Optimizing prophylactic cranial irradiation for patients with lung cancer

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曾海燕

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DISSERTATION

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By

Haiyan Zeng

曾海燕

Born on September 21st, 1988

in Ganzhou, Jiangxi, China

Promotor

Prof. dr. Dirk K.M. De Ruysscher

Co-promotors

Dr. Lizza E.L. Hendriks

Dr. Alberto Traverso

Assessment Committee

Prof. dr. Frits Franssen (Chair)

Dr. Monique Hochstenbag

Prof. dr. Ursula Nestle

Prof. dr. Sara Ramella

Dr. Leonard Wee

To my grandmother Kaoxiu Ning, a kindhearted nice lady

who lived in humble and optimistic.

致亲爱的奶奶宁考秀女士 —— 世间至纯至善至美的存在。

Contents

Abbreviations

Abbreviations	Full name	Chapters
ADLS	Activities of Daily Living Scale	7
AJCC	American Joint Committee on Cancer	1, 4
ALK	Anaplastic lymphoma kinase	1
ATE	Average Treatment Effect on the entire sample	2
ATT	Average Treatment Effect on the Treated	2
AUC-ROC	Area under the receiver operating characteristic curves	4, 9
BCI	Baseline cognitive impairment	8
BED	Biologically effective dose	2, 3
bid	Twice-daily	
BM	Brain metastases / Brain metastasis	1, 3, 4, 5, 6, 7, 8, 9
BMFS	Brain metastasis free survival	3
BMI	Body mass index	3, 4, 8
C	Control arm	1
CA125	Carbohydrate antigen 125	1
CA199	Carbohydrate antigen 199	1
CCRT	Concurrent chemoradiotherapy	1, 2, 3, 4, 7, 9
CEA	Carcinoembryonic antigen	1, 3
CEV	Cyclophosphamide-epirubicin-vincristine	3
Chemo	Chemotherapy	3
CI	Confidence interval	1, 2, 3, 4, 5, 7, 8
CNt	Chronic neurotoxicity	5
COC	Cognitive functioning category	8
COS	Cognitive functioning scale	8
COWA	Controlled Oral Word Association test	1, 5, 6, 7
CR	Cued recall	1, 7
CR	Complete response	3, 5
CRT	Chemoradiotherapy	3, 5
CRT-D	Chemoradiotherapy duration	3
CT	Computed tomography	1, 2, 3, 4, 5, 7
CTC	Circulating tumor cells	3
CTCAE	Common Terminology Criteria for Adverse Events	5
CVA	Cerebrovascular accident	7
DCA	Decision-curve analysis	4
DFS	Disease-free survival	5
DS-GPA	Disease-specific graded prognostic assessment	1
DTI	Dichotomize the outcome and then impute the binary response	8
E	Experiment arm	1
E	Expected number	3
ED	Extensive disease	1, 3, 5, 7, 9
EGFR	Epidermal growth factor receptor	1, 2
EORTC	European Organisation for Research and Treatment of Cancer	1
EORTC-QLQ-C30	The EORTC Quality-of-Life Questionnaire-C3	5, 6

Abbreviations	Full name	Chapters
EORTC QLQ-BN20	The EORTC Quality of Life Questionnaire–Brain Cancer Module	6
EP	Etoposide-platinum	1, 2, 3, 7
FACT-L	Functional Assessment of Cancer Therapy-Lung	1
FCSRT	Free and Cued Selective Reminding Test	1, 6, 7, 9
FR	Free recall	1, 7
GBM	Glioblastoma multiforme	5
GEE	Generalized estimating equation	7, 8
GTV	Gross tumor volume	1, 3, 4, 9
GTVn	Gross tumor volume of lymph nodes	1, 4, 9
GTVp	Gross tumor volume of primary tumor	1, 4, 9
HA-PCI	Hippocampal avoidance - prophylactic cranial irradiation	1, 5, 6, 7, 9
HA-WBRT	Hippocampal avoidance - whole-brain radiotherapy	5, 7, 9
HART	Hyperfractionated accelerated radiotherapy	1
HAZ	Hippocampal avoidance zone	7
HC	Healthy controls	5
HR	Hazard ratio	1, 2, 3, 4, 5, 9
HRQOL	Health-related quality of life	5
HT	Hypertension	5
HU	Hounsfield Units	4
HVLT-DR	Hopkins Verbal Learning Test-Delayed Recall	5
HVLT-R	Hopkins Verbal Learning Test-Revised	1, 5, 6, 8, 9
IBD	Impute the missing continuous outcome before dichotomizing the response	8
ICCTF	International Cognition and Cancer Task Force	5
ICI	Immune checkpoint inhibitors	1
IMRT	Intensity-modulated radiotherapy	3
IPTW	Inverse probability treatment weight	3
IPD	Individual patient data	3, 9
IQR	Interquartile range	2, 3, 4
IR	Incomplete response	3
KPS	Karnofsky Performance Status	1, 3, 5
KRAS	Kirsten rat sarcoma viral oncogene	1
LASSO	Least absolute shrinkage and selection operator regression	4
LC	Lung cancer	1, 9
LD	Limited disease	1, 3, 5, 7, 9
LDH	Lactate dehydrogenase	3
LS	The EORTC–RTOG Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale	5
LVI	Lymphovascular invasion	3
MDASI-BT	MD Anderson Symptom Inventory-Brain Tumor	6
MI	Multiple imputation	8
MMSE	Mini Mental Status Exam	5
MOS	Medical Outcomes Study	6
MRI	Magnetic resonance imaging	1, 2, 3, 4, 5, 6, 7, 8, 9

Abbreviations	Full name	Chapters
NA	Non-applicable	2, 3, 5
NCCN	National Comprehensive Cancer Network	1, 2
NCF	Neurocognitive function	5
ND	Neurologic deterioration	5
NI	No information	3, 5
NICE	National Institute for Health and Clinical Excellence	1
NLR	Neutrophil-to-lymphocyte ratio	3
NOS	The Newcastle-Ottawa-Scale	3
NPV	Negative predictive value	4, 9
NR	Non-response	3
NSCC	Non-squamous cell carcinoma	8
NSCLC	Non-small cell lung cancer	1, 3, 4, 5, 6, 8, 9
NSE	Neuron-specific enolase	1, 3
O	Observed number	3
ODRT	Once-daily radiotherapy	1, 2, 3, 4, 7, 9
OR	Odds ratio	3, 5, 8
OS	Overall survival	1, 3, 4, 5, 7, 8, 9
PCI	Prophylactic cranial irradiation	1, 3, 4, 5, 6, 7, 8, 9,
PD	Progressive disease	5
PD-L1	Programmed death ligand-1	1
PET-CT	Positron emission tomography- computed tomography	1, 2, 3, 4
PFS	Progression-free survival	1, 4, 9
PICO	Patient-Intervention-Comparison-Outcome	3, 5
PLR	Platelet-to-lymphocyte ratio	3
POMS	Profile of Mood States	5
PORT	Postoperative radiotherapy	3
PPV	Positive predictive value	4, 9
PR	Partial response	3
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses guideline	3, 5, 9
PS	Performance status	1, 3, 4, 5
PSM	Propensity score matching	9
qd	Once-daily	5
QOL	Quality of life	1, 2, 3, 5, 6, 7, 8, 9
RCI	Reliable changing index	1, 5
RCT	Randomized controlled trial	3, 5, 6, 9
RECIST	Response Evaluation Criteria in Solid Tumors	2
RoB2	Revised Cochrane risk-of-bias tool for randomized trials	3, 5
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions	3
ROI	Regions of interest	4
RS	Raw scores	1
RTOG	Radiation Therapy Oncology Group	1
SCC	Squamous cell carcinoma	8
SCLC	Small cell lung cancer	1, 3, 4, 5, 6, 7, 9
SCRT	Sequential chemoradiotherapy	1, 2, 3, 4, 7

Abbreviations	Full name	Chapters
SD	Stable disease	3
SD	Standard deviation	4, 5, 7, 8
SE	Standard error	8
SEOM	Sociedad Española de Oncología Médica (Spanish Society of Medical Oncology)	1
SER	Start of any therapy to the end of radiotherapy	2, 3
sHR	Subdistribution hazard ratio	1, 2, 3, 4, 7, 9
SRCF	Self-reported cognitive functioning	1, 5, 6, 7, 8, 9
SRS	Stereotactic radiosurgery	1, 3
SUV	Standardized uptake value	3
TD	Total irradiation dose	4
TDRT	Twice-daily radiotherapy	1, 2, 3, 4, 7, 9
TIA	Transient ischemic attack	7
TMT	Trail Making Test	1, 5, 6
TNM	Tumor Node Metastases	1, 3
TR	Total recall	1, 7
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guideline	4
TRT	Thoracic radiotherapy	3, 9
T2DM	Type 2 diabetes	5
UICC	Union for International Cancer Control	1
UK	United Kingdom	1
V	Variance	3
VALG	Veterans Administration Lung Study Group	1
WAIS-III	Wechsler Adult Intelligence Scale-III	7
WBRT	Whole brain radiation therapy / whole brain radiotherapy	1, 5, 6, 9
2D	Two-dimensional radiotherapy	3
3D	Three-dimensional radiotherapy	3

Chapter 1

General introduction and outline of the thesis

Haiyan Zeng

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1. Lung cancer

Lung cancer has become the second most common diagnosed cancer and the leading cause of cancer related deaths in men and women[1]. This is highly linked to cigarette smoking patterns, especially in small cell lung cancer (SCLC)[2]. When grouping all stages and pathologies together, the 5-year survival rate is 21%[3]. SCLC comprises 13-20% of all lung cancer cases[3,4]. Compared with non-small cell lung cancer (NSCLC), SCLC is much more aggressive. This is reflected in rapid growth, often already metastases at diagnosis, responsiveness to chemotherapy and radiotherapy, and short disease-free duration after initial treatment[5]. Consequently, SCLC and NSCLC are regarded as two distinct diseases and are managed differently.
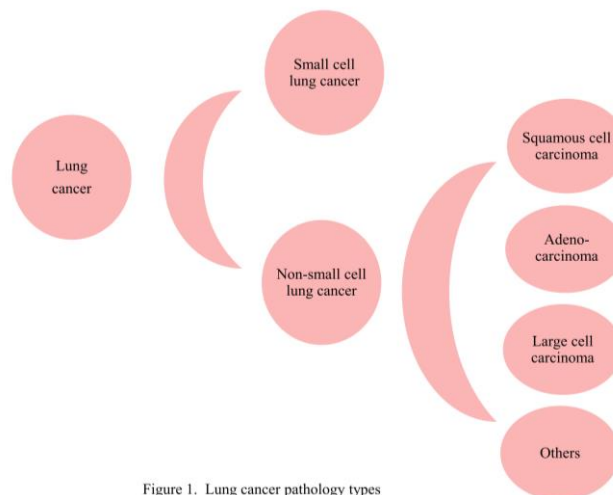
Figure 1. Lung cancer pathology types

Previously, the staging system was also different. For NSCLC, the Tumor Node Metastases (TNM) classification (T0-4, N0-3, M0-1, stage I-IV) has been used for decades. The TNM classification was invented and developed by Prof. Pierre Denoix between 1943-1952 and further developed and improved by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC)[6,7]. In contrast, for SCLC, the Veterans Administration Lung Study Group (VALG) staging system of simply "limited disease (LD)" and "extensive disease (ED)", mainly based on the radiation field, has been used for years, as it has proven to be adequate for most clinical situations[8,9]. Trials showed that surgery in early stage did not result in improved overall survival (OS) compared with radical radiotherapy[10] and chemotherapy[11]. Fortunately, with advances in staging procedures as well as multidisciplinary treatments, it has become clear that SCLC should also be further subdivided in more detailed stages[12-14]. Therefore, it was recommended that the VALG staging system should be replaced by the UICC/AJCC TNM classification system for patients with SCLC[15], particularly the revised 7th version (2007)[16] and the 8th version (2017)[17].

Furthermore, the progress in the development of new therapies is not balanced between the two histologies. In NSCLC, targeted agents for oncogene driven cancers (such as the third-generation epidermal growth factor receptor [EGFR] inhibitor, osimertinib; the next-generation anaplastic lymphoma kinase (ALK) inhibitors, alectinib, brigatinib, lorlatinib) and immune checkpoint inhibitors (ICI) for the others (like pembrolizumab, nivolumab[18,19] and durvalumab[20,21]) significantly improved the survival: the 3-year survival rate for all stages of NSCLC increased from 25% during 2004-2006 to 38% during 2016-2018[22].

Not only the 3-year, but also the 5-year survival improved. Specifically, the KEYNOTE-189 trial showed that pembrolizumab improved the 5-year OS from 11.3% to 19.4% (hazard ratio [HR]=0.6, 95% confidence interval [CI] 0.50-0.72) in patients with treatment naïve stage IV nonsquamous NSCLC who had no EGFR/ALK alterations[23]; the KEYNOTE-407 trial showed that pembrolizumab improved the 5-year OS from 9.7% to 18.4% (HR=0.71, 95%CI 0.59 - 0.85) in patients with treatment naïve stage IV squamous NSCLC[24], For those with a programmed death ligand-1 (PD-L1) tumor proportion score ≥50% who had no EGFR/ALK alterations, the KEYNOTE 024 trial showed that pembrolizumab improved the 5-year OS from 16.3% to 31.9% (HR=0.62, 95%CI 0.48 - 0.81)[25]. Also dual immunotherapy has been successful: for NSCLC patients who had no EGFR/ALK alterations, the CheckMate 227 trials showed that nivolumab alone did not improve OS significantly, but nivolumab + ipilimumab increased the 5-year OS from 14% to 24 % in patients with a PD-L1 expression≥1%, and the 5-year OS increased from 7% to 19% in those with a PD-L1 expression<1%[26]. In patients with stage IV EGFR mutated NSCLC, 5-year OS rate of those treated with first line gefitinib + carboplatin + pemetrexed versus monotherapy gefitinib was 39%, and 34%, respectively (HR, 0.822; 95% CI, 0.639-1.058, p=0.127) [27]. For first line osimertinib, 5-year survival rates are not available yet. For patients with ALK rearranged NSCLC, 5-year OS rate of those treated with alectinib improved to 62.5% compared with 34.9% for crizotinib (HR, 0.67; 95% CI, 0.46-0.98)[28] (Table 1).

Table 1. 5-year OS in first line treated metastatic NSCLC

Trials	Patients	Intervention and sample size	5-year OS
KEYNOTE-189[23]	Stage IV, nonsquamous, EGFR/ALK (-)	E: pembrolizumab + chemotherapy (n=410); C: placebo+ chemotherapy (n=206).	E: 19.4% (95% CI 15.7 - 23.4); C: 11.3% (95% CI 7.4 - 16.1); HR=0.6, 95%CI 0.50 - 0.72
KEYNOTE-407[24]	Stage IV, squamous	E: pembrolizumab+ chemotherapy (n=278); C: placebo + chemotherapy (n=281).	E: 18.4% (95%CI 13.8 - 23.4); C: 9.7% (95%CI 6.5 - 13.7); HR=0.71, 95%CI 0.59 - 0.85
KEYNOTE-024[25]	Stage IV, PD-L1≥50%; EGFR/ALK (-)	E: pembrolizumab (n=154); C: chemotherapy (n=151)	E: 31.9%; C: 16.3%; HR=0.62, 95%CI 0.48 - 0.81
CheckMate 227[26]	Stage IV, EGFR/ALK (-)	*PD-L1 ≥ 1%:* E1: nivolumab + ipilimumab (n=391); E2: nivolumab alone (n=391); C: chemotherapy (n=387).	*PD-L1 ≥ 1%:* E1: 24%; E2: 17%; C: 14%; E1 vs C: HR, 0.77; 95%CI, 0.66 - 0.91 E2 vs C: HR, 0.92; 95%CI, 0.79-1.07
		PD-L1 < 1%: E1: nivolumab + ipilimumab (n=185); E2: nivolumab + chemotherapy (n=172); C : chemotherapy (n=183).	*PD-L1 < 1%:* E1: 19%; E2: 10%; C: 7%; E1 vs C: HR, 0.65; 95% CI, 0.52-0.81 E2 vs C: HR, 0.80; 95% CI, 0.64 -1.00
NEJ009[27]	Stage IV, EGFR (+)	E: GCP (n=169); C: gefitinib alone (n=172)	GCP: 39%; Gefitinib: 34%; HR, 0.82; 95% CI,0.64-1.06, *p*=0.13
ALEX[28]	Stage III/IV, ALK (+)	E: alectinib (n=152); C: crizotinib (n=151).	Alectinib: 62.5%(95% CI 54.3-70.8) ; Crizotinib: 45.5%(95% CI 33.6-57.4); HR, 0.67; 95% CI, 0.46 - 0.98

Abbreviations: ALK, anaplastic lymphoma kinase; C, control; CI: confidence interval; E, experiment; EGFR, epidermal growth factor receptor; GCP, gefitinib+carboplatin+pemetrexe; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1.

In contrast, the achievements in SCLC have been more limited. The CheckMate 331 trial showed that compared with second-line chemotherapy (topotecan or amrubicin), nivolumab did not improve the OS of relapsed SCLC (median OS, 7.5 months in nivolumab versus 8.4 months in chemotherapy; HR 0.86; 95%CI 0.72-1.04; $p = 0.11$)[29], Although ICI in combination with chemotherapy (etoposide-platinum, EP) did result in survival benefit, and changed the first-line treatment for metastatic SCLC (ICI either being durvalumab[30] or atezolizumab[31]), the improvements were modest. For example in the CASPIAN trial durvalumab prolonged the median OS from 10.3 months to 13.0 months [HR=0.73, 95% CI 0.59–0.91; p=0.0047] [30]; while this was 12.3 versus 10.3 months in the IMpower133 trial with atezolizumab [HR=0.70, 95% CI 0.54–0.91; p=0.007][31]; CAPSTONE-1: adebrelimab prolonged the median OS from 12.8 months to 15.3 months [HR=0.72, 95% CI 0.58–0.90; p=0.0017][32]; ASTRUM-005: serplulimab

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improved the median OS from 10.9 months to 15.4 months [HR=0.63, 95% CI 0.49–0.82; p<0.001][33]). The 3-year OS rate for all stages of SCLC remained dismal and steady at 9% to 12%[22]. In the recent update of the CASPIAN trial, durvalumab improved the 3-year OS of stage IV SCLC from 5.8% to 17.6% (HR=0.71, 95%CI 0.60-0.86, p = 0.0003), while adding tremelimumab to chemotherapy plus durvalumab did not result in an OS improvement (3-year OS 15.3%)[34] (Table 2).

Table 2. OS in metastatic SCLC

Trials	Patients	Intervention and sample size	median OS / 3-year OS
CheckMate 331[29]	relapsed SCLC	E: nivolumab (n=284); C: chemotherapy (topotecan/amrubicin) (n=285)	E: 7.5 months (95% CI 5.6-9.2); C: 8.4 months (95% CI 7.0-10.0); HR 0.86; 95%CI 0.72-1.04; p=0.11
CASPIAN[30]	treatment-naïve ED-SCLC	E: durvalumab + EP (n=268); C : EP (n=269)	E: 13.0 months (95% CI 11.5-14.8); C: 10.3 months (95% CI 9.3–11.2); HR=0.73, 95% CI 0.59–0.91; p=0.0047
CASPIAN-updated OS[34]	treatment-naïve ED-SCLC	E1: durvalumab + EP (n=268); E2:durvalumab+tremelimumab+EP (n=268); C : EP (n=269)	*Median OS*: E1: 12.9 months (95% CI 11.3-14.7); E2: 10.4 months (95% CI 9.5-12.0); C : 10.5 months (95% CI 9.3-11.2); *3-year OS*: E1: 17.6% (95% CI 13.3-22.4); E2: 15.3% (95% CI 11.2-19.9); C: 5.8 % (95% CI 3.4-9.1); E1 vs C: HR=0.71, 95%CI 0.60-0.86, p = 0.0003; E2 vs C: HR 0.81, 95% CI 0.67-0.97, p= 0.0200
IMpower133[31]	treatment-naïve ED-SCLC	E: atezolizumab +EP (n=201) C: placebo+ EP(n=202)	E: 12.3 months (95% CI, 10.8–15.9); C: 10.3 months (95% CI, 9.3–11.3); HR=0.70, 95% CI 0.54–0.91; p=0.007
CAPSTONE-1[32]	treatment-naïve ED-SCLC	E: adebrelimab+EP (n=230) C: placebo+ EP(n=232)	E: 15.3 months (95% CI, 13.2-17.5); C: 12.8 months (95% CI, 11.3-13.7); HR=0.72, 95% CI 0.58–0.90; p=0.0017
ASTRUM-005[33]	treatment-naïve ED-SCLC	E: serplulimab + EP (n = 389); C: placebo + EP (n = 196).	E: 15.4 months (95%CI 13.3 –not evaluable); C: 10.9 months (95%CI 10.0-14.3); HR=0.63, 95% CI 0.49–0.82; p<0.001

Abbreviations: C, control; CI: confidence interval; E, experiment; EP, etoposide + cisplatin/carboplatin; HR, hazard ratio; ED-SCLC, extensive disease-small cell lung cancer; OS, overall survival.

Furthermore, patients with SCLC have a higher risk of brain metastases (BM), and management is different compared with NSCLC as discussed below.

2. Brain metastases

BM are frequently diagnosed in patients with lung cancer. Especially those with SCLC or NSCLC adenocarcinoma histology are at risk[35]. About 20% of patients with stage IV lung cancer will have BM at the time of diagnosis and up to 50% of patients will develop BM during the course of their disease[36]. Magnetic resonance imaging (MRI) is the best imaging method to detect BM and is superior to computed tomography (CT) of the brain[37-39]. According to guidelines, brain imaging (preferably MRI) is recommended to screen asymptomatic BM in patients with SCLC[40,41]. However, screening for BM by MRI is controversial in patients with NSCLC[42].

BM have a considerable impact on quality of life (QOL) because of the associated symptoms like headache, vomiting, seizures, limb weakness, gait disorders, sensory changes, language disorders, visual deficits, and cognitive decline[43]. BM are also associated with a decreased survival, as curative intent treatment is seldom possible, and except for some of the newer targeted therapies, systemic therapies often have a poor blood-brain barrier penetration, limiting the duration of disease control on systemic therapy[43,44]. Local treatments for BM mainly include brain irradiation (stereotactic radiosurgery [SRS] and/or whole brain radiation therapy [WBRT]) and surgical resection[36,43]. In the earlier reports from 1970s, the median OS was only 3 months[45]. If left untreated, it was less than 2 months[46].

Nowadays, although survival in general is still dismal, patients with NSCLC and favorable prognostic factors, such as younger age, good Karnofsky Performance Status (KPS), no extracranial metastases and especially the presence of an oncogenic driver, can reach a median survival of around 4 years[47]. The lung-molGPA score is an updated disease-specific graded prognostic assessment (DS-GPA) for patients with NSCLC using molecular markers, which includes six prognostic factors: age, KPS, extracranial metastases, number of BM, EGFR mutation, and ALK alteration[47]. In contrast, patients with SCLC usually have a median OS of less than half a year, and only those with favorable prognostic factors such as <50 years-old, KPS 90-100, no extracranial metastases, and solitary BM can reach a median OS of around 17 months[48].

The above data clearly demonstrates that the survival of patients varies a lot and depends on patient and tumor related factors. However, as the majority of patients diagnosed with BM have a poor OS, ideally, the development of BM should be prevented. Prophylactic cranial irradiation (PCI) is a proven effective preventive treatment, but comes at a risk of neurotoxicity, as is described in part 3 and 4 of this introduction. Lung cancer treatment could be further personalized if only patients at high risk of BM, but low risk of neurotoxicity, would receive PCI.

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Several studies evaluated the risk factors for BM in patients with lung cancer. In one retrospective series (N=185) including patients with SCLC who did not undergo PCI, 85 patients developed BM, the risk of BM was significantly higher in younger patients (<65) ($p < 0.03$). hypertension (which increases cerebral blood velocity and damages the arterial wall), sex, body mass index (BMI), and the location of SCLC were not associated[49]. In another retrospective study (N=175) including patients with SCLC who underwent PCI, 36 patients developed BM. Thoracic hyperfractionated accelerated radiotherapy (HART), or twice-daily radiotherapy (TDRT) (HR 2.171, 95% CI 1.111–4.243, $p = 0.023$) and stage IIIB-IV (HR 2.525, 95% CI 1.259–5.064, $p = 0.009$) were independent risk factors for BM after PCI. Other factors such as age, sex, smoking history, response to initial therapies, concurrent chemoradiotherapy (CCRT)/sequential chemoradiotherapy (SCRT) and chemotherapy cycles were not significant[50]. In contrast, a secondary analysis based on data from a prospective clinical trial, the CONVERT trial, showed that compared with once-daily radiotherapy (ODRT), TDRT was not associated with BM development (subdistribution hazard ratio [sHR] 0.95; 95%CI 0.60-1.50, $p = 0.83$), but gross tumor volume (GTV) (sHR 1.43, 95%CI 1.11-1.85, $p = 0.006$) and performance status (PS) (sHR 0.54, 95%CI 0.32–0.90, $p = 0.018$) were independent risk factors. PCI timing, PCI dose, weight loss, and type of baseline brain imaging (MRI versus CT scan) were not associated with the occurrence of BM ($p > 0.05$)[51]. As conflicting results were presented from relatively small and often retrospective studies, future studies are still warranted, especially thoracic TDRT, which is usually recommended for patients with SCLC in radiotherapy guidelines[52], If TDRT would be confirmed to be associated with BM, this should be taken into account in the treatment decision and plan[50].

For NSCLC, it has been suggested based on systematic reviews, including mainly small retrospective series, that younger age, higher PS, female sex; adenocarcinoma or non-squamous cell carcinoma pathology type; advanced TNM stage; EGFR mutation, ALK fusion, kirsten rat sarcoma viral oncogene (KRAS) gene mutation; higher levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), cytokeratin-19 fragment, neuron-specific enolase (NSE), and carbohydrate antigen 125 (CA125) are risk factors[53,54].

Unfortunately, in prospective clinical trials risk factors for BM are seldom evaluated, and as stated above, the available data is mainly from (small) retrospective series, limiting the applicability. Furthermore, risk prediction models solely based on clinical factors are not reliable enough to use in daily clinical care for decision making[55,56]. Therefore, other types of analysis are necessary.

As an emerging quantitative imaging analysis technique, radiomics provides more objective measures than a human-only visual analysis[57]. It is possible that radiomics parameters could be useful in the identification of patients at high risk of BM. Metastases develop through "wiring" of the primary to spread metastases to a certain organ, and that organ is prepared for future metastases homing ("seed and soil")[58], and the "seed" eventually grows into overt metastases sites ("fruit") (Figure 2). These cells remain dormant for some time in the target organ
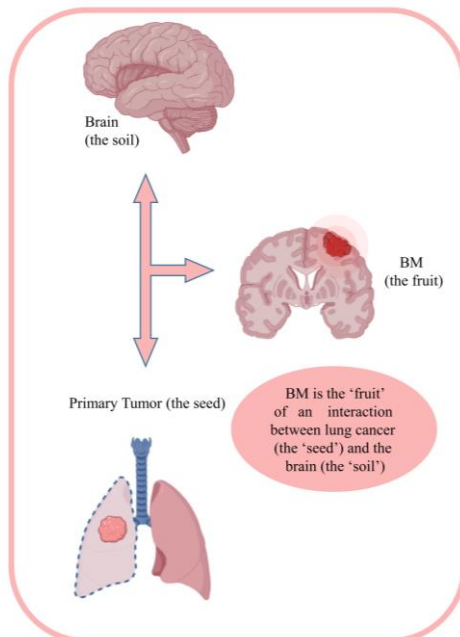
Figure 2. Lung cancer and BM (seed – soil – fruit)

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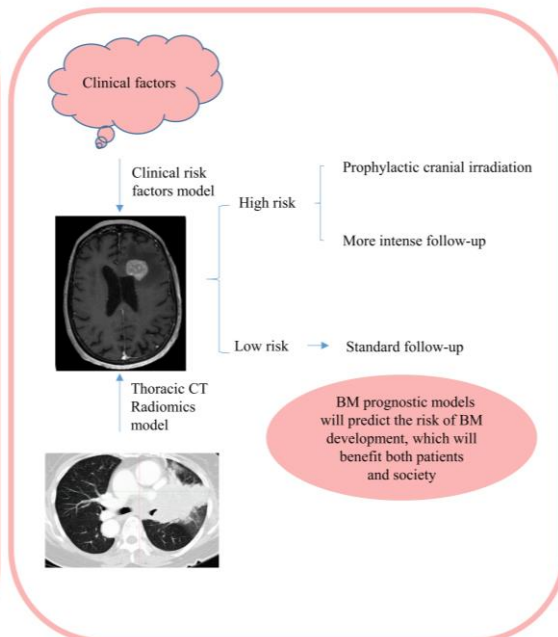
Figure 3. BM prognostic models

Abbreviations: BM, brain metastases

(metastatic niche, e.g. in the brain) and cannot be detected visually by radiologists. However, these microscopic metastases already change their tumor micro-environment to make it more susceptible to future outgrowth of macroscopic metastases. It could be that this can already be detected by radiomics analysis, but not by just looking at the images. Furthermore, there are more and more data that for example exosomes already prepare a certain organ for the future homing of a metastatic cell[59]. With the advances in radiomics, the genotype might be linked to the imaging phenotypes[60]. Indeed, animal experiments did show that texture features may quantitatively detect liver metastases before they become visually detectable by radiologists[61]. Human radiogenomics analysis also reveals that a prognostic radiomic signature, capturing intratumour heterogeneity, is associated with underlying gene-expression patterns[62]. In addition, data do indicate that radiomics can predict different somatic mutations drive radiographic phenotypes[63]. Furthermore, studies do show that chest computed tomography (CT)-based radiomics models using the primary tumor might have positive value to predict BM in patients

with NSCLC NSCLC[64,65]. However, the published studies are hampered by small sample size (89 patients and 105 patients, respectively), no positron emission tomography-computed tomography (PET-CT) for TNM staging, overfitting, selecting bias, no cranial magnetic resonance imaging (MRI) to exclude BM at baseline, etc. Therefore, better executed studies with a higher number of adequately staged patients are necessary to further evaluate the role of radiomics in the prediction of BM in lung cancer.

In short, BM prognostic models based on chest CT radiomics features and clinical factors could predict BM development in patients with lung cancer and in return help improve patients care, which will benefit both patients, family, and the whole society (Figure 3).

3. Prophylactic cranial irradiation (PCI) / hippocampal avoidance (HA)-PCI

Prophylactic cranial irradiation (PCI) is prophylactically irradiating the brain before overt BM involvement. PCI is not intended to prevent BM, but eradicates microscopic disease not visible on brain imaging. Ideally, PCI should be recommended only for patients who are at high risk of developing BM, as they are more likely to harbor occult microscopic metastases.

Historically, PCI was firstly proposed and applied in childhood acute lymphocytic leukemia who achieved an M1 marrow status (the percentages of residual blasts by morphological assessment<5%[66]), as the prolongation of OS had led to a growing recognition of the brain, a pharmacological sanctuary, as a major site of relapse[67,68]. Then, the PCI concept was extended to patients with SCLC[69], as the percentage of patients who will develop BM is as high as 50–80%[70]. Several randomized trials evaluated the usefulness of PCI in this setting and revealed that PCI not only reduces the prevalence of BM but also improves the OS in SCLC, especially in LD patients with complete response to chemoradiotherapy[68,71-75].

In the landmark randomized phase III EORTC trial, enrolling patients with ED-SCLC who had no progression after chemotherapy, PCI reduced the incidence of symptomatic BM from 41.3% to 16.8% (HR 0.27, 95% CI 0.16-0.44, $p<0.001$), prolonged median progression-free survival (PFS) from 12.0 weeks to 14.7 weeks (HR 0.76, 95% CI 0.59-0.96, $p=0.02$), and improved median OS from 5.4 months to 6.7 months (HR 0.68, 95% CI 0.52-0.88; $p=0.003$)[72]. In contrast, Takahashi *et al* conducted a phase III randomized controlled trial in Japan and showed that compared with MRI follow-up, even though PCI combined with MRI follow-up reduced BM incidence (1 year BM: 32.9% in the PCI group vs 59.2% in the control group, $p<0.0001$), it did not improve OS (HR 1.27, 95% CI 0.96-1.68; $p=0.094$) in patients with ED-SCLC who had no BM on MRI[76]. Major differences in trial design (primary endpoint, MRI

screening and follow-up) are probably the explanation for the differences in outcomes between the EORTC trial and the Japanese trial.

The results of the Japanese trial significantly changed the recommendations in the guidelines for patients with stage IV SCLC. Since then, both PCI and cranial MRI surveillance are recommended for patients with ED-SCLC[40,41,77-86]. The SEOM[41] and NCCN[83] recommend MRI surveillance regardless of PCI status. These MRI follow-up recommendations pose significant challenges to healthcare systems due to the lack of access to MRI. The NICE committee specified that the Japanese trial was not applicable for UK because UK has much less MRI scanners per million population than Japan (6 versus 52)[85]. Therefore, such a frequent MRI follow-up was impractical in UK[87], as in many other countries worldwide.

PCI might have negative effects on neurocognitive function and QOL[88,89], probably because of radiation injury to the hippocampal area, which plays an important role in memory and learning[90]. Inspired by the promising results from the RTOG 0933 trial, which showed that compared with historical control whole-brain radiotherapy (WBRT), HA-WBRT was associated with preservation of neurocognition and QOL[91], HA-PCI has been investigated in SCLC to evaluate the potential benefit on neurocognitive outcome[92] (Figure 4).
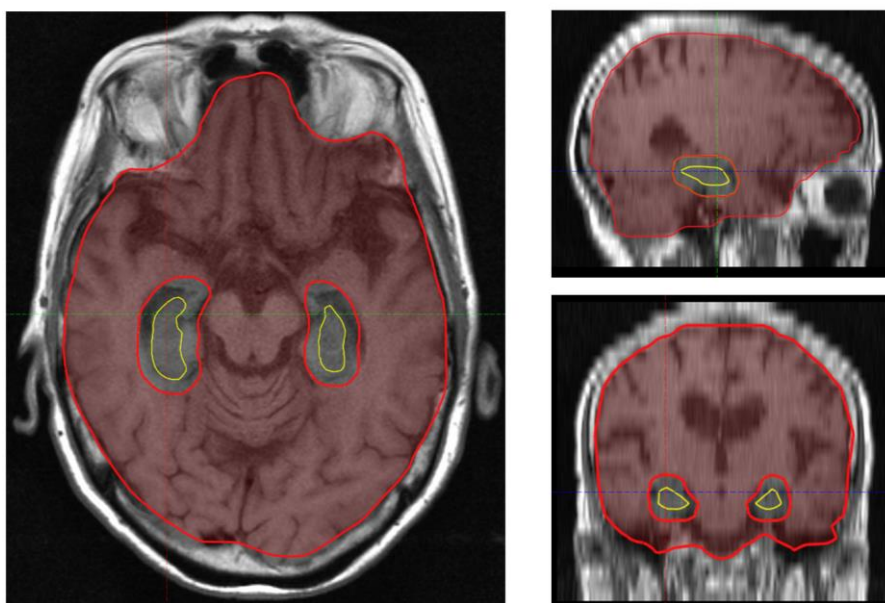
Figure 4. Hippocampal avoidance-prophylactic cranial irradiation (HA-PCI)

Prophylactic cranial irradiation (PCI) is prophylactically irradiating the whole brain before overt brain metastases involvement. Hippocampal avoidance-prophylactic cranial irradiation (HA-PCI) is a special PCI that irradiating the whole brain except for the hippocampal zone (the red shadow). The hippocampal avoidance zone is the hippocampus (contoured with the yellow line) with a 5mm margin.

A prematurely closed trial (20 patients enrolled, stopped early to support NRG CC003 trial) showed that HA-PCI resulted in less cognitive toxicities, but with a cost of higher risk of BM

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in the under-dosed zone[92]. In 2021, two comparable phase III randomized controlled trials, the Dutch-Flemish NCT01780675 trial[93] and the Spanish PREMER/NCT02397733 trial[94] were published with conflicting results about the role of HA-PCI on neurocognitive function in patients with SCLC. The Dutch trial showed that the percentage of patients with cognitive decline (measured by Hopkins Verbal Learning Test-Revised [HVLT-R]) was not significantly different between both arms (28% for HA-PCI vs 29% for PCI, p=1.000)[93]. In contrast, the Spanish trial revealed that the percentage of patients with cognitive decline (measured by Free and Cued Selective Reminding Test [FCSRT]) after HA-PCI was significantly lower compared with PCI (5.8% for HA-PCI vs 23.5% for PCI, p=0.003)[94]. The upcoming results of the phase III NRG-CC003 trial are eagerly awaited to provide more clarity[95].

Meanwhile, the effects of PCI have also been investigated in patients with NSCLC[96-98]. However, even with advances in multi-disciplinary treatments, PCI trials in patients with stage III NSCLC still failed to show the OS benefit despite a significant reduction in the incidence of BM [99-103]. Correspondingly, PCI remains not a standard of care in patients with NSCLC[42].

4. Cognitive impairment /Cognitive decline

Cognitive decline is a rising concern for patients who need cranial irradiation[104], especially regarding PCI for patients without BM[105], or WBRT for patients with BM[106]. However, the assessment of cognitive decline is difficult since patient compliance with longitudinal neurocognitive testing remains challenging[107]. In addition, cognitive function is influenced by various factors including the disease itself, paraneoplastic syndromes, undiagnosed micrometastases, depression, anxiety, age and smoking[108,109]. These factors were not systematically taken into account in the published trials evaluating the effects of (HA)-PCI on cognition. Furthermore, decline in patient self-reported cognitive functioning (SRCF) is not closely correlated with decline in objective neurocognition tested by neuropsychological tests[110]. On top of that, cognitive function is typically conceptualized in multiple domains of functioning, which are hierarchical from the bottom (more basic sensory and perceptual processes) to the top (executive functioning and cognitive control) and not independent from each other[111].

SRCF can be assessed using the cognitive functioning scale on the questionnaire EORTC-QLQ-C30[112]. This is a self-administered, cancer-specific, structured questionnaire containing 30 items, which consists of one global health status scale, three symptom scales (nausea/vomiting, pain, and fatigue), five functional scales (cognitive, physical, role, emotional and social), and six single items (appetite loss, dyspnea, constipation, diarrhea, insomnia, and

financial problems). Each scale score is calculated by averaging items within the scale and transforming average score linearly, which ranges from 0 to 100[113]. A higher score for a symptom scale (such as fatigue and pain) or item (like dyspnea and insomnia) represents a severer symptom or problem, while a higher score for a functional scale (such as cognitive functioning, role functioning) represents a better functioning.

The cognitive functioning scale consists of two items:

I_{20}, concentration: Have you had difficulty in concentrating on things, like reading a newspaper or watching TV?

I_{25}, memory: Have you had difficulty remembering things?

Each item has four possible raw scores (RS): 1=Not at all; 2=A little; 3=Quite a bit; 4=Very much. Therefore, the SRCF score has seven possibilities (0, 16.7, 33.3, 50.0, 66.7, 83.3, 100) according to the linear transformation formula: $S=[1-(RS-1)/range]\times100$, where $RS=(I_{20} + I_{25})/2$, rang =maximum possible RS–minimum possible RS=3 [113].

Self-reported cognitive impairment is defined as a score of SRCF <75[89].

Self-reported cognitive decline is defined as a delta SRCF between two time points (usually compared with baseline) ≤ -10. Stable is defined as a |delta SRCF| <10. Improvement is defined as a delta SRCF ≥ 10 [114].

Objective neurocognitive function is assessed by neuropsychological tests (Table 3).

Table 3. Commonly used neuropsychological tests

Domains	Tests
learning and memory	Hopkins Verbal Learning Test—Revised (HVLT-R) [114]; Free and Cued Selective Reminding Test (FCSRT) [115,116]
Attention	Trail Making Test (TMT) A and B[117,118], Digit symbol;
Memory	Wechsler Adult Intelligence Scale III digit span (Digit span forward, Digit span backward)
Speed of processing	Controlled Oral Word Association (COWA) test (COWAB/P, COWAD/M, COWAH/W, COWAtotal)[119]
Motor skills	Lafayette's Grooved Pegboard test (Dominant hand, Non-dominant hand)[120]

The HVLT-R test consists of a 12-item word list that is read to subjects on three successive learning trials. Free recall scores are recorded for each learning trial (Recall 1, Recall 2, Recall 3, Total recall). After 20-25 minutes break, subjects are asked to recall as many of the words as possible (Delayed recall). Then, a yes/no recognition task is presented (True positive hits, Semantic-related false-positives, Semantic-unrelated false-positives, False-positives, Recognition)[115].The FCSRT test consists of a 16-items presented four at a time on a card with three recall trials, which involves two parts (freely recall and cued recall), resulting in Free recall-1 (FR1), Cued recall-1(CR1), Total recall-1 (TR1); FR2, CR2, TR2; FR3, CR3, TR3; Total Free recall (FR1+FR2+FR3); Total recall (TR1+TR2+TR3). After 30 minutes break, the

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same procedure of freely recall and cued recall is done (delayed recall, DR), resulting in Free delayed recall (FDR), Cued DR (CDR), and Total DR (TDR)[122] .

The cut-off value (threshold) of objective neurocognitive decline is defined by reliable changing index (RCI)[123,124]: $RCI = 1.64 \times S_{diff}$; $S_{diff} = \sqrt{2(s_E)^2}$; $S_E = s_1\sqrt{1 - r_{xx}}$; where r_{xx} is the test-retest reliability statistic, s_1 is the standard deviation of the test. The threshold is rounded by the nearest whole number. Therefore, the thresholds of recall 1, recall 2, recall 3, total recall, delayed recall, true positive, false-positive of HVLT-R[115] are 3, 2, 2, 5, 3, 2, 1, and 2, respectively. The thresholds of free recall 1, total free recall, total recall, free delayed recall, total delayed recall of FCSRT[125] are 4, 9, 6, 5, and 3, respectively.

In this thesis, I focused more on the SRCF, as this is what patients think and feel based on their own needs and expectations towards a "normal" level. For example, younger patients might expect more for cognitive functioning in daily life, while elder patients might be less picky (do not report because of less sensitive to the cognitive functioning questionnaires or more acceptable to fact of having cancer).

5. Quality of life

Quality of life (QOL) is an important aspect of cancer patients, especially for those long-term survivors. Therefore, clinical trials that comparing two or more treatment strategies always report the QOL as one of the secondary endpoints. Questionnaires that are frequently used for evaluating QOL include: EORTC-QLQ-C30, EORTC QLQ-BN20 questionnaire[126], and Functional Assessment of Cancer Therapy-Lung (FACT-L)[127]. Cognitive functioning consists an important part of QOL, but QOL also includes other key aspects of daily life, such as role functioning, physical functioning, emotional functioning, fatigue, motor dysfunction, future uncertainty, visual disorder, communication deficit, headaches; seizures; drowsiness; itchy skin; hair loss; weakness of legs; bladder control. These are all indispensable for patients. Assessing these functions and symptoms thoroughly will help clinicians evaluate the effects of managements or new treatment strategies better.

6. Aim and outline of the present thesis

As stated above, lung cancer is the leading cause of cancer related deaths and has a high incidence of BM. PCI is an effective method to reduce the incidence of BM with a risk of cognitive impairment. Therefore, PCI treatment should be optimized and personalized for patients with SCLC as well as NSCLC, by identifying patients who are at high risk of

developing BM, and who are more likely to experience cognitive impairment. PCI should be administered only selectively to patients who are at high risk for BM, among whom who are at high risk for neurocognitive decline, personalized PCI should be considered and neuroprotective agents should be evaluated specifically. PCI should be forgone in patients who are at low risk for BM and at high risk for neurocognitive decline. An outline of the thesis is presented in Figure 3 and described below.
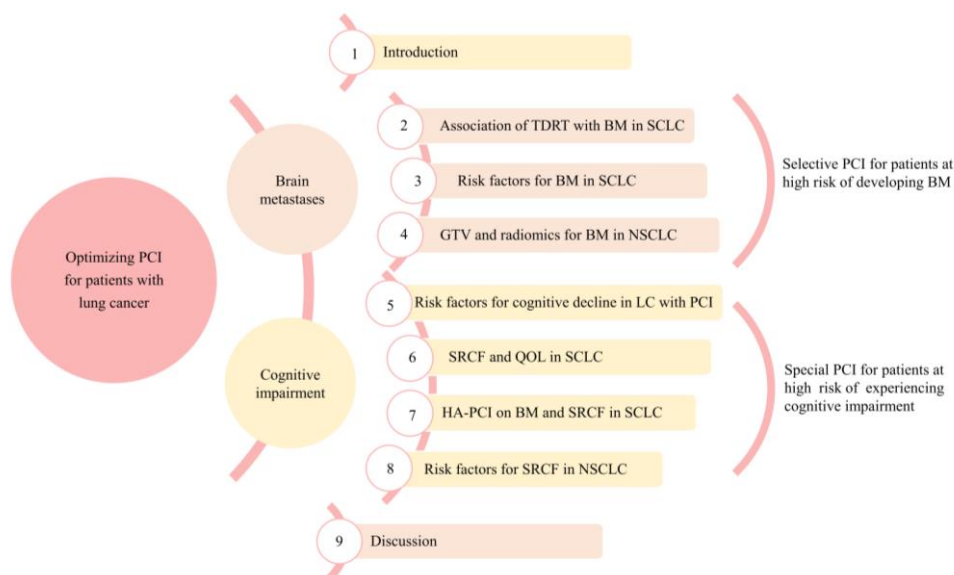
Figure 5. Thesis outline

Abbreviations: BM, brain metastases; GTV, gross tumor volume; LC, lung cancer; NSCLC, non-small cell lung cancer; PCI, prophylactic cranial irradiation; QoL, quality of life; SCLC, small cell lung cancer; SCRF, self-reported cognitive functioning; TDRT, twice-daily radiotherapy.

Chapter 2 is a multicenter retrospective study in patients with SCLC who underwent PCI. I compared whether the incidence of BM was different for thoracic ODRT and TDRT using a propensity score matching approach to control for confounders. This study was conducted in China to compare the findings with the European CONVERT trial.

In **Chapter 3**, I performed a systemic review and meta-analysis of the available literature to identify risk factors associated with BM development in SCLC.

In **chapter 4**, I investigated risk factors for BM in patients with adequately staged and radically treated stage III NSCLC. I developed prediction models for BM based on clinical (including GTVs) variables and radiomics features of GTV-lymph nodes [GTVn], GTV-primary tumor [GTVp] and GTV on the planning contrast-enhanced chest CT for thoracic radiotherapy.

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In **chapter 5**, I systematically evaluated risk factors associated with neurocognitive decline after PCI in patients with lung cancer.

As an important aspect for patients, SRCF and QOL should be evaluated in interventional trials. Therefore, in **Chapter 6,** I compared the SRCF and QOL between conventional PCI and HA-PCI in patients with SCLC based on the phase III randomized controlled trial NCT01780675.

In **Chapter 7**, I pooled the two most recent comparable multi-centric phase III RCTs, the Dutch-Flemish NCT01780675 trial and the Spanish PREMER/NCT02397733 trial, to compare the SRCF and BM (incidence and location) after conventional PCI versus HA-PCI in patients with SCLC.

In **chapter 8**, I investigated risk factors for cognitive impairment in patients with NSCLC using the longitudinal data from the phase III NVALT-11 trial, which evaluated PCI versus observation in radically treated stage III NSCLC.

Chapter 9 is a general discussion and future directions based on the aforementioned chapters.

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Chapter 2

Association of twice-daily radiotherapy with subsequent brain metastases in adults with small cell lung cancer

Zeng H[†], Li R[†], Hu C[†], Qiu G[†], Ge H, Yu H, Zhang K, Hu M, Zeng P, Xiao D, Miao C, Wei C, Ni M, Shen J, Li H, Yue J, Lu H, Fan B, Zhu H, Hu X, Kong FM, Yu J*, Yuan S*

[†] Equal contributing

*Corresponding authors

2

Abstract

Importance: Although thoracic twice-daily radiotherapy (TDRT) is one of standard of cares for small-cell lung cancer, its impact on brain metastases remains unknown.

Objective: To compare TDRT with once-daily radiotherapy (ODRT) for the brain metastases after prophylactic cranial irradiation in small-cell lung cancer.

Design: Consecutive small-cell lung cancer patients were retrieved from eight hospitals' databases in China between 2003 and 2016.

Setting: Multicenter.

Participants: A total of 894 patients were screened, among whom 778 with thoracic radiotherapy (609 in ODRT vs. 169 in TDRT), chemotherapy, and prophylactic cranial irradiation were eligible and included for further analysis. A 1:1 propensity score matching approach was used to control confounding between ODRT and TDRT groups. Confounding covariates included eight demographic variables and eight treatment related covariates.

Exposures: ODRT group: 50-66Gy/25-33f.

TDRT group: 45Gy/30f.

Main Outcomes and Measures: The primary endpoint was brain metastases. The secondary endpoints included progression-free survival and overall survival. Data analysis was conducted November 2017 to May 2018 and reanalyzed for revision.

Results: Of the 778 patients with median age of 55-year (interquartile range [IQR], 48-61), 204 (26.2%) were female. At a median follow-up time of 23.6 months (IQR, 14.2-38.2), 131 (16.8%) experienced brain metastases. The rates in TDRT were significantly higher than ODRT (3-year, 26.0% vs. 16.9%; subdistribution hazard ratio [sHR] = 1.55, 95% confidence interval [CI] 1.06-2.26, $P = 0.03$). Of the 338 matched patients (169 in ODRT vs. 169 in TDRT), 60 (17.8%) experienced brain metastases with 3-year rate of 14.9% in ODRT vs 26.0% in TDRT (sHR = 1.71, 95%CI 1.02-2.88, $P = 0.04$). Progression-free survival was similar in both the whole cohort and the matched one. Overall survival in ODRT tended to be significantly longer after matching (median, 47.2 months in ODRT vs. 32.8 months in TDRT; HR = 1.41, 95%CI 0.99-2.01, $P = 0.06$).

Conclusions and Relevance: Small-cell lung cancer patients who were treated with thoracic TDRT appeared to have higher risk of brain metastases than those with ODRT, which strongly supports the need for further prospective randomized controlled trials, especially in China or Asia.

Keywords

Small-cell lung cancer; Twice-daily radiotherapy; Once-daily radiotherapy; Brain metastasis; Prophylactic cranial irradiation

2

Key Points

Question: Whether thoracic twice-daily radiotherapy (TDRT) increases risks for brain metastases after prophylactic cranial irradiation in small-cell lung cancer?

Findings: This multicenter study, involving 778 patients from 2003-2016, revealed a significantly higher brain metastases rate in TDRT than once-daily radiotherapy (ODRT), which was further confirmed in subsequent propensity score analysis including 338 patients.

Meaning: Compared with small-cell lung cancer patients treated with ODRT, those treated with TDRT were more likely to experience brain metastases after prophylactic cranial irradiation.

Tweet:

Scholars Found Twice-daily Radiotherapy May Increase Brain Metastases in Patients with Small-Cell Lung Cancer in China.

2

Introduction

Twice-daily radiotherapy (TDRT) (1.5Gy bid 45Gy) or once-daily radiotherapy (ODRT) (1.8-2.0Gy, qd, 60-70Gy) is recommended for small-cell lung cancer in 2018 National Comprehensive Cancer Network (NCCN) guideline[1]. However, the effect of TDRT on brain metastases remains unknown.

The NCCTG 89-20-52 trial reported that brain metastases rates in TDRT was numerically higher than ODRT in 154 patients with limited-disease (11% vs. 9% for TDRT vs. ODRT, $P = 0.68$)[2]. In stage IIIA and IIIB non-small-cell lung cancer, hyperfractionated accelerated radiotherapy was associated with higher brain metastases rates than ODRT (20% vs. 13%), but the calculated time point and P value was not reported[3]. One retrospective study exploring risk factors for brain metastases after prophylactic cranial irradiation in small-cell lung cancer reported that compared to ODRT, patients with TDRT were more likely to develop brain metastases (3 year rates, 43% in TDRT vs 21% in ODRT; HR = 2.171, 95% CI 1.111–4.243, $P = 0.023$)[4]. Whereas, according to CONVERT trial using competing risk analysis, the brain metastases incidence of each arm was similar (5 year rates, 18.3% in TDRT vs 15.9% in ODRT; sHR = 1.15, 95% CI 0.75–1.79, $P = 0.42$)[5].

To further investigate the impact of thoracic TDRT/ODRT on brain metastases after prophylactic cranial irradiation, we conducted this real world study of small-cell lung cancer patients treated at eight institutes in China, using methods including competing risk analysis and propensity score matching approach.

Methods

No ethical approval or informed consent was required for this study under Chinese Ethic Standard. This report follows the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reporting guideline for comparative effectiveness studies according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements[6]. The eligibility criteria included: (1) Pathologically or cytologically confirmed small-cell lung cancer without mixture of other pathological types; (2) Received radiotherapy, chemotherapy, and once-daily prophylactic cranial irradiation before relapsing or progression from 2003 to 2016; (3) Performed contrast-enhanced cranial Computed tomography (CT) / Magnetic resonance imaging (MRI) to rule out brain metastases prior to prophylactic cranial irradiation (Former study[4] showed that patients performed CT or MRI before prophylactic cranial irradiation was not significantly related with brain metastases [$p= 0.362$] so we did not specified

CT or MRI in this study); (4) No evidence of prior malignant carcinoma over the past five years. Patients with incomplete medical records at diagnosis or treatment were excluded from this analysis (Figure 1). Notably, stage was not the excluding criteria in this study because Slotman *et al* found that patients with extensive-stage disease also benefit from prophylactic cranial irradiation and thoracic radiotherapy[7,8]. Instead, we matched and adjusted it in further analyses.

The most commonly used schedules for ODRT and TDRT were 50-66Gy/25-33f once-daily and 45Gy/30f twice-daily, respectively (Appendix Table 1). The main prophylactic cranial irradiation schedule was 25Gy/10f once-daily. Patients who received 24Gy/16f twice-daily were excluded.

Appendix Table 1. Thoracic radiotherapy dose details

Groups	Schedules	No.	Constituent ratio (%)
ODRT			
	50-66Gy/25-33F	569	93.4
	>66Gy	6	1.0
	<50Gy	34	5.6
	Total	609	100
TDRT			
	45Gy/30F/bid	145	85.8
	>45Gy*	23	13.6
	<45Gy**	1	0.6
	Total	169	100

Abbreviations: ODRT = once-daily radiotherapy; TDRT = twice-daily radiotherapy.
Note: *Including 9 patients with late course accelerated hyperfractionated radiotherapy; **37.5Gy/25F/bid.

The biologically effective dose (BED) of thoracic radiotherapy was calculated according to the linear-quadratic formula[9]: $BED = (nd)\{1 + [d/(\alpha/\beta)]\} - [0.693t/(\alpha T_{pot})]$, where n = the total number of fractions delivered; d = the dose per fraction (Gy); $\alpha/\beta = 10$; $\alpha = 0.3$ Gy; t = total days in which radiotherapy was delivered; and $Tpot$ = potential doubling time (5.6 days)[9,10].

Response to chemoradiotherapy was assessed with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[11] before prophylactic cranial irradiation but not specified in this study because an earlier research found that response was not associated with brain metastases ($P = 0.842$)[4].

The detailed follow-up strategy was showed in *supplementary specification*. Additional brain radiotherapy (radiosurgery or whole brain radiotherapy, depends on the relapsed numbers) and chemotherapy were adopted for patients with brain metastases but not specified in this study.

Statistical Analysis

2

The primary endpoint was brain metastases confirmed by cranial image at any time no matter with neurologic symptoms (like headache, vomit, etc) or not. The secondary endpoints were progression-free survival (progressed at the first time of any sites confirmed by image) and overall survival. All endpoints were analyzed as time-to-event data from thoracic radiotherapy commencement to respective events, which were subject to censoring at the last follow-up (data cutoff was November, 2017) if no events were observed. The brain metastases was evaluated using competing risk analysis (Gray's test for univariate analysis and Fine-Gray model for multivariable regression[12,13]), where death without brain metastases was treated as competing event. Both progression-free survival and overall survival were analyzed using Kaplan-Meier method and Cox regression model. Six clinically important covariates (year of diagnosis, performance status, stage, thoracic radiotherapy, combination of chemoradiotherapy, timing of prophylactic cranial irradiation) were included for multiple analysis.

A 1:1 optimal propensity-score matched method was used to control confounding between ODRT (Control) and TDRT (Treated)[14] to essentially estimate Average Treatment Effect on the Treated (ATT), instead of Average Treatment Effect on the entire sample (ATE). Propensity scores, i.e., the conditional probability of receiving TDRT, were calculated using a multivariable logistic regression model. Covariates used to calculate propensity scores included eight demographic variables (treating site, year of diagnosis, age at diagnosis, sex, performance status, smoking history, laterality, stage) and eight treatment related covariates (surgery, combination of chemoradiotherapy, type of initial chemotherapy regimen, types of chemotherapy regimen involved, chemotherapy cycles, thoracic radiotherapy time from diagnosis to commencement, timing of prophylactic cranial irradiation, prophylactic cranial irradiation dose classification), which were summarized and compared between TDRT and ODRT using chi-square tests, both prior to and after conducting matching. All tests were 2-sided and a *P* value less than 0.05 was considered to be statistically significant. Statistical analyses were performed November 2017 to May 2018 and reanalyzed for revision using IBM SPSS 22.0 and R 2.15.3.

Results

Patients' characteristics

Of the 894 consecutive patients queried, 778 met the study criteria with complete medical records were included (Figure 1). Of the 778 patients, 204 (26.2%) were female, 490 (63.0%) were smokers (among the 574 male patients, 478 [83.3%] were smokers), 321 (41.3%) underwent radiotherapy sequentially after 2-4 cycles of chemotherapy (sequential chemoradio-

894 patients were screened

116 were ineligible
  24 did not receive thoracic radiotherapy
    15 did not perform cranial CT/MRI before PCI
  13 performed PCI until relapsing or progression
  10 diagnosed after July 1,2016
  5 did not complete PCI (DT < 20 Gy)
  5 received TDRT for PCI (24Gy/16f/bid)
  3 was whole brain irradiation for brain metastasis
   2 were recorded repeatedly
   2 had prior carcinoma over the past 5 years
  1 did not receive chemotherapy
  1 mixed with adenocarcinoma
  1 had central nervous disease
  34 had incomplete information
      14 timing of chemoradiotherapy
      10 cranial CT/MRI before PCI
      7 thoracic radiotherapy scheme
      3 PCI scheme

778 patients were eligible
(ODRT: TDRT = 609: 169)

440 failed 1:1 propensity score matching

ODRT (N=169)

TDRT (N=169)

Follow-up strategy*

Examined for brain metastases

Examined for extracranial progression

Figure 1. CONSORT diagram
Shown are patients screening and matching procedures.
* Follow-up strategy: Provided in detail in *supplementary specification*
CT, computerized tomography; MRI, magnetic resonance imaging; ODRT, once-daily radiotherapy; PCI, Prophylactic cranial irradiation; TDRT, twice-daily radiotherapy.

Supplementary specification:
Follow-up Strategy

   The follow-up strategy was every month for the first three months, then every three months for the following two years, every six months for the next three years and annually thereafter until death. Investigations included at least taking a medical history and performance status evaluation. Work-up included laboratory test, contrast-enhanced thoracic and abdominal CT scan or more (like positron emission tomography- computed tomography [PET-CT]). Patients with key symptoms of brain metastases such as headache, dizzy, vision damage, nausea, vomit, extremities motionless had to be performed with contrast-enhanced CT or MRI of the head. Otherwise clinician specified whether perform it or not on the basis of patients' willingness. Patients could visit our institutes or the local institutes at their convenience for follow-up. And we interviewed all the patients or their caregivers by telephone at least twice to confirm their healthy status and quality of life (QoL). Patients were treated as lost to follow up if we failed to contact them or their caregivers. The follow-up data were cutoff in November, 2017.

   Of the 778 eligible patients, 157(19.9%) patients were lost to follow-up (123 [20.2%] from ODRT and 34 [20.1%] from TDRT, $p = 0.98$). For the whole 778 patients, the median follow-up time was 23.6 months (IQR, 14.2-38.2 months). For the 621 patients who followed up until November 2017, the median time was 26.5 months (IQR, 17.5-41.2 months). For the 157 patients lost to follow up, the median time was 12.0 months (IQR, 5.7-21.3 months). In the matched cohort with 338 patients, 74 (22.5%) lost to follow-up (40 [23.7%] were from ODRT and 34 [20.1%] from TDRT, $p = 0.430$). For the whole 338 patients, the median follow-up time was 23.9 months (IQR, 15.5-34.3 months). For the 264 patients who followed up until November 2017, the median follow-up time was 26.4 months (IQR, 17.7-38.1 months). For the 74 patients lost to follow up, the median follow-up time was 13.4 months (IQR, 5.5-24.3 months).

therapy, SCRT) rather than concurrently (concurrent chemoradiotherapy, CCRT) largely due to performance status or age consideration, 609 received ODRT and the other 169 (21.7%) received TDRT at treating physicians' discretions based on their department's inclinations (in some departments, physicians prefer ODRT for all of their patients while in other departments, physicians prefer TDRT) (Table 1). Their median age was 55-year (interquartile range [IQR], 48-61). The median thoracic radiotherapy time was 64 days (IQR, 42-102).

Table 1. Clinical features and brain metastases risk before propensity score matching (N=778)

Valuables	No.(ratio)	BM rate 3-yr	5-yr	Univariate P (sHR,95%CI)	Multivariate P	sHR	95%CI
Treating site							
A(SD)	258 (33.2)	19.7	24.7	0.86			
B(SC)	166 (21.3)	18.6	24.8	(0.99, 0.87 - 1.13)			
C(ZJ)	198 (25.4)	16.5	18.8				
D(HN)	77 (9.9)	24.7	NA				
E(BJ)	48(6.2)	16.1	NA				
F(TZ/NC/JX)	31 (4.0)	22.6	22.6				
Year of diagnosis							
2003-2010	292 (37.5)	18.0	22.0	0.88	0.39	0.83	0.55 - 1.27
2011-2016	486 (62.5)	19.6	24.2	(1.03, 0.72 - 1.46)			
Age at diagnosis – yr							
<60	527 (67.7)	16.9	22.3	0.32			
≥60	251 (32.3)	23.1	24.5	(1.20, 0.84 - 1.71)			
Gender							
Male	574 (73.8)	19.8	25.0	0.94			
Female	204 (26.2)	18.4	22.5	(1.01, 0.69 - 1.48)			
Performance status							
0	127 (16.3)	13.5	23.5	0.22	0.32	1.25	0.81 - 1.91
1	624 (80.2)	19.7	22.8	(1.29, 0.86 - 1.95)			

2

Table 1. Clinical features and brain metastases risk before propensity score matching (N=778)

Valuables	No.(ratio)	BM rate		Univariate	Multivariate		
		3-yr	5-yr	P (sHR,95%CI)	P	sHR	95%CI
2	27 (3.5)	20.9	NA				
Smoking history							
Yes	490 (63.0)	19.4	26.4	0.93			
No	288 (37.0)	18.4	21.4	(0.98, 0.69 - 1.39)			
Laterality							
Left	380 (48.8)	18.8	24.2	0.71			
Right	398 (51.2)	18.7	21.8	(0.94, 0.67 - 1.32)			
Stage							
Limited disease	684 (87.9)	17.9	21.8	0.03	0.04	1.69	1.03 - 2.77
Extensive disease	94 (12.1)	25.0	36.4	(1.64, 1.03 - 2.62)			
Surgery							
Yes	44 (5.7)	12.0	19.6	0.45			
No	734 (94.3)	19.2	23.2	(0.75, 0.36 - 1.58)			
Type of initial chemotherapy regimen							
EP	719 (92.4)	18.4	22.2	0.32			
Non-EP	59 (7.6)	22.3	31.6	(1.33, 0.76 - 2.33)			
Types of chemotherapy regimen involved							
1	668 (85.9)	18.2	22.5	0.48			
≥2	110 (14.1)	21.4	25.6	(1.17, 0.75 - 1.84)			
Chemotherapy cycles							
<4	27 (3.5)	9.2	9.2	0.13			
4-6	710 (91.3)	18.7	23.5	(1.50, 0.88 - 2.54)			
>6	41 (5.3)	25.2	25.2				
Thoracic radiotherapy time – days*							
≤64	393 (50.5)	18.0	22.7	0.62			
>64	385 (49.5)	19.5	23.6	(1.09, 0.78 - 1.53)			
Thoracic radiotherapy fractionation							
ODRT	609 (78.3)	16.9	21.6	0.03	0.03	1.57	1.04 - 2.37
TDRT	169 (21.7)	26.0	28.1	(1.55, 1.06 - 2.26)			
Combination of chemoradiotherapy							
SCRT	321 (41.3)	20.0	25.7	0.28	0.42	0.87	0.62 - 1.23
CCRT	457 (58.7)	17.8	21.1	(0.83, 0.59 - 1.17)			
Timing of prophylactic cranial irradiation							
Early**	155 (19.9)	23.1	26.2	0.17	0.69	1.10	0.70 - 1.79
Late	623 (80.1)	17.8	22.3	(1.33, 0.89 - 2.00)			
Prophylactic cranial irradiation dose classification							
Lower-standard	17 (2.2)	18.7	18.7	0.73			
Standard***	678 (87.1)	18.4	22.8	(1.09, 0.68 - 1.73)			
Higher-standard	83 (10.7)	20.6	24.8				

Abbreviations: BM = brain metastases; CI = confidence interval; A(SD) = Shandong Cancer Hospital; B(SC) = Sichuan Cancer Hospital; C(ZJ) = Zhejiang Cancer Hospital; D(HN) = Henan Cancer Hospital; E(BJ) = Peking University Cancer Hospital & Institute; F(TZ/NC/JX) = Tengzhou Central People's Hospital, The Second Affiliated Hospital of Nanchang University, Jiangxi Cancer Hospital; NA = non-applicable; EP = etopside-platinum; ODRT = once-daily radiotherapy; sHR = subdistribution hazard ratio; TDRT = twice-

Table 1. Clinical features and brain metastases risk before propensity score matching (N=778)

Valuables		BM rate		Univariate	Multivariate		
	No.(ratio)	3-yr	5-yr	*P* (sHR,95%CI)	*P*	sHR	95%CI

daily radiotherapy; SCRT = sequential chemoradiotherapy; CCRT = concurrent chemoradiotherapy.

Note: *Thoracic radiotherapy time was divided into two categories by median time;

**Early: receiving prophylactic cranial irradiation before the end of chemoradiotherapy;

**Standard: 25Gy/10F or 30Gy/10-15F.

Brain metastases risk and survival analyses

Of the 778 patients, 131 (16.8%) developed brain metastases at a median follow-up time of 23.6 months (IQR, 14.2-38.2 months) with 3-year rate of 18.5% (95%CI 15.6-21.7%). Univariate analyses showed that comparing with patients treated with ODRT, those treated with TDRT were more likely to experience brain metastases after prophylactic cranial irradiation (3-year, 16.9% in ODRT vs. 26.0% in TDRT; subdistribution hazard ratio [sHR] = 1.55, 95% confidence interval [CI] 1.06-2.26, *P* = 0.03) (Figure 2A).
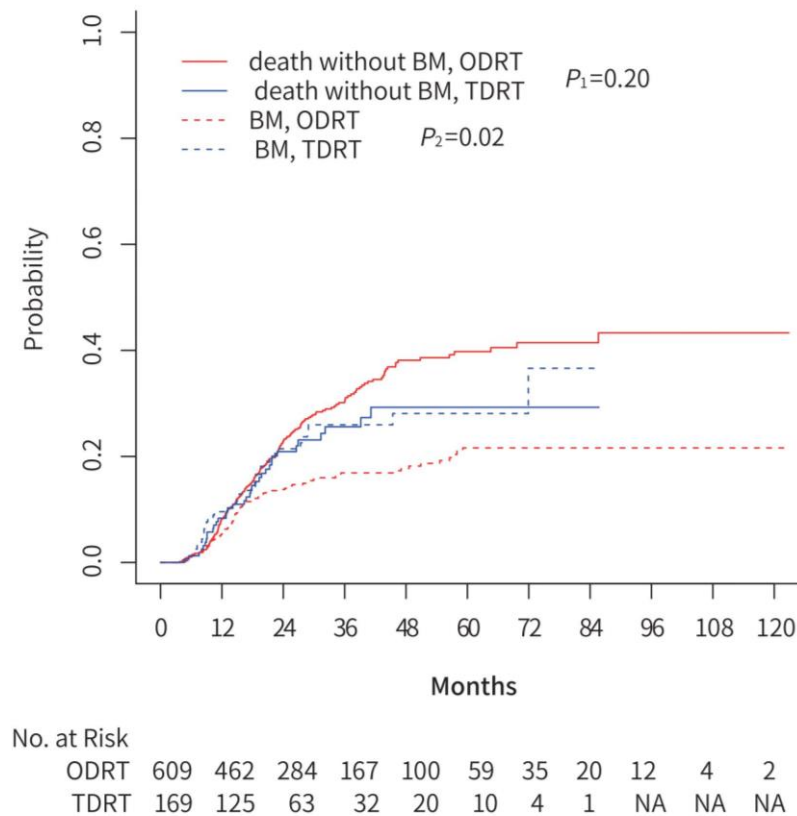
Figure 2A. Cumulative events incidences plots of the whole cohort (N=778)
The brain metastases incidence was significantly higher in TDRT than that in ODRT before matching.
ODRT, once-daily radiotherapy; TDRT, twice-daily radiotherapy; BM, brain metastases.

Stage (sHR = 1.64, 95%CI 1.03-2.62, *P* = 0.03) was significantly associated with brain metastases, too. Multivariable analysis confirmed that patients received TDRT (sHR = 1.57,

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95%CI 1.04-2.37, *P* = 0.03) or those with extensive disease (sHR = 1.69, 95%CI 1.03-2.77, *P* = 0.04) had higher brain metastases rate (Table 1). No significant difference between ODRT and TDRT was observed in overall survival (HR = 1.15, 95%CI 0.88-1.50, *P* = 0.31) or progression-free survival (HR = 1.10, 95%CI 0.87-1.37, *P* = 0.44). Multiple analysis showed that patients with worse performance status (overall survival, HR = 1.38, 95%CI 1.03-1.83, *P* = 0.03; progression-free survival, HR = 1.23, 95%CI 0.97-1.56, *P* = 0.08) or those underwent prophylactic cranial irradiation before the end of chemoradiotherapy (overall survival, HR = 1.37, 95%CI 1.05 - 1.78, *P* = 0.02; progression-free survival, HR = 1.34, 95%CI 1.07-1.68, *P* = 0.01) lived shorter. Additionally, patients diagnosed at earlier years (2003-2010) or with extensive disease experienced shorter progression-free survival (Table 2).

Table 2. Survival risk using multivariate Cox regression analysis (N=778)

Variables	Overall Survival			Progression-Free Survival		
	P	HR	95%CI	*P*	HR	95%CI
Year of diagnosis	0.11	0.82	0.65 - 1.04	0.03	0.79	0.64 - 0.97
Performance status	0.03	1.38	1.03 - 1.83	0.08	1.23	0.97 - 1.56
Stage	0.17	1.27	0.90 - 1.79	0.01	1.45	1.09 - 1.93
Thoracic radiotherapy fractionation	0.38	1.13	0.86 - 1.50	0.32	1.13	0.89 - 1.43
Combination of chemoradiotherapy	0.30	0.89	0.71 - 1.11	0.39	0.92	0.76 - 1.11
Timing of PCI	0.02	1.37	1.05 - 1.78	0.01	1.34	1.07 - 1.68

Abbreviations: CI = confidence interval; HR = hazard ratio; PCI = prophylactic cranial irradiation.

Propensity score matching was used to further evaluate the role of TDRT/ODRT. A total of 338 patients were matched successfully. As shown in Table 3, patients' clinical features excluding treating site were balanced between TDRT and ODRT after matching.

Table 3. Clinical features in the pre- and post-propensity score matching cohort

Characteristics	Before propensity score matching			After propensity score matching		
	ODRT (N=609)	TDRT (N=169)	*P* value	ODRT (N=169)	TDRT (N=169)	*P* value
Treating site - no. (%)						
A(SD)	185 (30.4)	73 (43.2)	<0.001	45 (26.6)	73 (43.2)	<0.001
B(SC)	132 (21.7)	34 (20.1)		24 (14.2)	34 (20.1)	
C(ZJ)	188(30.9)	10 (5.9)		36 (21.3)	10 (5.9)	
D(HN)	52(8.5)	25 (14.8)		32 (18.9)	25 (14.8)	
E(BJ)	29(4.8)	19 (11.2)		17 (10.1)	19 (11.2)	
F(TZ/NC/JX)	23(3.8)	8 (4.7)		15 (8.9)	8 (4.7)	
Year of diagnosis - no. (%)						
2003 - 2010	264(43.3)	28 (16.6)	<0.001	30 (17.8)	28 (16.6)	0.77
2011 - 2016	345 (56.7)	141 (83.4)		139 (82.2)	141 (83.4)	
Age at diagnosis - yr						
< 60	421 (69.1)	106 (62.7)	0.12	101 (59.8)	106 (62.7)	0.58
≥ 60	188 (30.9)	63 (37.3)		68 (40.2)	63 (37.3)	
Gender - no.						

Table 3. Clinical features in the pre- and post-propensity score matching cohort

Characteristics	Before propensity score matching			After propensity score matching		
	ODRT (N=609)	TDRT (N=169)	*P* value	ODRT (N=169)	TDRT (N=169)	*P* value
(%)						
Male	453 (74.4)	121 (71.6)	0.47	119 (70.4)	121 (71.6)	0.81
Female	156 (25.6)	48(28.4)		50 (29.6)	48(28.4)	
Perfomance status - no. (%)						
0	113 (18.6)	14 (8.3)	0.006	11 (6.5)	14 (8.3)	0.78
1	476 (78.2)	148 (87.6)		152 (89.9)	148 (87.6)	
2	20 (3.3)	7 (4.1)		6 (3.6)	7 (4.1)	
Smoking history - no. (%)						
Yes	388 (63.7)	102 (60.4)	0.42	89 (52.7)	102 (60.4)	0.15
No	221 (36.3)	67 (39.6)		80 (47.3)	67 (39.6)	
Laterality - no. (%)						
Left	296 (48.6)	84 (49.7)	0.80	73 (43.2)	84 (49.7)	0.23
Right	313 (51.4)	85(50.3)		96 (56.8)	85(50.3)	
Stage - no. (%)						
Limited disease	540 (88.7)	144(85.2)	0.22	143 (84.6)	144(85.2)	0.88
Extensive disease	69 (11.3)	25 (14.8)		26 (15.4)	25 (14.8)	
Surgery - no. (%)						
Yes	38 (6.2)	6 (3.6)	0.18	4 (2.4)	6 (3.6)	0.52
No	571 (93.8)	163 (96.4)		165 (97.6)	163 (96.4)	
Type of initial chemotherapy regimen - no. (%)						
EP	556 (91.3)	163 (96.4)	0.03	157 (92.9)	163 (96.4)	0.15
Non-EP	53 (8.7)	6 (3.6)		12 (7.1)	6 (3.6)	
Types of chemotherapy regimen involved - no. (%)						
1	520 (85.4)	148 (87.6)	0.47	147 (87.0)	148 (87.6)	0.87
≥2	89 (14.6)	21 (12.4)		22 (13.0)	21 (12.4)	
Chemotherapy cycles - no. (%)						
<4	20 (3.3)	7 (4.1)	0.47	11 (6.5)	7 (4.1)	0.63
4-6	554 (91.0)	156 (92.3)		152 (89.9)	156 (92.3)	
>6	35 (5.7)	26 (3.6)		6 (3.6)	26 (3.6)	
Thoracic radiotherapy time – days*						
≤64	313 (51.4)	80 (47.3)	0.35	81 (47.9)	80 (47.3)	0.91
>64	296 (48.6)	89 (52.7)		88 (52.1)	89 (52.7)	
Combination of chemoradiotherapy - no. (%)						
SCRT	231 (37.9)	90 (53.3)	<0.001	96 (56.8)	90 (53.3)	0.51
CCRT	378 (62.1)	79 (46.7)		73 (43.2)	79 (46.7)	
Timing of prophylactic cranial irradiation - no. (%)						
Early**	122 (20.0)	33 (19.5)	0.89	26 (15.4)	33 (19.5)	0.32
Late	487 (80.0)	136 (80.5)		143 (84.6)	136 (80.5)	
Prophylactic cranial irradiation dose classification - no. (%)						
Lower-standard	15 (2.5)	2 (1.2)	0.04	3 (1.8)	2 (1.2)	0.73
Standard***	521 (85.6)	157 (92.9)		153 (90.5)	157 (92.9)	
Higher-standard	73 (12.0)	10 (5.9)		13 (7.7)	10 (5.9)	

Abbreviations: ODRT = once-daily radiotherapy; TDRT = twice-daily radiotherapy; A(SD) = Shandong Cancer Hospital; B(SC) = Sichuan Cancer Hospital; C(ZJ) = Zhejiang Cancer Hospital; D(HN) = Henan Cancer Hospital; E(BJ) = Peking University Cancer Hospital & Institute; F(TZ/NC/JX) = Tengzhou Central People's Hospital, The Second Affiliated Hospital of Nanchang University, Jiangxi Cancer

Table 3. Clinical features in the pre- and post-propensity score matching cohort

Characteristics	Before propensity score matching			After propensity score matching		
	ODRT (N=609)	TDRT (N=169)	*P* value	ODRT (N=169)	TDRT (N=169)	*P* value

Hospital; CCRT = concurrent chemoradiotherapy; SCRT = sequential chemoradiotherapy; EP = etopside-platinum.

Note: * Thoracic radiotherapy time was divided into two categories by median time;
**Early: receiving prophylactic cranial irradiation before the end of chemoradiotherapy;
**Standard: 25Gy/10F or 30Gy/10-15F.

After a median follow-up of 25.9 months (IQR, 15.7-35.2 months), 60 (17.8%) of the 338 matched patients developed brain metastases, with 3-year rate of 14.9% for ODRT and 26.0% for TDRT (HR = 1.71, 95%CI 1.02-2.88, *P* = 0.04) (Appendix Table 2, Figure 2B). One hundred and twenty-three (36.4%) died, with median overall survival of 47.2 months in the ODRT and 32.8 months in the TDRT (HR = 1.41, 95%CI 0.99-2.01, *P* = 0.06) (Appendix figure 1A). One-hundred and eighty-eight (55.6%) experienced progression, with median progression-free survival of 20.1 months vs. 18.8 months for ODRT vs. TDRT (HR = 1.16, 95%CI 0.87-1.55, *P* = 0.30) (Appendix figure 1B).
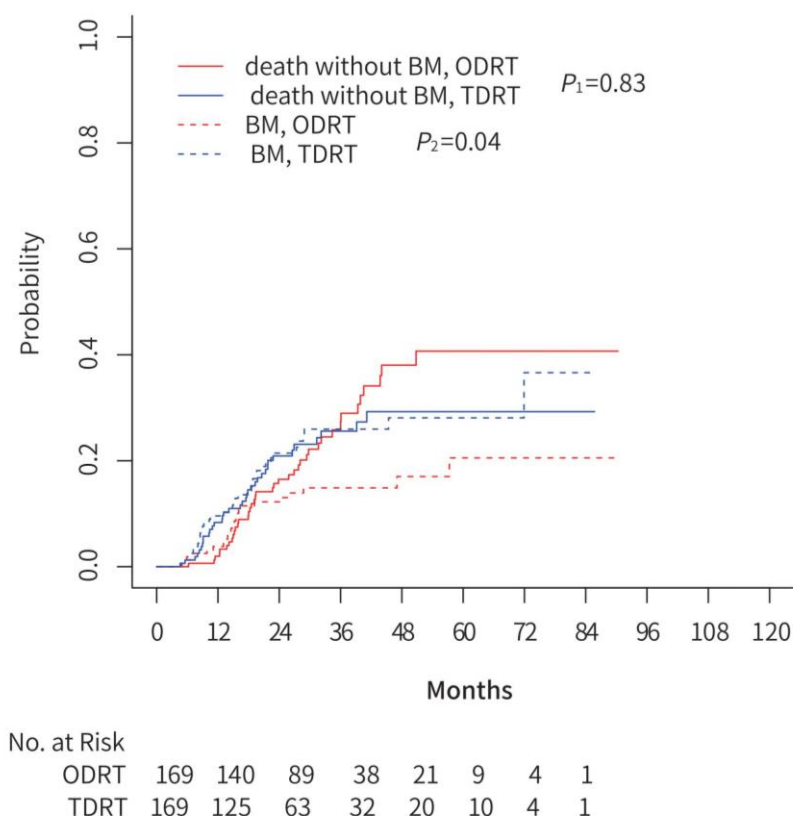
Figure 2B. Cumulative events incidences plots of the matched cohort (N=338)
The brain metastases incidence was still significantly higher in TDRT than that in ODRT after matching.
ODRT, once-daily radiotherapy; TDRT, twice-daily radiotherapy; BM, brain metastases.
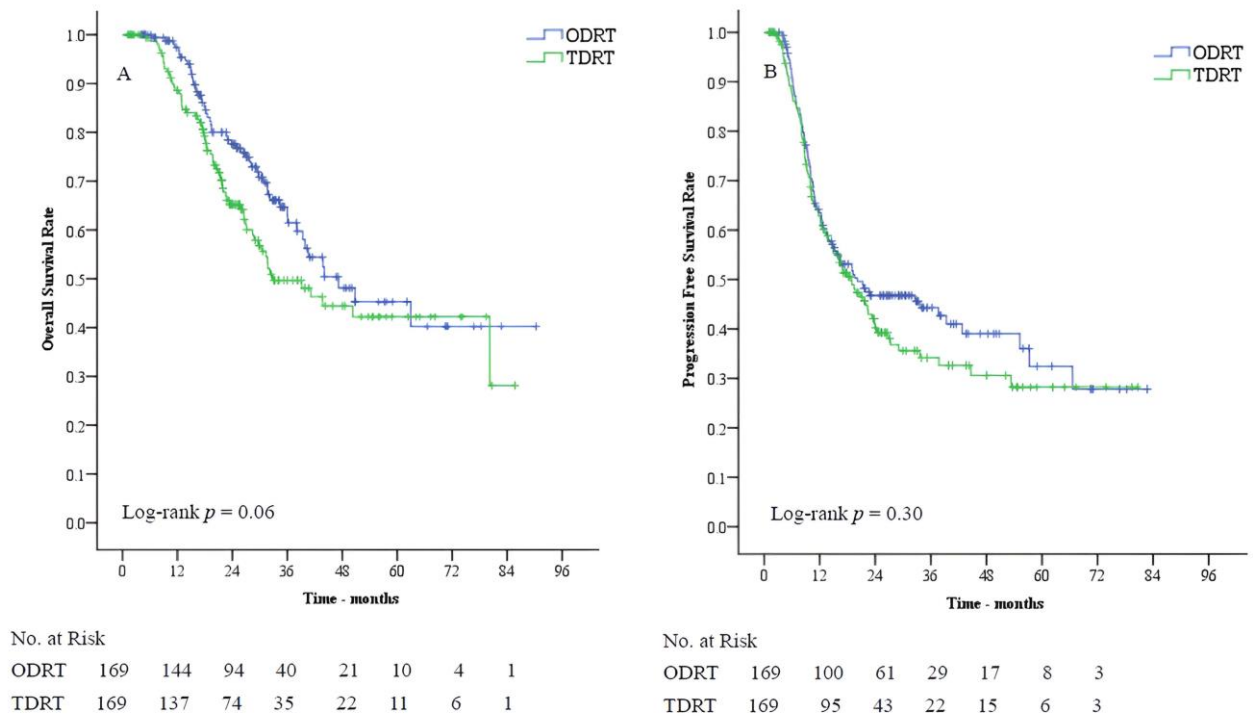
Appendix Figure 1. Overall survival and progression-free survival in ODRT and TDRT (N=338)
Shown are overall survival rate (Panel A) and progression-free survival rate (Panel B) in two groups. Overall survival tended to be significantly longer in ODRT while progression-free survival was not significantly different between ODRT and TDRT groups.
ODRT, once-daily radiotherapy; TDRT, twice-daily radiotherapy.

Appendix Table 2. Brain metastases rate in ODRT and TDRT group (N=338)

Events	Cumulative Rate (95%CI) - %					P value
	1-yr	2-yr	3-yr	4-yr	5-yr	(Gray's test)
Competing event*						
ODRT	2.0 (0.5-5.2)	16.5 (10.9-23.2)	25.8 (18.2-34.1)	38.0 (27.5-48.6)	40.7 (29.3-51.8)	0.83
TDRT	8.3 (4.7-13.4)	20.9 (14.6-28.0)	25.6 (18.2-33.6)	29.3 (20.7-38.3)	29.3 (20.7-38.3)	
Brain metastases						
ODRT	3.8 (1.6-7.7)	12.2 (7.5-18.1)	14.9 (9.5-21.4)	17.0 (10.6-24.7)	20.5 (11.8-31.0)	0.04
TDRT	9.6 (5.6-14.8)	21.4 (15.1-28.6)	26.0 (18.6-34.0)	28.1 (19.9-36.9)	28.1 (19.9-36.9)	

Abbreviations: CI = confidence interval; ODRT = once-daily radiotherapy; TDRT = twice-daily radiotherapy.
Note: *Competing event includes death without brain metastases.

For the matched cohort, BED was lower in TDRT (median, 51.8Gy for ODRT vs. 43.1Gy for TDRT, $P < 0.001$). Start of any therapy to the end of radiotherapy (SER) was shorter in TDRT (median, 108 days for ODRT vs. 81 days or TDRT, $P < 0.001$). Neither BED nor SER was associated with brain metastases, progression-free survival or overall survival. And the

differences in overall survival between ODRT / TDRT became more obvious after adjusting for BED and SER (HR = 1.69, 95%CI 1.05-2.71, *P* = 0.03) (Appendix table 3).

Appendix Table 3. Survival analysis with ODRT/TDRT, BED and SER (N=338)

Endpoints	Univariate			Multivariate		
	P	(s)HR	95%CI	*P*	(s)HR	95%CI
Brain metastases*						
ODRT/TDRT	0.04	1.71	1.02-2.88	0.03	1.98	1.09-3.59
BED	0.44	0.99	0.95-1.02	0.45	1.02	0.97-1.06
SER	0.95	1.00	1.00-1.01	0.58	1.00	1.00-1.01
Progression-free survival**						
ODRT/TDRT	0.30	1.16	0.87-1.55	0.31	1.20	0.84-1.72
BED	0.41	0.99	0.97-1.01	0.86	1.00	0.97-1.03
SER	0.18	1.00	1.00-1.01	0.11	1.00	1.00-1.01
Overall survival**						
ODRT/TDRT	0.06	1.41	0.99-2.01	0.03	1.69	1.05-2.71
BED	0.57	0.99	0.96-1.02	0.37	1.02	0.98-1.06
SER	0.31	1.00	1.00-1.01	0.14	1.00	1.00-1.01

Abbreviations: BED = biologically effective dose; CI = confidence interval; ODRT = once-daily radiotherapy; SER = Start of any therapy to the end of radiotherapy; (s)HR = (subdistribution) hazard ratio; TDRT = twice-daily radiotherapy.
Note: *Fine-Gray model (sHR); **Cox regression model (HR)

Of note, among the five excluded patients who received twice-daily prophylactic cranial irradiation (24Gy/16F, twice-daily) (screened among the 894 patients but not included in the 778 patients, Figure 1), 3 experienced brain metastases (60%). One of the five patients received thoracic TDRT, too. And he developed brain metastases.

In addition, the asymptomatic brain metastasis ratio was 65.6% in ODRT vs 60.5% in TDRT (*P* = 0.59) before matching and 57.1% in ODRT vs 60.5% in TDRT (*P* = 0.80) after matching.

Other prognostic factors and subgroup analyses

Subgroup analyses based on stage, year of diagnosis, and timing of prophylactic cranial irradiation were performed among the 338 matched patients. Patients treated with TDRT showed higher risks of developing brain metastases when adjusting by stage (sHR=1.71, 95%CI 1.02-2.87, *P* = 0.04). Possibly due to reduced sample size and statistical power, the rates of brain metastases in TDRT were only numerically higher in either limited stage or extensive stage subgroups (Appendix Table 4).

Appendix Table 4. BM rate in ODRT and TDRT by stratum of stage (N=338)

Subgroups	No. (Ratio)	BM rate (%)		Fine and Gray model		
		3-yr	5-yr	*P* value	sHR	95% CI
Limited disease						
ODRT	143 (49.8)	14.3	20.1	0.08	1.67	0.94 - 2.96
TDRT	144 (50.2)	24.6	26.7			
All limited	287 (84.9)*	20.4	NA	0.15*	1.65*	0.84 - 3.23*
Extensive disease						
ODRT	26 (51.0)	20.3	NA	0.29	1.91	0.58 - 6.32
TDRT	25 (49.0)	33.5	NA			
All extensive	51 (15.1)*	26.8	NA			
Adjusting by stage**				0.04	1.71	1.02 - 2.87

Abbreviations: BM = Brain metastases; CI = confidence interval; NA = non-applicable; ODRT = once-daily radiotherapy; sHR = subdistribution hazard ratio; TDRT = twice-daily radiotherapy.
Note:* Compare between limited and extensive disease; ** Compare between ODRT and TDRT.

For patients diagnosed small-cell lung cancer at recent years (2011-2016), no significant difference in brain metastases rate was observed (sHR=1.47, 95%CI 0.80-2.68, *P* = 0.21). While for those diagnosed at earlier years (2003-2010), the brain metastases rate was significantly higher in TDRT (sHR=3.05, 95%CI 1.09-8.53, *P* = 0.03). After adjusting for diagnosis years, TDRT remained to be significantly associated with higher brain metastases risks (sHR=1.78, 95%CI 1.05-3.00, *P* = 0.03) (Appendix Table 5).

Appendix Table 5. BM rate in ODRT and TDRT by stratum of diagnosis year (N=338)

Subgroups	No. (Ratio)	BM rate (%)		Fine and Gray model		
		3-yr	5-yr	*P* value	sHR	95% CI
Earlier years (2003-2010)						
ODRT	30 (51.7)	14.2	19.5	0.03	3.05	1.09 - 8.53
TDRT	28 (48.3)	45.2	45.2			
All earlier	58 (17.2)*	28.7	31.4	0.12*	0.63*	0.35 - 1.13*
Recent years (2011-2016)						
ODRT	139(49.6)	15.1	20.6	0.21	1.47	0.80 - 2.68
TDRT	141(50.4)	21.8	25.0			
All recent	280 (82.8)*	18.3	22.8			
Adjusting by earlier/recent years**				0.03	1.78	1.05 - 3.00

Abbreviations: BM = Brain metastases; CI = confidence interval; ODRT = once-daily radiotherapy; sHR = subdistribution hazard ratio; TDRT = twice-daily radiotherapy.
Note:* Compare between earlier and recent years; ** Compare between ODRT and TDRT.

In addition, the brain metastases rate in earlier/recent years by stratum of ODRT/TDRT was analyzed to see whether time itself would affect results. It showed that for patients with ODRT, the brain metastases rate of those diagnosed at earlier years was not significantly different to those diagnosed at recent years (sHR=0.97, 95%CI 0.37-2.55, *P* = 0.95). While for patients with TDRT, it was significantly higher for those diagnosed at earlier years than those diagnosed recently (sHR=0.46, 95%CI 0.22-0.96, *P* = 0.04). After adjusting for ODRT/TDRT,

time was not significantly associated with brain metastases risks (sHR=0.61, 95%CI 0.34-1.10, *P* = 0.10) (Appendix Table 6).

Appendix Table 6. BM rate in earlier and recent years by stratum of ODRT vs. TDRT (N=338)

Subgroups	No. (Ratio)	BM rate (%)		Fine and Gray model		
		3-yr	5-yr	*P* value	sHR	95% CI
ODRT						
Earlier years	30 (17.8)	14.2	19.5	0.95	0.97	0.37 - 2.55
Recent years	139 (82.2)	15.1	20.6			
All ODRT	169 (50.0)*	14.9	20.5	0.04*	1.71*	1.02 - 2.88*
TDRT						
Earlier years	28 (16.6)	45.2	45.2	0.04	0.46	0.22 - 0.96
Recent years	141 (83.4)	21.8	25.0			
All TDRT	169 (50.0)*	26.0	28.1			
Adjusting by ODRT/ODRT**				0.10	0.61	0.34 - 1.10

Abbreviations: BM = Brain metastases; CI = confidence interval; ODRT = once-daily radiotherapy; sHR = subdistribution hazard ratio; TDRT = twice-daily radiotherapy.
Note:* Compare between ODRT and TDRT;
    ** Compare between earlier (2003-2010) and recent years (2011-2016).

    For patients with late prophylactic cranial irradiation, the rates of brain metastases in TDRT were significantly higher (sHR=1.81, 95%CI 0.99-3.31, *P* = 0.05). While it was not significantly different for those received early prophylactic cranial irradiation (sHR=1.39, 95%CI 0.49-3.99, *P* = 0.54). But patients treated with TDRT showed higher risks of developing brain metastases when adjusting by timing of prophylactic cranial irradiation (sHR=1.71, 95%CI 1.01-2.89, *P* = 0.05) (Appendix Table 7).

Appendix Table 7. BM rate in ODRT and TDRT by stratum of early PCI vs. late PCI (N=338)

Subgroups	No. (Ratio)	BM rate (%)		Fine and Gray model		
		3-yr	5-yr	*p* value	sHR	95% CI
Early PCI						
ODRT	26 (44.1)	28.2	28.2	0.54	1.39	0.49 - 3.99
TDRT	33 (55.9)	32.3	32.3			
All early	59 (17.5)*	30.2	30.2	0.12*	1.58*	0.89 - 2.84*
Late PCI						
ODRT	143 (51.3)	12.8	19.5	0.05	1.81	0.99 - 3.31
TDRT	136 (48.7)	24.4	28.0			
All late	279 (82.5)*	17.9	30.2			
Adjusting by early/late PCI**				0.05	1.71	1.01 - 2.89

Abbreviations: BM = Brain metastases; CI = confidence interval; ODRT = once-daily radiotherapy; PCI, prophylactic cranial irradiation; sHR = subdistribution hazard ratio; TDRT = twice-daily radiotherapy.
Note:* Compare between late PCI and early PCI; ** Compare between ODRT and TDRT.

Discussion

    This multicenter study revealed that compared with ODRT, TDRT was associated with higher brain metastases incidences, as shown in both multivariable analysis based on the whole

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cohort (778 patients) and the propensity score matched cohort with smaller sample size (338 patients). Additional subgroup analyses also suggest such disparity may be independent of disease stages and timing of prophylactic cranial irradiation. Our analysis therefore suggests ODRT may be superior to TDRT in brain metastases control in small-cell lung cancer, with multiple unverified, hypothesis-generating underlying mechanisms.

One of the possibilities maybe related to the impairment of blood-spinal cord barrier/blood-brain barrier. Irradiation disrupts the blood-spinal cord barrier with an associated increase in vascular permeability at early times (24 hours)[15,16]. As late reaction tissues with a very slowly turning over rate[17,18], the repair of sublethal injury in spinal cord tissue and vascular endothelial cell appears to be somewhat longer[3]. TDRT involves the delivery of the target dose in shorter time interval between fractions and provides normal tissues with less time to repair sublethal radiation damage, which leads to an accumulation of incomplete repair and result in asymptomatic biologic response characterized by sequential physiological changes in the thoracic spinal cord[16,19,20]. Sublethal injury with protractedly less time for repair leads to more severe permeability disruption of the thoracic blood-spinal cord barrier and results in more transmigration of residual tumor cells in TDRT compared to ODRT. The transmigrated tumor cells metastasize to the brain along with cerebrospinal fluid, form metastatic niches, and generate colonization in the brain months later[21]. Actually, our animal experiences did show that the irradiated thoracic blood-spinal cord barrier responded differently to different irradiation schedules (which will be reported in details in another paper in future).

This inference can also be supported by the subgroup analyses. Spanning 13 years, during which significant advancements in radiotherapy technique and supportive care have been made, we thus have adjusted for the year of diagnosis to minimize the potential impact in our study. It showed that for patients diagnosed small-cell lung cancer at earlier years, the brain metastases rate was obviously higher in TDRT, which remained after adjusting years. We even compared brain metastases rate in earlier/recent years by stratum of ODRT/TDRT to see the impact of time itself. Again, it showed that for patients with TDRT, the brain metastases rate was significantly higher in those diagnosed at earlier years. But after adjusting for ODRT/TDRT, diagnosed time was not significantly associated with brain metastases risks. In another words, TDRT was more detrimental in earlier years. The improved radiological technics and better supportive care over years might minimize the difference of brain metastases between ODRT and TDRT. Thus, improved technics decrease the injury of thoracic blood-spinal cord / blood-brain barrier and mask the difference. This may also explain the results from Western Country, like CONVERT study, there was no difference in brain metastasis between TDRT and ODRT[5].

Additionally, the brain metastases incidence of patients who received prophylactic cranial irradiation twice-daily was much higher than other patients with once-daily prophylactic cranial irradiation, which further indicated that irradiated the whole brain twice-daily would injure the blood-brain barrier more obviously. In addition, data from other studies like RTOG 0212 on prophylactic cranial irradiation also showed that the brain metastases rate at 1-yr was 10.6% in twice-daily arm (36Gy/24f) vs. 6.2% in once-daily arm (36Gy/18f) (total, 21% in twice-daily vs. 10% in once-daily)[22], in which although the P value was not reported, the rate in twice-daily prophylactic cranial irradiation group was obviously higher in terms of numerical value.

The timing of prophylactic cranial irradiation was controversial over time. Data from *Lee et al* showed the trend that the overall incidence of brain metastases was higher in the late prophylactic cranial irradiation group (offered irradiation after 5-6 courses of chemotherapy) than in the early irradiation group (offered after 2-3 courses of chemotherapy) (23.6% vs. 14.3%, $P = 0.08$). There was no difference in overall survival between the two groups[23]. The pooled analysis conducted by Schild et al also showed that the timing did not have an impact on subsequent survival across all patients (HR = 1.00, 95% CI 0.99-1.01, $P = 0.76$)[24]. According to *Auperin et al*, via classifying the time interval between initiation of induction therapy and prophylactic cranial irradiation into less than 4, 4-6 and longer than 6 months, they identified a trend towards a reduction in brain metastases rate with earlier prophylactic cranial irradiation after the initiation of chemotherapy ($P = 0.01$) without overall survival difference ($P = 0.39$)[25]. *Sas-Korczynska et al* found that early prophylactic cranial irradiation (performed during chemoradiotherapy) was more effective compared with irradiation applied after combined therapy, which decreased brain metastases rate from 20% to 7.3% ($P = 0.009$)[26]. However, prophylactic cranial irradiation administration concurrent with systemic therapy inevitably increased the risk of neurotoxicity and hematotoxicity[10,27,28]. Some physicians do not like to apply prophylactic cranial irradiation too early because they think that prophylactic cranial irradiation decreases brain metastases rate via eliminating micro-metastases that cannot be detected by radiological methods, rather than preventing metastases[29]. Undergoing prophylactic cranial irradiation too early attenuates the effects since micro-metastases have not developed yet. In our study, early prophylactic cranial irradiation did not decrease brain metastases rate significantly compared to late irradiation but it significantly shortened overall survival and progression-free survival. In line with NCCN guideline[1], our data support that prophylactic cranial irradiation should be administered after the resolution of acute toxicities of initial chemoradiotherapy.

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Previous studies showed BED and SER may be associated with overall survival[10,30,31], and we also found BED was lower and SER was shorter in TDRT group in our study. However, the multivariable analysis that jointly evaluated BED, SER and TDRT/ODRT showed that BED and SER had no significant impacts on outcomes, which further supports the hypothesis that observed difference in brain metastases incidences may be attributed the radiotherapy frequency.

In our study, the lower brain metastases incidence in ODRT did not translate into improved outcome in overall survival in the whole cohort. In fact, such observation is not rare and has been reported before[32-34], which could be explained by the potential confounding of effective subsequent therapies with higher treatment-related financial costs[35]. But after matching with balanced cases, the longer overall survival in ODRT became marginally significant, which further indicates that the impact of ODRT/TDRT is of clinical significance.

In addition, our data showed that patients lived longer than former studies[36]. The longer overall survival resulted in higher long-term brain metastases incidence and might also have contributed to the observation of the significant brain metastases difference in our series. As for the causes for our longer survival, maybe because all of our patients were Chinese, while less than 1% were Asian origin in the CONVERT trial[36]. *Faivre-Finn et al* also discussed that their results might not be applicable to other ethnicities[36]. It is not unusual that different races may show different responses to the same treatment regimen. A good case in point is that tyrosine kinase inhibitor was turned out to be effect for Chinese patients while it was not so effective for Europeans or Americans[37,38], as there are more Chinese patients with epidermal growth factor receptor (EGFR) mutation. In addition, our patients were younger with less smokers, which was in line with Chinese official data[39,40]. According to *Jia et al*, among the enrolled 14,106 male patients, 11,750 (83.3%) were smokers[39]. In another study including 3320 cases, 2223 (67.0%) patients were smokers[40]. Other reasons were briefly discussed in an earlier study[4].

In summary, TDRT has been introduced to clinical practice based on radiobiological principles for decades[41]. It's time to review real-world experience and reconsider its value. Our findings may shed light on the TDRT treatment would benefit from use of the longest feasible interfraction interval[20], for example, 12 hours interval between fractions in the twice-daily regimen. And even stop adopting TDRT in small-cell lung cancer, especially in China or Asia where twice-daily irradiation is logistically less preferred comparing to once-daily irradiation, since more and more ODRT schedules showed non-inferior outcomes[42-44].

The study has several limitations. First, due to the retrospective nature of this study, a fraction of patients with missing data had to be excluded in our analysis, which may have leaded

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to bias (like incorrect estimates of difference between types of radiation), limited the generalizability of our findings and reduced the power to detect clinically meaning differences in clinical outcomes. Second, despite that we have made significant efforts to minimize the potential selection biases using regression and propensity score matching, the current analysis could still be subject to unobserved confounding. Third, centers are not balanced even after matching. But considering patients from the same institute had undergone the same treatment-related or follow up policy and the detection rate of asymptomatic brain metastasis via imaging is similar between ODRT group and TDRT group no matter for the whole cohort or for the matched one, we don't think centers would affect the results. In fact, our data showed that there was only very limited variability in brain metastases rates across centers.

In conclusion, compared with thoracic ODRT, TDRT are associated with higher risk of brain metastases after prophylactic cranial irradiation in Chinese patients with small-cell lung cancer. These findings might not only motivate more researches in vitro and in vivo to further investigate the underlying mechanisms but also affect the clinical option of thoracic radiotherapy schedule, especially in China or Asia.

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Academy of Medical Sciences, China and Prof. Chen Hu from Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, USA conducted and are responsible for the data analysis.

Conflicts of interest statement

The authors have no conflict of interest associated with this study.

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Chapter 3

Risk factors for brain metastases in patients with small cell lung cancer: a systematic review and meta-analysis

Zeng H, Zheng D, Witlox W, Levy A, Traverso A, Kong FM, Houben R, De Ruysscher DKM, Hendriks LEL.

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Abstract:

The use of prophylactic cranial irradiation (PCI) for small cell lung cancer (SCLC) patients is controversial. Risk factors for brain metastases (BM) development are largely lacking, hampering personalized treatment strategies. This study aimed to identify the possible risk factors for BM in SCLC. We systematically searched Pubmed database (01-01-1995 ~ 18-01-2021) according to the PRISMA guideline. Eligibility criteria: studies reporting detailed BM data with adequate sample size (randomized controlled trials [RCTs]: N≥50; non-RCTs: N≥100) in patients with SCLC. We summarized the reported risk factors and performed meta-analysis to estimate the pooled hazard ratios (HR) if enough qualified data (i.e. two or more studies; the same study type; the same analysis method; HRs retrievable) were available. In total, 61/536 records were eligible (18 RCTs and 39 non-RCTs comprising 13188 patients), in which 57 factors were reported. Ten factors had qualified BM data for meta-analysis: Limited stage disease (LD) (HR=0.34, 95% confidence interval [CI]: 0.17-0.67; P=0.002) and older age (≥65) (HR=0.70, 95%CI: 0.54-0.92; P=0.01) were associated with less BM; A higher T stage (≥T3) (HR=1.72, 95%CI: 1.16-2.56; P=0.007) was a significant risk factor for BM. Male sex (HR=1.24, 95%CI: 0.99-1.54; P=0.06) tended to be a risk factor and better PS (0-1) (HR=0.66, 95%CI: 0.42-1.02; P=0.06) tended to have less BM. Smoking, thoracic radiotherapy dose were not significant (P>0.05). PCI significantly decreased BM (P<0.001), but did not improve OS in ED-SCLC (P=0.81). A higher PCI dose did not improve OS (P=0.11). The impact on BM was conflicting between Cox regression data (HR=0.59, 95%CI: 0.26-1.31; P=0.20) and competing risk regression data (HR=0.74, 95%CI: 0.55-0.99; P=0.04). Compared to M0-M1a, M1b was a risk factor for OS (P=0.01) in ED-SCLC, but not for BM (P=0.19). As regular brain imaging was rarely performed, high-quality data is lacking. Other factors such as N-stage and blood biomarkers had no qualified data to perform meta-analysis. In conclusion, younger age, higher T stage, and ED are risk factors for BM, suggesting that PCI should be especially discussed in such cases. Individual patient data (IPD) meta-analysis and well-designed RCTs are needed to better identify more risk factors and further confirm our findings.

Keywords: small cell lung cancer (SCLC), brain metastases (BM), risk factors, systematic review, meta-analysis

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Contribution to the field

Evidence before this study: Prophylactic cranial irradiation (PCI) is controversial in small cell lung cancer (SCLC) because of its neurotoxicity and possible limited survival benefit for particular subgroups. Identifying risk factors for brain metastases (BM) can help clinicians to tailor the management for patients with SCLC and researchers to improve the design of SCLC randomized controlled trials (RCTs) by better controlling confounders. We systematically searched the Pubmed database for studies published in English from 01.01.1995-18.01.2021 using the terms "small cell lung cancer", "brain metastases" and their synonyms. Studies were eligible if the sample size was adequate (RCTs: N≥50; non-RCTs: N≥100).

Added value of this study: To our knowledge, this is the first systematic review and meta-analysis identifying risk factors for BM in SCLC. We systematically screened studies with adequate sample size, reviewed all the reported risk factors, and made a comprehensive summary which can be of use in the design of future studies evaluating BM prevention strategies. We found that risk factors for BM development are not systematically evaluated in clinical trials. Baseline brain imaging, with or without follow-up, is often lacking. We firstly assessed the quality of data before pooling everything together to perform meta-analysis. Our meta-analysis showed that younger age, higher T-stage, and extensive stage disease (ED) were statistically significant risk factors for BM; PCI reduced BM in ED-SCLC, but did not improve overall survival; higher PCI dose prevented BM more effectively, but did not improve overall survival.

Implications of all the available evidence: SCLC patients with younger age and higher T-stage have a higher risk of BM and could be preferably included in clinical trials evaluating BM prevention strategies, such as PCI. Higher PCI dose may be not necessary. Risk factors for BM need to be consistently evaluated and better designed clinical trials are warranted.

Introduction

Small cell lung cancer (SCLC) accounts for about 13% of newly diagnosed lung cancers worldwide[1]. Brain metastases (BM) are a very common metastatic site in SCLC: over 10% of patients have BM at initial diagnosis, more than 50% will develop BM within 2 years and up to 80% of all patients are found to have BM at autopsy[2]. Patients with SCLC and BM have a dismal survival, with a 2-year survival rate below 2%[3]. Furthermore, BM have a negative impact on quality of life (QoL). Prophylactic cranial irradiation (PCI) significantly reduces the incidence of BM in patients with SCLC[4,5]. However, because of potential neurotoxicity[6,7] and possible limited survival, especially in metastatic SCLC[8,9], PCI is increasingly questioned. In addition, stereotactic radiosurgery (SRS) has become more available and may represent an attractive therapeutic alternative[10]). As a consequence, SCLC guidelines encourage shared decision making regarding PCI for particular subgroup patients, such as elderly, very early stages, or extensive stage disease (ED)[11,12], However, shared decision making is hampered by the fact that risk factors for BM development are largely unknown in SCLC patients. The specific risk of BM (high vs low) could also be used as a stratification factor to better control confounders in trials evaluating BM prevention strategies such as PCI. Therefore, we performed a systematic review and meta-analysis to summarize the possible risk factors for BM in patients with SCLC to support a better management of SCLC patients and a better design of SCLC randomized controlled trials (RCTs).

Methods:

Study design and data extraction

We conducted this study according to the PRISMA guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[13] and registered it with PROSPERO (CRD42021228391)[14]. We performed a systematic literature search in the Pubmed database from 01-01-1995 to the search date (18-01-2021) adhering to the PICO method[15] (Appendix Table 1). The description of these components is presented in Appendix Table 2. Study eligibility criteria were as follows: 1. SCLC patients without baseline BM; 2. with detailed BM data; 3. had adequate sample size (defined as: retrospective studies or prospective observational/single arm studies [non-RCTs]: N≥100 patients; RCTs: N≥50). The detailed criteria are shown in Appendix Table 3. We assessed the "Risk of bias" for BM in eligible RCTs using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)[16,17]. We did not grade non-RCTs separately because of the inherent disadvantages of this type of studies.

Appendix Table 1. PICO searching strategy

PICO	Search terms
Patients	(("Carcinoma, Small Cell"[Majr] AND "Lung Neoplasms"[Majr]) OR "Small Cell Lung Carcinoma"[Mesh] OR sclc*[ti] OR (small cell*[ti] AND lung*[ti]) OR (small*[ti] AND cell*[ti] AND lung*[ti]) OR (oat cell*[ti] AND lung*[ti]) OR ("oat"[ti] AND cell*[ti] AND lung*[ti]) OR ((pneumoa*[ti] OR pneumob*[ti] OR pneumoc*[ti] OR pneumod*[ti] OR pneumoe*[ti] OR pneumof*[ti] OR pneumog*[ti] OR pneumoh*[ti] OR pneumoi*[ti] OR pneumok*[ti] OR pneumol*[ti] OR pneumom*[ti] OR pneumon*[ti] OR pneumoo*[ti] OR pneumop*[ti] OR pneumor*[ti] OR pneumos*[ti] OR pneumot*[ti] OR pneumou*[ti] OR pneumov*[ti] OR pneumow*[ti] OR pneumox*[ti] OR pulmon*[ti] OR respir*[ti] OR lung*[ti] OR bronche*[ti] OR bronchi*[ti] OR bronchoa*[ti] OR bronchob*[ti] OR bronchoc*[ti] OR bronchod*[ti] OR bronchoe*[ti] OR bronchof*[ti] OR bronchog*[ti] OR bronchoh*[ti] OR bronchoi*[ti] OR bronchok*[ti] OR bronchol*[ti] OR bronchom*[ti] OR bronchon*[ti] OR bronchoo*[ti] OR bronchop*[ti] OR bronchor*[ti] OR bronchos*[ti] OR bronchot*[ti] OR bronchou*[ti] OR bronchov*[ti] OR bronchoz*[ti] OR bronchu*[ti] OR endobronch*[ti] OR alveol*[ti] OR pleur*[ti] OR diaphragm*[ti] OR diaphragm*[ti] OR thorax*[ti] OR thorac*[ti] OR chest*[ti]) AND ((small*[ti] AND cell*[ti]) OR oat cell*[ti] OR ("oat"[ti] AND cell*[ti]))) NOT "non-small"[ti])
Intervention	Non-applicable
Comparison	Non-applicable
Outcome	(("brain metasta*") OR ("cranial metasta*") OR ("CNS metasta*") OR ("central nervous system metasta*") OR ("cerebral metasta*") OR "Brain Neoplasms/secondary" [Mesh] OR ("metastatic brain tum*") OR ("secondary brain tum*") OR ("intra-axial metastatic tum*"))

Appendix Table 2. Descriptions of the components of PICO

Acronym	Definition	Description
P	Patients	SCLC patients without BM at baseline
I	Intervention	NA
C	Comparison	NA
O	Outcome	BM during or after antitumor treatment (follow-up BM), time to BM development, and risk factors associated with BM, overall survival

Abbreviations: BM, Brain metastases; NA, non-applicable; SCLC, small cell lung cancer.

Appendix Table 3. Inclusion criteria

Subjects included	Human only
Language	English
Article type	Original article, full paper
Study type	Large scale retrospective studies (sample size ≥ 100); Prospective observational studies (sample size ≥ 100); Prospective randomized phase II trials (sample size ≥ 50); Prospective randomized phase III-IV trials
Primary tumor	Small cell lung cancer without brain metastasis at baseline
Period	Studies published since 01.01.1995 (as from 1995, brain MRI with gadolinium became more widely available)
Follow up period	All
Outcome	Brain metastases

We extracted data according to our published protocol[14] and reported the following critical items: title, first author, journal, publication year, study design, recruitment period, sample size, age, performance status (PS), sex, thoracic radiotherapy (TRT), surgery, chemotherapy, PCI, follow-up time, statistics analysis, the results of possible risk factors for BM and overall survival (OS) (numbers of events/patients, hazard ratio [HR], 95% confidence interval [CI], and P-value), and conclusion. We also reported the following items for each RCT: brain magnetic resonance imaging (MRI) or computed tomography (CT) at baseline and before PCI, scheduled brain CT or MRI during follow-up, brain imaging contrast-enhanced or not, BM as primary or secondary outcomes. We applied the Web Plot Digitizer[18] to extract survival data from plots if necessary.

Two investigators (HZ and DZ) independently screened the titles, abstracts, methods, and full texts for eligibility; extracted data; and assessed the risk of bias. Any conflicts in each step were resolved through discussion with a third investigator (LH).

Statistical analysis

Our primary endpoint was BM. We also analyzed OS to further interpret the clinical significance when such data were available. The factors' effect on BM and OS was expressed as a HR, being the most appropriate metric for summarizing time-to-event data[19]. We first analyzed each factor for BM per study. If two or more studies investigated the factor's impact on BM with homogenous methodology and outcomes, we performed a meta-analysis with Rev Man 5.4.1 using the EXP[(O-E)/Var] method. If the OS data were not available in one or more studies that were included for the BM meta-analysis, the meta-analysis for OS would not be performed to avoid missing outcome bias. To minimize bias, we used the adjusted rather than the univariate HR if possible. We calculated the observed (O) minus expected (E) number of events and its variance (V) for each study according to the methods of Tierney et al[20]. If similar data were reported by researchers from the same group, only the latest one was included for meta-analysis to avoid data overlapping. Meta-analysis was performed separately for RCTs and non-RCTs to avoid misleading conclusions. Meta-analysis for non-RCTs was not performed if there were sufficient RCTs addressing the issue[21]. We used I^2 to quantify inter-study heterogeneity, of which 25%, 50% and 75% can be considered as low, moderate, and high heterogeneity[22]. If $I^2 > 50\%$, we performed the random-effects meta-analysis[23,24] using R version 4.1.2 with "meta" package.

Results:

Study selection and quality assessment

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The systematic review identified 536 records, of which 61 records met the inclusion criteria (22 records for 18 RCTs comprising 5060 patients and 39 non-RCTs comprising 8128 patients [including two prospective observational studies comprising 544 patients]) (Figure 1). The 18 RCTs were published between 1995-2019, but only three were from 2010-2019[25-27]. As shown in Appendix Table 4-5, BM was the primary endpoint in three trials[5,28-30]. Brain MRI/CT was performed before treatment for patients in two trials[27,31] and before PCI in six trials[9,26,28,30-32]. In five trials brain CT/MRI was scheduled during follow-up [9,26,28,30,33] and in one trial (PCI85[28]) the number of performed CT scans at pre-specified time points was mentioned (which indicated low compliance). As regular brain imaging was not performed in most trials, asymptomatic BM will have been missed, which has resulted in high risk of bias at domain 4 (measurement method) or domain 3 (missing outcome) according to RoB2. Because of that, two RCTs were assessed to be at low risk of bias, the others were at high risk of bias (Figure 2). The 39 non-RCTs were published from 1995-2020, among which 32 were from 2010-2020. The study design, patients' characteristics and treatments are shown in Appendix Table 6.

In addition to symptomatic BM, we found that the pre-PCI BM (BM immediately before PCI) was investigated in one study[34] and the first isolated BM event, rather than overall BM during the whole disease course, was analyzed in five studies[35-39]. Both first isolated BM and overall BM were reported in eight papers[28-30,40-44] and showed that first isolated BM incidence was lower than overall BM incidence (Table 1). We only performed meta-analysis for overall BM because this is more relevant than a first isolated BM event.

We also found that the definition of time to BM events varied among studies, which indicates that heterogeneity also exists between RCTs: from the date of initial diagnosis (n=19)[43,45-62]; from the date of randomization (n=16)[5,9,25,26,28-32,39,44,63-67]; from the date of treatment initiation (n=6)[35,40,68-71]; from the end of chemoradiotherapy (CRT) (n=5)[42,50,69,72,73]; from the date of PCI (n=4)[27,74-76]; from the date of chemotherapy initiation (n=3)[33,36,37]; from the date of TRT initiation (n=2)[41,77]; from the date of surgery (n=1)[78]; five studies had no information[34,38,79-81], two studies applied two definitions[50,69].

More importantly, we noticed that the statistical analyses for BM varied considerably: Competing risk regression: n=12[57,69,77,81], RCT: N=8[5,9,26-30,44]; Cox proportional hazard regression:n=20[35,36,41,43,45,46,53,54,59-61,70,73,75,78,80], RCT: N=4[31,33,38,39]; Log-rank test n=16[41,42,47,49,50,52,55,58,62,76], RCT: N=6[25,32,63-66]; Logistic regression: n=3[34,74,79]; χ^2-test or Fisher exact 2-tailed test: n=7[37,51,56,68,71], RCT: N=2[67,72]; Descriptive: n=2[40,48]. Statistical analysis for OS was always using survival analysis (Kaplan-Meier, Log-rank test, and Cox regression).
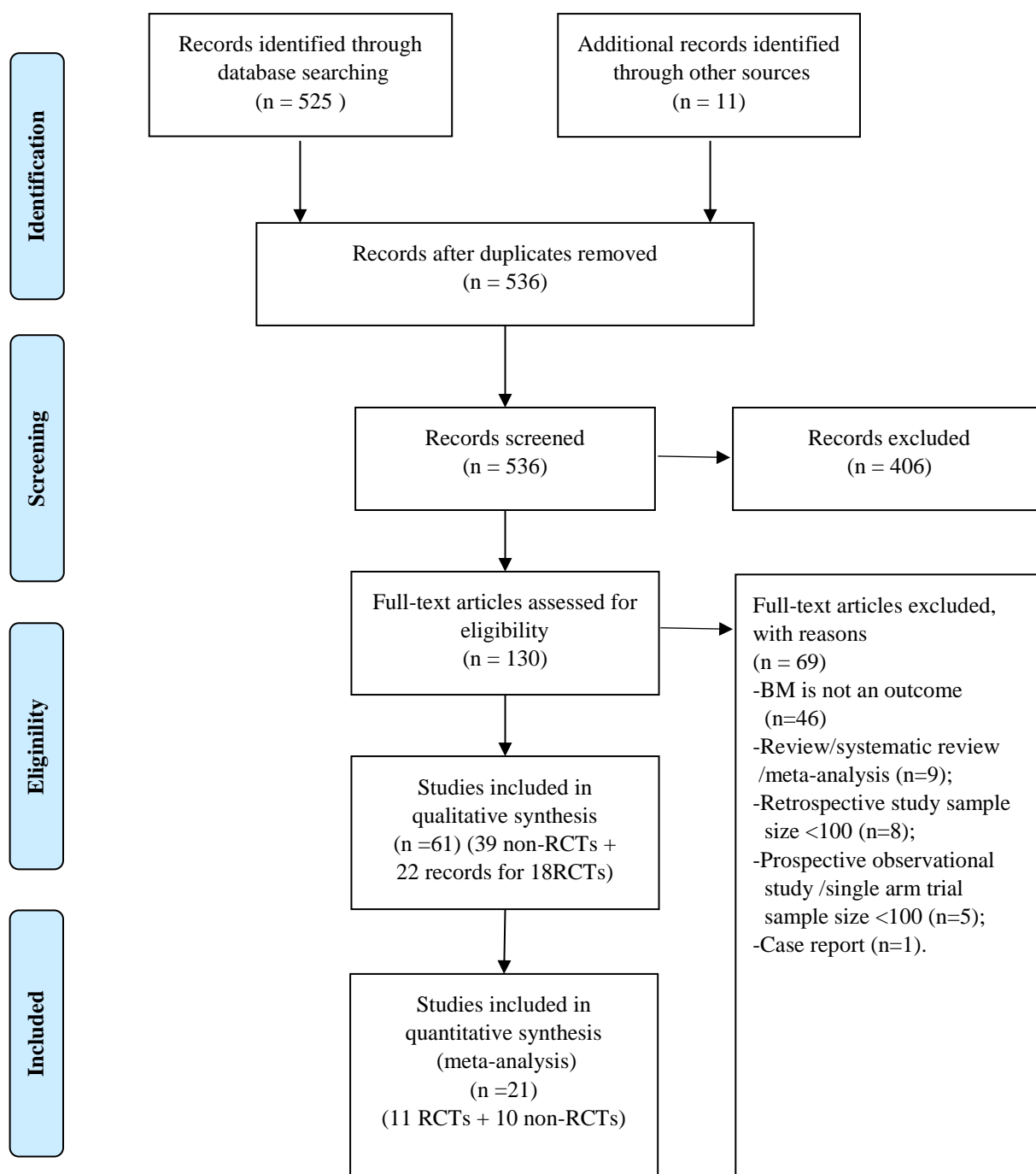
Figure 1. PRISMA flow diagram

Abbreviations: BM, brain metastases; Non-RCTs, non-randomized controlled trials; RCTs, Randomized controlled trials.

Appendix Table 4. Design of included randomized controlled trials

ID	First Author (Trial)	Journal	Study design	Brain CT or MRI before treatment	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Brain image contrast-enhanced or not	BM as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
1. PCI vs no PCI *1) LD-SCLC*										
487	Work, 1996[1]	J Clin Oncol	LD-SCLC: PCI vs no PCI	Only performed when indicated	Only performed when indicated.	Only performed when indicated.	NI	NI	03-1981 ~ 09-1989	100-> 200; 199 were eligible, PCI: 157; No PCI: 42.
148	Gregor, 1997[2] (UKCCCR /EORTC)	Eur J Cancer	Phase III, LD-SCLC, CR after induction therapy: PCI vs no PCI (PCI 24Gy vs 36Gy)	NI	16% patients had brain CT before PCI	No	NI	Secondary	10-1987 ~ 04-1995	300 required (Power: NI) 314 patients (194 PCI, 120 No PCI) were randomized.
62	Cao, 2005[3]	Chin Med J (Engl)	LD-SCLC: PCI vs no PCI	CT?[A]	CT?[A]	NI	NI	NI	01-1990 ~ 12-1995	NI for targeted size; 51 enrolled: 26 PCI, 25 no PCI
2) ED-SCLC										
415	Slotman, 2007[4] (EORTC)	N Engl J Med	Phase III, ED-SCLC: PCI vs no PCI	No	No	Only performed when indicated	Yes	Primary	02-2001 ~ 03-2006	287 required (Power 80%); 286 patients were recruited (143 in each arm).
445	Takahashi, 2017[5]	Lancet Oncol	Phase III, ED-SCLC: PCI vs no PCI	NI	MRI	Brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment	Yes	Secondary	03-04-2009 ~ 17-07-2013	330 required (power: 80%); 224 recruited: PCI: 113; No PCI: 111
3) SCLC										

Appendix Table 4. Design of included randomized controlled trials

ID	First Author (Trial)	Journal	Study design	Brain CT or MRI before treatment	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Brain image contrast-enhanced or not	BM as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
18	Arriagada, 1995[6] (PCI 85)	J Natl Cancer Inst	SCLC, CR after induction therapy: PCI vs no PCI	CT?[A]	CT?[A]	CT at 6, 18, 30, and 48 months after random assignment	NI	Primary	05-1985 ~ 03-1993	150 each arm (power: 95%); 300 randomized (149 PCI, 151 control), 145 received PCI, 149 no PCI
225	Laplanche, 1998[7] (PCI 88)	Lung Cancer	SCLC, CR after induction therapy: PCI vs no PCI	NI	NI	CT was performed when indicated.	NI	Secondary	10-1988 ~ 04-1994	550 per group (power: 95%); 211 included (100 PCI, 111 no PCI) (power: 37%)
19	Arriagada, 2002[8] (PCI 85 + PCI 88)	Ann Oncol	SCLC, CR after induction therapy: PCI vs no PCI	CT?[A]	CT?[A]	CT was performed when indicated.	NI	Primary	05-1985 ~ 04-1994	NI for targeted size; 505 enrolled: PCI85: 294 (145 PCI, 149 no PCI); PCI88: 211 (100 PCI, 111 no PCI)
	2. PCI dose									
231	Le Pechoux, 2009[9]	Lancet Oncol	Phase III, LD-SCLC with CR after CRT: PCI high dose (36Gy/24f/bid vs 36Gy/18f/qd) vs standard dose (25Gy).	NI	23% had MRI, 73% had CT	MRI/CT yearly or before in case of neurological symptoms	NI	Primary	09-1999 ~ 12-2005	NI for targeted size; 720 (360 in each arm) enrolled
	3. TRT vs no TRT in ED-SCLC									
526	Slotman, 2015[10] (CREST)	Lancet	Phase III, ED-SCLC: TRT vs no TRT	Brain CT/MRI was done for all patients with symptoms	A brain CT/MRI was done for all patients with symptoms	NI	NI	Secondary	18-02-2009 ~ 21-12-2012	483 required (power: 80%); 498 randomized (249 TRT, 249 no TRT), 495 analyzed

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Appendix Table 4. Design of included randomized controlled trials

ID	First Author (Trial)	Journal	Study design	Brain CT or MRI before treatment	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Brain image contrast-enhanced or not	BM as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
				230 (46%) of asympto-matic patients underwent a brain CT/MRI	43 (13%) of asymptomatic patients underwent a brain CT/MRI					(247 received TRT, 248 no TRT)
140	Gore, 2017[11] (RTOG 0937)	J Thorac Oncol	Phase II, ED-SCLC: TRT vs no TRT	No	Yes, MRI/CT	Brain imaging were required at 2, 6, 9, and 12 months; every 6 months for 2 to 3 years; and then annually.	NI	Secondary	18-03-2010 ~ 27-02-2015	154 required (power: 80%); 97 randomized (46 TRT, 51 no TRT), 86 eligible (44 received TRT, 42 no TRT)
	4. TRT timing									
488	Work, 1997[12]	J Clin Oncol	LD-SCLC: Early TRT (initial TRT) + PCI vs Late TRT (delayed 18 weeks) + PCI	Only performed when indicated.	Only performed when indicated.	Only performed when indicated.	NI	NI	03-1981 ~ 09-1989	100-> 200; 199 were eligible, 157 were given PCI: Early TRT: 99; Late TRT: 58.
532	Jeremic, 1997[13]	J Clin Oncol	LD-SCLC: Early vs Late TDRT (week 1 vs week 6)	CT or radionuclide	CT or radionuclide	NI	NI	Secondary	01-1988 ~ 12-1992	170 required, 107 enrolled, 103 included: Early: 52; Late: 51.
531	Skarlos, 2001[14] (HeCOG)	Ann Oncol	LD-SCLC: Early vs Late TDRT (1st vs 4th chemo)	NI	NI	Brain CT: During treatment: every 2 cycles of chemo; after treatment:	NI	Secondary	12-1993 ~ 11-1999	86 required, 81 included: Early: 42; Late: 39.

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ID	First Author (Trial)	Journal	Study design	Brain CT or MRI before treatment	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Brain image contrast-enhanced or not	BM as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
						every 3 months for the first year, every 4 months for the second year and every 6 months thereafter				
429	Spiro, 2006[15]	J Clin Oncol	LD-SCLC: Early vs Late TRT (2nd vs 6th chemo)	CT: 153/325=47%;	CT	Performed when indicated.	NI	Secondary	1993 ~ 1999	320 required (power: 80%); 325 recruited: Early TRT: 159; Late TRT: 166
	5.CRT sequence									
530	Gregor, 1997[16] (EORTC08877)	J Clin Oncol	Phase III, LD-SCLC: Alternating vs SCRT	NI	NI	NI	NI	Secondary	03-1989 ~ 01-1995	360 required (Power: 80%); 349 recruited (175 in arm A, 174 in arm S), 14 were ineligible (5 in arm A, 9 in arm S).
529	Takada, 2002[17] (JCOG 9104)	J Clin Oncol	LD-SCLC; SCRT vs CCRT	CT	NI	NI	NI	Secondary	05-1991 ~ 01-1995	220 required (Power 80%); 231 recruited, 228 eligible (114 in each arm).
	6.TRT fractionation									
239	Levy, 2019[18]; Faivre-Finn, 2017[19];	J Thorac Oncol; Lancet Oncol;	Phase III, LD-SCLC: TDRT vs ODRT	MRI/CT: CT: 79% (356/449); MRI: 18% (83/449)	No	No	NI	Secondary	17-04-2008 ~ 29-11-2013	532 required (Power 80%); 547 recruited (274 TDRT, 273 ODRT), 449

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	Faivre-Finn, 2016[20]. (CONVERT trial)	BMJ Open								received PCI (229 TDRT, 220 ODRT).
7. Topotecan vs observation in ED-SCLC										
388	Schiller, 2001[21] (E7593)	J Clin Oncol	Phase III, ED-SCLC: EP -> Topotecan vs EP -> Observation	No	No	No	NA	Secondary	03-1995 ~ 01-1999	284 patients for step 2 needed (Power 90%); 420 recruitment for step 1 required. 421 recruited (274 TDRT, 273 ODRT), 402 eligible. 242 randomized (122 Topotecan, 120 observation), 223 eligible (112 Topotecan, 111 observation)
536	Sundstrøm, 2002[22]	J Clin Oncol	Phase III, SCLC: EP vs CEV	No. Only performed when indicated.	No. Only performed when indicated.	No	NI	Secondary	01-1989 ~ 08-1994	436 randomized (218 EP, 218 CEV)

Notes:
[A]: Not sure the brain image was before treatment or before PCI.
Abbreviations:
CEV, cyclophosphamide-epirubicin-vincristine; CR, complete response; CRT, chemoradiotherapy; CT, Computerized Tomography; ED, extensive-stage disease; EP: Etoposide-platinum; LD, limited-stage disease; MRI, Magnetic Resonance Imaging; NI, no information; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; TRT, thoracic radiotherapy.
References:

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2. Gregor A, Cull A, Stephens RJ, et al: Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 33:1752-8, 1997

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16. Gregor A, Drings P, Burghouts J, et al: Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: a European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study. J Clin Oncol 15:2840-9, 1997

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Appendix Table 5. Baseline characteristics and treatments of the randomized controlled trials

ID	First Author, (Trial)	Median follow-up	Age	PS	Gender (Male percentage)	Surgery	TRT	Chemo	PCI
	1. PCI vs no PCI *1) LD-SCLC*								
487	Work, 1996[1]	NI	Median (range): PCI: 61 (36-70), No PCI: 59 (36-69), Total: 60 (36-70).	KPS 100: 11.6%; 90-80: 69.3%; 70-60: 14.6%; 50-40: 4.5%.	PCI: 60% No PCI: 71.4% Total: 61.5%	No	Before October 1984: 40 Gy; After October 1984: 45 Gy..	Yes	PCI: 157 No PCI: 42
148	Gregor, 1997[2] (UKCCCR/EORTC)	18 months	Median (range): No PCI:61 (28-76), PCI: 60 (37-79).	NI	No PCI: 74/120(62%), PCI: 125/194(64%).	NI	84% TRT (263/314)	Yes	PCI: 194/314 No PCI: 120/314
62	Cao, 2005[3]	>5 years	≤65; Mean±SD: No PCI:55.63 ± 7.29, PCI: 54.69 ± 7.56.	KPS ≥70	No PCI: 92%, PCI: 92%.	NI	Yes, 56-70Gy.	Yes	PCI: 26 (51%); No PCI: 25(49%)
	2) ED-SCLC								
415	Slotman, 2007[4] (EORTC)	NI	Median (range): No PCI:63 (39-75), PCI: 62 (37-75).	0:No PCI: 52/143(36.4%), PCI: 52/143(36.4%); 1:No PCI: 76/143(53.1%), PCI: 80/143(55.9%); 2:No PCI: 15/143(10.5%), PCI: 11/143(7.7%); 3:No PCI:0/177(0%), PCI: 1/163(1%); Unknown:No PCI: 0/177(0%), PCI: 1/163(1%). (0:No PCI: 105/177(59%), PCI: 77/163(47%); >0:No PCI: 68/177(41%), PCI: 86/163(53%)	No PCI: 82/143(57.3%), PCI: 97/143(67.8%).	NI	NI	Yes	PCI: 143/286 No PCI: 143/286

Appendix Table 5. Baseline characteristics and treatments of the randomized controlled trials

ID	First Author, (Trial)	Median follow-up	Age	PS	Gender (Male percentage)	Surgery	TRT	Chemo	PCI
445	Takahashi, 2017[5]	11.9 months	Median (range): No PCI:69 (37-86), PCI: 69 (43-83).	0-1:No PCI: 107/111(96%), PCI: 108/113(96%); 2:No PCI:4/111(4%), PCI: 5/113(4%).	No PCI: 98/111(88%), PCI: 95/113(84%).	NI	NI	Yes	PCI: 106/224 No PCI: 118/224
	3) SCLC								
18	Arriagada, 1995[6] (PCI 85)	NI	Mean±SD: No PCI:56 ± 9, PCI: 57 ± 8.	KPS 90-100:No PCI:62%, PCI: 62%; 70-80: No PCI:35%, PCI: 37%; ≤60: No PCI:3%, PCI: 1%.	No PCI: 86%, PCI: 88%.	8%	92%	99%	PCI: 145 (49%); No PCI: 149(51%)
225	Laplanche, 1998[7] (PCI 88)	5 years	Mean±SD: No PCI:57 ± 9, PCI: 58 ± 8.	KPS ≥90: No PCI:75%, PCI: 82%; <90: No PCI:25%, PCI: 18%.	No PCI: 92%, PCI: 89%.	NI	NI	Yes	PCI: 100(47%), no PCI: 111(53%)
19	Arriagada, 2002[8] (PCI 85 + PCI 88)	11 years	See above	KPS >80: No PCI:68%, PCI: 70%; 70-80: No PCI:31%, PCI: 29%; ≤60: No PCI:2%, PCI: 1%.	No PCI: 88%, PCI: 88%.	NI	NI	Yes	PCI: 245(51%), no PCI: 260 (49%)
	2. PCI dose								
231	Le Pechoux, 2009[9]	39 months	Median (range): standard dose: 60 (38-83), higher dose: 60 (34-78).	NI	Standard dose: 234/360 (65%); higher dose: 226/360 (63%).	NI	Yes (685/720=95%)	Yes	Yes (711/720=99%)
	3. TRT vs no TRT in ED-SCLC								
526	Slotman, 2015[10] (CREST)	24 months	Median (IQR): No TRT:63 (57-69); TRT: 63 (58-69).	0:No TRT:70/248 (28%), TRT: 97/247 (39%);	No TRT: 55%; TRT: 55%;	No	Yes (30Gy/10f): 248 (50%);	Yes	Yes

Appendix Table 5. Baseline characteristics and treatments of the randomized controlled trials

ID	First Author, (Trial)	Median follow-up	Age	PS	Gender (Male percentage)	Surgery	TRT	Chemo	PCI
				1:No TRT: 155/248(63%), TRT: 121/247(49%); 2:No TRT: 23/248(9%), TRT: 29/247(12%).			No TRT: 247 (50%)		
140	Gore, 2017[11] (RTOG 0937)	9 months	Median (range): No TRT:60.5 (47-81); TRT: 66 (35-86); Total: 63 (35-86).	0: 39/86 (45.3%); 1: 46/86 (53.5%); 2: 1/86 (1.2%).	No TRT: 42.9%; TRT: 47.7%; Total: 45.3%	No	Yes (45Gy/15f): 44 (51%); No TRT: 42 (49%)	Yes	Yes
	4. TRT timing								
488	Work, 1997[12]	NI	Median (range): Early TRT: 61 (36-70), Late TRT: 59 (36-69), Total: 60 (36-70).	KPS 100: 11.6%; 90-80: 69.3%; 70-60:14.6%; 50-40: 4.5%.	Early TRT: 54.5% Late TRT: 70.6% Total: 61.5%	No	Before October 1984: 40 Gy; After October 1984: 45 Gy..	Yes	PCI: 157 No PCI: 42
532	Jeremic, 1997[13]	NI	Median (range): Early TRT: 59 (40-67), late TRT: 59 (44-66),	90-100: 51/103 (49.5%), 50-80: 52/103 (50.5%)	Early TRT: 31/52 (59.6%), Late TRT: 31/51(60.8%).	NI	54Gy/36f, bid	Yes	PCI was given to patients achieving a complete response.
531	Skarlos, 2001[14] (HeCOG)	35 months	Median (range): Early TRT: 61 (40-76), Late TRT: 60 (37.5-76),	0: Early: 11/42 (26%), Late: 16/39 (41%). 1: Early: 21/42 (50%), Late: 17/39 (44%). 2: Early: 10/42 (24%), Late: 6/39 (15%).	Early TRT: 39/42 (93%), Late TRT: 35/39 (90%).	NI	45Gy/30f, bid	Yes	PCI was given to patients achieving a complete response.

Appendix Table 5. Baseline characteristics and treatments of the randomized controlled trials

ID	First Author, (Trial)	Median follow-up	Age	PS	Gender (Male percentage)	Surgery	TRT	Chemo	PCI
429	Spiro, 2006[15]	63 months	Median (range): Early TRT: 62 (34-74), Late TRT: 62 (33-74).	0-1: Early TRT:144/159 (91%), Late TRT: 148/166 (89%). 2-3: Early TRT:15/159 (9%), Late TRT: 18/166 (11%).	Early TRT: 95/159 (60%), Late TRT: 94/166 (57%).	NI	Yes: 40Gy/15f;	Yes	Responding to CRT: Yes:
	5.Treatment sequence: CCRT vs SCRT, Alternating vs SCRT:								
530	Gregor, 1997[16] (EORTC08877)	43 months	Median (range): A:61 (34-74), S: 61 (33-75).	0:A:80/170 (47%), S: 76/165 (46%); 1:A:76/170 (45%), S: 79/165 (48%); 2:A:10/170 (6%), S: 7/165 (4%); 3.A:3/170 (2%), S: 3/165 (2%);	A:112/170 (66%), S: 112/165 (68%);	No	Alternating: 50Gy/20f, 4 1-week courses. SCRT: 50Gy/20f, 4 consecutive weeks.	Yes	No
529	Takada, 2002[17] (JCOG 9104)	NI	Median (range): SCRT: 64 (30-74), CCRT: 65 (39-74),	0: SCRT: 33/114 (29%), CCRT: 25/114(22%). 1: SCRT: 75/114 (66%), CCRT: 83/114(73%). 2: SCRT: 6/114 (5%), CCRT: 6/114 (5%).	SCRT: 93/114(82%), CCRT: 91/114(80%).	NI	45Gy/30f, bid	Yes	PCI was administered to patients with a complete or near-complete response
	6.TRT fractionation: ODRT vs TDRT								
239	Levy, 2019[18] (CONVERT trial)	45 months	Median (range): 62 (29-81)	0: 215 (48%); 1: 222 (49%); 2: 12 (3%).	252 (56%)	NI	Yes	Yes	Yes (449)

7. Chemo: Topotecan vs observation in ED-SCLC, EP vs CEV in SCLC

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ID	First Author, (Trial)	Median follow-up	Age	PS	Gender (Male percentage)	Surgery	TRT	Chemo	PCI
388	Schiller,2001 [21] (E7593)	21 months	Median: Topotecan: 62.5, Observation: 62.	0: Topotecan: 29%, Observation: 34%; 1: Topotecan: 60%, Observation: 54%; 2: Topotecan: 12%, Observation: 12%.	Topotecan: 64%, Observation: 61%;	Topotecan: 37%; observation: 22%;	NI	Yes	NI
536	Sundstrøm, 2002 [22]	>5 years	Median (range): EP: 64 (41-75); CEV: 64 (39-76)	0: EP: 22%, CEV: 18%; 1: EP: 47%, CEV: 44%; 2: EP: 28%, CEV: 35%; 3: EP: 3%, CEV: 3%.	EP: 66%, CEV: 63%;	NI	LD-SCLC: Yes	Yes, EP vs CEV	PCI was administered to LD-SCLC patients with a complete response: EP: 20%; CEV: 23%.

Abbreviations:

CCRT, concurrent chemoradiotherapy; CEV, cyclophosphamide-epirubicin-vincristine; chemo, chemotherapy; CRT, chemoradiotherapy; ED-SCLC, extensive-stage disease small cell lung cancer; EP: Etoposide-platinum; IQR, Interquartile range; LD-SCLC, limited-stage disease small cell lung cancer; KPS, Karnofsky performance status scale; NI: no information; ODRT, once-daily radiotherapy; PCI, prophylactic cranial irradiation; PS, performance status; SCRT, sequential chemoradiotherapy; TDRT, twice-daily radiotherapy; TRT, thoracic radiotherapy.

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Figure 2. Risk of bias assessments -- randomized controlled trials

Interventions	Trials	R	D	Mi	Me	S	O
1.1 PCI vs no PCI in ED-SCLC	415.Slotman, 2007	+	+	+	-	+	-
	445.Takahashi, 2017	+	+	+	+	+	+
1.2 PCI vs no PCI in LD-SCLC	487.Work, 1996	-	+	+	-	+	-
	148. Gregor, 1997, UKCCCR/EORTC	+	?	-	+	+	-
	62.Cao, 2005	?	+	+	-	+	-
1.3 PCI vs no PCI in SCLC	18. Arriagada, 1995, PCI85	+	+	-	+	+	-
	225. Laplanche, 1998, PCI88	+	+	+	-	+	-
	19. Arriagada, 2002, PCI85 + PCI88	+	+	-	-	+	-
2. PCI dose in LD-SCLC: high (36Gy) vs standard (25Gy)	231.Le Pechoux, 2009	+	+	+	+	+	+
3. TRT vs no TRT in ED-SCLC	526.Slotman, 2015, CREST	+	+	+	-	+	-
	140. Gore, 2017, RTOG 0937	?	+	+	-	+	-
4.1 CRT sequence in LD-SCLC: CCRT vs SCRT	529. Takada, 2002, JCOG 9104	+	+	+	-	?	-
4.2 CRT sequence in LD-SCLC: alternating vs SCRT	530. Gregor, 1997, EORTC08877	+	+	+	-	?	-
5.1 TRT timing in LD-SCLC: early vs late (initial vs delayed 18 weeks)	488.Work, 1997	+	+	-	-	+	-
5.2 TRT timing in LD-SCLC: early vs late (week 1 vs week 6)	532. Jeremic, 1997	+	+	+	-	+	-
5.3 TRT timing in LD-SCLC: early vs late (1st vs 4th chemo)	531. Skarlos, 2001, HeCOG	+	+	-	+	+	-
5.4 TRT timing in LD-SCLC: early vs late (2nd vs 6th chemo)	429. Spiro, 2006	+	+	+	-	+	-

6. TRT fractionation in LD-SCLC: TDRT vs ODRT	239. Levy, 2019, CONVERT	+	?	+	-	+	-
7.1 Chemo in ED-SCLC: topotecan vs observation	388. Schiller, 2001, E7593	+	+	+	-	?	-
7.2 Chemo in SCLC: EP vs CEV	536. Sundstrøm, 2002	+	+	+	-	+	-

Figure 2. Risk of bias assessments

Risk of bias legend. **R** Bias arising from the randomisation process. **D** Bias due to deviations from intended interventions. **Mi** Bias due to missing outcome data. **Me** Bias in measurement of the outcome. **S** Bias in selection of the reported results. **O** Overall risk of bias.

Domain 1: Risk of bias arising from the randomization process: The study conducted by Work et al (1996) was at high risk of bias because PCI vs no PCI was not strictly randomized. The study conducted by Cao et al had "some concerns" because of no information about the random allocation sequence. RTOG 0937 had "some concerns" because baseline age was unbalanced between arms (P = 0.03). The other 16 studies were assessed as at low risk of bias.

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): The CONVERT trial was assessed to have "some concerns" because it is unclear whether there were deviations from the intended intervention that arose because of the trial context. The UKCCCR/EORTC trial was assessed to have "some concerns" since there were deviations from the intended intervention that arose because of the trial context. The others were at low risk.

Domain 3: Missing outcome data: This domain is difficult to tell because most trials did not have a regular brain CT/MRI scan plan during the follow-up. In the trials that did have a pre-planned brain CT/MRI scan schedule, only one trial (IPC85) mentioned the compliance at some time point. Readers do not know how many data were missing. The UKCCCR/EORTC trial and HeCOG were at high risk because of no information about missing data. IPC85, the pooled analysis of IPC85+ IPC88, and the study conducted by Work et al (1997) were at high risk because many data were missing but there were no evidence that the result was not biased by missing data. The other 14 studies were at low risk.

Domain 4: Risk of bias in measurement of the outcome: 14 studies were judged to be at high risk because the method of measuring the outcome (BM) was inappropriate. They performed brain MRI/CT when patients experience neurological symptoms. The other five trials were at low risk because they had pre-planned brain MRI/CT scan during follow-up.

Domain 5: Risk of bias in selection of the reported result: JCOG 9104, E7593, and the trial conducted by Gregor et al (EORTC) had "some concerns" because of no information about pre-specified analysis plan or selection from multiple eligible analysis.

Overall risk of bias: Only the studies conducted by Le Pechoux et al and Takahashi et al were judged to be at low risk of bias. The other 17 trials were judged as high risk of bias. This is mainly because of domain 3 and domain 4.

Abbreviations:
CCRT, concurrent chemoradiotherapy; CEV, cyclophosphamide-epirubicin-vincristine; chemo, chemotherapy; CRT, chemoradiotherapy; ED, extensive-stage disease; EP, etoposide-platinum; LD, limited-stage disease; ODRT, once-daily radiotherapy; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer; SCRT, sequential chemoradiotherapy; TDRT, twice-daily radiotherapy; TRT, thoracic radiotherapy.

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
	Retrospective studies												
28	Bang, 2018[1]	Int J Radiat Oncol Biol Phys	ED-SCLC, without baseline BM, at least PR to chemo: PCI vs no PCI	01-01-2005 ~ 31-12-2011	397 screened 155 eligible	NI	66 (43-89);	0: 13/155 (8.4%); 1: 86/155 (55.5%); 2: 31/155 (20%); 3: 23/155 (14.8%); 4: 2/155 (1.3%);	57.4%	NI	PCI: 62%; No PCI: 55%; (P=0.40)	Yes	PCI: 68 No PCI: 87
34	Bernhardt, 2017[2]	Clin Lung Cancer	ED-SCLC, PCI	2007 ~ 2015	136	NI	62 (45-86);	KPS: 80 (50-100)	85/136 (62.5%)	NI	NI	Yes	Yes
52	Brewster, 1995[3]	Radiother Oncol	LD-SCLC, PCI 8Gy	07.1986 - 03.1989.	106; patients with CR:73.	≥ 24 m	58	NI	59/106 (55.7%)	NI	12.5 Gy, 1 fraction	Yes	Yes
80	Chen, 2016[4]	Strahlenther Onkol	ED-SCLC, without baseline BM, at least PR to chemo: PCI vs no PCI	04.2005 - 05.2014	204	11.2 m (range 2.9–71.7 m).	58 (IQR 52–63).	0: 71/204 (34.8%); 1: 124/204 (60.8%); 2: 9/204 (4.4%);	171/204 (83.8%)	NI	NI	Yes	Yes: 45/204 (22.1%)
81	Chen, 2018[5]	Strahlenther Onkol	ED-SCLC: Early vs late PCI	11.2011 - 07.2016	103	12 m (range: 3–36 m).	59 (IQR: 53–65)	0: 37/103 (35.9%); 1: 61/103 (59.2%); 2: 5/103 (4.9%);	89/103	NI	Yes	Yes	Yes: 59/103 (57.3%)

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Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
82	Choi, 2017[6]	Clin Lung Cancer	LD-SCLC with PET-CT or not: PCI vs no PCI	04.2001 ~ 04.2013	1423 screened, 280 eligible	NI	<60: 103/280 (36.8%); 60-70: 129/280 (46.1%); ≥70 years: 48/280 (17.1%).	0: 54/280 (19.3%); 1: 213/280 (76.1%); 2: 13/280 (4.6%).	247/280 (88.2%)	NI	Yes	Yes	PCI: 90/280 (32.1%); No PCI: 190/280 (67.9 %)
86	Chu, 2019[7]	Radiat Oncol	risk factors for pre-PCI BM	2011-2017	283 screened, 110 eligible	For OS: 22.7 m (range 6.4–92.0 m); For BM: 5.2 m (range 2.8–9.2 m).	38-79	NI	95/110 (86.4%)	NI	Yes: CCRT: 93/110; SCRT: 17/110	Yes	No
108	El Sharouni, 2009[8]	Anticancer Res	LD-SCLC: SCRT vs CCRT;	1996-2005	151 eligible, 16 lost to follow-up: SCRT: 95; CCRT:40. SCRT+PCI: 67; CCRT+PCI: 23	NI	32-81.7	NI	94/151 (62.3%)	NI	Yes	Yes	Yes
112	Eze, 2017[9]	Clin Lung Cancer	LD-SCLC with MRI: PCI vs no PCI	1998 ~ 2012	184 eligible	NI	63 (34-83).	median: 1 (range, 0-3).	111/184 (60%)	NI	Yes	Yes	PCI: 71/184 (39%); No PCI:

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
													113/184 (61%)
115	Farooqi, 2017[10]	Radiother Oncol	LS-SCLC: PCI vs no PCI	1986 ~ 2012	658 (PCI: 364; No PCI: 294)	21.2 m (range 1.2–240.8 m)	62 (27–95); ≥70 years: 151/668 (22.9%).	KPS: ≥ 80: 550/658 (83.6%); < 80: 108/658 (16.4%)	342/658 (52.0%)	No	Yes	Yes	PCI: 364 (55.3%); No PCI: 294 (44.7%)
134	Giuliani, 2010[11]	Cancer	LD-SCLC: PCI vs no PCI	1997 ~ 2007	796 screened, 207 analyzed	18.8 m (range, 2.2-130.1 m).	65.7 (38.6-88.1).	NI	111/207 (53.6%)	NI	4005 cGy / 15 fractions	Yes	PCI: 127/207(61.4%) No PCI: 80/207(38.6%)
139	Gong, 2013[12]	Int J Radiat Oncol Biol Phys	SCLC with surgery	01.1998 - 12.2009	126 eligible	NI	59 (28–79).	NI	91/126 (72.2%)	Yes	Yes: 50/126 (39.7%)	Induction: 51/126 (40.5%); adjuvant: 112/126 (88.9%)	No
145	Greenspoon, 2011[13]	J Thorac Oncol	risk factors for BM in ED-SCLC	01.01.2004 - 31.12.2006	130, 101 without baseline BM	NI	NI	0: 3/130 (2.3%); 1: 49/130 (37.7%); 2: 48/130 (36.9%); 3: 21/130 (16.2%); 4: 9/130 (6.9%).	66/130 (50.8%)	Yes: 111/130 (85.4%)	NI	NI	No

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Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
203	Kim, 2019[14]	J Radiat Res	LD-SCLC: PCI vs no PCI	11.1994 ~ 06.2010	320 screened, 235 analyzed	22 m (range 1–150 m).	61 (34–77).	0: 29; 1-2: 205	204/234 (87%)	NI	Yes	Yes	PCI: 139/234 (59.4%); No PCI: 95/234 (40.6%)
263 (Manapov, 2012[16])	Manapov, 2012[15]	Strahlenther Onkol (J Neurooncol)	LD-SCLC, PS 2-3	1997-2008	149, 125 completed CRT: SCRT: 51/125 (41%); CCRT:74/125 (59%)	NI	Median: 63.2	2 (2-3)	78/125(62%)	NI	Yes	Yes	CCRT: 16 (31%); SCRT: 20 (27%).
265	Manapov, 2013[17]	Tumori	LD-SCLC	1998-2007	125: SCRT: 51/125 (41%); CCRT:74/125(59%)	448 d (range, 35-3432).	Median: 63	2 (1-3)	78/125(62%)	NI	Yes	Yes	36/125 (29%) patients who achieved a CR.
303	Nakamura, 2018[18]	J Radiat Res	LD-SCLC: PCI vs no PCI	01.2006~ 12.2014	162 analyzed	38 m (range, 6–105 m).	67.5 (23–85)	0: 71 (44%); 1-2: 91 (56%)	130 (80%)	NI	Yes (45Gy/bid, or 50Gy/qd)	Yes	PCI: 93/162 (57%); No PCI: 69/162 (43%)

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
312	Nicholls, 2016[19]	Asia Pac J Clin Oncol	SCLC: PCI vs no PCI	01.2008 - 12.2013	203	7.6 m (range 0.5–76.5)	65.4 (±10.7)	0: 50/203 (24.6%); 1: 91/203 (44.8%); 2: 34/203 (16.7%); 3: 19/203 (9.4%); 4: 3/203 (1.5%);	160/203 (79%)	NI	LD: Yes: 55/74; ED: Yes: 63/129;	LD: Yes: 55/74; ED: Yes: 101/129;	LD: 32/74 (43.2%); ED: 17/129 (13.1%)
342	Pezzi, 2020[20]	JAMA Netw Open	LD-SCLC with MRI: PCI vs no PCI	1992 ~ 2012	297 eligible, 168 matched	PCI: 83.64 m; no-PCI: 83.97 m	Before matching: PCI: 62.2 (range, 27.0-85.0); No PCI: 68.6 (range, 40.0-86.0). After matching: PCI: 65.0 (44.0-85.0) No PCI: 67.5 (40.0-86.0)	before matching: 0: 72/297 (24.2%); 1: 189 /297 (63.6%); 2: 30/297 (10.1%); 3: 6/ 297 (2.0%). after matching: 0: 38/168 (22.6%); 1: 105 /168 (62.5%); 2: 21/168 (12.5%); 3: 4/ 168 (2.4%).	before matching: 162/297 (54.5%); after matching: 96/168 (57.1%)	NI	Yes	Yes	before matching: PCI: 205/297(69%); No PCI: 92/297(3 1%); after matching: PCI: 84/168 (50%) No PCI: 84/168 (50%)

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
356	Ramlov, 2012[21]	Lung Cancer	SCLC with PCI	01.2007 ~ 08.2010	118	All: 16.6 m (range 3–54 m); alive: 33 m (20–54 m)	65 (46–80).	NI	51/118 (43.2%)	Yes: 7/118 (6%)	Yes: 65/118 (53.4%)	Yes: 111/118	Yes
368	Roengvoraphoj, 2017[22]	Strahlenther Onkol	LD-SCLC with CRT: Male vs female	1998 - 2012	179	NI	63 (range, 35–83)	1 (range, 0–3)	110/179 (61.5 %)	NI	Yes	Yes	Yes: 70/179 (39%)
371	Rubenstein, 1995[23]	Int J Radiat Oncol Biol Phys	LD-SCLC: PCI vs no PCI	06.1986 ~ 12.1992	197 analyzed	mean:19 m, median:11.5 m (range, 1.1 - 89.8 m)	mean: 66 (range, 33 - 86)	Baseline KPS: ≤80: 79 (41.8%); >80: 110 (58.2%). Pre-RT KPS: ≤80: 70 (37.0%); >80: 119 (63.0%).	NI	10 (5.1%)	Yes: 195/197 (99%)	Yes	PCI: 112/197 (56.9%); No PCI: 69/197 (43.1%)
376	Sahmoun, 2004[24]	Anticancer Res	SCLC without PCI: Risk factors for BM in SCLC: HT vs no HT	06.1986 - 06.2003	232 screened, 185 eligible	NI	67 (44-89);	NI	130/185 (70%)	NI	NI	NI	No

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
377	Sahmoun, 2005[25]	Anticancer Res	Risk factors for BM and OS in SCLC: Site, gender	01.1989 - 12.2002	230 eligible, 209 without baseline BM	NI	67 (41-89);	NI	148/230 (64%)	NI	Yes: 134/230	Yes: 182/230	Yes: 12/209 (5.7%)
384	Sas-Korczyńska, 2010[26]	Strahlenther Onkol	LD-SCLC: Early PCI vs Late PCI	1995 - 2004	129	19 m (range: 4-135 m)	57 (33-73) (Mean: 56.02)	80 (60-90)	83/129 (64.3%)	NI	Yes, CCRT	Yes	Yes: 86/129, 66.7%; (Early: 41/86. 47.7%; late: 45/86, 52.3%)
393	Scotti, 2014[27]	Tumori	TRT timing in LD-SCLC	06.2000 - 05.2010	124: CCRT: 53/124 (42.8%); SCRT: 71/124 (57.2%)	2.2 y (range, 0.2-12.4)	≤ 55: 34/124 (27.4%); 56-65: 42/124 (33.9%); ≥ 66: 48/124 (38.7%)	0: 95/124 (76.6%); 1: 29/124 (23.4%)	101/124 (81.5%)	NI	Yes	Yes	Yes: 38/124 (25.9%)
439	Suzuki, 2018[28]	Radiother Oncol	Risk factors for BM in SCLC: Hematologic variables	2001–2015	293	14.3 m (IQR: 9.3–22.8 m)	64 years (IQR, 58–71 years)	0–1: 239/293 (82%)	48%	No	≥ 45 Gy: 200/293 (68%)	yes	Yes: 125/293 (43%)

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ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
441	Tai, 2013[29]	Clin Lung Cancer	LD-SCLC: PCI vs no PCI	1981 ~ 2007	289 analyzed	NI	65 (range, 38-86)	NI	168/289 (58.1%)	NI	Yes	Yes	PCI: 177/289 (61.2%);
461	van der Linden, 2001[30]	Respir Med	LD-SCLC with CR: PCI vs no PCI	01.1985 ~ 10.1994	135 screened, 102 analyzed	17 m (range 7 - 117 m)	NI	NI	NI	9/135	yes: 67/102 (65.7%): PCI: 55/65; No PCI: 12/37.	Yes	PCI: 65/102; No PCI: ˆ37/102.
491	Wu, 2017[31]	Radiother Oncol	LD-SCLC, TNM vs BM	1993-2013	333 screened, 283 eligible	21.4 m	NI	KPS: ≥ 80: 241/283 (85.2%); < 80: 42/283 (14.8%)	127/283 (44.9%)	Yes: 69/283 (24.4%)	Yes: 236/283 (83.4%)	Yes: 264/283 (93.3%)	Yes: 116/283 (41.0%)
493	Xu, 2017[32]	J Thorac Oncol	Resected SCLC: PCI vs no PCI	01.2006 ~ 01.2014	438 screened, 349 eligible	NI	median: NI (range, 38–79); <60: 155/349 (44.4%) ≥60: 194/349 (55.6%).	NI	337/389 (85.1%)	Yes, all	yes: 229 (65.6%); median: 52 Gy (range 30–80 Gy).	Yes: 321 (92%); No: 28 (8.0%)	PCI: 115/349; No PCI: 234/349

Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
513	Zeng, 2019[33]	JAMA Netw Open	SCLC, with TRT, chemo, and PCI: TDRT vs ODRT	01-07-2003 ~ 30-6-2016	894 screened, 778 eligible, 338 matched (1:1 PSM)	23.6 m (IQR, 14.2-38.2 m),	55 (IQR, 48-61),	0: 127/778 (16.3%); 1: 624/778 (80.2%); 2: 27/778 (3.5%)	574/778 (73.8%)	Yes: 44 (5.7%)	ODRT: 609/778 (78.3%); TDRT: 169/778 (21.7%)	Yes	Yes
514	Zeng, 2017[34]	Sci Rep	SCLC with PCI: Risk factors for BM	2003 ~ 2014	204 screened, 175 eligible	42.1 m (range, 7.4–119.4)	55 (29-76)	0: 10/175(5.7%); 1: 162/175(92.6%); 2: 3/175(1.7%)	129/175 (73.7%)	NI	ODRT: 123/175; TDRT: 46/175	Yes	Yes
519	Zheng, 2018[35]	Strahlenther Onkol	LD-SCLC without PCI: Risk factors for BM	01.2010 ~ 12.2016	153	42.5 m (range, 5.8–93.2 m).	59 (23–80);	0: 64/153 (41.8%); 1: 75/153 (49.0%); 2: 6/153 (3.9%)	104/153 (68%)	NI	ODRT (mean: 56.9Gy, range:50–66Gy): 120; TDRT (45Gy/bid): 19	Yes	No
520	Zhu, 2014[36]	Radiat Oncol	Resected SCLC: Risk factors for BM	01.2003 ~ 12.2009	211 screened, 126 eligible	56.0 m (range, 30.4–96.8 m).	55 (34–74); <65: 91/126 (72.2%); ≥65: 35/126 (27.8%).	KPS: ≥ 80: 80/126 (64.0%); < 80: 46/126 (36.0%)	101/126 (80.2%)	Yes, all	yes: 55/126; 50–60 Gy	yes	No

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ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not
521	Zhu, 2014[37]	Lung Cancer	Resected SCLC: PCI vs no PCI	01.2003 ~ 12.2009	211 screened, 193 eligible	All: 39.4 m (range,4.0–96.8 m); surviving patients: 52.7 m (range,30.4–96.8 m).	56 (34-78); <65 y: 143/193 (74.1%); ≥65 y: 50/193 (25.9%).	KPS: ≥ 80: 126/193 (65.3%); < 80: 67/193 (34.7%)	150/193 (77.7%)	Yes, all	Yes: 94/193; 50–60 Gy	Yes	PCI: 67/193; No PCI: 126/193
Prospective observation studies													
397	Seute, 2004[38]	Cancer	SCLC, Observe neurologic disorders	10.1980 - 09. 2001	432 (11 were diagnosed SCLC with BM at autopsy)	NI	66 (32–89)	NI	347/432 (80.3%)	NI	occasionally applied	yes	45/432 (10.4%)
122	Fu, 2014[39]	Jpn J Clin Oncol	SCLC with PCI	11.2006 -02.2010	129 enrolled, 112 eligible	25 m (5–66 m)	58.5 (IQR 49–69)	NI	NI	NI	Yes	Yes	Yes

Abbreviations:
BM, brain metastasis; CCRT, concurrent chemoradiotherapy; chemo, chemotherapy; CR, complete response; CRT, chemoradiotherapy; ED-SCLC, extensive-stage disease small cell lung cancer; IQR, interquartile range; HT: Hypertension; KPS, Karnofsky performance status scale; LD-SCLC, limited-stage disease small cell lung cancer; MRI, magnetic resonance imaging; NI, no information; ODRT, once-daily radiotherapy; OS, overall survival; PCI, prophylactic cranial irradiation; PET-CT, positron emission tomography and computed tomography; PR, partial response; PS, performance status; SCLC, small cell lung cancer; SCRT, sequential chemoradiotherapy; TDRT, twice-daily radiotherapy; TRT, thoracic radiotherapy.

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ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not

6.   Choi M, Lee Y, Moon SH, et al: Effect of Accurate Staging Using Positron Emission Tomography on the Outcomes of Prophylactic Cranial Irradiation in Patients With Limited Stage Small-Cell Lung Cancer. Clin Lung Cancer 18:77-84, 2017

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11.   Giuliani M, Sun A, Bezjak A, et al: Utilization of prophylactic cranial irradiation in patients with limited stage small cell lung carcinoma. Cancer 116:5694-9, 2010

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13.   Greenspoon JN, Evans WK, Cai W, et al: Selecting patients with extensive-stage small cell lung cancer for prophylactic cranial irradiation by predicting brain metastases. J Thorac Oncol 6:808-12, 2011

14.   Kim TG, Pyo H, Ahn YC, et al: Role of prophylactic cranial irradiation for elderly patients with limited-disease small-cell lung cancer: inverse probability of treatment weighting using propensity score. J Radiat Res 60:630-638, 2019

15.   Manapov F, Klöcking S, Niyazi M, et al: Chemoradiotherapy duration correlates with overall survival in limited disease SCLC patients with poor initial performance status who successfully completed multimodality treatment. Strahlenther Onkol 188:29-34, 2012

16.   Manapov F, Klöcking S, Niyazi M, et al: Primary tumor response to chemoradiotherapy in limited-disease small-cell lung cancer correlates with duration of brain-metastasis free survival. J Neurooncol 109:309-14, 2012

17.   Manapov F, Klöcking S, Niyazi M, et al: Timing of failure in limited disease (stage I-III) small-cell lung cancer patients treated with chemoradiotherapy: a retrospective analysis. Tumori 99:656-60, 2013

18.   Nakamura M, Onozawa M, Motegi A, et al: Impact of prophylactic cranial irradiation on pattern of brain metastases as a first recurrence site for limited-disease small-cell lung cancer. J Radiat Res 59:767-773, 2018

19.   Nicholls L, Keir GJ, Murphy MA, et al: Prophylactic cranial irradiation in small cell lung cancer: A single institution experience. Asia Pac J Clin Oncol 12:415-420, 2016

20.   Pezzi TA, Fang P, Gjyshi O, et al: Rates of Overall Survival and Intracranial Control in the Magnetic Resonance Imaging Era for Patients With Limited-Stage Small Cell Lung Cancer With and Without Prophylactic Cranial Irradiation. JAMA Netw Open 3:e201929, 2020

21.   Ramlov A, Tietze A, Khalil AA, et al: Prophylactic cranial irradiation in patients with small cell lung cancer. A retrospective study of recurrence, survival and morbidity. Lung Cancer 77:561-6, 2012

22.   Roengvoraphoj O, Eze C, Niyazi M, et al: Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. Strahlenther Onkol 193:150-155, 2017

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Appendix Table 6. Characteristics and treatments of non-randomized controlled trials

ID	(Trial)	Journal	Study design	Reviewed period	Sample size	Median follow-up	Age	PS	Gender (Male%)	Surgery	TRT	Chemo	PCI or not

23.   Rubenstein JH, Dosoretz DE, Katin MJ, et al: Low doses of prophylactic cranial irradiation effective in limited stage small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 33:329-37, 1995

24.   Sahmoun AE, Case LD, Chavour S, et al: Hypertension and risk of brain metastasis from small cell lung cancer: a retrospective follow-up study. Anticancer Res 24:3115-20, 2004

25.   Sahmoun AE, Case LD, Santoro TJ, et al: Anatomical distribution of small cell lung cancer: effects of lobe and gender on brain metastasis and survival. Anticancer Res 25:1101-8, 2005

26.   Sas-Korczyńska B, Korzeniowski S, Wójcik E: Comparison of the effectiveness of "late" and "early" prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. Strahlenther Onkol 186:315-9, 2010

27.   Scotti V, Meattini I, Franzese C, et al: Radiotherapy timing in the treatment of limited-stage small cell lung cancer: the impact of thoracic and brain irradiation on survival. Tumori 100:289-95, 2014

28.   Suzuki R, Wei X, Allen PK, et al: Hematologic variables associated with brain failure in patients with small-cell lung cancer. Radiother Oncol 128:505-512, 2018

29.   Tai P, Assouline A, Joseph K, et al: Prophylactic cranial irradiation for patients with limited-stage small-cell lung cancer with response to chemoradiation. Clin Lung Cancer 14:40-4, 2013

30.   van der Linden YM, van Kempen ML, van der Tweel I, et al: Prophylactic cranial irradiation in limited disease small-cell lung cancer in complete remission: a retrospective analysis. Respir Med 95:235-6, 2001

31.   Wu AJ, Gillis A, Foster A, et al: Patterns of failure in limited-stage small cell lung cancer: Implications of TNM stage for prophylactic cranial irradiation. Radiother Oncol 125:130-135, 2017

32.   Xu J, Yang H, Fu X, et al: Prophylactic Cranial Irradiation for Patients with Surgically Resected Small Cell Lung Cancer. J Thorac Oncol 12:347-353, 2017

33.   Zeng H, Li R, Hu C, et al: Association of Twice-Daily Radiotherapy With Subsequent Brain Metastases in Adults With Small Cell Lung Cancer. JAMA Netw Open 2:e190103, 2019

34.   Zeng H, Xie P, Meng X, et al: Risk factors for brain metastases after prophylactic cranial irradiation in small cell lung cancer. Sci Rep 7:42743, 2017

35.   Zheng Y, Wang L, Zhao W, et al: Risk factors for brain metastasis in patients with small cell lung cancer without prophylactic cranial irradiation. Strahlenther Onkol 194:1152-1162, 2018

36.   Zhu H, Bi Y, Han A, et al: Risk factors for brain metastases in completely resected small cell lung cancer: a retrospective study to identify patients most likely to benefit from prophylactic cranial irradiation. Radiat Oncol 9:216, 2014

37.   Zhu H, Guo H, Shi F, et al: Prophylactic cranial irradiation improved the overall survival of patients with surgically resected small cell lung cancer, but not for stage I disease. Lung Cancer 86:334-8, 2014

38.   Seute T, Leffers P, ten Velde GP, et al: Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. Cancer 100:801-6, 2004

39.   Fu L, Liu F, Fu H, et al: Circulating tumor cells correlate with recurrence in stage III small-cell lung cancer after systemic chemoradiotherapy and prophylactic cranial irradiation. Jpn J Clin Oncol 44:948-55, 2014

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
A. Baseline characteristics							
1. Age							
1) <70 *vs* ≥70: Meta-analysis for BM is not applicable because of different statistics							
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	<70 *vs* ≥70: SHR 1.07, 95% CI 0.71–1.62, P= 0.734;	HR 1.34, 95% CI 1.08–1.66, P=0.007; Multivariate (adjusted factors: NI): P>0.05	Age is not an independent risk factor for BM or OS in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	34	Bernhardt, 2017[2]	Cox proportional hazard regression	<70 *vs* ≥70: HR 0.90, 95% CI 0.34-2.33, P= 0.83;	<70 *vs* ≥70: HR 1.47, 95% CI 0.28-2.45, P= 0.13;	Age is not a significant risk factor for BM or OS in ED-SCLC with PCI	No report of patients distribution in each group
2) <65 vs ≥ 65: 3 studies (376, 439, 203) have qualified BM data to perform meta-analysis, no qualified data for OS meta-analysis							
	376	Sahmoun, 2004[3]	Cox proportional hazard regression.	≥ 65 vs <65 (adjust for hypertension, sex, BMI, laterality): HR=1.59, 95%CI: 1.03-2.5; P: NI.	NI	Compared to age ≥ 65, age <65 is an independent risk factor for BM in SCLC.	Investigated only demographic factors, did not consider tumor and treatment related factors
	520	Zhu, 2014[4]	Cox proportional hazard regression.	<65 vs ≥65: p=0.802	<65 vs ≥65 (adjust for PS, stage, LVI, and BM): HR=1.798, 95%CI: 1.027-3.148; P=0.04.	Compared to age <65, age ≥65 is an independent risk factor for OS in resected LD-SCLC, but not for BM.	BM was included in the multivariate model of OS
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤ 64 vs > 64: HR: 0.846, 95%CI: 0.584–1.225; P= 0.375.	NI	Age is not a significant risk factor for BM in SCLC	
	203	Kim, 2019[6]	Cox proportional	<65 vs ≥65: HR=0.418, 95%CI: 0.187–0.938, P=0.034;	P>0.05	Compared to age ≥ 65, age <65 is a risk factor for BM	Inverse probability treatment weight

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression.	adjust for Sex, T, and PCI: P=0.037.		in LD-SCLC, but not for OS.	(IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
3) <60 vs ≥60: Meta-analysis for BM is not applicable because of different statistics and no enough HR data							
	514	Zeng, 2017[7]	Cox proportional hazard regression.	BM: <60 : 24/117 (20.5%); ≥60: 12/58 (20.7%); HR=1.07, 95%CI: 0.53-2.14; p=0.85	NI	Age is not a significant risk factor for BM after PCI in SCLC	
	81	Chen, 2018[8]	BM: Logistic regression. OS: Cox proportional hazard regression.	<60 vs ≥60 (adjust for sex, PS, tumor load, number of metastatic sites, PCI timing): OR=1.077, 95%CI: 0.428–2.708; p >0.05.	<60 vs ≥60: HR=1.477, 95%CI: 0.823–2.653; P=0.191.	Age is not a significant risk factor for BM or OS in ED-SCLC	Logistic regression was used for BM analysis.
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<60 vs ≥ 60: HR: NI, 95%CI: NI; p=0.808	P=0.823	Age is not a significant risk factor for BM or OS in LD-SCLC without PCI	Investigated multiple factors (N=21) with limited sample size (n=153).
	513	Zeng, 2019[10]	Competing-risk regression	<60 vs ≥60: HR=1.20, 95%CI: 0.84-1.71; P=0.32	NI	Age is not a significant risk factor for BM after PCI in SCLC	
4) ≤ 60 vs > 60							
	139	Gong, 2013[11]	Cox proportional hazard regression.	≤ 60 vs > 60: HR: NI, 95%CI: NI; P= 0.841.	≤ 60 vs > 60: HR: NI, 95%CI: NI; P= 0.841.	Age is not a significant risk factor for BM or OS in resected LD-SCLC.	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129).
5) <68 vs ≥ 68							

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	377	Sahmoun, 2005[12]	Cox proportional-hazard regression	≥ 68 vs <68: (adjust for treatment, stage, BMI, sex, laterality, anatomical site, PCI): HR=0.67, 95%CI: 0.41-1.12; P: NI.	≥ 68 vs <68: (adjust for treatment, stage, BMI, sex, laterality, anatomical site): HR=0.62, 95%CI: 0.41-0.95; P: NI.	Compared to age <68, age ≥68 is an independent risk factor for OS in SCLC, but not for BM.	The hazards model of OS did not include PCI.
6) ≤ 58 vs > 58							
	80	Chen, 2016[13]	Cox proportional hazard regression	≤ 58 vs > 58: HR, 1.065; 95%CI: 0.722–1.571; p>0.05;	≤ 58 vs > 58: HR, 1.302; 95%CI: 0.898–1.889; p>0.05;	Age is not a significant risk factor for BM or OS in ED-SCLC	
7) <58.5 vs ≥ 58.5							
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: ≥ 58.5 vs <58.5 (adjust for sex, PS, stage, CTC at baseline, CTC post-first cycle, CTC post-fourth cycle, response): HR=0.983, 95%CI: 0.953–1.015; P=0.290.	NI	Age is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group
8) Continuous: Meta-analysis for BM is not applicable because of different statistics and no HR data							
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	(Continuous) : P>0.05	(Continuous): HR= 1.01; 95%CI: 0.99–1.03; P= 0.23	Age is not a significant risk factor for BM or OS in LD-SCLC	No details on BM results, i.e. HR, 95%CI, and detailed P value.
	28	Bang, 2018[16]	Cox proportional hazard regression	(Continuous) : P>0.05	(Continuous) : P>0.05	Age is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	86	Chu, 2019[17]	Pre-PCI BM: binary logistic regression; OS: Cox proportional hazard regression.	OR=0.976, 95%CI: 0.924–1.032, P=0.400.	HR=1.022, 95%CI: 0.986–1.059, P=0.235	Age is not a significant risk factor for pre-PCI BM or OS in LD-SCLC	Investigated risk factors for Pre-PCI BM in LD-SCLC using logistic regression.

2. Race/ethnicity: Meta-analysis for BM is not applicable because of different statistics

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	White, non-Hispanic *vs* all others: SHR 1.35, 95%CI: 0.90–2.04; P=0.145;	HR 0.91, 95%CI: 0.71–1.16; P=0.438;	Race is not a significant risk factor for BM or OS in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	White vs non-white: HR: 1.098, 95%CI: 0.677–1.779; P= 0.705.	NI	Race is not a significant risk factor for BM in SCLC	

3. Sex: 5 studies (368, 80, 377, 514, 439) have qualified BM data to perform meta-analysis, no qualified data for OS meta-analysis
1) LD-SCLC: 368 has available data for meta-analysis

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	520	Zhu, 2014[4]	Cox proportional hazard regression.	P= 0.906	P= 0.901	Sex is not a significant risk factor for BM or OS in resected LD-SCLC	
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: male vs female (adjust for age, PS, stage, CTC at baseline, CTC post-first cycle, CTC post-fourth cycle, response):	NI	Sex is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group; Data overlapped with No.514.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				HR= 1.502, 95%CI: 0.751–3.004; P=0.250.			
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	Female *vs* male: SHR 1.00, 95%CI: 0.72–1.4; P=0.981	HR 1.09, 95%CI: 0.91–1.30; P=0.345;	Sex is not a significant risk factor for BM or OS in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	368	Roengvoraphoj, 2017[18]	BM: log-rank; OS: Cox proportional-hazard regression	Mean BMFS: Female: 96 (95% CI 77–114), Male: 64 m (95% CI 51–75) (HR= 1.79, 95%CI: 1.05–3.04; p = 0.031).	Median OS: 16.8 m (95% CI 14.8–18.9): Female: 20 (95% CI 15–25), Male: 14 (95% CI: 11–17). female vs male (Adjust for PCI, response, chemo regimen, and age) HR= 1.404, 95%CI: 1.082–1.917; P=0.033.	Compared to female, male is a significant risk factor for BM and OS in LD-SCLC.	
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	male vs female: P>0.05	male vs female:: HR= 1.24; 95%CI: 0.92–1.67; P= 0.16	Sex is not a significant risk factor for BM or OS in LD-SCLC	No details on BM results, i.e. HR, 95%CI, and detailed P value.
	519	Zheng, 2018[9]	Cox proportional hazard regression.	P=0.293	P=0.150	Sex is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	86	Chu, 2019[17]	Pre-PCI BM: binary logistic regression;	male vs female: OR=0.510, 95%CI: 0.107–2.437, P=0.399.	male vs female: HR=1.725, 95%CI: 0.728–4.086, P=0.215	Sex is not a significant risk factor for pre-PCI BM or OS in LD-SCLC	13.6% (15/110) patients were female; Investigated risk factors for Pre-PCI BM

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			OS: Cox proportional hazard regression.				in LD-SCLC using logistic regression.
2) ED-SCLC: 80 has available data for meta-analysis							
	80	Chen, 2016[13]	Cox proportional hazard regression	HR, 1.254; 95%CI: 0.774–2.033; p>0.05;	HR, 0.991; 95%CI: 0.603–1.628; p>0.05;	Sex is not a significant risk factor for BM or OS in ED-SCLC	
	81	Chen, 2018[8]	BM: Logistic regression. OS: Cox proportional hazard regression	Female *vs* male: (adjust for age, PS, tumor load, number of metastatic sites, PCI timing): OR=0.616, 95%CI: 0.200–1.896; P >0.05.	Female *vs* male: HR=0.976, 95%CI: 0.314–1.368; P=0.945.	Sex is not a significant risk factor for BM or OS in ED-SCLC	Logistic regression was used for BM analysis.
	28	Bang, 2018[16]	Cox proportional hazard regression	P>0.05	P>0.05	Sex is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
3) SCLC: 377, 514, 439 have available data for meta-analysis							
	376	Sahmoun, 2004[3]	Cox proportional hazard regression.	male vs female (adjust for hypertension, age, BMI, laterality): HR=1.01, 95%CI: 0.6-1.6; P: NI.	NI	Sex is not a significant risk factor for BM in SCLC without PCI.	Investigated only demographic factors, did not consider tumor and treatment related factors Data overlapped with No.377.
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	male vs female (adjust for treatment, stage, BMI, age, laterality, anatomical site, PCI):	male vs female (adjust for treatment, stage, BMI, age, laterality, anatomical site): HR=0.55, 95%CI: 0.34-0.88; P: NI.	Compared to female, male is an independent risk factor for OS, but not for BM in SCLC.	The hazards model of OS did not include PCI.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				HR=1.11, 95%CI: 0.67-1.83; P: NI.			Observed events were different in table II and table III.
	514	Zeng, 2017[7]	Cox proportional hazard regression.	HR=1.12, 95%CI: 0.53-2.36; P=0.760	NI	Sex is not a significant risk factor for BM after PCI in SCLC	
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	male vs female: HR: 1.109, 95%CI: 0.766–1.604; P= 0.584.	NI	Sex is not a significant risk factor for BM in SCLC	
	203	Kim, 2019[6]	Cox proportional hazard regression.	male vs female: HR: 0.500, 95%CI: 0.270–0.368, P=0.027; adjust for age, T, and PCI: P=0.167.	P>0.05	Male is a risk factor for BM in LD-SCLC, but not for OS.	No HR in the 95%CI. Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
	513	Zeng, 2019[10]	Competing-risk regression	HR=1.01, 95%CI: 0.69-1.48; P= 0.94;	NI	Sex is not a significant risk factor for BM after PCI in SCLC	

4. Smoking: 2 studies (519, 514) have qualified BM data to perform Meta-analysis, no qualified data for OS meta-analysis

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	520	Zhu, 2014[4]	Cox proportional hazard regression.	Yes vs No: P= 0.559	P= 0.594	Smoking is not a significant risk factor for BM or OS in resected LD-SCLC	

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	514	Zeng, 2017[7]	Cox proportional hazard regression.	Yes vs No: HR=0.82, 95%CI: 0.41–1.63; P=0.572	NI	Smoking is not a significant risk factor for BM after PCI in SCLC	
	519	Zheng, 2018[9]	Cox proportional hazard regression.	No *vs* Yes (adjust for NLR, blood glucose, NSE, T, TRT timing, chemo cycles): HR=1.47, 95%CI: 0.78–2.75; P =0.235.	P=0.277	Smoking is not a significant risk factor for BM in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	Current smoking vs no: HR: 1.218, 95%CI: 0.831–1.786; P= 0.312.	NI	Current smoking is not a significant risk factor for BM in SCLC	No data for ever smoking or not.
	28	Bang, 2018[16]	Cox proportional hazard regression	Smoking during chemo vs no: P>0.05	Smoking during chemo vs no: P>0.05	Smoking during chemo is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
	513	Zeng, 2019[10]	Competing-risk regression	Yes vs No: HR: 0.98, 95%CI: 0.69–1.39; P= 0.93.	NI	Smoking is not a significant risk factor for BM after PCI in SCLC	
	86	Chu, 2019[17]	Pre-PCI BM: binary logistic regression; OS: Cox proportional hazard regression.	Yes vs no (adjust for CRT-D, T, and N): OR=4.376, 95%CI: 0.895–21.394, P=0.068	Yes vs no: HR=1.205, 95%CI: 0.614–2.366, P=0.588	Smoking is not a significant risk factor for pre-PCI BM or OS in LD-SCLC	Investigated risk factors for Pre-PCI BM in LD-SCLC using logistic regression.

5. BMI: 2 studies (377, 376) have overlapped BM data for meta-analysis. Therefore, meta-analysis was not performed to avoid bias.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	376	Sahmoun, 2004[3]	Cox proportional hazard regression.	<25 vs ≥ 25 kg/m^2 (adjust for hypertension, age, sex, laterality): HR=1.01, 95%CI: 0.6-1.6; P: NI.	NI	BMI is not a significant risk factor for BM in SCLC without PCI.	Investigated only demographic factors, did not consider tumor and treatment related factors Data overlapped with 377.
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression	<25 vs ≥ 25 kg/m^2 (adjust for treatment, stage, age, sex, laterality, anatomical site, PCI): HR=0.94, 95%CI: 0.57-1.54; P: NI.	<25 vs ≥ 25 kg/m^2 (adjust for treatment, stage, age, sex, laterality, anatomical site): HR=1.85, 95%CI: 1.25-2.86; P: NI.	Compared to normal weight, overweight is an independent risk factor for OS, but not for BM.	The hazards model of OS did not include PCI.
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<25 vs ≥ 25 kg/m^2: P=0.075	P=0.404	BMI is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
6. Weight loss: No qualified data to perform meta-analysis (different statistical analysis).							
	239[C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	$\leq 10\%$ vs $> 10\%$ (adjust by Log (tGTV), ODRT/TDRT, Brain MRI/CT, PS, PCI timing, PCI dose): HR: 1.83; 95% CI: 0.69–4.89; P=0.230	$\leq 10\%$ vs $> 10\%$ (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, PS, PCI timing, PCI dose): HR: 1.98; 95% CI: 0.14–3.43; P=0.015	Weight loss >10% is an independent risk factor for OS in LD-SCLC with PCI, but not for BM.	Data from RCT
	145	Greenspoon, 2011[20]	logistic regression	≥ 5 kg vs <5kg (adjust for chemo response): OR=0.69, 95%CI: 0.49-0.97; P= 0.03	NI	Weight loss more than 5kg was an independent risk factor for BM in ED-SCLC.	Logistic regression was used for BM analysis . BM time definition and follow-up period were not reported. No report of patients distribution in each group.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
7. Chronic disease							
	519	Zheng, 2018[9]	Cox proportional hazard regression.	Yes vs No: P=0.056	P=0.879	Chronic disease is not a significant risk factor for BM or OS in LD-SCLC.	Investigated multiple factors (N=21) with limited sample size (n=153).
8. Hypertension							
	376	Sahmoun, 2004[3]	Cox proportional hazard regression.	No vs Yes (adjust for, age, sex, laterality, BMI): HR=1.11, 95%CI: 0.7-1.8; P: NI.	NI	Hypertension is not a significant risk factor for BM in SCLC without PCI.	Investigated only demographic factors, did not consider tumor and treatment related factors
B. Tumor related factors							
1. Histology (SCLC vs combined SCLC): Meta-analysis for BM is not applicable because of different statistics and no HR data							
	139	Gong, 2013[11]	Cox proportional hazard regression.	(Adjust for surgical resection, stage, induction chemo, adjuvant chemo, and PORT): HR=2.002, 95%CI: NI; P=0.099.	NI	Combined SCLC is not a significant risk factor for BM in resected LD-SCLC.	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129). The impact of histology on OS was not analyzed.
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	P>0.05	HR= 1.15; 95%CI: 0.60–2.20; P= 0.67.	Combined SCLC is not a significant risk factor for BM or OS in LD-SCLC	Only 6% (17/283) patients were with combined SCLC and NSCLC; No details on BM results, i.e. HR, 95%CI, and detailed P value.
2. Tumor size: Meta-analysis for BM is not applicable because of different analysis methods							
	239[C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	Log (tGTV) (adjust by ODRT/TDRT, brain CT/MRI, weight loss, PS, PCI timing, PCI dose): HR: 1.43; 95% CI: 1.11–1.85; P=0.006	Log (tGTV) (adjust by ODRT/TDRT, brain CT/MRI, weight loss, PS, PCI timing, PCI dose): HR: 1.33; 95% CI: 1.16–1.54; P<0.001	tGTV is an independent risk factor for BM and OS in LD-SCLC with PCI	Data from RCT.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	<5 *vs* ≥5 cm: HR 1.77, 95% CI 1.22–2.55, P=0.002; SHR 1.66, 95% CI 1.15–2.40, P=0.007; Multivariate (adjusted factors: NI): P>0.05	HR 1.16, 95% CI 0.96–1.40, P=0.114	Tumor size is not an independent risk factor for BM or OS in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<5 *vs* ≥5 cm: P=0.065	P=0.764	Tumor size is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	203	Kim, 2019[6]	Cox proportional hazard regression.	<50 *vs* ≥50 ml: HR=0.909, 95%CI: 0.413–2.000, P=0.812.	P>0.05	Tumor volume is not a significant risk factor for BM or OS in LD-SCLC.	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.

3. T stage: 3 studies (519, 34, 203) have qualified BM data for meta-analysis, no qualified data for OS meta-analysis

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	34	Bernhardt, 2017[2]	Cox proportional hazard regression	1-2 vs 3-4: HR 0.76, 95% CI 0.39-1.46, P= 0.41;	HR 1.10, 95% CI 0.72-1.69, P= 0.64;	T is not a significant risk factor for BM or OS in ED-SCLC with PCI	No report of patients distribution in each group
	519	Zheng, 2018[9]	Cox proportional hazard regression.	1-2 vs 3-4 (adjust for smoking, blood glucose, NSE, NLR, TRT timing, chemo cycles): HR=2.27, 95%CI:1.11–4.61, P= 0.024;	P=0.614	T stage is an independent risk factor for BM in LD-SCLC, but not for OS	Investigated multiple factors (N=21) with limited sample size (n=153).

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	86	Chu, 2019[17]	Pre-PCI BM: Logistic regression; OS: Cox proportional hazard regression.	1-2 vs 3-4 (adjust for smoking, CRT-D, and N): OR=1.099, 95%CI: 0.411–2.941, P=0.851	T1-2 vs T3-4 (adjust for CRT-D and N): HR=2.610, 95%CI: 1.364–4.993, P=0.004	T is an independent risk factor for OS in LD-SCLC, but not for pre-PCI BM.	Investigated risk factors for Pre-PCI BM in LD-SCLC using logistic regression.
	203	Kim, 2019[6]	Cox proportional hazard regression.	0-2 vs 3-4: HR=1.787, 95%CI: 0.894–3.573, P=0.101; adjust for age, sex, and PCI: P=0.253.	P>0.05	T is not a significant risk factor for BM or OS in LD-SCLC	male vs female: HR: 0.500, 95%CI: 0.270–0.368, P=0.027; adjust for age, T, and PCI: P=0.167

4. N stage: Meta-analysis for BM is not applicable because of different statistics and no HR data

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	519	Zheng, 2018[9]	Cox proportional hazard regression.	N0-1 vs N2-3: p=0.542	P=0.419	N stage is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	203	Kim, 2019[6]	Cox proportional hazard regression.	0-1 vs 2-3: HR=1.452, 95%CI: 0.731–2.884, P=0.286.	Adjust for PS, LDH, stage, TRT dose, TRT timing, PCI: P>0.05	N is not a significant risk factor for BM or OS in LD-SCLC.	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
	86	Chu, 2019[17]	Pre-PCI BM: Logistic regression; OS: Cox proportional	N0-2 vs N3 (adjust for smoking, CRT-D, and T): OR=1.389, 95%CI: 0.456–4.235, P=0.564	N0-2 vs N3 (adjust for CRT-D and T): HR=2.160, 95%CI: 1.056–4.417, P=0.035	N is an independent risk factor for OS in LD-SCLC, but not for pre-PCI BM.	Investigated risk factors for Pre-PCI BM in LD-SCLC using logistic regression.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression.				

5. c-stage

1) I-II vs III: Meta-analysis for BM is not applicable because of different statistics and no HR data

	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	I-II vs III (adjust for PCI, chemo): HR, 2.09; 95% CI, 1.08–4.04; P = 0.028.	I-II vs III (adjust for PCI, chemo): HR, 1.97; 95% CI, 1.38–2.80; P <0.001.	Compared to stage 1-II, stage III is an independent risk factor for BM and OS in LD-SCLC.	
	519	Zheng, 2018[9]	Cox proportional hazard regression.	I-II vs III: p= 0.093	P=0.503	cTNM stage is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	203	Kim, 2019[6]	Cox proportional hazard regression.	I-II vs III : HR=1.305, 95%CI: 0.660–2.580, P=0.444.	Adjust for PS, N, LDH, TRT dose, TRT timing, PCI: P>0.05.	Stage is not a significant risk factor for BM or OS in LD-SCLC.	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
	303	Nakamura, 2018[21]	BM: χ^2-test; OS: Cox proportional hazard regression	BM as a first recurrence site: Stage II: 22% (5/23); Stage III: 29% (40/139); P=0.485	III vs II (adjust for age, ODRT/TDRT, pulmonary effusion, PCI, SER): HR=0.51, 95%CI: 0.27–0.94, P=0.031.	Stage was an independent risk factor for OS in LD-SCLC, but not for BM	χ^2-test was used for BM analysis; No overall BM results

2) ≤IIIA vs ≥IIIB: Meta-analysis for BM is not applicable because of overlapped data

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: IIIA vs IIIB (adjust for age, sex, PS, CTC at baseline, CTC post-first cycle, CTC post-fourth cycle, response): HR=1.601, 95%CI: 0.762–3.366; P=0.214.	NI	Stage is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group; Data overlapped with 514.
	514	Zeng, 2017[7]	Cox proportional hazard regression.	I-IIIA vs IIIB-IV (adjust for sex, age, smoking, response, TDRT/ODRT, CCRT/SCRT, chemo cycles, brain CT/MRI): HR = 2.119, 95%CI 0.932–4.821, p = 0.073.	HR = 2.002, 95% CI 1.180–3.395, p = 0.010	Compared to stage I-IIIA, stage IIIB-IV was a significant risk factor for OS and tended to be an independent risk factor for BM after PCI in SCLC.	
3) I-III vs IV							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	I-III vs IV (adjust for PS, number of extrathoracic metastatic sites, TRT dose, PCI, pretreatment LDH, Pretreatment PLR): HR: 1.062, 95% CI: 0.618–1.826, P=0.826	NI	Stage is not a significant risk factor BM in SCLC	
4) LD vs ED: 2 studies (377, 514) have qualified BM and OS data for meta-analysis							
	397	Seute, 2004[22]	Log-rank test	2-year BM: LD: 49%, ED: 65%; P: NI	Median OS: 8.5 m (range, 0–154 m): ED (n=284): 7.2 m (range, 0–124 m), LD (n=137): 11.9 m (range, 0–154 m) (P<0.0005).	ED is a risk factor for BM and OS in SCLC,	No HR or P value for BM.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	LD vs ED (adjust for treatment, BMI, age, sex, laterality, anatomical site, PCI): HR=4.63, 95%CI:1.80-11.9; P: NI	LD vs ED (adjust for treatment, BMI, age, sex, laterality, anatomical site, PCI): HR=2.24, 95%CI: 1.17-4.3; P: NI.	Compared to LD, ED is an independent risk factor for BM and OS.	The hazards model of OS did not include PCI.
	356	Ramlov, 2012[23]	Log-rank test	BM prevalence: 21/118 (17.8%): LD: 14/74 (18.9%); ED: 7/44 (15.9) (p>0.05).	Median OS: 16.0 m (95%CI 13.0–19.0): LD: 24.0 m (19.6–28.3), ED: 12.0 m (9.6–14.4) (p < 0.001).	ED is a risk factor for OS in SCLC with PCI, but not for BM.	No HR reported.
	514	Zeng, 2017[7]	Cox proportional hazard regression.	LD vs ED (adjust for sex, age, smoking, response, TDRT/ODRT, CCRT/SCRT, chemotherapy cycles, brain CT/MRI): HR=1.76y, 95%CI: 0.63-4.92; P=0.280.	HR=1.141, 95% CI 0.543-2.395 , P= 0.728	LD/ED is not a significant risk factor for BM or OS in SCLC with PCI.	
	513	Zeng, 2019[10]	BM: Competing-risk regression; OS: Cox proportional-hazards regression models	LD vs ED (adjust for era, PS, CCRT/SCRT, ODRT/TDRT, timing of PCI): HR=1.69, 95%CI:1.03-2.77, P=0.04	LD vs ED (adjust for era, PS, CCRT/SCRT, ODRT/TDRT, timing of PCI): HR=1.27, 95%CI: 0.90-1.79, P=0.17.	ED is an independent risk factor for BM after PCI in SCLC, but not for OS.	

6. p-stage: I,II,III: Meta-analysis for BM is not applicable because of different statistical analysis.

	139	Gong, 2013[11]	Cox proportional hazard regression.	(Adjust for surgical resection, histology, induction chemo, adjuvant chemo, and	(Adjust for surgical resection, BM, induction chemo, adjuvant chemo, and PORT): HR=2.391, 95%CI: NI; P=0.001.	Stage is an independent risk factor for BM and OS in resected LD-SCLC.	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129);

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				PORT): HR=2.458, 95%CI: NI; P=0.002.			The factors in multivariate model of BM and OS were different.
	520	Zhu, 2014[4]	Cox proportional hazard regression.	(Adjust for LVI and PORT): HR = 2.013, 95%CI: 1.135 ~ 3.569; p = 0.017.	(adjust for age, PS, LVI, and BM): HR=2.093, 95%CI: 1.399-3.132; P=0.001.	Stage is an independent risk factor for BM and OS in resected LD-SCLC.	BM was included in the multivariate model of OS.
7. LVI	520	Zhu, 2014[4]	Cox proportional hazard regression.	Yes vs no (adjust for p-stage and PORT): HR = 1.924, 95%CI: 1.002 ~ 3.291; p = 0.039.	(adjust for age, PS, stage, and BM): HR=0.935, 95%CI: 0.507-1.723; P=0.829.	LVI is an independent risk factor for BM in resected LD-SCLC, but not for OS.	BM was included in the multivariate model of OS.
8. M status in ED-SCLC: 3 studies (80, 34, 28) have qualified BM and OS data for meta-analysis							
	80	Chen, 2016[13]	Cox proportional hazard regression	Distant metastases vs. locally advanced: HR, 1.234; 95%CI: 0.826–1.843; p>0.05;	HR, 1.410; 95%CI: 0.959–2.084; p>0.05;	Distant metastases is not a significant risk factor for BM or OS in ED-SCLC	
	34	Bernhardt, 2017[2]	Cox proportional hazard regression	M1b or not: HR 0.69, 95% CI 0.27-1.78, P= 0.44;	M1b or not: HR 1.25, 95% CI 0.63-2.48, P= 0.51;	M1b is not a significant risk factor for BM or OS in ED-SCLC with PCI	No report of patients distribution in each group
	28	Bang, 2018[16]	Cox proportional hazard regression	Extrathoracic metastases (No vs Yes) (adjust for PCI): HR 2.59; 95% CI: 1.12-7.56; P=0.02;	Extrathoracic metastases (No vs Yes) (adjust for PS, PCI): HR 1.75; 95% CI:1.04-3.17; P = 0.03	Extrathoracic metastases is an independent risk factor for BM and OS in ED-SCLC.	Backward stepwise multivariate analysis
	81	Chen, 2018[8]	BM: Logistic regression. OS: Cox proportional	Distant metastases vs. locally advanced (adjust for age, sex, PS, number of metastatic sites, PCI timing): OR=2.944,	Distant metastases vs. locally advanced: HR=2.018, 95%CI: 1.159–3.517; P =0.013.	Distant metastases is a significant risk factor for OS in ED-SCLC, but not for BM.	Logistic regression was used for BM analysis.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	95%CI: 1.049–8.261; P >0.05.			

9. Number of metastatic sites: Meta-analysis for BM is not applicable because of different statistical analysis

| | 80 | Chen, 2016[13] | Cox proportional hazard regression | ≥2 *vs* <2: HR, 1.124; 95% CI, 0.688–1.835; p> 0.05; | ≥2 *vs* <2: (adjust for PCI, liver metastasis, PS): HR, 1.146; 95%CI: 0.722–1.820; p>0.05. | Number of metastatic sites is not a significant risk factor for BM or OS in ED-SCLC. | |
| | 81 | Chen, 2018[8] | BM: Logistic regression. OS: Cox proportional hazard regression | ≥2 *vs* <2 (adjust for age, sex, PS, tumor load, PCI timing): OR=1.445, 95%CI: 0.284–7.354; P >0.05. | ≥2 *vs* <2: HR=1.758, 95%CI: 0.697–4.435; P=0.232. | Number of metastatic sites is not a significant risk factor for BM or OS in ED-SCLC. | Logistic regression was used for BM analysis. |

10. Number of extrathoracic metastatic sites

| | 439 | Suzuki, 2018[5] | Cox proportional hazard regression. | ≤ 4 vs > 4 (adjust for PS, stage, TRT dose, PCI, pretreatment LDH, Pretreatment PLR): HR: 0.978, 95% CI: 0.620–1.543, P=0.924. | NI | Number of extrathoracic metastatic sites is not a significant risk factor BM in SCLC. | |

11. Metastatic organs

1) Bone metastasis: Meta-analysis for BM is not applicable because of different statistical analysis.

| | 145 | Greenspoon, 2011[20] | logistic regression | Yes vs No: OR=0.68, 95%CI: 0.24-1.94; P= 0.47. | NI | Bone metastasis is not a significant risk factor for BM in ED-SCLC. | Logistic regression was used for BM analysis . BM time definition and follow-up period were not reported. No report of patients distribution in each group. |

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	80	Chen, 2016[13]	Cox proportional hazard regression	Yes vs no: HR, 1.234; 95%CI: 0.826–1.843; p>0.05;	HR, 1.083; 95%CI: 0.692–1.694; p>0.05;	Bone metastases is not a significant risk factor for BM or OS in ED-SCLC.	

2) Liver metastasis: Meta-analysis for BM is not applicable because of different statistical analysis.

| | 145 | Greenspoon, 2011[20] | logistic regression | Yes vs No: OR=0.80, 95%CI: 0.27-2.34; P= 0.68. | NI | Liver metastasis is not a significant risk factor for BM in ED-SCLC. | Logistic regression was used for BM analysis . BM time definition and follow-up period were not reported. No report of patients distribution in each group. |
| | 80 | Chen, 2016[13] | Cox proportional hazard regression | Yes *vs* no (adjust for PCI, Number of metastatic sites): HR, 2.511; 95%CI: 1.408–4.477; p<0.05; | Yes *vs* no (adjust for PCI, Number of metastatic sites, PS): HR, 2.193; 95%CI: 1.284–3.747; p<0.05; | Liver metastasis is an independent risk factor for BM and OS in ED-SCLC | |

3) Adrenal metastasis: Meta-analysis for BM is not applicable because of different statistical analysis.

| | 145 | Greenspoon, 2011[20] | logistic regression | Yes vs No: OR=0.84, 95%CI 0.22-3.24; P= 0.80. | NI | Adrenal metastasis is not a significant risk factor for BM in ED-SCLC. | Logistic regression was used for BM analysis . BM time definition and follow-up period were not reported. No report of patients distribution in each group. |
| | 80 | Chen, 2016[13] | Cox proportional hazard regression | Yes vs no: HR, 1.778; 95%CI: 0.946–3.344; p>0.05; | HR, 1.396; 95%CI: 0.725–2.687; p>0.05; | Adrenal metastases is not a significant risk factor for BM or OS in ED-SCLC. | |

4) Lung metastasis

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	80	Chen, 2016[13]	Cox proportional hazard regression	Yes vs no: HR, 0.886; 95%CI: 0.526–1.493; p>0.05;	HR, 0.828; 95%CI: 0.499–1.374; p>0.05;	Lung metastases is not a significant risk factor for BM or OS in ED-SCLC.	
12. Laterality: Meta-analysis for BM is not applicable because of different analysis and overlapped data.							
	376	Sahmoun, 2004[3]	Cox proportional hazard regression.	Left vs right (adjust for hypertension, age, sex, BMI): HR=1.11, 95%CI: 0.7-1.8; P: NI.	NI	Laterality is not a significant risk factor for BM in SCLC without PCI.	Investigated only demographic factors, did not consider tumor and treatment related factors Data overlapped with 377.
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression	Left vs right (adjust for treatment, stage, BMI, age, sex, anatomical site, PCI): HR=1.25, 95%CI: 0.84-1.89; P: NI.	Left vs right (adjust for treatment, stage, BMI, age, sex, anatomical site): HR=1.52, 95%CI: 1.01-2.3; P: NI.	Compared to left , right SCLC is an independent risk factor for OS, but not for BM.	The hazards model of OS did not include PCI.
	513	Zeng, 2019[10]	Competing-risk regression	left vs right: HR=0.94, 95%CI: 0.67-1.32; P=0.71.	NI	Laterality is not a significant risk factor for BM after PCI in SCLC	
13. Anatomical site							
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	lower vs upper lobe (adjust for treatment, stage, BMI, age, sex, laterality, PCI): HR=0.70, 95%CI: 0.42-1.16; P: NI.	lower vs upper lobe (adjust for treatment, stage, BMI, age, sex, laterality): HR=0.90, 95%CI: 0.54-1.53; P: NI.	Anatomical site is not a significant risk factor for BM or OS in LD-SCLC	The hazards model of OS did not include PCI.
14. KPS[D]: Meta-analysis for BM is not applicable because of different analysis methods.							
	520	Zhu, 2014[4]	Cox proportional hazard regression.	≥80 *vs* <80: P= 0.272	(adjust for age, stage, LVI, and BM): HR=1.149, 95%CI: 0.631-2.092; P=0.649.	KPS is not a significant risk factor for BM or OS in resected LD-SCLC	BM was included in the multivariate model of OS

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	≥80 *vs* <80: SHR 0.89, P=0.668;	HR 1.41, 95% CI 1.09–1.83, P=0.010; Multivariate (adjusted factors: NI): P>0.05	KPS is not an independent risk factor for BM or OS in LD-SCLC.	Two definitions for time to development of BM, unclear which one is used
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	≥80 *vs* <80: P>0.05	≥80 *vs* <80: HR= 0.75; 95%CI: 0.50–1.11; P= 0.15	KPS is not a significant risk factor for BM or OS in LD-SCLC	No details on BM results, i.e. HR, 95%CI, and detailed P value.
	34	Bernhardt, 2017[2]	Cox proportional hazard regression	≤ 70 vs > 70: HR 0.71, 95% CI 0.35-1.41, P= 0.33;	HR 0.85, 95% CI 0.55-1.33, P= 0.49;	KPS is not a significant risk factor for BM or OS in ED-SCLC with PCI	No report of patients distribution in each group
	371	Rubenstein, 1995[24]	Multivariate Cox regression	Pre-RT KPS (≤ 80 vs > 80) (adjusted factors: PCI, response, age, treatment intent): HR: NI, P=0.04.	pre-RT KPS (≤ 80 vs > 80) (adjusted factors: PCI, response, age, CCRT/SCRT): HR: NI, P = 0.0001	Pre-RT KPS was a significant risk factor for BM and OS in LD-SCLC	Did not report HR;

15. PS[D]

1) 0-1 vs ≥ 2: 2 studies (80, 439) have qualified BM data for meta-analysis, no qualified data for OS meta-analysis.

| | 80 | Chen, 2016[13] | Cox proportional hazard regression | 0-1 vs 2: HR, 2.383; 95% CI, 0.866–6.560; p> 0.05; | 0-1 vs 2: (adjust for PCI, liver metastasis, number of metastatic sites) : HR, 3.182; 95%CI: 1.534–6.599; p<0.05; | PS is an independent risk factor for OS in ED-SCLC, but not for BM. | |
| | 81 | Chen, 2018[8] | BM: Logistic regression. OS: Cox proportional | 0-1 vs 2: (adjust for age, sex, tumor load, number of metastatic sites, PCI timing): OR=6.001, | 0-1 vs 2: (adjust for age, sex, tumor load, number of metastatic sites, PCI timing): | PS is not a significant risk factor for BM or OS in ED-SCLC | Logistic regression was used for BM analysis. |

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	95%CI: 0.509–70.727; P >0.05.	HR=2.545, 95%CI: 0.788–8.217; P=0.118.		
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	0-1 vs ≥ 2 (adjust for stage, number of extrathoracic metastatic sites, TRT dose, PCI, pretreatment LDH, Pretreatment PLR): HR: 1.369, 95% CI: 0.834–2.246, P=0.214.	NI	PS is not a significant risk factor BM in SCLC	
	28	Bang, 2018[16]	Cox proportional hazard regression	0-1 vs 2-4: P>0.05	0-1 vs 2-4 (adjust for PS, PCI, Extrathoracic metastases): HR 1.75; 95% CI:1.04-3.17; P = 0.03	PS is an independent risk factor for OS in ED-SCLC, but not for BM.	Backward stepwise multivariate analysis

2) 0 vs 1-2: Meta-analysis for BM is not applicable because of different analysis methods and no HR data.

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	239[C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	0 vs 1-2 (adjust by Log (tGTV), ODRT/TDRT, Brain MRI/CT, Weight loss, PCI timing, PCI dose): HR: 0.54; 95% CI: 0.32–0.90; P=0.018	0 vs 1-2 (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, Weight loss, PCI timing, PCI dose): HR: 1.1; 95% CI: 0.86–1.46; P=0.348	Better PS is an independent risk factor for BM after PCI in LD-SCLC, but not for OS.	Data from RCT,
	519	Zheng, 2018[9]	Cox proportional hazard regression.	0 vs 1-2: P= 0.455	P=0.805	PS is not a significant risk factor for BM in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	203	Kim, 2019[6]	Cox proportional hazard regression.	0 vs 1-2: HR=1.788, 95%CI: 0.554–5.773, P=0.331.	Adjust for LDH, N, stage, TRT dose, TRT timing, PCI: P>0.05.	PS is not a significant risk factor for BM or OS in LD-SCLC.	Inverse probability treatment weight (IPTW) was used to minimize bias;

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
							No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
3) Others: Meta-analysis for BM is not applicable because of different analysis methods.							
	513	Zeng, 2019[10]	BM: Competing risk regression; OS: Cox proportional hazard regression	0,1,2 (adjust for era, stage, ODRT/TDRT, SCRT/CCRT, PCI timing): HR=1.25, 95%CI: 0.81–1.91, P=0.32.	0,1,2 (adjust for era, stage, ODRT/TDRT, SCRT/CCRT, PCI timing): HR=1.38, 95%CI: 1.03–1.83, P=0.03.	PS is an independent risk factor for OS in SCLC with PCI, but not for BM.	
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: 0-3 vs >3 (adjust for age, sex, stage, CTC at baseline, CTC post-first cycle, CTC post-fourth cycle, response): HR= 0.397, 95%CI: 0.046–3.432; P=0.401.	NI	PS is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group.
	145	Greenspoon, 2011[20]	logistic regression	0-2 vs 3-4: OR=0.39, 95%CI: 0.08-1.86; P= 0.24.	NI	PS is not a significant risk factor for BM in ED-SCLC.	Logistic regression was used for BM analysis. BM time definition and follow-up period were not reported. No report of patients distribution in each group.
16. Response[E]: Meta-analysis for BM is not applicable because of different analysis methods and no HR data.							
	371	Rubenstein, 1995[24]	Multivariate Cox regression	Response to induction chemo (CR/Near CR vs others) (adjusted factors:	Response to induction chemo (CR/Near CR vs others) (adjusted factors: PCI, Pre-RT	Response was a significant risk factor for OS in LD-SCLC, but not for BM.	NoHR given;

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				PCI, KPS, age, treatment intent) HR: NI, P>0.05.	KPS, age, CCRT/SCRT): HR: NI, P = 0.0173		Did not report compared response in detail.
	519	Zheng, 2018[9]	Cox proportional hazard regression.	PR vs CR: P= 0.308	P=0.102	Response is not a significant risk factor for BM in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	28	Bang, 2018[16]	Cox proportional hazard regression	PR vs CR: P>0.05	PR vs CR: P>0.05	Response is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
	514	Zeng, 2017[7]	Cox proportional hazard regression.	PR/SD vs CR: P=0.842	NI	Response is not a significant risk factor for BM after PCI in SCLC	
	122	Fu, 2014[14]	Cox proportional-hazard regression	(adjust for age, sex, PS, CTC at baseline, CTC post-first cycle, CTC post-fourth cycle, stage): HR= 1.727, 95%CI: 0.718–4.152; P=0.222.	NI	Response is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group; Data overlapped with No. 514.
	145	Greenspoon, 2011[20]	Logistic regression	Chemo response (adjust for weight loss): OR=5.49, 95%CI: 1.08-27.91; P= 0.03	NI	Chemo response was an independent risk factor for BM in ED-SCLC.	Logistic regression was used for BM analysis. BM time definition and follow-up period were not reported. No report of patients distribution in each group.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	264	Manapov, 2012[25]	Log-rank test	BMFS: CR: 567 days, PR: 298 days, NR (SD/PD): 252 days; p <0.0001.	NI	Response significantly affects BMFS in LD-SCLC with poor initial PS	No HR given.

17. Pretreatment LDH (lactate dehydrogenase): Meta-analysis for BM is not applicable because of different cut-off values

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤543 IU/L vs > 543IU/L (adjust for PS, stage, number of extrathoracic metastatic sites, TRT dose, PCI, pretreatment platelet count): HR: 1.373, 95% CI: 0.922–2.046, P =0.119.	NI	Pretreatment LDH is not a significant risk factor for BM in SCLC	
	203	Kim, 2019[6]	Cox proportional hazard regression.	< 400 IU/L vs ≥400 IU/L: HR=1.240, 95%CI: 0.703–2.187, P=0.458.	Adjust for PS, N, stage, TRT dose, TRT timing, PCI: P>0.05	LDH is not a significant risk factor for BM or OS in LD-SCLC.	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.

18. Neutrophil count

1) Pretreatment

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤3.9×10³/μL vs >3.9×10³/μL: HR: 0.807, 95%CI: 0.540–1.207; P= 0.296.	NI	Pretreatment neutrophil count is not a significant risk factor for BM in SCLC	

2) Pre-PCI

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤3.6×10³/μL vs >3.6×10³/μL: HR: 0.764, 95%CI: 0.382–1.525; P= 0.445.	NI	Pre-PCI neutrophil count is not a significant risk factor for BM in SCLC	Cut-off value changed

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
19. TLC, total lymphocyte count							
1) Pretreatment							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq 1.7 \times 10^3/\mu L$ vs $>1.7 \times 10^3/\mu L$: HR: 1.024, 95%CI: 0.708–1.481; P= 0.898.	NI	Pretreatment TLC is not a significant risk factor for BM in SCLC	
2) Pre-PCI							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq 1.1 \times 10^3/\mu L$ vs $>1.1 \times 10^3/\mu L$ (adjust for stage): HR: 2.512, 95%CI: 1.196–5.277; P= 0.015.	NI	Higher Pre-PCI TLC is an independent risk factor for BM in SCLC	Cut-off value changed
20. NLR, neutrophil-to-lymphocyte ratio							
1) Pretreatment: Meta-analysis for BM is not applicable because of different cut-off values							
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<2.55 vs ≥ 2.55 (adjust for smoking, blood glucose, NSE, T, TRT timing, chemo cycles): HR= 2.07, 95%CI: 1.08–3.97, P= 0.029.	<2.55 vs ≥ 2.55 (adjust for TRT timing) HR= 2.11, 95%CI:1.28-3.59; P= 0.005	Higher pretreatment NLR is an independent risk factor for BM and OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤ 1.6 vs >1.6: HR: 0.758, 95%CI: 0.433–1.326; P= 0.332.	NI	Pretreatment NLR is not a significant risk factor for BM in SCLC	
2) Pre-PCI							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	≤ 2.3 vs >2.3: HR: 0.498, 95%CI: 0.240–1.033; P= 0.061.	NI	Pre-PCI NLR is not a significant risk factor for BM in SCLC	Cut-off value changed
21. Platelet count							
1) Pretreatment							

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq270\times10^9$/L vs $>270\times10^9$/L(adjust for PS, stage, number of extrathoracic metastatic sites, TRT dose, PCI, pretreatment LDH): HR: 1.516, 95% CI: 1.024–2.245, P =0.038	NI	High pretreatment platelet count is an independent risk factor for BM in SCLC	
2) Pre-PCI							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq247\times10^9$/L vs $>247\times10^9$/L(adjust for stage): HR: 1.847, 95% CI: 0.927–3.681, P =0.081	NI	Pre-PCI platelet count is not a significant risk factor for BM in SCLC	
22. PLR, platelet-to-lymphocyte ratio							
1) Pretreatment: Meta-analysis for BM is not applicable because of different cut-off values							
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<125.7 vs $\geq$ 125.7: P= 0.477	P=0.401	Pretreatment PLR is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq$119.4 vs >119.4 (adjust for PS, stage, number of extrathoracic metastatic sites, TRT dose, PCI, pretreatment LDH): HR: 1.557, 95% CI: 0.939–2.582, P =0.086	NI	Pretreatment PLR is not a significant risk factor for BM in SCLC	
2) Pre-PCI							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	$\leq$69.3 vs >69.3 (adjust for stage): HR: 0.409, 95% CI: 0.173–0.969, P = 0.042	NI	Lower Pre-PCI PLR is an independent risk factor for BM in SCLC	Cut-off value changed
23. Pretreatment NSE							

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<17 vs ≥ 17 ng/ml (adjust for smoking, blood glucose, NLR, T, TRT timing, chemo cycles): HR= 3.84, 95%CI: 0.90–16.40, P= 0.069.	P=0.280	NSE is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
24. Pretreatment CEA							
	519	Zheng, 2018[9]	Cox proportional hazard regression.	<3.4 vs ≥3.4 ng/ml: P= 0.111	P=0.272	CEA is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
25. Pretreatment blood glucose							
	519	Zheng, 2018[9]	Cox proportional hazard regression.	≤6.2 vs >6.2 mmol/L (adjust for smoking, NSE, NLR, T, TRT timing, chemo cycles): HR=1.09, 95%CI: 0.50–2.41, P= 0.826.	P=0.182	Blood glucose is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
26. CTC, circulating tumor cells							
1) CTC at baseline							
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: (adjust for age, sex, PS, CTC post-first cycle, CTC post-fourth cycle, stage, response): HR=5.243; 95% CI, 2.133–10.574; P < 0.001. Median BM time: CTCs ≤ 218 vs CTCs > 218: 11.6 (22.3–67.7) vs 7.3 (6.8–35.2) m (p=0.001).	NI	Higher CTC at baseline is an independent risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group
2) CTC post-first cycle							

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: (adjust for age, sex, PS, CTC at baseline, CTC post-fourth cycle, stage, response): HR=1.066; 95% CI, 0.585–4.318; P =0.546.	NI	CTC post-first cycle is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group
3) CTC post-fourth cycle							
	122	Fu, 2014[14]	Cox proportional-hazard regression	BM as a first recurrence site: (adjust for age, sex, PS, CTC post-first cycle, CTC post-fourth cycle, stage, response): HR=1.002; 95% CI, 0.776–2.371; P =0.857.	NI	CTC post-fourth cycle is not a significant risk factor for BM after PCI in stage III SCLC	Analyzed BM as a first site of recurrence; No report of patients distribution in each group
27. SUVmax							
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	(continuous): P>0.05	(continuous): HR= 1.02; 95%CI: 0.99–1.05; P= 0.21.	SUVmax is not a significant risk factor for BM or OS in LD-SCLC	No detailed BM results reported, i.e. HR, 95%CI, and detailed P value.
Treatment related factors							
1. PCI vs no PCI: 3 RCTs have qualified overall BM data for meta-analysis based on Cox regression (148, 487, 19); 2 have overall BM data based on competing risk regression (415, 445); 2 have OS data (415, 445)							
1) LD-SCLC: 2 RCTs have qualified overall BM data for subgroup meta-analysis (487, 148)							
	62[c]	Cao, 2005[26]	χ^2-test	BM prevalence: PCI: 3.8% (1/26); No PCI: 32.0% (8/25) (χ^2=5.15, P =0.02)	χ^2 =2.25, P =0.13	PCI significantly decreased BM in LD-SCLC, but did not significantly improve OS	RCT; χ^2-test was used for BM analysis
	487[c]	Work, 1996[27]	Log-rank test	BM prevalence: PCI: 9.6%(15/157);	2-year OS: PCI: 24.9%; No PCI: 16.9%; HR: NI; P=0.31	PCI significantly decreased BM in LD-	RCT;

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				No PCI: 31% (13/42); (HR = 0.30, 95% CI 0.12-0.75, P =0.01);		SCLC, but did not significantly improve OS	Not strictly randomized;
	148[C]	Gregor, 1997[28] (UKCCCR/ EORTC)	Log-rank test	2-year BM: PCI: 30%, No PCI: 54%; HR = 0.44, 95% CI 0.29-0.67, P = 0.00004.	HR= 0.86, 95% CI 0.66-1.12, P= 0.25).	PCI significantly decreased BM in LD-SCLC, but did not significantly improve OS	RCT;
	461	van der Linden, 2001[29]	Cox proportional hazard regression.	Overall BM: PCI: 17%; No PCI: 57%; HR: 7.3; 95% CI: 3.3 - 16.4, P<0.001	2-year OS: PCI: 42%, No PCI: 27%; HR: 1.8; 95%CI: 1.1 - 2.9, P = 0.016;	PCI significantly decreased BM and improved OS in LD-SCLC.	
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	No vs Yes (adjust for treatment, stage, BMI, age, sex, laterality, anatomical site): HR=0.56, 95%CI: 0.20-1.57; P: NI.	NI	PCI did not significantly decrease BM in LD-SCLC	Only 5.7% (12/209) patients received PCI.
	384	Sas-Korczyńska, 2010[30]	BM prevalence: χ^2-test; BMFS: Log-rank test.	PCI: 12/86 (14%), No PCI: 20/43 (46.5%); P=0.00005. 4-year BMFS: All: 67.8%, PCI: 81.8%, No PCI: 32.2% (P<0.0001).	NI	PCI significantly decreased BM in LD-SCLC	
	134	Giuliani, 2010[31]	Cox proportional hazard regression.	HR:3.4; 95% CI: 1.9-6.1;P<0.001; multivariate (adjusted for age): HR:3.8; 95% CI: 2.1-6.8; P<0.001;	(adjusted for age) PCI: HR 2.0 (95% CI, 1.4 to 2.8; P=0.0001).	PCI significantly decreased BM and improved OS in LD-SCLC.	

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	264	Manapov, 2012[25]	Log-rank test	BM prevalence: PCI: 13.9% (5/36), No PCI: 28.1%(25/89); BMFS in patients with CR: PCI: 640 days; No PCI: 482 days; (P=0.047).	NI	PCI prolongs BMFS in LD-SCLC with poor initial PS who had CR to CRT	No HR reported.
	441	Tai, 2013[32]	BM prevalence: χ^2-test or Fisher exact 2-tailed test; BM time, OS: Kaplan-Meier method, Wilcoxon test.	1. Overall BM: 1) CR: PCI: 24/128 (18.8%); no PCI: 20/49 (40.8%) (Fisher P=0.002); 2) IR: PCI: 11/40 (27.5%); no PCI: 15/48 (31.3%) (Fisher P=0.70); 2. BM as first recurrence: 1) CR: PCI: 6/128 (4.7%); no PCI: 5/49 (10.2%) (Fisher P=0.18); 2) IR: PCI: 2/40 (20%); no PCI: 8/48 (16.7%) (Fisher P=0.10); 3. BM as first recurrence time: 20.7 vs. 10.6 m (P<0.0001)	PCI vs No PCI: 1. All: P=0.0011; 2. pts with IR: P=0.32; 3. pts with CR: P=0.15;	PCI decreases BM, improves OS	
	393	Scotti, 2014[33]	Log-rank test.	PCI: 8/38 (21.1%); No PCI: 19/54 (35.2%); P: NI	P=0.21	BM prevalence in the PCI group was lower, but the p was not reported.	No P values for BM.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
						PCI did not improve OS in LD-SCLC.	
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	No PCI *vs* PCI: HR 0.54, 95% CI 0.39–0.76, P<0.001; SHR 0.56, 95% CI 0.40–0.78, P=0.001; Multivariate (adjusted factors: NI): SHR 0.57, 95% CI 0.41–0.79, p=0.001;	Multivariate (adjusted factors: NI): HR 0.76, 95% CI 0.63–0.91, p=0.003	PCI significantly improved OS and decreased BM in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	82	Choi, 2017[34]	Cox proportional hazard regression.	cumulative first isolated BM: whole: PCI: 25.4%; No PCI: 38.9% (P = 0.014); PET: PCI: 34.3%; No PCI: 41.1% (P = 0.243); No PET: PCI: 13.3%; No PCI: 37.0% (P = 0.020).	whole: PCI: 33.1 m; No PCI: 30.7 m (P = 0.938); PET: PCI: 33.0 m; No PCI: 42.2 m (P = 0.474); No PET: PCI: 34.9 m; No PCI: 22.5 m (P = 0.569).	1. PCI decreased first isolated BM, did not improve OS in the whole group and no PET group; PCI did not decrease first isolated BM or improve OS the PET group.	Analyzed BM as a first site of recurrence; Characteristics were not balanced between groups; Less patients underwent MRI in the no-PET group (68.4% vs 82.8%, P=0.001).
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	No vs Yes: Univariate : HR, 0.81; 95% CI, 0.48–1.39, P = 0.45: Multivariate (adjust for stage, chemo): P>0.001.	No vs Yes (adjust for stage, chemo): HR= 0.67; 95%CI: 0.49–0.92; P= 0.014	PCI did not significantly decrease BM, but significantly improved OS in LD-SCLC	
	303	Nakamura, 2018[21]	BM: χ^2-test; OS: Cox proportional hazard regression	BM as a first recurrence site: PCI: 18% (17/93); No PCI: 41% (28/69); P=0.002; BM as a first recurrence site time:	(adjust for age, stage, pulmonary effusion, TDRT/ODRT, SER): HR=0.54, 95%CI: 0.36–0.82, P=0.004.	PCI significantly decreased first isolated BM and improved OS in LD-SCLC	Unbalanced characteristics between PCI and non-PCI group (in no PCI group, more patients had longer SER, more patients had ODRT);

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				No PCI: 7.5 m, PCI: 10 m (P = 0.012).			χ^2-test was used for BM analysis; No overall BM results
	203	Kim, 2019[6]	Cox proportional hazard regression.	HR 0.588, 95% CI 0.338–1.024, P = 0.060. adjust for age, T, and PCI: P=0.068.	whole cohort: PCI: HR 0.543, 95% CI 0.383–0.771, P = 0.001.	PCI improved OS and BMFS in LD-SCLC	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
2) LD-SCLC with MRI: Meta-analysis for BM is not applicable because of different methods.							
	112	Eze, 2017[35]	BM: Log-rank test; OS: Cox proportional hazard regression	PCI: 16/71 (23%); No PCI: 42/113 (37%); P<0.0001	Yes vs No (adjust for sex, chemo cycles, chemo regimen, response) : HR=1.899; 95% CI, 1.370-2.632; P < 0.0001;	PCI improves OS and decreases BM in LD-SCLC staged with brain MRI	
	342	Pezzi, 2020[36]	BM: Competing risk regression; OS: Cox proportional hazard regression	3-year BM: PCI 20.40% vs no PCI 11.20%; P = 0.10; No PCI vs PCI (adjust for tumor size, radiation dose): 0.513 (95%CI, 0.239-1.098; P = .09)	No PCI vs PCI (adjust for age, sex, PS, tumor size, radiation dose): HR=0.787; 95%CI, 0.558-1.110; P = 0.17;	PCI does not significantly improve OS or decrease BM in LD-SCLC staged with brain MRI	
3) Resected SCLC: Meta-analysis for BM is not applicable because of no HR data.							
	521	Zhu, 2014[37]	BM: Log-rank test; OS: Cox proportional	2-year BMFS: PCI: 96.8%, non-PCI: 79.4%;	2-year OS: All: 73.4%, PCI: 92.5%, non-PCI: 63.2%;	PCI improves OS and BMFS in resected LD-SCLC, but not in p-stage I.	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	5-year BMFS: PCI: 76.6%, non-PCI: 75.5% (p = 0.014).	5-year OS: All: 52.3%, PCI: 54.9%, non-PCI: 47.8% (p = 0.001). Yes vs No (adjust for sex, age, KPS, stage, LVI, PORT, chemo cycles): HR= 2.339; 95%CI: 1.414–3.869; P= 0.001. p-stage I: 2-year OS: All: 91.7%, PCI: 100%, non-PCI: 87.1%, 5-year OS: All: 69.3%, PCI: 58.3%, non-PCI: 74.4% (p = 0.601)		
	493	Xu, 2017[38]	BM: Log-rank test; OS: Cox proportional hazard regression	All: PCI: 15/115 (13.0%), No PCI: 53/234 (22.6%), P=0.009; p-stage I: PCI: 2/19 (10.5%), No PCI: 8/59(13.6%), P=0.389; p-stage II: PCI: 5/39 (12.8%), No PCI:15/67 (22.4%), P=0.094; p-stage III: PCI: 8/57 (14.0%), No PCI: 30/108 (27.8%), P=0.018;	PCI: 36.40 m, 95% CI:23.36–49.44; non–PCI: 25.62 m, 95% CI: 18.86–32.39). No vs Yes (adjust for age, sex, smoking, histology, stage, tumor size, PORT, Surgery type, chemo cycles, and PET/CT scan) HR = 0.69, 95% CI: 0.50–0.95, p= 0.023. p-stage III:HR=0.54, 95% CI: 0.34–0.86, p =0.009). p-stage II: HR=0.54, 95% CI: 0.30–0.99, p =0.047). p-stage I: HR= 1.61, 95% CI: 0.68–3.83, p=0.282).	PCI improves OS and decreases BM in resected LD-SCLC, but not in p-stage I.	
4) ED-SCLC: 2 RCTs have qualified BM data for meta-analysis (415, 445).							
	415[C]	Slotman, 2007[39] (EORTC)	BM: Competing risk regression;	BM prevalence: PCI: 16.8% (24/143); No PCI: 41.3% (59/143);	Median OS: PCI: 6.7 m, No PCI: 5.4 m;	PCI significantly decreased BM and improved OS in ED-SCLC	RCT;

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			OS: log-rank test	1-year BM: PCI: 14.6%; No PCI: 40.4%; HR, 0.27; 95%CI, 0.16-0.44; P<0.001.	HR=0.68; 95% CI, 0.52- 0.88; P = 0.003.		Symptomatic BM, no brain images at baseline.
	445[C]	Takahashi, 2017[40]	BM: Competing risk regression; OS: Cox proportional hazard regression	BM prevalence: PCI: 48% (54/113); No PCI: 69% (77/111); 1-year BM: PCI: 32.9%; No PCI: 59% (HR, 0.49; 95%CI, 0.33-0.74; Gray's p<0·0001)	Median OS: PCI: 11.6 m, No PCI: 13.7 m; HR=1.27; 95% CI, $0.96–1.68$; p=0.094	PCI significantly decreased BM, but did not improve OS in ED-SCLC	RCT; Contains asymptomatic BM, have brain images at baseline.
	80	Chen, 2016[13]	Cox proportional hazard regression	Yes vs No (adjust for liver metastasis, number of metastatic sites) : HR, 0.410; 95% CI, 0.218–0.770; p< 0.05;	Yes vs No (adjust for PS, liver metastasis, number of metastatic sites) : HR, 0.638; 95% CI, 0.413–0.982; p <0.05;	PCI significantly decreased BM and improved OS in ED-SCLC.	
	28	Bang, 2018[16]	Cox proportional hazard regression	Yes vs No (adjust for extrathoracic metastases): HR 2.53; 95% CI: 1.51-4.29; P=0.0004);	Yes vs No (adjust for PS, extrathoracic metastases): HR 1.81; 95% CI: 1.29-2.54; P=0.0005	PCI significantly decreased BM and improved OS in ED-SCLC.	Backward stepwise multivariate analysis
5) SCLC	18[C]	Arriagada, 1995[41] (PCI 85)	First isolated BM: Competing risk regression; Overall BM, OS: log-rank test	Overall BM (2-year): PCI: 40%; No PCI: 67%; RR=0.35, P<10^{-13} (Log-rank test); First BM (2-year): PCI: 19%; No PCI: 45%: P<10^{-6} (Gray's test).	2-year OS: PCI: 29%; No PCI: 21.5%; (adjust for center and stage): RR=0.83, p=0.14	PCI significantly decreased first isolated BM in SCLC, but did not improve OS	RCT; The incidence of first isolated BM is lower than overall BM. Data overlapped with No.19.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	225[c]	Laplanche, 1998[42] (PCI 88)	First isolated BM: Competing risk regression; Overall BM, OS: log-rank test	Overall BM (4-year): PCI: 44%; No PCI: 51%: RR=0.71, 95%CI 0.45–1.12, P=0.14; First BM (4-year): PCI: 21%; No PCI: 27%: RR=0.69, P=0.26.	4-year OS: PCI: 22%; No PCI: 16%; RR=0.84, p=0.25	PCI did not significantly decrease BM or improve OS in SCLC	RCT; Closed earlier, Power=37%. The incidence of first isolated BM is lower than overall BM. Data overlapped with No.19.
	19[c]	Arriagada, 2002[43] (PCI 85 + PCI 88)	First isolated BM: Competing risk regression; Overall BM, OS: log-rank test	Overall BM (5-year): PCI: 43%; No PCI: 59%: RR=0.50, P<0.001; First BM (5-year): PCI: 20%; No PCI: 37%: P<0.001.	5-year OS: PCI: 18%; No PCI: 15%; RR=0.84, p=0.06	PCI significantly decreased BM in SCLC, but did not improve OS.	Pooled analysis of 2 RCTs; The incidence of first isolated BM is lower than overall BM; HR is estimated by RR.
	312	Nicholls, 2016[44]	OS, BMFS: Kaplan-Meier method, Wilcoxon signed-rank test; BM incidence: Fisher's exact test	LD: PCI: 3 (9.4%), No PCI: 8 (19%), p=0.33; ED: PCI: 4 (23.5%), No PCI: 13 (17.8%), p=0.24 Median BMFS: LD: PCI: 11.8 m (range 11.6–50.2); no PCI: 6.4 m (range 0.2–21.0) (P = 0.22). ED: PCI: 13.6 m (range 8.8–33.1); No PCI: 6.5 m (range 5.2–28.6) (P = 0.04).	LD-SCLC: 8.2 m (0.1–51.5), PCI: 18.8 m (0.9–69.4), No PCI: 8.2 m (0.1–34.4), (P < 0.001). ED-SCLC: 5.7 m (0.1–37.5); PCI: 13.6 m (5.2–37.5), No PCI: 5.6 m (0.1–73.6), (P < 0.001).	PCI improved OS in SCLC	Fisher's exact test was used for BM incidence analysis.
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	No vs Yes (adjust for PS, stage, number of extrathoracic metastatic sites, TRT dose, pretreatment LDH, Pretreatment PLR): HR:	NI	PCI significantly decreases BM in SCLC	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				0.317, 95% CI: 0.207–0.485, P <0.001			

2. PCI dose: ≤25 Gy *vs* > 25 Gy: 2 RCTs have qualified overall BM data for meta-analysis based on Cox regression (148, 231); 2 have overall BM data based on competing risk regression (231, 239); 2 have OS data (231, 239).

25Gy vs 33Gy

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	487[C]	Work, 1996[27]	Log-rank test	5-year BM: 33Gy: 14.9± 7.0%; 25 Gy: 22.9 ± 6.6%; P>0.05	NI	High dose PCI didn't significantly decrease BM.	RCT;

24Gy vs 36Gy

| | 148 [C] | Gregor, 1997[28] (UKCCCR/ EORTC) | Log-rank test | 2-year BM (data from plot): 36Gy: 16%; 24 Gy: 55%; HR 0.34; 95%CI 0.13–0.86; p<0.05. | NI | High dose PCI decreased BM more effectively in LD-SCLC. | RCT; |

25Gy vs 36Gy

| | 231 [C] | Le Pechoux, 2009[45] | Overall BM, first isolated BM: Competing risk regression; Overall BM, OS: Cox proportional hazard regression | Overall BM (2-year): 36Gy: 23%; 25Gy: 29%: HR 0.80; 95%CI 0.57–1.11; p=0.18;

Overall BM (2-year) (Gray): 36Gy: 16%; 25Gy: 22%: HR= 0.76, 95% CI 0.54–1.05, p=0.10;

First BM (2-year) (Gray): 36Gy: 12%; 25Gy: 6%: HR= 0.48, 95% CI 0.29–0.81, p=0.005. | 2-year OS: 36Gy: 37%; 25Gy: 42%; HR 1.20; 95%CI 1.00–1.44; p=0.05. | High dose PCI decreased OS and first BM, but did not decrease overall BM in LD-SCLC. | RCT. |

≤25 Gy *vs* > 25 Gy

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	≤25 Gy *vs* > 25 Gy (adjust by Log (tGTV), ODRT/TDRT, Brain MRI/CT, Weight loss, PS, PCI timing): HR: 0.67; 95% CI: 0.34–1.28; P=0.220.	≤25 Gy *vs* > 25 Gy (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, Weight loss, PS, PCI timing): HR: 0.93; 95% CI: 0.65–1.34; P=0.776.	PCI dose is not a significant risk factor for BM or OS in LD-SCLC with PCI.	Data from RCT
	371	Rubenstein, 1995[24]	Actuarial survival techniques, log-rank tests.	≤25.2 Gy *vs* > 25.2 Gy: HR: NA, P=0.1091.	NI	PCI dose was not a significant risk factor for BM in LD-SCLC.	Did not report HR.
	52	Brewster, 1995[46]	Descriptive	Single fraction, 8Gy: 2-yr BM: 22% (16/73); 2-yr BM only: 12.3% (9/73).	2-yr OS: 35%	Single fraction PCI was effective	Included 106 patients, but only 73 with CR were reported for BM incidence,
	513	Zeng, 2019[10]	Competing-risk regression	lower, standard, higher: HR: 1.09; 95% CI: 0.68–1.73; P=0.73.	NI	PCI dose is not a significant risk factor for BM after PCI in SCLC	

3. PCI timing: Meta-analysis for BM is not applicable because of different analysis methods

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	log(PCI) timing from randomization (adjust by Log (tGTV), ODRT/TDRT, Brain MRI/CT, Weight loss, PS, PCI dose): HR: 1.82; 95% CI: 0.04–8.62; P=0.760	log(PCI) timing from randomization (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, Weight loss, PS, PCI dose): HR: 0.66; 95% CI: 0.11–4.14; P=0.659	PCI timing from randomization is not a significant risk factor for BM or OS in LD-SCLC with PCI	Data from RCT
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional	log(PCI) timing from end of CRT (adjust by Log (tGTV), ODRT/TDRT, Brain	log(PCI) timing from end of CRT (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, Weight loss, PS, PCI	PCI timing from end of CRT is not a significant risk factor for BM or OS in LD-SCLC with PCI	Data from RCT

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	MRI/CT, Weight loss, PS, PCI dose): HR: 0.83; 95% CI: 0.48–1.45; P=0.520	dose): HR: 1.32; 95% CI: 0.93–1.87; P=0.189		
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	log(PCI) timing from beginning of chemo (adjust by Log (tGTV), ODRT/TDRT, Brain MRI/CT, Weight loss, PS, PCI dose): HR: 1.68; 95% CI: 0.03–10.67; P=0.810	log(PCI) timing from beginning of chemo (adjust by Log (tGTV), TDRT vs ODRT, Brain MRI/CT, Weight loss, PS, PCI dose): HR: 1.07; 95% CI: 0.15–7.84; P=0.945	PCI timing from beginning of chemo is not a significant risk factor for BM or OS in LD-SCLC with PCI	Data from RCT
	384	Sas-Korczyńska, 2010[30]	χ^2-test;	(early: PCI was given immediately after the end of thoracic radiotherapy and prior to the last cycles of chemotherapy): Early PCI: 3/41 (7.3%), Late PCI: 9/45 (20%), p= 0.00901.	NI	Early PCI is more effective to decrease BM than late PCI in LD-SCLC	χ^2-test was used for BM analysis.
	356	Ramlov, 2012[23]	Log-rank test	(Early: <5 m from the diagnosis to PCI): p = 0.26.	NI	PCI timing is not a significant risk factor for BM after PCI in SCLC	No HR reported.
	34	Bernhardt, 2017[2]	Cox proportional hazard regression	PCI timing from chemo: 120-170 days vs ≤ 120 days: HR 0.91, 95% CI 0.35-2.36, P= 0.85;	PCI timing from chemo: 120-170 days vs ≤ 120 days: HR 0.72, 95% CI 0.40-1.29, P= 0.27;	PCI timing from chemo is not a significant risk factor for BM or OS in ED-SCLC with PCI	No report of patients distribution in each group
	34	Bernhardt, 2017[2]	Cox proportional	PCI timing from brain CT: <80 days *vs* ≥ 80	PCI timing from brain CT: <80 days *vs* ≥ 80 days: HR 0.62, 95% CI 0.32-1.17, P= 0.14;	PCI timing from brain MRI/CT is not a significant risk factor for	No report of patients distribution in each group

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	days: HR 0.52, 95% CI 0.19-1.37, P= 0.18; PCI timing from brain MRI: <80 days *vs* ≥ 80 days: HR 2.30, 95% CI 0.87-6.05, P= 0.09.	PCI timing from brain MRI: <80 days *vs* ≥ 80 days: HR 1.49, 95% CI 0.79-2.80, P= 0.21.	BM or OS in ED-SCLC with PCI	
	81	Chen, 2018[8]	BM: Logistic regression. OS: Cox proportional hazard regression	(Early: <6 m from the start of initial chemo to PCI): early PCI: 10/47 (21.3%), late PCI: 23/56 (41.1%); multivariate (adjust for age, sex, PS, tumor load, number of metastatic sites): OR=0.367, 95%CI: 0.145–0.933; P <0.05.	Early vs late: HR=0.917, 95%CI: 0.542–1.551; P=0.748.	Early PCI is more effective to decrease BM than late PCI in ED-SCLC, but not for OS.	Logistic regression was used for BM analysis.
	513	Zeng, 2019[10]	BM: Competing risk regression; OS: Cox proportional hazard regression	Before vs after completing CRT (adjust for era, PS, stage, ODRT/TDRT, SCRT/CCRT): HR: 1.10; 95% CI: 0.70–1.79; P=0.69.	Before vs after completing CRT (adjust for era, PS, stage, ODRT/TDRT, SCRT/CCRT): HR: 1.37; 95% CI: 1.05–1.78; P=0.02.	Undergoing PCI before completing CRT is an independent risk factor for OS in SCLC with PCI, but not for BM.	

4. TRT vs no TRT: Meta-analysis for BM is not applicable because of different methods and no HR data.
1) LD-SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	519	Zheng, 2018[9]	Cox proportional hazard regression.	2-year BM: Yes: 41.7%, No: 35.7%; HR: NI, p=0.521.	P=0.182	TRT or not is not a significant risk factor for BM or OS in LD-SCLC	9.2% (14/152) patients did not undergo TRT; Investigated multiple factors (N=21) with limited sample size (n=153).

2) ED-SCLC: Meta-analysis for BM is not applicable because of different statistics

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	526 [C]	Slotman, 2015[47] (CREST)	Log-rank test	BM: TRT: 24/247 (9.7%), No TRT: 13/248 (5.2%), p=0.09	2-year OS: TRT: 13%, No TRT: 3%, p=0.004	TRT improved OS, but did not decrease BM in ED-SCLC	RCT;
	140 [C]	Gore, 2017[48] (RTOG 0937)	BM: Competing risk regression; OS: Cox proportional hazard regression	1-year BM: No TRT: 17% (95% CI: 6.6–40.2); TRT: 18.5% (95% CI: 8.5–37.6); P: NI.	No TRT: 15.8 m, 13.8 m, p=0.21 HR:1.44; 95% CI: 0.82–2.53	TRT is not a significant risk factor for OS in ED-SCLC	RCT;
3) Resected SCLC: Meta-analysis for BM is not applicable because of different patients							
	139	Gong, 2013[11]	Cox proportional hazard regression.	Yes (PORT) vs no (Adjust for stage, histology, induction chemo, adjuvant chemo, and surgical resection): HR= 0.607, 95%CI: NI; P= 0.226.	Yes (PORT) vs no (Adjust for stage, BM, induction chemo, adjuvant chemo, and surgical resection): HR=0.630, 95%CI:NI; P=0.057.	PORT or not is not a significant risk factor for BM in resected LD-SCLC, but tended to improve OS.	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129).); The factors in multivariate model of BM and OS were different.
	520	Zhu, 2014[4]	Cox proportional hazard regression.	Yes (PORT) vs no (adjust for p-stage and LVI): HR = 0.825, 95%CI: 0.329 ~ 2.064; p = 0.680.	P=0.866	PORT or not is not a significant risk factor for BM or OS in resected LD-SCLC	
5. TRT dose: 2 studies (439, 203) have qualified BM data for meta-analysis, no qualified data for OS meta-analysis.							
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	<45Gy *vs* ≥ 45Gy (adjust for PS, stage, number of extrathoracic metastatic sites, PCI, pretreatment LDH, Pretreatment PLR): HR: 0.425, 95% CI: 0.267–0.677, P <0.001	NI	Lower TRT dose is an independent risk factor BM in SCLC	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	203	Kim, 2019[6]	Cox proportional hazard regression.	52.5Gy *vs* 44Gy: HR=0.990, 95%CI: 0.563–1.742, P=0.973;	Adjust for PS, N, stage, TRT dose, LDH, PCI: P>0.05	TRT dose is not a significant risk factor for BM or OS in LD-SCLC	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
6. BED	513	Zeng, 2019[10]	BM: Competing-risk regression; OS: Cox proportional hazard regression.	(adjust for ODRT/TDRT, SER) HR=1.02, 95%CI:0.97-1.06, P=0.45;	(adjust for ODRT/TDRT, SER) HR=1.02, 95%CI:0.98-1.06, P=0.37;	BED is not a significant risk factor for BM or OS in SCLC with PCI.	

7. TRT timing: Meta-analysis for BM is not applicable because of different methods.

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	488 [C]	Work, 1997[49]	Log-rank test	Initial TRT vs delayed 18 weeks: BM prevalence: Early: 11% (11/99); Late: 7% (4/58). 2-year BMFS: Early: 80.8 ± 5.5%; Late: 87.0 ± 6.6% (p=0.24).	Median OS: Early: 10.5 m; Late: 12.0 m, p=0.41	TRT timing is not a significant risk factor for BM or OS in LD-SCLC	RCT;
	532 [C]	Jeremic, 1997[50]	Cox proportional hazard regression	CCRT at week 1 vs week 6: 5-year BM: Early TRT: 11%; Late TRT: 10%; P=0.9.	Median OS: Early: 34 m; Late: 26 m. 5-year OS: Early: 30%; Late:15%; *P* = 0.052.	Early TRT improved OS in LD-SCLC, but not significant for BM.	RCT;
	531 [C]	Skarlos, 2001[51] (HeCOG)	Cox proportional hazard regression	CCRT at 1st vs 4th chemo: Early TRT: 26% (11/42); Late TRT: 23% (9/39); p>0.05	Death: Early TRT: 69% (29/42); Late TRT: 82% (32/39); P = 0.65.	TRT timing is not a significant risk factor for BM or OS in LD-SCLC	RCT;

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	429 [C]	Spiro, 2006[52]	Log-rank test	CCRT at 2nd vs 6th chemo: BM: Early: 24%; late: 17%; HR=1.00, 95%CI:0.62-1.61, P=0.12	HR= 1.16; 95% CI, 0.91-1.47; log-rank P=0.23.	TRT timing is not a significant risk factor for BM or OS in LD-SCLC	RCT;
	519	Zheng, 2018[9]	Cox proportional hazard regression.	≤ 2.93 vs > 2.93 m (adjust for smoking, blood glucose, NSE, NLR, T, chemo cycles): HR=0.34, 95%CI: 0.17–0.67, P=0.002.	≤ 2.93 vs > 2.93 m (adjust for NLR) HR= 1.95, 95%CI:1.16-3.26; P= 0.011	Earlier TRT is an independent risk factor for BM in LD-SCLC, but benefits OS.	Authors speculated that earlier TRT might promote metastasis when tumor is larger and active, and the brain is thought to represent a 'sanctuary' site as systemic control improves; Investigated multiple factors (N=21) with limited sample size (n=153).
	513	Zeng, 2019[10]	Competing-risk regression	≤ 64 days vs >64 days: HR=1.09, 95%CI: 0.78–1.53, P=0.62.	NI	TRT timing is not a significant risk factor for BM after PCI in SCLC	
	203	Kim, 2019[6]	Cox proportional hazard regression.	Early (start TRT at 1st chemo) *vs* late (start TRT at 3rd chemo): HR=1.033, 95%CI: 0.547–1.956, P=0.918.	Adjust for PS, N, stage, TRT dose, LDH, PCI: P>0.05	TRT timing is not a significant risk factor for BM or OS in LD-SCLC	Inverse probability treatment weight (IPTW) was used to minimize bias; No report of patients distribution in each group after IPTW; Details of multivariate model not reported.
8. SER	513	Zeng, 2019[10]	BM: Competing-risk regression;	(Adjust for ODRT/TDRT, BED) HR=1.00, 95%CI: 1.00-1.01, P=0.58.	(Adjust for ODRT/TDRT, BED) HR=1.00, 95%CI: 1.00-1.01, P=0.14.	SER is not a significant risk factor for BM or OS in SCLC with PCI.	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			OS: Cox proportional hazard regression.				
9. CRT-D							
	86	Chu, 2019[17]	Pre-PCI BM: Logistic regression; OS: Cox proportional hazard regression.	(Adjust for smoking, T, and N): OR=1.406, 95%CI: 1.007–1.964, P=0.045	(Adjust for T and N): HR=1.227, 95%CI: 1.026–1.466, P=0.025	CRT-D is an independent risk factor for pre-PCI BM and OS in LD-SCLC	Investigated risk factors for Pre-PCI BM in LD-SCLC using logistic regression.
10. TRT technique							
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression.	IMRT *vs* 2D/3D: SHR 0.46, 95% CI 0.29–0.71, P=0.001; Multivariate (adjusted factors: NI): SHR 0.46, 95% CI 0.30–0.73, p=0.001.	Multivariate (adjusted factors: NI): HR 0.79, 95% CI 0.64–0.99, p=0.037	Compared to 2D/3D, IMRT is an independent risk factor for BM and OS in LD-SCLC.	Two definitions for time to development of BM, unclear which one is used
11. Era: Meta-analysis for BM is not applicable because of different methods.							
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression.	<2000 *vs* ≥ 2000: SHR 0.57, 95% CI 0.40–0.80, P=0.001; Multivariate (adjusted factors: NI): P>0.05	HR 0.76, 95% CI 0.63–0.90, P=0.002; Multivariate (adjusted factors: NI): P>0.05	Era is not an independent risk factor for BM or OS in LD-SCLC	Two definitions for time to development of BM, unclear which one is used
	28	Bang, 2018[16]	Cox proportional hazard regression	<2008 *vs* ≥ 2008: P>0.05	<2008 *vs* ≥ 2008: P>0.05	Era is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	513	Zeng, 2019[10]	BM: Competing-risk regression; OS: Cox proportional hazard regression.	2003-2010 vs 2011-2016 (adjust for PS, stage, ODRT/TDRT, SCRT/CCRT, PCI timing): HR=0.83, 95% CI 0.55–1.27, p=0.39.	(Adjust for PS, stage, ODRT/TDRT, SCRT/CCRT, PCI timing): HR=0.82, 95% CI 0.65–1.04, p=0.11.	Era is not a significant risk factor for BM or OS in SCLC with PCI	

12. CRT sequence: Meta-analysis for BM is not applicable because of different methods and no HR data.

1) Alternating vs SCRT

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	530 [C]	Gregor, 1997[53] (EORTC)	Cox proportional hazard regression	First isolated BM: Alternating: 20% (34/169); SCRT: 16% (26/165); P: NI.	Death: Alternating: 81.2% (138/170); SCRT: 81.8% (135/165); P=0.24.	A/S was not a significant factor for OS in LD-SCLC. The significance of difference on BM was unclear.	Analyzed first isolated BM instead of overall BM. HR or P of BM was not reported.

2) CCRT vs SCRT

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	529 [C]	Takada, 2002[54] (JCOG 9104)	Cox proportional hazard regression	First isolated BM: SCRT: 27% (31/114); CCRT: 19% (22/114); P=0.16.	Median OS: SCRT:19.7m, CCRT: 27.2 m, P=0.094; (Adjust for PS, stage, age, and sex): HR=0.70, 95%CI: 0.52-0.94, P=0.02.	CCRT significantly improved OS in LD-SCLC, but not for first isolated BM.	Analyzed first isolated BM instead of overall BM.
	108	El Sharouni, 2009[55]	BM: χ2 test; OS: Log-rank test	SCRT+PCI: 16.4% (11/67); CCRT+PCI: 8.7% (2/23). (P=0.502)	SCRT (N=95): 14.0 m; CCRT (N=40): 21.8 m; P: NI	CCRT/SCRT is not a significant risk factor for BM after PCI in SCLC	χ2 test was used for BM in SCRT + PCI vs CCRT + PCI but with low number of events. Statistic significance of OS was not reported.
	264	Manapov, 2012[25]	Log-rank test	BMFS: CCRT: 332 days, SCRT: 267 days, p = 0.522.	NI	CCRT/SCRT is not a significant risk factor for BM in LD-SCLC with poor initial PS	No HR.

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	263	Manapov, 2012[56]	Descriptive	SCRT: 19% (14/74); CCRT:31% (16/51); p: NI.	CCRT: 14.9 m (95% CI 11.7–18.2); SCRT: 16.1 m (95% CI 12.2–20) ; p = 0.6.	In LD-SCLC patients with poor initial PS, more patients developed BM in the CCRT group than in the SCRT group. But the P value was not reported. CCRT/SCRT is not a significant risk factor for OS.	No statistic analysis details and no statistic interpretation.
	265	Manapov, 2013[57]	Log-rank test	CCRT: 37% (19/51); SCRT:20% (15/74); P=0.049. BM time from initial diagnosis: CCRT: 330 days (95%CI: 216-444), SCRT: 273 days (95%CI :221-325), P=0.7; from end of chemotherapy: CCRT: 123 days (95%CI:15-231), SCRT: 151 days (95%CI:101-210), P=0.7; from end of TRT: CCRT: 213 days (95%CI: 104-322), SCRT: 73 days (95%CI: 17-129), P=0.2;	14.9 m (SCRT vs CCRT: P=0.6)	CCRT/SCRT is not a significant risk factor for OS in LD-SCLC. The conclusion of impact on BM is contradictory	The BM conclusion is contradictory with the detailed BM time.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression	CCRT *vs* induction chemo→CRT: SHR 1.36, 95% CI 0.92–2.02, P=0.120; CCRT *vs* induction chemo→RT: SHR 1.14, 95% CI 0.75–1.75, P=0.534.	CCRT vs introduction chemo→CRT): HR 1.55, 95% CI 1.25–1.92, P<0.001. Multivariate (adjusted factors: NI): P>0.05	CCRT/SCRT is not an independent risk factor for BM or OS in LD-SCLC.	Two definitions for time to development of BM, unclear which one is used
	514	Zeng, 2017[7]	Cox proportional hazard regression.	P=0.163	NI	CCRT/SCRT is not a significant risk factor for BM after PCI in SCLC	
	519	Zheng, 2018[9]	Cox proportional hazard regression.	P=0.062	P=0.440	CCRT/SCRT is not a significant risk factor for BM or OS in LD-SCLC	Investigated multiple factors (N=21) with limited sample size (n=153).
	513	Zeng, 2019[10]	BM: Competing-risk regression; OS: Cox proportional hazard regression	(adjust for PS, stage, ODRT/TDRT, era, PCI timing): HR=0.87, 95% CI 0.62–1.23, P=0.42.	(adjust for PS, stage, ODRT/TDRT, era, PCI timing): HR=0.89, 95% CI 0.71–1.11, P=0.30.	CCRT/SCRT is not a significant risk factor for BM or OS in SCLC with PCI.	

13.TRT fractionation: Meta-analysis for BM is not applicable because of different methods and no HR data.

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	TDRT vs ODRT (adjust by Log (tGTV), brain CT/MRI, weight loss, PS, PCI timing, PCI dose): HR: 0.93; 95% CI: 0.57–1.53; P=0.770	TDRT vs ODRT (adjust by Log (tGTV), brain CT/MRI, weight loss, PS, PCI timing, PCI dose): HR: 1.16; 95% CI: 0.89–1.51; P=0.275.	ODRT/TDRT is not a significant risk factor for BM or OS in LD-SCLC with PCI.	Data from RCT
	514	Zeng, 2017[7]	Cox proportional	ODRT vs TDRT (adjust for sex, age, smoking, response, TNM stage,	*p* = 0.570	TDRT is an independent risk factor for BM after	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression.	CCRT/SCRT, chemotherapy cycles, brain CT/MRI): 3-year BM: ODRT: 21%; TDRT: 43%; HR = 2.748, 95%CI 1.227–6.157, p = 0.014		PCI in SCLC, but not for OS.	
	115	Farooqi, 2017[1]	BM: Competing-risk regression. OS: Cox proportional hazard regression.	ODRT *vs* TDRT: SHR 1.01, 95%CI 0.72–1.41, P=0.971; ODRT *vs* Mixed: SHR 1.02, 95%CI 0.25–1.45, P=0.981.	HR 0.75, 95%CI 0.63–0.90, P=0.002. Multivariate (adjusted factors: NI): P>0.05	ODRT/TDRT is not an independent risk factor for BM or OS in LD-SCLC.	Two definitions for time to development of BM, unclear which one is used
	519	Zheng, 2018[9]	Cox proportional hazard regression.	ODRT vs TDRT: P=0.187	P=0.453	ODRT/TDRT is not a significant risk factor for BM or OS in LD-SCLC	13.7%(19/139) were TDRT; Investigated multiple factors (N=21) with limited sample size (n=153).
	303	Nakamura, 2018[21]	BM: χ^2-test; OS: Cox proportional hazard regression	BM as a first recurrence site: ODRT: 34% (23/68); TDRT: 23% (22/94); P=0.144.	ODRT vs TDRT (adjust for age, stage, pulmonary effusion, PCI, SER): HR=0.49, 95%CI: 0.27–0.88, P=0.016.	ODRT/TDRT is not a significant risk factor for BM in LD-SCLC, but TDRT improved OS.	No overall BM results. χ^2-test was used for BM analysis.
	513	Zeng, 2019[10]	BM: Competing-risk regression; OS: Cox proportional hazard regression.	ODRT vs TDRT (adjust for era, PS, CCRT/SCRT, stage, timing of PCI): HR=1.57, 95%CI: 1.04-2.37, p=0.03; After propensity score matching: ODRT vs	ODRT vs TDRT (adjust for era, PS, CCRT/SCRT, stage, timing of PCI): HR=1.13, 95%CI: 0.86-1.50, p=0.38; After propensity score matching: ODRT vs TDRT (adjust for BED, SER):	TDRT is an independent risk factor for BM and OS in SCLC with PCI.	Propensity score matching was used to minimize bias.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
				TDRT (adjust for BED, SER): HR=1.98, 95%CI: 1.09-3.59, p=0.03.	HR=1.69, 95%CI: 1.05-2.71, p=0.03.		

14. Treatment intent: Meta-analysis is not applicable because of different methods.

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	371	Rubenstein, 1995[24]	Multivariate Cox regression	Curative vs not (adjusted factors: PCI, response, age, KPS) HR: NI, P>0.05.	NI	Treatment intention was not a significant risk factor for BM in LD-SCLC.	Did not report HR.
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	CRT vs Chemo alone (adjust for stage, BMI, age, sex, laterality, anatomical site, PCI): HR=2.46, 95%CI: 1.41-4.28; P: NI	CRT vs Chemo alone (adjust for stage, BMI, age, sex, laterality, anatomical site): HR=1.17, 95%CI: 0.74-1.8; P: NI	Compared to CRT, chemo alone is an independent risk factor for BM, but not for OS.	The hazards model of OS did not include PCI.
	377	Sahmoun, 2005[12]	Cox proportional-hazards regression models	CRT vs No treatment (adjust for stage, BMI, age, sex, laterality, anatomical site, PCI): HR=2.65, 95%CI: 1.26-5.64; P: NI	CRT vs No treatment (adjust for stage, BMI, age, sex, laterality, anatomical site): HR=3.30, 95%CI: 1.87-5.8; P: NI	Compared to CRT, no treatment is an independent risk factor for BM and OS.	The hazards model of OS did not include PCI.

15. Chemo cycles: Meta-analysis for BM is not applicable because of different methods and no HR data.

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	520	Zhu, 2014[4]	Cox proportional hazard regression.	<4 vs ≥ 4: P= 0.624	P= 0.638	Chemo cycles is not a significant risk factor for BM or OS in resected LD-SCLC	
	439	Suzuki, 2018[5]	Cox proportional hazard regression.	<4 vs ≥ 4: HR: 0.939, 95%CI: 0.457–1.928; P= 0.863.	NI	Chemo cycles is not a significant risk factor for BM in SCLC	

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	519	Zheng, 2018[9]	Cox proportional hazard regression.	≤4 vs >4 (adjust for smoking, blood glucose, NSE, NLR, T, TRT timing): HR=0.49, 95%CI:0.25–0.95, P= 0.036.	P=0.345	Chemo cycles is a significant risk factor for BM in LD-SCLC, but not for OS.	Investigated multiple factors (N=21) with limited sample size (n=153).
	514	Zeng, 2017[7]	Cox proportional hazard regression.	≤6 vs >6: P=0.960	NI	Chemo cycles is not a significant risk factor for BM after PCI in SCLC	
	491	Wu, 2017[15]	BM: Competing risk regression; OS: Cox proportional hazard regression	No vs Yes (Adjust for PCI, Stage):P>0.05	No vs Yes (Adjust for PCI, Stage): HR=0.45, 95%CI: 0.25–0.81, P= 0.008	Chemo did not decrease BM, but improved OS in LD-SCLC	Only 6.7% (17/283) patients did not get chemotherapy.
	28	Bang, 2018[16]	Cox proportional hazard regression	(Continuous): P>0.05	(Continuous): P>0.05	Chemo cycles is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
	513	Zeng, 2019[10]	Competing-risk regression	<4, 4-6, >6: HR=1.50, 95%CI: 0.88–2.54; P= 0.13.	NI	Chemo cycles is not a significant risk factor for BM after PCI in SCLC	
16. Chemo regimen: Meta-analysis is not applicable because of different methods.							
	388[C]	Schiller, 2001[58] (E7593)	Log-rank test	Observation: 25%; Topotecan: 31%. p>0.05	1-year OS: Observation: 28%; Topotecan: 25%; P=0.43	Compared to observation, Topotecan after first line EP chemo did not improve OS or BM in ED-SCLC	
	536[C]	Sundstrøm, 2002[59]	BM: χ^2-test; OS: Cox proportional	325 of the 436 patients had available follow-up information. 290 were relapsed. 46% recurred	Median OS: EP: 10.2 m; CEV: 7.8 m; P=0.0004.	Compared to CEV, EP improved OS in SCLC.	χ^2-test was used for BM analysis.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
			hazard regression	in the brain: EP: 57% (82/143); CEV: 46% (68/147); P=0.06			
	28	Bang, 2018[16]	Cox proportional hazard regression	Cisplatin vs Carboplatin: P>0.05	Cisplatin vs Carboplatin: P>0.05	Chemo regimen is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
	513	Zeng, 2019[10]	Competing-risk regression	EP vs non-EP: HR=1.33, 95%CI: 0.76–2.33; P= 0.32.	NI	Chemo regimen is not a significant risk factor for BM after PCI in SCLC	
	513	Zeng, 2019[10]	Competing-risk regression	Types of chemo regimen involved (1 vs ≥ 2): HR=1.17, 95%CI: 0.75–1.84; P= 0.48.	NI	Types of chemo regimen involved is not a significant risk factor for BM after PCI in SCLC	

17. chemo or not in resected LD-SCLC

1). Induction chemo

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	139	Gong, 2013[11]	Cox proportional hazard regression.	Yes vs no (Adjust for stage, histology, PORT, adjuvant chemo, and surgical resection): HR= 1.556, 95%CI: NI; P= 0.274.	Yes vs no (Adjust for stage, BM, PORT, adjuvant chemo, and surgical resection): HR=1.201, 95%CI:NI; P=0.423.	Induction chemo or not is not a significant risk factor for BM or OS in resected LD-SCLC.	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129); The factors in multivariate model of BM and OS were different.

2). Adjuvant chemo

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	139	Gong, 2013[11]	Cox proportional hazard regression.	Yes vs no (Adjust for stage, histology, induction chemo, PORT, and surgical resection): HR=2.515, 95%CI: NI; P= 0.373.	Yes vs no (Adjust for stage, BM, induction chemo, PORT, and surgical resection): HR=0.524, 95%CI:NI; P=0.067.	Adjuvant chemo or not is not a significant risk factor for BM in resected LD-SCLC, but tended to improve OS.	Only 11.1% (14/126) patients did not undergo adjuvant chemo; Contained many patients with combined SCLC and NSCLC (53.5%, 69/129);

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
							The factors in multivariate model of BM and OS were different.
18. Surgery or not							
	513	Zeng, 2019[10]	Competing-risk regression	HR=0.75, 95%CI: 0.36–1.58; P= 0.45.	NI	Surgery is not a significant risk factor for BM after PCI in SCLC	Only 5.7% (44/778) patients underwent surgery.
19. Surgical resection complete or not							
	139	Gong, 2013[11]	Cox proportional hazard regression.	Complete vs incomplete (Adjust for stage, histology, induction chemo, adjuvant chemo, and PORT): HR=3.563, 95%CI: NI; P=0.020.	Complete vs incomplete (Adjust for stage, BM, induction chemo, adjuvant chemo, and PORT): HR=1.712, 95%CI:NI; P=0.117.	Compared to complete resection, incomplete resection is an independent risk factor for BM, but not for OS in resected LD-SCLC	Contained many patients with combined SCLC and NSCLC (53.5%, 69/129); The factors in multivariate model of BM and OS were different.
20. Brain CT/MRI before PCI: Meta-analysis is not applicable because of different methods.							
	239 [C]	Levy, 2019[19] (CONVERT trial)	BM: Competing risk regression; OS: Cox proportional hazard regression	MRI vs CT (adjust by Log (tGTV), ODRT/TDRT, weight loss, PS, PCI timing, PCI dose): HR: 1.28; 95% CI: 0. 67–2.46; P=0.450	MRI vs CT (adjust by Log (tGTV), TDRT vs ODRT, weight loss, PS, PCI timing, PCI dose): HR: 1.41; 95% CI: 0.99–2.00; P=0.151	Brain MRI/CT is not a significant risk factor for BM or OS in LD-SCLC with PCI	Data from RCT
	514	Zeng, 2017[7]	Cox proportional hazard regression.	MRI vs CT: P=0.362	MRI vs CT: P=0.239	Brain MRI/CT is not a significant risk factor for BM or OS in SCLC with PCI	
	28	Bang, 2018[16]	Cox proportional hazard regression	MRI vs CT: P>0.05	MRI vs CT: P>0.05	Postchemo brain MRI/CT is not a significant risk factor for BM or OS in ED-SCLC	Backward stepwise multivariate analysis
21. PET-CT or not at diagnosis							

Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments
	82	Choi, 2017[34]	Cox proportional hazard regression.	cumulative first isolated BM: whole: PET: 38.7%; No PET: 30.1% (P = 0.718); PCI: PET: 34.3%; No PET: 13.3% (P = 0.177); No PCI: PET: 41.1%; No PET: 37.1% (P = 0.942);	5-year OS: whole: PET: 38.2%; No PET: 30.5% (P = 0.023); PCI: PET: 38.3%; No PET: 33.6% (P = 0.985); No PCI: PET: 38.6%; No PET: 29.3% (P = 0.011); Yes vs no (Adjust for age, sex, PS, and PCI): HR=1.452, 95%CI: 1.071-1.968; P=0.016	With initial PET or not did not significantly correlate with first isolated BM in LD-SCLC, but improved OS.	Analyzed BM as a first site of recurrence; Characteristics were not balanced between groups.
22. Treating site (hospital)							
	513	Zeng, 2019[10]	Competing-risk regression	HR=0.99, 95%CI: 0.87–1.13; P= 0.86.	NI	Treating hospital is not a significant risk factor for BM after PCI in SCLC	

Notes: [A]: All the results are in univariate analysis for overall BM unless specified; [B]: Only factors with BM results will be presented with the OS results; [C]: Highlighted studies are RCTs. [D]: Baseline performance status unless specified; [E]: Response to chemoradiotherapy unless specified.

Abbreviations: BED, biologically effective dose; BM, brain metastasis; BMFS, brain metastasis free survival; BMI, body mass index; CCRT, concurrent chemoradiotherapy; CEA, carcinoembryonic antigen; CEV, cyclophosphamide-epirubicin-vincristine; chemo, chemotherapy; CI, confidence interval; CR, complete response; CRT, chemoradiotherapy; CRT-D: Chemoradiotherapy duration; CT, computerized tomography; CTC, circulating tumor cells; ED, extensive-stage disease; EP, etoposide-platinum; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; IPTW, inverse probability treatment weight; IR, incomplete response; KPS, Karnofsky performance status scale; LD, limited-stage disease; LDH, lactate dehydrogenase; LVI, lymphovascular invasion; MRI, magnetic resonance imaging; NA, not applicable; NI, no information; NLR, neutrophil-to-lymphocyte ratio; NR: Non-response; NSCLC, non-small cell lung cancer; NSE, neuron-specific enolase; ODRT, once-daily radiotherapy; OR, odds ratio; OS, overall survival; PCI, prophylactic cranial irradiation; PET-CT, positron emission tomography and computed tomography; PLR, platelet-to-lymphocyte ratio; PORT, postoperative radiotherapy; PS, performance status; SCLC, small cell lung cancer; SCRT, sequential chemoradiotherapy; SD, stable disease; SER, start of any treatment until the end of chest irradiation; SHR, subdistribution hazard ratio; SUV, standardized uptake value, tGTV, thoracic gross tumor volume; TRT, thoracic radiotherapy; TDRT, twice-daily radiotherapy; 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy.

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments

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Table 1. Risk factors for BM in SCLC

Risk factors	Studies ID	First Author (Trial)	Statistics	BM Results[A]	OS results[B]	Conclusion	Comments

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Risk factors

In total, 57 factors were reported in all studies, including 8 baseline factors, 27 tumor-related factors, and 22 treatment-related factors (Table 1). However, they were investigated in various ways with different participants, such as LD, or ED, or resected SCLC, or patients with PCI. Details are shown in the comments in table 1. Hence, 10 factors had qualified BM data from 21 studies (11 RCTs + 10 non-RCTs [all were retrospective studies]) and four factors had qualified OS data for meta-analysis (Table 1-2):

Table 2. Summary of the 10 factors for BM with meta-analysis

		BM	
		Risk	Non-significant
OS	Risk	ED	M1b stage
	Non-significant	PCI in ED-SCLC, PCI dose	
	Unclear	Age, Male (P=0.06), cT-stage, PS (P=0.06), PCI in SCLC	Smoking
	No information		TRT dose

Abbreviations:
BM, brain metastasis; ED, extensive-stage disease; OS, overall survival; PCI, prophylactic cranial irradiation; PS, performance status; SCLC, small cell lung cancer; TRT, thoracic radiotherapy.

A. baseline characteristics:

1. Age: Age was investigated in 18 studies with seven different methods (different age groups, continuous vs group) (Table 1). It concluded that age was not an independent risk factor for BM or OS in 14 studies[34,36,41,45,46,57,59-61,69,70,74,75,77]. Three studies[53,61,80] were eligible to perform BM meta-analysis and showed that patients with older age (≥65) had less BM than younger patients (HR=0.70, 95%CI: 0.54-0.92; P=0.01) (Fig 3A).
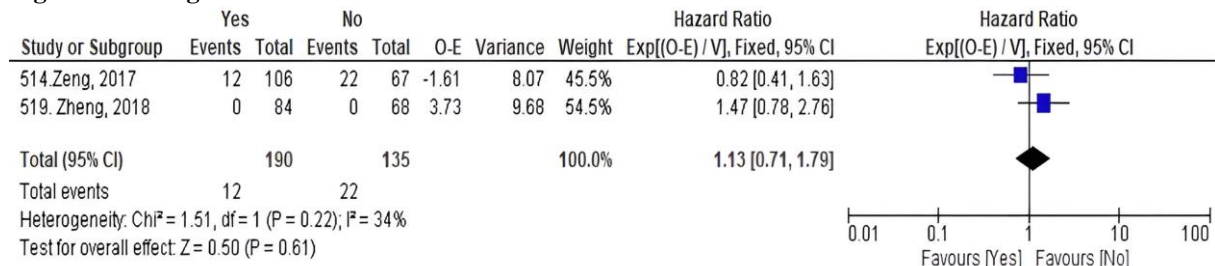
Fig 3A. Age:
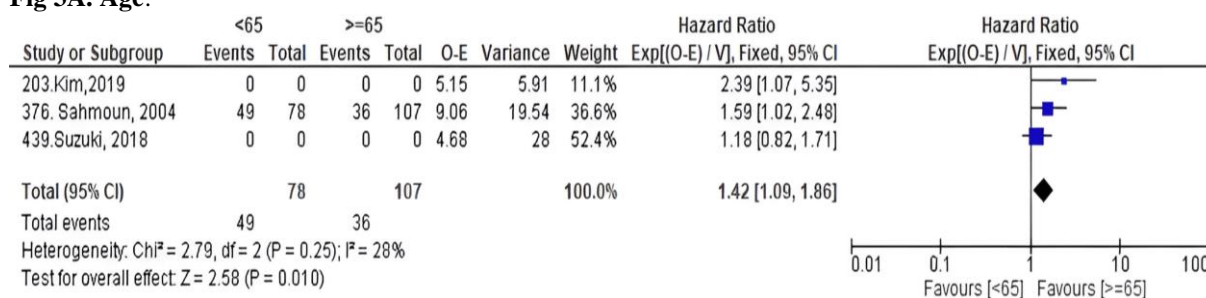
2. Sex: Sex was investigated in 16 studies. It concluded that sex was not an independent risk factor for BM or OS in 13 studies[34,36,45,46,53,57,59-61,69,74,77,78]. Five studies[46,52,54,59,61] were eligible to perform meta-analysis for BM and showed that male sex tends to be a risk factor for BM (HR=1.24, 95%CI: 0.99-1.54; P=0.06) (Fig 3B).
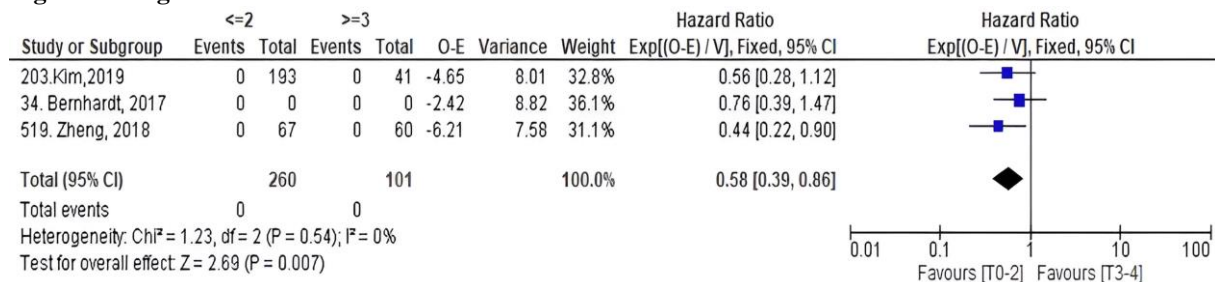
Fig 3B. Sex

	Male		Female					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
368.Roengvoraphoj, 2017	40	110	18	69	8	13.74	17.1%	1.79 [1.05, 3.04]	
377. Sahmoun, 2005	0	138	0	71	1.59	15.22	18.9%	1.11 [0.67, 1.83]	
439.Suzuki, 2018	0	142	0	151	2.91	28.13	34.9%	1.11 [0.77, 1.60]	
514.Zeng, 2017	27	129	9	46	0.81	6.98	8.7%	1.12 [0.53, 2.36]	
80.Chen, 2016	0	171	0	33	3.73	16.48	20.5%	1.25 [0.77, 2.03]	
Total (95% CI)		690		370			100.0%	1.24 [0.99, 1.54]	
Total events	67		27						
Heterogeneity: Chi² = 2.46, df = 4 (P = 0.65); I² = 0%									
Test for overall effect: Z = 1.90 (P = 0.06)									

Favours [Male]   Favours [Female]

3. Smoking: Smoking was investigated in seven studies. It showed that smoking was not a significant risk factor for BM or OS[34,45,59-61,77,78]. Two studies[59,60] were eligible to perform meta-analysis for BM and showed that smoking (ever vs never) was indeed not a significant risk factor for BM (HR=1.13, 95%CI: 0.71-1.79; P=0.61) (Fig 3C).

Fig 3C. Smoking:

	Yes		No					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
514.Zeng, 2017	12	106	22	67	-1.61	8.07	45.5%	0.82 [0.41, 1.63]	
519. Zheng, 2018	0	84	0	68	3.73	9.68	54.5%	1.47 [0.78, 2.76]	
Total (95% CI)		190		135			100.0%	1.13 [0.71, 1.79]	
Total events	12		22						
Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34%									
Test for overall effect: Z = 0.50 (P = 0.61)									

Favours [Yes]   Favours [No]

B. Tumor related factors

1. TNM cT stage: T stage was investigated in four studies with conflicting conclusions[34,60,75,80]. Three studies[60,75,80] had qualified BM data for meta-analysis and showed that patients with a higher T stage(T≥3) had a statistically significantly higher risk of BM than lower T stages (HR=1.72, 95%CI: 1.16-2.56; P=0.007) (Fig 3D).

Fig 3D. T stage:

	<=2		>=3					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
203.Kim,2019	0	193	0	41	-4.65	8.01	32.8%	0.56 [0.28, 1.12]	
34. Bernhardt, 2017	0	0	0	0	-2.42	8.82	36.1%	0.76 [0.39, 1.47]	
519. Zheng, 2018	0	67	0	60	-6.21	7.58	31.1%	0.44 [0.22, 0.90]	
Total (95% CI)		260		101			100.0%	0.58 [0.39, 0.86]	
Total events	0		0						
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%									
Test for overall effect: Z = 2.69 (P = 0.007)									

Favours [T0-2]   Favours [T3-4]

2. c-stage: c-stage was investigated in different ways in 11 studies with conflicting conclusions[36,37,54,55,57,59-61,76,77,80](Table 1). Two studies[54,59] were eligible to perform meta-analysis for BM and OS. It showed that compared to ED, LD patients had less BM (HR=0.34, 95%CI: 0.17-0.67; P=0.002) (Fig 3E) and a better OS (HR=0.60, 95%CI: 0.37-0.98; P=0.04) (Fig 4A).
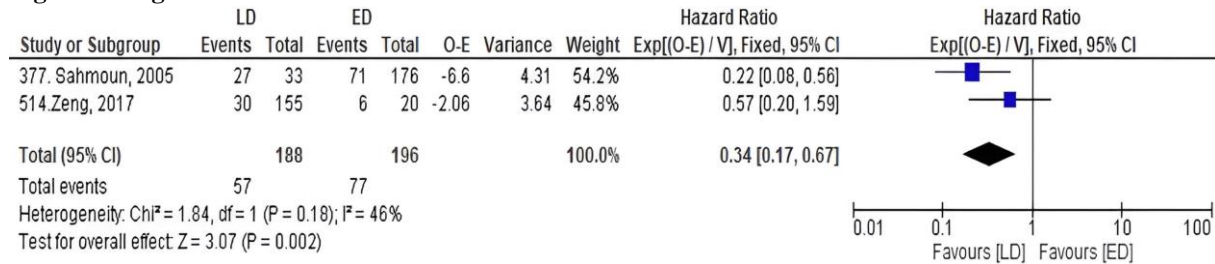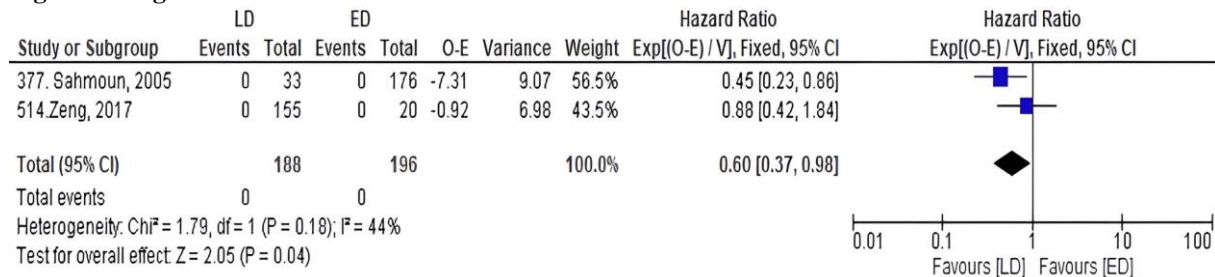
Fig 3E. c-stage :

	LD		ED					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
377. Sahmoun, 2005	27	33	71	176	-6.6	4.31	54.2%	0.22 [0.08, 0.56]	
514.Zeng, 2017	30	155	6	20	-2.06	3.64	45.8%	0.57 [0.20, 1.59]	
Total (95% CI)		188		196			100.0%	0.34 [0.17, 0.67]	
Total events	57		77						

Heterogeneity: Chi² = 1.84, df = 1 (P = 0.18); I² = 46%
Test for overall effect: Z = 3.07 (P = 0.002)

Favours [LD] Favours [ED]

Fig 4A. c-stage for OS:

	LD		ED					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
377. Sahmoun, 2005	0	33	0	176	-7.31	9.07	56.5%	0.45 [0.23, 0.86]	
514.Zeng, 2017	0	155	0	20	-0.92	6.98	43.5%	0.88 [0.42, 1.84]	
Total (95% CI)		188		196			100.0%	0.60 [0.37, 0.98]	
Total events	0		0						

Heterogeneity: Chi² = 1.79, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 2.05 (P = 0.04)

Favours [LD] Favours [ED]

3. M-status in ED-SCLC: M status (M1b or M0-M1a) was investigated in patients with ED-SCLC in four studies[45,46,74,75]. Three were eligible to perform meta-analysis for BM and OS[45,46,75]. It showed that M1b was a significant risk factor for OS (HR=1.46, 95%CI: 1.10-1.95; P=0.01; Fig 4B) but not for BM (HR=1.26, 95%CI: 0.89-1.77; P=0.19; Fig 3F) in ED-SCLC.

Fig 3F. Tumor load in ED-SCLC:

	M1b		<M1b					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
28. Bang, 2018	0	0	0	0	4.01	4.21	13.0%	2.59 [1.00, 6.74]	
34. Bernhardt, 2017	0	0	0	0	-1.6	4.32	13.3%	0.69 [0.27, 1.77]	
80.Chen, 2016	0	129	0	75	5.02	23.86	73.7%	1.23 [0.83, 1.84]	
Total (95% CI)		129		75			100.0%	1.26 [0.89, 1.77]	
Total events	0		0						

Heterogeneity: Chi² = 3.76, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.31 (P = 0.19)

Favours [M1b] Favours [<M1b]

Fig 4B. M status in ED-SCLC for OS:

Study or Subgroup	M1b Events	Total	M0-M1a Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
28. Bang, 2018	0	136	0	19	6.92	12.37	26.9%	1.75 [1.00, 3.05]
34. Bernhardt, 2017	0	0	0	0	1.83	8.18	17.8%	1.25 [0.63, 2.48]
80.Chen, 2016	0	129	0	75	8.76	25.51	55.4%	1.41 [0.96, 2.08]
Total (95% CI)		265		94			100.0%	1.46 [1.10, 1.95]
Total events	0		0					

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)
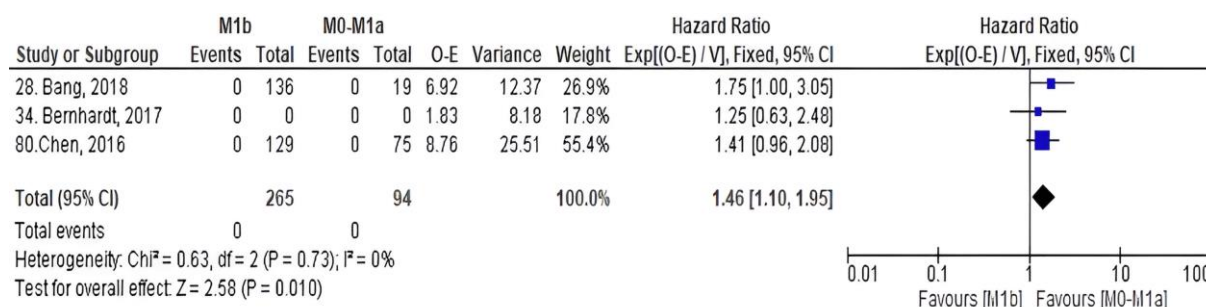
4. PS: PS was investigated in 10 studies in different ways. It concluded that PS was not a significant risk factor for BM or OS in six SCLC studies[36,60,61,74,79,80]. Two non-RCTs[46,61] were eligible to perform meta-analysis for BM and showed that better PS (0-1) tended to be associated with less BM (HR=0.66, 95%CI: 0.42-1.02; P=0.06) (Fig 3G).

Fig 3G. PS:

Study or Subgroup	0-1 Events	Total	>=2 Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
439.Suzuki, 2018	0	239	0	54	-4.92	15.66	80.7%	0.73 [0.45, 1.20]
80.Chen, 2016	0	195	0	9	-3.25	3.75	19.3%	0.42 [0.15, 1.16]
Total (95% CI)		434		63			100.0%	0.66 [0.42, 1.02]
Total events	0		0					

Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)
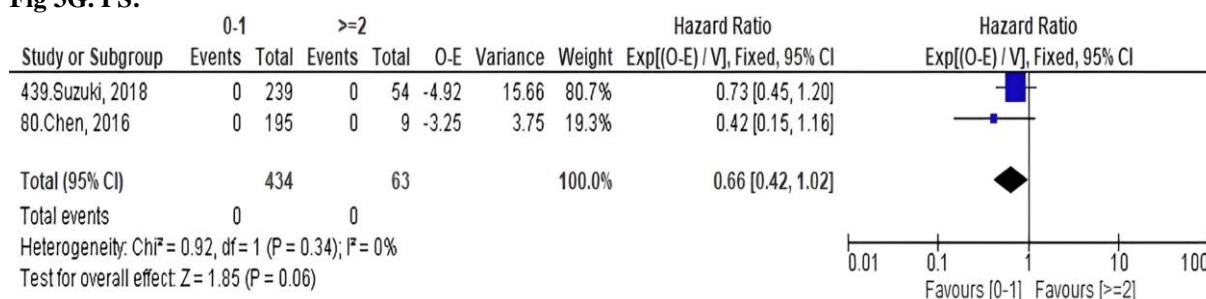
C. *Treatment related factors:*

1. PCI vs no PCI: PCI was investigated in 28 studies, including 8 RCTs. Three RCTs had qualified overall BM data for meta-analysis based on Cox regression[29,63,64] and showed that PCI significantly decreases BM in SCLC (HR=0.47, 95%CI: 0.38-0.58; P<0.00001) and LD-SCLC (HR=0.41, 95%CI: 0.28-0.60; P<0.00001) (Fig 3H1); two had overall BM data based on competing risk regression[5,9] and also showed that PCI significantly decreased BM in ED-SCLC (HR=0.37, 95%CI: 0.20-0.65; P=0.0007) (Fig 3H2); two had OS data[5,9] and showed that PCI did not significantly improve OS in ED-SCLC (HR=0.93, 95%CI: 0.50-1.71; P=0.81) (Fig 4C).

Two retrospective studies[47,81] investigated PCI in LD-SCLC staged with brain MRI and reported controversial conclusions. Meta-analysis was not applicable. Two retrospective studies[58,62] investigated PCI in resected LD-SCLC and showed that PCI improved OS and decreased BM in resected LD-SCLC, but not in p-stage I. Meta-analysis was also not applicable.

Fig 3H1. PCI in SCLC:

Study or Subgroup	PCI Events	PCI Total	No PCI Events	No PCI Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
7.1.1 SCLC									
19. Arriagada, 2002	105	245	153	260	-44.71	64.5	70.8%	0.50 [0.39, 0.64]	
Subtotal (95% CI)		245		260			70.8%	0.50 [0.39, 0.64]	
Total events	105		153						
Heterogeneity: Not applicable									
Test for overall effect: Z = 5.57 (P < 0.00001)									
7.1.2 LD-SCLC									
148. Gregor, 1997	0	194	0	120	-17.99	21.91	24.1%	0.44 [0.29, 0.67]	
487. Work 1996 PCI	15	157	13	42	-5.56	4.66	5.1%	0.30 [0.12, 0.75]	
Subtotal (95% CI)		351		162			29.2%	0.41 [0.28, 0.60]	
Total events	15		13						
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%									
Test for overall effect: Z = 4.57 (P < 0.00001)									
Total (95% CI)		596		422			100.0%	0.47 [0.38, 0.58]	
Total events	120		166						
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%									
Test for overall effect: Z = 7.15 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%									

Scale: 0.01 0.1 1 10 100 — Favours [PCI] Favours [No PCI]

Fig 3H2. PCI in ED-SCLC:

First author	logHR	logSE	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
Slotman	-1.31	0.2161		0.27	[0.18; 0.41]	47.6%	49.4%
Takahashi	-0.71	0.2060		0.49	[0.33; 0.73]	52.4%	50.6%
Common effect model				0.37	[0.28; 0.49]	100.0%	--
Random effects model				0.37	[0.20; 0.65]	--	100.0%
Heterogeneity: I² = 75%, p = 0.05							

Scale: 0.2 0.5 1 2 5

Fig 4C. PCI in ED-SCLC for OS:

First author	logHR	logSE	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
Slotman	-0.39	0.1342		0.68	[0.52; 0.88]	53.1%	50.3%
Takahashi	0.24	0.1428		1.27	[0.96; 1.68]	46.9%	49.7%
Common effect model				0.91	[0.75; 1.10]	100.0%	--
Random effects model				0.93	[0.50; 1.71]	--	100.0%
Heterogeneity: I² = 90%, p < 0.01							

Scale: 0.75 1 1.5
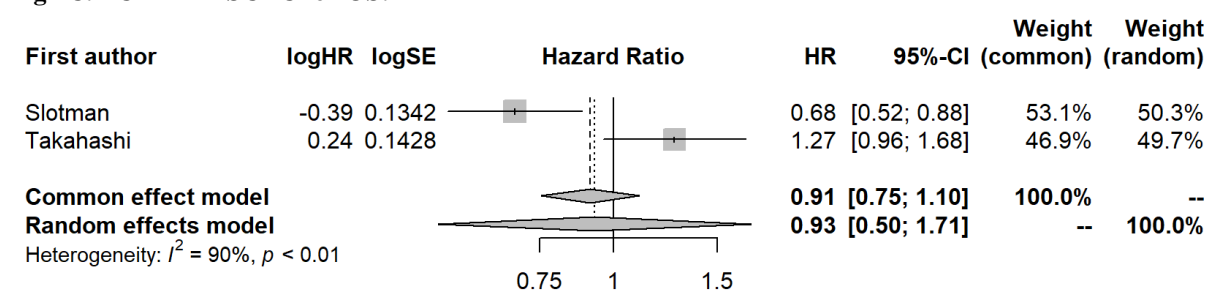
2. PCI dose: PCI dose was investigated in four RCTs[27,30,63,64] and three retrospective studies[40,41,77]. Two RCTs had qualified overall BM data for meta-analysis based on Cox regression[30,63] and showed that PCI dose (≤25Gy vs >25Gy) was not a significant risk factor for BM (HR=0.59, 95%CI: 0.26-1.31; P=0.20) (Fig 3I1); two RCTs had overall BM data based on competing risk regression[27,30] and showed that high dose (>25Gy) decreased BM more effectively (HR=0.74, 95%CI: 0.55-0.99; P=0.04) (Fig 3I2); Two had OS data[27,30] and showed

that higher dose did not significantly improve OS (HR=1.14, 95%CI: 0.97-1.34; P=0.11) (Fig 4D).

Fig 3I1.PCI dose (Cox):

First author	logHR	logSE	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
Gregor	-1.08	0.4820		0.34	[0.13; 0.87]	10.6%	36.0%
Le Pechoux	-0.22	0.1656		0.80	[0.58; 1.11]	89.4%	64.0%
Common effect model				0.73	[0.54; 0.99]	100.0%	--
Random effects model				0.59	[0.26; 1.31]	--	100.0%

Heterogeneity: I^2 = 65%, p = 0.09

0.2   0.5   1   2   5

Fig 3I2.PCI dose (Gray):

Study or Subgroup	>25 Gy Events	Total	<=25 Gy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
231. Le Pechoux, 2009	63	360	82	360	-9.95	36.25	80.6%	0.76 [0.55, 1.05]
239. Levy 2018, CONVERT	0	0	0	0	-3.5	8.74	19.4%	0.67 [0.35, 1.30]
Total (95% CI)		360		360			100.0%	0.74 [0.55, 0.99]
Total events	63		82					

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)

0.01   0.1   1   10   100
Favours [>25Gy]   Favours [=25Gy]

Fig 4D. PCI dose in SCLC for OS:

Study or Subgroup	>25 Gy Events	Total	<=25 Gy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
231. Le Pechoux, 2009	252	360	226	360	21.79	119.5	80.3%	1.20 [1.00, 1.44]
239. Levy 2018, CONVERT	0	57	0	392	-2.13	29.36	19.7%	0.93 [0.65, 1.34]
Total (95% CI)		417		752			100.0%	1.14 [0.97, 1.34]
Total events	252		226					

Heterogeneity: Chi² = 1.53, df = 1 (P = 0.22); I² = 35%
Test for overall effect: Z = 1.61 (P = 0.11)

0.01   0.1   1   10   100
Favours [>25Gy]   Favours [<=25Gy]

3. TRT dose: TRT dose (<45Gy vs ≥45Gy) was investigated in patients with SCLC in two studies[61,80] and obtained different conclusions. Meta-analysis showed that high dose (≥45Gy) was not a significant risk factor for BM (HR=1.55, 95%CI: 0.66-3.61; P=0.31) (Fig 3J).

Fig 3J. TRT dose:

First author	logHR	logSE	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
Kim	-0.01	0.2892		0.99	[0.56; 1.75]	40.2%	48.2%
Suzuki	0.85	0.2372		2.35	[1.48; 3.74]	59.8%	51.8%
Common effect model				1.66	[1.16; 2.38]	100.0%	--
Random effects model				1.55	[0.66; 3.61]	--	100.0%

Heterogeneity: I^2 = 81%, p = 0.02

0.5   1   2
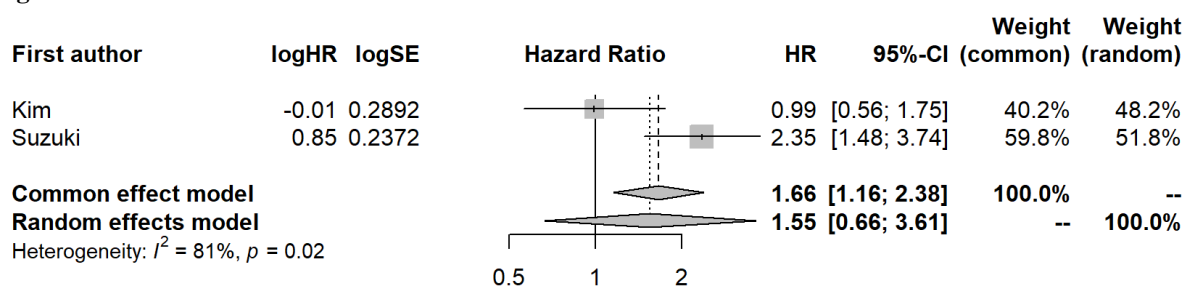
The other 47 factors did not have sufficient qualified data to perform meta-analysis, such as N-stage, number of distant metastasis, and blood biomarkers. Detailed reasons are summarized in Appendix Text 1. Detailed results are provided in Appendix Text 2 with a brief summary table (Appendix Table 7).

Appendix text 1. Reasons of not performing meta-analysis

After careful assessment for the data, we found that many factors did not have qualified data to perform meta-analysis. Reasons are shown as follows:

1. The factor was investigated with the same method in only one study:
1) Age: ≤ 60 vs > 60;
2) Age: <68 vs ≥ 68;
3) Age: ≤ 58 vs > 58;
4) Age: <58.5 vs ≥ 58.5;
5) Chronic disease;
6) Hypertension;
7) c-stage: I-III vs IV;
8) LVI;
9) Number of extrathoracic metastatic sites;
10) Lung metastasis;
11) Anatomical site;
12) Neutrophil count;
13) TLC, total lymphocyte count;
14) Platelet count;
15) NSE;
16) CEA;
17) CTC;
18) SUVmax;
19) BED;
20) SER;
21) CRT-D;
22) TRT technique;
23) chemo or not in resected LD-SCLC;
24) Surgery or not;
25) Surgical resection complete or not;
26) PET-CT or not at diagnosis;
27) Treating site (hospital).

2. The factor was analyzed with different statistics or analysis methods in different studies:
1) Age: <70 *vs* ≥70;
2) Age: <60 vs ≥60;
3) Age: Continuous:
4) Race/ethnicity;
5) Histology (SCLC vs combined SCLC);
6) Tumor size;
7) N stage;
8) c-stage: I-II vs III;
9) Laterality;
10) KPS;
11) PS: 0 vs 1-2;
12) PS: others;
13) Response;
14) LD-SCLC with MRI: PCI or not;
15) PCI timing;

16) SCLC: TRT vs no TRT;
17) TRT timing;
18) Era;
19) CRT sequence;
20) TRT fractionation;
21) Treatment intent;
22) Chemo cycles;
23) Chemo regimen;
24) Brain CT/MRI before PCI.

3. The continuous variable was analyzed using different cut-off values:
1) LDH, lactate dehydrogenase
2) NLR, neutrophil-to-lymphocyte ratio
3) PLR, platelet-to-lymphocyte ratio

4. No HR data (not reported, and also no enough information to calculate):
1) Age: <60 vs ≥60;
2) Age: Continuous;
3) Histology (SCLC vs combined SCLC);
4) N stage;
5) c-stage: I-II vs III;
6) PS: 0 vs 1-2;
7) Response;
8) Resected SCLC: PCI vs no PCI;
9) SCLC: TRT vs no TRT;
10) CRT sequence;
11) TRT fractionation;
12) Chemo cycles.

5. Data overlapped:
1) BMI;
2) c-stage: ≤IIIA vs ≥IIIB:
1) Laterality.

6. Different statistical analysis:
1) Weight loss;
2) p-stage: I,II,III;
3) Number of metastatic sites:
4) Bone metastasis;
5) Liver metastasis;
6) Adrenal metastasis.

7. Different patients:
1) resected SCLC: PORT or not

Appendix text 2. Risk factors without meta-analysis

This is a summary for risk factors that have no qualified data to perform meta-analysis for BM or OS. Detailed data are shown in table 1.

A. baseline characteristics:

1. Race: Two studies investigated race and showed that race was not a significant risk factor for brain metastasis (BM) or overall survival (OS) [1,2].

2. Body mass index (BMI): Three studies investigated BMI and showed that BMI (<25 vs ≥ 25 kg/m^2) was not a significant risk factor for BM[3-5]. Two studies have overlapping BM data[3,4]. Therefore, meta-analysis was not performed. The impact of BMI on OS was controversial but no qualified data were available to perform meta-analysis.

3. Weight loss: Two studies investigated weight loss with conflicting results[6,7]. The CONVERT trial showed that weight loss >10% was an independent risk factor for OS in limited disease small cell lung cancer (LD-SCLC) with prophylactic cranial irradiation (PCI), but not for BM[7]. No data were available to perform Meta-analysis. Therefore, it's unclear whether weight loss is a risk factor for BM.

4. Chronic disease: Zheng *et al* investigated chronic disease and showed that it was not a significant risk factor for BM or OS in LD-SCLC[5].

5. Hypertension: Sahmoun *et al* investigated hypertension and showed that it was not a significant risk factor for BM in SCLC[3].

B. Tumor related factors

1. Histology (SCLC vs combined SCLC)**:** Two studies investigated SCLC vs combined SCLC and showed that it was not a significant risk factor for BM or OS[8,9].

2. Tumor size: Four studies investigated tumor size in different ways with conflicting conclusions[1,5,7,10] . The CONVERT trial showed that tGTV, thoracic gross tumor volume (tGTV) was an independent risk factor for BM and OS in LD-SCLC with PCI[7]. No qualified data were available to perform Meta-analysis. Therefore, it's unclear whether tumor size is a risk factor for BM.

3. N-stage: Three studies investigated N and showed that N was not a significant risk factor for BM in LD-SCLC[5,10,11]. No qualified data were available to perform meta-analysis. The impact of N on OS was controversial but no qualified data were available to perform meta-analysis.

4. p-stage: Two studies investigated p-stage (I, II, III) and showed that p-stage was an independent risk factor for BM and OS in resected LD-SCLC[8,12]. Of note, both studies analyzed this 3-category variable without setting dummy variables or merging into two categories. Therefore, no qualified data were available to perform meta-analysis.

5. Lymphovascular node invasion (LVI): Zhu *et al* investigated LVI and showed that LVI was an independent risk factor for BM in resected LD-SCLC, but not for OS[12].

6. Number of metastatic sites: Chen *et al* investigated number of metastatic sites and showed that it was not a significant risk factor for BM or OS in extensive disease small cell lung cancer (ED-SCLC)[13,14].

7. Number of extrathoracic metastatic sites: Suzuki *et al* investigated number of extrathoracic metastatic sites and showed that it was not a significant risk factor BM in SCLC[2].

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8. Metastatic organs: Two studies investigated bone metastasis, liver metastasis, and adrenal metastasis[6,13]. Chen *et al* investigated lung metastasis as well[13]. It showed that bone, adrenal, and lung metastasis were not significant risk factors for BM or OS in ED-SCLC. Liver metastasis was a risk factor for OS, the BM conclusions were conflicting. No qualified data were available for meta-analysis.

9. Laterality: Three studies[3,4,15] investigated laterality and showed that laterality was not a significant risk factor for BM in SCLC, right SCLC was an independent risk factor for OS. No qualified data were available for meta-analysis.

10. Anatomical site: Sahmoun *et al* investigated anatomical site and showed that it was not a significant risk factor for BM or OS in LD-SCLC[4].

11. Karnofsky performance status (KPS): Four studies investigated KPS (≥80 *vs* <80 / ≤ 70 vs > 70) and showed that KPS was not a significant risk factor for BM or OS in LD-SCLC[1,9,12,16]. Rubenstein *et al* investigated pre-radiotherapy (RT) KPS (≤ 80 vs > 80) and showed that pre-RT KPS was a significant risk factor for BM and OS in LD-SCLC[17]. No qualified data were available for meta-analysis.

12. Response: Seven studies investigated response with conflicting conclusions[5,6,17-21]. As studies investigated response in different ways with different patients, no effective data were available to perform meta-analysis. Therefore, it's unclear whether response is a risk factor for BM.

13. Lactate dehydrogenase (LDH): Two studies investigated pretreatment LDH with different cut-off values and found that LDH was not a significant risk factor for BM or OS in LD-SCLC[2,10]. Meta-analysis was not applicable.

14. Neutrophil count: Suzuki *et al* investigated pretreatment and pre-PCI neutrophil count and showed that they were not significant risk factors for BM in SCLC[2].

15. Total lymphocyte count (TLC): Suzuki *et al* investigated pretreatment and pre-PCI TLC and showed that higher pre-PCI TLC was an independent risk factor for BM in SCLC but pretreatment TLC was not.

16. Neutrophil-to-lymphocyte ratio (NLR): Two studies investigated pretreatment NLR with different cut-off values and got controversial conclusions[2,5]. Meta-analysis was not applicable. Therefore, it's unclear whether pretreatment NLR is a risk factor for BM in SCLC. Suzuki *et al* also investigate pre-PCI NLR and showed that pre-PCI NLR was not a significant risk factor for BM in SCLC[2].

17. Platelet count: Suzuki *et al* investigated pretreatment and pre-PCI platelet count and showed that higher pretreatment platelet count was an independent risk factor for BM in SCLC but pre-PCI platelet count was not[2].

18. Platelet-to-lymphocyte ratio (PLR): Two studies investigated pretreatment NLR with different cut-off values and showed that it was not a significant risk factor for BM or OS in SCLC[2,5]. Suzuki *et al* also investigated pre-PCI PLR and showed that lower pre-PCI PLR was an independent risk factor for BM in SCLC[2].

19. Neuron-specific enolase (NSE): Zheng *et al* investigated pretreatment NSE and showed that NSE was not a significant risk factor for BM or OS in LD-SCLC[5].

20. Carcinoembryonic antigen (**CEA):** Zheng *et al* investigated pretreatment CEA and showed that CEA was not a significant risk factor for BM or OS in LD-SCLC[5].

21. Blood glucose: Zheng *et al* investigated pretreatment blood glucose and showed that it was not a significant risk factor for BM or OS in LD-SCLC[5].

22. Circulating tumor cells (CTC): Fu *et al* investigated CTC at baseline, post-first cycle, post-fourth cycle and showed that CTC at baseline was an independent risk factor for BM after PCI in stage III SCLC, while CTC post-first cycle and post-fourth cycle were not[19].

23. Maximum standardized uptake value (SUVmax): Wu *et al* investigated SUVmax and showed that it was not a significant risk factor for BM or OS in LD-SCLC[9].

C. *Treatment related factors:*

1. PCI timing: Six studies investigated PCI timing and got different conclusions[7,14-16,22,23]. The only one randomized controlled trial (RCT) showed that PCI timing was not a significant risk factor for BM or OS in LD-SCLC with PCI[7]. As studies investigated PCI timing in different ways with different patients, no effective data are available to perform Meta-analysis. Therefore, it's unclear whether PCI timing is a risk factor for BM.

2. Thoracic radiotherapy (TRT) vs no TRT: Zheng *et al* investigated TRT in LD-SCLC, Zhu *et al*[12] and Gong *et al*[8] investigated adjuvant TRT in resected LD-SCLC. Two RCTs[24,25] investigated TRT in ED-SCLC and got different conclusions. Meta-analysis was not applicable.

3. Biologically effective dose (BED): Zeng *et al* investigated BED and showed that BED was not a significant risk factor for BM or OS in SCLC with PCI.

4. TRT timing: Four RCTs[26-29] and three retrospective studies[5,10,15] investigated TRT timing and got different conclusions. As studies investigated TRT timing in different ways with different patients, no effective data were available to perform meta-analysis. Therefore, it's unclear whether TRT timing is a risk factor for BM.

5. Start of any treatment until the end of chest irradiation (SER): Zeng *et al* investigated SER and found that SER was not a significant risk factor for BM or OS in SCLC with PCI[15].

6. Chemoradiotherapy duration (CRT-D): Chu *et al* investigated CRT-D and found that CRT-D was an independent risk factor for pre-PCI BM and OS in LD-SCLC. Of note, they only investigated pre-PCI BM with logistic regression. The BM time definition and the impact of CRT-D on total BM was unclear.

7. TRT technique: Farooqi *et al* investigated intensity-modulated radiotherapy (IMRT) vs 2D/3D and found that compared to 2D/3D, IMRT was an independent risk factor for BM and OS in LD-SCLC[1]. Of note, they used competing risk analysis but the competing event was inappropriate. They also used two definitions for BM time, it's unclear which definition was used for the data. Therefore, the impact of TRT technique on total BM was unclear.

8. Era: Three studies[1,15,18] investigated era and showed that it was not a significant risk factor for BM or OS in SCLC. Meta-analysis was not applicable.

9. Chemoradiotherapy (CRT) sequences: One RCT[30] investigated the impact of alternating CRT vs sequential CRT (SCRT) on first isolated BM in LD-SCLC and showed that it was not a significant factor for OS in LD-SCLC. The significance of difference on first isolated BM was unclear. One RCT[31] investigated the impact of SCRT vs concurrent CRT (CCRT) on first isolated BM in LD-SCLC and showed that CCRT significantly improved OS in LD-SCLC, but not for first isolated BM. Eight retrospective studies[1,5,15,20,21,32-34] showed that SCRT or CCRT was not a significant risk factor for BM or OS in SCLC. Meta-analysis was not applicable.

10. TRT fractionation: One RCT[7] investigated once-daily radiotherapy (ODRT) vs twice-daily radiotherapy (TDRT) and showed that ODRT/TDRT was not a significant risk factor for BM or OS in LD-SCLC with PCI. Five retrospective studies[1,5,15,21,35] got conflicting conclusions. As studies investigated TRT fractionation in different ways with different patients, no effective data were available to perform meta-analysis. Therefore, it's unclear whether TRT fractionation is a risk factor for BM.

11. Treatment intent: Rubenstein *et al* investigated curative vs not and found that it was not a significant risk factor for BM or OS in LD-SCLC[17]. Sahmoun *et al* investigated CRT vs chemotherapy (chemo) alone and CRT vs no treatment[4]. It showed that compared to CRT, no treatment was an independent risk factor for BM and OS. Compared to CRT, chemo alone was an independent risk factor for BM, but not for OS.

12. Chemo cycles: Seven studies[2,5,9,12,15,18,21] investigated chemo cycles with conflicting conclusions. As studies investigated it in different ways with different patients, no effective data were available to perform Meta-analysis. Therefore, it's unclear whether chemo cycles is a risk factor for BM.

13. Chemo regimen: One RCT[36] investigated topotecan after first line etopside-platinum (EP) chemo and showed that compared to observation, topotecan after first line EP chemo did not improve OS or BM in ED-SCLC. One RCT[37] investigated EP vs cyclophosphamide-epirubicin-vincristine (CEV) in SCLC and found that EP improved OS. Zeng *et al* investigated EP vs non-EP and types of chemo regimen involved[15]. Bang *et al* investigated cisplatin vs carboplatin[18]. It showed that chemo regimen and types of chemo regimen were not significant for BM or OS in SCLC. Meta-analysis was not applicable.

14. Chemo or not in resected LD-SCLC: Gong *et al* investigated induction chemo and adjuvant chemo in resected LD-SCLC[8]. It showed that induction chemo or not was not a significant risk factor for BM or OS in resected LD-SCLC. Adjuvant chemo or not was not a significant risk factor for BM in resected LD-SCLC, but tended to improve OS. Of note, only 11.1% patients did not undergo adjuvant chemo and the majority patients were combined SCLC (53.5%). Therefore, it's unclear whether induction and adjuvant chemo was a risk factor for BM or OS in pure LD-SCLC with surgery.

15. Surgery: Zeng *et al* investigated surgery and found that surgery was not a significant risk factor for BM after PCI in SCLC[15]. Of note, only 5.7% (44/778) patients underwent surgery. Therefore, it's unclear whether surgery was a risk factor for BM in SCLC.

16. Surgical resection complete or not: Gong *et al* investigated surgical resection and found that compared to complete resection, incomplete resection was an independent risk factor for BM in resected LD-SCLC, but not for OS[8]. Of note, the majority patients were combined SCLC patients (53.5%); The factors in multivariate model of BM and OS were different. Therefore, it's unclear whether induction and adjuvant chemo was a risk factor for BM.

17. Brain CT/MRI before PCI: One RCT[7] and 2 retrospective studies[18,21] investigated brain CT vs MRI before PCI and found that it was not a significant risk factor for BM or OS in SCLC with PCI. Meta-analysis was not applicable.

18. PET-CT or not at diagnosis: Choi *et al* investigated with or without PET-CT at staging and found that with initial PET or not did not significantly correlate with first isolated BM, but improved OS. Of note, this study only analyzed BM as a first site of recurrence and characteristics were not balanced between groups. Therefore, it is unclear whether PET-CT at staging was associated with total BM in LD-SCLC.

19. Hospital: Zeng *et al* investigated treating hospital and found it was not a significant risk factor for BM after PCI in SCLC[15].

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Appendix table 7. Summary of the 47 risk factors without meta-analysis

		BM		
		Risk	Non-significant	Unclear
OS	Risk	p-stage, pre-RT KPS, no treatment vs CRT	Laterality,	Weight loss, liver metastasis, pre-treatment NLR, CRT-D, IMRT vs 2D/3D, diagnosis PET-CT or not, EP vs CEV
	Non-significant	LVI, chemo alone vs CRT,	Race, chronic disease, histology, number of metastatic sites, bone metastasis, adrenal metastasis, lung metastasis, anatomical site, KPS, LDH, NSE, CEA, blood glucose, SUVmax, BED, SER, era, treatment intent curative or not, chemo regimen, brain CT vs MRI before PCI	
	Unclear	pre-PCI TLC, pretreatment platelet count	BMI, N-stage, pretreatment TLC, pre-PCI platelet count	Tumor size, response, PCI timing, TRT or not, TRT timing, CRT sequences, TRT fractionation, chemo cycles, adjuvant chemo or not
	No information		Number of extrathoracic metastatic sites, neutrophil count, pre-PCI NLR, CTC, hypertension, hospital.	Surgery;

Abbreviations: BED, biologically effective dose; BM, brain metastasis; BMFS, brain metastasis free survival; BMI, body mass index; CCRT, concurrent chemoradiotherapy; CEA, carcinoembryonic antigen; CEV, cyclophosphamide-epirubicin-vincristine; chemo, chemotherapy; CI, confidence interval; CR, complete response; CRT, chemoradiotherapy; CRT-D: Chemoradiotherapy duration; CT, computerized tomography; CTC, circulating tumor cells; ED, extensive-stage disease; EP, etoposide-platinum; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; IPTW, inverse probability treatment weight; IR, incomplete response; KPS, Karnofsky performance status scale; LD, limited-stage disease; LDH, lactate dehydrogenase; LVI, lymphovascular invasion; MRI, magnetic resonance imaging; NA, not applicable; NI, no information; NLR, neutrophil-to-lymphocyte ratio; NR: Non-response; NSE, neuron-specific enolase; ODRT, once-daily radiotherapy; OR, odds ratio; OS, overall survival; PCI, prophylactic cranial irradiation; PET-CT, positron emission tomography and computed tomography; PLR, platelet-to-lymphocyte ratio; PORT, postoperative radiotherapy; PS, performance status; SCLC, small cell lung cancer; SCRT, sequential chemoradiotherapy; SD, stable disease; SER, start of any treatment until the end of chest irradiation; SHR, subdistribution hazard ratio; SUV, standardized uptake value, tGTV, thoracic gross tumor volume; TRT, thoracic radiotherapy; TDRT, twice-daily radiotherapy; 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy.

Discussion:

Data on risk factors for BM in SCLC are largely lacking, which makes personalized treatment (e.g. shared decision making regarding PCI) difficult. It also impairs the design as well as the interpretation of RCTs evaluating PCI. We identified several factors that were associated with a higher risk of BM: higher T-stage, ED, male sex, and younger age. As has already been reported previously[4,82], we also found that PCI reduced BM incidence significantly, but did not improve OS in ED-SCLC. Of note, most data were derived from studies reporting only development of symptomatic BM since brain imaging before treatment or during follow-

up was rarely performed unless indicated by neurological symptoms, indicating that asymptomatic BM data have been missed; and only two RCTs were at low risk of bias. IPD meta-analysis of RCTs could help revealing more clues.

It is not surprising that ED and higher T stage, which means more advanced tumor load, were risk factors for BM. It is more than interesting to note that compared to M0-M1a, M1b was a risk factor for OS but not for BM in patients with ED-SCLC. This could possibly be explained by the aggressive nature of ED-SCLC per se, resulting in a short OS, making M-status factors less relevant as a risk factor for BM development.

We also found younger age (<65) as a risk factor for BM. This is probably because younger SCLC patients generally live longer[54,78] and therefore have more time to experience BM. Of note, the cut-off value of age varied among studies, but only age<65 have qualified data to perform meta-analysis in our current study.

Similarly, the cut-off value of PS also varied among studies, resulting in that only PS≥2 had qualified data to perform meta-analysis based on two retrospective studies. It showed that worse PS (≥2) tended to be at higher risk for BM. This is conflicting with a secondary analysis of CONVERT trial showing that poorer PS (1-2 vs 0) patients had a lower risk (HR: 0.54; 95% CI: 0.32–0.90; P=0.018) of brain progression[27], likely because they die earlier before developing BM[45,46,77].

We also showed a marginally significant risk for developing BM in males. This is consistent with former reports illustrating that female patients had better prognosis than male, in SCLC[52], NSCLC[83], or other cancer sites[84]. Reasons of this is not clear, but could include lower proliferation indexes[85], lower levels of p-glycoprotein[86,87], more frequently expressed thyroid transcription factor-1 (TTF-1)[88], and sex hormone patterns[84].

Furthermore, we found that PCI reduced BM in SCLC, but did not improve OS in ED-SCLC, which is based on the EORTC phase III trial[5] and the Japanese phase III trial[9]. The conflicting results of these two trials has made PCI in ED-SCLC a reviving area of debates. Details about these two RCTs have been thoroughly discussed in other papers[89,8,59]. Several literature-based meta-analysis reported conflicting OS results after PCI in ED-SCLC[82,90,91]. Differences might be explained by including different studies, although all those meta-analyses included the aforementioned two RCTs. Interestingly, the two RCTs' meta-analysis results of Maeng *et al* were similar with ours (HR=0.93, 95%CI: 0.50-1.71; P=0.81)[82]. This also indicates that inclusion criteria for meta-analysis are very crucial and that pooling retrospective studies with RCTs together could result in misleading conclusions because of the methodological downsides of retrospective studies.

Interestingly, we noticed that the meta-analysis results based on competing risk regression and Cox regression could be different, which indicates that data based on different statistical analysis methods should not be pooled together to perform meta-analysis. In this current study, only PCI dose (≤25Gy vs >25Gy) had qualified data to perform meta-analysis for both regressions. The Cox regression data showed that PCI dose was not a significant risk factor for BM (HR=0.59, 95%CI: 0.26-1.31; P=0.20), while the competing risk regression data showed that higher dose (>25Gy) could prevent BM more effectively (HR=0.74, 95%CI: 0.55-0.99; P=0.04). Of note, both analyses contained the same RCT conducted by Le Pechoux et al[30], in which the results of competing risk regression (HR= 0.76, 95% CI 0.54–1.05, p=0.10) and Cox regression (HR=0.80; 95%CI 0.57–1.11; p=0.18) were similar. It is unknown whether the meta-analysis results of the same trials would be different. We preferred the competing risk result because it treats death without BM as a competing event. We have not found other systematic reviews or meta-analysis answering the same question. IPD meta-analysis is needed to further clarify these data. Since higher dose PCI did not improve OS significantly, we do not recommend increasing the PCI dose, especially because higher PCI dose was associated with a higher risk of cognitive decline[7].

PCI best timing is also unknown. Current guidelines do not have a definite consensus on this issue[89]. We identified six studies which had investigated PCI timing[27,71,74-77]. The RCT showed that PCI timing was not a significant risk factor for BM or OS in LD-SCLC[27]. Two retrospective studies showed that early PCI was more effective to reduce BM[71,74], but three others showed the opposite[75-77]. As studies investigated PCI timing in different ways, and the definitions of "early" were also different, there were no qualified data to perform meta-analysis. Therefore, it remains unclear what the best PCI timing is. More RCTs or meta-analysis of RCTs are warranted to further answer this question.

Similarly, four RCTs[31-33,65] and three retrospective studies[60,77,80] have reported the impact of TRT timing on BM with different definitions of "early TRT", which made the meta-analysis not applicable. Therefore, it is unclear whether TRT timing is a risk factor for BM. However, it has already been shown in an IPD meta-analysis that early TRT (within 30 days after the start of chemotherapy) improves OS (2-year survival: OR: 0.73, 95% CI 0.51-1.03, P = 0.07; 5-year survival: OR: 0.64, 95% CI 0.44-0.92, P = 0.02)[92]. Consequently, most guidelines recommend starting TRT at the 1st or 2nd cycle of chemotherapy[89].

It is well known that risk of bias assessment is very important in systematic reviews and meta-analyses. We assessed the risk of bias for RCTs using the RoB2 tool and noticed that it has its limitations. It assesses the process of data collection and data report, but does not assess

the methods of data analysis. However, inappropriate analysis can lead to different/misleading conclusions. It also does not evaluate trials closed earlier, which results in much less powerful conclusions. Therefore, improvement of the RoB2 tool is needed to assess the risk of bias more thoroughly and help to improve the design of RCTs.

As for the non-RCTs, Wells *et al* proposed the Newcastle-Ottawa-Scale (NOS) for assessing the quality in a website rather than in a peer-reviewed journal[93]. Till now, NOS has been widely used and tends to become more and more popular for non-RCTs in meta-analysis. However, a discussion in depth showed that the NOS has unknown validity and using this score may produce arbitrary results[94]. Lo *et al* also found that the assessment between reviewers and authors of the studies were very different[95]. Interestingly, many studies that used the NOS cited this critical discussion instead of the original web-based link[96-99], suggesting that researchers were using the problematic tool even though they were aware of the limitations.

The Cochrane community recommends Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for assessing the risk of bias in non-RCTs of interventions[100]. However, in our study, the baseline characteristics and tumor-related factors are not interventions, so, ROBINS-I is not appropriate as well. In addition, since most of the included RCTs were at high risk of bias and all the RCTs in which BM was the primary endpoint did not perform regular brain imaging examination during follow-up, we decided not to perform risk of bias assessment for non-RCTs because the additional work would not add much value to the current study.

Additionally, current risk of bias assessment tools mainly assesses risk of bias per study. This is fine for studies that mainly investigate interventions. However, as a meta-analysis aiming to identify all related risk factors, it is necessary to assess risk of bias per factor in each study. Therefore, we assessed the quality of data per factor mainly focusing on the analysis methods in each study and summarized the possible problems in the comments. In this way, readers can interpret the results clearly.

To our knowledge, this is the first systematic review and meta-analysis to identify risk factors for BM in SCLC. Most current meta-analyses focused on one aspect, such as PCI or not in SCLC[101], ED-SCLC[82,90], and resected SCLC[102]. Chen *et al* conducted a meta-analysis to identify risk factors for BM in NSCLC[97]. Unfortunately, they only searched observational studies instead of RCTs. They used odds ratio (OR) rather than HRs to measure the effects. Therefore, the conclusions of this study were not comparable to this current study of identifying risk factors for BM in SCLC. We suggest a well design following the PRISMA guideline and Cochrane handbook before jumping into meta-analysis by simply pooling everything together.

In addition, we firstly used a simple and effective method to assess the quality of data before pooling everything together to perform meta-analysis. That is, only studies of the same type using the same method with proper statistical analysis should be pooled together under the premise that the patients belonged to the same category. This will avoid misleading conclusions based on heterogeneous data.

Furthermore, we noticed that many studies retrieved in our search (46, among which 17 were RCTs) did not report BM related outcomes. Moreover, brain imaging is often lacking in the published studies. To evaluate BM risk factors better, it is very crucial to document baseline characteristics, treatment, as well as adequate and regular brain imaging. Brain imaging should be preferably MRI, as this is the best imaging modality to detect asymptomatic BM. Regular brain imaging is important in clinical trials, as even after a negative baseline brain MRI, in a study by Manapov *et al*, the second cranial MRI after completion of chemoradiotherapy revealed asymptomatic BM in 11/40 (32.5%) LD-SCLC complete responders[103]. In some RCTs[9,26,28,30,33], MRI was indeed scheduled at specified time points, but it was in general not reported whether these time points were adhered to, which might influence the results. In this current study, only one RCT reported the MRI compliance indirectly. Current trials on SCLC patients without BM are assessing if MRI surveillance could be non-inferior to (hippocampal-avoidance)-PCI in terms of both OS and neurotoxicity[104,105], in which the regular brain imaging are scheduled. Hope they will also report the compliance data.

We also noticed that many studies which reported BM data did not report OS data. This hampers the interpretation of clinical significance. For example, if a factor (A) is a risk for BM but not for OS, a factor (B) is a risk for both BM and OS, while another factor (C) is a risk for BM but unknown for OS, clinicians will put much higher weight on considering factor B and much less weight on considering C when making an individualized management strategy. Therefore, we suggest researchers report OS data as well when reporting BM data to enhance the clinical application value.

Conclusion:

In conclusion, multiple studies evaluated risk factors for SCLC BM, but limited data was qualified to perform a meta-analysis. We found that younger age, higher T stage, and ED were risk factors for BM; suggesting that PCI should be especially discussed in such cases and shared decision making is necessary; and higher PCI dose is not necessary. IPD meta-analysis and well-designed RCTs with high quality data are needed to identify more risk factors such as blood biomarkers, and further confirm our findings. Regular MRI with contrast-enhancement

before PCI and during follow-up is helpful to detect asymptomatic BM, especially for patients with high risks for BM. The MRI compliance at each pre-specified time point should also be reported in prospective trials. Better collaboration with statisticians is needed in future studies. We suggest amendment of the ROB2 tool to assess the statistical methods as well.

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Conflict of interests

None related to this manuscript.

Author contributions

HZ, DDR, and LH conceived this study. HZ and DDR searched papers in Pubmed. HZ and DZ screening the papers from titles to full texts, extracted the data, and assessed the risk of bias; LH checked the screening, extraction and assessments. HZ, WW, and RH analyzed the results. DDR and LH supervised the whole process. HZ, LH and DDR draft the manuscript, AL, AT, WW, RH, FMK, and DZ revised it.

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Chapter 4

The association of gross tumor volume and its radiomics features with brain metastases development in patients with radically treated stage III non-small cell lung cancer

Zeng H, Tohidinezhad F, De Ruysscher DKM, Willems Y, Degens JHRJ, van Kampen-van den Boogaart VEM, Pitz C, Cortiula F, Brandts L, Hendriks LEL, Traverso A.

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Abstract:

Purpose: To identify which model, based on clinical risk factors, gross tumor volume (GTV) radiomics features, and both, is superior in predicting brain metastases (BM) in patients with radically treated stage III non-small cell lung cancer (NSCLC).

Methods: Clinical data and planning computed tomography (CT) scans for thoracic radiotherapy were retrieved from patients with radically treated stage III NSCLC treated in five hospitals between 2012-2021. Radiomics features were extracted for the GTV, primary lung tumor (GTVp), and involved lymph nodes (GTVn), separately. Backward stepwise competing risk analysis was used to develop models (clinical, radiomics, and combined model). Bootstrapping samples with 1000 iterations and least absolute shrinkage and selection operator (LASSO) regression was performed to select radiomics features and train models. Area under the receiver operating characteristic curves (AUC-ROC), calibration were performed to assess the models' performance. Decision-curve and nomograms were developed for clinical utility.

Results: In total, 310 patients were eligible. Within a median follow up of 51.3 months (95% CI 43.0-59.7 months), 176 (56.8%) patients died, 52 (16.8%) developed BM. GTV, GTVn, GTVp were available in 282, 254, and 260 patients, respectively. Sixteen clinical variables and 861 radiomics features were analyzed. Three clinical variables (age, NSCLC subtype, and GTVn) and five radiomics features from each radiomics model were significantly associated with BM. Radiomic features measuring tumor heterogeneity extracted from the tumor volumes were the most relevant. The AUCs and calibration curves of the models showed that the GTVn radiomics model had the best performance (AUC: 0.74; 95%CI: 0.71-0.86; Sensitivity: 84%; Specificity: 61%; positive predictive value [PPV]: 29%; negative predictive value [NPV]: 95%; Accuracy: 65%).

Conclusion: Age, NSCLC subtype, and GTVn were significant clinical factors associated with BM development in patients with stage III NSCLC. GTVn radiomics features provided higher predictive value than GTVp and GTV for BM development. GTVp and GTVn should be separated in clinical and research practice.

Keywords: Non-small cell lung cancer (NSCLC), brain metastases (BM), gross tumor volume (GTV), radiomics, thoracic radiotherapy.

Introduction:

Up to 30% of patients with stage III non-small cell lung cancer (NSCLC) receiving radical chemoradiotherapy will develop symptomatic brain metastases (BM) during the course of their disease[1]. Identifying risk factors for BM can help improve the management of these patients. Known risk factors are female sex, adenocarcinoma or non-squamous cell carcinoma histology, advanced tumor stage[2-4]. Whether a higher gross tumor volume (GTV) is a risk factor for subsequent BM development remains unclear. It has been reported that GTV is a prognostic factor for locoregional control[5], progression-free survival (PFS)[6], and OS[6-9] in patients with NSCLC. *Ji et al* found that GTV is not a significant risk factor for BM in patients with NSCLC (N=335, p=0.687)[10], whereas a larger GTV was associated with an increased risk of BM in patients with small-cell lung cancer (SCLC) (hazard ratio [HR]=1.37, 95% confidence interval [CI] 1.09-1.73, $p = 0.007$)[11].

Radiomics is increasingly being used in cancer risk prediction[12,13] and is, based on the seed-and-soil hypothesis, also of interest to evaluate in stage III NSCLC (primary tumor and/or involved lymph nodes) and in the BM prediction setting [14]. It is a quantitative imaging analysis technique that provides image-derived metrics capable of quantifying textures at a higher granularity, beyond the ability of the naked eye. Four studies showed that radiomic models based on pretreatment computed tomography (CT) might predict BM in NSCLC, but the models did not always add value to clinical models [15-19]. Important limitations of these studies were: small sample sizes, inadequate baseline staging, only evaluating the primary tumor and not the involved lymph nodes, and the use of heterogeneous CT protocols. Thus, it is difficult to draw firm conclusions.

According to the backgrounds and rationales above, we conducted the current study to explore risk factors and develop prognostic models for BM in radically treated stage III NSCLC. We used a large dataset with adequately staged patients (baseline ^{18}F-labeled fluorodeoxyglucose positron emission tomography–CT scan [[18]FDG-PET-CT] and brain magnetic resonance imaging [MRI]) and evaluated clinical data together with radiomics features of GTVs on the uniformly scanned planning contrast-enhanced chest CT for thoracic radiotherapy.

Patients and Methods:

Patients with stage III NSCLC were retrospectively screened in five hospitals in the Netherlands and Italy (MUMC, Zuyderland, Venlo, Roermond, Udine) from 01.03.2012 to 31.07.2021. AJCC 7th edition was used for staging[20]. Eligibility criteria for this study included:

pathologically confirmed NSCLC, [18]FDG-PET-CT and brain MRI performed at baseline (before antitumor therapy), treatment with chemoradiotherapy with radical intent (concurrent or sequential chemoradiotherapy, CCRT/SCRT). Exclusion criteria were: participation in interventional clinical trials (NVALT-11 trial [because of prophylactic cranial irradiation [PCI] administration in one arm][1], PET-boost trial [because of radiotherapy dose-escalation][21], and NICOLAS trial [because of nivolumab] [22], other malignancy within 5 years before NSCLC diagnosis; surgery for NSCLC before chemoradiotherapy, and a total irradiation dose (TD) <54Gy. Proton therapy, all types of platinum doublet chemotherapy and adjuvant durvalumab were allowed. This study was conducted in accordance with the Helsinki Declaration of the World Medical Association and approved by the institutional review boards (W 22 01 00010). Informed consent from individuals for the use of their medical data was waived because no additional interventions were performed.

Acquisition of images:

The original planning CTs were retrieved from the clinical workstation database. All the images were acquired with contrast enhancement and with a slice thickness of 3 mm with consistent acquisition parameters on the two scanner manufacturers (Philips or SIEMENS). The pixel spacing varied from a minimum of 0.976 mm to a maximum of 1.52 mm in the X and Y directions.

Delineation of regions of interest (ROI) / GTV:

The ROIs were the original GTVs obtained from the planning CT scan. The GTVs were delineated by a team of specialists in lung cancer radiotherapy in each slice of the planning CT based on the most recent [18]FDG-PET information using the ARIA workstation (Varian, Palo Alto, CA). GTV of the primary tumor (GTVp) and lymph nodes (GTVn) were delineated separately if anatomically distinguishable. When it was difficult to distinguish the primary tumor or lymph nodes, the tumor was contoured as either GTVp or GTVn (the choice was left to experienced radiation oncologist). GTV was calculated as the morphological union of GTVp and GTVn. The lung window setting (W=200HU and L=-1000 HU [Hounsfield Units]) was used to contour tumors surrounded by lung tissue and the mediastinum window setting (W=220HU and L= -180 HU) was applied for the contouring of lymph nodes and primary tumors invading the mediastinum or chest wall[23]. The contouring of each patient was confirmed by a senior radiation oncologist (experience >10 years).

GTV radiomics features extraction:

The pipeline for radiomic feature extraction consisted of the following steps: data conversion and pre-processing, radiomic extraction configuration and feature extraction. The data conversion was performed using an in-house Python script that converts the original DICOM and RTSTRUCT images into the .nrrd format that is mineable by pyradiomics. The Python packages simpleITK v2.1 and pyplastimatch v1.9.3 were used to convert the original DICOM CT images and the contours GTV, GTVp, GTVn into .nrrd images and corresponding binary masks. The radiomic extraction configuration included the following operations: re-sampling of the original images to the same pixel spacing of [1,1,1] using B-spline interpolation, removal of outliers from the binary masks above 3σ from the distribution of intensity values for each patient, application of wavelet filtering in all the 13 directions to generate wavelet features. The following feature categories were extracted from both original and wavelet-filtered images: first order statistical features, and texture feature matrixes (GLCM, GLSZM, GLRLM, NGTDM). Morphological features were extracted only from the original images. The fixed-bin width approach (N=25) was chosen for the quantization of statistical and texture features. The details of the source code are published on a public repository (https://github.com/Maastro-CDS-Imaging-Group/GTVNSCLC). The features were normalized to Z-score, as is common practice in statistical analyses.

Clinical and treatment-related variables:

In addition to GTV, other potential factors for BM were also recorded and investigated, including age, sex, smoking history, body mass index (BMI), performance status (PS), histology type, TNM stage at diagnosis; chemoradiotherapy type (concurrent or sequential chemoradiotherapy, CCRT/SCRT), total dose of radiotherapy, type of radiotherapy (once-daily radiotherapy, ODRT; twice-daily radiotherapy, TDRT/mix [TDRT+ODRT]), and immunotherapy.

Statistics:

Missing data of the clinical variables were imputed by multiple imputation. Then, GTV, GTVn, and GTVp were divided into three categories by interquartile range (IQR) for risk analysis. The primary endpoint was BM confirmed by cranial imaging at any time regardless of presence of neurologic symptoms (e.g., headache or vomiting). The secondary endpoints were PFS (progression of disease at the first time in any sites confirmed by imaging or death) and OS. All endpoints were analyzed as time-to-event data from the pathological diagnosis to

the respective events, which were subject to censoring at the last follow-up if no events were observed. The BM analyzed using competing risk analysis, in which death without BM was treated as a competing event. The significant clinical risk factors (including volume of GTVs, which was excluded from the radiomic features analysis) for BM were identified using the multivariate Fine-Gray model with backward stepwise elimination[24,25].

Radiomic feature selection was performed using 1000 bootstrap resamples[26-28]. Within each of the 1000 bootstrap resamples, Spearman's correlation was performed to identify and eliminate the highly correlated features ($|r| > 0.9$). Then, the least absolute shrinkage and selection operator (LASSO) embedded with the Fine-Gray model was used to select features (lambda=0.01). The features were sorted according to how frequently they were retained by LASSO in 1000 bootstrap resamples. We arbitrarily selected the top 13 features as the input for the backward stepwise competing risk model on the same 1000 bootstrap resamples. Then, we arbitrarily selected the top signature (more than one radiomic feature) to build the radiomic models. The coefficients were fitted using the original sample. A maximum number of five predictors was considered for each model to reduce the risk of overfitting. To build the combined model, one feature with the highest effect estimate (according to subdistribution hazard ratio[sHR]) from each model (Clinic + GTV + GTVp + GTVn) was selected.

The performance of competing-risk models at the 24-months' time point was evaluated by area under the receiver operating characteristic curves (AUC-ROC) and calibration. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of each model was also reported. The net-benefit decision-curve analysis (DCA) was performed to compare the models' utility/application value[26]. A nomogram would be developed for the clinical model. If the radiomics model or combined model performed better, a nomogram would also be developed for the best one[28] (Figure 1). The time point of 24-months was chosen because most of BM develop within 2 years[1].The effect of significant BM risk factors (features) on PFS and OS were investigated by Cox proportional hazards regression models. All tests were 2-sided, and $p < 0.05$ were considered as statistically significant. Statistical analyses were performed using R version 4.2.2 (R Project for Statistical Computing).
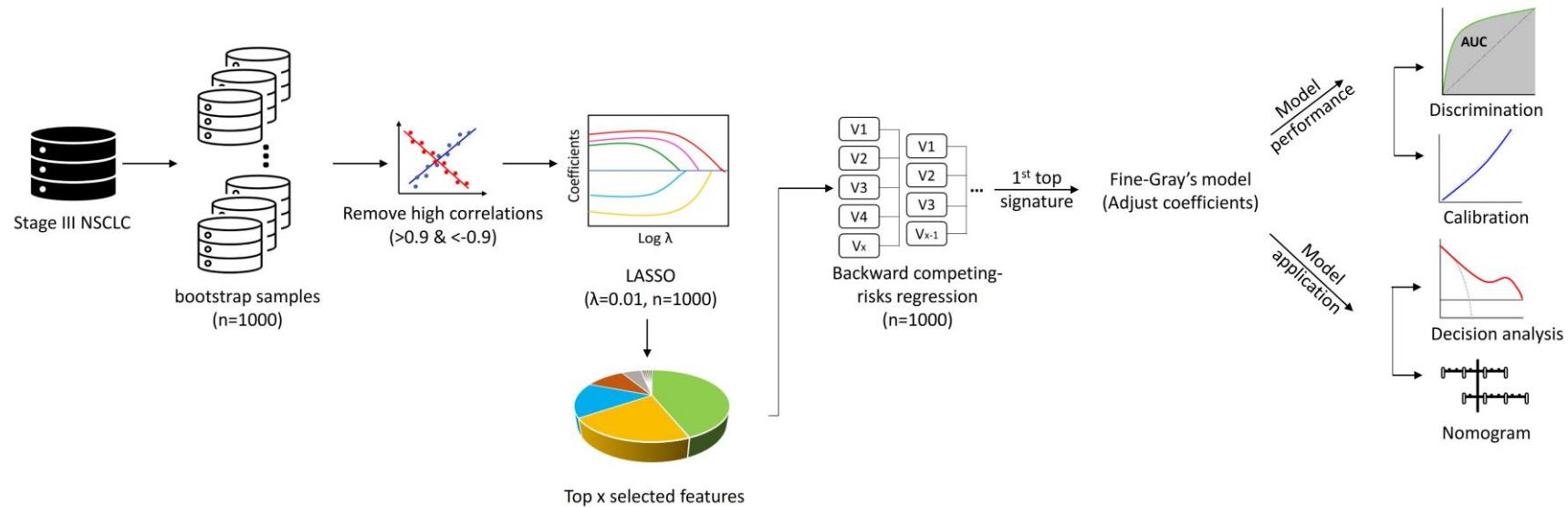
Figure 1. Analysis pipeline of radiomics models
This figure shows the analysis pipeline for development and evaluation of the radiomics prediction models:
I, resample by 1000 bootstrap;
II, eliminate highly correlated features;
III, select features by LASSO regression embedded with the Fine-Gray model;
IV, select top features retained by LASSO in 1000 bootstrap resamples;
V, evaluate the features' associations with BM using backward stepwise competing risk model;
VI, select the top signatures to build the radiomic models using the original sample;
VII, evaluate the performance of the models by AUC and calibration curve;
VIII, evaluate the utility of the models by the net-benefit decision-curve analysis;
IX, develop a nomogram for the best model.
Abbreviations: AUC, area under the receiver operating characteristic curves; LASSO, least absolute shrinkage and selection operator; NSCLC, non-small cell lung cancer.

This type 2A study was conducted according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guideline[29]. The TRIPOD checklist was reported in Appendix Table 1.

Section/Topic	Item	Checklist Item	Page
Appendix Table 1. TRIPOD Checklist: Prediction Model Development			
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2-3
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	3
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	3
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	3
	5b	Describe eligibility criteria for participants.	3
	5c	Give details of treatments received, if relevant.	3
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	3-5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	3
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	5
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5-6, Fig1
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6, Fig 2
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6, Table 1
Model development	14a	Specify the number of participants and outcome events in each analysis.	6-7
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	NA

Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6-7. Table 2-3
	15b	Explain how to the use the prediction model.	7,Fig 3
Model performance	16	Report performance measures (with CIs) for the prediction model.	7
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	10-11
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	8-11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	10
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	5
Funding	22	Give the source of funding and the role of the funders for the present study.	Title page

Results:

In total, 310 out of 524 patients were eligible, 282 of the 310 patients had available DICOM images for radiomic analysis (260 had GTVp, 254 had GTVn, 231 had GTVp+GTVn) (CONSORT diagram in Figure 2). Twenty-one patients had indistinguishable GTVp/GTVn, of which 12 were contoured as GTVn, nine as GTVp. Among the 310 patients, 54.5% were male, 51.6% had stage IIIA, and 37.4% had squamous-cell carcinoma (SCC), the median GTV was 71.2 (IQR: 35.2-115.2) cm^3, the median GTVn was 16.4 (IQR: 0.88-244.1) cm^3 and the median GTVp was 41.4 (IQR: 9.8-89) cm^3 (Table 1). The median follow-up was 51.3 months (95% CI: 42.9-59.7 months), during which 176 (56.8%) patients died, 183 (59.0%) progressed, and 52 (16.8%) developed BM. The median OS was 34.8 months (95% CI: 28.4-41.2 months) and the median PFS was 19.3 months (95% CI: 15.1-23.5 months). For the 52 patients who developed BM, the median time to BM diagnosis was 10.5 months (95% CI: 9.2-11.9 months), the BM incidence at 2-year was 14.5%.
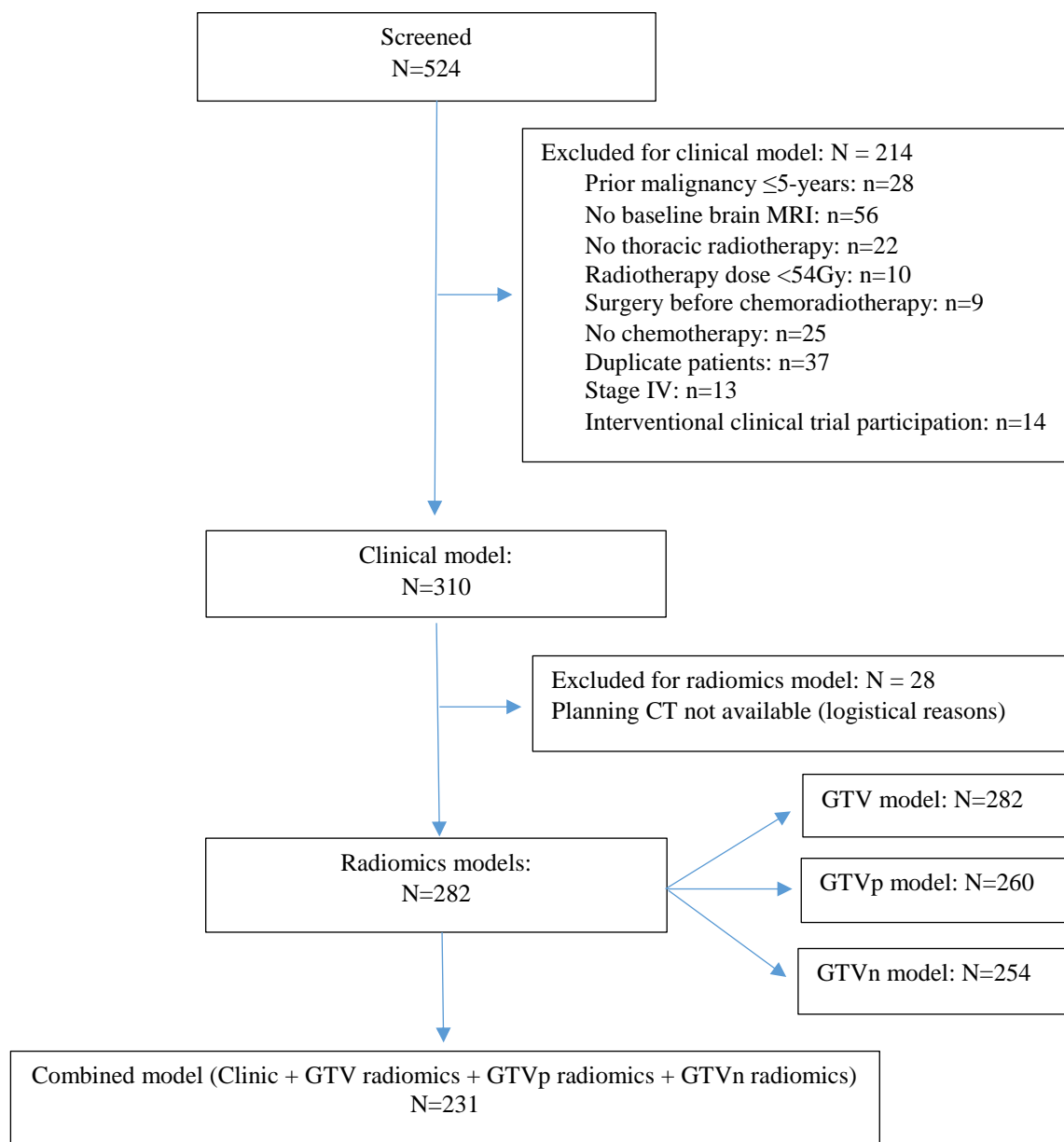
Figure 2. CONSORT diagram.

This diagram shows the patients screening and available sample size for each model.
Abbreviations: CT, computed tomography; GTV, gross tumor volume; GTVp, GTV of the primary tumor; GTVn, GTV of the involved lymph nodes; MRI, magnetic resonance imaging.

Table 1. Patients characteristics (N=310)

Characteristics	Number (%)	Characteristics	Number (%)
Age		Squamous-cell	116 (37.4)
Mean ± SD	65.7 ± 8.4	Non-Squamous-cell	194 (62.6)
≤60	80 (25.8)	Chemoradiotherapy	
>60	230 (74.2)	Concurrent	277 (89.4)
Male gender	169 (54.5)	Sequential	33 (10.6)
Body mass index-kg/m^2		Type of radiation	
Normal (18.5-24.9)	137 (44.2)	OD	205 (66.1)
Underweight (<18.5)	13 (4.2)	TD/TD+OD	105 (33.9)
Overweight (25.0-29.9)	113 (36.5)	Total dose (Gy)	
Obese (≥30)	47 (15.2)	≤66	226 (72.9)
Smoking		>66	84 (27.1)
Never/Former	174 (56.1)	Adjuvant immunotherapy	84 (27.1)
Current	136 (43.9)	GTV (cm^3)	
Performance status		Median (range)	71.2 (4.3 - 1252.8)
0	123 (39.7)	<35.2	78 (25.2)
1	160 (51.6)	35.2-115.2	153 (49.4)
2-3	27 (8.7)	>115.2	79 (25.5)
TNM_T		GTVn (cm^3)	
0/X/1/2/3	171 (55.2)	Median (range)	16.4 (0 -244.1)
4	139 (44.8)	<6	78 (25.2)
TNM_N		6-36.4	154 (49.7)
0-1	38 (12.3)	>36.4	78 (25.2)
2	210 (67.7)	GTVp (cm^3)	
3	62 (20.0)	Median (range)	41.4 (0 - 1195.6)
Stage		<9.8	78 (25.2)
IIIA	160 (51.6)	9.8-89	154 (49.7)
IIIB	150 (48.4)	>89	78 (25.2)
Histology			

Abbreviations: GTV, gross tumor volume; GTVp, gross tumor volume-primary lung tumor; GTVn, gross tumor volume-metastatic lymph nodes; ODRT, once-daily radiotherapy; SD, standard deviation; TDRT, twice-daily radiotherapy.

BM risk models:

The clinical model identified three significant factors associated with BM: a higher age (>60 years) was protective (sHR 0.56, 95%CI 0.32- 0.99, p = 0.05), while non-squamous histology (sHR 2.64, 95%CI 1.28 - 5.46, p = 0.009), and a larger GTVn (median IQR: sHR 3.76, 95%CI 1.33-10.61, p = 0.012; upper IQR: sHR 3.86, 95%CI 1.28-11.65, p = 0.017) were associated with an increased risk. GTV, GTVp, the use of adjuvant durvalumab, and other clinical variables were not significantly associated with BM development (Table 2).

We extracted 861 radiomic features in total and identified five GTV features, five GTVn features, and five GTVp features that were associated with BM (Table 2). The combined model of the 1st top feature from each model showed that the GTVn radiomics feature (LLH glrlm Run Variance: sHR 1.53, 95%CI 1.05 - 2.24, $p = 0.028$) and the GTVp radiomics feature (HLH glszm Grey Level Non Uniformity: sHR 1.52, 95%CI 1.29 - 1.79, $p < 0.001$) were significantly associated with an increased risk of BM development, while the clinical variable (volume of GTVn) and GTV radiomics feature were not (Table 2).

Table 2. BM competing risk models

	sHR	95% CI	*p*
Clinical model (n=310, 52 BM)			
Age (>60 vs ≤60)	0.56	0.32 - 0.99	**0.045**
Histology (Non - Squamous vs squamous)	2.64	1.28 - 5.46	**0.009**
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	3.76	1.33 - 10.61	**0.012**
>36.4	3.86	1.28 - 11.65	**0.017**
GTV radiomic model (n=282, 46 BM)			
HLH firstorder Median	0.63	0.50 - 0.78	**<0.001**
HLH glcm Imc1	1.72	1.13 - 2.61	**0.011**
Original firstorder Skewness	1.39	1.17 - 1.64	**<0.001**
Original glszm Zone Entropy	0.66	0.50 - 0.87	**0.003**
HHH glszm Small Area Emphasis	1.66	1.17 - 2.35	**0.004**
GTVn radiomic model (n=254, 44 BM)			
LLH glrlm Run Variance	1.77	1.26 - 2.48	**0.001**
HLH glcm Imc1	1.67	1.14 - 2.46	**0.009**
HLH glszm Small Area Low Grey Level Emphasis	0.58	0.38 - 0.89	**0.012**
LLH glszm Size Zone Non Uniformity Normalized	1.54	1.27 - 1.87	**<0.001**
HHL glszm Grey Level Non Uniformity Normalized	0.67	0.48 - 0.93	**0.018**
GTVp radiomic model (n=260, 39 BM)			
LHH glszm Small Area Low Grey Level Emphasis	1.66	1.29 - 2.14	**<0.001**
LLH glcm Cluster Shade	1.40	1.10 - 1.80	**0.007**
HLH glszm Grey Level Non Uniformity	1.90	1.58 - 2.29	**<0.001**
HLL firstorder Root Mean Squared	0.62	0.43 - 0.90	**0.013**
LLL glcm Imc1	1.93	1.06 - 3.51	**0.032**
Combined model (n=231, 37 BM)			
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	3.09	0.68 - 13.98	0.143
>36.4	2.49	0.50 - 12.53	0.268
GTV HLH glcm Imc1	1.33	0.82 - 2.16	0.242
GTVn LLH glrlm Run Variance	1.53	1.05 - 2.24	**0.028**
GTVp HLH glszm Grey Level Non Uniformity	1.52	1.29 - 1.79	**<0.001**

Abbreviations: BM, brain metastases; CI, confidence interval; GTV, gross tumor volume; GTVp, gross tumor volume-primary lung tumor; GTVn, gross tumor volume-metastatic lymph nodes; SD, standard deviation; sHR, subdistribution hazard ratio.

Evaluation of the models' performance

The AUCs at each time point showed that the GTVn radiomics model performed best to discriminate the patients that did and did not develop BM (AUC range: 0.71-0.74) (Figure 3A). At 24-months, the GTVn radiomics model had the highest AUC (0.74, 95%CI: 0.71-0.86), sensitivity (84%), and the NPV (95%); the GTVp radiomics model has the highest specificity (80%), PPV (34%), and accuracy (76%) (Table 3). The calibration plot also visually showed that the GTVn radiomic model had the best calibration within 24-months (Figure 3B). The decision curve analysis showed that compared with the other models, the GTVn radiomic model provided a better net benefit for the threshold probabilities smaller than 0.3 (Figure 3C). Therefore, a nomogram was developed for the clinical model (Figure 3D) and the GTVn radiomics model (Figure 3E), respectively.
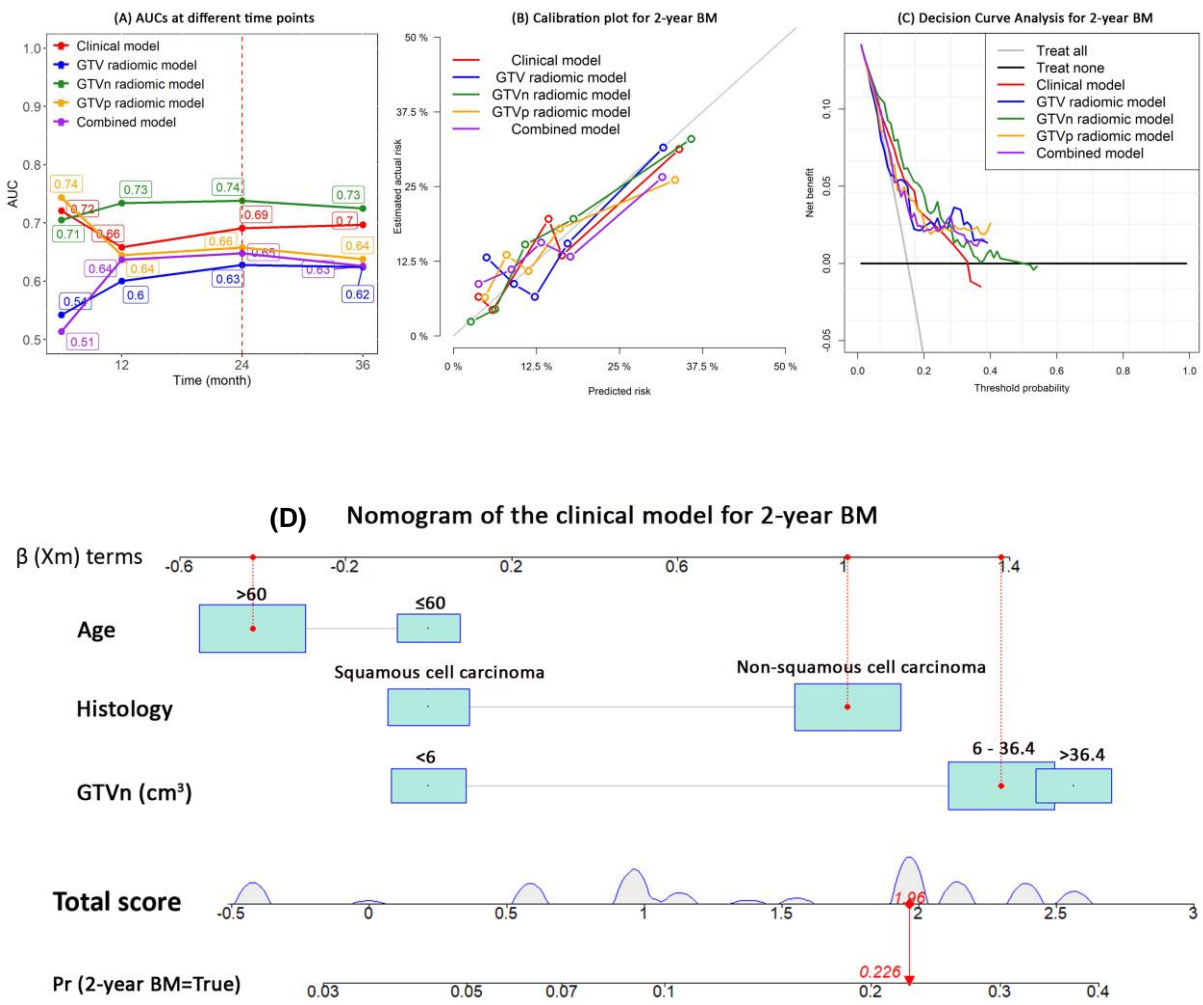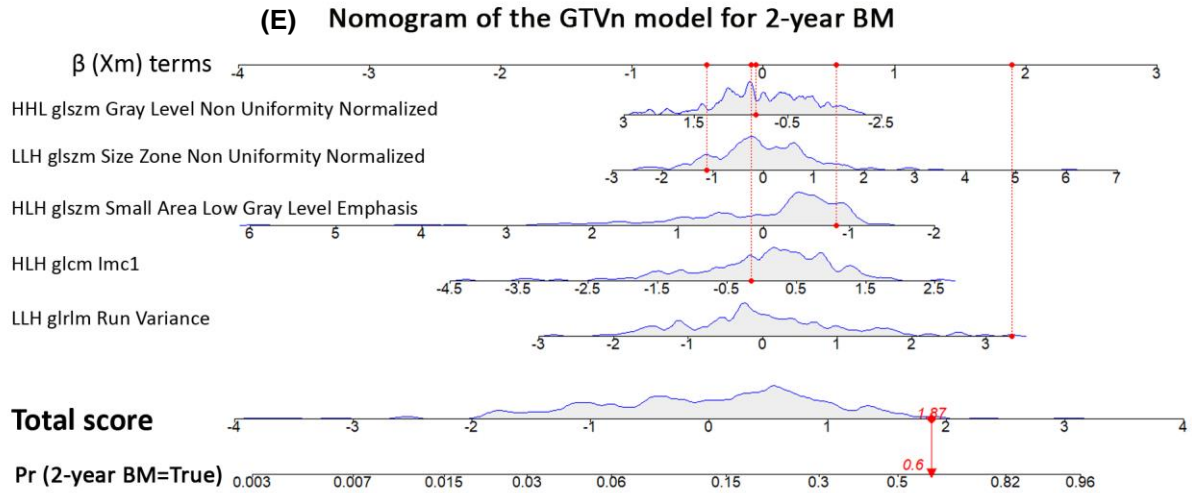
Figure 3. Models performance and nomogram.

This figure shows the performance of the competing risk models for BM development in patients with radically treated stage III NSCLC (clinical, GTV, GTVn, GTVp, and combined models): (A) AUC; (B) Calibration plots; (C) Net-benefit decision curves; (D) nomogram of the clinical model; (E) nomogram of the GTVn radiomics model. *Abbreviations:* AUC, area under the receiver operating characteristic curves; BM, brain metastases; GTV, gross tumor volume; GTVp, GTV of the primary tumor; GTVn, GTV of the involved lymph nodes; NSCLC, non-small cell lung cancer.

Table 3. Model Performance at 24-months

Models	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Accuracy
Clinical	0.69 (0.66 - 0.82)	59%	77%	33%	91%	74%
GTV	0.63 (0.57 - 0.77)	65%	67%	27%	91%	67%
GTVn	0.74 (0.71 - 0.86)	84%	61%	29%	95%	65%
GTVp	0.66 (0.62 - 0.81)	54%	80%	34%	90%	76%
Combined	0.65 (0.60 - 0.78)	70%	60%	25%	91%	62%

Abbreviations: GTV, gross tumor volume; GTVp, gross tumor volume-primary lung tumor; GTVn, gross tumor volume-metastatic lymph nodes; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

OS, PFS

The above factors and radiomics features were checked for their impact on PFS and OS. A larger GTVn was significantly associated with decreased OS (median IQR: HR 1.49, 95%CI 1.01-2.21, $p = 0.045$; upper IQR: HR 2.32, 95%CI 1.50-3.59, $p < 0.001$) and PFS (median IQR: HR 1.93, 95%CI 1.30-2.85, $p = 0.001$; upper IQR: HR 2.08, 95%CI 1.31-3.30, $p = 0.002$). Patients with non-squamous carcinoma were at higher risk for progression (HR 1.35, 95%CI 1.00 - 1.83, $p = 0.05$), but no significant association with OS was found. Age was not significantly correlated with OS or PFS (Appendix Table 2-3).

All the five GTV radiomics features were not correlated with OS. HLH firstorder Median of the GTV was correlated with PFS (HR 0.87, 95%CI 0.78 -0.98, $p = 0.02$) (Appendix Table

2-3).

LLH glrlm Run Variance (HR 1.20, 95%CI 1.04-1.39, *p* = 0.016) and HLH glszm Small Area Low Grey Level Emphasis of the GTVn (HR 0.78, 95%CI 0.63-0.97, *p* = 0.026) was associated with OS, but not PFS (Appendix Table 2-3).

LLL glcm Imc1 of GTVp was correlated with OS (HR 1.32, 95%CI 1.09-1.60, *p* = 0.005) and PFS (HR 1.38, 95%CI 1.15-1.65, *p* = 0.001). HLH glszm Grey Level Non Uniformity of

Appendix Table 2. Overall survival Cox models

	HR	95% CI	*p*
Clinical model (n=310, 176 death)			
Age (>60 vs ≤60)	1.44	0.98 - 2.11	0.066
Histology (Non - Squamous vs squamous)	1.08	0.79 - 1.46	0.645
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	1.49	1.01 - 2.21	**0.045**
>36.4	2.32	1.50 - 3.59	**<0.001**
GTV radiomic model (n=282, 168 death)			
HLH firstorder Median	1.00	0.91 - 1.11	0.977
HLH glcm Imc1	1.08	0.91 - 1.28	0.392
Original firstorder Skewness	0.95	0.81 - 1.12	0.55
Original glszm Zone Entropy	1.19	0.98 - 1.43	0.081
HHH glszm Small Area Emphasis	1.01	0.85 - 1.18	0.95
GTVn radiomic model (n=254, 158 death)			
LLH glrlm Run Variance	1.20	1.04 - 1.39	**0.016**
HLH glcm Imc1	1.01	0.86 - 1.20	0.873
HLH glszm Small Area Low Grey Level Emphasis	0.78	0.63 - 0.97	**0.026**
LLH glszm Size Zone Non Uniformity Normalized	1.03	0.88 - 1.20	0.717
HHL glszm Grey Level Non Uniformity Normalized	1.04	0.88 - 1.23	0.648
GTVp radiomic model (n=260, 153 death)			
LHH glszm Small Area Low Grey Level Emphasis	1.15	0.96 - 1.39	0.132
LLH glcm Cluster Shade	1.02	0.88 - 1.18	0.83
HLH glszm Grey Level Non Uniformity	1.17	1.00 - 1.37	**0.047**
HLL firstorder Root Mean Squared	0.97	0.79 - 1.20	0.797
LLL glcm Imc1	1.32	1.09 - 1.60	**0.005**
Combined model (n=231, 142 death)			
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	1.10	0.67 - 1.78	0.716
>36.4	1.70	0.94 - 3.09	0.081
GTV HLH glcm Imc1	1.05	0.85 - 1.29	0.655
GTVn LLH glrlm Run Variance	1.12	0.93 - 1.35	0.23
GTVp HLH glszm Grey Level Non Uniformity	1.17	1.02 - 1.33	**0.023**

Abbreviations: BM, brain metastases; CI, confidence interval; GTV, gross tumor volume; GTVp, gross tumor volume-primary lung tumor; GTVn, gross tumor volume-metastatic lymph nodes; HR, hazard ratio; SD, standard deviation.

GTVp was correlated with OS (HR 1.17, 95%CI 1.00-1.37, *p* = 0.047) but not PFS. LLH glcm Cluster Shade of GTVp was correlated with PFS (HR 1.16, 95%CI 1.02-1.33, *p* = 0.026) but not OS. (Appendix Table 2-3).

The combined model showed that HLH glszm Grey Level Non Uniformity of GTVp was correlated with OS (HR 1.17, 95%CI 1.02-1.33, *p* = 0.023) but not PFS. GTVn was associated with PFS (median IQR: HR 1.63, 95%CI 0.99-2.69, *p* = 0.054; upper IQR: HR 2.37, 95%CI 1.28-4.38, *p* = 0.006) but not OS (Appendix Table 2-3).

Appendix Table 3. Progression-free survival Cox models

	HR	95% CI	*p*
Clinical model (n=310, 183 progression)			
Age (>60 vs ≤60)	1.12	0.78 - 1.63	0.537
Histology (Non - Squamous vs squamous)	1.35	1.00 - 1.83	0.054
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	1.93	1.30 - 2.85	**0.001**
>36.4	2.08	1.31 - 3.30	**0.002**
GTV radiomic model (n=282, 167 progression)			
HLH firstorder Median	0.87	0.78 - 0.98	**0.02**
HLH glcm Imc1	1.06	0.90 - 1.25	0.51
Original firstorder Skewness	1.07	0.89 - 1.27	0.494
Original glszm Zone Entropy	1.02	0.86 - 1.22	0.787
HHH glszm Small Area Emphasis	1.05	0.90 - 1.23	0.531
GTVn radiomic model (n=254, 156 progression)			
LLH glrlm Run Variance	1.03	0.87 - 1.23	0.733
HLH glcm Imc1	1.12	0.94 - 1.32	0.204
HLH glszm Small Area Low Grey Level Emphasis	0.84	0.69 - 1.01	0.065
LLH glszm Size Zone Non Uniformity Normalized	1.14	0.97 - 1.33	0.105
HHL glszm Grey Level Non Uniformity Normalized	1.01	0.85 - 1.19	0.944
GTVp radiomic model (n=260, 157 progression)			
LHH glszm Small Area Low Grey Level Emphasis	1.17	0.99 - 1.38	0.06
LLH glcm Cluster Shade	1.16	1.02 - 1.33	**0.026**
HLH glszm Grey Level Non Uniformity	1.16	0.96 - 1.40	0.121
HLL firstorder Root Mean Squared	0.93	0.77 - 1.13	0.453
LLL glcm Imc1	1.38	1.15 - 1.65	**0.001**
Combined model (n=231, 145 progression)			
GTVn (cm^3)			
<6	[Reference]		
6 - 36.4	1.63	0.99 - 2.69	0.054
>36.4	2.37	1.28 - 4.38	**0.006**
GTV HLH glcm Imc1	1.06	0.86 - 1.30	0.593
GTVn LLH glrlm Run Variance	0.96	0.78 - 1.18	0.679
GTVp HLH glszm Grey Level Non Uniformity	1.13	0.98 - 1.31	0.1

Abbreviations: BM, brain metastases; CI, confidence interval; GTV, gross tumor volume; GTVp, gross tumor volume-primary lung tumor; GTVn, gross tumor volume-metastatic lymph nodes; HR, hazard ratio; SD, standard deviation.

Discussion:

Although it has been reported that the GTV volume is associated with OS and PFS, the association of the GTV volume and the subsequent risk of BM development is unclear in patients with radically treated stage III NSCLC. Our study indicated that a larger GTVn was a risk factor for BM, OS, and PFS in patients with stage III NSCLC, but GTV and GTVp were not significantly associated with BM. In contrast, *Ji et al* reported that GTV was not a significant risk factor for BM (p=0.687)[10]. A possible explanation could be that they analyzed the BM risk factors using Cox regression, which does not consider the competing event of death. Additionally, GTVp and GTVn were not specified. To the best of our knowledge, this is the first work reporting that GTVn is associated with subsequent BM development, while GTVp and GTV are not. The finding that lymph nodes involvement is more prognostic than the primary tumor volume warrants to be validated in further studies. A biological explanation could be that lung cancer cells are already more aggressive when migrating to lymph nodes and that the volume of GTVn correlates with the aggressiveness.

Interestingly, colleagues in Denmark investigated GTVp and GTVn for the first failure site in patients with locally advanced NSCLC. They found that neither GTVp nor GTVn was significantly correlated with first failure site (either locoregional failure or distant metastases)[30]. In this study, the main idea of separating GTVn from GTVp was similar to ours. However, patients with stage I-II or stage IV (20.5%) were also included, and they only explored the associations with the first failure site without specifying BM or metastases to other organs. We focused on BM, regardless of whether the brain was the first site of failure and we also evaluated the association with PFS and OS. This approach is more inclusive and therefore of greater clinical practice value, as patients can still develop BM after extracranial progression.

In line with other studies [2-4,31], we also found that higher age and squamous cell carcinoma were independent protective factors for developing BM, while smoking history, thoracic radiotherapy dose, and the use of adjuvant durvalumab were not significantly associated with the development of BM. The latter is in contrast to the PACIFIC trial, in which the percentage of patients with BM halved in the durvalumab arm compared with placebo (31/476 [6.5%] vs 28/237 [11.8%], p=0.015)[32]. A possible explanation could be that in the PACIFIC study only fit patients without disease progression after CCRT were selected[33], while we included NSCLC patients who had stage III at the initial diagnosis, patients who progressed after CCRT were not excluded. In addition, in the PACIFIC trial, brain MRI was not required (brain CT was allowed) and PET-CT was not mandatary, while in this current study, only patients who underwent baseline PET-CT and brain MRI to fully stage and exclude occult BM were included.

As far as we are aware, this is the first study which found that the GTVn radiomics model performed better than the clinical, GTVp radiomics, GTV radiomics, and combined model, with the highest AUC (0.74), sensitivity (84%), and NPV (95%). Consistent with earlier studies, the GTVp radiomics model was not as good as the clinical model[18]. Generally, a high sensitivity leads to a better ability of ruling a disease out, and a high specificity leads to a better ability of ruling in a disease[34]. As our aim of this study is to identify patients who are at higher risk to develop BM, it is better in ruling out BM (higher sensitivity) than ruling in BM, which indicates that managements to prevent or detect BM (such as PCI and regular brain MRI surveillance) are needed for these patients. Therefore, although the GTVp radiomics model had a better specificity, we considered the GTVn radiomics model as a better one. Furthermore, a NPV of 95 % is very good. Although the PPV and overall accuracy of the GTVn model were not great, the model may still be very valuable in clinical practice, as it can predict with a high likelihood that a patient will not develop BM and hence should not be considered for PCI (currently only within a clinical trial) nor for brain image follow-up. In addition, the specificity and sensitivity do not change when the incidence/prevalence changes, while the PPV and NPV are dependent on the prevalence/incidence of the outcome[34]. The relatively low PPV of all the models are mainly because of the relatively low incidence of BM (14.5% at 2-years) in this cohort, which was probably due to better staging (PET-CT and MRI were performed at diagnosis of stage III NSCLC). Therefore, the GTVp and GTVn should be separately delineated and analyzed in clinical practice and related studies.

Our results showed that wavelet features were the most prominent class associated with BM development as well as OS and PFS, independently from the region of interest of choice (GTV, GTVp, GTVn). Wavelet features decompose the original CT scan into a frequency space (like an "MR-like" image) and they are able to quantify granular textures based on the differences among harder and softer tissues. Our results showed that a combination of high-pass (HLH) and low-pass filtered (LLH) wavelet features are capable of quantifying tumor heterogeneity, which is a potential surrogate for a higher tumor aggressiveness. Although in the literature there is a lack of the understanding about the biological meaning of radiomic features, our results suggest that tumors (and more specifically lymph nodes) that have more enhanced textures (GLSZM features) are more likely to spread to the brain, probably suggesting a higher proliferation of aggressive cells. Also, there are few studies that focused on extracting the radiomic features from both the GTVp and GTVn. However, previous radiomic studies[35,36] have shown that for the prediction of distant metastases it is better to focus on a larger region than just the GTVp, the so-called peri-tumoral ring.

In addition, we provided nomograms for the clinical model and the GTVn radiomics model, together with the codes for extracting radiomics features from GTVs on the planning CT scan, which clinicians and researchers could use for conducting future studies.

Strengths of this study are the relatively large dataset, the gold standard staging (baseline PET-CT and brain MRI), the administration of radical treatment to every patient, the inclusion of immunotherapy data in a real-world setting, and the long follow-up. All GTVs were rigorously contoured and evaluated by a team of specialists in lung cancer radiotherapy. Planning CTs were homogeneous regarding the scanning protocol. One limitation lies in the fact that we used the planning CT rather than the staging CT before anti-tumor treatment. In CCRT, most patients already had received one chemotherapy administration before having the planning CT. In SCRT, only patients with a reasonable performance status and without progression after chemotherapy were sent for thoracic radiotherapy. One can question the necessity of predicting the risk of BM in patients intended to undergo SCRT but not eligible (progression, poor PS) to undergo thoracic radiotherapy. On the other hand, the use of expertly contoured GTVs is reliable as well as convenient because no additional contouring is necessary, and therefore extracting radiomics features from GTVs is feasible in clinical application for all patients with a radiotherapy treatment plan. Another limitation is the lack of external validation. To overcome this limitation, we performed bootstrapping 1000 times and LASSO regression to develop the radiomics models. Our results can be further tested in future external validation studies (evaluating our model on a separate dataset, TRIPOD type 4 studies), or further confirmed using the same methods with a larger sample size training dataset and an independent validation dataset (TRIPOD type 3 studies)[29].

Conclusion

To our knowledge, this is the first study that demonstrates the prognostic value of the GTVn volume on BM development in patients with stage III NSCLC. Younger patients and those with non-squamous cell carcinoma are at higher risk to develop BM. Radiomics features of GTVn have greater prognostic value than GTVp and GTV for BM development. Therefore, the GTVp and GTVn shall be contoured and analyzed separately in clinical practice and future studies.

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Chapter 5

Risk factors for neurocognitive decline in lung cancer patients treated with prophylactic cranial irradiation: A systematic review

Zeng H, Hendriks LEL, van Geffen WH, Witlox WJA, Eekers DBP, De Ruysscher DKM.

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Abstract:

Background: Prophylactic cranial irradiation (PCI) reduces brain metastasis incidence in lung cancer, however with risk of neurocognitive decline. Nevertheless, risk factors for neurocognitive decline after PCI remain unclear.

Methods: We systematically reviewed the PubMed database according to the PRISMA guideline. Included were: randomized controlled trials (RCTs) and observational/single arm trials evaluating PCI, including ≥20 patients, reporting neurocognitive test results for lung cancer. Primary aim: evaluate risk factors associated with neurocognitive decline after PCI.

Results: Twenty records were eligible (8 different RCTs, 8 observational studies), including 3553 patients in total (858 NSCLC, 2695 SCLC) of which 73.6% received PCI. Incidence of mild/moderate cognitive decline after PCI varied from 8-89% (grading not always provided); for those without PCI, this was 3.4-42%. Interestingly, 23-95% had baseline cognitive impairment. Risk factors were often not reported. In one trial, both age (>60 years) and higher PCI dose (36 Gy) including twice-daily PCI were associated with a higher risk of cognitive decline. In one trial, white matter abnormalities were more frequent in the concurrent or sandwiched PCI arm, but without significant neuropsychological differences. One trial identified hippocampal sparing PCI to limit the neurocognitive toxicities of PCI and another reported an association between hippocampal dose volume effects and memory decline. As neurocognition was a secondary endpoint in most RCTs, and was assessed by various of instruments with often poor/moderate compliance, high-quality data is lacking.

Conclusions: Age, PCI dose, regimen and timing might be associated with cognitive impairment after PCI in lung cancer patients, but high-quality data is lacking. Future PCI trials should collect and evaluate possible risk factors systematically.

Keywords: lung cancer, prophylactic cranial irradiation (PCI), neurocognitive decline, cognitive impairment, risk factor

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Highlights:

- Prophylactic cranial irradiation (PCI) increases the risk of neurocognitive decline.
- The risk factors for cognitive decline after PCI remain unclear.
- 20 records were identified but no enough validated data has been published until now.
- Dose, frequency, timing of PCI, and age might be associated with cognitive decline.
- Future PCI trials should collect and evaluate possible risk factors systematically.

Introduction

Lung cancer patients frequently develop brain metastases (BM). For example, approximately 30% of radically treated stage III non-small cell lung cancer (NSCLC) patients present with symptomatic BM in the course of their disease, despite being treated with radical chemoradiotherapy[1]. In metastatic NSCLC with an oncogenic driver, BM incidence is up to 60%[2]. BM incidence of small cell lung cancer (SCLC) patients is even higher (up to 80% at autopsy)[3].

BM are associated with a negative impact on quality of life (QoL) and survival[4-6]. Therefore, prevention of BM is necessary. In an individual patient data meta-analysis of patients with SCLC, prophylactic cranial irradiation (PCI) reduced the 3-year BM rate by 25.3% (58.6% in the control versus 33.3% in the PCI arm, P<0.001) and increased the 3-year overall survival (OS) rate by 5.4% (P=0.01). The majority had limited disease SCLC [LD-SCLC]) with complete response on a simple chest X-ray after induction chemotherapy[7]. In extensive disease SCLC (ED-SCLC) patients responding to first line chemotherapy, the 1-year BM rate was reduced by 25.8% (40.4% in the control versus 14.6% in the PCI arm, P<0.001). The 1-year OS rate increased with 13.8% (P = 0.003)[8]. Thus, PCI became standard of care in SCLC patients responding to initial therapy. However, a Japanese randomized controlled trial (RCT) showed that in ED-SCLC patients without BM on baseline magnetic resonance imaging (MRI), PCI followed by MRI follow-up did not result in a survival benefit compared with MRI follow-up alone (1-year OS 48.4% versus 53.6% for PCI versus observation, P=0.094). PCI did reduce the BM rate by 26.1% at 1-year (59.0% in the control versus 32.9% in the PCI arm, P<0.0001)[9]. For NSCLC, PCI also significantly reduced the risk of BM development by 10.3-29.6%, but this did not translate into an OS benefit, and therefore did not become standard of care in NSCLC [1,10-13].

As a downside, PCI increases short-term adverse events (mainly low-grade toxicities such as headache, nausea, vomiting, fatigue, and alopecia). PCI is also associated with a long term and irreversible decline in neurocognitive functions, such as intellectual impairment, abnormalities on brain imaging, and in rare cases also dementia and ataxia[1,6]. Chronic neurocognitive decline has a negative impact on QoL and daily functioning[14,15]. According to the NVALT-11/DLCRG02 phase III RCT evaluating PCI versus observation in stage III NSCLC patients, total incidence of Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[16] grade 1-2 cognitive disturbance (20.9% versus 3.4%) and memory impairment (30.2% versus 8.0%) were significantly increased in the PCI arm[1]. However, no

statistically significant nor clinically relevant impact of PCI on health-related QoL was observed (P-values, 0.641-0.914)[17].

Personalized treatment is important to avoid treatments that are not beneficial or even harmful for certain patients. Ideally, PCI is only administered to patients with a positive risk-benefit balance: i.e. preventing BM without a significant neurocognitive decline. For shared decision making, it is important to know the patients' personal risk factors for PCI associated cognitive decline. However, little is known about these risk factors. In 1994, Crossen *et al* proposed that the neurotoxicities of cranial irradiation might be related to age, radiation dose, fraction size, and timing of chemotherapy[18]. However, both imaging (i.e. the introduction of MRI for BM screening) and treatment modalities (i.e. more accurate radiation) have improved significantly the last 20 years and it is unclear whether the conclusions of Crossen *et al* are applicable to more recent literature. Furthermore, attention should be paid to potential confounding factors that might influence neurocognition such as anemia, depression and co-medication, and previous literature did not focus on these factors. Therefore, we performed a systematic review to evaluate potential risk factors for cognitive decline after PCI in patients with lung cancer based on literature from 1995.

Materials and Methods

Study design

This systematic review was conducted according to the PRISMA guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[19]. Before initiation we registered the protocol in the International prospective register of systematic reviews (PROSPERO 2020: Registered number: CRD42020155776)[20] .

Main outcomes and measures

The primary exposure was PCI, primary outcomes were cognitive functioning and risk factors associated with neurocognitive decline. Other outcomes (e.g. survival, BM incidence) were not reported as these have been reported extensively elsewhere[6,21-27].

Participants and search strategy

The literature search was performed in the Pubmed database using the PICO method[28] (Table A.1) and included trials published from 01-jan-1995 to the search date (15-nov-2019). The full search terms are in Table A.2. The search was limited to full papers only, published in English. Eligibility criteria were: humans, lung cancer (SCLC/NSCLC), clinical trials containing cognitive function tests conducted at baseline and/or during follow up (with neurocognitive decline set as the primary endpoint or one of the secondary/exploratory

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endpoints), prospective phase II-IV trials (if two or more arms: randomized). The start date of 01-Jan-1995 was chosen for this review, as from 1995, brain MRI with gadolinium became more widely available (i.e. better exclusion of baseline BM). Exclusion criteria were: phase I trials, retrospective studies, reviews, duplicates, studies including < 20 patients, studies including patients without (pathological evidence of) lung cancer, and studies in which neurocognitive outcomes were not reported. The detailed criteria are shown in Table A.3.

Appendix Table 1. Descriptions of the components of PICO

Acronym	Definition	Description
P	Patients	All lung cancer patients, no matter SCLC or NSCLC, including all stages without brain metastases before prophylactic cranial irradiation
I	Intervention	Prophylactic cranial irradiation or not
C	Comparison	We will compare patients with PCI or not, whether the outcome would be different. We hypothesize that PCI might increase neurocognitive decline, either temporary or permanently. And we try to find out high risks for neurocognitive decline in patients with lung cancer treated with prophylactic cranial irradiation.
O	Outcome	Cognitive decline, including kinds of questionnaires conducted at a series of batteries.

Abbreviations: NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; PCI: Prophylactic cranial irradiation.

Appendix Table 2. PICO searching strategy

PICO	Search terms	
Patients	1) lung cancer	OR
	2) small cell lung cancer	
	3) non-small cell lung cancer	
	4) SCLC	
	5) NSCLC	
	6) pulmonary neoplasm	
	7) lung neoplasms	
	8) lung neoplasm	
	9) cancer of the lung	
	10) cancer of lung	
	11) lung cancers	
	12) pulmonary cancer	
	13) pulmonary cancers	
	14) thoracic tumor	
	15) thoracic tumors	
	16) thoracic tumour	
	17) thoracic tumours	
	18) MeSH term: Lung Neoplasms	
Intervention	1) prophylactic cranial irradiation	OR
	2) PCI	
	3) prophylactic cranial radiotherapy	
	4) irradiation of the head	
	5) irradiation of head	
	6) prophylactic central nervous system therapy	
	7) prophylactic cerebral irradiation	
	8) prophylactic central nervous system irradiation	
	9) prophylactic CNS therapy	

	10) irradiation of the brain	
	11) irradiation of brain	
	12) prophylactic irradiation of the central nervous system	
	13) MeSH term: cranial irradiation	
Control	NA	
Outcome	1) cognitive impairment	OR
	2) cognitive dysfunction	
	3) cognitive functioning	
	4) cognitive side effects	
	5) cognitive adverse event	
	6) cognitive adverse events	
	7) cognitive deficit	
	8) cognitive deficits	
	9) cognitive disturbance	
	10) cognitive disturbances	
	11) cognition deficit	
	12) cognition deficits	
	13) cognition disturbances	
	14) cognition disturbance	
	15) cognition disorders	
	16) cognition disorder	
	17) cognition	
	18) neurocognition	
	19) neurocognition deficit	
	20) neurocognition deficits	
	21) neurocognitive	
	22) neurotoxicity	
	23) neurotoxicities	
	24) intellectual impairment	
	25) memory impairment	
	26) amnesia	
	27) dementia	
	28) MeSH term: neurocognitive disorders	
	29) MeSH term: memory disorders	

Abbreviations: NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; PCI: Prophylactic cranial irradiation; CNS: central nervous system; NA: not applicable.

Appendix Table 3. Inclusion criteria

Subjects included	Human only
Language	English
Article type	Original article, full paper
Study type	Prospective phase II-IV trials; for two-arm trials, should be randomized
Period	Studies published from 01.01.1995 to 15.11.2019
Number of patients	≥ 20
Primary tumor	Lung cancer with pathological evidence
Treatment	Prophylactic cranial irradiation
Follow up period	All
Outcome	Cognitive function

Study selection and risk of bias assessment

Two authors (HZ and WHVG) independently selected papers for inclusion based on titles, abstracts, and full texts. A third author (LH) evaluated all papers with disagreement and consensus was sought through discussion.

A risk of bias assessment was done for the selected RCTs, using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[29,30]. Cognitive function was the outcome being assessed.

Data extraction

HZ extracted the following information from eligible full texts: title; first author; journal; publication year; recruitment period; study type; sample size (planned and actual enrollment); details of included patients (age, pathology, disease stage, smoking history, gender, comorbidities); MRI or computed tomography (CT) of the brain before PCI and during follow-up; PCI details (fractionation schedule, initiation time); endpoints of the trial; type and timing of, and compliance to neurocognitive and QoL questionnaires; cognitive results and cognition conclusions. The results were checked by LH.

Results

Study selection and characteristics

The electronic literature search yielded 198 records after applying the preset filters (Human, English, publication date). Another five records were added through reference searching. Among these 203 records, 20 fulfilled the inclusion criteria (Figure 1). Six were published between 1995-1998[31-36], and 14 between 2007- 2019[1,8,11,17,37-46]. None of the records that were published between 1996 and 2006 met the inclusion criteria. Twelve records were published out of eight different RCTs[1,8,11,17,32,33,37,39,40,44-46] (NVALT-11[1,17], RTOG0214[11,45], Le Pechoux's trial[39,40], Slotman's trial[8,44] had two related publications), the other eight were observational studies[31,34-36,38,41-43]). All the eligible observational trials were primarily designed to evaluate cognitive consequences of PCI, while most RCTs were primarily comparing OS or the BM incidence of PCI versus observation, or high dose PCI versus standard dose. Cognitive results were mostly included as secondary endpoints. The RTOG 0212 trial was the only RCT designed to evaluate cognitive consequences of PCI dose in LD-SCLC patients[46] (Table 1).

The eligible trials involved 3553 patients in total, including 858 (24.1%) with NSCLC and 2695 (75.9%) with SCLC, among whom 2616 (73.6%) received PCI and the other 937 (26.4%) did not. The median age was approximately 60 years in all trials, and about 60% in most trials was male[1,8,11,17,31,33,34,37-40,44-46]. Only three trials reported smoking history[17,42,43], three trials

recorded comorbidities like hypertension and diabetes[34,36,43], and seven trials did not report performance status[33,35,36,39-42,46] (Table 2).
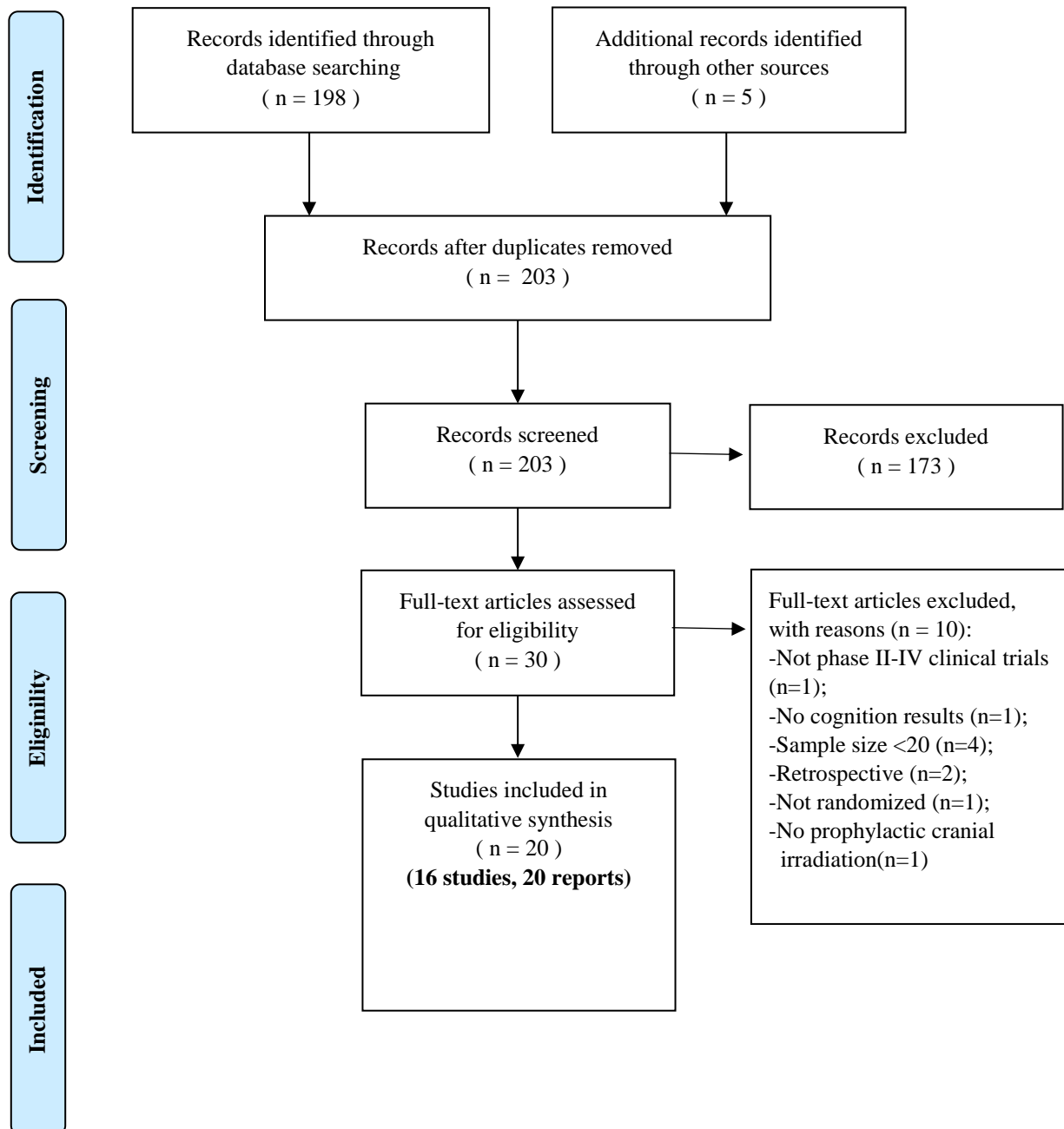
Figure 1. PRISMA flow diagram

Table 1. Design of included studies

First Author (Trial)	Study design	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Primary endpoints	Secondary endpoints	Cognition as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
Randomized controlled trials								
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	Phase III, PCI vs no PCI	MRI/CT	MRI/CT were performed if patients experience key neurologic symtoms	symptomatic BM at 24 months	Adverse effects, OS, QoL, quality-adjusted survival, health care costs	Secondary	2009 ~ 2015	150 each arm (power 90%); registered 195, 174 randomly assigned (86 in PCI, 88 in No PCI)(power 73%)
Sun, 2011[3] & Gore, 2011[4] (RTOG 0214)	Phase III, PCI vs no PCI	MRI/CT	No	OS	DFS, NCF, QoL, BM incidence	Secondary	19-09-2002 ~ 30-12-2007	529 per arm (power 80%); 356 accrued, 340 (176 allocated to PCI, 158 received PCI, 163 in PCI analyzed vs 180 allocated, 177 analyzed in No PCI)
Wolfson, 2011[5] (RTOG 0212)	Phase II, High dose vs standard dose PCI	MRI/CT	No	Cognitive function and QoL	BM incidence	Primary	19-02-2003 ~ 12-02-2008	NI for targeted size; 265 accrued,131 in Arm 1, 67 in Arm 2, and 66 in Arm 3 eligible
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	Pooled analysis (RTOG 0212 + RTOG 0214), PCI vs no PCI	MRI/CT	No	Exploratory: self-reported cognitive functioning	Exploratory: HVLT-R and QoL	Primary	NI*1: 19-09-2002 ~ 12-02-2008	NI for targeted size; 621 accrued (441 PCI, 180 No PCI): RTOG 0212 (n=265), RTOG 0214 (n=356). 583 analyzed (410 PCI, 173 No PCI): RTOG 0212 (n=252, 95%), RTOG 0214 (n=331, 93%).

Table 1. Design of included studies

First Author (Trial)	Study design	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Primary endpoints	Secondary endpoints	Cognition as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]	Phase III, High dose vs standard dose PCI	MRI/CT	MRI/CT yearly or before in case of neurological symptoms	BM incidence	Survival, neurological functions, QoL and late sequelae.	Secondary	09-1999 ~ 12-2005	NI for targeted size; 720 (360 in each arm) enrolled
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	Phase III, PCI vs no PCI	No	MRI/CT were performed if patients experience key neurologic symtoms	symptomatic BM	HRQOL, patient-reported symptoms, survival, toxic effects, and treatment costs.	Secondary	02-2001 ~ 03-2006	287 required (Power 80%); 286 patients were recruited (143 in each arm). A total of 280 patients had at least one valid HRQOL form and 268 (93.7%) had a baseline assessment.
Gregor, 1997[11] (UKCCCR/EORTC)	Phase III, PCI vs no PCI	16% patients had brain CT before PCI	No	OS	BM, cognitive function, and QoL.	Secondary	10-1987 ~ 04-1995	300 required (Power: NI) 314 patients (194 PCI, 120 No PCI) were randomised. 136 patients (84 PCI, 52 No PCI) were included in the optional assessments of cognitive function and QoL.
Arriagada, 1995[12]	NI, PCI vs no PCI	CT	CT at 6, 18, 30, and 48 months after random assignment	BM, especially BM as the first isolated site of recurrence.	The neurological complication rate and overall survival	Secondary	05-1985 ~ 03-1993	150 each arm (power: 95%); 300 randomized (149 PCI, 151 control), 145 received PCI, 149 No PCI

Observational studies

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Table 1. Design of included studies

First Author (Trial)	Study design	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Primary endpoints	Secondary endpoints	Cognition as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
Simó, 2016[13]	SCLC-PCI vs NSCLC-chemotherapy vs HCs	MRI	MRI at 3 months after treatment	Observe cognition function, structural imaging change and QoL 3 months after PCI	NA	Primary	12-2010 ~ 01-2014	NI for targeted size; 22 SCLC, 13 NSCLC, and 21 HCs enrolled.
Ahles, 1998[14]	Randomized phase III trial*2, CRT + PCI, with or without warfarin	NI	NI	Psychological and neuropsychological (cognitive) functioning	NA	Primary	NI (before 1997)	NI for targeted size; 295 patients were recruited for the psychologic study at baseline, and 224 and 177 patients completed the pre-RT and post-RT assessments, respectively.
Redmond, 2017[15]	Hippocampal-sparing PCI.	MRI	MRI at 6, 12, 18, and 24 months after PCI.	Memory (HVLT-R) at 6 months after PCI	BM, OS, DFS, and other cognitive tests.	Primary	04-03-2013 ~ 08-09-2015	125 patients were needed but only recruited 20
Ma, 2017[16]	Pooled analysis, Hippocampal-sparing PCI for SCLC or WBRT for GBM	MRI	MRI at at 6,12,18, and 24 months after PCI.	Memory decline (HVLT-R) baseline vs 6 months	Memory decline on standardized battery of neurocognitive tests	Primary	12-2011 ~ 01-2016	NI for targeted size; 60 were accrued but only 30 patients were analyzable.
Van Oosterhout, 1995[17]	PCI vs. matched controls	CT	No	Treatment-related cognitive impairment until	NA	Primary	NI (before 1993)	NI for targeted size; 32, in their pretherapeutic condition

Table 1. Design of included studies

First Author (Trial)	Study design	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Primary endpoints	Secondary endpoints	Cognition as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)
				5 months after PCI				were compared to matched controls
Van Oosterhout, 1996[18]	Chemotherapy vs Sequential PCI vs concurrent/sandwiched PCI vs. matched controls	MRI/CT	NA	Long term effects on neurologic and structural change in SCLC patients who survived more than 2 years	NA	Primary	01-1991 ~ 01-1993	NI for targeted size; 51 patients were divided into three groups: group 1: chemotherapy alone (n = 21), group 2: sequential PCI (n = 19), group 3: concurrent or sandwiched PCI (n = 11).
Komaki, 1995[19]	PCI	NI	NI	Cognition deficits before and after PCI	NA	Primary	NI (before 1993, ASCO)	NI for targeted size; 30
Grosshans, 2008[20]	PCI	MRI/CT	No	Cognition function before and after PCI	NA	Primary	1989-2002	NI for targeted size; 96 recruited, but 3 were excluded because of BM before PCI. So, 93

Note: *1. Inferred from RTOG 0214 and RTOG 0212;

*2. Randomly compared warfarin vs no warfarin, NI on which phase trial, PCI was not different between groups, so here classified as observational trials.

Abbreviations: PCI, prophylactic cranial irradiation; CT, computed tomography; MRI, magnetic resonance imaging; BM, brain metastases; OS, overall survival; QoL, quality of life; DFS, disease-free survival; NCF, neurocognitive function; NI, no information; HVLT-R, Hopkins Verbal Learning Test-Revised; HRQOL, Health-related quality of life; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HCs, healthy controls; CRT, chemoradiotherapy; NA, not applicable; WBRT, whole brain radiation therapy; GBM, glioblastoma multiforme.

References:

1.	De Ruysscher D, Dingemans AC, Praag J, et al: Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. J Clin Oncol 36:2366-2377, 2018

2.	Witlox WJA, Ramaekers BLT, Joore MA, et al: Health-related quality of life after prophylactic cranial irradiation for stage III non-small cell lung cancer patients: Results from the NVALT-11/DLCRG-02 phase III study. Radiother Oncol 144:65-71, 2019

3.	Sun A, Bae K, Gore EM, et al: Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 29:279-86, 2011

Table 1. Design of included studies

First Author (Trial)	Study design	Brain CT or MRI before PCI	Scheduled Brain CT or MRI during follow-up	Primary endpoints	Secondary endpoints	Cognition as primary or secondary endpoints	Recruitment period	Sample size (planned and actual enrollment)

4. Gore EM, Bae K, Wong SJ, et al: Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol 29:272-8, 2011

5. Wolfson AH, Bae K, Komaki R, et al: Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 81:77-84, 2011

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8. Le Pechoux C, Dunant A, Senan S, et al: Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 10:467-74, 2009

9. Slotman BJ, Mauer ME, Bottomley A, et al: Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 27:78-84, 2009

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20. Grosshans DR, Meyers CA, Allen PK, et al: Neurocognitive function in patients with small cell lung cancer : effect of prophylactic cranial irradiation. Cancer 112:589-95, 2008

Table 2. Baseline characteristics of included studies

First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)
Randomized controlled trials							
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	J Clin Oncol & Radiother Oncol	Mean±SD: No PCI:62 ± 7.68; PCI: 61 ± 8.35.	WHO PS 0:No PCI:34/88(39%), PCI: 32/86(37%); 1:No PCI:49/88(56%), PCI: 50/86(58%); 2:No PCI:5/88(6%), PCI: 4/86(5%).	IIIA/IIIB NSCLC treated with CRT +/- surgery, without PD	Smoker: No PCI:25/88 (28%), PCI: 35/86 (41%); former smoker: No PCI:60/88 (68%), PCI: 46/86 (53%); never smoker: No PCI:3/88 (3%), PCI: 4/86 (5%); Unknown: No PCI:0/88 (0%), PCI: 1/86 (1%).	No PCI: 56/88 (63.6%), PCI: 58/86 (67.4%).	NI
Sun,2011[3] & Gore,2011[4] (RTOG 0214)	J Clin Oncol & J Clin Oncol	Median (range): No PCI: 62 (39-83), PCI: 63 (39-84).	Zubrod PS 0:No PCI:105/177(59%), PCI: 77/163(47%); 1:No PCI:68/177(38%), PCI: 76/163(47%); 2:No PCI:4/177(2%), PCI: 8/163(5%); 3:No PCI:0/177(0%), PCI: 1/163(1%); unknown:No PCI:0/177(0%), PCI: 1/163(1%). (0:No PCI:105/177(59%), PCI: 77/163(47%); >0:No PCI:68/177(41%), PCI: 86/163(53%).)	IIIA/IIIB NSCLC, definitive therapy completed, without PD	NI	No PCI: 110/177(62%), PCI: 102/163(63%).	NI
Wolfson, 2011[5] (RTOG 0212)	Int J Radiat Oncol Biol Phys	Median(range): arm 1:62 (39-86), arm 2: 62 (39-78), arm 3: 61 (44-77).	NI	LD-SCLC achieving CR after CRT	NI	arm 1: 78/131(60%), arm 2: 34/67(51%), arm 3:34/66(52%)	NI

Table 2. Baseline characteristics of included studies

First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	Int J Radiat Oncol Biol Phys	Median (range): No PCI:62 (39-83), PCI: 62 (39-86).	Zubrod PS 0:No PCI:102/173(59.0%), PCI: 133/410(32.4%); 1:No PCI:67/173(38.7%), PCI: 123/410(30.0%); 2-3:No PCI:4/173(2.3%), PCI: 9/410(2.2%).	IIIA/IIIB NSCLC+ LD-SCLC	NI	No PCI: 108/173(62.4%), PCI: 242/410(59.0%).	NI
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]	Ann Oncol & Lancet Oncol	Median (range): standard dose: 60 (38-83), higher dose: 60 (34-78).	NI	LD-SCLC with CR after CRT	NI	standard dose: 234/360 (65%); higher dose: 226/360 (63%).	NI
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	J Clin Oncol & N Engl J Med	Median (range): No PCI:63 (39-75), PCI: 62 (37-75).	0:No PCI:52/143(36.4%), PCI: 52/143(36.4%); 1:No PCI:76/143(53.1%), PCI: 80/143(55.9%); 2:No PCI:15/143(10.5%), PCI: 11/143(7.7%); 3:No PCI:0/177(0%), PCI: 1/163(1%); Unknown:No PCI:0/177(0%), PCI: 1/163(1%). (0:No PCI:105/177(59%), PCI: 77/163(47%); >0:No PCI:68/177(41%), PCI: 86/163(53%).)	ED-SCLC responding to chemotherapy	NI	No PCI: 82/143(57.3%), PCI: 97/143(67.8%).	NI
Gregor, 1997[11] (UKCCCR /EORTC)	Eur J Cancer	Median (range): No PCI:61 (28-76), PCI: 60 (37-79).	NI	LD-SCLC, CR after induction therapy	NI	No PCI: 74/120(62%), PCI: 125/194(64%).	NI

Table 2. Baseline characteristics of included studies

First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)
Arriagada, 1995[12]	J Natl Cancer Inst	Mean±SD: No PCI:56 ± 9, PCI: 57 ± 8.	KPS 90-100:No PCI:62%, PCI: 62%; 70-80: No PCI:35%, PCI: 37%; <=60: No PCI:3%, PCI: 1%.	SCLC	NI	No PCI: 86%, PCI: 88%.	NI
Observational studies							
Simó, 2016[13]	J Thorac Oncol	Mean±SD: SCLC: 59.64±4.84; NSCLC: 59.92±6.14; HC: 62.86±7.91.	KPS: SCLC: 80 (70-100); NSCLC: 90 (80-100).	SCLC, IIB-IIIB NSCLC, HC	Smoking:SCLC:22/ 22(100%), NSCLC: 12/13(92%), HC: 11/21(52%).	SCLC:16/22(72.7%), NSCLC: 12/13(92.3%), HC: 19/21(90.5%).	HT:SCLC:6/22(27%), NSCLC: 5/13(38.5%), HC: 8/21(38%); T2DM:SCLC:3/22(14%), NSCLC: 6/13(46%), HC: 2/21(9.5%); Dyslipidemia:SCLC: 4/22(18%), NSCLC: 7/13(54%), HC: 11/21(52%); Vascular risk factors (high): SCLC:10/22(45.5%), NSCLC: 11/13(85%), HC: 12/21(57%).
Ahles, 1998[14]	J Clin Oncol	<40-49: 36/295; 50-59: 86/295; 60-69: 147/295; 70+: 26/295.	ECOG PS 0:166/295(56.3%); 1:124/295(42.0%); 2:15/295(5.1%).	LD-SCLC	NI	188/295(63.7%).	NI
Redmond, 2017[15]	Int J Radiat Oncol Biol Phys	Median (range): 61 (38 - 76)	NI	LD-SCLC, CRT completed	Smoker: 6/20 (30%);	8/20 (40%).	NI

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Table 2. Baseline characteristics of included studies

First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)
					former smoker: 14/20 (70%); never smoker: 0/20 (0%);		
Ma, 2017[16]	Radiother Oncol	Median (range): SCLC: 59 (48-76)	NI	LD-SCLC (CRT completed) + GBM	NI	6/16 (37.5%).	NI
Van Oosterhout, 1995[17]	Int J Radiat Oncol Biol Phys	Median (range): 64 (45-78)	NI	SCLC	NI	26/32(81.3%).	NI
Van Oosterhout, 1996[18]	Int J Radiat Oncol Biol Phys	Mean±SD: Group 1: 64.5±7.2; Group 2: 59.7±9.1; Group 3: 64.7±9.9.	NI	SCLC	NI	NI	Cardiovascular risk factors have been recognized in 17 patients (32%); 9 patients group 1, 5 patients group 2, and 3 patients group 3, respectively.
Komaki, 1995[19]	Int J Radiat Oncol Biol Phys	Median (range): 61 (34-73)	KPS: 70-80: 3/30 (10%); 90-100: 27/30 (90%).	LD-SCLC	NI	18/30(60%).	Of the 30 patients, 9 had a previous history that would be expected to influence neuropsychological testing. These problems included a history of stroke, mild mental retardation or

Table 2. Baseline characteristics of included studies

First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)
							learning disability, and alcohol abuse.
Grosshans, 2008[20]	Cancer	Median (range): 59 (34-77)	KPS: <70: 4/96 (4%); 70-80: 24/96 (25%); 90-100: 68/96 (71%).	SCLC	NI	52/96(54%).	NI

*Abbreviations***:** PS, performance status; SD, standard deviation; PCI, prophylactic cranial irradiation; NSCLC, non-small cell lung cancer; CRT, chemoradiotherapy; PD, progressed disease; NI, no information; LD-SCLC, limited disease small cell lung cancer; CR, complete response; ED-SCLC, extensive disease small cell lung cancer; KPS, Karnofsky performance status scale; HC, healthy controls; HT: hypertension; T2DM: type 2 diabetes; GBM, glioblastoma multiforme.

References:

1.   De Ruysscher D, Dingemans AC, Praag J, et al: Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. J Clin Oncol 36:2366-2377, 2018

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First Author, (Trial)	Journal	Age	PS	Patients and stage	Smoking status	Gender (Male)	Comorbidities (diabetes, hypertension…)

11.   Gregor A, Cull A, Stephens RJ, et al: Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 33:1752-8, 1997

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20.   Grosshans DR, Meyers CA, Allen PK, et al: Neurocognitive function in patients with small cell lung cancer : effect of prophylactic cranial irradiation. Cancer 112:589-95, 2008

Risk of bias assessment

All observational trials were judged as high risk of bias, because of lack of a comparator arm. Six of the eight RCTs were assessed as high risk of bias[1,8,11,17,32,37,44-46], the remaining two had "some concerns"[33,39,40]. None were assessed as low risk of bias (Figure 2). This was mainly because cognitive function was secondary endpoint in most RCTs, while many data were missing because of poor assessment compliance (Figure 2).

	R	D	Mi	Me	S	O
De Ruysscher,2018 &Witlox,2019(NVALT-11)	+	+	?	−	+	−
Sun, 2011&Gore, 2011 (RTOG 0214)	+	+	?	−	+	−
Wolfson, 2011 (RTOG 0212)	+	+	?	−	+	−
Gondi, 2013 (RTOG0212+RTOG0214)	?	+	?	−	+	−
Le Pechoux, 2011 & Le Pechoux, 2009	+	+	?	+	+	?
Slotman, 2009 &Slotman, 2007	+	+	−	−	+	−
Gregor, 1997 (UKCCCR/EORTC)	+	?	+	+	+	?
Arriagada,1995	+	+	?	−	+	−

Figure 2. Risk of bias assessments

Risk of bias legend
R Bias arising from the randomisation process;   **D** Bias due to deviations from intended interventions
Mi Bias due to missing outcome data;   **Me** Bias in measurement of the outcome
S Bias in selection of the reported results;   **O** Overall risk of bias

Domain 1: Risk of bias arising from the randomization process: All trials were assessed as at low risk of bias except the pooled analysis of RTOG 0212 and RTOG 0214: this had "some concerns" because the educational level was unbalanced between arms (P = 0.02)[37].

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention): the UKCCCR/EORTC trial is the only one that was assessed to have "some concerns" because the poor accrual during the first four years was mainly due to some radiotherapists not wishing to use the mandated PCI regimens[33]. The others were at low risk.

Domain 3: Missing outcome data: all RCTs were hampered by the decreasing compliance of cognitive assessments throughout time, although with balance in both arms. Therefore, six trials were assessed to have some concerns. The Slotman's trial was judged to be at high risk of bias because data might not be missing at random (23.8% forms were not filled in since the patient was or felt too ill to complete the questionnaire and the return rate of forms for patients with BM was lower than those without BM)[8,44]. The UKCCCR/EORTC trial was judged

as at low risk since the missing data were balanced between arms and mainly due to logistical or protocol factors, rather than patients' deteriorating conditions[33].

Domain 4: Risk of bias in measurement of the outcome: Six trials were judged to be at high risk because the assessors were aware of the intervention received by study participants[1,44] or the assessment of the outcome probably could have been influenced by knowledge of whether PCI was received or not [32,37,45,46]. The UKCCCR/EORTC trial was judged to be at low risk of bias because centers performed evaluation blinded to PCI status[33]. The Le Pechoux's trial[39,40] was at low risk of bias because they were comparing high dose vs standard dose instead of PCI or not, based on patient-reported data.

Domain 5: Risk of bias in selection of the reported result: All trials were assessed as at low risk of bias because they reported the cognitive results in accordance with a pre-specified analysis plan.

Overall risk of bias: Only the Le Pechoux's trial[39,40] and UKCCCR/EORTC trial[33] were judged to have some concerns. The other six trials were judged as high risk of bias. This is mainly because of domain 3 and domain 4.

Cognitive function tests and results

The detailed cognition and QoL tests used are shown in Table 3. The most frequently used tests were the EORTC Quality-of-Life Questionnaire-C30 (QLQ-C30) (7 trials[1,8,11,17,39,40,42-46]), the EORTC QLQ Brain Cancer Module (BN20) (6 trials[1,8,11,17,39,40,42,44-46]), Trail Making Test Part A (TMT-A) (6 trials[34,35,38,42,43,46]), Trail Making Test Part B (TMT-B) (7 trials[31,34,35,38,42,43,46]), Hopkins Verbal Learning Test (HVLT) (4 trials[11,41,42,45,46]), and Controlled Oral Word Association Test (COWAT) (4 trials[34,38,42,46]).

The definition of cognitive decline varied between trials. It was defined by comparing scores in seven trials[31,34-36,38,43,44,47] or reliable change index (RCI) in five trials [11,37,41,42,45,46]. Other definitions are shown in Table A.4. Most RCTs noted a cognitive decline after PCI (incidence varied from 8-89%[1,33,39,40,45,46]), but in some trials the effect was mild or moderate and did not result in a clinically significant decline. Some observational trials conducted in earlier years found that cognitive impairment was also found before PCI or before lung cancer treatment in general (Table 3, Table A.4).

Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions
Randomized controlled trials						
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	PCI should start ≤6 weeks after the last chemotherapy administration.	36 Gy/18 f; 30 Gy/12 f; 30 Gy/10 f.	30/12: 38; 30/10: 34; 25/10: 3; 36/18: 1; 20/12: 1; 3/1: 1; 0 Gy (No PCI): 8.	1. QLQ-C30; 2. BN20; 3. EuroQol 5D; 4. CTCAE 3.0.	Baseline, 4 weeks, 3, 6, 12, 24 and 36 months, earlier when symptoms of brain metastasis occurred	No PCI:48.8 months, PCI: 48.5 months; PCI results in cognition decline (based on CTCAE 3.0)
Sun, 2011[3] & Gore, 2011[4] (RTOG 0214)	NI (pre-PCI therapy had to be completed wthin 16 weeks of study entry)	30 Gy/15 f.	NI	1.MMSE; 2.ADLS; 3.HVLT; QoL: 4. QLQ-C30; 5. BN20;	Baseline. NCF was reassessed at 3, 6, 12, 18, 24, 30, 36, and 48 months and then yearly. QoL was assessed, and brain imaging was performed at 6, 12, 24, 36, and 48 months and then yearly.	23.8 months, reported cognition at 12 months: 1. There was greater decline in HVLT in the PCI arm at 1 year; 2. No significant differences in MMSE, ADLS or QoL. PCI results in cognition decline
Wolfson, 2011[5] (RTOG 0212)	after chemotherapy and chest radiotherapy	Arm 1: 25 Gy/10 f; Arm 2: 36 Gy/18 f; Arm 3: 36 Gy/24 f/ bid;	NI	1.HVLT; 2.COWAT; 3.TMT-A; 4.TMT-B; QoL: 5.QLQ-C30; 6.BN20.	At baseline, at 6 and 12 months for the first year after treatment, then annually for 3 years and at disease progression or relapse and at death	25.3 months, PCI results in cognition decline
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	after chemotherapy and chest radiotherapy	See RTOG 0212 and RTOG 0214	NI	1.HVLT; 2.SRCF in QLQ-C30	Baseline (before PCI and after locoregional therapy), 6 months, 12 months after study entry (24,36, 48 months were not available for analysis)	12 months, PCI results in cognition decline

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Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]	after induction therapy	Standard dose: 25 Gy/10 f; High dose: 36 Gy/18 f; or: 36 Gy/24 f/ bid;	Standard dose group: 0 Gy: 5; 25/10: 341(95%); <25Gy: 3; 26–36 Gy:11; 36 Gy/24 f/ bid:2 High dose group: 0 Gy: 4; 36 Gy: 335 (93%) bid: 79(22%); qd: 277 (78%); <25Gy: 6; 25Gy: 2; 26–36 Gy:13.	1.QLQ-C30; 2.BN20; 3.LS scale	At baseline (before PCI or randomization), 6 and 12 months and then yearly	39 months, PCI results in cognition decline
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	4-6 weeks after chemotherapy	20 Gy/5f; 20 Gy/8f; 24 Gy/12f; 25 Gy/10f; 30 Gy/10f, 30 Gy/12f	20/5: 89; 30/10: 23; 30/12: 9; 25/10: 7; Others: 6.	1.QLQ-C30; 2.BN20.	At random assignment, 6 weeks, 3 months, and then 3-monthly up to 1 year and 6-monthly thereafter	NI for median follow-up; PCI results in cognition decline ; PCI did not cause significant cognition decline
Gregor, 1997[11] (UKCCCR /EORTC)	4 - 8 weeks after completion of induction chemotherapy. Can be simultaneously delivered with thoracic radiotherapy.	1. 36 Gy/18 f; 2. 24 Gy/12 f; after 11-1991: 3. 30 Gy /10 f; 4. 20 Gy/ 5 f; 5. 24 Gy /8f	Randomized to 36/18: 32 36/18: 27 24/12: 1 40/15: 1 none: 3 Randomized to 24/12: 32 24/12: 31 24/10: 1 PCI regimen chosen by clinician 130 8/1: 25	1. NART (at randomization only); 2. PASAT; 3. CFT; 4. AVLT; 5.RSCL (QoL); 6.HADS (anxiety and depression)	Baseline, 6 months, 1 year, 2 years.	18 months, Cognition decline before PCI ; PCI did not cause significant cognition decline

Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions
			20/5: 7 24/8: 1 24/12: 2 25/10: 2 26/13: 1 30/8: 1 30/10: 61 30/12: 9 30/15: 13 30/20: 1 36/18: 2 none: 5			
Arriagada, 1995[12]	Concurrent chemotherapy during PCI was not allowed, a week interval was requested before and after radiotherapy	24 Gy/ 8f, 4f per week	24 Gy: 126 (89%), 30 Gy: 8 (6%), < 24 Gy/>34 Gy: 7 (5%); 1/149 of the control group received the treatment by mistake.	MMSE and neurocognitive testing, type of test not specified (temporospatial orientation and memory, judgment, language, praxis, mood status, neurological testing)	At the time of random assignment, at 6, 18, 30, and 48 months after random assignment	NI for median follow-up; PCI did not cause significant cognition decline
Observational studies						
Simó, 2016[13]	NI	25 Gy/10f	NI	1. WAIS-III; 2. AVLT; 3. ROCF; 4. the Verbal Fluency Test; 5.TMT-A; 6.TMT-B; 7. BDI; 8. QLQ-C30.	At baseline (NSCLC before chemotherapy and SCLC before PCI) and at the 3-month evaluations.	3 months; PCI results in cognition decline
Ahles, 1998[14]	simultaneously with thoracic radiotherapy and chemotherapy	36 Gy/18f	NI	1. POMS; 2. TMT-B.	Baseline, week 9 (after chemotherapy), week 17(after chemotherapy and RT), year 1 and year 2	17 weeks; PCI results in cognition decline

Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions
Redmond, 2017[15]	NI	25 Gy/10 f;	NI	1. HVLT-R; 2. COWAT; 3. TMT-A; 4. TMT-B; 5. measures of estimated premorbid intelligence quotient (IQ) (Hopkins Adult Reading Test); 5. MMSE; 6. BVMT-R; 7. BTA; 8. PCT; 9. CIFA; 10. QLQ-C30; 11. BN20	At baseline and at 6 and 12 months after completion of PCI.	16.7 months; hippocampal-sparing technics benefits in neuropsychological sequelae
Ma, 2017[16]	NI	25 Gy/10 f; GBM: 46 Gy/ 23f + 14 Gy/7f	NI	HVLT-R	At baseline, at 6- and 12-month follow up	NI for median follow-up; hippocampal-sparing technics benefits in neuropsychological sequelae
Van Oosterhout, 1995[17]	After chemotherapy, CR	30 Gy/15f	Only 5 patients were treated with PCI	1. the Groninger Intelligentie Test; 2. AVLT; 3. the Stroop color-word test; 4. TMT-A; 5. TMT-B.	Pretherapeutically; during chemotherapy (session 2); after chemotherapy (session 3); 1 month after PCI (session 4); 5 months after PCI (session 5);	NI for median follow-up; Cognition decline because of lung cancer

Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions
Van Oosterhout, 1996[18]	NI	NA	30/15: Group 2: 3/19(15.8%), Group 3: 1/11(9.1%); 30/12: Group 2: 10/19(52.6%), Group 3: 5/11(45.5%); 30/10: Group 2: 6/19(31.6%), Group 3: 5/11(45.5%).	1. AVLT; 2. the Digit Span; 3. MST; 4. CST; 5. the Stroop Color-Word Test	> 2 years from diagnosis	NI for median follow-up; Cognition decline because of lung cancer
Komaki, 1995[19]	PCI was started between 12 - 20 weeks after the start of chemotherapy	25 Gy/10f	28 completed, 2 refused PCI	1. WAIS-R; 2. WCST; 3. COWAT; 4. Verbal Selective Reminding and the Benton Visual Retention Test; 5. TMT-A; 6. TMT-B; 7. Grooved Pegboard.	Pre-PCI and post-PCI (mean, 11 months, range 5-20 months)	NI for median follow-up; Cognition decline before PCI; PCI did not cause significant cognition decline
Grosshans, 2008[20]	mean, 12 weeks after primary therapy	NI	25/10: 67; 30/10: 1; 24/12: 1.	1. Verbal Selective Reminding Test; 2. Benton Visual Retention Test; 3. WCST; 4. TMT-B; 5. WAIS-R; 6. TMT-A; 7. COWAT; 8. Motor coordination tests.	Baseline (after primary treatment), 80-1400 days, divided into 4 groups	23 months; Cognition decline before PCI; PCI did not cause significant cognition decline

Abbreviations: PCI, prophylactic cranial irradiation; QoL, quality of life; NCF, neurocognitive function; NI, no information; bid, twice-daily; qd, once-daily; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; GBM, glioblastoma multiforme; CR: complete response; NA, not applicable;

Abbreviations for cognition/QoL tests:
1. QLQ-C30, The EORTC Quality-of-Life Questionnaire-C30;
2. BN20, the EORTC QLQ Brain Cancer Module;
3. CTCAE 3.0, Common Terminology Criteria for Adverse Events (version 3.0);
4. MMSE, Mini Mental Status Exam;
5. ADLS, Activities of Daily Living Scale;

Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions

6. HVLT, Hopkins Verbal Learning Test;
7. HVLT-R, Hopkins Verbal Learning Test-Revised;
8. HVLT-IR: Hopkins Verbal Learning Test-Immediate Recall;
9. HVLT-DR: Hopkins Verbal Learning Test-Delayed Recall;
10. COWAT, Controlled Oral Word Association Test;
11. TMT, Trail Making Test;
12. TMT-A, Trail Making Test Part A;
13. TMT-B, Trail Making Test Part B;
14. SRCF, self-reported cognitive functioning;
15. LS scale, the EORTC–RTOG Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale;
16. NART, The National Adult Reading Test;
17. PASAT, The Paced Auditory Serial Addition Task;
18. CFT, the Rey Osterrieth Complex Figure Test;
19. AVLT, Auditory Verbal Learning Test;
20. RSCL, Rotterdam Symptom Checklist;
21. HADS, Hospital Anxiety and Depression Scale;
22. WAIS-III, Wechsler Adult Intelligence Scale-III;
23. WAIS-R, Wechsler Adult Intelligence Scale-Revised;
24. ROCF, the Rey-Osterreith Complex Figure Test;
25. BDI, the Beck Depression Inventory;
26. POMS, Profile of Mood States;
27. MST, Memory Scanning Test;
28. CST, Concept Shifting Test;
29. BTA, Brief Test of Attention;
30. BVMT-R, Brief Visuospatial Memory Test-Revised;
31. CIFA, Calibrated Ideational Fluency Assessment;
32. PCT, Perceptual Comparison Test;
33. WCST, Wisconsin Card Sorting Test.

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Table 3. Treatments and cognitive assessments in the included studies

First Author (Trial)	PCI initial time	PCI schedules	Completed PCI schedules Gy/ fr/ N patients	Cognition/ QoL tests	Assessment battery	Median follow up time and Cognitive conclusions

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Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores		P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
Randomized controlled trials					
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	Groups	PCI	No PCI		The decline of memory impairment and cognitive disturbance were assessed according to CTCAE 3.0:
	Memory impairment	30.2%	8%	<0.001	1.Grade 1-2 memory impairment and cognitive disturbance
	Cognitive disturbance	20.9%	3.4%	<0.001	were significantly increased in the PCI arm.
	QoL-physical functioning (median score) (3 months) EuroQoL-5D-3L (linear mixed effects models)	73	87	0.0017	2.QoL was worse in the PCI arm at 3 months after PCI, particularly in physical functioning. At 6, 12, and 18 months, QoL was similar between both arms, but long term—24, 36, and 48 months—there was a slight, nonsignificant advantage in QoL in the observation arm.
	Utility score	NA	NA	0.641	3.None of the health-related QoL metrics were clinically
	Visual analogue scale	NA	NA	0.914	relevant or statistically significantly different between the PCI and the observation arm.
Sun, 2011[3]& Gore, 2011[4] (RTOG 0214)	Groups	PCI	No PCI		Decline was defined based on RCI:
	HVLT-IR (3 months)	45%	13%	<0.001*	1. There was greater decline in HVLT–IR (P=0.03) and
	HVLT-IR (6 months)	19%	5%	0.045*	HVLT-DR (P= 0.008) in the PCI arm at 1 year;
	HVLT-IR (12 months)	26%	7%	0.03*	2. No significant differences in MMSE (P= 0.60) or ADLS
	HVLT-DR (3 months)	44%	10%	<0.001*	(P=0.88);
	HVLT-DR (6 months)	15%	14%	0.81*	3. No significant differences at 1 year between the two arms
	HVLT-DR (12 months)	32%	5%	0.008*	in EORTC-QLQC30 or QLQBN20 (P>0.05);
	ADLS (12 months)	NI	NI	0.88	4. Early changes of NCF (ie, 3 months) after PCI were more
	MMSE (3 months)	36%	17%	0.04	dramatic and significant than later changes (ie, 6, 12
	MMSE (6 months)	28%	25%	0.68	months).
	MMSE (12 months)	23%	18%	0.60	
	QLQ-C30 (Global health status)	35%	32%	0.98*	
	QLQ-C30 (6 months)	22%	34%	0.98*	
	QLQ-C30 (12 months)				
	BN20 (Cognitive functioning)	35%	18%	0.24*	
	BN20 (6 months)	41%	25%	0.98*	
	BN20 (12 months)				
Wolfson, 2011[5] (RTOG 0212)	Groups	High dose PCI	Standard PCI		Decline was defined based on RCI:
	HVLT (baseline)	NI	NI	>0.05	36 Gy increased risk of developing CNt.
	TMT-B (baseline)	NI	NI	>0.05	

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores		P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
	QLQ-C30 (baseline)	NI	NI	>0.05	
	BN20 (baseline)	NI	NI	>0.05	
	COWAT (baseline)	NI	NI	0.03	
	TMT-A (baseline)	NI	NI	0.03*	
	HVLT (12 months - baseline)	NI	NI	>0.05	
	TMT-B (12 months - baseline)	NI	NI	>0.05	
	COWAT (12 months - baseline)	NI	NI	>0.05	
	TMT-A (12 months - baseline)	NI	NI	>0.05	
	QLQ-C30 (12 months-baseline)	NI	NI	>0.05	
	BN20 (12 months - baseline)	NI	NI	>0.05	
	ND[*1](12 months - baseline)	85% in qd, 89% in bid;	62%	0.03	
	CNt[*2](12 months - baseline)	85% in qd, 89% in bid	60%	0.02	
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	Groups	No PCI (Reference) vs PCI:			Decline was defined based on RCI:
	HVLT-R (6 months)	OR 3.91 (95%CI 1.68-9.08)		0.002	1.PCI is associated with decline in HVLT-tested and self-reported cognitive functioning
	HVLT-R (12 months)	OR 4.96 (95%CI 1.84-13.38)		0.002	
	HVLT-DR (6 months)	OR 1.89 (95%CI 0.94-3.81)		0.08	
	HVLT-DR (12 months)	OR 2.49 (95%CI 0.96-6.48)		0.06	
	SRCF (6 months)	OR 3.60 (95%CI 2.34-6.37)		<0.0001	
	SRCF (12 months)	OR 3.44 (95%CI 1.84-6.44)		<0.0001	
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]		High dose PCI	Standard PCI		Decline defined as a binomial distribution with the event being all unfavourable classes ([0–75] for QoL functional scales, [25–100] for QoL symptoms scales and ≥1 for LS):
	QoL-cognitive functioning			0.40	1.Over the 3 years studied, there was no significant difference between the two groups in any of the 17 selected items assessing QoL and neurological and cognitive functions.
	Baseline	25%	23%		
	At 6 months	34%	35%		
	At 12 months	41%	38%		
	At 24 months	46%	41%		
	At 36 months	47%	35%		
	LS-intellectual deficit			0.02	2.They observed in both groups a mild deterioration across time of communication deficit, weakness of legs, intellectual deficit and memory (all P < 0.005).
	Baseline	9%	10%		
	At 12 months	20%	12%		
	At 24 months	28%	20%		
	At 36 months	34%	27%		

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Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores		P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	Groups	PCI	No PCI		Decline defined by comparing scores:
	QoL-Overall			0.1134	1.The impact of PCI was limited for role, emotional, and
	Baseline	66.5±1.68	66.1±1.72	0.8633	cognitive functioning.
	At 6 weeks	60.2±2.34	67.9±2.25	0.0183	2.None of the *P* values were below 0.01 nor was the 10-
	At 3 months	51.7±2.85	59.7±3.03	0.0554	point clinical significant difference reached at any time
	At 6 months	52.8±3.41	52.8±3.67	0.9919	point.
	At 9 months	52.4±4.81	54.4±5.21	0.7764	
Gregor, 1997[11] (UKCCCR/EORTC)	Groups	PCI	No PCI		Decline defined respectively according to tests:
	At baseline				1. The proportions of patients showing impairment at
	PASAT	24%	24%	>0.05	baseline in each test were substantial but similar in the two
	CFT	42%	41%	>0.05	groups.
	AVLT-learning	38%	31%	>0.05	2. In both groups, there was impairment of cognitive
	AVLT-retention	24%	27%	>0.05	function and QoL before PCI and additional impairment at 6
	Occur impairment in patients without impairment at baseline:				months and 1 year, but no consistent difference between the two groups and thus no evidence over 1 year of major
	At 6 months				impairment attributable to PCI.
	PASAT	19%	14%	>0.05	
	CFT	22%	5%	>0.05	
	AVLT-learning	30%	31%	>0.05	
	AVLT-retention	15%	18%	>0.05	
	At 12 months				
	PASAT	31%	17%	>0.05	
	CFT	15%	17%	>0.05	
	AVLT-learning	69%	40%	>0.05	
	AVLT-retention	0%	38%	>0.05	
Arriagada, 1995[12]	Groups	PCI	No PCI		Each test score was binary; normal was considered as the
	Higher functions (2-year)	30%	36%	0.58	absence of abnormality as indicated by the specific test or
	Mood (2-year)	19%	28%	0.55	examination:
	Walking (2-year)	8%	11%	0.72	1. The 2-year cumulative incidence of neuropsychological
	Cerebellar function (2-year)	15%	13%	0.61	changes were not significantly different between the two
	Tendon reflexes (2-year)	48%	39%	0.83	groups;
	Sensibility (2-year)	16%	8%	0.97	
	Cranial nerves (2-year)	54%	42%	0.19	

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores	P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
Observational studies				
Simó, 2016[13]	Main groups effects	SCLC vs NSCLC vs HCs		Decline defined by comparing scores:
	Phonemic fluency	$F(2,53) = 6.02$	< 0.004	1.The SCLC group performed worse than the HC group in verbal fluency (phonemic fluency), processing speed (TMT A), and verbal working memory (AVLT A1);
	TMT-A	$F(2,51) = 3.97$	< 0.025	2. The SCLC group also performed worse than the HCs and patients with NSCLC in visuospatial abilities (ROCF first copy);
	AVLT	$F(2,53) = 3.51$	< 0.037	3. Patients with SCLC deteriorated over time in verbal fluency (P < 0.03), no significant changes were observed in the NSCLC group;
	ROCF	$F(2,52) = 9.85$	< 0.001	4. The HC group showed an improvement over time in visual memory and processing speed because of learning effects;
	BDI	$H(2) = 0.10$	> 0.95	5. No significant differences between groups were found for the difference in BDI scores between the baseline and the follow-up sessions;
				6. Statistically significant group differences were observed for the QLQ-C30 in most of the evaluated items
				8. The SCLC group deteriorated over time in terms of cognitive functioning (P < 0.05) and nausea (P < 0.03) whereas no significant changes over time were observed in the NSCLC and HC groups
	Others	1. Verbal fluency declined in SCLC(P=0.03); 2. AVLT-B1 declined in SCLC(P=0.04); 3. AVLT-B1 did not decline in NSCLC(P>0.05); 4. ROCF-delayed increase in HC (P=0.002); 5. Compared to SCLC and NSCLC, Phonemic fluency is higher in HC (P=0.004); 6. Compared to SCLC and NSCLC, TMT A is higher in HC (P=0.025); 7. Compared to HC and NSCLC, ROCF first copy is lower in SCLC (P=0.001); 8. Compared to SCLC and NSCLC, AVLT-A1 is higher in HC (P=0.037);		Decline defined by comparing scores: 1.The SCLC group exhibited cognitive deficits together with brain-specific structural changes after platinum-based chemotherapy and PCI, compared with both the HC and NSCLC groups with a limited impact on their quality of life.

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores		P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
Ahles, 1998[14]	Groups	Warfarin	No Warfarin		Decline defined by comparing scores:
	POMS				1.There were no significant differences on psychologic and
	pre-radiotherapy (9 weeks)	-4.18	-2.73	0.825	neuropsychologic functioning between warfarin arm and
	post-radiotherapy (17 weeks)	-4.52	2.19	0.539	observational arm.
	TMT-B				2. Cognitive functioning was improved from baseline to
	pre-radiotherapy (9 weeks)	-16.37	-12.15	0.514	post-ACE chemotherapy, but a significant worsening post-
	post-radiotherapy (17 weeks)	16.69	-0.49	0.271	radiotherapy compared with the pre- radiotherapy assessments(P <0.0001).
					3. This combination of chemotherapy and RT had a negative impact on cognitive functioning
Redmond, 2017[15]	Comparison	Baseline vs Post PCI			Decline was defined based on RCI:
	HVLT-R (6 months)	NI (shown in Figures)		0.34	1.There was no significant decline in performance between
	HVLT-R (12 months)	NI (shown in Figures)		0.17	baseline and 6 or 12 months for any of the tests
	COWAT (6 months)	NI (shown in Figures)		1.0	2. Patient-reported evaluations of cognitive functioning
	COWAT (12 months)	NI (shown in Figures)		0.67	significantly declined at 6 months but did not persist at 1
	TMT-A(6 months)	NI (shown in Figures)		0.1	year.
	TMT-A(12 months)	NI (shown in Figures)		0.38	3. The decline in the subjective patient-reported
	TMT-B(6 months)	NI (shown in Figures)		0.25	QOL measures at 6 months was not confirmed in the more
	TMT-B(12 months)	NI (shown in Figures)		0.81	detailed
	MMSE(6 months)	NI (shown in Figures)		0.06	and quantitative cognitive evaluations.
	MMSE(12 months)	NI (shown in Figures)		0.13	
	BVMT-R(6 months)	NI (shown in Figures)		0.18	
	BVMT-R(12 months)	NI (shown in Figures)		0.89	
	BTA(6 months)	NI (shown in Figures)		0.47	
	BTA(12 months)	NI (shown in Figures)		0.24	
	PCT(6 months)	NI (shown in Figures)		0.94	
	PCT(12 months)	NI (shown in Figures)		0.78	
	CIFA(6 months)	NI (shown in Figures)		0.62-0.67	
	CIFA(12 months)	NI (shown in Figures)		0.80-1.00	
	QLQ-C30-cognitive (6 months)	NI (shown in Figures)		≤0.05	
	QLQ-C30-cognitive(12 months)	NI (shown in Figures)		≤0.1	
		NI (shown in Figures)		≤0.005	
	BN20-communication improved (6 months)	NI (shown in Figures)		>0.1	

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores	P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
	BN20-communication improved (12 months)			
Ma, 2017[16]	Comparison	Baseline vs Post PCI 1.D100% to the bilateral hippocampi leading to a 20% probability of HVLT-R DR decline (tolerated dose at 20% risk, TD20) was estimated to be 10.9 Gy; 2.Dose leading to a 50% probability of HVLT-R DR decline (TD50) was 59.3 Gy; 3.The slope parameter (c50) of the dose–response curve in the logistic normal-tissue complication probability model without volume effect was estimated to be 0.42; 4.TD20 and TD50 for D50% to bilateral hippocampi were 22.1 Gy and 62.9 Gy, respectively; 5.TD20 and TD50 for Dmax to bilateral hippocampi were 37.0 Gy and 101.4 Gy, respectively; 6.Dmax was significantly associated with change in HVLT-R DR score in a linear regression model (P = 0.032)		Decline was defined based on RCI: 1.This study demonstrates an association between hippocampal dose volume effects and memory decline measured by HVLT-R DR over a wide dose range. 2. Dmax correlated significantly with change in HVLT-R DR score.
Van Oosterhout, 1995[17]	Comparison	Pretherapeutically vs during chemotherapy vs after chemotherapy vs 1 month after PCI vs 5 months after PCI vs matched controls: 1.There were significant differences between patients before therapy vs. matched controls (P = <0.001); 2. There were no significant deterioration either during or after therapy (0.1 < P < 0.8).		Decline defined by comparing scores: 1.This study indicates a nontreatment-related cognitive impairment could exist in patients with SCLC.
Van Oosterhout, 1996[18]	Comparison Learning and memory Memory span Speed of information processing	Patients vs Matched controls: Wilks' λ = 0.634, $F_{(9,175)}$ = 4.005, P< 0.001; Wilks' λ = 0.685, $F_{(9, 170)}$ = 3.562, P < 0.000; Wilks' λ = 0.600, $F_{(15, 174)}$ = 2.289, P < 0.006; Wilks' λ = 0.735, $F_{(6, 140)}$ = 3.555, P < 0.003;		Decline defined by comparing scores: Different patient groups were significantly worse than those of matched controls. Comparisons of the three patient groups did not show differences within the four cognitive domains.

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)		Testing deterioration rate or scores		P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion
	Attention shifting	Chemotherapy vs sequential PCI vs sandwiched PCI: did not show differences within the four cognitive domains.			
Komaki, 1995[19]	Comparison	Pre-PCI	Post-PCI		Decline defined by comparing scores:
	Wisconsin Card Sorting Test	37.2	36.8	0.95	1. An unexpected 97% of patients had evidence of cognitive
	COWAT	38.6	38.4	0.90	dysfunction prior to PCI.
	TMT-A	30.0	28.3	0.59	2. No significant deterioration were found after PCI.
	TMT-B	35.4	32.1	0.21	
	Grooved Pegboard				
	Right	39.0	34.4	0.38	
	Left	32.8	35.5	0.50	
Grosshans, 2008[20]	Comparison	Pre-PCI	Post-PCI		Decline defined by comparing scores:
	WCST	15.6 ±11.5	27.1 ±17.6	0.008	1.Before undergoing PCI, 47% of the patients displayed
	COWAT	33.8 ± 9.9	31.0 ± 9.0	0.049	deficits on 1 of the neurocognitive tests.
	Patients without progression				2.After PCI, univariate analysis revealed significant
	WCST	17.0 ±13.4	24.9 ±20.1	0.08	transient declines in executive function and language at early time points. Controlling for noncentral nervous system disease progression the deficit in executive function was no longer significant. Moreover, these deficits were not sustained, and significant improvements in language and motor coordination were recorded. 3.On multivariate analysis, no significant differences before and after PCI were found.

Notes:*1. CNt is defined as the deterioration in at least one of the following without the development of brain metastasis at 12 months:
   HVLT-recall, HVLT-recognition, HVLT-delayed recall, COWAT, TMT-A, or TMT-B.
   *2. ND is defined as the deterioration in at least one of the following regardless of the development of brain metastasis at 12 months:
   HVLT-recall, HVLT-recognition, HVLT-delayed recall, COWAT, TMT-A, or TMT-B.
Abbreviations: PCI, prophylactic cranial irradiation; QoL, quality of life; NA, not applicable; NI, no information; RCI, reliable change index; NCF, neurocognitive function; CNt, chronic neurotoxicity; ND, neurologic deterioration; qd, once-daily; bid, twice-daily; OR, odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HC, health control.
Abbreviations for cognition/QoL tests:
   1. QLQ-C30, The EORTC Quality-of-Life Questionnaire-C30;
   2. BN20, the EORTC QLQ Brain Cancer Module;
   3. CTCAE 3.0, Common Terminology Criteria for Adverse Events (version 3.0);

Appendix Table 4. Detailed Cognitive Results

First Author (Trial)	Testing deterioration rate or scores	P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion

4. MMSE, Mini Mental Status Exam;
5. ADLS, Activities of Daily Living Scale;
6. HVLT, Hopkins Verbal Learning Test;
7. HVLT-R, Hopkins Verbal Learning Test-Revised;
8. HVLT-IR: Hopkins Verbal Learning Test-Immediate Recall;
9. HVLT-DR: Hopkins Verbal Learning Test-Delayed Recall;
10. COWAT, Controlled Oral Word Association Test;
11. TMT, Trail Making Test;
12. TMT-A, Trail Making Test Part A;
13. TMT-B, Trail Making Test Part B;
14. SRCF, self-reported cognitive functioning;
15. LS scale, the EORTC–RTOG Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale;
16. NART, The National Adult Reading Test;
17. PASAT, The Paced Auditory Serial Addition Task;
18. CFT, the Rey Osterrieth Complex Figure Test;
19. AVLT, Auditory Verbal Learning Test;
20. RSCL, Rotterdam Symptom Checklist;
21. HADS, Hospital Anxiety and Depression Scale;
22. WAIS-III, Wechsler Adult Intelligence Scale-III;
23. WAIS-R, Wechsler Adult Intelligence Scale-Revised;
24. ROCF, the Rey-Osterreith Complex Figure Test;
25. BDI, the Beck Depression Inventory;
26. POMS, Profile of Mood States;
27. MST, Memory Scanning Test;
28. CST, Concept Shifting Test;
29. BTA, Brief Test of Attention;
30. BVMT-R, Brief Visuospatial Memory Test-Revised;
31. CIFA, Calibrated Ideational Fluency Assessment;
32. PCT, Perceptual Comparison Test;
33. WCST, Wisconsin Card Sorting Test.

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Appendix Table 4. Detailed Cognitive Results

First Author (Trial)	Testing deterioration rate or scores	P-value (*:adjusted P)	Cognitive decline definition and cognitive conclusion

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Nine records showed that PCI leads to increased cognitive decline. In the pooled analysis of RTOG 0212 and 0214, the odds ratio (OR) of PCI versus observation varied from 3.44-4.96, all statistically significant[37]. In RTOG 0212, incidence of chronic neurotoxicity at 12 months after PCI varied from 60-89% in arms with different PCI doses[46]. In RTOG 0214, incidence of cognitive decline varied from 15-45% for PCI versus 5-17% for observation at different time points (3-12 months), all statistically significant[45]. In the NVALT-11, grade 1-2 cognitive disturbance (20.9% in PCI versus 3.4% in observation) and memory impairment (30.2% in PCI versus 8.0% in observation) were statistically significantly different (P < 0.001)[1]. In Le Pechoux's trial, the incidence of cognitive decline after PCI varied from 34-47% at different time points (6-36 months)[39,40]. In Slotman's trial, according to the scores of the QoL tests, there was a maximum mean difference of 7.4 at week 6 for emotional functioning, 9.4 at week 6 for role functioning, and 8.8 at month 3 for cognitive functioning, all favoring the control arm (P > 0.01)[44]. In Ahles' trial, there was a significant worsening in TMT-B after radiotherapy (including thoracic radiotherapy and PCI) (about 100 versus 130 in females and 120 versus 150 in males [extracted from figures], P<0.0001)[31]. In Simó's longitudinal study, the cognitive functioning score dropped from 96.67 ± 7.42 at baseline to 89.17 ± 15.57 at 3 months after PCI (P=0.05)[43].

Results of five records observed no statistically significant cognitive decline increase by PCI. In Slotman's trial, the impact of PCI was minor for cognitive functioning, only a difference of 8.8 at month 3, which did not reach the 10-point clinically significant difference (P = 0.07)[8,44]. In the UKCCCR/EORTC trial, the incidence of impairment in patients without baseline impairment varied from 0-69% for PCI and 5-40% for observation in different tests at different time points (all P>0.05)[33]. In the Arriagada's trial, the 2-year cumulative incidence of neuropsychological changes was not significantly different between PCI and observation (8-54% versus 8-42%, P-values 0.19-0.97)[32]. In Komaki's study, there were no significant differences between pre-PCI and post-PCI noted on any of the tests (30.0-39.0 before PCI versus 28.3-38.4 after PCI, P-values 0.21-0.95)[34]. In Grosshans' study, for patients without progression, it was also not significantly different (17.0 ±13.4 before PCI versus 24.9 ±20.1 after PCI, P=0.08)[38].

Five records reported that cognitive decline could already be detected before PCI. In Le Pechoux's trial, baseline cognitive decline was detected in 23-25% of patients[40]. In the UKCCCR/EORTC trial, 24-42% had baseline cognitive impairment[33]. In Arriagada's trial, only 94 of 229 (41%) assessed patients did not show abnormalities at the initial neuropsychological examination[32]. In Komaki's trial, 97% (29 out of 30) of the patients had evidence of cognitive

dysfunction before PCI and 20 out of 21 (95%) patients with no prior neurologic or substance abuse history had impairments on cognitive assessment[34]. In Grosshans' trial, 47% displayed cognitive impairment prior to PCI[38].

Two studies found that cognitive decline existed in lung cancer. Van Oosterhout's two studies on SCLC showed clear differences between the pre-therapeutic performance of patients and that of matched controls (P<0.001[35], P<0.006[36]).

Risk factors for cognitive impairment after PCI

Although all the eligible records reported on whether PCI resulted in cognitive decline, risk factors for neurocognitive decline after PCI were mentioned in only a few trials (Table 4).

RTOG 0212 found that age (>60 years) was a risk factor for developing cognitive impairment (P=0.005) in patients with LD-SCLC[46]. Le Pechoux's trial confirmed the importance of age (continuous) as a risk factor of neurocognitive decline (memory impairment: hazard ratio [HR] = 1.04, P=0.005)[40]. The pooled analysis of RTOG 0212 and RTOG 0214 also indicated that age (>60 years) was associated with higher rates of HVLT-delayed recall decline at 12 months (OR 2.52, 95%CI 1.06-5.99, P=0.04)[37].

In addition, RTOG 0212 also reported that patients with a high PCI dose (36 Gy) were more likely to develop cognitive decline compared to those with standard dose (25 Gy) PCI (P=0.03)[46]. However, Le Pechoux's trial showed that there were no statistically significant differences between the higher dose (36 Gy) and standard dose (25 Gy) PCI arms (all P-values >0.02)[40]. Of note, the patients of the RTOG 0212 trial were included in Le Pechoux's trial. Another pooled analysis of RTOG 0212 and RTOG 0214 also demonstrated no difference between high- and low-dose PCI in terms of cognitive decline[37]. However, all these trials concluded that 25Gy should still be the standard of care for PCI in SCLC since higher doses did neither reduce the incidence of BM nor improve OS compared with standard dose[39,40,46]. Possibly, twice-daily fractions for PCI also contributed to the increase in cognitive decline, because in RTOG 0212 the cognitive functioning in QLQ-C30 declined more obviously in the twice-daily PCI arm (mean change scores: -14.0 in 25Gy arm, -13.5 in 36Gy with once-daily 18 fractions arm, and-19.6 in 36 Gy with twice-daily 24 fractions arm) and the incidence of BM was higher in the twice-daily arm (10% in once-daily 18 fractions arm versus 21% in twice-daily 24 fractions arm)[46].

Van Oosterhout *et al* assessed whether treatment variables had an effect on cognitive functioning, but they found that there were no significant correlations between neurocognitive outcomes and number of chemotherapy courses, type of chemotherapy, total and fraction dose

of PCI[36]. The only difference was that white matter abnormalities were more frequent in the arm of concurrent or sandwiched PCI (PCI between chemotherapies). Ahles's study[31] noticed that female patients performed worse in psychological tests, suggesting that female patients might be more distressed than male patients, and might need more psychological support. Two records evaluated hippocampus avoidance (HA) techniques to protect cognitive function (Redmond's trial[42] and Ma's pooled-analysis[41]) and indicated that there was a potential benefit of HA in limiting neuropsychological toxicities of brain radiation, with an association between hippocampal dose volume effects and memory decline.

Cognitive assessment compliance

Most trials were designed to assess cognitive functioning at baseline and to repeat this assessment at a series of time points during follow up. However, compliance dropped down rapidly from baseline to follow-up (median, 3-48.8 months[1,11,33,37-40,43,46]) in almost every trial (19-100%[1,11,17,31-35,37-42,44-47]) (Table A.5). Therefore most trials failed to obtain enough data to perform a neurocognitive results analysis after 12 months. The highest compliance rate at 12 months was in Redmond's trial (88.2%)[42]. The longest follow-up data was from Le Pechoux's trial (33-39% at 48 months)[40]. As a whole, the compliance in NVALT-11 was the best, ranging from 71.3% to 100% at every time point except at 18 months, which was not a pre-planned assessment point according to the protocol[1,17]

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Table 4. Risk factors for cognitive decline except PCI *per se*

First Author (Trial)	Risk factors	Results	Conclusion	Other findings
Randomized controlled trials				
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	NI	NA	NA	NA
Sun, 2011[3] & Gore, 2011[4] (RTOG 0214)	Age, other patient factors such as hypertension or diabetes.	1.No clear differences at 1 year emerged in NCF or QoL between patients≤60 or > 60 years on either arm (all adjusted *P* values >0.05). 2.The data of other factors were too limited to allow any meaningful analysis.	1.PCI did not cause significant cognitive decline stratified by age.	Early changes of NCF (ie, 3 months) after PCI were more dramatic and significant than later changes (ie, 6, 12 months)
Wolfson, 2011[5] (RTOG 0212)	Incidence of CNt* at 12 months between PCI dose, gender, education level, marital status, age,	1.PCI dose: 60% in 25Gy/10f vs 85% in 36 Gy/18f vs 89% in 36Gy/24f/bid, p=0.02; 2. Gender: 72% in male vs 74% in female, p=0.84; 3. Education level: 66% in ≤High school vs 79% in > High school, p=0.20; 4. Marital status: 72% in Married/living as married vs 74% in Single/divorced/widowed, p=0.83; 5. Age: 56% in ≤60y vs 83% in > 60y, p=0.009	1. Higher dose (36 Gy) and age (>60 y) were significant risk factors for the development of CNt; 2. Gender, education level, and marital status were not risk factors for CNt.	1.Use of hyperfractionated radiotherapy in this randomized trial did not yield a significant reduction in late neurologic effects;
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	Baseline impairment, age, PCI dose	1.Baseline impairment vs no impairment: HVLT-R (6 months): OR 4.62, 95%CI 2.09-10.22, P=0.0002; HVLT-R (12 months): OR 4.13, 95%CI 1.63-10.43, P=0.003; HVLT-DR (6 months): OR 4.51, 95%CI 1.85-10.97, P=0.0009; HVLT-DR (12 months): 3.33, 95%CI 1.10-10.09, P=0.03; 2.Age(≤60y vs > 60y): HVLT-DR (12 months): OR 2.52, 95%CI 1.06-5.99, P=0.04;	1. For HVLT-R and -DR, baseline impairment was associated with lower rates of decline at 6 months and 12 months; 2. For SRCF, baseline impairment was not associated with subsequent decline at 6 or 12 months. 3. Age >60 years was associated with higher rates of HVLT-DR decline at 12 months; 4. PCI dose was not associated with HVLT or SRCF decline;	1.HVLT-R at 6 and 12 months was not closely correlated with decline in SRCF (P=.05 and P=.86, respectively). 2. patients with baseline impairment in HVLT-R or -DR were significantly less likely to develop subsequent HVLT decline

Table 4. Risk factors for cognitive decline except PCI *per se*

First Author (Trial)	Risk factors	Results	Conclusion	Other findings
		3.Comparisons demonstrated no difference between high- and low-dose PCI in terms of HVLT or SRCF decline. 4.Patient factors associated with higher baseline HVLT-R scores included female gender (P<0.0001), more advanced education level (P<0.0001), partnered status (P=0.04), and age ≤60 years (P<0.0001). 5.Patient factors associated with higher baseline HVLTDR scores were female gender (P<0.0001), more advanced education level (P<0.0001), and age ≤60 years (P=0.03). 6.Comparisons of baseline EORTC QLQ-C30 scores demonstrated no significant associations of SRCF with any patient factors.	5. Patient factors associated with higher baseline HVLT-R scores included female, more advanced education level, partnered status, and age≤60 years; 6. Patient factors associated with higher baseline HVLT-DR scores were female, more advanced education level, and age ≤60 years; 7. No significant associations of SRCF with any patient factors.	
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]	PCI dose, time, baseline and age	1.There was no significant difference between PCI dose groups in any of the 17 QoL/LS selected scales (all P-values >0.02). 2.Four QoL/LS scales worsen with time after randomization (communication deficit: HR = 1.40, P = 0.005; weakness of legs: HR = 1.31, P = 0.004; intellectual deficit: HR = 1.53, P = 0.003; LS-memory: HR = 1.43, P = 0.001); Social functioning becomes better with time: HR =0.78, P = 0.009; There is a trend for memory deterioration over time but only two patients developed a grade 4 memory deficit (at 24 months). 3.Four scales worsen with age considering age at baseline: physical functioning: HR = 1.04, P = 0.0007; motor dysfunction: HR = 1.03, P = 0.01; LS-memory: HR = 1.04, P = 0.005; MRI and/or CT: HR = 1.06, P = 0.002; 4. There was no significant interaction between time and age (all P-values >0.08).	1.There was no significant difference between high dose and standard dose groups in QoL and eurological and cognitive functions. 2. Many patients experienced a mild cognitive decline over time, but only few developed severe deterioration of QoL or neurological and cognitive functions 3. Clinicians found memory and cognitive deficits (grade ≥1) at baseline in 17% and 12% of patients, respectively. 4. Age is a cofactor of neurocognitive decline.	1. The trial showed some relationship between radiological and neurological abnormalities (P<0.04)

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Table 4. Risk factors for cognitive decline except PCI *per se*

First Author (Trial)	Risk factors	Results	Conclusion	Other findings
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	NI	NA	NA	NA
Gregor, 1997[11] (UKCCCR/EORTC)	NI	NA	NA	NA
Arriagada, 1995[12]	Dose, concurrent chemotherapy with PCI	NA	Compared with other retrospective studies, this trial showed that PCI did not cause neuropsychological decline possibly because they use 24 Gy instead of 30 Gy or more dose and they precluded concurrent chemotherapy with PCI.	There were no significant differences Between PCI group and no PCI group in terms of abnormalities indicated by computed tomography brain scans.
Observational studies				
Simó, 2016[13]	NI	NA	NA	NA
Ahles, 1998[14]	Age, Gender	1.Women had significantly higher (P < 0.004) POMS scores at baseline (age ≥ 60, mean = 73.2±4.8; age < 60, mean = 74.6 ±4.6) compared with men (age ≥ 60, mean = 59.2 ± 2 8; age < 60, mean = 66.5±3.5). 2.TMT-B data revealed a significant effect for gender (P <0.03), age (P <0.03), and gender by age (P <0.01).	1.Women showed a higher scores in POMS at the baseline, which indicated a higher level of distress; 2. Performance on TMT-B worsens with age.	
Redmond, 2017[15]	NI	NA	NA	NA
Ma, 2017[16]	NI	NA	NA	NA
Van Oosterhout, 1995[17]	NI	NA	NA	NA
Van Oosterhout, 1996[18]	Chemotherapy (Group1), Sequential PCI (Group 2),	1.The extent of cortical atrophy did not differ significantly between groups (P = 0.3); 2.The predominately periventricular localized white matter lesions were significantly more	White matter abnormalities were found more frequently in the group of concurrent or sandwiched PCI	

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Table 4. Risk factors for cognitive decline except PCI *per se*

First Author (Trial)	Risk factors	Results	Conclusion	Other findings
	Concurrent or sandwiched PCI (Group 3)	extensive in group 3 than in groups 1 and 2 (P = 0.02)		
Komaki, 1995[19]	NI	NA	NA	NA
Grosshans, 2008[20]	NI	NA	NA	NA

Note: * CNt is defined as the deterioration in at least one of the following without the development of brain metastasis at 12 months: HVLT-recall, HVLT-recognition, HVLT-delayed recall, COWAT, TMT-A, or TMT-B.

Abbreviations: PCI, prophylactic cranial irradiation; NI, no information; NA, not applicable; NCF, neurocognitive function; QoL, quality of life; CNt, chronic neurotoxicity; OR, odds ratio; CI, confidence interval; HR, hazard ratio; HVLT, Hopkins Verbal Learning Test; HVLT-R, Hopkins Verbal Learning Test-Revised; HVLT-DR: Hopkins Verbal Learning Test-Delayed Recall; SRCF, self-reported cognitive functioning; QLQ-C30, The EORTC Quality-of-Life Questionnaire-C30; LS, the EORTC–RTOG Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale; POMS, Profile of Mood States; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; COWAT, Controlled Oral Word Association Test.

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1.	De Ruysscher D, Dingemans AC, Praag J, et al: Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. J Clin Oncol 36:2366-2377, 2018

2.	Witlox WJA, Ramaekers BLT, Joore MA, et al: Health-related quality of life after prophylactic cranial irradiation for stage III non-small cell lung cancer patients: Results from the NVALT-11/DLCRG-02 phase III study. Radiother Oncol 144:65-71, 2019

3.	Sun A, Bae K, Gore EM, et al: Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 29:279-86, 2011

4.	Gore EM, Bae K, Wong SJ, et al: Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol 29:272-8, 2011

5.	Wolfson AH, Bae K, Komaki R, et al: Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 81:77-84, 2011

6.	Gondi V, Paulus R, Bruner DW, et al: Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. Int J Radiat Oncol Biol Phys 86:656-64, 2013

7.	Le Pechoux C, Laplanche A, Faivre-Finn C, et al: Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). Ann Oncol 22:1154-63, 2011

8.	Le Pechoux C, Dunant A, Senan S, et al: Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 10:467-74, 2009

9.	Slotman BJ, Mauer ME, Bottomley A, et al: Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 27:78-84, 2009

Table 4. Risk factors for cognitive decline except PCI *per se*

First Author (Trial)	Risk factors	Results	Conclusion	Other findings

10.   Slotman B, Faivre-Finn C, Kramer G, et al: Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357:664-72, 2007

11.   Gregor A, Cull A, Stephens RJ, et al: Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 33:1752-8, 1997

12.   Arriagada R, Le Chevalier T, Borie F, et al: Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 87:183-90, 1995

13.   Simo M, Vaquero L, Ripolles P, et al: Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. J Thorac Oncol 11:475-86, 2016

14.   Ahles TA, Silberfarb PM, Herndon J, 2nd, et al: Psychologic and neuropsychologic functioning of patients with limited small-cell lung cancer treated with chemotherapy and radiation therapy with or without warfarin: a study by the Cancer and Leukemia Group B. J Clin Oncol 16:1954-60, 1998

15.   Redmond KJ, Hales RK, Anderson-Keightly H, et al: Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 98:603-611, 2017

16.   Ma TM, Grimm J, McIntyre R, et al: A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation. Radiother Oncol 125:234-240, 2017

17.   van Oosterhout AG, Boon PJ, Houx PJ, et al: Follow-up of cognitive functioning in patients with small cell lung cancer. Int J Radiat Oncol Biol Phys 31:911-4, 1995

18.   Van Oosterhout AG, Ganzevles PG, Wilmink JT, et al: Sequelae in long-term survivors of small cell lung cancer. Int J Radiat Oncol Biol Phys 34:1037-44, 1996

19.   Komaki R, Meyers CA, Shin DM, et al: Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. Int J Radiat Oncol Biol Phys 33:179-82, 1995

20.   Grosshans DR, Meyers CA, Allen PK, et al: Neurocognitive function in patients with small cell lung cancer : effect of prophylactic cranial irradiation. Cancer 112:589-95, 2008

Appendix Table 5. compliance of clinical trials

	Baseline	4 w	6 w	9 w	3 m	17 w	6 m	9 m	12 m	18 m	24 m	30 m	36 m	48 m	Adjacent time windows
Randomized controlled trials															
De Ruysscher, 2018[1] & Witlox, 2019[2] (NVALT-11)	80.2-84.1%	82.6-85.2%	NA*1	NA	75.9-84.5%%	NA	71.3-79.7%	NA	79.7-80.3%	49.1-55.6 %*2	75.6-82.5%	NA	85.7-100%	NA	NI
Sun, 2011[3] & Gore, 2011[4] (RTOG 0214)	90-96%	NA	NA	NA	40-50%	NA	39-47%	NA	34-37%	NI*3	NI	NI	NI	NI	±2 weeks
Wolfson, 2011[5] (RTOG 0212)	87-93%	NA	NA	NA	NA	NA	51-69%	NA	19-50%	NA	NI	NA	NI	NA	±4 weeks for 6 months and 12 months assessments
Gondi, 2013[6] (RTOG 0212 + RTOG 0214)	93.6-97.1%	NA	NA	NA	NA	NA	55.4-61.8%	NA	42.6-51.5%	NA	NI	NA	NI	NI	±4 weeks for 6 months and 12 months assessments
Le Pechoux, 2011[7] & Le Pechoux, 2009[8]	92-94%	NA	NA	NA	NA	NA	67-75%	NA	68-72%	NA	57-64%	NA	49-57%	33-39%	Until the start of PCI for the baseline evaluation, within ±2 months for the 6-month evaluation (QoL) and within ±3 months for all subsequent evaluations (QoL/LS).
Slotman, 2009[9] & Slotman, 2007[10] (EORTC)	93.7%	NA	60.0%	NA	54.5%	NA	60.8%	46.3%	48.9%	NI	NI	NI	NI	NI	< 2 weeks before or 3 weeks after randomization, and before the start of PCI for baseline; ±3 weeks for 6 weeks assessment, <3 weeks before and <6 weeks after at 3 months,<6 weeks before

Appendix Table 5. compliance of clinical trials

	Baseline	4 w	6 w	9 w	3 m	17 w	6 m	9 m	12 m	18 m	24 m	30 m	36 m	48 m	Adjacent time windows
															and after every 3 months and <3 months before and after for assessments collected every 6 months.
Gregor, 1997[11] (UKCCCR/EORTC)	92%	NA	NA	NA	NA	NA	56%	NA	63%	NA	45%	NA	NA	NA	NI
Arriagada, 1995[12]	77.9%	NA	NA	NA	NA	NA	NI	NA	NA	56.9%	NA	62.9%	NA	NI	Baseline definition within 3 months from the date of random assignment.
Observational studies															
Simó, 2016[13]	NI	NA	NA	NA	NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NI
Ahles, 1998[14]	85%	NA	NA	76%	NA	60%	NA	NA	NI	NA	NI	NA	NA	NA	NI
Redmond, 2017[15]	100%	NA	NA	NA	NA	NA	84.2%	NA	88.2%	NA	NA	NA	NA	NA	NI
Ma, 2017[16]	NI	NA	NA	NA	NA	NA	SCLC: 95.0%; GBM:48.6%	NA	SCLC: 73.7%; GBM:47.3%	NA	NA	NA	NA	NA	NI
Van Oosterhout, 1995[17]	7.5% (28/32)	NA	During chemo: 100% (14/14)	NA	After chemo: 100% (11/11)	NA	1 m after PCI: 100% (5/5)	NA	5 m after PCI: 100% (5/5)	NA	NA	NA	NA	NA	NI
Van Oosterhout, 1996[18]	Tested once for patients who survived more than 2 years after diagnosis of SCLC.														

Appendix Table 5. compliance of clinical trials

	Baseline	4 w	6 w	9 w	3 m	17 w	6 m	9 m	12 m	18 m	24 m	30 m	36 m	48 m	Adjacent time windows
Komaki, 1995[19]	100%	After PCI: only 11 patients repeated tests, and the time varies from 5 to 20 months (mean=11 months)													
Grosshans, 2008[20]	100%	After PCI: only 37 of the 69 patients who received PCI repeated tests, and the time varies from 80 to 1400 days.													

Note: *1. NA: not planned to assess at this time point;

    *2. The 18 months' time point was not a pre-planned assessment point according to the protocol;

    *3. NI: planned to assess but did not report the data.

Abbreviations: chemo, chemotherapy; NA, not applicable; NI, no information; PCI, prophylactic cranial irradiation; QoL, quality of life; LS, the EORTC–RTOG Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale.

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1.   De Ruysscher D, Dingemans AC, Praag J, et al: Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. J Clin Oncol 36:2366-2377, 2018

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19.   Komaki R, Meyers CA, Shin DM, et al: Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. Int J Radiat Oncol Biol Phys 33:179-82, 1995

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Discussion

Cognitive toxicities of PCI in patients with lung cancer remain a concern and it is not clear which patients are at the highest risk of cognitive decline after PCI. In order to inform physicians and patients, and to personalize selection for PCI with the aim to select only those patients for PCI without a high risk of developing cognitive toxicities, we performed this systematic review. We found that age, PCI dose, PCI frequency (twice-daily instead of once daily), and timing of PCI might be associated with cognitive impairment after PCI in lung cancer patients.

However, not enough validated data has been published until now. The eight included RCTs and eight observational trials did not report detailed assessments of risk factors for neurocognitive decline. Furthermore, none of the trials were judged to be at low risk of bias. The compliance of cognitive assessments dropped rapidly during follow-up, resulting in significant missing data. In addition, assessments for cognitive functioning and definition for cognitive decline also varied between different trials.

Two trials showed that age was a cofactor for cognitive decline after PCI in patients with LD-SCLC (RTOG 0212[younger or older than 60 years][46] and Le Pechoux's trial [continuous][40]. However, RTOG 0214 did not observe significant differences in neurocognitive functioning between the PCI and the observational arm stratified by age (younger or older than 60 years) in stage III NSCLC patients[45]. Nevertheless, it was not reported whether there were significant differences in cognitive function between younger and older patients stratified by PCI. Since the pooled analysis of RTOG 0212 (43.2% patients) and RTOG 0214 (56.8% patients) confirmed the association between age ($\leq$ 60 years or > 60 years) and cognitive decline[37], it is reasonable that for elderly patients, especially SCLC, specific caution should be taken to administer PCI. But it is unknown whether 60 years is the proper cut-off age, as the inclusion criteria regarding age and the actual age range of recruited patients varied between the different trials and in general, a low percentage of older patients was included. Some trials did not set age limitations[11,45,46] while others mandated that recruited patients had to be younger than 70 years[32,39,40,43] or 75 years[8,44]. In some trials, age was analyzed as a continuous variable[40]. Furthermore, biological age is not the same as chronological age and it could be that some older patients could be more vulnerable to neurocognitive decline than others.

RTOG 0212 also showed that compared to standard dose, the incidence of chronic neurotoxicity at 12 months was higher in patients treated with a high PCI dose[46]. In contrast, two other trials containing the patients of RTOG 0212 indicated that there were no significant differences in cognitive decline between high and standard dose PCI[37,40]. Notably, in Le

Pechoux's trial, only 22% patients received 36 Gy PCI with twice-daily 24 fractions regimen[39], while in RTOG 0212, 50% were from this arm[46]. Administration of twice-daily fractions may also have contributed to higher cognitive decline. In addition, PCI concurrent or sandwiched with chemoradiotherapy was found to increase neurotoxicity and hematotoxicity[18,36,48,49], and it was recently shown that it also shortened survival[50]. Therefore, PCI concurrent with chemoradiotherapy should be avoided[51].

It has been suggested that neurocognitive decline is caused especially by irradiation of the hippocampus, and hippocampal-sparing techniques have been evaluated. In patients with BM, the RTOG 0933 trial (N=42) showed that compared with historical series, HA during whole-brain radiotherapy (WBRT) was associated with preservation of memory and QoL[52]. A single blinded, randomized phase II trial was (N=70, 65 completed treatment) recently reported in abstract form. Compared with conformal WBRT, patients receiving HA-conformal WBRT had better preservation in late verbal memory, but not in verbal fluency or executive function[53]. Redmond's single-arm observational trial suggested that HA-PCI was associated with less cognitive toxicities at the cost of higher risk of failures in the spared region: two patients developed a metastasis in the under-dosed region[42]. As only 20 of the 125 planned SCLC patients were included, firm conclusions cannot be made. A recent open-label phase II trial showed that for patients with LD-SCLC (N=44, 38 were evaluable), early HA-PCI does not appear to be better than those receiving sequential PCI without HA in terms of neurocognitive function preservation[54]. Of note, results of this trial were compared with RTOG 0212 data. In this trial, HA-PCI was administered to all patients concomitantly to the 2nd cycle of chemotherapy and thoracic radiotherapy, while in RTOG 0212, patients received PCI after completing of chemotherapy and thoracic radiotherapy[46]. Since PCI concurrent with chemoradiotherapy was found to increase neurotoxicity in several other trials [18,36,48,49], it is questionable whether HA-PCI concurrent with chemo(radio)therapy would be beneficial to patients. Recently, the results of a phase III RCT evaluating PCI with or without HA in SCLC have been reported (abstract form)[55]. The primary aim was to evaluate decline in the HVLT-R total recall at 4 months, where a decline of ≥5 out of a possible 36 points was considered a failure. With 168 patients being randomized, it was found that the cognitive decline rate at 4 months was not significantly different for PCI versus HA-PCI (28% versus 29% [P=0.99]). Moreover, rates at 8 months were similar (34% versus 26% [P=0.46]) [55]. The incidence of BM was not significantly different between groups and none of the patients developed BM in the spared zone [55,56]. Results were similar for patients with localized (stage I-III) and metastatic SCLC[57]. In contrast, the Spanish PREMER trial reported contrary results[58]. Among the 118

eligible patients (60 PCI and 58 HA-PCI), there was a significant decline in memory in the PCI versus the HA-PCI group (at 3 months, 21.7 vs 5.1%, p= 0.01; at 6 months, 32.6 vs 7.3%, p= 0.008; and at 12 months, 18.5 vs 3.8%; p=0.09). Neurocognitive function was assessed by Free and Cued Selective Reminding Test (FCSRT) which was not used in other HA-PCI trials to the best of our knowledge[58].Other ongoing RCTs will provide more data on HA-PCI: North America NRG-CC003 (NCT02635009)[59], America (NCT01797159)[60], Zhejiang, China (NCT02906384)[61], and Taiwan, China (NCT02448992)(NSCLC)[62].

In addition, Ma *et al* combined Redmond's trial with two glioblastoma multiforme (GBM) trials to evaluate hippocampal radiation dose volume effects and memory decline following cranial irradiation. They observed a dose-response of radiation to the hippocampus with regard to decline in memory: D50% of the bilateral hippocampi of 22.1Gy was associated with 20% risk of decline[41]. In this combined analysis, 16 out of 30 included patients had SCLC, the others had GBM. As GBM is a completely different disease entity, generally occurring in younger patients, and is treated with different radiation schedules, we think that these results cannot be combined or extrapolated. For example, less co-morbidities could result in less neurocognitive decline, and the higher radiation dose in GBM could result in "collateral damage" of neurons in the region of the hippocampus, responsible for transmitting the information stored earlier by the hippocampus[63]. Therefore, more high quality prospective trials addressing the true dose volume effects of HA-PCI in patients with lung cancer are needed.

Moreover, neuroprotectants during cranial irradiation might also be helpful to prevent or reduce neurotoxicities, although all data till now come from WBRT trials. The randomized phase III RTOG 0614 trial did show positive protection effects of memantine on neurocognitive function in patients treated with WBRT for BM[64]. However, only 149 of the targeted 536 patients were available for analysis, resulting in a statistical power of only 35%. The phase III NRG Oncology CC001 Trial evaluated the effects of memantine plus WBRT with or without HA in cognition preservation by randomly assigned 518 patients with BM and showed that compared to WBRT plus memantine, HA-WBRT plus memantine better preserves cognitive function (adjusted HR, 0.74; 95% CI, 0.58 to 0.95; P = 0.02) and patient-reported symptoms (P < 0.05)[65]. Whether this preservation effects should be attributed to HA or memantine or both is unknown. Moreover, we could not identify memantine-related PCI trials. Donepezil combined with vitamin E is another possible neuroprotective agent. However, the double blind, placebo controlled trial set up to test this combination in SCLC patients after completion of all cancer therapy including PCI was closed prematurely due to poor accrual (9 [5 received placebos and 4 received donepezil/vitamin E] of targeted 104 patients were recruited over 15 months) and

conclusions could not be drawn[66]. Again, RCTs are needed to evaluate neuroprotectants in the PCI setting.

Importantly, several studies have demonstrated that cognitive impairments often exists prior to PCI[32-34,38,46]. Some trials showed that patients with lung cancer performed significantly worse than healthy controls in cognitive tests[35,36,67].This indicates that other factors may also have impact on cognition impairment, such as disease related factors including cancer (e.g. paraneoplastic syndromes)[34,38], undiagnosed brain micrometastases[34] and treatment related factors such as chemotherapy, or chemotherapy induced anemia[32,34,38]. Lifestyle habits such as smoking and alcohol abuse could influence cognition, as are drugs such as steroids[38]. Comorbidities such as depression[34] and anxiety can cause cognitive impairment[6]. Hypertension, hyperlipidemia, and diabetes that can cause vascular damage and cerebral hypoperfusion could also exacerbate toxicity of cancer treatment and influence results of cognitive functioning tests[6,38,68,69]. However, these were not taken into account in any of the PCI trials included in this systematic review.

In summary, PCI *per se* can result in cognition decline, with an incidence varying from 8-89%. Based on the current evidence, to reduce the risk for cognitive decline, PCI concurrently with chemotherapy should be avoided, and PCI should not be given twice-daily or at higher doses (>25 Gy). Age might be a risk factor for developing cognitive decline. Other potential risk factors have not been studied thoroughly. HA-PCI and neuro-protective drugs are still under investigation. More high-quality clinical trials are warranted to further address this issue, but several challenges in the evaluation of neurocognitive functioning should be addressed.

First, long-term compliance to neurocognitive testing is very challenging. Possible reasons are administrative failure (logistical problems, assessors training)[33,40,44], patients being too ill to complete tests because of disease progression or BM[32,34,35,38,40,44,70], refusal to repeat the tests[40], assessments being voluntary in some protocols[33], and assessments being time-consuming[33]. Possible solutions are minimizing logistical failure by having certified and motivated people doing the tests[32], providing extra funding for education and professional training on cognitive assessments[44], emphasizing necessity and importance of assessments in the protocol, choosing some effective and sensitive but less time-consuming testing instruments, enhancing cooperation from patients by offering reimbursement, performing tests when patients are in clinic for routine oncologic evaluations by the original oncology team[42], and considering to select only good recruiting centers to participate in cognitive trials when studies involve patients in the palliative setting[44]. Innovative neurocognitive testing apps[71] or an electronic web-based system could be developed to complete the questionnaires at home.

According to RTOG 0828, the web-based strategy appears to be feasible to increase the QoL compliance rate[72].

Second, although neuropsychological testing is very important, testing may be difficult to perform during office practice or at the bedside since it is time-consuming (1–2 hours) and demanding for the patient[63]. Cognitive screening tests like Mini Mental Status Exam (MMSE) can provide a quick and easy, although not sensitive, rough measure of a person's cognitive function. Neuropsychological testing is much longer because it comprehensively examines multiple cognitive domains to provide a detailed assessment of the nature and severity of cognitive impairments[73]. Even so, it is probable that "one size does not fit all" exists for cognitive assessments, leading to development of many specialized tests for particular types of impairment[74]. In consist with the International Cognition and Cancer Task Force (ICCTF) published consensus recommendations, the most frequently used instruments in the eligible trials were TMT, HVLT and COWAT[15]. In addition, some factors may also cause potential bias in neuropsychological testing. For example, some medications like antidepressants may ameliorate cognitive deficits, while opioids may worsen cognitive symptoms. Disease progression by itself could also cause neurocognitive decline. Practice may improve performance, so it should be avoided to repeat psychological assessments within 6 months since learning effects may bias short-interval repeated evaluation, except when using parallel versions of tests[63]. Furthermore, some trials assessed the cognitive toxicities of PCI using the QLQ-C30, BN20, or CTCAE, which only contained a domain of cognitive functioning, instead of any cognitive screening tests or neuropsychological testing[1,8,17,44]. To complicate matters, patient and physician scored toxicity is not always concordant[1]. Some studies even indicate that proxy sources of QoL data collection like clinician assessments are unreliable and only consider assessments based on patient-reported data for research[75]. However, according to the ICCTF recommendations, objective tests remain the gold standard for measuring cognitive function because self-reported complaints have not been validated as a means to assess cognition, and research shows a stronger association between subjective complaints of cognitive dysfunction and mood and fatigue[15].

Neuroimaging may provide unique objective and important biomarkers of cognitive changes[76]. However, at present, this is experimental[43,67,77]. Biomarkers in cerebrospinal fluid are also investigated[78], but not practical for routine use. In contrast, a blood sample is relatively easier to be obtained[79], but no studies have been reported in patients with lung cancer. If validated, blood biomarkers would be very easy to implement to select those who are at risk of neuro-cognitive decline after PCI.

Last, based on our findings, we propose some suggestions for future RCTs. To improve cognitive function research, the following items should be implemented: 1. The use of an instrument as broad as possible, but still practical neurocognitive testing battery. This is very important to recruit patients, administer interventions and assess outcomes more successfully; 2. Blinding the assessors to intervention status. This will make the assessment more objective; 3. Trying to increase the patients' compliance of cognitive assessments, for example with a web-based system. This will lower the trial's risk of bias and make the conclusions more reliable; 4. A systems biology framework incorporating multimodality neuroimaging, genetics and other biomarkers. This will be very informative regarding individual differences in risk and protective factors and disease- and treatment-related mechanisms on cognitive decline[80]; 5. A prober and workable window definition of assessment time point is useful to expand the analyzable data; 6. Briefly specifying in the trial report how the randomization was conducted. This would be helpful for readers to assess randomization bias precisely and interpret the results better.

Conclusion

In conclusion, our literature search did not yield enough high quality data to define risk factors for developing cognitive decline after PCI. However, it is likely that higher age, PCI dose, twice-daily PCI, and timing of PCI might be associated with cognitive impairment after PCI in lung cancer patients. Protecting cognitive function is an important issue, but there is still a long way to go on cognitive function (or QoL) research in patients with PCI. Future trials should focus on risk factors for both BM development and neurocognitive decline, in order to select those that benefit most from PCI.

Author contributions:

DDR, LH and HZ conceived this study. HZ and LH searched papers in Pubmed. HZ and WVG screening the papers from titles to full texts. HZ extracted the data and assessed the risk

of bias, LH checked the screening, extraction and assessments. HZ analyzed the results, DDR and HZ supervised the whole process. HZ, LH and DDR draft the manuscript, WVG, WW and DE revised it.

Conflict of interests:

None.

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Chapter 6

Self-reported cognitive function and quality of life in small cell lung cancer patients in the hippocampal avoidance prophylactic cranial irradiation (HA-PCI) vs. PCI in randomized phase III trial (NCT01780675)

Albers EAC**, Zeng H,** De Ruysscher DKM, Kuenen MA, Kessels R, Hendriks LEL, Belderbos JSA, Schagen SB.

Chapter 6

6

Abstract

Background: In the randomized controlled trial (RCT) in patients with small cell lung cancer (SCLC) comparing standard prophylactic cranial irradiation (PCI) with hippocampal avoidance PCI (HA-PCI), we did not observe beneficial effects of HA-PCI on tested cognition. Here we report findings on self-reported cognitive functioning (SRCF) and Quality of Life (QoL).

Methods: SCLC patients were randomized to receive PCI with or without HA (NCT01780675) and assessed at baseline (82 HA-PCI and 79 PCI patients) and at 4, 8, 12, 18, 24 months follow-up, using the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires. SRCF was assessed with the cognitive functioning scale of the EORTC QLQ-C30 and the Medical Outcomes Study (MOS) questionnaire. A change of 10 points was used for minimal clinically important differences. Percentages of patients classified as improved, stable or deteriorated were compared between groups using chi-square tests. Changes in mean scores were analyzed using linear mixed models.

Results: There was no significant difference in the percentage of patients with deteriorated, stable, or improved SRCF between the treatment arms. Depending on the evaluated time point, 31-46% and 29-43% of patients in the HA-PCI and PCI arm, respectively, reported a deteriorated SRCF based on the EORTC QLQ-C30 and MOS. QoL outcomes were not significantly different between the study arms, except for physical functioning at 12 months (23% [n=7] in the PCI arm versus 14% [n=4] in the HA-PCI arm, P=0.019) and motor dysfunction at 24 months (33% [n=5] in PCI versus 23% [n=5] in HA-PCI, P=0.02).

Conclusion: Our trial did not show beneficial effects of HA-PCI over PCI on self-reported cognition and QoL. The cognitive benefit of sparing the hippocampus in the context of PCI is still subject of debate.

Keywords: Small cell lung cancer (SCLC); Prophylactic cranial irradiation (PCI); Hippocampus; Self-reported cognitive functioning (SRCF); Quality of Life (QoL).

Introduction

Small-cell lung cancer (SCLC) is characterized by early dissemination, including the brain[1]. At time of death, 50% to 65% of patients with SCLC have been diagnosed with brain metastases (BM)[2-4]. BM are associated with a significant reduction in quality of life (QoL) and life expectancy[5]. Once BM have occurred, patients are treated palliative, aiming to maintain their QoL during their remaining lifespan.

Prophylactic cranial irradiation (PCI) reduces the incidence of BM and may prolong the overall survival[4,6,7]. One concern of PCI is the potential for cognitive impairment and its effect on QoL[8,9].

The NVALT-11/DLCRG-02 trial, in which PCI was compared with observation in patients with non-small cell lung cancer (NSCLC), showed increased self-reported memory impairment (30% versus 8% respectively) and cognitive disturbances (19% versus 3% respectively)[10]. However, no statistically significant nor clinically relevant impact of PCI compared to no-PCI on patients' overall QoL was reported[11].

Hippocampal-avoidance PCI (HA-PCI) has the potential to preserve cognitive function, which may retain patients' QoL. A recent phase 3 trial (NRG CC001) of HA during whole-brain radiotherapy (WBRT) plus memantine versus WBRT plus memantine in 518 patients with overt BM mainly from NSCLC, reported a better preserved cognitive function assessed with neuropsychological tests (including the Hopkins Verbal Learning Test-Revised (HVLT-R), Controlled Oral Word Association (COWA) and Trail Making Test (TMT) A and B) and fewer self-reported cognitive symptoms (measured with the EuroQol-5D-5L (EQ-5D-5L) and MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) questionnaire) among patients treated with HA-WBRT plus memantine compared with patients in the WBRT plus memantine arm[12]. No other significant differences between arms were observed over time on several aspects of QoL (measured with the EQ-5D-5L)[12]. The phase 3 PREMER-trial conducted in 150 patients with SCLC without BM who were randomized to receive PCI or HA-PCI, also showed better preserved cognitive function assessed by the Free and Cued Selective Reminding Test (FCSRT) in the HA-PCI compared with the PCI arm[13]. In contrast, no significant differences were observed between arms on any scale of the EORTC QLQ-C30 and brain cancer module (BN20) up to 24 months follow-up [13].

The Dutch-Flemish phase 3 trial's main objective was to investigate the benefit of HA-PCI on memory function in SCLC patients compared to standard PCI using the HVLT-R total score[14]. No differences between the treatments were found at 4 months. Furthermore, no differences were found for other additional cognitive outcomes, despite an observed reduction

in hippocampal atrophy in the HA-PCI compared with the PCI arm[15]. However, both treatment modalities were associated with considerable brain injury[15]. Here, we report the study's secondary objectives: comparing patients' QoL, in particular their self-reported cognitive performance (SRCF) between HA-PCI and PCI.

Methods

Patient selection

Eligibility criteria of the multicenter phase 3 trial (NCT01780675) have been published before [14]. In short, patients were included when they: i) had histologic- or cytologic-proven SCLC, stages I to III ("limited stage") or stage IV ("extensive stage"); ii) had clinical or radiologic evidence of BM on a contrast-enhanced magnetic resonance imaging (MRI) scan; and iii) had no progressive disease after first line chemo-radiotherapy in stages I to III or after chemotherapy alone in stage IV[14]. Excluded were: i) younger than 18 years; ii) previous radiotherapy to the brain; or iii) received anticancer agents concurrently with PCI. All patients gave written informed consent. This trial (NCT01780675) was conducted according to the Declaration of Helsinki and approved by the Medical Ethics Committee of the Netherlands Cancer Institute.

Patients first received four courses of platinum-etoposide alone (stage IV) or concurrent chemo-radiotherapy (stage I-III), followed by PCI. The interval between the last chemotherapy and the start of PCI was at least 3 weeks. The detailed MRI acquisition and radiation treatment procedures have been previously described[14, 15]. Briefly, patients were irradiated with a total dose of 25 Gy in 10 fractions, five times a week. The mean dose of the hippocampal avoidance zone of the HA-PCI was limited to 8.5 Gy.

QoL assessment

Questionnaires were administered at baseline and at 4, 8, 12, 18, 24 months after completion of (HA) PCI in the same session as the neuropsychological assessment. QoL and symptom burden were assessed by i) The EORTC QLQ-C30, a 30-item questionnaire applicable for patients with cancer in general[16]. In addition to the domain of cognitive functioning (SRCF), four domains were selected for the current analyses: physical functioning, emotional functioning, role functioning and fatigue. Based on the literature, we expected that these domains were relevant to the patients' daily life[13,17]. ii) The EORTC QLQ-BN20 questionnaire[18], a 20-item questionnaire specific for patients with brain cancer, from which four domains were selected based on similar studies involving patients with SCLC or NSCLC and

BM [19,20]: motor dysfunction, future uncertainty, visual disorder and communication deficit. For both the EORTC QLQ-C30 and BN20, symptoms over the past week were scored in a range from 1 (not at all) to 4 (very much). All raw scores were linearly transformed and scored from 0 to 100. A higher score on the functional domains indicated higher QoL, whereas a higher score on the symptom domains indicates poorer QoL. iii) The cognitive functioning questionnaire from the Medical Outcomes Study (MOS). The six-item questionnaire assessed day-to-day problems in cognitive functioning, asking patients whether in the past month they became confused, reacted slowly to things, had difficulty reasoning, were forgetful, had trouble keeping attention or had difficulty concentrating. Symptoms over the past month were scored in a range from 1 (not at all) to 6 (all of the time). Scores were transformed to a range of 0-100, with higher scores indicating better cognitive functioning.

Statistical analyses

Power calculation for the primary study cognitive outcome has been previously described[14]. In total, 168 patients were randomized. In this current study, QoL data were available for 161 patients. Patients' baseline characteristics, the proportion of QoL responses, as well as the QoL scores were analyzed over time using descriptive statistics.

Analyses were performed on individual and group level. For all three questionnaires, the following analyses are performed: i) analyzing mean scores at each time interval, ii) analyzing clinical minimally important differences from baseline versus follow-up scores, using 10-points as cut-off for deterioration or improvement in scores[21]. Differences in percentage of patients that reported deteriorated, improved, or stable scores between the arms were investigated using Fisher's exact test.

On the group level, linear mixed models were used for all the three questionnaires, adding an interaction term for time by group to check for differences between the arms. Level of significance was set at $P<0.05$. Statistical analyses were performed using R-studio.

Results

Study patients

Figure 1 shows a flowchart of patients completing the SRCF and QoL questionnaires over time. According to intention to treat, 79/83 patients (95%) treated with PCI and 82/84 patients (98%) treated with HA-PCI completed questionnaires at baseline. This decreased to 16/26 patients (62%) treated with PCI and 22/25 patients (88%) treated with HA-PCI at the final 24 months follow-up. Reasons for drop-out were mainly: deceased, decline, and disease progression.

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                        ┌──────────────────────┐
                        │ N=168 patients enrolled │
                        └──────────────────────┘
┌──────────────────────┐                          ┌──────────────────────┐
│ N=79/83 (95%) completed │ ◄──────────────────► │ N=82/84 (98%) completed │
│ questionnaires at baseline │                   │ questionnaires at baseline │
└──────────────────────┘                          └──────────────────────┘
            │                                                  │
            ▼                                                  ▼
┌──────────────────────┐                          ┌──────────────────────┐
│ N=46/71 (65%) completed │                        │ N=55/72 (76%) completed │
│ questionnaires at 4 months │                     │ questionnaires at 4 months │
└──────────────────────┘                          └──────────────────────┘
            │                                                  │
            ▼                                                  ▼
┌──────────────────────┐                          ┌──────────────────────┐
│ N=35/61 (57%) completed │                        │ N=42/60 (70%) completed │
│ questionnaires at 8 months │                     │ questionnaires at 8 months │
└──────────────────────┘                          └──────────────────────┘
            │                                                  │
            ▼                                                  ▼
┌──────────────────────┐                          ┌──────────────────────┐
│ N=31/52 (60%) completed │                        │ N=29/50 (58%) completed │
│ questionnaires at 12 months │                    │ questionnaires at 12 months │
└──────────────────────┘                          └──────────────────────┘
            │                                                  │
            ▼                                                  ▼
┌──────────────────────┐                          ┌──────────────────────┐
│ N=28/41 (68%) completed │                        │ N=28/36 (78%) completed │
│ questionnaires at 18 months │                    │ questionnaires at 18 months │
└──────────────────────┘                          └──────────────────────┘
            │                                                  │
            ▼                                                  ▼
┌──────────────────────┐                          ┌──────────────────────┐
│ N=16/26 (62%) completed │                        │ N=22/25 (88%) completed │
│ questionnaires at 24 months │                    │ questionnaires at 24 months │
└──────────────────────┘                          └──────────────────────┘
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Figure 1. Flow chart

HA, hippocampal avoidance; PCI, prophylactic cranial irradiation

Baseline characteristics are described in Table 1. Median age was 64 (range: 36-87 years). In both arms, 71% of patients had SCLC stage I-III and 29% had stage IV. The majority of patients had a performance status of 1 (61% in PCI) versus 71% in HA-PCI).

Table 1. Baseline characteristics according to PCI and HA-PCI group of all randomized patients.

	PCI (N=79)	HA-PCI (N=82)	Total (N=161)
Age			
Median	64	63	64
Q1, Q3	59, 69	59, 70	59, 70
Min-Max	43-87	36-80	36-87
Sex			
Male	42 (53%)	38 (46%)	80 (50%)
Stage			
I-III	56 (71%)	58 (71%)	114 (71%)
IV	23 (29%)	24 (29%)	47 (29%)
Performance Status			
0	20 (25%)	19 (23%)	39 (24%)
1	48 (61%)	58 (71%)	106 (66%)
2	5 (6%)	4 (5%)	9 (5%)
3	1 (1%)	0 (0%)	1 (1%)
Missing	5 (7%)	1 (1%)	6 (4%)
Cognitive functioning			
Mean	78	85	82
Physical functioning			
Mean	70	74	72
Emotional functioning			
Mean	78	80	79
Role functioning			
Mean	63	70	67
Fatigue			
Mean	43	34	39
Motor dysfunction			
Mean	14	8	11
Future uncertainty			
Mean	27	26	27
Visual disorder			
Mean	12	8	10
Communication deficit			
Mean	10	8	9

Abbreviations: HA, hippocampus avoidance; HVLT-R, Hopkins Verbal Learning Test-Revised; Max, maximum; Min, minimum; PCI, prophylactic cranial irradiation; Q1, quartile 1; Q3, quartile 3.

SRCF measured with the EORTC QLQ-C30

At an individual level, there was no significant difference in percentage of patients who reported deteriorated, stable, or improved SRCF between the treatment arms at each time point: P=0.771 at 4 months, P=0.338 at 8 months, P=0.538 at 12 months, P=0.779 at 18 months and P=0.831 at 24 months (Table 2). Dependent on the evaluated time point, a deterioration in SRCF was reported by 33-41% of patients treated with PCI compared with 36-45% of patients treated with HA-PCI. Improvement was reported by 7-24% and 10-23% of patients respectively. Mean scores of SRCF of the EORTC QLQ-C30 are presented Figure 2.

At group level, mixed effect modelling for SRCF showed no significant interaction between treatment arm and time (P=0.71) (Figure 2).

Table 2. Change of SRCF and difference between arms at each time point.

	EORTC QLQ-C30			MOS		
	PCI	HA-PCI	P-value	PCI	HA-PCI	P-value
4 months	***(n=45)***	***(n=54)***	0.771	***(n=46)***	***(n=55)***	0.869
Deterioration	17 (38%)	20 (37%)		16 (35%)	17 (31%)	
Improvement	9 (20%)	8 (15%)		10 (22%)	11 (20%)	
Stable	19 (42%)	26 (48%)		20 (43%)	27 (49%)	
8 months	***(n=33)***	***(n=42)***	0.338	***(n=35)***	***(n=42)***	0.184
Deterioration	13 (39%)	16 (38%)		10 (29%)	16 (38%)	
Improvement	8 (24%)	5 (12%)		6 (17%)	12 (29%)	
Stable	12 (36%)	21 (50%)		19 (54%)	14 (33%)	
12 months	***(n=30)***	***(n=29)***	0.538	***(n=31)***	***(n=29)***	0.100
Deterioration	10 (33%)	13 (45%)		11 (35%)	10 (34%)	
Improvement	6 (20%)	3 (10%)		11 (35%)	4 (14%)	
Stable	14 (47%)	13 (45%)		9 (29%)	15 (52%)	
18 months	***(n=27)***	***(n=28)***	0.799	***(n=28)***	***(n=28)***	0.879
Deterioration	11 (41%)	11 (39%)		12 (43%)	13 (46%)	
Improvement	2 (7%)	4 (14%)		6 (21%)	4 (14%)	
Stable	14 (52%)	13 (46%)		10 (36%)	11 (39%)	
24 months	***(n=16)***	***(n=22)***	0.831	***(n=16)***	***(n=22)***	0.123
Deterioration	6 (38%)	8 (36%)		6 (38%)	7 (32%)	
Improvement	2 (12%)	5 (23%)		6 (38%)	3 (14%)	
Stable	8 (50%)	9 (41%)		4 (25%)	12 (55%)	

Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation; n, number; MOS, Medical Outcomes Study.
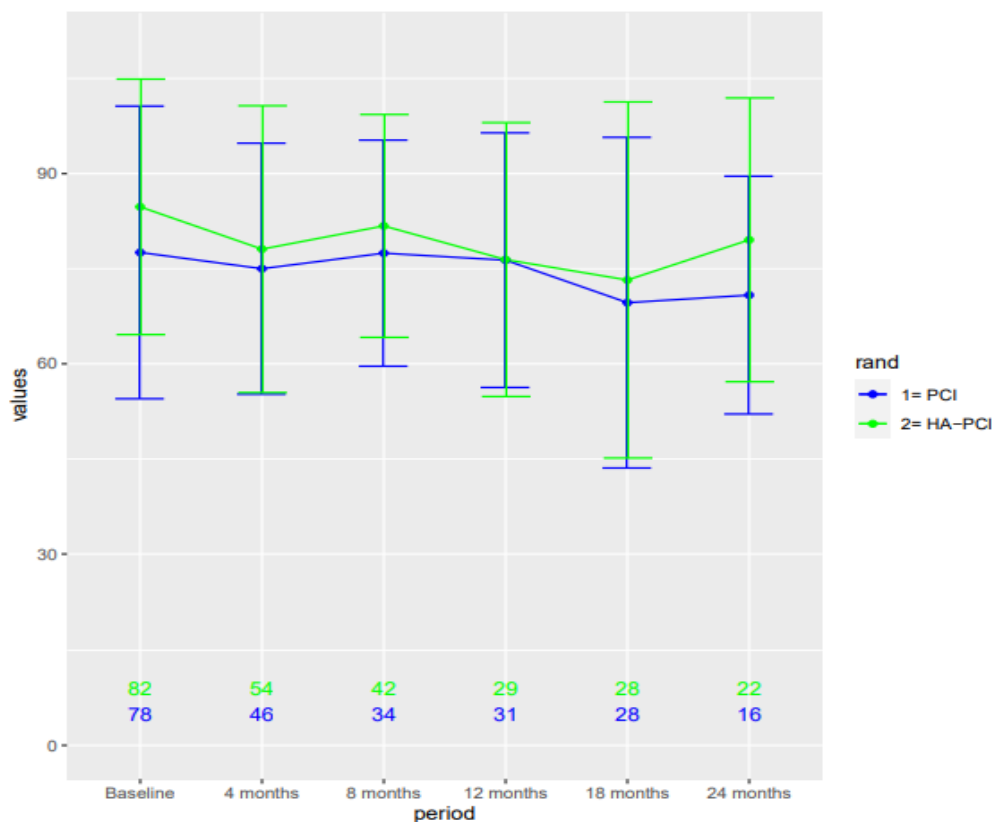
Figure 2. Mean scores of Cognitive Functioning on the EORTC QLQ-C30.

Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

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SRCF measured with the MOS

At an individual level, there was no significant difference in the percentage of patients who reported deteriorated, stable, or improved SRCF between the treatment arms at each time point: P=0.869 at 4 months, P=0.184 at 8 months, P=0.100 at 12 months, P=0.879 at 18 months, and P=0.123 at 24 months (Table 2). Dependent on the evaluated time point, a deterioration in SRCF was reported by 29-43% of patients treated with PCI compared with 31-46% of patients treated with HA-PCI. Improvement was reported by 17-38% and 14-29% of patients respectively. Mean scores of SRCF of the MOS are presented in Figure 3.

At group level, mixed effect modelling for cognitive functioning measured with the MOS showed no significant interaction between treatment arm and time (P=0.94) (Figure 3).
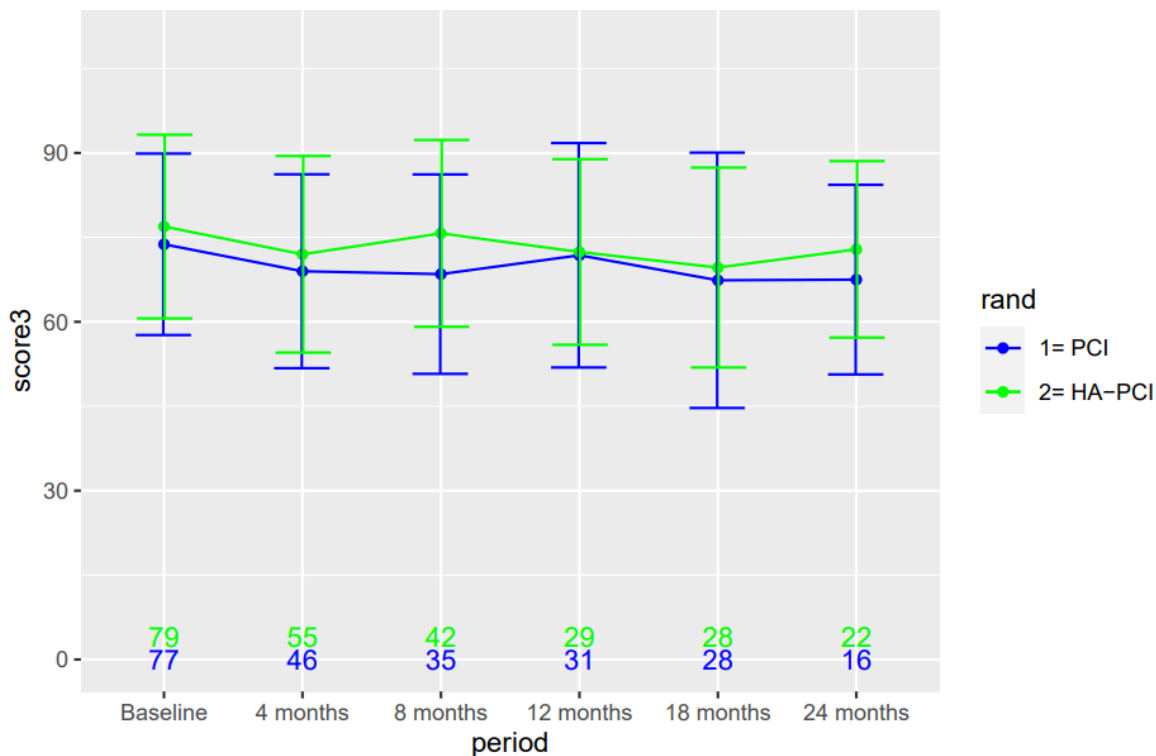
Figure 3. Mean scores of Cognitive Functioning on the Medical Outcomes Study (MOS).
Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

QoL measured with the EORTC QLQ-C30

At an individual level, there were no significant differences in the percentage of patients reporting deteriorated, stable, or improved role or emotional functioning after receiving treatment with PCI or HA-PCI. The same was found for fatigue. For physical functioning, a significant difference between the treatment arms was observed only at 12 months: 23% (n=7)

of patients in the PCI arm reported a deterioration in physical functioning, compared with 14% (n=4) of patients in the HA-PCI arm (P=0.019). Furthermore, 48% (n=15) of patients in the PCI arm reported improved physical functioning compared with 21% (n=6) of the patients in the HA-PCI arm at 12 months.

At group level, mixed effect modeling for symptoms of fatigue, role, emotional and physical functioning showed no significant interaction between group and time (Supplementary Figure 1).
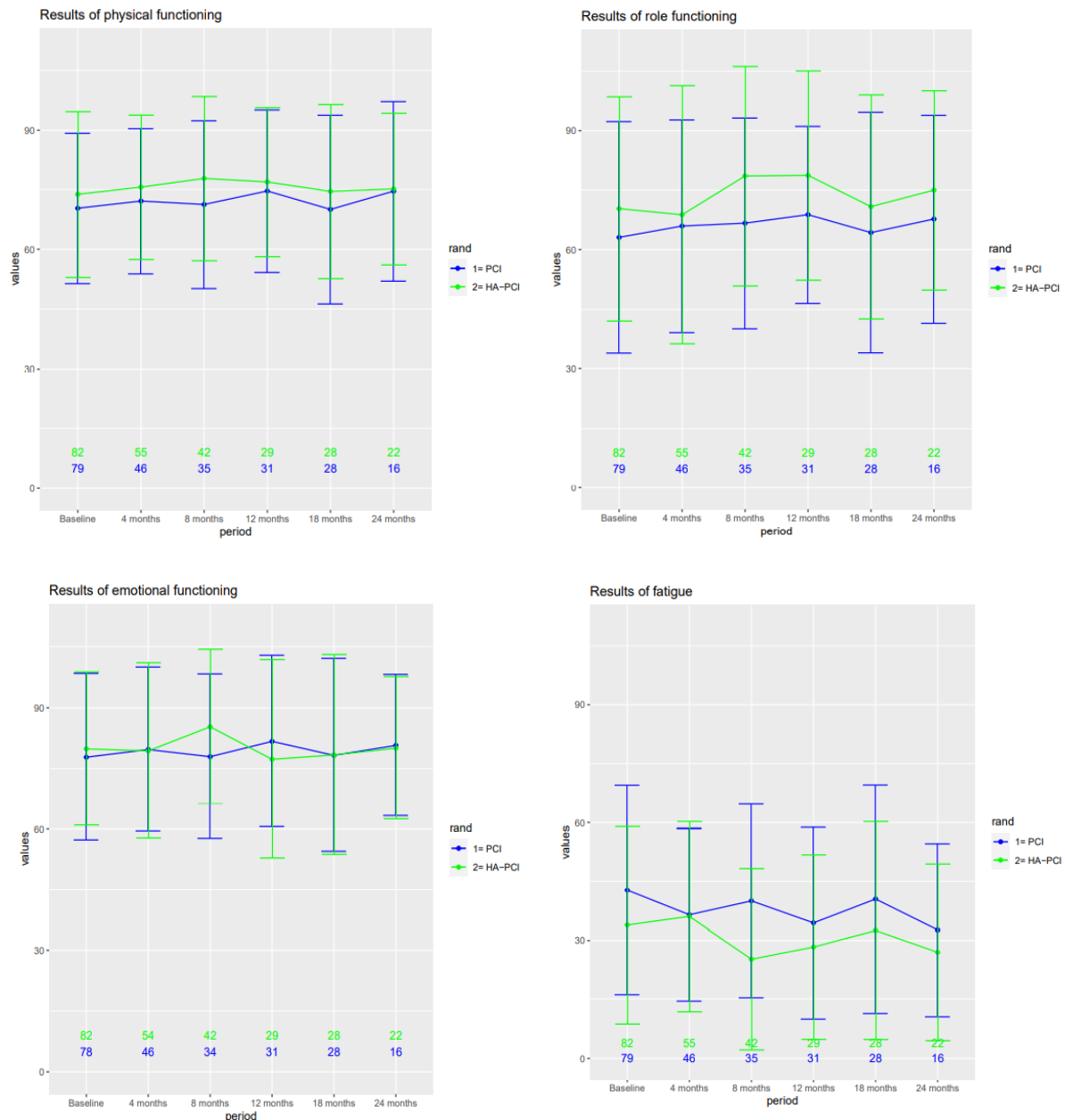
Supplementary Figure 1. Mean scores of physical functioning, role functioning, emotional functioning, and fatigue on EORTC QLQ-C30.

Abbreviations: HA; hippocampal avoidance. PCI; prophylactic cranial irradiation.

QoL measured with EORTC QLQ-BN20

At an individual level, domains of future uncertainty, visual disorder, and communication deficit showed no significant differences in the percentage of patients who deteriorated, remained stable, or improved over time between the two treatment arms. An exception was motor dysfunction at the 24 months follow-up, where a significant difference between the two treatment arms was observed: 33% (n=5) of patients treated with PCI reported a deterioration, while this was 23% (n=5) for HA-PCI (P=0.020). Furthermore, 60% (n=9) of patients in the PCI arm reported improved motor dysfunction compared with 27% (n=6) in the HA-PCI arm. The percentage of patients who deteriorated or improved over time on all EORTC QLQ-C30 and BN20 scales is reported in Supplementary Table 1.

At group level, no significant interaction between treatment arm and time was found for future uncertainty, visual disorder, motor dysfunction and communication deficit (Supplementary Figure 2).

Supplementary Table 1. Mean scores of the EORTC QLQ-C30 and BN20 at each time point.

		Baseline	4 months	8 months	12 months	18 months	24 months
EORTC QLQ-C30 functioning domains							
CF	PCI	78	75	78	76	69	71
	HA-PCI	85	78	82	76	73	80
PF	PCI	70	72	71	75	70	75
	HA-PCI	74	76	78	77	75	75
RF	PCI	63	66	67	69	64	68
	HA-PCI	70	69	79	79	71	75
EF	PCI	78	80	78	82	78	81
	HA-PCI	80	79	85	77	78	80
SF	PCI	75	78	79	81	74	85
	HA-PCI	76	77	85	88	85	86
EORTC QLQ-C30 symptom domains							
FA	PCI	43	37	40	34	41	33
	HA-PCI	34	36	25	28	33	27
NV	PCI	11	9	9	10	7	7
	HA-PCI	10	16	9	6	9	4
PA	PCI	19	16	21	23	26	24
	HA-PCI	15	18	16	11	20	17
DY	PCI	36	30	33	33	38	44
	HA-PCI	32	35	31	36	36	41
SL	PCI	17	14	27	23	23	21
	HA-PCI	24	22	17	22	27	22
AP	PCI	20	20	17	10	13	8
	HA-PCI	16	32	17	14	18	9
CO	PCI	15	18	7	12	7	13
	HA-PCI	11	10	6	9	6	6
DI	PCI	4	4	7	12	8	6
	HA-PCI	4	3	6	0	6	3
FI	PCI	11	14	12	4	5	4
	HA-PCI	14	14	15	15	12	18
EORTC QLQ-C30 Total scores							
Total	PCI	77	79	78	79	77	79
	HA-PCI	80	77	83	83	79	82

Supplementary Table 1. Mean scores of the EORTC QLQ-C30 and BN20 at each time point.

		Baseline	4 months	8 months	12 months	18 months	24 months
GHS	PCI	70	72	74	74	71	75
	HA-PCI	70	70	76	79	70	77
EORTC QLQ-BN20 functioning domains							
FU	PCI	27	19	24	22	24	19
	HA-PCI	26	25	19	26	29	21
VD	PCI	12	14	12	17	14	15
	HA-PCI	8	11	11	10	9	9
MD	PCI	14	15	16	18	20	21
	HA-PCI	8	11	9	10	13	9
CD	PCI	10	12	15	14	16	13
	HA-PCI	8	9	8	5	8	10
EORTC QLQ-BN20 symptom domains							
HA	PCI	10	11	13	17	10	16
	HA-PCI	8	17	13	20	24	21
SZ	PCI	0	0	2	2	5	0
	HA-PCI	0	0	2	4	0	0
DR	PCI	16	14	21	17	17	24
	HA-PCI	13	13	10	8	13	11
IS	PCI	21	17	17	16	11	18
	HA-PCI	12	16	15	20	23	15
HL	PCI	32	11	5	3	16	11
	HA-PCI	38	19	8	7	15	11
WL	PCI	20	20	19	18	26	18
	HA-PCI	16	15	18	17	20	11
BC	PCI	9	9	9	12	14	7
	HA-PCI	4	7	3	4	8	6

Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation; CF, Cognitive Functioning; PF, Physical Functioning; RF, Role Functioning; EF, Emotional Functioning; SF, Social Functioning; FA, Fatigue; NV, Nausea and vomiting; PA, Pain; DY, Dyspnea; SL, Sleep loss; AP, Appetite loss, CO, Constipation; DI, Diarrhea; FI, Financial difficulties; GHS, Global Health Score; FU, Future uncertainty; VD, Visual disorder; MD, Motor dysfunction; CD, Communication deficit; HA, Headaches; SZ, Seizures; DR, Drowsiness; IS, Itchy skin; HL, Hair loss; WL, Weakness of legs; BC, Bladder control.

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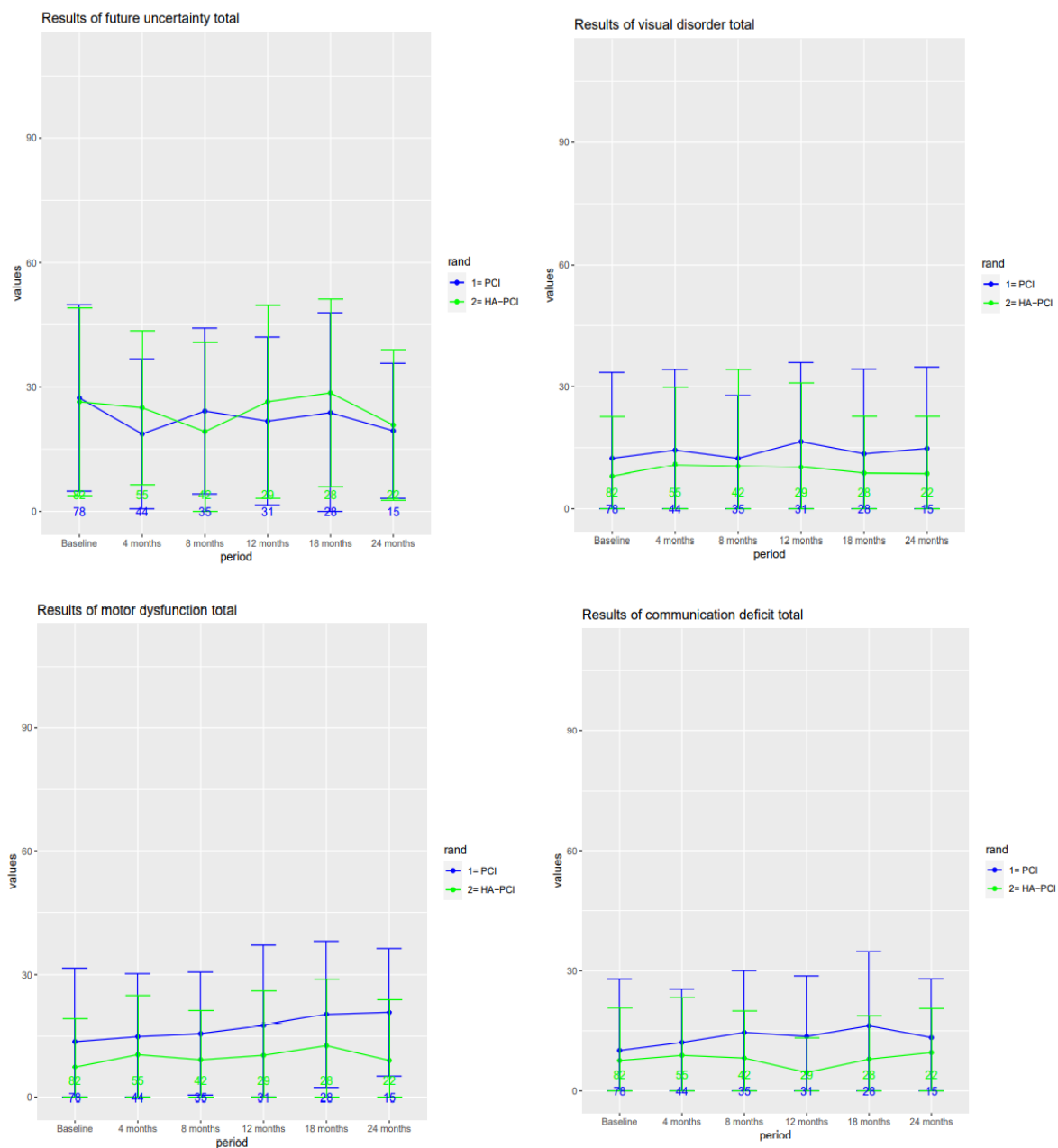
Supplementary Figure 2. Mean scores of EORTC QLQ-BN20 for future uncertainty, visual disorder, motor dysfunction and communication deficit.

Abbreviations: HA; hippocampal avoidance. PCI; prophylactic cranial irradiation.

Discussion

Much research is being conducted into hippocampal avoidance during prophylactic irradiation (HA-PCI) to preserve cognition. This trial previously reported no observed beneficial effects of HA-PCI compared to PCI on tested cognition in SCLC patients. Here we report the findings on SRCF and QoL. This trial did not find a clinically relevant nor statistically significant benefit in SRCF, using the EORTC QLQ-C30 and the MOS in patients with SCLC treated with HA-PCI compared with PCI. There was also no clinically relevant nor statically significant benefit for patients treated with HA-PCI regarding overall QoL. With two exceptions, no significant differences between arms were demonstrated for self-reported physical functioning, emotional functioning, role functioning and fatigue, neither at the individual nor the group level. The exceptions were a significant difference in physical functioning at 12 months and a significant difference in motor functioning at 24 months (more patients improved and deteriorated over time in the PCI arm and more patients remained stable in the HA-PCI arm). Given the large number of comparisons and the small sample sizes (n=16 in the PCI arm and n=22 in the HA-PCI arm at 24 months follow-up) at the later measurement points, we think that this statistical significance at a single time point is not clinically significant. Nevertheless, independent of treatment, more than one-third of patients treated with PCI and HA-PCI reported a deterioration of cognitive function at any given time point, regardless of treatment arms.

These findings are consistent with the primary endpoint of the trial, demonstrating that compared with PCI alone, HA-PCI did not preserve learning and memory, nor other aspects of cognitive functioning [14].

Two other phase III randomized trials also have investigated the potential benefit of HA-PCI/WBRT compared with regular PCI/WBRT[12,13]. Our results differ from the positive yet also conflicting findings of these two randomized trials: in the PREMER trial (patients with SCLC) it was found that compared with PCI, HA-PCI preserved objective cognitive functioning assessed by FCSRT but not SRCF[13], and in the NRC CC001 trial (patients with BM) it was demonstrated that compared with WBRT plus memantine, HA-WBRT plus memantine better preserved cognition both objectively assessed (including the HVLT-R, COW and TMT-A and B) and self-reported cognitive symptoms (measured with the EQ-5D-5L) and MDASI-BT questionnaire)[12]. Interestingly, all three trials reported that there were no significant differences between treatment arms regarding QoL, including global health status, physical functioning, emotional functioning, role functioning, fatigue, and pain/discomfort.

Conducted in parallel to the NRG CC001, the phase II/III trial of HA during PCI for SCLC was developed: The NRG CC003[22]. This trial has completed the accrual phase and the results are eagerly awaited as it would add evidence to the discussion about the use of HA-PCI in patients with SCLC.

Similar to other trials, the interpretation of our results is hampered by the high dropout rates at later time points. However, this dropout was balanced between both treatment arms and reflects the aggressive natures of SCLC and as such daily clinical practice. Another limitation is that as secondary endpoints, the trial was not powered to detect a statistically significant difference between arms for SRCF and QoL, especially at later time points. However, this was similar as for other trials such as the PREMER and NRC CC001 trial.

Furthermore, the same cut-off of 10 points is used for all sub-scales to measure minimal clinical important differences. This cut-off is often used in studies of QoL[21]. However, different subscales might require different cut-off points. Furthermore, the same cut-off of 10 points was used to determine deterioration or improvement of scores, while scoring changes into trivial, small, medium or large improvement or deterioration might be more informative. Therefore, this cut-off may be too simplistic and clinically meaningful change can be underestimated.

In conclusion, in line with previously published primary results of the NCT01780675 trial that reported no reduced probability of cognitive decline in patients receiving HA-PCI compared to PCI, we did not observe a statistically significant nor a clinically significant benefit of HA-PCI versus PCI regarding SRCF and QoL among patients with SCLC.

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6

Chapter 7

Impact of hippocampal avoidance-prophylactic cranial irradiation on brain metastases and self-reported cognitive functioning: pooled findings of NCT01780675 and PREMER trials

Zeng H*, Schagen SB*, Hendriks LEL, Sánchez-Benavides G, Jaspers JPM, Manero RM, Lievens Y, Mejía MM, Kuenen M, Rico-Oses M, Albers EAC, Samper P, Houben R, de Ruiter MB, Dieleman EMT, López-Guerra JL, de Jaeger K, Couñago F, Lambrecht M, Calvo-Crespo P, Belderbos JSA, De Ruysscher DKM**, Rodríguez de Dios N**.

*Equal contributing

** Equal contributing

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Abstract

Purpose: To investigate whether hippocampal avoidance-prophylactic cranial irradiation (HA-PCI) increases the risk of brain metastases (BM) development within the HA area and protects self-reported cognitive functioning (SRCF) in small cell lung cancer (SCLC) using the pooled individual patient data of two phase III randomized controlled trials: NCT01780675 (Dutch-Flemish) and PREMER/NCT02397733 (Spanish).

Methods: Patients with stage I-IV SCLC were randomized to PCI or HA-PCI. Brain magnetic resonance imaging (MRI) with contrast enhancement was performed and SRCF was assessed up to 24 months follow-up. The primary endpoints were BM location and longitudinal SRCF.The main secondary endpoints included BM incidence and self-reported cognitive impairment (defined as SRCF<75).

Results: In total, 168 and 150 patients were randomized in the Dutch and Spanish trial, respectively. The median follow up was 41.7 (95%CI 35.7-47.6) months, during which 61 patients developed BM (PCI:30, HA-PCI: 31, p=0.9). BM site was solitary in 15 patients (PCI:7, HA-PCI:8, p=0.8). Nine of the 61 patients had BM within the HA area (PCI:4, HA-PCI:5, p=1.0).The BM incidence was not significantly different between arms (subdistribution hazard ratio [sHR] 1.03, 95%CI 0.62-1.70, p=0.91). The incidence of cognitive impairment was significantly lower in the HA-PCI arm at 4-months (PCI arm 54.8% vs HA-PCI 26.0%, p^*=0.04), but not significantly different at other time points. Longitudinal generalized estimating equation (GEE) analysis showed that HA-PCI neither had a significant impact on SRCF (β = 1.406, p=0.515) nor on cognitive impairment (SRCF<75) (OR 0.811, 95%CI 0.526 – 1.251, p = 0.344) over time.

Conclusion: HA-PCI did not lead to an increased incidence of BM within or out of the HA zone, nor preserve longitudinal SRCF over time. HA-PCI reduced self-reported cognitive impairment incidence only at 4-months.

Keywords:

hippocampal avoidance-prophylactic cranial irradiation (HA-PCI), brain metastases (BM), self-reported cognitive functioning (SRCF), small cell lung cancer (SCLC).

Trials registration:

ClinicalTrials.gov (NCT01780675)

ClinicalTrials.gov (NCT02397733)

Introduction

Small cell lung cancer (SCLC) is an aggressive disease with a high (>50%) cumulative incidence of brain metastases (BM) and a poor 5-year overall survival (OS) rate (<10%)[1]. Prophylactic cranial irradiation (PCI) is an effective treatment to reduce BM incidence and it improves the OS[2,3]. However, it is an ongoing concern that PCI could cause neurocognitive impairment[4]. It has been shown that the hippocampus plays an important role in neurocognitive functioning and that the risk of BM within the hippocampal area is low (4/503, 0.8%)[5]. Therefore, hippocampal avoidance (HA) PCI and HA-whole-brain radiotherapy (HA-WBRT) have been proposed and explored in clinical trials to maintain the beneficial effects but to reduce the neurotoxicity of PCI/WBRT in patients with SCLC[6-9]. The phase II single arm RTOG0933 trial compared HA-WBRT for BM in SCLC with historical series and found that HA-WBRT was associated with preservation of memory ($p<0.001$)[6]. A single arm phase II trial (SAKK 15/12) showed that early HA-PCI was similar to historical control in terms of neurocognitive function decline and BM prevention[9].

Two comparable phase III randomized controlled trials (RCTs) resulted in conflicting conclusions on the role of HA-PCI on cognitive function as assessed with neuropsychological tests in patients with SCLC[7,8]. The NCT01780675 (Dutch-Flemish) study showed that the percentage of patients with cognitive decline was not significantly different between both arms (28% for HA-PCI vs 29% for PCI, $p=1.000$)[7]. In contrast, the PREMER/NCT02397733 (Spanish) trial revealed that the percentage of patients with cognitive decline after HA-PCI was significantly lower compared with PCI (5.8% for HA-PCI vs 23.5% for PCI, $p=0.003$)[8]. Of note, despite high similarities in design, these two trials used different neurocognitive tests to evaluate cognitive decline, which could have contributed to the different outcomes. Interestingly, both trials demonstrated that the self-reported cognitive functioning (SRCF), using the same instrument (EORTC-QLC-C30), was not significantly different between the HA-PCI and PCI treatment[8,10]. BM incidence and OS were also not significantly different between the HA-PCI and PCI arms in both trials (2-year BM incidence: Dutch: 16% vs 20%, $p=0.6$; Spanish: 22.8% vs 17.7%, $p=0.43$; median OS: Dutch: 18.5 months vs 19.9 months, $p=0.7$; Spanish: 23.4 months vs 24.9 months, $p=0.56$).

As number of patients with events (neurocognitive decline or BM) was relatively low in both trials, it is difficult to draw firm conclusions. To further investigate the role of HA-PCI on BM prevention and cognitive functioning preservation for patients with SCLC, we compared and pooled these two phase III RCTs in the current study. We investigated the safety (BM incidence and location) and benefits (preservation of SRCF) of HA-PCI based on the pooled

individual patient data. We only pooled the SRCF data, as the object cognitive tests did not overlap in these two trials.

Patients and Methods:

The time of enrollment and patient eligibility criteria of the two trials have been published previously[7,8]. Briefly, between April 2013 and October 2019, patients (age ≥18 years) with pathologically confirmed stage I-IV SCLC, without progression after chemoradiotherapy or chemotherapy, and without BM on a contrast-enhanced magnetic resonance imaging (MRI) scan were randomized to PCI or HA-PCI. Written informed consent was obtained from all patients. Both trials (NCT01780675, NCT02397733) were approved by the Medical Ethics Committee of each institute and conducted according to the Declaration of Helsinki.

Each patient underwent a high-resolution, three-dimensional T1-weighted gadolinium-contrasted brain MRI scan at baseline (after chemoradiotherapy or chemotherapy), 4-, and 12-months in the Dutch trial and at baseline, 3-, 12-, and 24-months in the Spanish trial. The baseline MRI scan was co-registered with the simulation computed tomography (CT) scan to delineate the hippocampi according to the RTOG 0933 atlas[11]. The prescribed PCI dose was 25 Gy in 10 fractions, five fractions per week. For the HA-PCI arm, the HA zone (HAZ) (hippocampus with 5mm volumetric expansion) was irradiated to a limited dose (Dutch: maximum (D1%) ≤ 10 Gy, mean ≤ 8.5 Gy; Spanish: optimum maximum ≤ 16 Gy, D100% ≤ 9 Gy, mean dose was not reported). Additionally, brain MRI or CT was performed ad interim when patients developed new neurological symptoms during follow-up. In patients diagnosed with BM on imaging, the BM location was recorded. In case of BM in the proximity of the underdosed regions, the MRI/CT-scans were matched to the planning CT-scan and visually inspected to see if the BM were located in the HAZ.

Different neurocognitive tests were performed at pre-specified time points to evaluate patients' objective cognitive function in these two trials. In both trials, the EORTC-QLQ-C30 questionnaire[12] was used to evaluate the quality of life (QoL) at the forementioned time points (both: baseline, 12-, and 24-months after completion of PCI; Dutch: 4-, 8-, and 18-months; Spanish: 3- and 6-months) (Appendix Table 1). In this current pooled analysis, SRCF was evaluated with the cognitive functioning scale of the EORTC-QLQ-C30 at baseline, 3-, 4-, 6-, 8-, 12-, 18-, and 24-months. Measurements within the time window (until the start of PCI for baseline, within 2 weeks for 3~8 months, within 1 month for 12~24 months) were analyzed, others (outside the window) were scored as missing. The assessment compliance at each time point was calculated among alive patients who had a pre-specified assessment plan. For patients

alive, who missed a SRCF assessment at at least one of the pre-specified time points, the SCLC disease progression rates were compared between the HA-PCI and PCI arms to check whether the missing was balanced between arms. The threshold of SRCF<75 was used to examine clinically relevant cognitive impairment[13,14]. Cognitive impairment incidence was calculated among all patients who had an assessment within the time window. Self-reported cognitive impairment was classified into four types according to the dynamic change over time: sustained, reversible, recurring, and alternating[13].

Appendix Table 1. Comparison of the trials

	NCT01780675 (Dutch-Flemish)	PREMER (Spanish)
Patients and randomization	**SCLC without BM and PD, HA-PCI vs PCI (25 Gy in 10 fractions)**	
Hippocampi dose constraits	Maximum (D1%) ≤ 10 Gy, mean ≤ 8.5 Gy	Maximum ≤ 16 Gy, D100% ≤ 9 Gy
Sample size	168 (84 in each arm)	150 (75 in each arm)
Recruitment period	April 2013 ~ March 2018	March 2015 ~ October 2019
Cognitive tests, QoL questionnaires	1. HVLT-R; 2. Trail making A, B; 3. COWAT; 4. WAIS III Digit Span; 5. WAIS III Digit Symbol; 6. Grooved Pegboard; 7. **QLQ-C30**; 8. **CTCAE 4.0**.	1. FCSRT; 2. **QLQ-C30**; 3. BN20; 4. **CTCAE 4.0**.
Assessment battery	**Baseline, 4, 8, 12, 18, and 24 months**	**Baseline, 3, 6, 12, and 24 months**
Brain MRI	**Baseline, 4, and 12 months**	**Baseline, 3, 12, and 24 months**
Primary endpoint	The total recall on HVLT-R at 4 months (decline ≥5 points).	The delayed free recall on FCSRT at 3 months (decline ≥3 points).

Abbreviations: SCLC, small cell lung cancer; BM, brain metastases; PD, progressive disease; PCI, prophylactic cranial irradiation; HA, hippocampal avoidance; QoL: quality of life; MRI, magnetic resonance imaging. .
Cognition/QoL tests:
1. QLQ-C30, The EORTC Quality-of-Life Questionnaire-C30;
2. BN20, the EORTC QLQ Brain Cancer Module;
3. CTCAE 4.0, Common Terminology Criteria for Adverse Events (version 4.0);
4. ADLS, Activities of Daily Living Scale;
5. HVLT-R, Hopkins Verbal Learning Test-Revised;
6. COWAT, Controlled Oral Word Association Test;
7. WAIS-III, Wechsler Adult Intelligence Scale-III;
8. FCSRT, Free and Cued Selective Reminding Test.

Statistical analyses:

The primary endpoints were BM location and SRCF. The secondary endpoints were whether patients developed BM during follow-up, time-to-BM, BM incidence over time, OS, and self-reported cognitive impairment (SRCF<75), Characteristics of patients, brain MRI compliance at each time point, overall BM incidence, and BM location during follow-up were compared using χ^2-test/Fisher's exact test. Patients who were diagnosed with BM or died during follow-up were excluded for MRI compliance analysis at the subsequent time points. Time to BM was calculated from the date of randomization to imaging diagnosis date. BM incidence

over time was estimated using cumulative incidence function[15] and compared using competing risk analysis (Fine-Gray model), in which death without BM was regarded as a competing event[16,17]. OS was calculated from randomization to death or the last follow-up, and estimated using the Kaplan-Meier method, and compared via log-rank test. Compliance of SRCF assessment and incidence of cognitive impairment (SRCF<75) at each time point were compared between arms using χ^2-test/Fisher's exact test. Longitudinal impacts of HA on SRCF and cognitive impairment (SRCF<75) were evaluated by performing generalized estimating equation (GEE) analysis. All tests are 2-sided and *p values* < 0.05 are considered statistically significant. For multiple comparisons, adjustments were performed by the Holm-Bonferroni method (*p**). All analyses were performed using IBM SPSS, version 27.0 (IBM Corp) and R, version 4.1.2 (R Project for Statistical Computing).

Results:

Patients characteristics:

A total of 168 (84 in each arm) and 150 (75 in each arm) patients were randomized in the Dutch and the Spanish trial, respectively. Fourteen patients in the PCI arm and 10 in the HA-PCI arm did not receive PCI (Figure 1). The median age was 64 years (range: 36-86), 131 of the 318 (41.2%) patients were female. Generally the patients were in good performance (95.8% WHO 0-1) and 29.2% of the patients had extensive disease (stage IV), 58.8% received concurrent chemoradiotherapy (CCRT), and 53.6% underwent twice-daily radiotherapy (TDRT). Patients and tumor characteristics were not significantly different between the arms (Table 1).

Compared with the Spanish trial, there were more females (50.6% vs 30.7%, *p* < 0.001) in the Dutch trial, more current smokers (73.0% vs 50.7%, *p* < 0.001), worse performance status (0: 24.4% vs 72.0%; 1: 69.4% vs 26.0%; 2: 5.6% vs 2.0%; 3: 0.6% vs 0.0%; *p*<0.001), more patients had non-malignant medical history, and more patients reported cognitive impairment at baseline (32.7% in Dutch vs 18.0% in Spanish, *p* = 0.003). In addition, more patients received an etoposide-platinum based chemotherapy regimen and TDRT in the Dutch trial. Furthermore, more patients received chemotherapy alone without thoracic radiotherapy in the Dutch trial (Appendix Table 2). Other characteristics did not differ significantly between the trials.

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┌─────────────────────────────────────────────────────┐
│        Enrolled and randomized patients (n=318)       │
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Allocation

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┌──────────────────────────────────┐   ┌──────────────────────────────────┐
│  Allocated to PCI arm (n=159)     │   │  Allocated to HA-PCI (n=159)      │
└──────────────────────────────────┘   └──────────────────────────────────┘
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Treatment

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┌──────────────────────────────────┐   ┌──────────────────────────────────┐
│ Received PCI (n=145)              │   │ Received HA-PCI (n=149)           │
│ Did not receive PCI (n=14)        │   │ Did not receive HA-PCI (n=10)     │
│   Ineligible (brain metastases)(n=2)│  │   Ineligible (brain metastases)(n=2)│
│   Ineligible (progression) (n=7)  │   │   Ineligible (progression) (n=2)  │
│   Refused (n=3)                   │   │   Refused (n=4)                   │
│   Received HA-PCI (n=2)           │   │   Other concomitant disease (n=2) │
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Analysis

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┌──────────────────────────────────┐   ┌──────────────────────────────────┐
│ Brain metastases (n=157)          │   │ Brain metastases (n=157)          │
│ Overall survival (n=159)          │   │ Overall survival (n=159)          │
│ SRCF (n=159)                      │   │ SRCF (n=159)                      │
└──────────────────────────────────┘   └──────────────────────────────────┘
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Figure 1. The CONSORT diagram.

*Abbreviations***:** HA, hippocampal avoidance; PCI, prophylactic cranial irradiation; SRCF, Self-reported cognitive functioning.

Table 1. Patients characteristics

		Number (%)		
		PCI (n=159)	HA-PCI(n=159)	*p*
Trials				1.0
	NCT01780675	84 (52.8)	84 (52.8)	
	PREMER	75 (47.2)	75 (47.2)	
Demographic features at randomization				
Age-years				1.0
	Median (range)	64 (43-86)	65 (36-82)	
	Mean ± SD	63.5 ± 8.0	63.7 ± 8.8	
	≤60	54 (34.0)	54 (34.0)	
	>60	105 (66.0)	105 (66.0)	
Gender				0.57
	Male	96 (60.4)	91 (57.2)	
	Female	63 (39.6)	68 (42.8)	
Smoking history				0.17
	Current smoker	88 (57.5)	102 (67.1)	
	Former smoker	61 (39.9)	45 (29.6)	
	Never	4 (2.6)	5 (3.3)	
	Missing	6	7	
Prior malignancy				1.0
	No	145 (91.8)	145 (91.8)	

Table 1. Patients characteristics

	Number (%) PCI (n=159)	HA-PCI(n=159)	p
Yes	13 (8.2)	13 (8.2)	
Missing	1	1	
Non-malignant medical history			
Stroke/TIA/CVA			0.58
No	144 (94.1)	149 (95.5)	
Yes	9 (5.9)	7 (4.5)	
Missing	6	3	
Cardiovascular			
No	71 (46.4)	66 (42.3)	0.47
Yes	82 (53.6)	90 (57.7)	
Missing	6	3	
Pulmonary			0.48
No	120 (78.4)	117 (75.0)	
Yes	33 (21.6)	39 (25.0)	
Missing	6	3	
Diabetes			0.81
No	133 (86.9)	137 (87.8)	
Yes	20 (13.1)	19 (12.2)	
Missing	6	3	
Others*			0.29
No	116 (75.8)	126 (80.8)	
Yes	37 (24.2)	30 (19.2)	
Missing	6	3	
Multiple history**			0.40
No	106 (69.3)	101 (64.7)	
Yes	47 (30.7)	55 (35.3)	
Missing	6	3	
Tumor related features			
Stage			0.90
LD (I-III)	113 (71.1)	112 (70.4)	
ED (IV)	46 (28.9)	47 (29.6)	
Performance status			0.56
0	76 (50.0)	71 (44.9)	
1	70 (46.1)	80 (50.6)	
2	5 (3.3)	7 (4.4)	
3	1 (0.7)	0 (0.0)	
Missing	7	1	
Baseline cognitive impairment***			0.38
No	112 (72.3)	121 (76.6)	
Yes	43 (27.7)	37 (23.4)	
Missing	4	1	
Treatment related features			
Chemotherapy type			0.70
EP	151 (97.4)	153 (98.1)	
Non-EP	4 (2.6)	3 (1.9)	
Missing	4	3	
Chemoradiotherapy			0.34
Chemo alone	32 (20.8)	42 (26.9)	
SCRT	25 (16.2)	28 (17.9)	
CCRT	97 (63.0)	86 (55.1)	
Missing	5	3	
Thoracic radiotherapy			0.18
No	31 (20.3)	42 (26.8)	
Yes	122(79.7)	115 (73.2)	
Missing	6	2	
Thoracic radiotherapy regimen			0.82
ODRT	57 (47.1)	52 (45.6)	

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Table 1. Patients characteristics

		Number (%)		
		PCI (n=159)	HA-PCI(n=159)	*p*
	TDRT	64 (52.9)	62 (54.4)	
	Missing	1	1	

Note:
* Other non-malignant medical history includes: psychosis disease, immune system disease, epilepsy, hypothyroidism, alcoholism, insomnia/somnolence, headache, dizziness, and meningitis;
**Multiple non-malignant medical history means two or more of the five types of non-malignant medical history (stroke/TIA/CVA, cardiovascular, pulmonary, diabetes, and others)
*** Cognitive impairment is defined as <75 on the cognitive functioning scale of QLQ-C30.
Abbreviations:
CCRT, concurrent chemoradiotherapy; CVA, cerebrovascular accident; ED, extensive stage disease; EP: etoposide-platinum; HA-PCI, hippocampus-avoidance prophylactic cranial irradiation; LD, limited stage disease; ODRT, once-daily radiotherapy; PCI, prophylactic cranial irradiation; SCRT, sequential chemoradiotherapy; SD, standard deviation; TDRT, twice-daily radiotherapy; TIA, transient ischemic attack.

Appendix Table 2. Patients characteristics between trials

		NCT01780675 (n=168)	PREMER (n=150)	*p*
Demographic features at randomization				
Age-years				0.47
	≤60	54 (32.1)	54 (36.0)	
	>60	1145 (67.9)	96 (64.0)	
Gender				**<0.001**
	Male	83 (49.4)	104 (69.3)	
	Female	85 (50.6)	46 (30.7)	
Smoking history				**<0.001**
	Current smoker	116 (73.0)	74 (50.7)	
	Former/Never	43 (27.0)	72 (49.3)	
Prior malignancy				0.17
	No	149 (89.8)	141 (94.0)	
	Yes	17 (10.2)	9 (6.0)	
Non-malignant medical history				
Stroke/TIA/CVA				0.75
	No	153 (94.4)	140 (95.2)	
	Yes	9 (5.6)	7 (4.8)	
Cardiovascular				
	No	78 (48.1)	59 (40.1)	0.16
	Yes	84 (51.9)	88 (59.9)	
Pulmonary				**<0.001**
	No	107 (66.0)	130 (88.4)	
	Yes	55 (34.0)	17 (11.6)	
Diabetes				0.06
	No	147 (90.7)	123 (83.7)	
	Yes	15 (9.3)	24 (16.3)	
Others*				**<0.001**
	No	107 (66.0)	135 (91.8)	
	Yes	55 (34.0)	12 (8.2)	
Multiple history**				**<0.001**
	No	93 (57.4)	114 (77.6)	
	Yes	69 (42.6)	33 (22.4)	
Tumor related features				
Stage				0.83
	LD (I-III)	118 (70.2)	107 (71.3)	
	ED (IV)	50 (29.8)	43 (28.7)	
Performance status				**<0.001**
	0	39 (24.4)	108 (72.0)	

Appendix Table 2. Patients characteristics between trials

	NCT01780675 (n=168)	PREMER (n=150)	p
1	111 (69.4)	39 (26.0)	
2	9 (5.6)	3 (2.0)	
3	1 (0.6)	0 (0)	
Baseline cognitive impairment***			**0.003**
No	107 (67.5)	123 (82.0)	
Yes	53 (32.5)	27 (18.0)	
Treatment related features			
Chemotherapy type			**0.04**
EP	161 (99.4)	143 (96.0)	
Non-EP	1 (0.6)	6 (4.0)	
Chemoradiotherapy			**<0.001**
Chemo alone	52 (32.5)	22 (14.7)	
SCRT	13 (8.1)	40 (26.7)	
CCRT	95 (59.4)	88 (58.7)	
Thoracic radiotherapy			**<0.001**
No	51 (31.9)	22 (14.7)	
Yes	109 (68.1)	128 (85.3)	
Thoracic radiotherapy regimen			**<0.001**
ODRT	15 (14.0)	94 (73.4)	
TDRT	92 (86.0)	34 (26.6)	

Note:
* Other non-malignant medical history includes: psychosis disease, immune system disease, epilepsy, hypothyroidism, alcoholism, insomnia/somnolence, headache, dizziness, and meningitis;
**Multiple non-malignant medical history means two or more of the five types of non-malignant medical history (stroke/TIA/CVA, cardiovascular, pulmonary, diabetes, and others)
*** Cognitive impairment is defined as <75 on the cognitive functioning scale of QLQ-C30.
Abbreviations:
CCRT, concurrent chemoradiotherapy; CVA, cerebrovascular accident; ED, extensive stage disease; EP: etoposide-platinum; HA-PCI, hippocampus-avoidance prophylactic cranial irradiation; LD, limited stage disease; ODRT, once-daily radiotherapy; PCI, prophylactic cranial irradiation; SCRT, sequential chemoradiotherapy; SD, standard deviation; TDRT, twice-daily radiotherapy; TIA, transient ischemic attack.

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BM:

The median follow up was 41.7 months (95%CI 35.7-47.6), during which 202 patients died (104 in PCI, 98 in HA-PCI). The MRI compliance at each pre-specified time point dropped from 100% at baseline to 55% at 24-months. No significant difference between arms was observed at each time point (Figure 2). Sixty-one patients developed BM (30 in PCI, 31 in HA-PCI, *p*=0.9). Fifteen patients had a solitary BM (7 in PCI arm, 8 in HA-PCI arm, *p*=0.8). Nine of the 61 patients had BM within the HA zone (4 in PCI, 5 in HA-PCI, *p*=1.0). One had a solitary BM within the HA area (HA arm, *p*=1.0) (Table 2). The cumulative BM incidence over time was not significantly different between arms (2-year BM incidence: 18.3% in PCI vs 19.3% in HA-PCI, subdistribution hazard ratio [sHR] 1.03, 95%CI 0.62-1.70, *p*=0.91) (Figure 3).

OS:

The OS was not significantly different between arms (median: 22.9 months [95%CI: 17.9-27.9] in PCI vs 22.8 months [95%CI: 14.9-30.8 months] in HA-PCI, HR 0.91, 95%CI 0.69-1.19, *p*=0.48) (Appendix Figure 1).
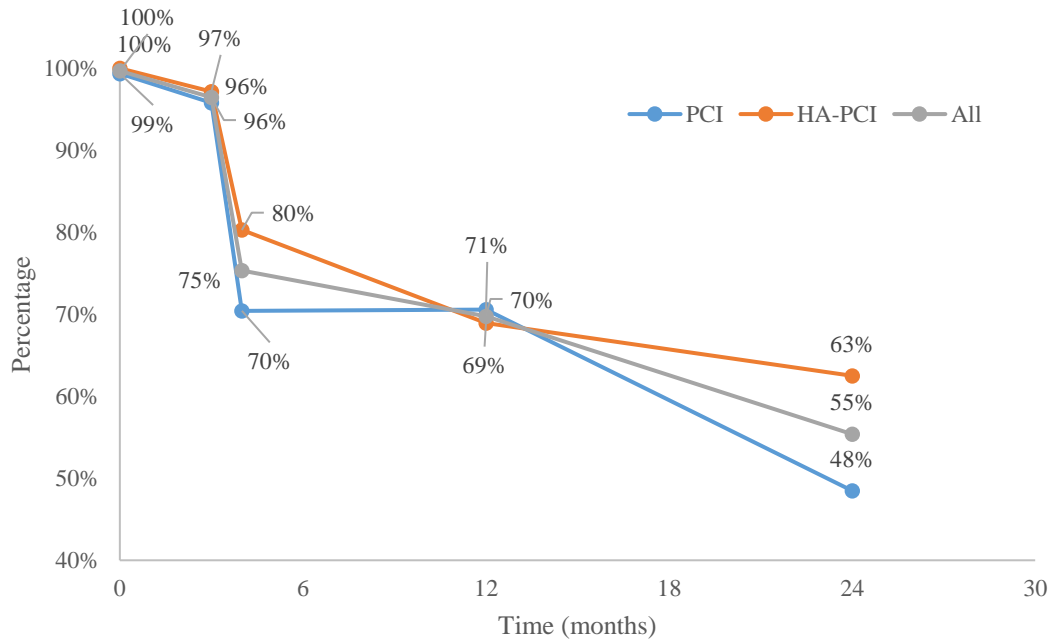
Figure 2. Compliance of brain MRI at each time point.

The compliance of brain MRI at each time point was calculated among alive patients who had a pre-specified surveillance plan. Patients who had been diagnosed with BM or died during follow-up were excluded for MRI compliance analysis at the subsequent time points. The MRI compliance dropped over time but no significant differences were found between arms at each time point ($p > 0.05$).
Abbreviations: MRI, magnetic resonance imaging; HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

Table 2. Overall BM incidence and location during follow-up

		PCI	HA-PCI	*p*
BM				0.9
	Yes	30	31	
	No	127	126	
BM number				0.8
	Multiple	23	23	
	Solitary	7	8	
Solitary BM within HAZ				1.0
	No	7	7	
	Yes	0	1	
BM within HAZ*				1.0
	No	26	25	
	Yes	4	5	

Note: * One patient was unknown.
Abbreviations: BM, brain metastases; HA-PCI, hippocampus-avoidance prophylactic cranial irradiation; HAZ, hippocampus-avoidance zone.
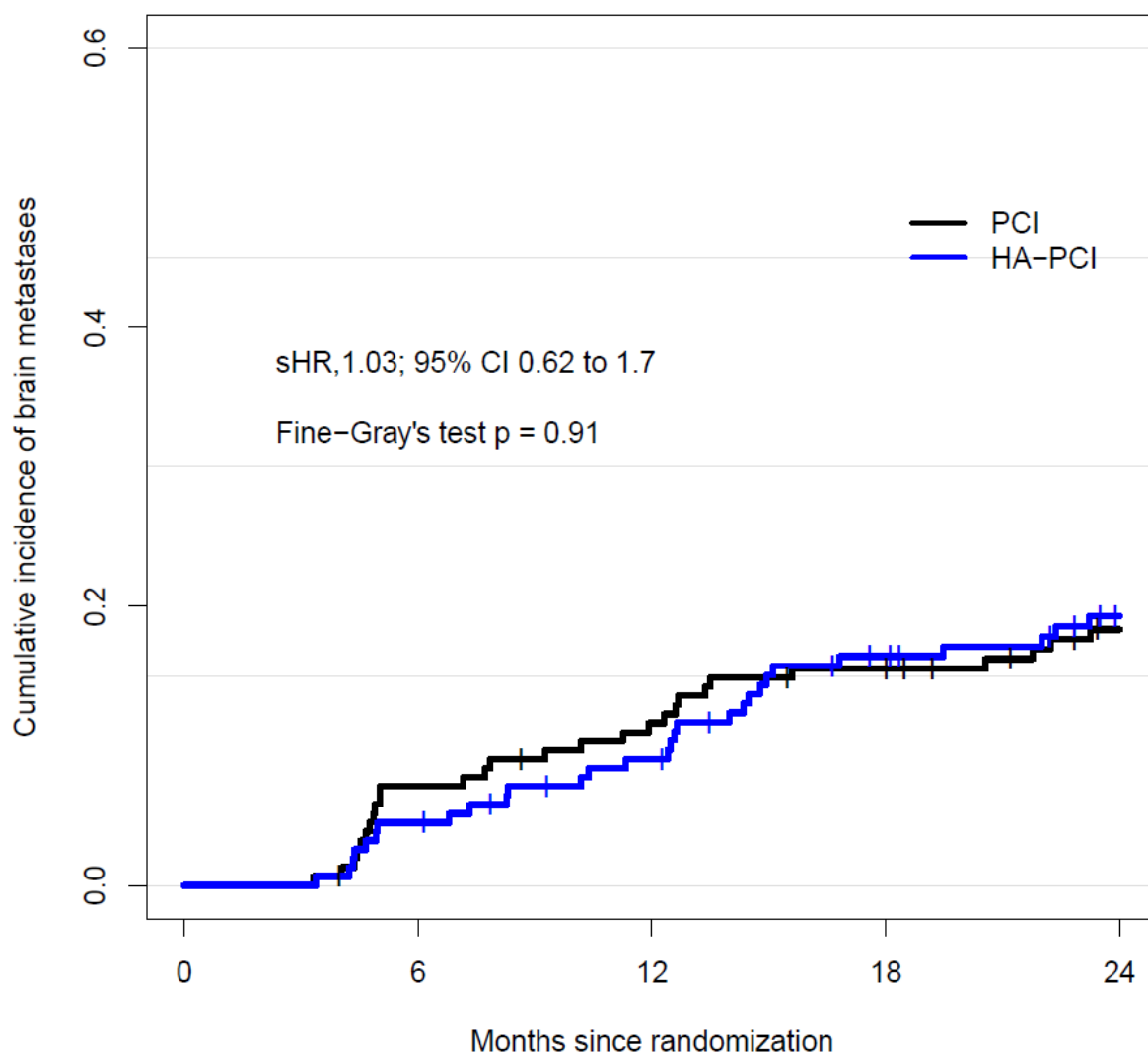
Figure 3. Brain metastases incidence

The incidence of brain metastases was not significantly different between arms (*p*=0.91).

*Abbreviations***:** HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

SRCF:

Overall, 54 out of 1016 (5.3%) SRCF assessments were evaluated at the time point out of the pre-specified time window. The compliance rate within the pre-specified time window dropped from 98.7% at baseline to 64.7% at 24-months. No significant difference in compliance rate between the two arms were observed at each time point (*p** > 0.05) (Figure 4a). The progression rate among the alive patients who did not complete the questionaires were not significantly different between arms (Appendix Table 3).
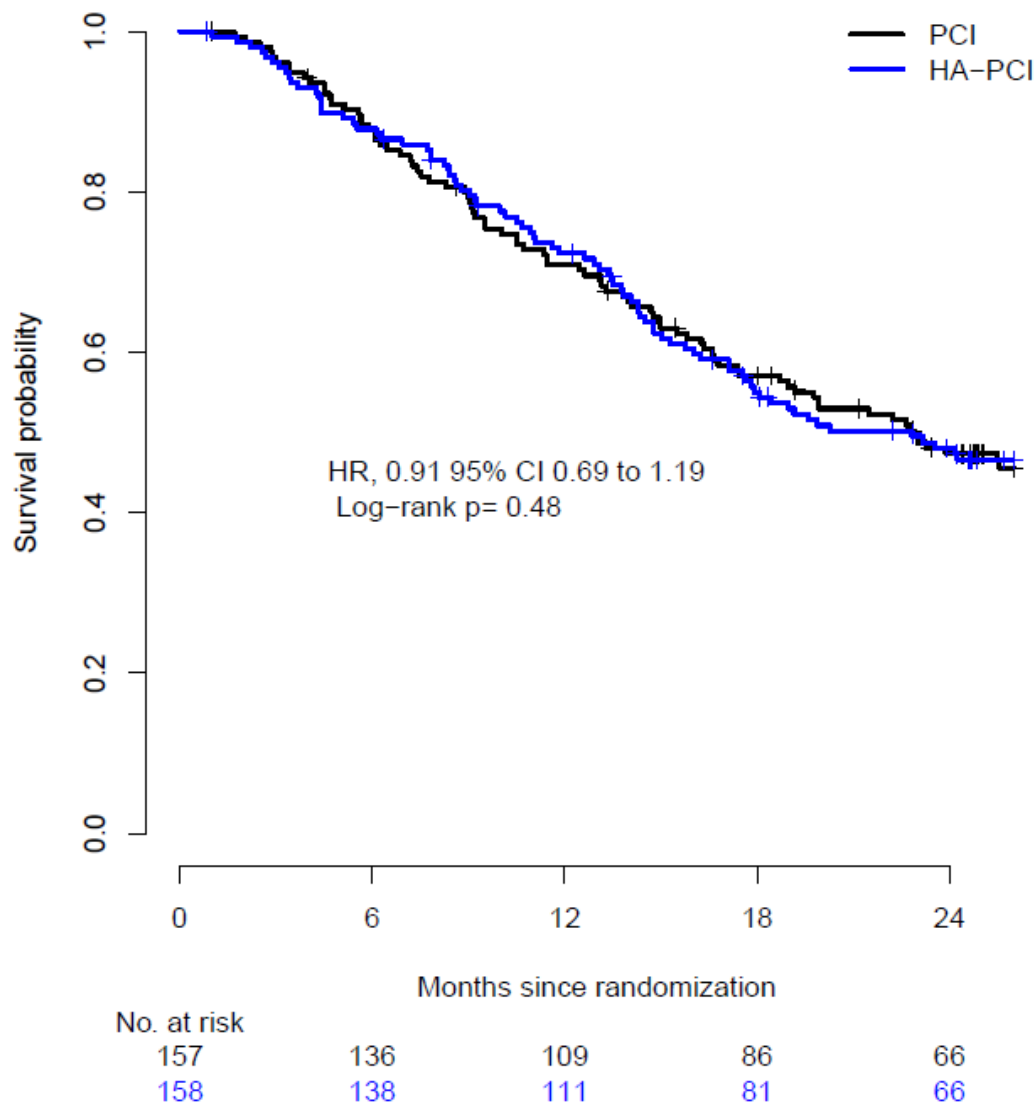
Appendix Figure 1. Overall survival.

The overall survival was not significantly different between arms (*p*=0.48).
Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

Five patients did not complete the EORTC-QLQ-C30 questionnaire at any time point. Among the other 313 patients, the self-reported cognitive impairment incidence ranged from 25.6% to 52.5% at each time point. Eighty (25.6%) patients reported cognitive impairment at baseline and 147 (47.0%) patients experienced cognitive impairment at least once (78 in PCI, 69 in HA-PCI, *p*=0.24). Among the 147 patients who reported cognitive impairment, 49 sustained, 31 reversed, 15 recurred, 3 reversed and recurred alternatingly, and 49 were not evaluable because of missing data. The constituent ratio of cognitive impairment types was not significantly different between the arms (*p*=0.32) (Appendix Figure 2). Among patients without cognitive impairment at baseline (n=233), 50 patients did not reassess SRCF, 67 of the rest 183 (36.6%) patients experienced cognitive impairment at least once (35/86 in PCI, 32/98 in
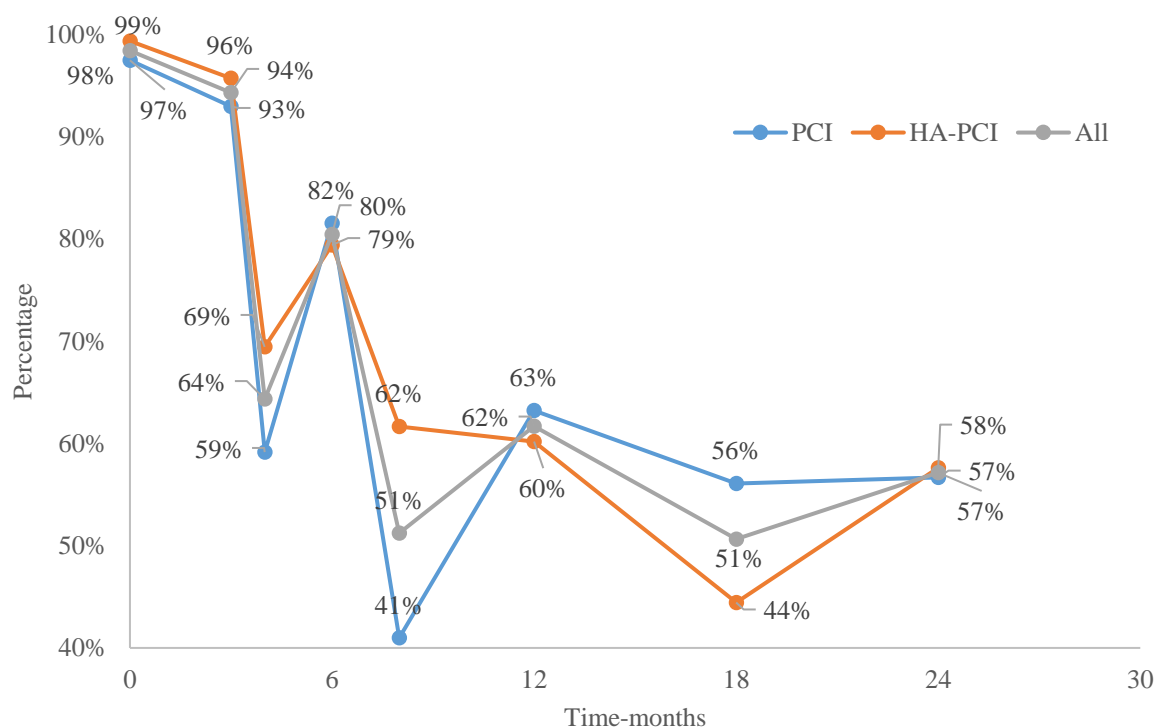
No. assessed/should assess

Time	0	3	4	6	8	12	18	24
All	313/318	133/141	92/143	108/133	63/121	132/214	39/77	77/119
HA-PCI	158/159	67/70	50/72	54/68	37/60	65/108	16/36	44/59
PCI	155/159	66/71	42/71	53/65	25/61	67/106	23/41	34/60
*p**	*1.00*	*1.00*	*1.00*	*1.00*	*0.18*	*1.00*	*1.00*	*0.92*

Figure 4a. Compliance of cognitive functioning assessment at each time point:

The compliance at each time point was calculated among alive patients who had a pre-specified assessment plan. It was significantly higher in the HA-PCI arm compared with the PCI-arm at 8 months (61.7% vs 41.3%, *p*=0.02). No significant difference was observed at other time points.
Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

HA-PCI, *p*=0.26). Self-reported cognitive impairment incidence at each time point was not significantly different between arms except for that at 4-months, which favored the HA-PCI arm (PCI arm 54.8% vs HA-PCI 26.0%, *p**=0.04) (Figure 4b).

GEE analysis showed that HA-PCI did not have a significant impact on longitudinal SRCF (β = 1.406, *p*=0.515) nor cognitive impairment (SRCF<75) (odds ratio [OR] 0.811, 95%CI 0.526 – 1.251, *p* = 0.344) (Appendix Figure 3).

Discussion:

Compared with conventional PCI, this pooled phase III trials analysis confirmed that HA-PCI is safe, does not increase the risk of BM within or beyond the hippocampal avoidance zone

Appendix Table 3. Alive patients who missed SRCF at pre-specified time points

Time points - months		PCI	HA-PCI	*p*
0				NA
	Progression	0 (0.0)	0 (0.0)	
	No progression	4 (100.0)	1 (100.0)	
3				1.0
	Progression	1(20.0)	0 (0.0)	
	No progression	4 (80.0)	3 (100.0)	
4				0.64
	Progression	2 (6.9)	3 (13.6)	
	No progression	27 (93.1)	19 (86.4)	
6				0.68
	Progression	5 (41.7)	4 (28.6)	
	No progression	7 (58.3)	10 (71.4)	
8				0.50
	Progression	11 (30.6)	9 (39.1)	
	No progression	25 (69.4)	14 (60.9)	
12				0.34
	Progression	15 (38.5)	21 (48.8)	
	No progression	24 (61.5)	22 (51.2)	
18				0.78
	Progression	10 (55.6)	12 (60.0)	
	No progression	8 (44.4)	8 (40.0)	
24				0.86
	Progression	10 (38.5)	9(36.0)	
	No progression	16 (61.5)	16 (64.0)	

Abbreviations:
HA-PCI, hippocampus-avoidance prophylactic cranial irradiation.
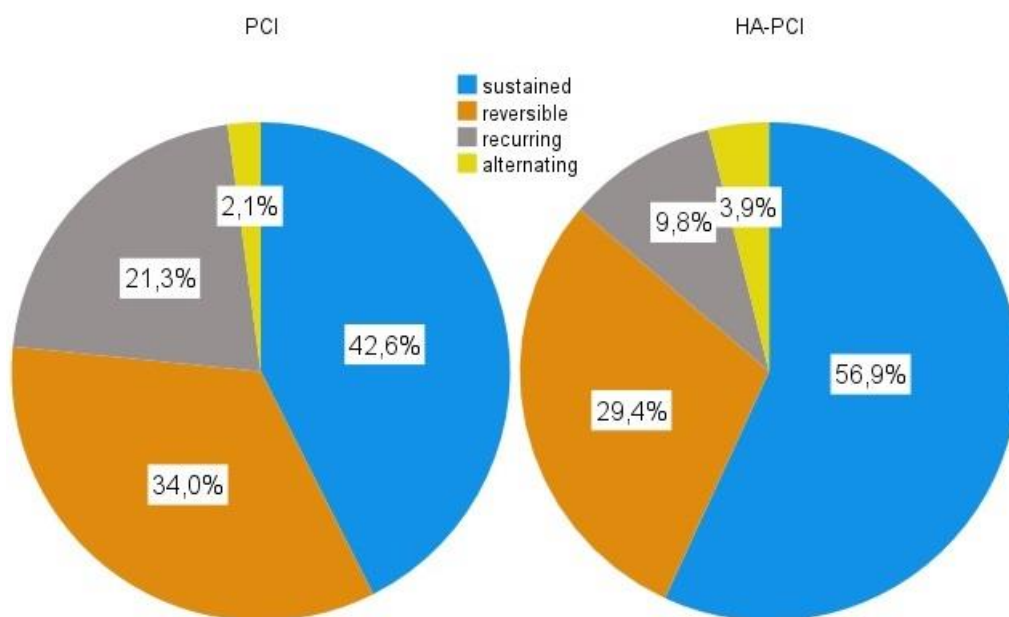
Appendix Figure 2. Cognitive impairment types.

The constituent ratios of cognitive impairment types were not significantly different between arms ($\chi2 = 3.53$, *p*=0.32).
Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.
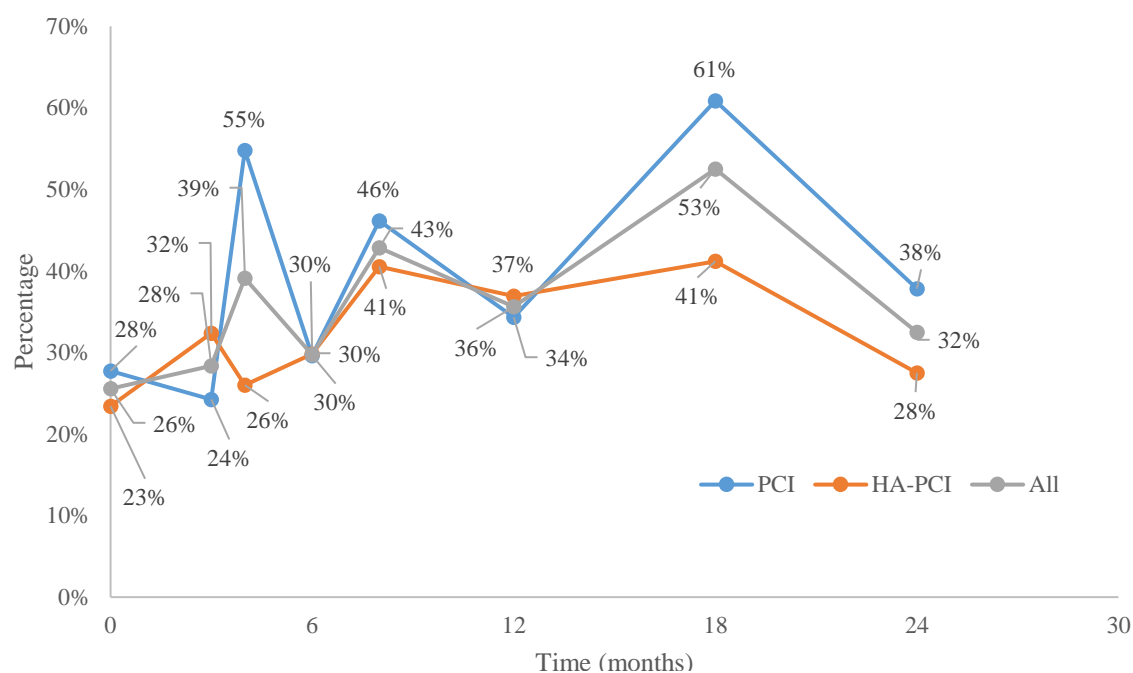
No. event/assessed

Time	0	3	4	6	8	12	18	24
All	80/313	38/134	36/92	33/111	27/63	47/132	21/40	25/77
HA-PCI	37/158	22/68	13/50	17/57	15/37	24/65	7/17	11/40
PCI	43/155	16/66	23/42	16/54	12/26	23/67	14/23	14/37
*p**	*1.00*	*1.00*	*0.04*	*0.98*	*1.00*	*1.00*	*1.00*	*1.00*

Figure 4b. Cognitive impairment incidence at each time point

The cognitive impairment incidence was calculated among all patients who had an assessment within the time window. It was significantly higher in the PCI arm compared with the HA-PCI arm at 4 months (54.8% vs 26.0%, *p*=0.005). No significant difference was observed at other time points.
Abbreviations: HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

Abbreviations: SRCF, self-reported cognitive functioning score; HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.
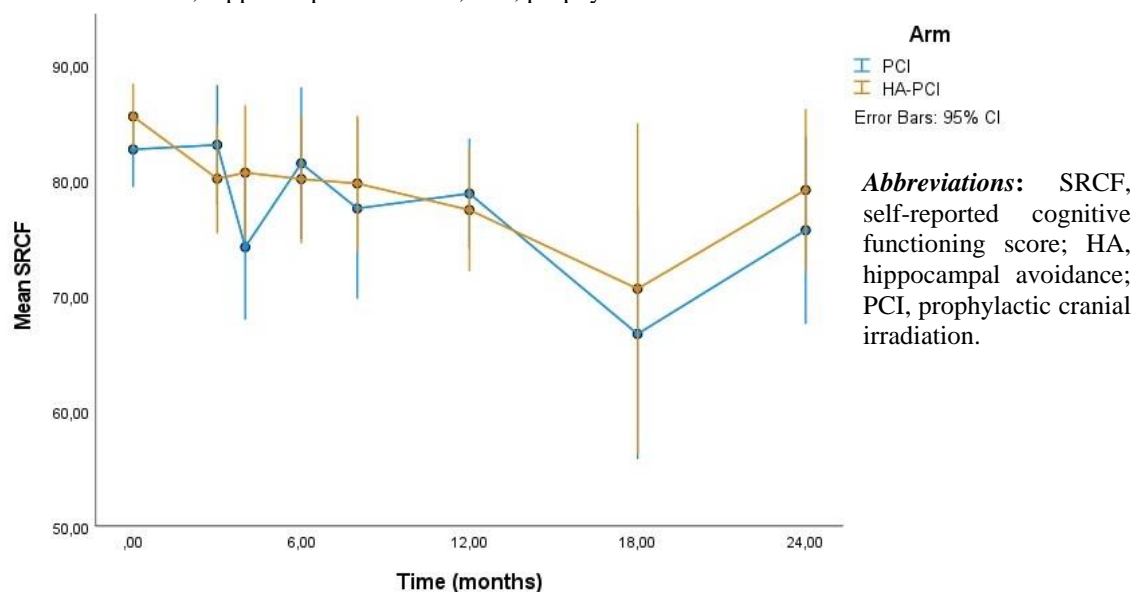
Appendix Figure 3. Mean scores of SRCF over time.

The plots showed that longitudinal SRCF over time was not significantly different between arms (*p*=0.52).

(hippocampus with 5mm volumetric expansion), and does not compromise OS. On the other hand, HA-PCI does not result in better longitudinal SRCF or cognitive impairment (SRCF<75) over time.

Our results affirmed, with a larger series, previous studies in which also a low incidence of BM within the HA zone was found, both for SCLC[18] and NSCLC[19], because of the relatively small volume of hippocampus[20]. Importantly, in our pooled analysis, the incidence of BM within the HA zone was not significantly different between HA-PCI and PCI. Only one patient developed a solitary BM within the HA zone. Therefore, HA-PCI is as effective and safe as conventional PCI. To the best of our knowledge, our pooled analysis provides the most robust evidence on the safety of HA-PCI in SCLC up to now with the largest sample size based on the only two recently published prospective phase III RCTs with a brain MRI pre-PCI. Furthermore, this is the first report on MRI compliance at each pre-specified time point in the prospective clinical trial setting, which was always lacking in earlier reports, even clinical trials[21]. It revealed that similar with neurocognitive tests, the MRI compliance dropped over time, indicating that managements are needed to improve the MRI compliance, as regular MRI can detect BM before they manifest symptoms. However, as the MRI compliance was not significantly different between arms, we can safely draw a stronger conclusion that HA-PCI does not result in an increased risk of BM development compared with conventional PCI.

This double-sample size pooled analysis further confirmed the separate analyses of each trial that longitudinal SRCF results were not significantly different between treatment arms[8,10]. Even though the compliance of SRCF assessment dropped over time, we assumed that the dropout was evenly distributed between arms and probably not informative. This was confirmed by the insignificantly different SRCF compliance rates and progression disease rate of dropouts between arms at each time point.

Interestingly, when inspecting the self-reported cognitive impairment (SRCF <75) at each time point, the HA-PCI arm demonstrated a lower cognitive impairment incidence at a single time point (4-months), which came from the Dutch trial. Considering the dynamic nature of self-reported cognitive impairment[13] and missing data of 35.7% patients, the positive finding at a single time point might fluctuate by chance. In line with the NSCLC trial[13], our current SCLC trials also showed that for individuals who have reported cognitive impairment, the impairment can be sustained, reversible, recurring, or alternating. This indicates that cognitive impairment is dynamic and needs longitudinal surveillance to draw meaningful conclusions. Another possibility could be that 4-months after PCI might be a sensitive time point to detect the preservation role of HA-PCI on SRCF, as the impairment incidence was not significantly

different at 3-months (data from the Spanish trial) nor 6-months (data from both trials). But when comparing the SRCF decline from baseline using a clinically relevant cut-off of 10 points, the self-reported cognitive decline was not significantly different between arms at 4-months or other time points[10]. Therefore, such a significantly higher incidence of self-reported cognitive impairment at a single time point might be of no clinical relevance.

Intriguingly, when evaluating the objective cognitive functioning using neuropsychological tests, the Dutch trial is more consistent towards null findings (no tested benefit on any time points)[7], while the Spanish trial stands out by its large difference in tested cognition and its total lack of difference in SRCF[8]. Causes for the above phenomenon could lie in the difference between the two trials, the difference between tested cognition and self-reported cognition in general, and the difference between neurocognitive tests.

First, participants were not completely comparable between the two trials. Despite similar eligibility criteria, we noticed that in the Dutch trial, more patients reported cognitive impairment at baseline, worse performance status, more females, more current smokers, and more pulmonary disease history, which could have influenced the neurocognitive results, especially the baseline cognitive impairment[13]. In addition, the first line chemo-radiotherapy percentages were also different between trials, even though it is unclear yet whether these treatments are correlated with neurocognitive function. Other differences have been thoroughly discussed earlier, such as close quality assurance on hippocampal delineation in the Spanish trial[22]. The quality of the HA-PCI irradiation in the Dutch trial was also assessed and showed that the adherence to the trial protocol was excellent[23].

Second, SRCF is not closely correlated with objective neurocognitive performance[24-26], which has also been found in patients with glioma[27,28]. SRCF may represent distinct elements of cognition or elements outside cognition such as anxiety, depression, coping, and fatigue[29]. These factors express a general feeling of well-being and not specifically cognitive functioning. Poor cognitive performance can and often will impair one's own judgment of his/her cognitive performance[30]. It is also interesting to look at the viewpoint of the caregiver, and indeed significant disagreements were found there[31].

Third, although both Hopkins Verbal Learning Test – Revised (HVLT-R)[32] (used in the Dutch trial) and Free and Cued Selective Reminding Test (FCSRT)[33,34] (used in the Spanish trial) are tools to evaluate memory and learning, they are not the same and likely capture different aspects of neurocognitive function (Appendix Table 4). It is unknown if both trials would have assessed the objective neurocognitive function using the same tool, the conclusion on objective neurocognitive function would have become consistent or not.

Appendix Table 4. Free and Cued Selective Reminding Test vs Hopkins Verbal Learning Test- Revised

	FCSRT	HVLT-R
Words	16	12
	self-read, 4 items a time on a card (words or pictures)	Listen, 12 words
Versions	2	6
First part	3 trials, each has 20s break (to prevent recall from short-term memory)	3 trials, no break
Trial 1		
Free recall-1 (FR1)	Maximum 2min (0-16)	0-12, no time limits
Cued recall-1 (CR1)	0~ (16-FR1)	/
Total recall-1 (TR1)	0-16	/
Trial 2		
Free recall-2 (FR2)	Maximum 2min (0-16)	0-12, no time limits
Cued recall-2 (CR2)	0~ (16-FR2)	/
Total recall-2 (TR2)	0-16	/
Trial 3	Cued recall (0-16)	0-12
Free recall-3 (FR3)	Maximum 2min (0-16)	0-12, no time limits
Cued recall-3 (CR3)	0~ (16-FR3)	/
Total recall-3 (TR3)	0-16	/
Total Free recall (FR1+FR2+FR3)	0-48	0-36
Total recall (TR1+TR2+TR3)	0-48	/
Delayed interval	30 min, non-verbal tasks	20-25 min, other neurocognitive tests
Delayed recall (DR)		
Free DR (FDR)	Maximum 2min (0-16)	0-12, no time limits
Cued DR (CDR)	0~ (16-FR3)	/
Total DR (TDR)	0-16	/
Standard score	Corrected by age and education	Corrected by age

Longitudinal neuroimaging may provide more insight in the neural damage following radiation[35]. The Dutch trial demonstrated that compared with traditional PCI, HA-PCI did result in less hippocampal atrophy at 4 and 12 months[36]. However, the hippocampal atrophy was not significantly correlated with neurocognitive decline. The Dutch trial also showed that both treatment arms with specific dose distributions were equally associated with considerable brain injury as seen on various MRI sequences. Whereas, the preliminary results of the first 60 patients in the Spanish trial showed that the reduction in hippocampal volume in the PCI arm (p=0.006) was correlated with a reduction in the total free recall of FCSRT at 6 months (Spearman correlation coefficient: 0.47, p=0.004)[37]. The total number of patients remains to be analyzed to see if the correlation persists.

In short, the pooled trials showed that self-reported cognitive impairment is dynamic in patients with SCLC after treatment. Compared with conventional PCI, HA-PCI did not significantly improve longitudinal SRCF over time, but it was associated with lower cognitive impairment at one single time point (4-months). As for the objective neurocognitive function (Dutch: no significant difference; Spanish: significantly different), no pooled-conclusion can be drawn because different tests were performed (Dutch: HVLT-R; Spanish: FSCRT), and the

test compliance at the primary end point were also different (Dutch: 63.4% at 4-months; Spanish: 93.7% at 3-months) in these two trials. Considering the cost-effectiveness[38,39] and safety, HA-PCI remains a promising irradiation technique that is worthy of more exploration in clinical trials. The upcoming results of the phase III NRG-CC003 trial will hopefully provide more clarity[40], since the same instrument (HVLT-R) was used as in the Dutch trial for objective cognition evaluation, and the same EORTC-QLQ-C30 questionnaire was used for the SRCF assessments. Besides, adding memantine in future studies might increase the possibility of cognitive preservation when administering PCI/HA-PCI, as the NRG-CC001 trial did show that HA-WBRT plus memantine preserved cognitive function better than WBRT plus memantine[41].

Conclusion:

In conclusion, compared with conventional PCI, HA-PCI was safe in terms of BM prevention and survival outcome. HA-PCI reduced self-reported cognitive impairment only at 4-months. HA-PCI did not have a benefit over PCI in terms of longitudinal SRCF. More research is warranted to identify the preservation role of HA-PCI on neurocognitive function and the results of the ongoing phase III NRG-CC003 trial are eagerly awaited.

Author contributions:

Conception and design: Haiyan Zeng, Dirk K.M. De Ruysscher

Provision of study materials or patients: Núria Rodríguez de Dios, Felipe Couñago, Maurico Murcia-Mejía, Mikel Rico-Oses, Patricia Calvo-Crespo, Pilar Samper, José Luis López-Guerra, Gonzalo Sánchez-Benavides, Rosa María Manero, José S.A. Belderbos, Dirk K.M. De Ruysscher, Sanne B. Schagen, Jaap P.M. Jaspers, Yolande Lievens, Edith M.T. Dieleman, Katrien De Jaeger, Maarten Lambrecht.

Collection and assembly of data: Haiyan Zeng, Sanne B. Schagen, José S.A. Belderbos, Michiel B. de Ruiter, Marianne Kuenen, Elaine A.C. Albers, Núria Rodríguez de Dios, Felipe Couñago, Maurico Murcia-Mejía, Mikel Rico-Oses, Patricia Calvo-Crespo, Pilar Samper, José Luis López-Guerra.

Data analysis and interpretation: Haiyan Zeng, Ruud Houben, Dirk K.M. De Ruysscher, Lizza E.L. Hendriks, Sanne B. Schagen, José S.A. Belderbos, Jaap P.M. Jaspers, Núria Rodríguez de Dios, Gonzalo Sánchez-Benavides.

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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N Rodríguez de Dios:

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F Couñago:

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The other authors declare no conflicts of interest.

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Chapter 8

Risk factors for cognitive functioning in radically treated stage III NSCLC: Secondary findings of the NVALT-11 study

Zeng H, Hendriks LEL, Witlox WJA, Groen HJM, Dingemans AC, Praag J, et al Belderbos J, Houben R, van der Noort V, De Ruysscher DKM.

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Abstract:

Aim: To identify risk factors for self-reported cognitive impairment in radically treated stage III non-small cell lung cancer (NSCLC).

Methods: Cognitive functioning was assessed using the EORTC-QLQ-C30 at seven pre-specified time points in the phase III NVALT-11 trial (observation versus prophylactic cranial irradiation [PCI] in stage III NSCLC treated with chemo-radiotherapy±surgery). Cognition was analyzed as binary (impairment or not) and continuous outcome, respectively, using generalized estimating equation (GEE) before and after multiple imputation. A score <75 was defined as cognitive impairment. A mean difference by <10, 10-<20, $\geq$ 20 points was regarded as no, moderate, and large clinical effect, respectively. We categorized the cognitive impairment into four types based on changes over time: sustained, reversible, recurring, and alternating.

Results: In the no-PCI arm, 43/84 [51.2%] reported cognitive impairment at least once, of which 31.4% were sustained, 25.7% reversible, 28.6% recurring, and 14.3% alternating. Results were similar in the PCI arm. Cognitive functioning at baseline was comparable in two arms and a score <75 was a significant risk factor with large effect for subsequent cognitive impairment (no-PCI: β = -22.30, $p<0.001$; PCI arm: β = -22.34, $p<0.001$; All: β = -23.47, $p<0.001$). Younger age ($\leq$ 60y), squamous histology, and PCI were risk factors without clinical relevance (β > -10, $p<0.05$). Cognitive functioning declined over time (β = -0.26, $p=0.001$) except for patients with cognitive impairment at baseline ($\beta=0.141$, $p=0.33$).

Conclusion: Cognitive impairment is dynamic over time with four types. Baseline cognitive impairment (score <75) is the most important risk factor for subsequent cognitive impairment in stage III NSCLC.

Keywords: cognitive impairment, non-small cell lung cancer (NSCLC), multi-modality treatment, concurrent chemo-radiotherapy, multiple imputation-generalized estimating equation (MI-GEE)

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Highlights:

- Cognitive impairment is dynamic in individuals.
- Cognitive impairment has 4 types: sustained, reversible, recurring, alternating.
- Baseline cognitive impairment is the most important risk factor.
- Cognitive functioning should be assessed at multiple time points.
- Patients who have sustained cognitive impairment should avoid neurotoxic treatments.

Introduction

The identification of risk factors for cognitive impairment becomes increasingly important for patients with stage III non-small cell lung cancer (NSCLC), as survival has improved due to rapid treatment developments, especially by technical improvements in radiotherapy and introducing immunotherapy into the multimodality treatment[1,2]. Multiple factors may cause cognitive impairment, such as the disease itself, brain metastases (BM), depression, anxiety, lifestyle (drugs/alcohol), higher age, and antitumor treatments (chemotherapy, surgery, immunotherapy, and cranial irradiation)[3-8]. Yet, contrary results were also reported in the literature[9]. Moreover, concomitant diseases such as cerebral vascular disease, heart failure, hypertension, hyperlipidemia, and diabetes influence the toxicity of cancer treatments[10]. However, high-quality data on risk factors for cognitive impairment are lacking, as neurocognition was only a secondary endpoint in most prospective clinical trials, and was assessed by various instruments, without good compliance[11]. Neurocognitive assessments include objective neurocognitive tests (such as using the Hopkins Verbal Learning Test [HVLT]) and self-reported questionnaires (such as the EORTC-QLQ-C30), and outcomes of objective and self-reported cognitive functioning (SRCF) do not correlate well[12].

Furthermore, to the best of our knowledge, there are no prospective data on risk factors for neurocognitive impairment in patients with stage III NSCLC receiving standard of care (chemo-radiotherapy ± surgery) alone. Most studies compared one intervention such as prophylactic cranial irradiation (PCI) versus no-PCI but do not focus on other potential factors[11,12]. In the NVALT-11 randomized phase III trial[13], though designed to determine the incidence of BM with or without PCI, the control arm (chemotherapy with a radical local thoracic therapy, mainly radiotherapy) is highly suitable to determine risk factors for cognitive impairment without confounding by immunotherapy, as the SRCF has been assessed prospectively at multiple pre-specified time points using the EORTC-QLQ-C30[14], and the NVALT-11 trial was conducted before the immunotherapy era.

Patients and Methods

Study design

Patients with radically treated stage III NSCLC were recruited from 2009 to 2015 in the NVALT-11 trial. Details have been reported previously[13]. Briefly, eligibility was limited to patients with stage III NSCLC who did not show tumor progression after radical treatment. Eligible patients were 1:1 randomly assigned to PCI or observation (no-PCI) (Figure 1). For this study, the same criteria were used, with the addition of excluding those with central nervous

system disease such as meningioma or psychiatric disorders, as these medical histories could influence the SRCF. The SRCF was evaluated using EORTC-QLQ-C30 [14] at baseline, 1, 3, 6, 12, 24, and 36 months. Data obtained within the following time windows were used: before randomization for baseline assessment; ±2 weeks for the 1-month, 3-month, and 6-month assessments; or ±1 month for the 12-months, 24-months, and 36-months assessments. Assessments out of the time window were handled as missing.
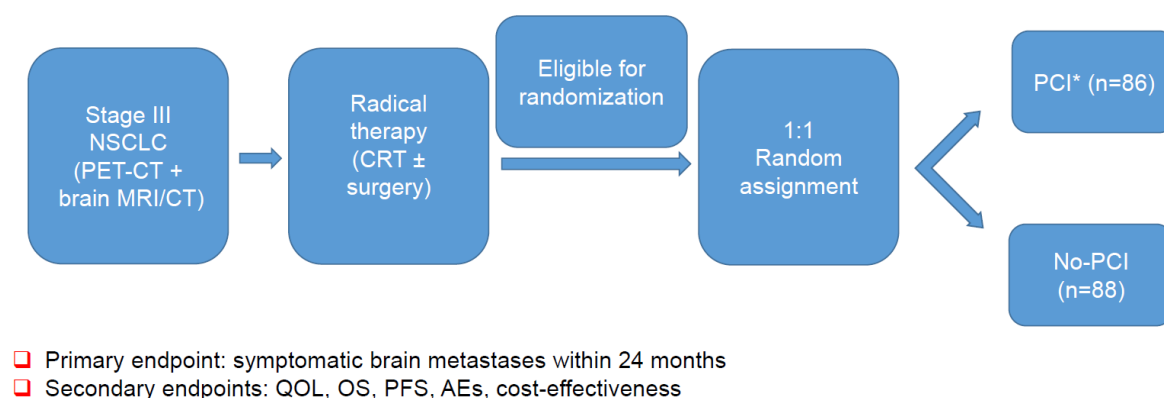
Figure 1. The study diagram.

Patients were fully staged with contrast-enhanced brain magnetic resonance imaging (MRI) or computed tomography (CT) and a whole-body ^{18}F-labeled fluorodeoxyglucose positron emission tomography–CT scan (^{18}FDG-PET/CT). The choice of the PCI dose was left to the participating hospitals—30 Gy in 12 fractions, 36 Gy in 18 fractions, or 30 Gy in 10 fractions. The primary endpoint was symptomatic brain metastases within 24 months. The secondary endpoints included QOL, OS, PFS , adverse events, and health care costs.
Abbreviations:
AEs, adverse events; CRT, chemoradiotherapy; CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PCI, prophylactic cranial irradiation; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; QOL, quality of life.

The EORTC-QLQ-C30 is a self-administered, cancer-specific questionnaire containing 30 items, which consists of cognitive functioning scale and other 14 scales and items[14]. Each scale score is transformed average score linearly, which ranges from 0 to 100[15]. A higher score for the cognitive functioning scale (COS) represents a better functioning.

The COS was compared between subgroups of factors. A mean difference of less than 10 points was considered as not clinically significant. A mean difference by ≥ 10 points but <20 points was regarded as a moderate effect. Mean differences ≥ 20 points were classified as large effects[16,17]. Changes over time (cognitive decline/improvement) were investigated as well. Meanwhile, we also adopted the binomial distribution concept (cognitive functioning category, COC) and dichotomized the cognition into cognitive impairment (COS <75) or not (COS ≥75)[18].

For patients who experienced cognitive impairment, we inspected the change over time per patient and classified the impairment into four types: "Sustained" refers to cognitive impairment presented at each measured time point; "Reversible" refers to impairment that recovered at later time points; "Recurred" refers to impairment that recovered at some time points, but appeared again at later time points; "Alternating" refers to impairment that recovered at some time points but recurred again at later time points, and recovers again later, or vice versa (Figure 2). The type was not evaluable if cognitive impairment was reported at one single time point and not reassessed thereafter.
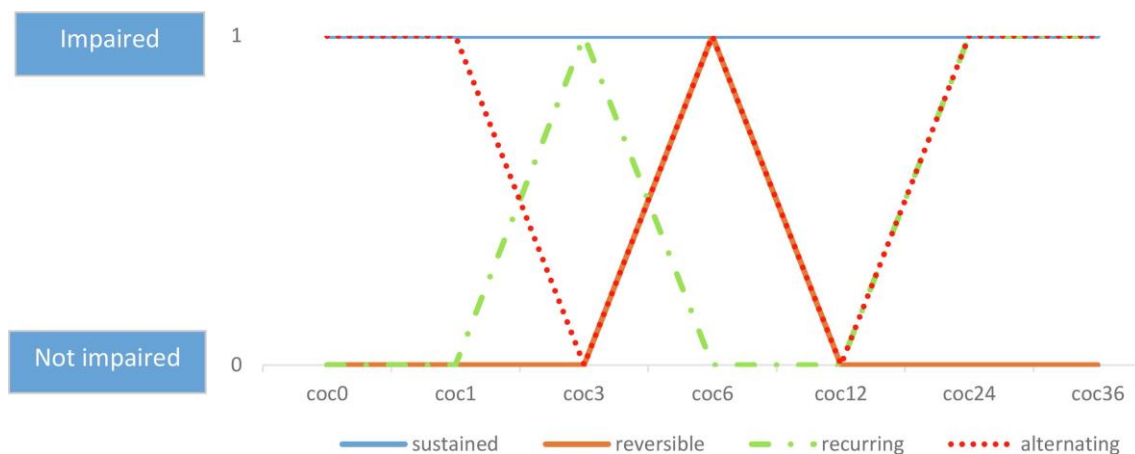
Figure 2. The definition of cognitive impairment types

The cognitive impairment can be categorized into four types based on its dynamic nature:
Sustained: cognitive impairment presents at each measured time point;
Reversible: cognitive impairment recovers at later time points;
Recurring: cognitive impairment recovers at some time points, but then presents again at later time points;
Alternating: cognitive impairment recovers at some time points, recurs again at later time points, and recovers again later, or vice versa.
Abbreviations: COC, cognitive functioning category.

Seven demographic factors (such as age, baseline cognitive impairment [BCI]), three tumor-related factors, three therapeutic factors, and two dynamic factors (BM and time) were investigated. We mainly focused on the standard of care, i.e. the no-PCI arm. We also compared the results in the PCI arm and the whole cohorts by adjusting for PCI.

Statistics:

First, scatter plots were performed to inspect the mean change of cognitive functioning over time in each subgroups. Then, multiple imputation-generalized estimating equation (MI-GEE) models with exchangeable covariance matrix structure were performed to identify the risk factors for cognitive impairment[19,20]. The cognitive functioning was analyzed as a continuous outcome (COS) and a binary outcome (COC: impairment or not), respectively. Multivariate

analysis was performed for the GEE models both before (COS-origin, COC-origin) and after multiple imputation (COS-MI, COC-MI) to interpret the results more thoroughly.

Multiple imputation (m=10) was performed using the fully conditional specification method[21]. The imputed values for COSs were limited to 0-100. For dichotomized variables, practitioners can either impute the missing continuous outcome before dichotomizing the response (IBD) or dichotomize the outcome and then impute the binary response (DTI)[21]. We performed multiple imputation in both ways to compare the results. Variables with ≥50% missing were excluded.

Significant risk factors were further inspected in the no-PCI arm and PCI arm, respectively. Cognitive impairment types were compared between arms and significant risk factors using $\chi 2$ test. SPSS27.0 and STATA16 were used for statistical analyses. All tests are 2-sided and a p-value <0.05 is considered statistically significant.

Results

A total of 174 patients (88 no-PCI, 86 PCI) were randomized in the NVALT-11 trial. Five patients (3 no-PCI, 2 PCI) were excluded according to the additional criteria (a history of craniotomy or psychosis) for this current study. Patient characteristics are shown in Table 1. The median follow-up was 60.2 months (95% CI: 59.8-60.7 months), including 118 OS events and 34 BM events (eTable 1 in the Supplement).

The compliance rates of SRCF assessment ranged from 72.7-86.7% in the no-PCI arm (eFigure 1 in the Supplement). The cognitive impairment rate ranged from 17.7-34.6% (Figure 3). The mean COS changed from 84.8 (95%CI 80.6-89.0) at baseline to 79.5 (95%CI 72.4-86.6) at 36 months (eFigure 2A in the Supplement). Results were similar in the PCI arm (eFigure 1-2A in the Supplement). The mean score plots indicated that all patients experienced a decline tendency over time except for patients with BCI and patients who developed BM (eFigure 2B-N in the Supplement).

Cognitive impairment presented at least once in 43/84 (51.2%) patients in the no-PCI arm and 43/80 (53.8%) in the PCI arm (p=0.7). One third of patients reported sustained impairment and one fourth was reversible in the no-PCI arm (11/33 sustained, 9/33 reversible, 10/33 recurring, 5/33 alternating, and 10 not assessable), which was similar in the PCI arm (p=0.4) (Figure 4A). Most cognitive impairment firstly occurred within the first six months after randomization (both no-PCI and PCI: 38/43 [88.4%]). The detailed cognitive impairment per patient is shown in eFigure 3 in the Supplement.

Table 1. Patient characteristics

Characteristics	No. (%) (N=169)
Demographic features at randomization	
Age-y	
Median (range)	61 (37-83)
Mean ± SD	60.8 ± 8.4
≤60	78 (46.2)
>60	91 (53.8)
Gender	
Male	109 (64.5)
Female	60 (35.5)
Smoking history	
Current smoker	59 (34.9)
Former smoker	103 (60.9)
Never	7 (4.1)
BMI-kg/m^2*	
Median (range)	24.8 (15.4- 38.9)
Mean ± SD	25.2 ± 3.9
<25	80 (51.9)
≥25	74 (48.1)
No information	15
Prior malignancy	
No	147 (87.0)
Yes	22 (13.0)
Significant medical history*	
No	105 (62.1)
Yes	64 (37.9)
Baseline cognitive impairment**	
No	105 (78.4)
Yes	29 (21.6)
No information	35
Tumor related features	
Pathology	
Squamous cell	60 (35.5)
Non-squamous cell	109 (64.5)
Stage (AJCC 7th edition)	
IIIA	91 (53.8)
IIIB	78 (46.2)
Performance status	
0	65 (38.9)
1	93 (55.7)
2	9 (5.4)
No information	2
Treatment related features	
Surgery	
No	150 (88.8)
Yes	19 (11.2)
Arm	
PCI	84 (49.7)
No-PCI	85 (50.3)
Chemotherapy type	
Single agent platinum based***	35 (21.1)
Combination agent platinum based	131 (78.9)
No information	3

Note: *Significant medical history includes: transient ischemic attack, cerebrovascular accident, cardiovascular diseases (hypertension, hyperlipidemia), and diabetes mellitus;
    **Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30;
    ***daily low dose cisplatin (6 mg/m^2).
Abbreviations: BMI, Body mass index; PCI, prophylactic cranial irradiation; SD: standard deviation.

eTable 1. Events at each pre-specified time point (N=169)

		Time points - months						
		0	1	3	6	12	24	36
OS								
Died		*0*	*0*	*11*	*20*	*46*	*84*	*106*
	No PCI	0	0	4	8	20	44	55
	PCI	0	0	7	12	26	40	51
Alive		*169*	*169*	*158*	*149*	*123*	*85*	*62*
	No PCI	85	85	81	77	65	41	30
	PCI	84	84	77	72	58	44	32
No information		*0*	*0*	*0*	*0*	*0*	*0*	*1*
	No PCI	0	0	0	0	0	0	0
	PCI	0	0	0	0	0	0	1
BM								
*Yes**		*0*	*0*	*7*	*13*	*20*	*29*	*33**
	No PCI	0	0	4	10	16	23	26
	PCI	0	0	3	3	4	6	7
No		*169*	*169*	*154*	*142*	*115*	*77*	*58*
	No PCI	85	85	78	71	58	35	27
	PCI	84	84	76	71	57	42	31
No information		*0*	*0*	*0*	*0*	*0*	*0*	*1*
	No PCI	0	0	0	0	0	0	0
	PCI	0	0	0	0	0	0	1
*Not applicable (died)***		*0*	*0*	*8*	*14*	*34*	*63*	*77*
	No PCI	0	0	3	4	11	27	32
	PCI	0	0	5	10	23	36	45

*Note***:** * 34 BM in total. One patient (in the no-PCI arm) was diagnosed with BM at 57.6 months.

**The number of not applicable was smaller than the death event because some patients developed BM before death.

*Abbreviations***:** BM, brain metastases; OS, overall survival.
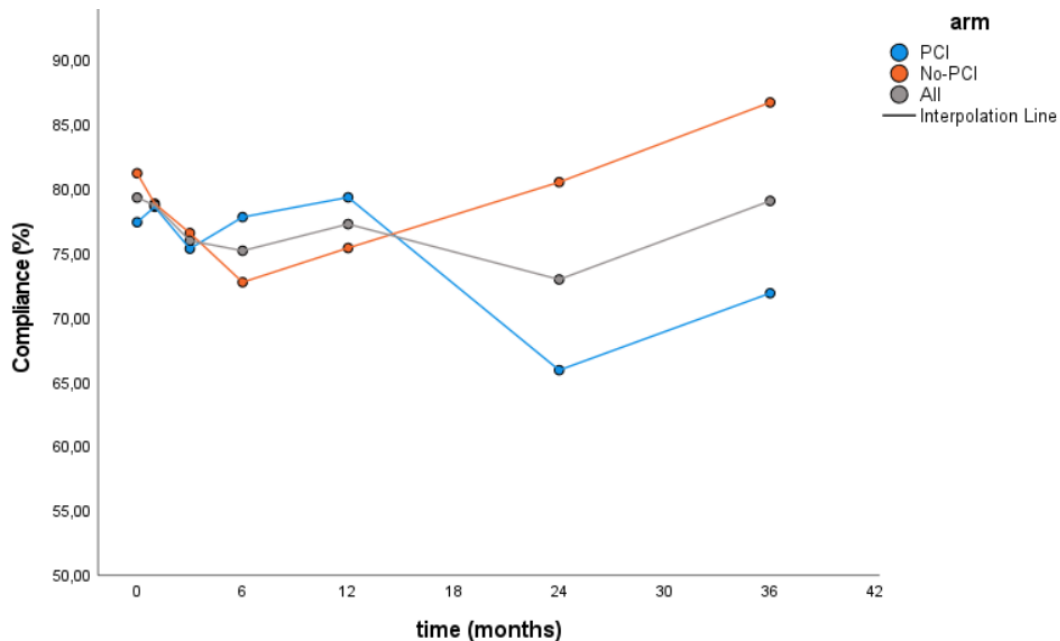
No. assessed / alive

All	134/169	112/149	95/123	62/85	49/62
No-PCI	69/ 85	56/77	49/65	33/41	26/30
PCI	65/84	56/72	46/58	29/44	23/32

eFigure 1. Compliance of cognitive functioning assessment at each time point

The mean compliance was not significantly different between arms (78.8% in no-PCI vs 75.2% in PCI, t-test *p*=0.17).
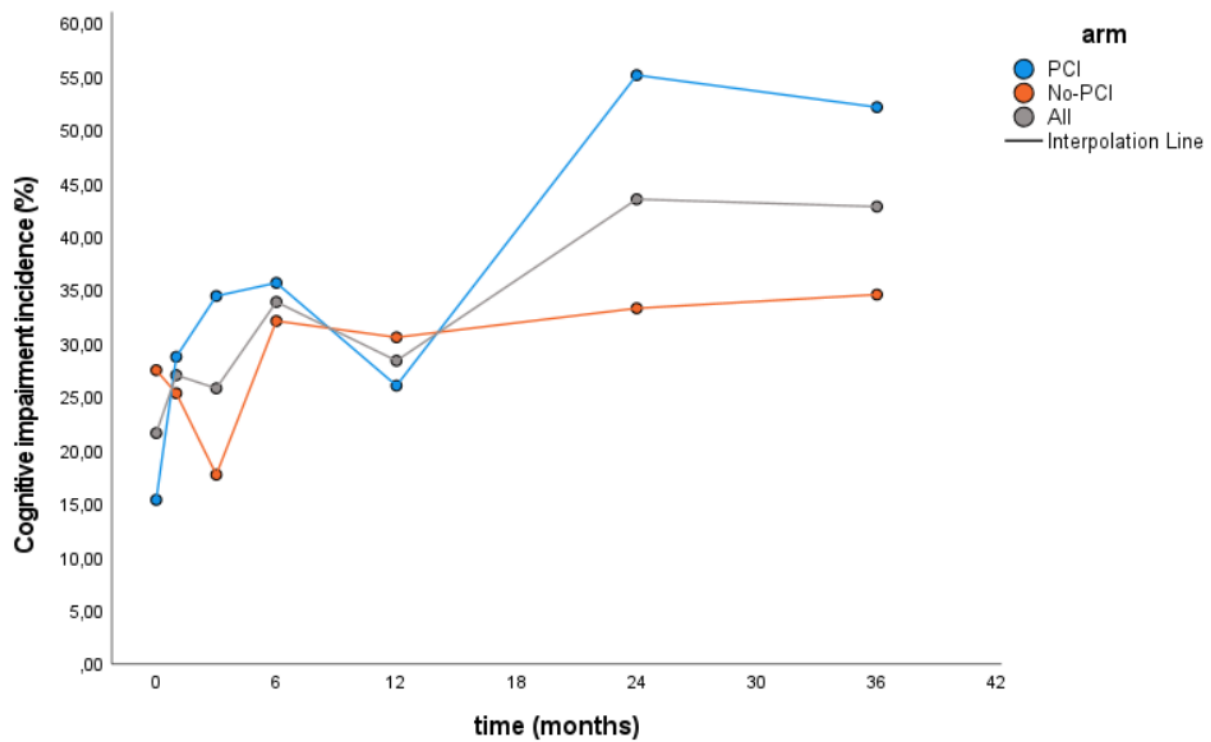
No. event / assessed

All	29/134	38/112	27/95	27/62	21/49
No-PCI	19/69	18/56	15/49	11/33	9/26
PCI	10/65	20/56	12/46	16/29	12/23

Figure 3. Cognitive impairment incidence at each time point

The mean cognitive impairment incidence was not significantly different between arms (28.8% in no-PCI vs 35.4% in PCI, t-test p=0.27)
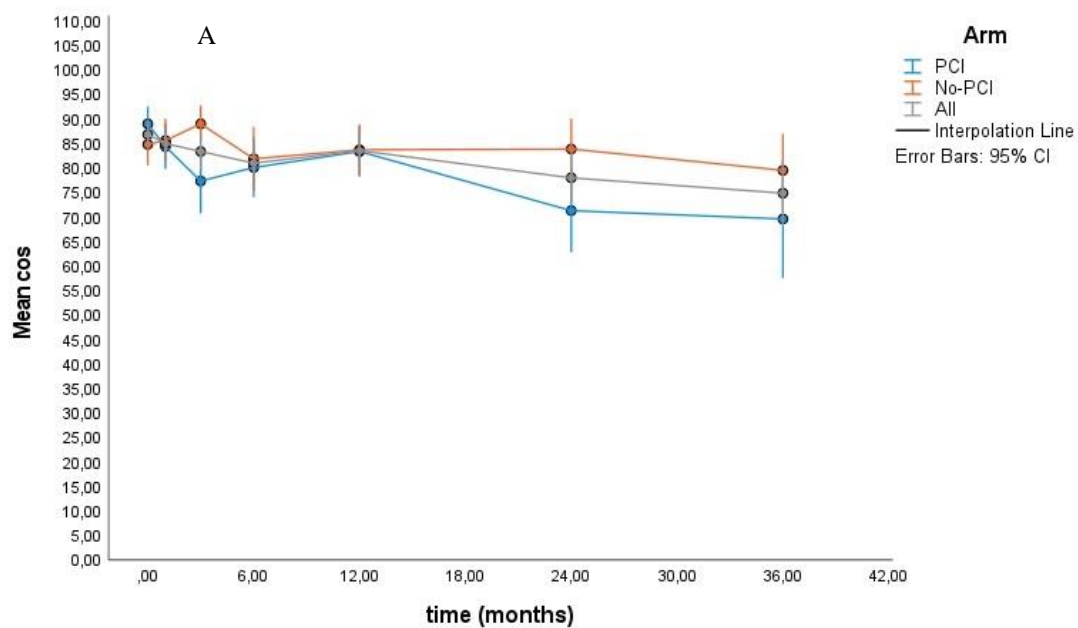
eFigure 2. Cognitive functioning score plots: (A) Arm: PCI, prophylactic cranial irradiation.
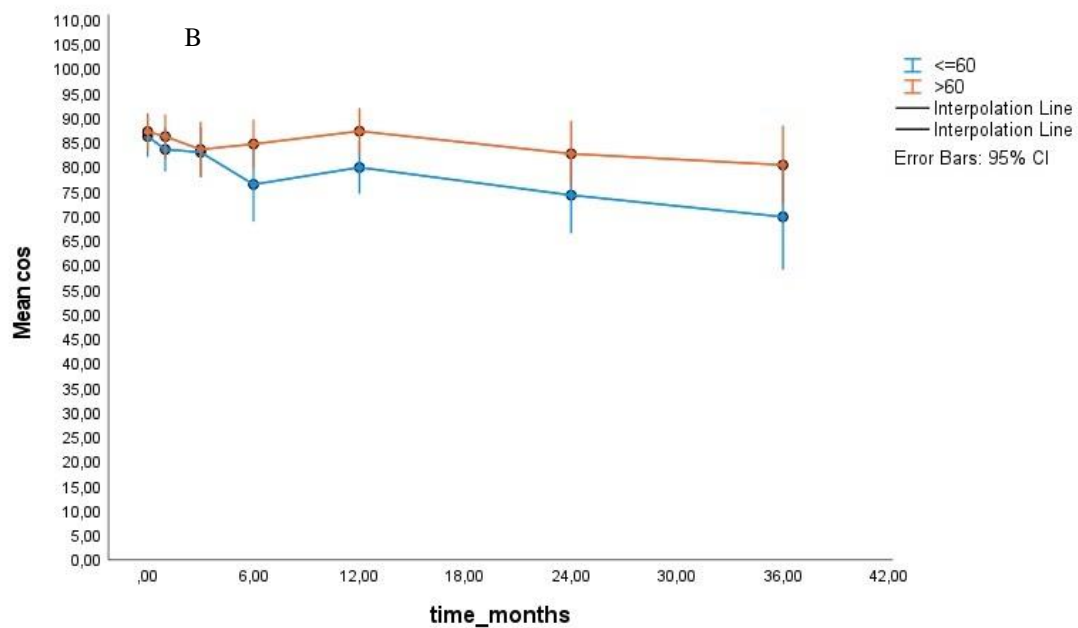
eFigure 2. Cognitive functioning score plots: (B) Age.

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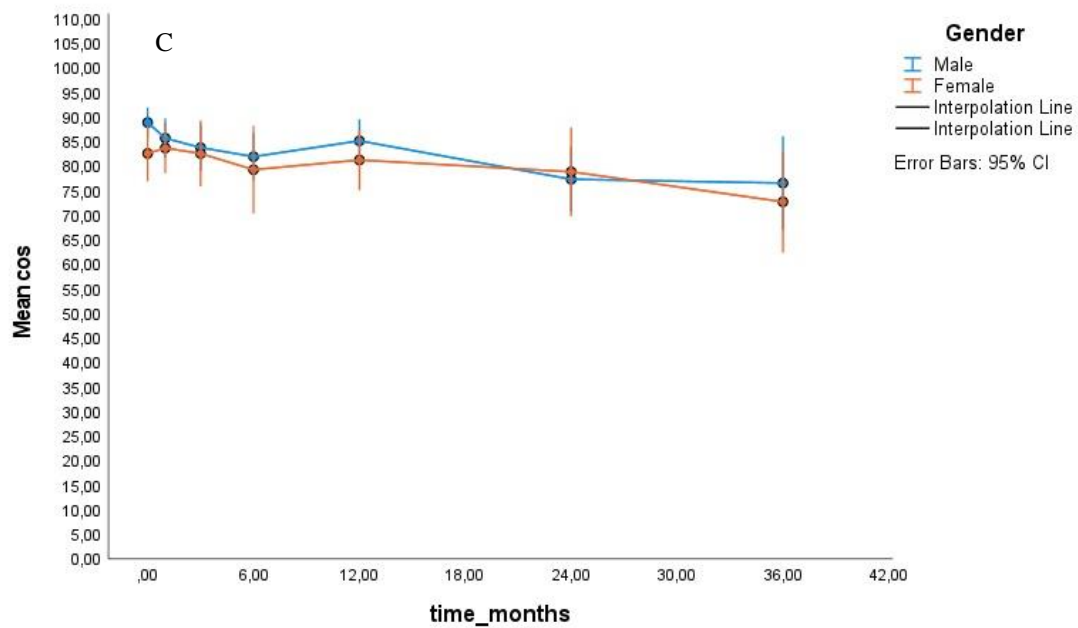
eFigure 2. Cognitive functioning score plots: (C) Gender.
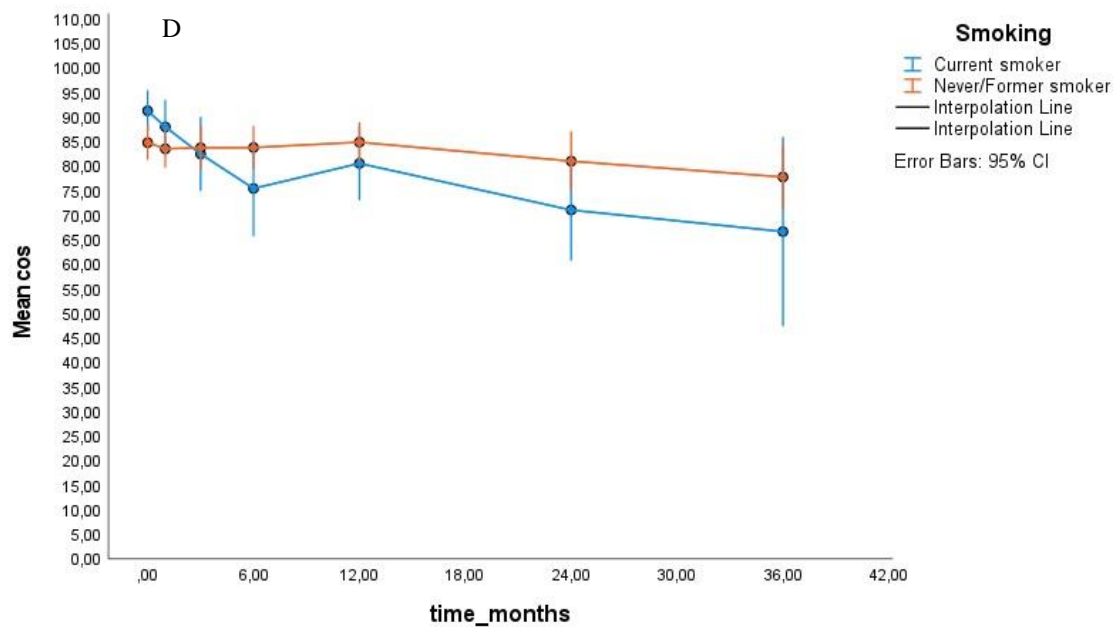
eFigure 2. Cognitive functioning score plots: (D) Smoking.

E
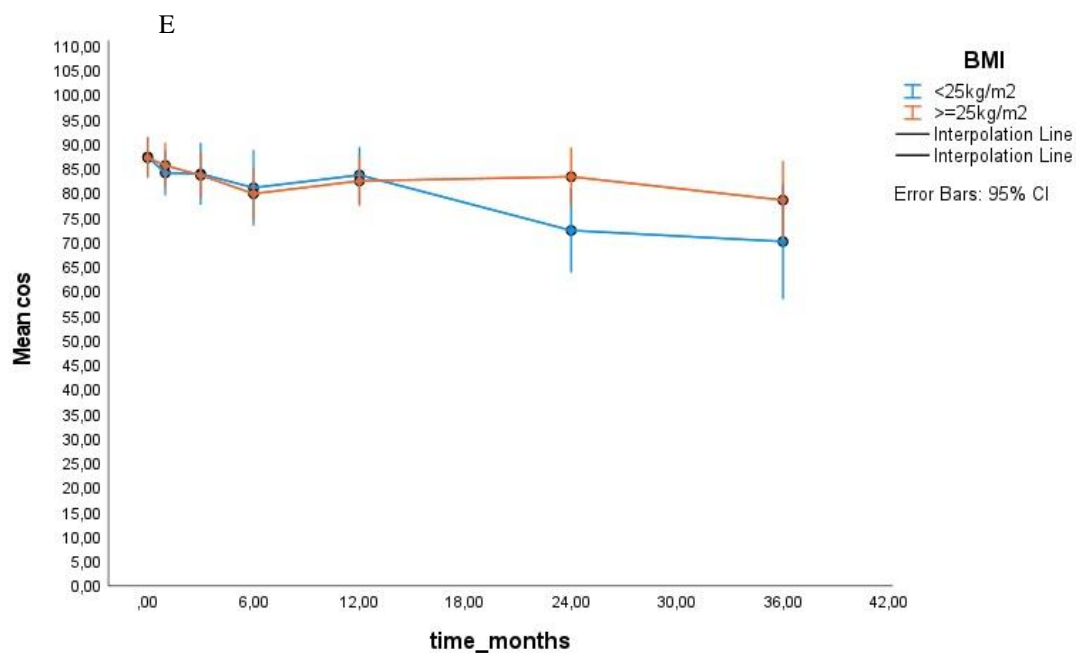
eFigure 2. Cognitive functioning score plots: (E) BMI, body mass index.

F
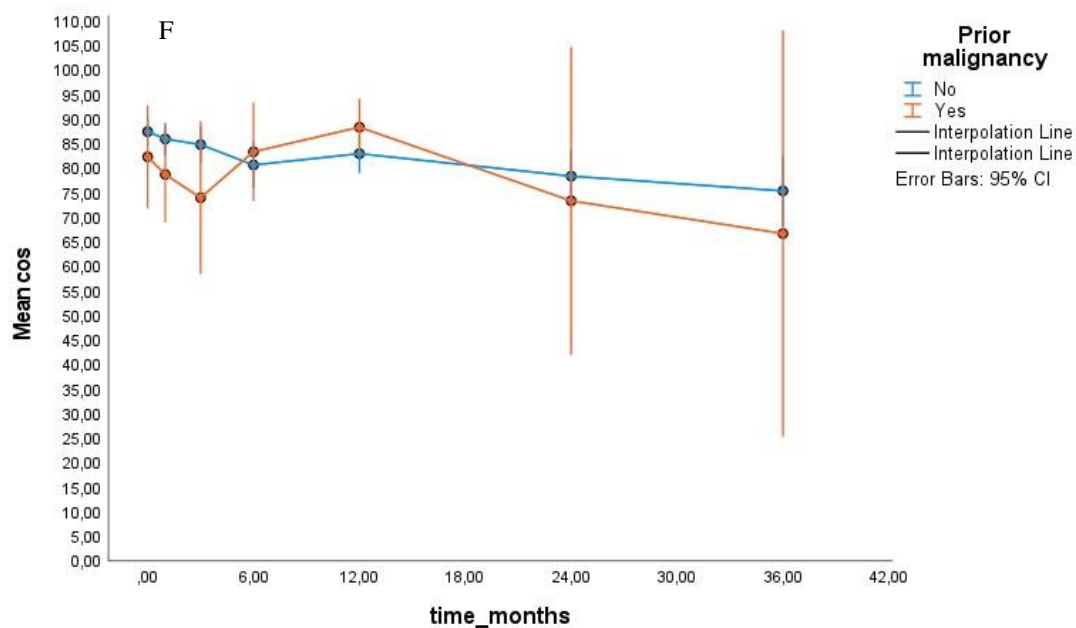
eFigure 2. Cognitive functioning score plots: (F) Prior malignancy.
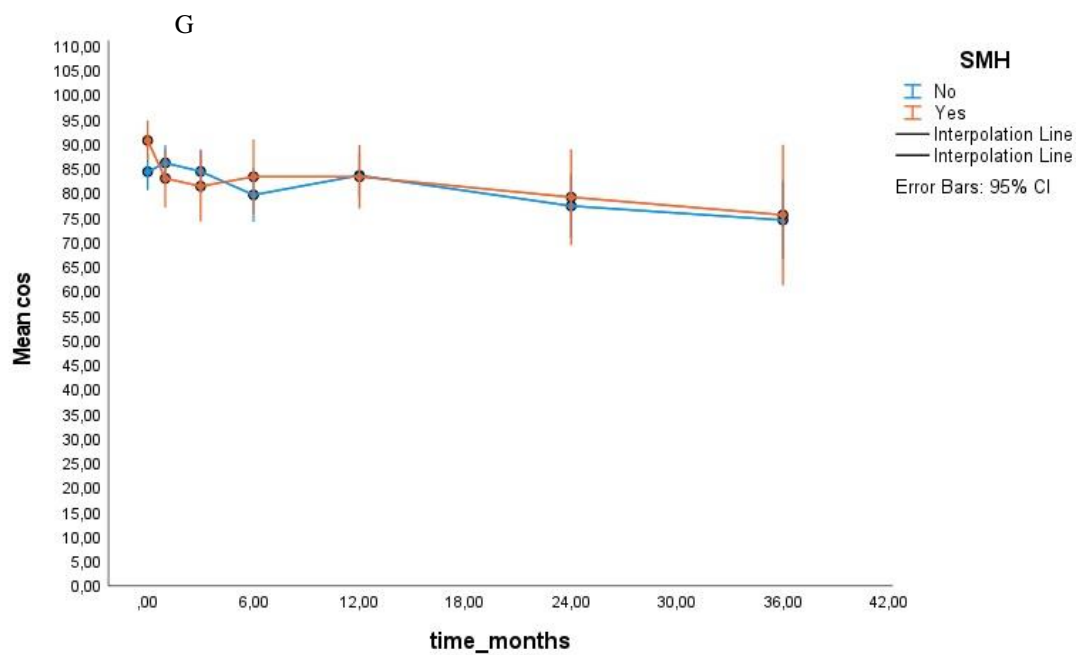
eFigure 2. Cognitive functioning score plots: (G) significant medical history (SMH)
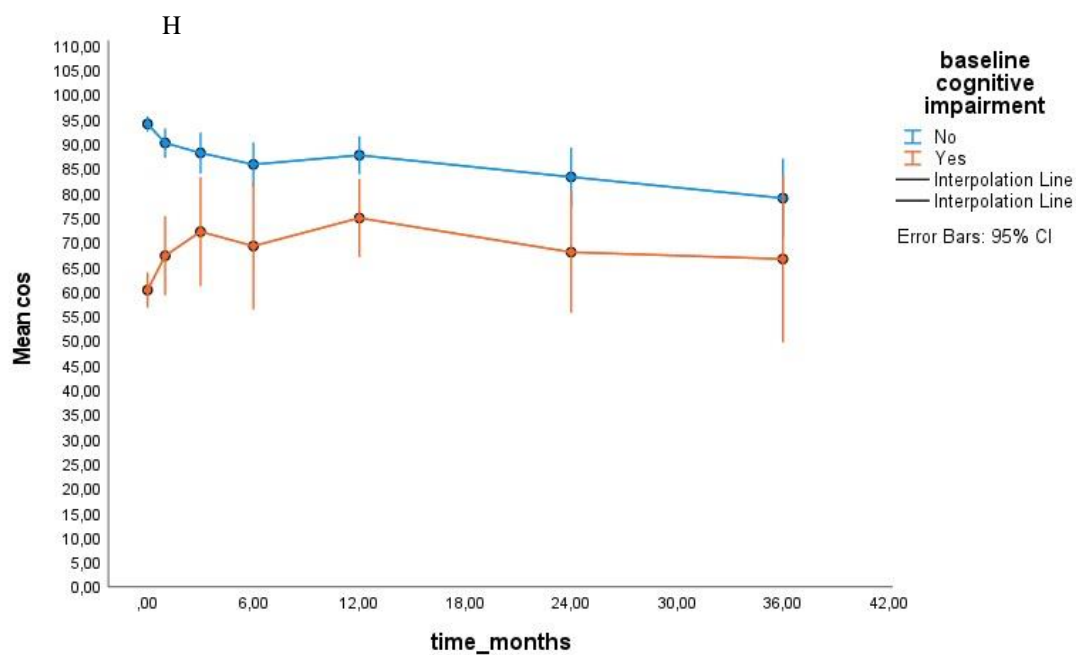
eFigure 2. Cognitive functioning score plots: (H) Baseline cognitive impairment.
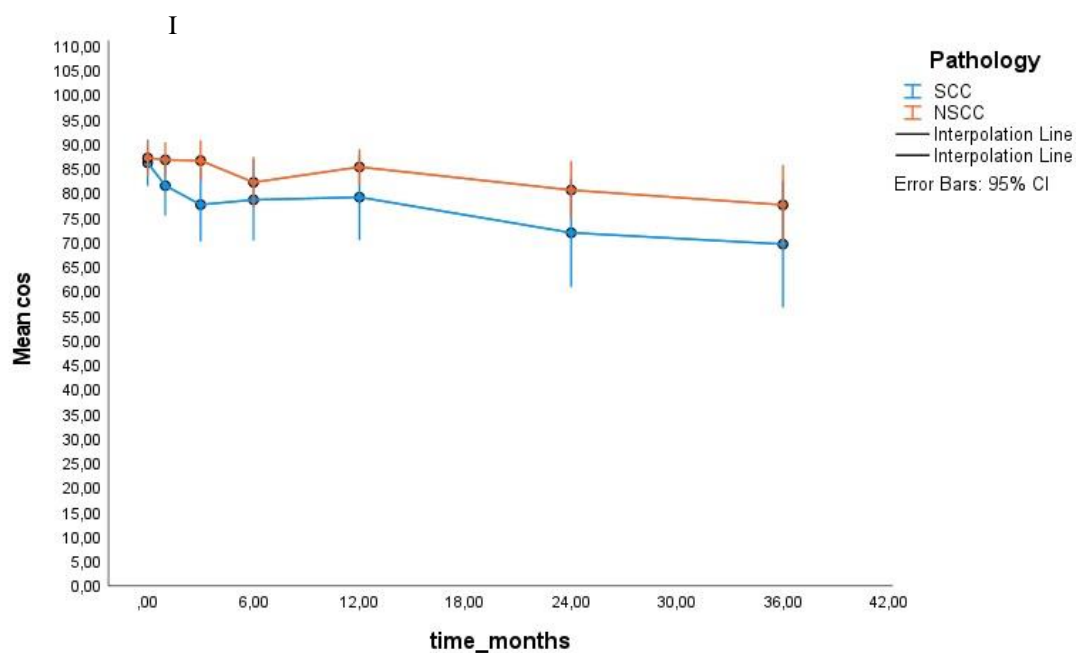
eFigure 2. Cognitive functioning score plots: (I) Pathology: NSCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma.
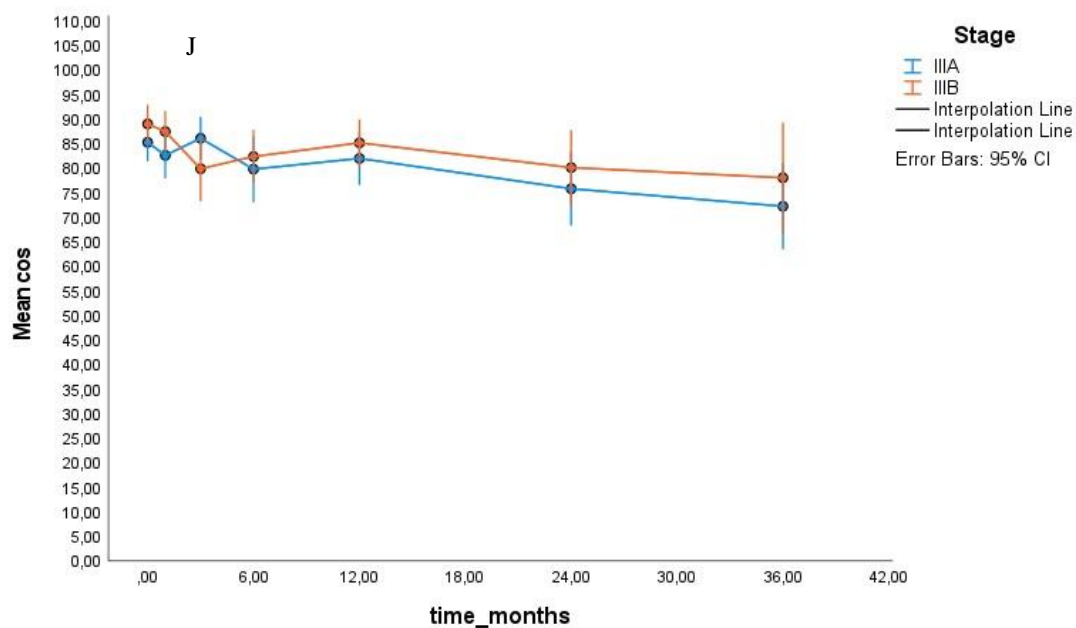
eFigure 2. Cognitive functioning score plots: (J) Stage.
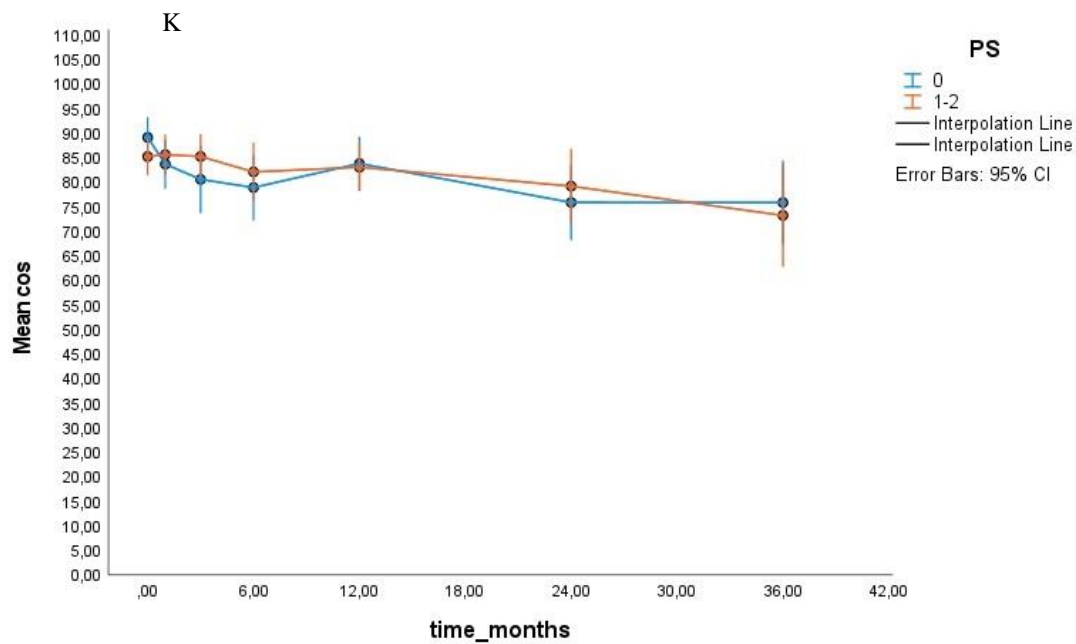
eFigure 2. Cognitive functioning score plots: (K) Performance status (PS).
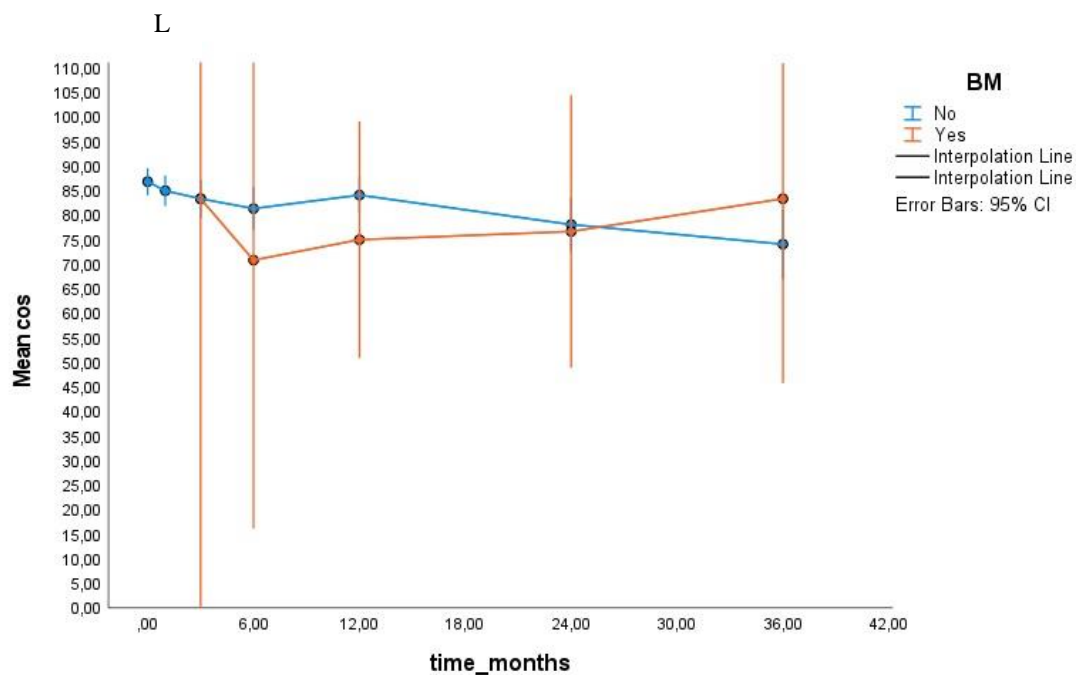
eFigure 2. Cognitive functioning score plots: (L) brain metastases (BM).
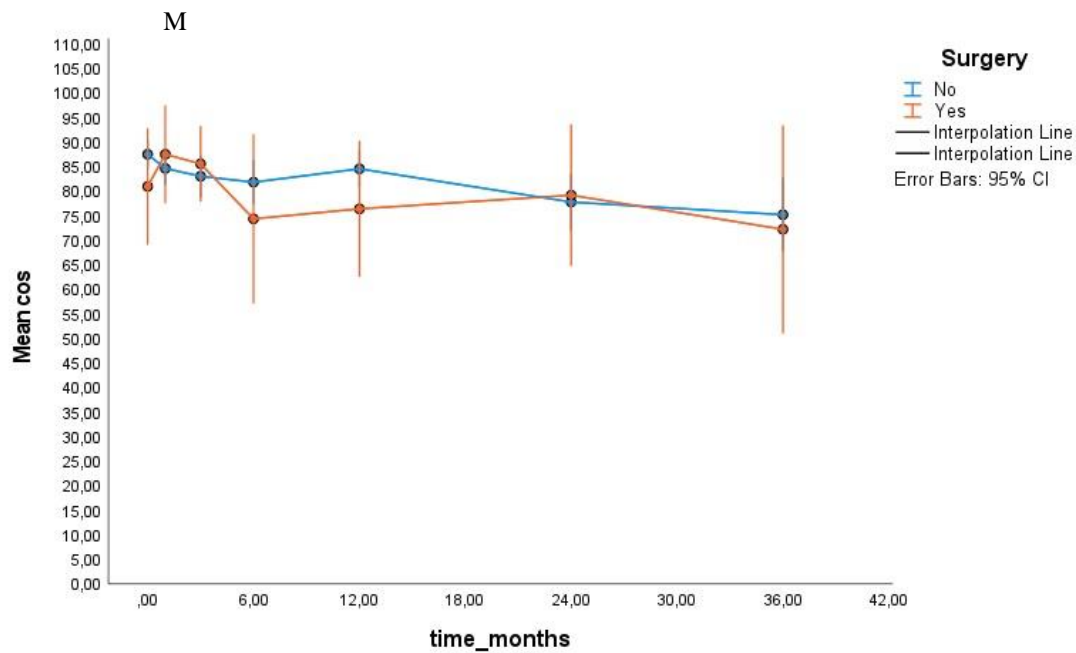
eFigure 2. Cognitive functioning score plots: (M) Surgery.
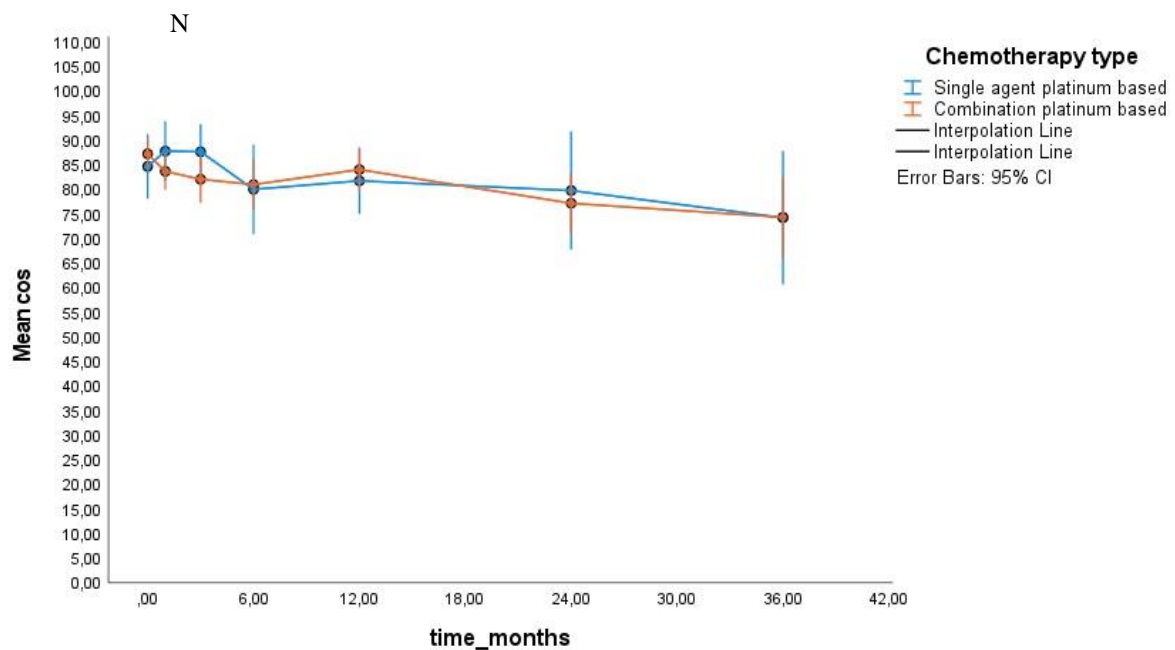
eFigure 2. Cognitive functioning score plots: (N) chemotherapy type.

eFigure 2. Cognitive functioning score plots: The plots showed that all patients experienced a decline tendency over time except for patients with BCI and patients with BM. For patients with BCI, the cognitive functioning improved to some degree, and then slightly declined. For patients who experienced BM, the cognitive functioning declined sharply, and then improved gradually.

*Abbreviations***:** BCI, baseline cognitive impairment; BM, brain metastases; CI, confidence interval; COS, cognitive functioning score.

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A

Arm

B

baseline cognitive impairment

C

Age

<=60

>60

- sustained
- reversible
- recurring
- alternating

D

pathology

SCC

NSCC

- sustained
- reversible
- recurring
- alternating

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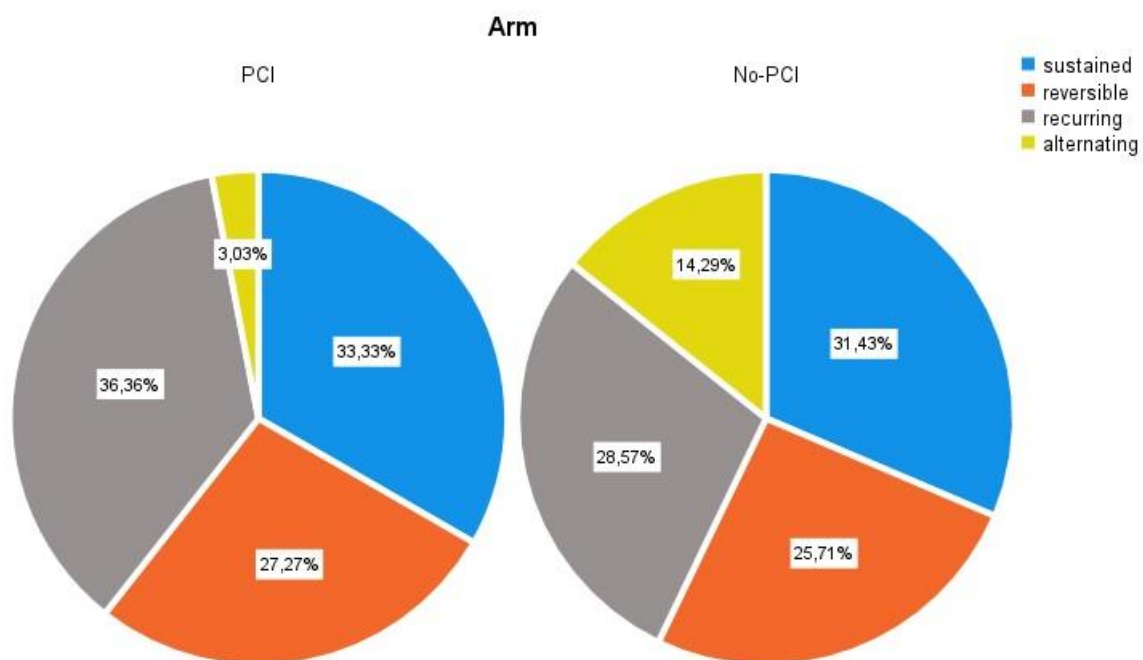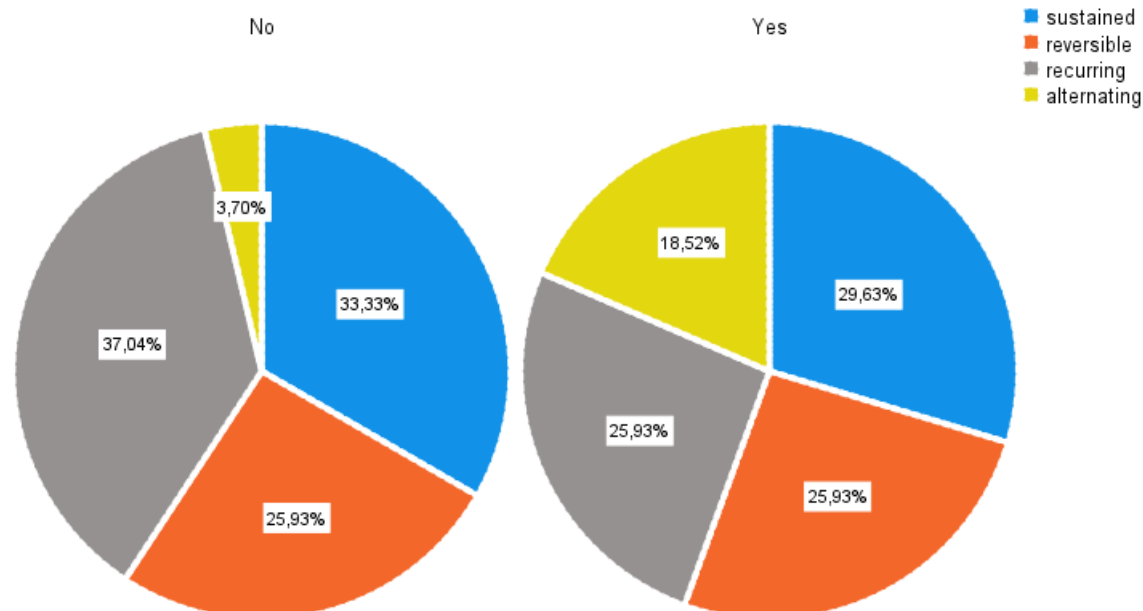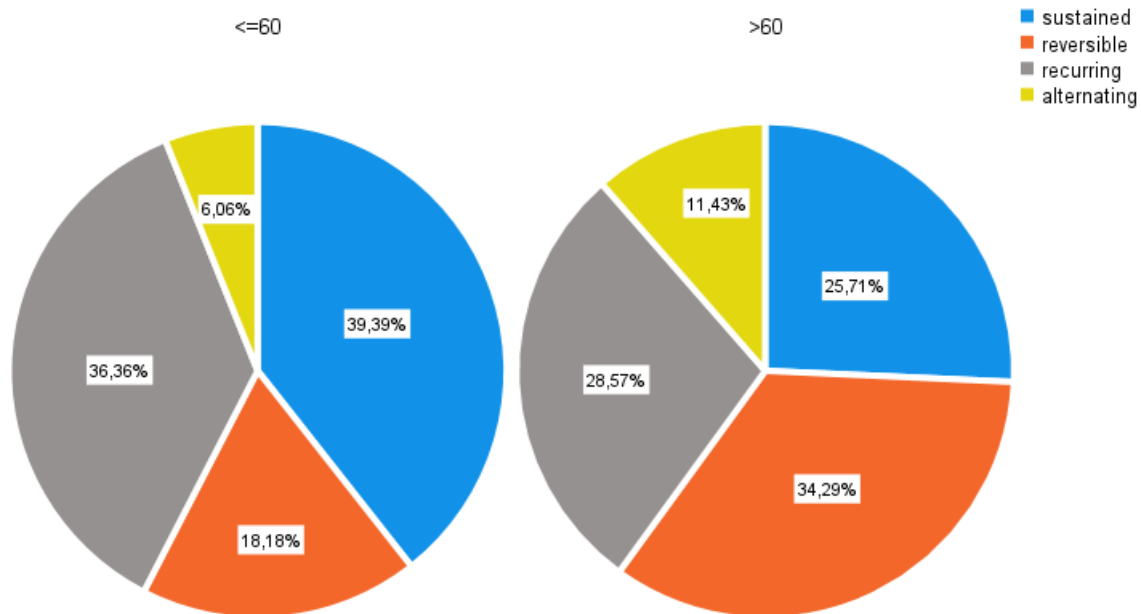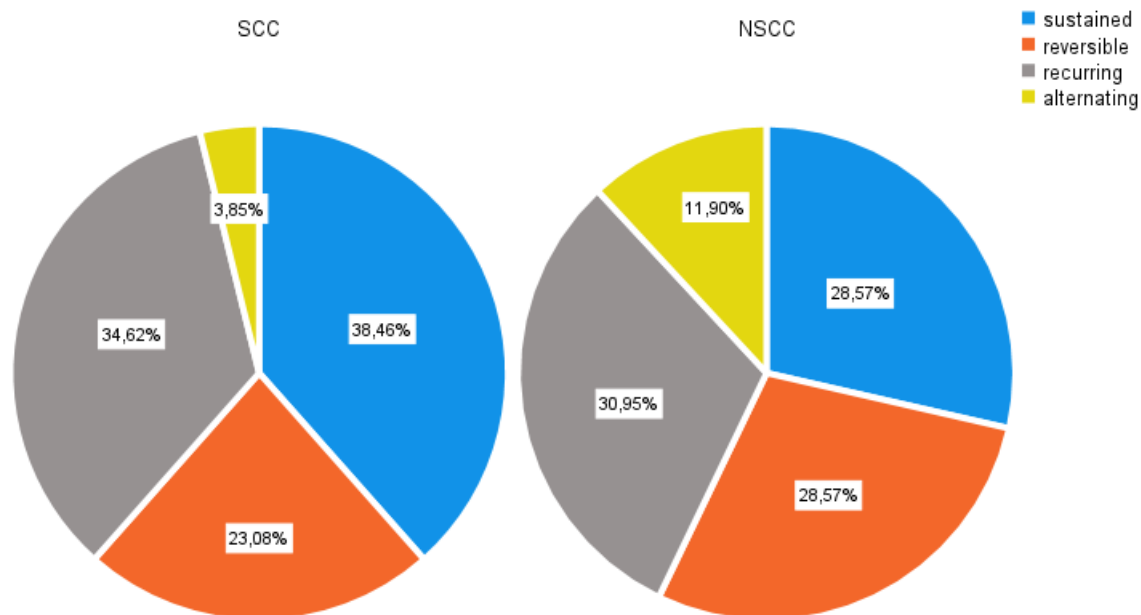
E
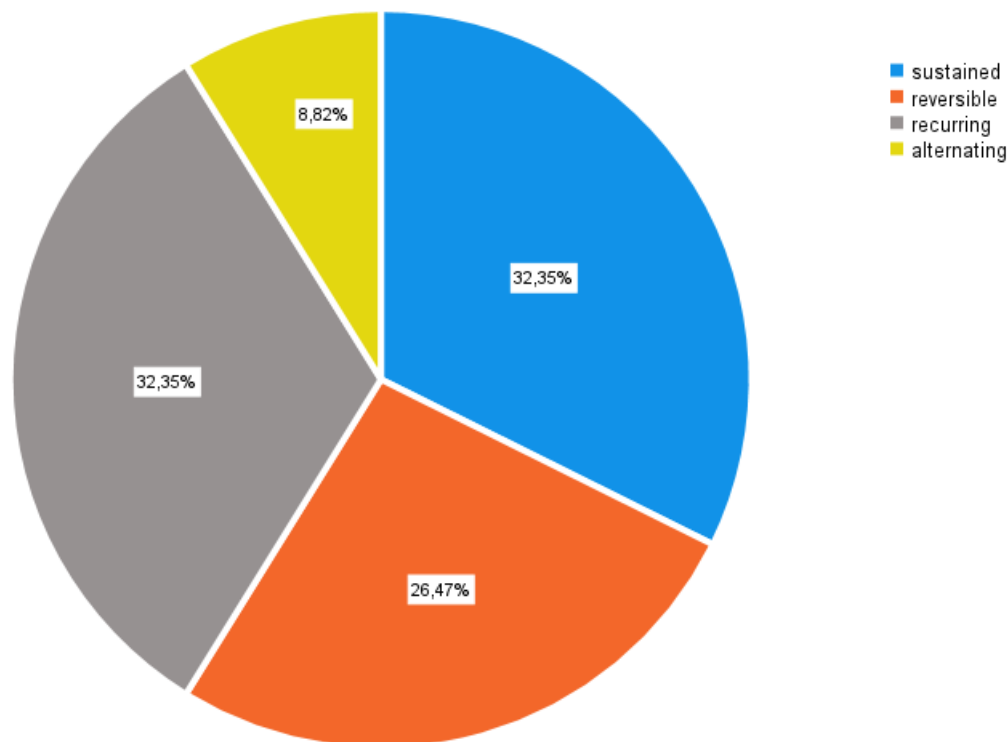
Figure 4. Constituent ratios of cognitive impairment types

The constituent ratios of cognitive impairment types were not significantly different in subgroups of (A) arm ($\chi 2$ $= 2.79, p=0.43$); (B) BCI ($\chi 2 = 3.26, p=0.35$); (C) age ($\chi 2 = 3.52, p=0.32$); or (D) pathology ($\chi 2 = 1.92, p=0.59$). Cognitive impairment was dynamic and can be reversible. Only one third were sustained impairment: (E) All. The cognitive impairment type was not evaluable in 18 patients (8 no-PCI vs 10 PCI) because there were no available reassessed QOL data after presenting cognitive impairment. Cognitive impairment type was not compared in the BM vs no BM group because BM was a dynamic factor changing over time.
*Abbreviations***:** BCI, baseline cognitive impairment; QOL, quality of life; NSCC, non-squamous cell carcinoma; PCI, prophylactic cranial irradiation; SCC, squamous cell carcinoma.
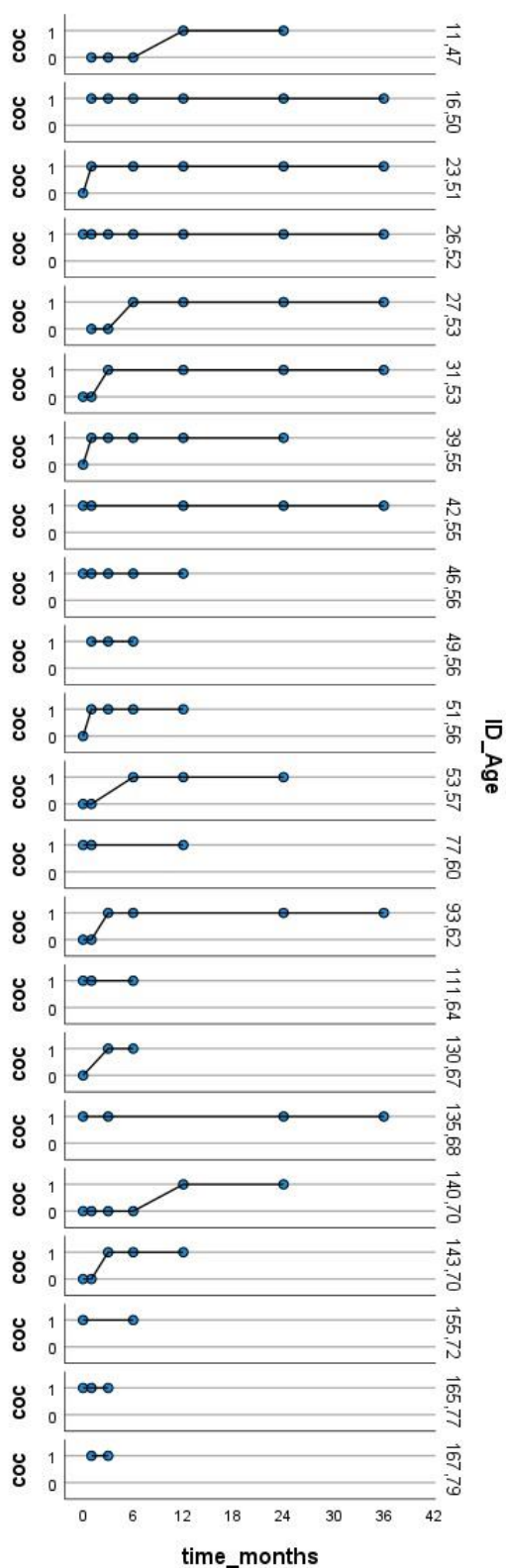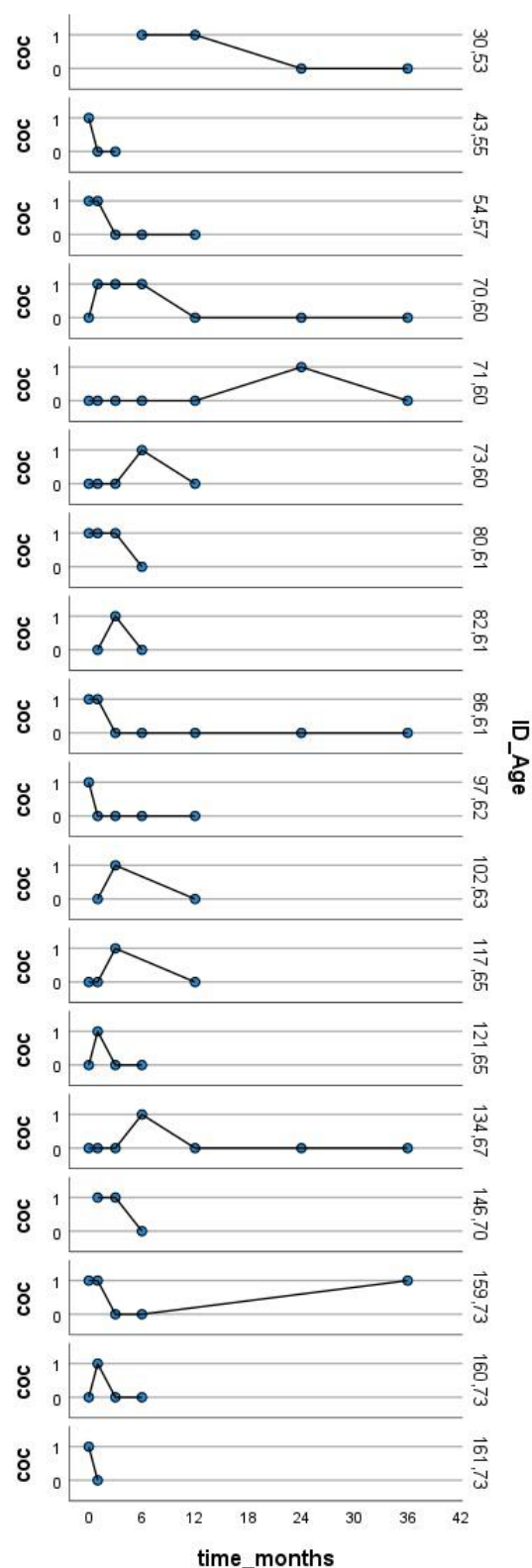
eFigure 3. Cognitive assessment per patient by cognitive impairment types: (A) Sustained (N=22); (B) Reversible (N=18).

eFigure 3. Cognitive assessment per patient by cognitive impairment types: (C) Recurring (N=22); (D) Alternating (N=6); (E) Not assessable (N=22). ***Abbreviations*****:** cognitive functioning category, COC
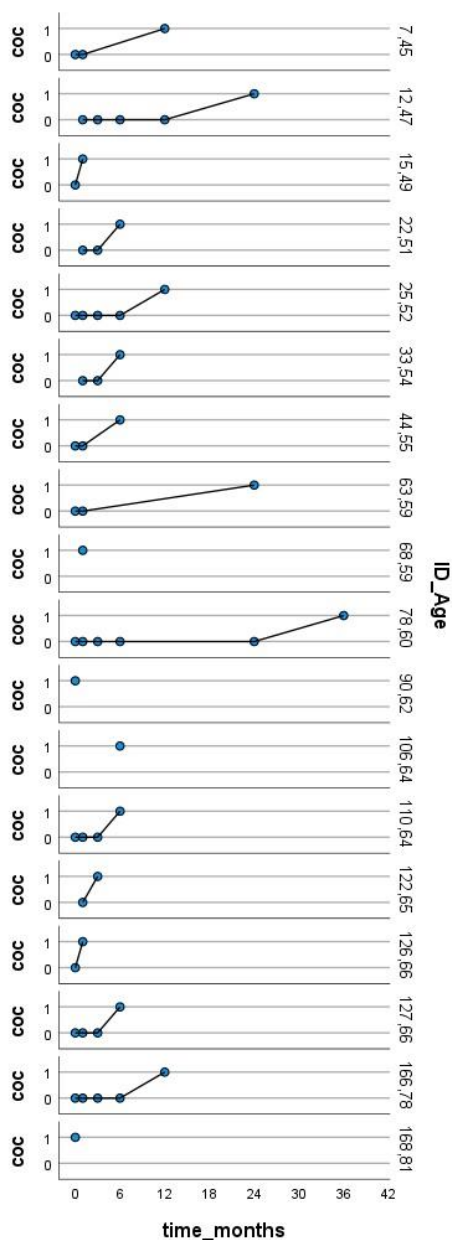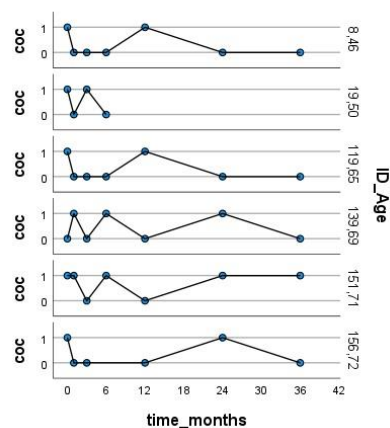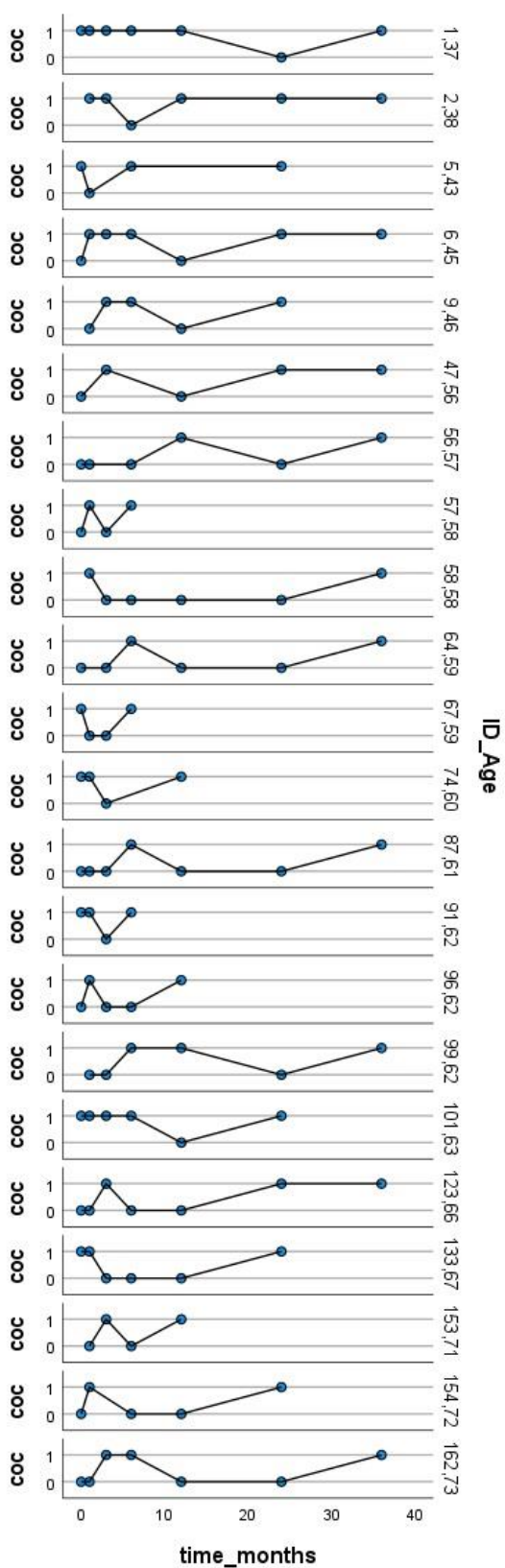
Multiple imputation showed that: (1) DTI: COC24 and COC36 were not imputed because of >50% missing values (including missing because of death); (2) IBD: Multiple imputation stopped because COS6 did not meet the imputation constraints.

Therefore, two GEE models before imputation (COS-origin, COC-origin), and one after imputation (COC-MI) were performed (Table 2). All the three models showed that cognitive functioning declined over time (COS-origin: β = -0.26, p=0.001; COC-origin: OR 1.04, 95%CI 1.02 - 1.06, p=0.001; COC-MI: OR 1.03, 95%CI 1.01 – 1.04, p=0.004). BCI had a large negative effect on cognitive functioning (COS-origin: β = -23.47, p<0.001; COC-origin: OR 20.99, 95%CI 10.21 - 43.13, p<0.001; COC-MI: OR 7.66, 95%CI 4.29 – 13.68, p<0.001). Patients in the PCI arm reported worse cognitive functioning compared with the no-PCI arm but the difference was not clinically relevant (COS-origin: β = -5.56, p=0.003; COC-origin: OR 2.53, 95%CI 1.34 - 4.78, p=0.004; COC-MI: OR 1.87, 95%CI 1.14 - 3.06, p=0.01). Older patients (>60 years) (COS-origin: β = 6.43, p=0.002) and patients with non-squamous cell carcinoma (COS-origin: β =6.22, p=0.009) reported better cognitive functioning, also with no clinical relevance. Other factors were not clinically nor statistically significant (p<0.05) (Table 2).

Table 2. Risk factors for cognitive impairment (N=169)

Factors	COS-origin* β (SE)*	COS-origin* p	COC-origin** β (SE)	COC-origin** OR(95%CI)	COC-origin** p	COC-MI** β(SE)	COC-MI** OR (95%CI)	COC-MI** p
Demographic variates								
Age-years								
≤60	Ref		Ref			Ref		
>60	6.43 (2.12)	0.002	-1.12 (0.34)	0.33 (0.17 - 0.64)	0.001	-0.71 (0.25)	0.49 (0.30- 0.79)	0.004
Gender								
Male	Ref		Ref			Ref		
Female	2.06 (2.25)	0.36	-0.60 (0.37)	0.55 (0.27 – 1.13)	0.10	-0.12 (0.25)	0.88 (0.54 – 1.45)	0.63
Smoking history								
Current smoker	Ref		Ref			Ref		
Never/Former smoker	3.94 (2.33)	0.09	-0.34 (0.34)	0.71 (0.37 - 1.37)	0.31	-0.39 (0.24)	0.67 (0.42 – 1.08)	0.11
BMI-kg/m^2								
<25	Ref		Ref			Ref		
≥25	-1.09 (2.10)	0.61	0.30 (0.30)	1.35 (0.75 – 2.41)	0.32	0.12 (0.25)	1.12 (0.68 – 1.85)	0.65
Prior malignancy								
No	Ref		Ref			Ref		
Yes	-1.82 (2.51)	0.47	0.28 (0.43)	1.33 (0.58 – 3.06)	0.51	0.38 (0.32)	1.46 (0.78 – 2.73)	0.24
Significant medical history ***								
No	Ref		Ref			Ref		
Yes	1.67 (2.09)	0.42	0.18 (0.30)	1.19 (0.66 – 2.16)	0.56	0.25 (0.21)	1.29 (0.85 – 1.96)	0.24
Baseline cognitive impairment ****								

Table 2. Risk factors for cognitive impairment (N=169)

Factors	COS-origin* β (SE)*	COS-origin* p	COC-origin** β (SE)	COC-origin** OR(95%CI)	COC-origin** p	COC-MI** β(SE)	COC-MI** OR (95%CI)	COC-MI** p
No	Ref		Ref			Ref		
Yes	-23.47 (2.26)	<0.001	3.04 (0.37)	20.99 (10.21-43.13)	<0.001	2.04 (0.30)	7.66 (4.29-13.68)	<0.001
Tumor related variates								
Pathology								
Squamous cell	Ref		Ref			Ref		
Non-squamous cell	6.22 (2.01)	0.009	-0.72 (0.35)	0.48 (0.24 - 0.96)	0.04	-0.41 (0.24)	0.66 (0.41 – 1.06)	0.09
Stage								
IIIA	Ref		Ref			Ref		
IIIB	2.49 (2.02)	0.22	-0.29 (0.30)	0.75 (0.42 – 1.33)	0.32	-0.19 (0.22)	0.83 (0.54 – 1.26)	0.34
Performance status								
0	Ref		Ref			Ref		
1-2	3.49 (2.03)	0.09	-0.57 (0.32)	0.57 (0.30 – 1.05)	0.07	-0.44 (0.24)	0.64 (0.40 – 1.03)	0.07
Treatment related variates								
Surgery								
No	Ref		Ref			Ref		
Yes	1.88 (3.46)	0.59	-0.58 (0.52)	0.56 (0.20 – 1.54)	0.26	-0.46 (0.37)	0.63 (0.31 – 1.29)	0.21
Chemotherapy type								
Single agent platinum based	Ref		Ref			Ref		
Combination agent platinum based	-0.31 (2.40)	0.90	0.16 (0.38)	1.17 (0.56 – 2.46)	0.68	0.10 (0.31)	1.10 (0.60 – 2.02)	0.75
Arm								
No-PCI	Ref		Ref			Ref		
PCI	-5.56 (1.89)	0.003	0.93 (0.33)	2.53 (1.34 - 4.78)	0.004	0.63 (0.25)	1.87 (1.14 - 3.06)	0.01
Dynamic variates								
BM								
No	Ref		Ref			Ref		
Yes	-5.10 (6.90)	0.46	1.34 (0.78)	3.82 (0.84-17.44)	0.08	0.99 (0.60)	2.70 (0.83 – 8.75)	0.10
Time-months	-0.26 (0.08)	0.001	0.04 (0.01)	1.04 (1.02 - 1.06)	0.001	0.03 (0.01)	1.03 (1.01 – 1.04)	0.004

*Note***:** * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

    ** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

    *** Significant medical history includes transient ischemic attack, cerebrovascular accident, cardiovascular diseases (hypertension, hyperlipidemia), and diabetes mellitus.

    **** Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30.

*Abbreviations***:** BM, brain metastases; BMI, Body mass index; CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; PCI, prophylactic cranial irradiation; Ref, reference; SE, standard error.

When splitting the dataset by arms, BCI still had a large negative effect on cognitive functioning in both the no-PCI arm ($\beta = -22.30$, $p<0.001$) and the PCI arm ($\beta = -22.34$, $p<0.001$). Pathology remained significant without clinical relevance in the no-PCI arm ($\beta = 5.97$, $p=0.05$), but became insignificant in the PCI arm ($\beta = 4.41$, $p=0.19$). Age became insignificant in either arm (no-PCI: $\beta = 4.50$, $p=0.10$; PCI arm: $\beta = 5.57$, $p=0.08$). Results were somewhat different in the three models, mainly due to the halved sample size (eTable 2 in the Supplement).

eTable 2a. Risk factors for cognitive impairment in patients with no-PCI (N=85)

	Models							
	COS-origin*		COC-origin**			COC-MI**		
Fctors	β (SE)*	p	β (SE)	OR (95%CI)	p	β (SE)	OR (95%CI)	p
Demographic variates								
Age-years								
≤60	Ref		Ref			Ref		
>60	4.50 (2.72)	0.10	-0.88 (0.42)	0.41 (0.18 - 0.93)	0.03	-0.36 (0.30)	0.70 (0.39 – 1.26)	0.24
Baseline cognitive impairment***								
No	Ref		Ref			Ref		
Yes	-23.30 (3.22)	<0.001	2.61 (0.41)	13.60 (6.12 - 30.25)	<0.001	1.62 (0.32)	5.04 (2.69 – 9.45)	<0.001
Tumor related variates								
Pathology								
Squamous cell	Ref		Ref			Ref		
Non-squamous cell	5.97 (2.98)	0.05	-1.02 (0.46)	0. 36 (0.15 - 0.90)	0.03	-0.48 (0.36)	0.62 (0.30 – 1.26)	0.19
Dynamic variates								
Time-months	-0.14 (0.07)	0.06	0.03 (0.01)	1.03 (1.00 - 1.06)	0.05	0.01 (0.01)	1.01 (0.99 – 1.04)	0.28

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

*** Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30.

Abbreviations: CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; PCI, prophylactic cranial irradiation; Ref, reference; SE, standard error.

eTable 2b. Risk factors for cognitive impairment in patients with PCI (N=84)

Factors	COS-origin* β (SE)*	COS-origin* p	COC-origin** β (SE)	COC-origin** OR (95%CI)	COC-origin** p	COC-MI** β (SE)	COC-MI** OR (95%CI)	COC-MI** p
				Models				
Demographic variates								
Age-years								
≤60	Ref		Ref			Ref		
>60	5.57 (3.19)	0.08	-0.72 (0.44)	0.49 (0.21 - 1.14)	0.10	-0.82 (0.33)	0.44 (0.23 – 0.85)	0.02
Baseline cognitive impairment***								
No	Ref		Ref			Ref		
Yes	-22.34 (3.83)	<0.001	2.31 (0.52)	10.08 (3.62 - 28.03)	<0.001	1.82 (0.43)	6.18 (2.68 – 14.22)	<0.001
Tumor related variates								
Pathology								
Squamous cell	Ref		Ref			Ref		
Non-squamous cell	4.41 (3.35)	0.19	-0.49 (0.43)	0.61 (0.26 - 1.44)	0.26	-0.60 (0.31)	0.55 (0. 30 – 1.01)	0.06
Dynamic variates								
Time-months	-0.32 (0.12)	0.008	0.04 (0.01)	1.04 (1.01 - 1.07)	0.01	0.04 (0.01)	1.04 (1.01 – 1.07)	0.002

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

   ** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

   *** Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30.

Abbreviations: CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; PCI, prophylactic cranial irradiation; Ref, reference; SE, standard error.

As patients were treated by different schedules in the PCI arm (30Gy in 10 fractions [n=33], 30Gy in 12 fractions [n=37], and others [n=14]), we compared the effects of these PCI schedules on cognitive outcome as well and observed neither clinically relevant nor statistically significant differences in any of the three models (COS-origin: *p*>0.7; COC-origin: *p*>0.5; COC-MI: *p*>0.8) (eTable 3 in the Supplement).

eTable 3. Effect of PCI schedule on cognitive impairment

Factors	COS- origin* β (SE)*	COS- origin* p	COC-origin** β (SE)	COC-origin** OR (95%CI)	COC-origin** p	COC-MI** β (SE)	COC-MI** OR (95%CI)	COC-MI** p
				Models				
PCI schedule***								
30Gy/10f	Ref		Ref			Ref		
30Gy/12f	0.98 (4.04)	0.81	0.03 (0.38)	1.03 (0.49 - 2.17)	0.95	0.02 (0.34)	1.02 (0.52 – 2.00)	0.96
Others	1.73 (6.03)	0.77	-0.31 (0.56)	0.74 (0.24 - 2.22)	0.59	-0.06 (0.43)	0.94 (0.41 – 2.18)	0.89
Time-months	-0.37 (0.10)	<0.001	0.03 (0.01)	1.03 (1.01 - 1.05)	0.002	0.04 (0.01)	1.04 (1.01 - 1.06)	0.002

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

    ** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

    ***PCI schedules include 30Gy in 10 fractions (n=33), 30Gy in 12 fractions (n=37), and others (n=14): 36Gy in 18 fractions (n=1), 25Gy in 10 fractions (n=3), 20Gy in 12 fractions (n=1), 3Gy in 1 fraction (n=1), 0 Gy (no PCI) (n=8).

Abbreviations: CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; PCI, prophylactic cranial irradiation; Ref, reference; SE, standard error.

Patients who developed BM reported worse cognitive functioning, but the differences were insignificant (COS-origin: $p=0.46$; COC-origin: $p=0.08$; COC-MI: $p=0.10$). Taking into account the bias that patients who developed BM died earlier, we performed a specific GEE analysis including BM, time, and the interaction of BM*time. It showed that the interaction effect was statistically significant (COS-origin: $p=0.01$; COC-origin: $p=0.04$; COC-MI: $p=0.03$). After adjusting for time and the interaction effect, we observed a moderate negative effect on cognitive functioning (β =-18.25, $p=0.04$) (eTable 4 in the Supplement). Subgroup analysis using the COS-origin model showed that the cognitive functioning did not further decline over time in patients who developed BM (β=0.03, $p=0.93$), while it declined in those who did not experience BM (β=-0.256, $p<0.001$). As few patients who developed BM assessed cognitive functioning (eTable 5 in the Supplement), the results were unreliable.

eTable 4. Interaction effect of BM with time on cognitive impairment

				Models				
	COS- origin*		COC-origin**			COC-MI**		
Factors	β (SE)*	*p*	β (SE)	OR (95%CI)	*p*	β (SE)	OR (95%CI)	*p*
BM								
No	Ref		Ref			Ref		
Yes	-18.25 (8.80)	0.04	6.80 (0.78)	6.80 (1.53 – 30.22)	0.01	1.98 (0.75)	7.24 (1.68 – 31.24)	0.009
Time-months	-0.26 (0.07)	<0.001	0.02 (0.007)	1.02 (1.01 - 1.04)	<0.001	0.02 (0.007)	1.02 (1.01 - 1.04)	0.001
BM × time	0.80 (0.31)	0.01	-0.07 (0.03)	0.93 (0.87-1.00)	0.04	-0.07 (0.03)	0.93 (0.87-0.99)	0.03

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

    ** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

Abbreviations: BM, brain metastases; CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; Ref, reference; SE, standard error.

eTable 5. COS by subgroup of BM at each time points

	COS0	0	16.7	33.3	50	66.7	88.3	100	Total
BM0	Yes	0	0	0	0	0	0	0	0
	No	0	0	1	9	19	37	68	134
	Total	0	0	1	9	19	37	68	134
	COS1	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM1	Yes	0	0	0	0	0	0	0	0
	No	0	0	4	9	23	31	66	133
	Total	0	0	4	9	23	31	66	133
	COS3	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM3	Yes	0	0	0	0	1	0	1	2
	No	1	2	2	11	14	33	55	118
	Total	1	2	2	11	15	33	56	120
	COS6	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM6	Yes	0	0	1	1	0	0	2	4
	No	3	1	3	4	25	24	48	108
	Total	3	1	4	5	25	24	50	112
	COS12	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM12	Yes	0	0	0	2	1	1	2	6
	No	0	0	3	3	18	28	37	89
	Total	0	0	3	5	19	29	39	95
	COS24	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM24	Yes	0	0	0	1	2	0	2	5
	No	0	1	2	6	15	14	19	57
	Total	0	1	2	7	17	14	21	62
	COS36	**0**	**16.7**	**33.3**	**50**	**66.7**	**88.3**	**100**	**Total**
BM36	Yes	0	0	0	1	0	1	2	4
	No	1	1	1	8	9	13	12	45
	Total	1	1	1	9	9	14	14	49

Abbreviations: BM, brain metastases; COS, cognitive functioning score.

A time interaction analysis was also performed for significant risk factors. It showed that the interaction effect of time with BCI was significant as well (COS-origin: $p=0.003$; COC-origin: $p<0.001$; COC-MI: $p<0.001$). After adjusting for time and the interaction effect, the role of BCI was more negative (COS-origin: $\beta=-25.17$, $p<0.001$) (eTable 6 in the Supplement). Subgroup analysis with the COS-origin model showed that in patients with BCI, no significant improvement or decline over time occurred ($\beta=0.141$, $p=0.33$), while patients without BCI experienced a decline over time ($\beta=-0.33$, $p<0.001$).

eTable 6. Interaction effect of BCI with time on cognitive impairment

	COS- origin*		COC-origin**			COC-MI**		
Factors	β (SE)*	p	β (SE)	OR (95%CI)	p	β (SE)	OR (95%CI)	p
Baseline cognitive impairment***								
No	Ref		Ref			Ref		
Yes	-25.17 (2.53)	<0.001	2.94 (0.29)	18.83 (10.57 –33.55)	<0.001	1.97 (0.22)	7.18 (4.62 – 11.15)	<0.001
Time-months	-0.33 (0.08)	<0.001	0.05 (0.009)	1.05 (1.03 - 1.07)	<0.001	0.04 (0.008)	1.03 (1.01 – 1.04)	<0.001
Baseline cognitive impairment × time								
	0.47 (0.16)	0.003	-0.07 (0.01)	0.93 (0.90 – 0.96)	<0.001	-0.06 (0.02)	0.94 (0.91 – 0.97)	<0.001

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

*** Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30.

Abbreviations: BCI, baseline cognitive impairment; CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; Ref, reference; SE, standard error.

Arm (β=0.24, *p*=0.07) had marginal interaction effect with time. In the PCI arm, cognitive functioning declined over time without clinical relevance (β=-0.37, *p*<0.001), while in the no-PCI arm, the cognitive functioning did not decline significantly (β=-0.132, *p*=0.101). Age (β=0.14, *p*=0.28) and pathology (β=0.05, *p*=0.71) had no interaction effect with time. Compared with younger (≤60y) patients (β = -0.30, *p*=0.005), cognitive functioning declined less in elder (>60y) patients (β = -0.16, *p*=0.04). Both squamous cell (β = -0.26, *p*=0.001) and non-squamous cell (β = -0.23, *p*=0.01) experienced slight cognition decline over time.

We also performed the time interaction analysis for other factors using the COS-origin model. It showed that the interaction effect of gender with time was significant as well (β=0.26, *p*=0.05). Smoking (β=0.35, *p*=0.06) had marginal interaction effects with time. Subgroup analysis showed that women reported similar cognitive functioning over time (β=-0.08, *p*=0.70), while male patients experienced a decline over time (β=-0.35, *p*<0.001). Both current smokers (β=-0.50, *p*=0.005) and never/former smokers (β=-0.15, *p*=0.01) experienced cognitive functioning decline over time, but the current smokers declined more. Therefore, we reran the GEE models by adjusting the interaction effects with time. It confirmed that BCI was the most important risk factor (COS-origin: β = -26.46, *p*<0.001; COC-origin: OR 38.54, 95%CI 17.891 - 83.023, *p*<0.001; COC-MI: OR 13.07, 95%CI 7.14 – 23.93, *p*<0.001). The effect of BM became larger after adjusting the interactions (COS-origin: β =-22.86, *p*=0.07; COC-origin: OR 32.66, 95%CI 3.77 – 282.74, *p*=0.002; COC-MI: OR 9.65, 95%CI 1.88 – 49.56, *p*=0.008).

Younger age (<60), squamous cell, and PCI were risk factors without clinical relevance (β>-10, *p*<0.05) (eTable 7 in the Supplement).

eTable 7. Risk factors for cognitive impairment (adjusted by interactions with time)

	Models							
	COS-origin*		COC-origin**			COC-MI**		
Factors	β (SE)*	*p*	β (SE)	OR (95%CI)	*p*	β(SE)	OR (95%CI)	*p*
Demographic variates								
Age-years								
≤60	Ref		Ref			Ref		
>60	6.33 (2.08)	0.002	-1.14 (0.35)	0.32 (0.16 - 0.63)	0.001	-0.73 (0.25)	0.48 (0.29 – 0.79)	0.004
Gender								
Male	Ref		Ref			Ref		
Female	1.03 (2.16)	0.63	-0.68 (0.40)	0.51 (0.23 – 1.10)	0.09	-0.13 (0.26)	0.88 (0.53 – 1.45)	0.61
Smoking history								
Current	Ref		Ref			Ref		
Never/ Former	3.59 (2.28)	0.12	-0.34 (0.35)	0.71 (0.36 - 1.417)	0.33	-0.41 (0.25)	0.66 (0.41 – 1.08)	0.10
BMI-kg/m^2								
<25	Ref		Ref			Ref		
≥25	-0.49 (2.10)	0.84	0.17 (0.30)	1.18 (0.65 – 2.15)	0.58	0.04 (0.26)	1.04 (0.62 – 1.72)	0.89
Prior malignancy								
No	Ref		Ref			Ref		
Yes	-1.92 (2.53)	0.45	0.35 (0.46)	1.42 (0.58 – 3.49)	0.44	0.41 (0.34)	1.50 (0.78 – 2.89)	0.23
Significant medical history [***]								
No	Ref		Ref			Ref		
Yes	1.39 (2.11)	0.51	0.22 (0.32)	1.25 (0.67 – 2.32)	0.48	0.26 (0.22)	1.30 (0.84 – 2.01)	0.24
Baseline cognitive impairment [****]								
No	Ref		Ref			Ref		
Yes	-26.46 (2.26)	<0.001	3.65 (0.39)	38.54 (17.89 - 83.02)	<0.001	2.57 (0.31)	13.07 (7.14-23.93)	<0.001
Tumor related variates								
Pathology								
Squamous cell	Ref		Ref			Ref		
Non-squamous cell	6.77 (2.39)	0.005	-0.89 (0.36)	0.41 (0.20 - 0.84)	0.01	-0.47 (0.25)	0.62 (0.39 – 1.01)	0.05
Stage								
IIIA	Ref		Ref			Ref		
IIIB	2.42 (2.00)	0.23	-0.30 (0.30)	0.74 (0.41 – 1.35)	0.33	-0.18 (0.22)	0.83 (0.54 – 1.29)	0.41
Performance status								
0	Ref		Ref			Ref		
1-2	3.55 (2.02)	0.08	-0.62 (0.33)	0.54 (0.28 – 1.02)	0.06	-0.47 (0.25)	0.63 (0.39 – 1.02)	0.06
Treatment related variates								
Surgery								
No	Ref		Ref			Ref		
Yes	1.14 (3.50)	0.74	-0.54 (0.52)	0.58 (0.21 – 1.61)	0.30	-0.46 (0.38)	0.67 (0.32 – 1.39)	0.28
Chemotherapy type								
Single agent	Ref		Ref			Ref		

eTable 7. Risk factors for cognitive impairment (adjusted by interactions with time)

	Models							
	COS-origin*		COC-origin**			COC-MI**		
Factors	β (SE)*	p	β (SE)	OR (95%CI)	p	β(SE)	OR (95%CI)	p
platinum based Combination agent platinum based	0.32 (2.44)	0.90	0.02 (0.40)	0.98 (0.45 – 2.16)	0.97	0.006 (0.32)	1.01 (0.54 – 1.87)	0.99
Arm								
No-PCI	Ref		Ref			Ref		
PCI	-5.84 (1.89)	0.002	0.97 (0.34)	2.643 (1.36 - 5.16)	0.004	0.64 (0.25)	1.89 (1.15 - 3.11)	0.01
Dynamic variates								
BM								
No	Ref		Ref			Ref		
Yes	-22.86 (12.54)	0.07	3.49 (1.11)	32.66 (3.77-282.74)	0.002	2.27 (0.83)	9.65 (1.88-49.56)	0.008
Time-months	-0.44 (0.11)	<0.001	0.06 (0.01)	1.06 (1.04 - 1.08)	<0.001	0.05 (0.01)	1.05 (1.03 – 1.07)	<0.001
Interactions								
Gender × time	0.17 (0.13)	0.20	-0.002 (0.02)	1.00 (0.97 - 1.03)	0.88	-0.002 (0.02)	1.00 (0.97 – 1.03)	0.92
Baseline cognitive impairment × time								
Yes	0.42 (0.17)	0.01	-0.07 (0.02)	0.93 (0.90 – 0.96)	<0.001	-0.07 (0.02)	0.93 (0.90 - 0.97)	0.001
BM × time								
Yes	0.86 (0.46)	0.06	-0.11 (0.05)	0.89 (0.80 – 0.99)	0.03	-0.08 (0.04)	0.92 (0.85-1.00)	0.05

Note: * In the COS model, regression coefficient β >0 indicates better cognitive functioning (better cognitive functioning score). A mean difference by <10, 10-<20, ≥ 20 points was regarded as no, moderate, and large clinical effect, respectively.

** In the COC model, regression coefficient β <0 (OR<1) indicates better cognitive functioning (lower odds ratio for cognitive impairment).

*** Significant medical history includes transient ischemic attack, cerebrovascular accident, cardiovascular diseases (hypertension, hyperlipidemia), and diabetes mellitus.

**** Cognitive impairment: a score<75 on the cognitive functioning scale of QLQ-C30.

Abbreviations: BM, brain metastases; BMI, Body mass index; CI, confidence interval; COC, cognitive functioning category; COS, cognitive functioning score; MI, multiple imputation; OR, odds ratio; PCI, prophylactic cranial irradiation; Ref, reference; SE, standard error.

$\chi 2$ tests were conducted to compare cognitive impairment types distribution among BCI, age, and pathology subgroups. It showed that the type was not significantly different among all the subgroups (BCI: *p*=0.4; age: *p*=0.3; pathology: *p*=0.6) (Figure 4B-D). Cognitive impairment was dynamic and could be reversible. Only one third of patients reported sustained impairment (Figure 4E).

We also compared the age distribution according to the cognitive impairment type and found that the age was not significantly different in each type (ANOVA *p*=0.31; multiple comparisons using Bonferroni test: *p*>0.4).

Discussion

Cognitive impairment becomes a rising concern in patients with stage III NSCLC with the radiotherapy improvements and the development of immunotherapy. Unfortunately, even immunotherapy may cause cognitive impairment[22]. Identifying risk factors for cognitive impairment is the first step to prevent cognitive problems. Therefore, we conducted this MI-GEE analysis using the longitudinal data from the NVALT-11 trial, in which patients were enrolled in a time period when immunotherapy was not introduced. This avoided a possible confounding of immunotherapy-associated cognitive effects. We also categorized the cognitive impairment into four types based on the changing over time – sustained, reversible, recurring, and alternating.

We found that cognitive functioning declined slightly over time without a clinical relevance. Moreover, cognitive impairment was dynamic in the majority of patients. Importantly, one fifth of patients already reported cognitive impairment at baseline. Furthermore, BCI was the most important risk factor for subsequent cognitive impairment, both in the standard observation arm and in the experimental PCI arm. Interestingly, the cognitive functioning did not further decline over time in patients who reported BCI, i.e. a low score (<75) at baseline was associated with subsequent cognitive impairment, but not with further cognitive decline.

It has been reported that self-reported cognitive impairment at baseline was not associated with subsequent decline at 6 or 12 months[12]. However, when defining the cognitive impairment using HVLT, which is an international standardized method to evaluate memory and recognition, the investigators observed different results. Of note, logistic regression analysis was performed separately at each time point, which neglected the correlation of measurements within subjects in longitudinal assessments[23]. It is unknown whether the conclusions would be different if they performed GEE or generalized linear mixed model analysis. Although the data showed fair agreement between SRCF and other QLQ domains[12], the decline in HVLT and decline in SRCF were not closely correlated, indicating that objective neurocognitive tests and SRCF may represent distinct elements of the cognitive spectrum, which was confirmed in a cross-sectional study[5].

Nevertheless, it is necessary to assess cognitive functioning at multiple time points since diagnosis because of the dynamic nature of cognitive impairment. One measurement at one single time point is not sufficient to conclude that there is permanent cognitive impairment. Clarifying the cognitive impairment type will further help clinicians and researchers to better predict and prevent cognitive impairment. For example, treatments with a risk of neurotoxicity should probably not be administered to patients at risk of sustained cognitive impairment, while

treatments could be more aggressive to achieve better survival in those with a reversible type. The reasons for reversible, sustained, recurring, or alternating cognitive impairment should be evaluated in future studies to test strategies that could improve cognitive functioning, such as exercise and nutrition[24].

Studies have shown that higher age is associated with long term cognitive dysfunction in cancer survivors[25]. Unexpectedly, we observed that older patients (>60y) reported better cognitive functioning than younger patients. However, the difference was not clinically relevant. A possible explanation is that younger patients have higher requirements for their cognitive functioning, and therefore notice a slight impairment more easily compared with older patients. This is also in line with breast cancer[26].

In addition, we confirmed that patients who developed BM are at higher risk for experiencing cognitive impairment[11]. Interestingly, the cognitive functioning in the BM group did not further decline over time. This could be due to BM directed therapies, but could also be biased due to a short survival, without subsequent time to develop further decline. Same as in the RTOG0214 trial[17], this finding was hampered by a small number of patients.

Trials have shown that adding whole-brain radiotherapy (WBRT) to stereotactic radiosurgery (SRS) for patients with 1-3 BM could result in more cognitive decline[27,28], in which cognition was assessed using objective neurocognitive tests and cognitive decline was compared at one time point from baseline. It would be interesting to explore whether the longitudinal SRCF would be different for SRS with or without WBRT in patients with BM in future trials.

Last, PCI is not standard of care in stage III NSCLC and nowadays is also less often given in SCLC due to concerns for neurotoxicity[29]. In the present study, patients who received PCI indeed reported worse cognitive functioning, however, the clinical relevance was negligible. Similar findings were reported in the RTOG 0214 trial[17]. A pooled analysis showed a higher risk of cognitive decline at 6 and 12 months in the PCI arm[12], however, as stated above, the within-subjects correlation of longitudinal data was not considered, and the concept of "decline" was defined differently using the reliable change index method[30]. Furthermore, a recent study showed that PCI is cost effective in NSCLC[31]. Therefore, it is necessary to prevent BM, especially as patients live longer with more effective treatments. Additionally, cognition preservation managements have shown encouraging effects, such as hippocampus avoidance-PCI (HA-PCI)[32], memantine[33], or HA-PCI plus memantine[34]. On top of that, cognitive impairment is dynamic and complex, as shown in the four types. Therefore, it is time to reassess

the stigma of PCI-toxicity in stage III NSCLC using high quality data, especially for patients who are at high risk of developing BM and do not have cognitive impairment at baseline.

Besides, PCI dose and regimen might be correlated with cognitive impairment after PCI in patients with lung cancer[11]. The RTOG 0212 trial showed that compared with 25Gy (once-daily), patients receiving 36Gy (once-daily or twice-daily) were at higher risk to develop cognitive decline[35]. However, Le Pechoux's trial demonstrated no significant differences between the higher dose (36 Gy) and standard dose (25 Gy) PCI arms[18]. Of note, in the latter, fewer patients received a twice-daily regimen in the high dose arm. In contrast, in the NVALT-11 trial, only one patient received 36Gy, and three received 25Gy, with 30Gy in 10 or 12 fractions being the most commonly used regimen. When comparing the these regimens, no significant effect on SRCF was found. In the Netherlands, a prospective RCT (NVALT-28 trial, NCT04597671) is currently ongoing to investigate the incidence of BM in patients with stage III NSCLC treated with adjuvant durvalumab and low-dose PCI (15 Gy in 10 fractions) versus adjuvant durvalumab only. Neurocognition is the key secondary outcome. The results will be helpful to further clarify the role of PCI on neurocognitive function in addition to immunotherapy[36].

Strengths of the present study are the use of prospectively collected data, obtained standardized in the NVALT-11 clinical trial, the long follow-up period, the relatively high compliance for cognitive functioning assessments, and the relevance for patients (as this is what they report about their cognitive functioning). Limitations can be found in the dropout of individuals during follow-up, but we have performed GEE models before and after multiple imputation to mitigate its bias.

Conclusion

To our knowledge, this study firstly demonstrated that cognitive impairment can be categorized into four types based on the dynamic nature: sustained, reversible, recurring, and alternating. Therefore, cognitive functioning assessment should be assessed at multiple time points. BCI was the most important risk factor for subsequent cognitive impairment, but it did not further deteriorate. Patients who developed BM were at higher risk to experience cognitive impairment. Younger age (≤ 60), non-squamous cell carcinoma, and PCI were risk factors without clinical relevance. These findings will be helpful to stratify patients and to design specific interventions.

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Conflict of Interest:

The authors declare no conflicts of interest.

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Chapter 9

General discussion and future perspectives

Haiyan Zeng

1. Introduction

Brain metastases (BM) is a common problem in patients with lung cancer. Prevention and treatment of BM is a significant challenge for clinicians and scientists. On one hand, the risk factors for BM remain largely unknown. On the other hand, prophylactic cranial irradiation (PCI) can effectively reduce the incidence of BM but has a risk of neurotoxicity and neurocognitive decline. Furthermore, although having completed PCI, 17%-21% of patients still will be diagnosed with BM during the course of their disease[1,2]. For these patients, BM management becomes even more limited due to the earlier cranial irradiation. So, ideally, PCI should only be offered to patients who are at high risk of developing BM and should not be recommended in patients who would experience BM even with PCI, for whom periodic brain magnetic resonance imaging (MRI surveillance) would be a better option to detect BM earlier. In addition, for patients who respond well to PCI, efforts should be done to reduce the risk of neurocognitive decline on the condition of identifying patients who are at high risk of experiencing neurocognitive decline after PCI. Therefore, in my thesis I performed several studies in order to optimize PCI for patients with lung cancer, to maximize the benefit and minimize the toxicity of PCI, by identifying risk factors for BM and neurocognitive impairment in patients with lung cancer, including small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

2. Summary of main findings

In **chapter 2**, as a retrospective study in China[2] and a prospective phase III trial in Europe (not powered for this question)[3] showed conflicting results regarding the association of thoracic twice-daily radiotherapy (TDRT) versus once-daily radiotherapy (ODRT) and the development of BM after PCI in patients with small cell lung cancer (SCLC), I conducted a larger multi-centric retrospective study in China to further evaluate this question. In contrast to the previous studies, I controlled the potential confounding factors by performing 1:1 propensity score matching (PSM). I found that the incidence of BM in patients treated with thoracic TDRT was significantly higher than those with ODRT (before PSM [N=778]: 3-year BM incidence 26.0% in TDRT vs. 16.9% in ODRT; subdistribution hazard ratio [sHR] = 1.55, 95%CI 1.06-2.26, $p = 0.03$; after PSM [N=338]: 3-year BM incidence 26.0% in TDRT vs. 14.9% in ODRT; sHR = 1.71, 95%CI 1.02-2.88, $p = 0.04$), which favors the previously published Chinese results[2]. Progression-free survival (PFS) was similar in both the whole cohort and the matched one. After PSM, there was a trend for a longer median overall survival (OS) in the ODRT subgoup

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(median, 47.2 months in ODRT vs. 32.8 months in the TDRT subgroup; HR = 1.41, 95%CI 0.99-2.01, p = 0.06). This non-significant difference is consistent with both earlier studies[1,2].

To further evaluate factors associated with BM development in SCLC, in **Chapter 3,** I systematically reviewed all the risk factors that have been reported in the literature and performed meta-analysis for factors with qualified data. I found that among the 57 factors that were reported, 10 factors had qualified BM data for meta-analysis (i.e. two or more studies; the same study type; the same analysis method; HRs retrievable): Limited stage disease (LD) (HR=0.34, 95%CI: 0.17-0.67; p=0.002) and older age (≥65) (HR=0.70, 95%CI: 0.54-0.92; p=0.01) were associated with less BM, a higher T stage (≥T3) (HR=1.72, 95%CI: 1.16-2.56; p=0.007) was a significant risk factor for BM. Male sex (HR=1.24, 95%CI: 0.99-1.54; p=0.06) tended to be a risk factor and better PS (0-1) (HR=0.66, 95%CI: 0.42-1.02; p=0.06) tended to be protective. Smoking, and thoracic radiotherapy dose were not significantly associated with BM development (p>0.05). PCI significantly decreased BM (p<0.001), but did not improve OS in extensive disease (ED)-SCLC (p=0.81). A higher PCI dose did not improve OS (p=0.11). The impact on BM was conflicting between Cox regression analysis (HR=0.59, 95%CI: 0.26-1.31; p=0.20) and competing risk regression analysis (sHR=0.74, 95%CI: 0.55-0.99; p=0.04). Compared to M0-M1a, M1b was associated with a poorer OS (p=0.01) in ED-SCLC, but was not associated with BM development (p=0.19). As regular brain imaging was rarely performed in the included studies, high-quality data is lacking. Other factors such as N-stage and blood biomarkers had no qualified data to perform a meta-analysis. In conclusion, younger age, higher T stage, and ED are risk factors for BM, suggesting that PCI should be especially discussed in such cases. Individual patient data (IPD) meta-analysis and well-designed randomized controlled trials (RCTs) are needed to better identify more risk factors and further confirm our findings.

In this systematic review, I identified six studies that have investigated the association of thoracic radiotherapy fractionation (ODRT/TDRT) and BM development, which drew conflicting conclusions (Table 1). The only RCT (the CONVERT trial) recruited 547 patients (TDRT: 274; ODRT: 273) with limited disease (LD)-SCLC in Europe[4]. Competing risk analysis showed that ODRT/TDRT was not a significant risk factor for BM in LD-SCLC[1,3]. One retrospective study in China (N=175) explored risk factors for BM after PCI in patients with SCLC showed that compared to ODRT, patients with TDRT were more likely to develop BM[2]. Another retrospective study in China (N=139) explored risk factors for BM in LD-SCLC patients who did not undergo PCI showed that ODRT vs TDRT was not correlated with BM (p=0.187)[5], in which only 13.7% (19/139) patients were treated with TDRT. One retrospective

study in America (N=658) also showed negative results in patients with LD-SCLC. Another retrospective study in Japan (N=162) investigated BM as a first recurrence site in patients with LD-SCLC and showed no significant difference between ODRT and TDRT[6]. In this study, the overall BM results (including BM after extracranial progression) were not reported, and χ^2-test was used for BM analysis. The last one was our multicenter retrospective study, in which the PSM method was used to minimize bias of confounders. The competing risk analysis showed that TDRT increased BM incidence after PCI in patients with SCLC in both the whole cohort and the PSM cohort[7].

As studies investigated thoracic radiotherapy (TRT) fractionation in different ways (competing risk regression, Cox regression, and χ^2-test) with different patients (SCLC including patients with LD/ED treated with PCI, or patients with LD-SCLC treated with or without PCI), no qualified data were available to perform meta-analysis. Therefore, it is unclear whether TRT fractionation is a risk factor for BM. Among the above six studies, the most comparable two studies were the CONVERT trial and our multicenter PSM study, as both investigated patients who received PCI with competing risk analysis, which considers death as a competing event of BM. The potential mechanism of the conflicting results has been discussed in detail in **Chapter 2** (more severe injury to thoracic blood-spinal cord barrier/blood-brain barrier in the TDRT irradiation, and races/ ethnicities differences in the Chinese and European population). Better designed studies incorporating translational research are needed to answer this question, especially prospective RCTs in China or Asia. Future studies should adequately stage, better document all potential risk factors, plan periodic brain MRI surveillance at pre-specified time points, and improve the compliance of MRI examination. In the translational part of prospective randomized trials there should be a focus on the radiobiology mechanisms of ODRT versus TDRT behind BM development in SCLC, and preclinical studies are also needed to further evaluate this.

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Table 1. Studies on thoracic radiotherapy fractionation (ODRT/TDRT) and BM development

Studies	Patients	Study location	BM analysis	Conclusion
Faivre-Finn C, 2017[3]; Levy, 2019[1] (CONVERT trial)	LD-SCLC: PCI (N=449); CCRT (N=489); CCRT+PCI (N=437)	Europe, multicenter, prospective randomized trial (ODRT vs TDRT)	Competing risk regression;	TDRT is not a significant risk factor for BM: with PCI: sHR = 1.05, 95%CI 0.67-1.67, $p = 0.83$; with CCRT: sHR = 1.15, 95% CI 0.75–1.79, $p = 0.42$; with CCRT+PCI: sHR = 1.02, 95% CI 0.65–1.61, $p = 0.92$.
Zeng, 2017[2]	SCLC with PCI (N=175)	China, single center, retrospective	Cox regression.	TDRT is a risk factor for BM after PCI in SCLC: 3-year BM: ODRT: 21%; TDRT: 43%; HR = 2.171, 95% CI 1.111–4.243, $p = 0.023$.
Farooqi, 2017[8]	LD-SCLC (N=658)	America, single center, retrospective	Competing-risk regression.	TDRT is not a risk factor for BM in LD-SCLC: sHR 1.01, 95%CI 0.72–1.41, $p=0.971$
Zheng, 2018[5]	LD-SCLC without PCI (N=139)	China, single center, retrospective	Cox regression.	TDRT is not a significant risk factor for BM in LD-SCLC patients who did not undergo PCI: $p=0.187$.
Nakamura, 2018[6]	LD-SCLC (N=162)	Japan, single center, retrospective	χ^2-test	BM as a first recurrence site is not significantly different in ODRT and TDRT in LD-SCLC: ODRT: 34% (23/68); TDRT: 23% (22/94); $p=0.144$.
Zeng, 2019[7]	SCLC with PCI (N=778; after matching: N=338)	China, multicenter, retrospective PSM (ODRT vs TDRT)	Competing risk regression	TDRT is a risk factor for BM in SCLC with PCI: before PSM: 3-year BM 26.0% in TDRT vs. 16.9% in ODRT; sHR = 1.55, 95%CI 1.06-2.26, $p = 0.03$; after PSM: 3-year BM 26.0% in TDRT vs. 14.9% in ODRT; sHR = 1.71, 95%CI 1.02-2.88, $p = 0.04$.

Abbreviations: BM, brain metastases; CCRT, concurrent chemoradiotherapy; LD-SCLC, limited-disease small cell lung cancer; ODRT, once-daily radiotherapy; PSM, propensity score matching; sHR, subdistribution hazard ratio; TDRT, twice-daily radiotherapy.

After summarizing the current progress on BM risk factors in patients with SCLC, I take a further step to patients with NSCLC, since there is a lack of knowledge on how to predict BM in NSCLC as well, especially in patients with stage III, for whom PCI has been found to reduce the incidence of BM without OS benefit[9-11]. If PCI could be selectively administered only in patients who are at high risk of developing BM, the OS outcome might be different. Therefore, in **chapter 4**, I investigated risk factors for BM in patients with adequately staged and radically treated stage III NSCLC. I found that three clinical variables (younger age, NSCLC non-squamous subtype, and larger gross tumor volume of lymph nodes [GTVn]) were risk factors for BM, five radiomics features from each radiomics model (GTVn, GTV of primary tumor [GTVp], GTV) were significantly associated with BM development. Radiomic features measuring tumor heterogeneity extracted from the tumor volumes were the most relevant. The

Area under the receiver operating characteristic curves (AUCs) and calibration curves of the models showed that the GTVn radiomics model had the best performance (AUC: 0.74; 95%CI: 0.71-0.86; Sensitivity: 84%; Specificity: 61%; Positive predictive value [PPV]: 29%; Negative predictive value [NPV]: 95%; Accuracy: 65%). To our knowledge, this is the first study that demonstrates the prognostic value of the GTVn volume and GTVn radiomics features on BM development in patients with stage III NSCLC. It indicates that the GTVp and GTVn should be contoured separately in clinical practice and related studies. Furthermore, we also show that these models can be especially useful to predict which patient will NOT develop BM. If validated in other studies, our model could help in selecting patients that will not need PCI and do not need MRI follow-up.

Although not many patients received durvalumab in this cohort (84/310, 27%), I think the results might still be valid in the era of PACIFIC[12,13], as younger age, non-squamous subtype, and larger GTVn were the only three independent risk factors among the 16 factors in the multivariate competing risk analysis model. For patients with younger age, non-squamous subtype, and larger GTVn, selective PCI might have the potential to improve the OS. This could be prospectively validated in the ongoing NVALT-28 trial (NCT04597671)[14], which compares durvalumab with or without low dose PCI (15Gy in 10 fractions) in radically treated stage III NSCLC.

This study also showed a very good example of solving clinical problems by interdisciplinary collaboration (close collaboration with clinicians, computer scientists, and data scientists). As a clinician who usually does not have much background knowledge on computer science, the most challenging parts for interpreting radiomics results is to understand the principles of radiomics features and the process of extracting radiomics features. But only a basic learning would help a lot. After that, clinicians can work much better together with data scientists on related projects to improve health care in clinical practice.

As mentioned above, PCI is an effective management to reduce the incidence of BM in patients with lung cancer, however, it does not improve OS in NSCLC or in metastatic SCLC. In addition, it could cause neurocognitive decline in a subgroup of patients. Since it remains unknown what factors are associated with neurocognitive decline after PCI, I conducted a systematic review in **chapter 5**. I systematically reviewed the PubMed database according to the PRISMA guideline. Eligibility criteria were: RCTs and observational/single arm trials evaluating PCI, including ≥20 patients, reporting neurocognitive test results for lung cancer. I identified 20 records (8 RCTs, 8 observational studies) and found that the incidence of mild/moderate cognitive decline after PCI varied from 8-89% (grading not always provided);

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for those without PCI, this was 3.4-42%. Interestingly, 23-95% of the patients already had baseline cognitive impairment. Risk factors were often not reported in detail. Most trials only evaluated PCI vs no PCI, or HA-PCI vs PCI, but did not consider other potential risk factors. In one trial, both age (>60 years) and higher PCI dose (36 Gy) including twice-daily PCI were associated with a higher risk of cognitive decline. In another trial, white matter abnormalities were more frequent in the concurrent or sandwiched PCI arm, but without significant neuropsychological differences. One trial identified hippocampal sparing PCI to limit the neurocognitive toxicities of PCI and another reported an association between hippocampal dose volume effects and memory decline. In summary, age, PCI dose, regimen and timing might be associated with cognitive impairment after PCI in patients with lung cancer. As neurocognition was a secondary endpoint in most RCTs, and was assessed by various of instruments with often poor/moderate compliance, high-quality data is lacking. Further research is therefore needed.

To improve cognitive function research, the following items should be implemented: 1. Using as broad as possible, but still practical neurocognitive testing batteries, which needs close collaborations with neuropsychologists. This is very important to recruit patients, administer interventions and assess outcomes more successfully; 2. Trying to increase the patients' compliance of cognitive assessments, for example explaining the importance and value of the neurocognitive functioning assessments, reminding, encouraging, and rewarding patients and caregivers to do so by offering them reimbursements or small gifts, or involving the patient foundation to come up with a better solution together. This will lower the trial's risk of bias and make the conclusions more reliable; 3. Blinding the assessors to the intervention status as this will make the assessment more objective; 4. A systemic biology framework incorporating multimodality neuroimaging, genetics and other biomarkers. This will be very informative regarding individual differences in risk and protective factors and disease- and treatment-related mechanisms on cognitive decline[15]; 5. A proper and workable window definition of each assessment time point is useful to expand the analyzable data; 6. Briefly specifying in the trial report how the randomization was conducted. This would be helpful for readers to assess randomization bias precisely and interpret the results better.

After obtaining/gaining an overview on the current status and pitfalls of cognitive related studies worldwide, I dived deep into a specific topic: HA-PCI vs PCI, in patients with SCLC. HA-PCI is presumed to preserve neurocognitive function by avoiding to irradiate the hippocampal zone, which plays a key role in learning and memory[16]. However, the phase III Dutch-Flemish RCT, NCT01780675, showed that the percentage of patients with cognitive decline (defined as a decrease ≥5 points of total recall on the Hopkins Verbal Learning Test-

Revised [HVLT-R]) was not significantly different between HA-PCI and PCI arms (28% for HA-PCI vs 29% for PCI, p=1.000)[17]. HVLT-R is a psychological test that measures the objective neurocognitive function. However, it is also important to know how patients themselves rate their neurocognitive functioning and how their QoL is influenced by PCI. Therefore, I compared the self-reported cognitive functioning (SRCF) and quality of life (QOL) between conventional PCI and hippocampal avoidance (HA)-PCI in patients with SCLC based on the longitudinal data from the Dutch trial in **chapter 6**. I found that there was no significant difference in the percentage of patients with deteriorated, stable, or improved SRCF between the treatment arms. Depending on the evaluated time point, 31-46% and 29-43% of patients in the HA-PCI and PCI arm, respectively, reported a deteriorated SRCF based on the EORTC QLQ-C30 and MOS. QoL outcomes were not significantly different between the study arms, except for physical functioning at 12 months (23% [n=7] in the PCI arm versus 14% [n=4] in the HA-PCI arm, p=0.019) and motor dysfunction at 24 months (33% [n=5] in PCI versus 23% [n=5] in HA-PCI, p=0.02). That is to say, according to the Dutch trial, HA-PCI makes no difference in QOL and neurocognitive function (both SRCF and tested cognitive function).

In contrast with the Dutch-Flemish trial, the comparable Spanish PREMER/NCT02397733 trial reported contrasting results on the role of HA-PCI on neurocognitive function preservation in patients with SCLC: the percentage of patients with cognitive decline after HA-PCI (defined as a decrease ≥3 points of delayed free recall on the Free and Cued Selective Reminding Test [FCSRT]) was significantly lower compared with PCI (5.8% for HA-PCI vs 23.5% for PCI, p=0.003)[18]. As the number of patients with events was relatively low in both trials and the cognitive test for the primary endpoint was different, it is difficult to draw firm conclusions. Furthermore, one can argue whether a difference in HVLT-R or the FCSRT testing on one single time point is the most relevant for patients, as this does not take into account the evaluation of the patient of his/her cognition and it does not take into account variations over time. Additionally, another reason to choose HA-PCI or PCI is the safety regarding BM development which might be higher for HA-PCI. Therefore, in **Chapter 7**, I pooled the individual data of these two trials together to compare the SRCF and BM between conventional PCI and HA-PCI in patients with SCLC. I found that HA-PCI has no impact on SRCF. On the other hand, sparing the hippocampus did not lead to a higher incidence of brain failure within or out of the hippocampal avoidance zone. This is so far the most robust evidence worldwide. The ongoing NRG CC003 trial will provide more data to further clarify this issue. According to the experience on whole brain radiotherapy (WBRT) that comparing with WBRT plus memantine, HA-WBRT plus memantine can better preserve neurocognitive function [19], it is

reasonable to postulate that adding memantine to HA-PCI might achieve promising results on cognitive function maintenance, especially for patients at risk of neurocognitive decline. Yet, RCTs are warranted to confirm this hypothesis.

As stated above (summary of **chapter 5**), PCI is not the only cause that can cause neurocognitive decline and 23-95% of patients already reported cognitive impairment before PCI. Chemotherapy, which is the backbone in the treatment of stage III NSCLC, might also cause cognitive impairment (chemobrain[20]). However, there is paucity of data on neurocognitive functioning after chemotherapy given for NSCLC. I therefore investigated the cognitive impairment in the phase III NVALT-11 trial (observation versus PCI in stage III NSCLC) with the focus on the standard of care arm without PCI in **chapter 8**. I observed cognitive impairment (score <75) also in patients not having received PCI and found that baseline cognitive impairment is the most important risk factor for subsequent cognitive functioning. I also found that cognitive impairment is dynamic in individuals and can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating, which was also confirmed in patients with SCLC (**Chapter 7**). This classification is very innovative and can inspire numerous further investigations, which should be incorporated in future clinical trials, as this could identify patients who may benefit most from interventions that are increasingly investigated, such as immunotherapy and PCI. For patients who are more likely to have sustained cognitive impairment, a potentially neurotoxic therapy should only be administered after counseling with a shared decision. Furthermore, studies evaluating potentially neuroprotective treatments should especially focus on this high-risk population, while for patients who are more likely to have reversible cognitive impairment, the treatments can be more aggressive to achieve a maximum curative effect. But on top of that, long term follow-up with periodic neurocognitive assessment is needed to identify the patients' impairment types correctly.

Strengths and limitations:

The strengths and limitations of each chapter are shown in Table 2. I also summarized the challenges we have met in conducting the studies, what we have done to mitigate the bias, and how we can improve it in future work.

Table 2. Strengths and limitations of each project

Chapters	Strengths	Challenges	Limitations	Mitigations	Future work
2. TDRT and BM in SCLC	1. Multicenter study; 2. Propensity score matching; 3. Competing risk analysis	Collaboration with colleagues from multiple centers	Retrospective study	Propensity score matching; Multicenter; Large sample size	1. RCTs; 2. Translational studies focusing on the radiobiology mechanisms of thoracic ODRT versus TDRT behind BM development.
3. Risk factors for BM in SCLC: meta-analysis	1. Proposed data qualification criteria for performing meta-analysis; 2. Analyzed BM risk factors' impact on OS as well if applicable; 3. Found out pitfalls of current studies and proposed suggestions for improvement in future studies.	Systematic literature searching and reviewing	Studies themselves were often poorer quality so difficult to draw reliable conclusions	Set qualification criteria for data assessment to perform meta-analysis	1. Better designed prospective clinical trials; 2. Individual patient data meta-analysis
4. GTV and BM in NSCLC	1. Adequately staged with PET-CT and brain MRI; 2. Uniform planning CT scans; 3. Large sample size; 4. 1000-bootstrapping and LASSO regression for features selection; 5. Competing risk analysis; 6. Evaluate GTVn and GTVp separately; 7. Including patients with immunotherapy (durvalumab); 8. Precision GTVs contouring by specialists in lung cancer radiotherapy; 9. Evaluated the impact of BM risk factors/features on OS.	Distinguish GTVn and GTVp	1. Type 2A study without external validation; 2. Retrospective study without pre-specified brain MRI surveillance	Performed bootstrapping 1000 times and LASSO regression to develop the radiomics models.	1. External validation studies (evaluating our model on a separate dataset, TRIPOD type 4 studies); 2. Same methods with a larger sample size training dataset and an independent validation dataset (TRIPOD type 3 studies) 3. Deep learning, machine learning, and artificial intelligence studies with big data.
5. Cognitive decline in LC: systematic review	1. Focus on prospective studies; 2. Set a sample size criteria; 3. Found out pitfalls of current studies and proposed suggestions for improvement in future studies.	Systematic literature searching and reviewing	Studies themselves were often poorer quality so difficult to draw reliable conclusions	Only included prospective trials with adequate sample size	1. Designed clinical trials with the neurocognitive functioning as the primary endpoint; 2. Better conducted clinical trials with higher compliance of neurocognitive function assessment.

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Table 2. Strengths and limitations of each project

Chapters	Strengths	Challenges	Limitations	Mitigations	Future work
6. SRCF and QOL in the Dutch trial	1. Phase III RCT; 2. Longitudinal data collected prospectively at each pre-specified time point.	1.Design a phase III RCT trial; 2. Perform HA-PCI; 3.International collaboration within multiple centers; 4.Neurocognitive tests and QOL assessments compliance	1. Dropouts of patients; 2. Secondary endpoints, not powered enough.	1. Dropout was balanced between both treatment arms and reflects the aggressive natures of SCLC; 2. Longitudinal linear mixed models were performed; 3. It is a common practice in clinical trials to design QOL as a secondary endpoint without power calculation.	1. Pooled analysis of comparable clinical trials with individual patient data; 2. Better conducted clinical trials with higher compliance of neurocognitive function assessment for alive patients;
7. SRCF and BM in the pooled trials	1. Two phase III RCTs; 2. Most recent available data worldwide 3. Longitudinal data collected prospectively at each pre-specified time point; 4. Set a time window for neurocognitive function assessments at each time point; 5. Reported the brain MRI compliance, which is novel and hasn't been reported in any earlier studies; 6. Large sample size.	1.Design and conduct two phase III RCT trials; 2. Perform HA-PCI; 3.International collaboration within multiple centers; 4.Neurocognitive tests and brain MRI assessments compliance; 5. Retrieve data	1. No comparable objective neurocognitive functioning data (different neuropsychological tests were used); 2. Dropouts of patients	Pooled-analysis of the only two comparable RCTs to double the sample size	Waiting for the results of the ongoing NRG CC003 trial[21] and pooling the objective neurocognitive functioning data with the Dutch trial, as same neurocognitive tests were used in both trials.
8. SRCF in NSCLC	1. Phase III RCT; 2. Longitudinal data collected prospectively at each pre-specified time point; 3. Set a time window for neurocognitive function assessments at each time point; 4. Long follow-up and relatively high compliance of neurocognitive function assessment compliance; 5. Proposed a novel classification for cognitive impairment types; 6. Multiple imputation for missing data.	1. Design a phase III RCT trial; 2. International collaboration within multiple centers; 3. Neurocognitive tests and QOL assessments compliance; 4. Retrieve data.	1.Relatively small sample size; 2.Dropouts of patient.	1. Longitudinal generalized estimating equation (GEE) analysis before and after multiple imputation.	1.Pooled analysis with the comparable RTOG 0214 trial.

Abbreviations: BM, brain metastases; GTV, gross tumor volume; LC, lung cancer; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ODRT, once-daily radiotherapy; PCI, prophylactic cranial irradiation; QoL, quality of life; SCLC, small cell lung cancer; RCT, randomized controlled trial; SCRF, self-reported cognitive functioning; TDRT, twice-daily radiotherapy.

Conclusion:

In conclusion, serial projects of this thesis (including secondary analyses of 3 phase III RCTs) showed that TDRT is a risk factor for BM in Chinese patients with SCLC. Younger age, higher T stage, and ED are risk factors for BM in patients with SCLC. Younger age (≤ 60 years), non-squamous cell carcinoma, and larger GTVn were significant clinical factors associated with BM development in patients with stage III NSCLC, GTVn radiomics features provided higher predictive value for BM development than GTVp and GTV. Age (>60 years), higher PCI dose (36Gy), regimen (twice-daily PCI), and timing (concurrent or sandwiched PCI) might be associated with cognitive impairment after PCI in lung cancer patients. There were no significant difference in BM incidence and location, cognitive decline and QOL between HA-PCI and PCI arms in patients with SCLC. Baseline cognitive impairment is the most important risk factor for subsequent cognitive functioning in patients with NSCLC. Cognitive impairment is dynamic in individuals and can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating.

As extensively discussed above, future studies are warranted to investigate the mechanism of TDRT injury to the irradiated thoracic blood-spinal cord barrier/blood-brain barrier. RCTs comparing BM incidence of thoracic TDRT and ODRT in SCLC patients in China or Asia are essential. Radiomics studies with more extensive data and external validation are warranted to evaluate which patients are at high risk of BM (or no risk at all). IPD meta-analysis and well-designed RCTs with high quality data are needed to identify more risk factors such as blood biomarkers for BM and cognitive impairment. Periodic brain MRI with contrast-enhancement, cognitive assessments should be performed before anti-tumor therapy, before PCI, and during follow-up to detect asymptomatic BM, to identify cognitive impairment types, and to better establish prognostic models. On top of that, the compliance of brain MRI and cognitive assessments at pre-specified time points shall be improved, for example, by offering reimbursements or additional funding, which shall be included in the budget of research grants. Memantine with PCI/HA-PCI shall be investigated to further protect cognitive function. And to conclude, better collaboration with statisticians are needed to conduct studies with high quality and reliability by performing proper statistical analysis.

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Chapter 10

Summary

Haiyan Zeng

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Lung cancer is the leading cause of cancer related deaths. Brain metastases (BM) are very common in patients with lung cancer, and are associated with a decrease in quality of life (QOL) and overall survival (OS). Identifying risk factors for BM development can help clinicians to select patients who are at higher risk to develop BM during the disease course, and accordingly propose strategies to reduce the risk, such as administering prophylactic cranial irradiation (PCI). PCI is an effective method to reduce the incidence of BM in patients with lung cancer. However, it is associated with a risk of neurocognitive decline. Therefore, PCI should be selectively applied only to patients who are more likely to develop BM. Importantly, PCI is not the only cause that could give rise to neurocognitive impairment. Hence, revealing the risk factors for cognitive impairment is also very important, which can help improve the QOL by modifying the treatments, such as proposing hippocampal avoidance (HA)-PCI. Based on the above described rationales, I conducted serial studies to optimize PCI for patients with lung cancer in this thesis.

Chapter 1 is the first part of the thesis, where I provided a detailed background for this thesis, including lung cancer and its main pathology types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the differences between the two diseases. I described BM in lung cancer and its prognosis, together with currently known risk factors and the needs for further research. Next, I summarized how to reduce the incidence of BM by PCI, the pros and cons of PCI, and how to reduce the toxicity of PCI by HA-PCI. Last, I specified the definition of cognitive impairment and how to assess the cognitive function and QOL. I tried to solve the open questions described in chapter 1 in the subsequent chapters.

I started with evaluating the risk factors for BM in patients with SCLC and in patients with NSCLC. In **Chapter 2**, I conducted a propensity score matching multi-centric retrospective study in China to investigate whether thoracic twice-daily radiotherapy (TDRT) is associated with a higher incidence of BM compared with once-daily radiotherapy (ODRT) in patients with SCLC. It showed that TDRT increased the risk of BM without affecting the OS. Then, I systematically reviewed all the risk factors that have been reported for patients with SCLC in the current literature and conducted meta-analysis when applicable (**Chapter 3**). It domenstrated that the most important risk factors were younger age, higher T stage, and extensive disease (ED). Six studies have investigated the association of thoracic radiotherapy fractionation (ODRT/TDRT) with BM development and showed conflicting conclusions. No qualified data were available to perform meta-analysis for this factor. Future studies are warranted to confirm this issue. After that, I took a further step to NSCLC and investigated risk factors for BM in patients with radically treated stage III NSCLC, including radiomics features

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of the gross tumor volume (GTVs) on the planning CT scan for thoracic radiotherapy (**Chapter 4**). I developed a clinical model, three radiomics model (GTV, GTV of the involved lymph nodes [GTVn], GTV of the primary tumor [GTVp]), and a combined model. I compared their performance and clinical utility and found that the radiomics model of GTVn was the best one. Younger age, NSCLC non-squamous subtype, and larger GTVn were risk factors for BM. The GTVn volume and GTVn radiomics features were most prognostic for BM development in patients with stage III NSCLC. The GTVp and GTVn should be contoured separately in clinical practice.

The next part handles neurocognitive impairment and QOL in patients with SCLC and in patients with NSCLC. In **Chapter 5**, I systematically reviewed risk factors for neurocognitive decline in patients with lung cancer who were treated with PCI. To ensure the conclusions are reliable, I focused on reports from prospective clinical trials with adequate sample size. The main message is that high-quality data is lacking. Age, PCI dose, regimen and timing might be associated with cognitive impairment after PCI, but further research is needed.

With an overview on the status and pitfalls of current neurocognitive function related studies, I investigated the self-reported cognitive functioning (SRCF) and QOL in SCLC patients who were treated with PCI or HA-PCI from the phase III Dutch-Flemish randomized controlled trial (RCT), NCT01780675 (**Chapter 6**). The conclusion is: HA-PCI or PCI do not result in a difference in QOL and SRCF. Then, I pooled the two comparable phase III RCTs, the Dutch-Flemish NCT01780675 trial and the Spanish PREMER/NCT02397733, to investigate the impact of HA-PCI on SRCF and BM, including BM incidence and location (**Chapter 7**). It revealed that HA-PCI has no impact on SRCF, sparing the hippocampus did not lead to a higher incidence of isolated brain failure within or out of the hippocampal avoidance zone. Meanwhile, I also investigated the risk factors for cognitive impairment in patients with radically treated stage III NSCLC based on the longitudinal data from the phase III NVALT-11 trial (**Chapter 8**). I found that cognitive impairment is dynamic in individuals and can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating, which was also confirmed in patients with SCLC (**Chapter 7**). Baseline cognitive impairment is the most important risk factor for subsequent cognitive functioning.

The last part of the thesis (**Chapter 9**) provides the main findings of each project and a general discussion on the findings, including the value of the findings, together with strengths and contributions of our studies, challenges we have met in conducting the studies, limitations that need attention in each study, what we have done to mitigate the corresponding bias, how we can improve it in future work, and future perspectives.

Hoofdstuk 10

Samenvatting

Haiyan Zeng

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Longkanker is de belangrijkste oorzaak van kankergerelateerde sterfgevallen. Hersenmetastasen (brain metastases, BM) komen zeer vaak voor bij patiënten met longkanker en worden in verband gebracht met een afname van de kwaliteit van leven (quality of life, QOL) en de algehele overleving (overall survival, OS). Het identificeren van risicofactoren voor de ontwikkeling van BM kan clinici helpen om patiënten te selecteren die een hoger risico lopen om BM te ontwikkelen tijdens het ziekteverloop, en dienovereenkomstig strategieën voor te stellen om het risico te verminderen, zoals profylactische schedelbestraling (prophylactic cranial irradiation, PCI). PCI is een effectieve methode om de incidentie van BM bij patiënten met longkanker te verminderen. Het wordt echter geassocieerd met een risico op neurocognitieve achteruitgang. Daarom moet PCI alleen selectief worden toegepast bij patiënten die meer kans hebben om BM te ontwikkelen. Belangrijk is dat PCI niet de enige oorzaak is die aanleiding kan geven tot neurocognitieve stoornissen. Daarom is het identificeren van de risicofactoren voor cognitieve stoornissen ook erg belangrijk. Dit is nuttig om de QOL te verbeteren door de behandelingen aan te passen, zoals het voorstellen van hippocampus sparende (hippocampal avoidance, HA)-PCI. Op basis van de hierboven beschreven achtergrond heb ik in dit proefschrift verschillende onderzoeken uitgevoerd om PCI te optimaliseren voor patiënten met longkanker.

Hoofdstuk 1 is het eerste deel van het proefschrift, waarin ik een gedetailleerde achtergrond voor dit proefschrift heb gegeven, inclusief longkanker en de belangrijkste pathologietypes, kleincellige longkanker (small-cell lung cancer, SCLC) en niet-kleincellige longkanker (non-small-cell lung cancer, NSCLC), en de verschillen van de twee ziekten. Ik heb BM bij longkanker en de prognose ervan beschreven, samen met de momenteel bekende risicofactoren en de behoefte aan verder onderzoek. Vervolgens heb ik samengevat hoe de incidentie van BM door PCI kan worden verminderd, de voor- en nadelen van PCI en hoe de toxiciteit van PCI door HA-PCI kan worden verminderd. Als laatste specificeerde ik de definitie van cognitieve stoornissen en hoe de cognitieve functie en de QOL te beoordelen. De beschreven open vragen in hoofdstuk 1 heb ik in de volgende hoofdstukken geprobeerd op te lossen.

Ik begon met het evalueren van de risicofactoren voor BM bij patiënten met SCLC en bij patiënten met NSCLC. In **Hoofdstuk 2** heb ik een propensity score matching multicentrische retrospectieve studie in China uitgevoerd om te onderzoeken of thoracale tweemaal daagse radiotherapie (twice-daily radiotherapy, TDRT) geassocieerd is met een hogere incidentie van BM in vergelijking met eenmaal daagse radiotherapie (twice-daily radiotherapy, ODRT) bij

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patiënten met SCLC. Het toonde aan dat TDRT het risico op BM verhoogde zonder de OS te beïnvloeden.

Vervolgens heb ik een systematisch review uitgevoerd om alle risicofactoren die in de huidige literatuur zijn gerapporteerd voor patiënten met SCLC samen te vatten en heb ik indien van toepassing meta-analyse uitgevoerd (**Hoofdstuk 3**). Het liet zien dat de belangrijkste risicofactoren jongere leeftijd, hoger T-stadium en extensive disease (ED) waren. Zes onderzoeken hebben de associatie van fractionaring van thoracale radiotherapie (ODRT/TDRT) met de ontwikkeling van BM onderzocht en toonden tegenstrijdige conclusies. Er waren geen gekwalificeerde data beschikbaar om meta-analyse voor deze factor uit te voeren. Toekomstige studies zijn nodig om deze vraag te beantwoorden.

Daarna ben ik een stap verder gegaan naar NSCLC en onderzocht ik risicofactoren voor BM bij patiënten met radicaal behandeld stadium III NSCLC, inclusief radiomic kenmerken van het bruto tumorvolume (gross tumor volume, GTV's) op de plannings CT-scan voor de thoracale radiotherapie (**Hoofdstuk 4**). Ik ontwikkelde een klinisch model, drie radiomics-modellen (GTV, GTV van de betrokken lymfeklieren [GTVn], GTV van de primaire tumor [GTVp]) en een gecombineerd model. Ik vergeleek hun prestaties en klinische bruikbaarheid en ontdekte dat het radiomics-model van GTVn het beste was. Jongere leeftijd, niet-plaveiselcelsubtype NSCLC en groter GTVn waren risicofactoren voor BM. Het GTVn-volume en de GTVn-radiomics-kenmerken waren het meest prognostisch voor de ontwikkeling van BM bij patiënten met stadium III NSCLC. De GTVp en GTVn moeten in de klinische praktijk afzonderlijk worden ingetekend.

Het volgende deel behandelt neurocognitieve stoornissen en QOL bij patiënten met SCLC en bij patiënten met NSCLC. In **Hoofdstuk 5** heb ik systematisch de risicofactoren voor neurocognitieve achteruitgang bij patiënten met longkanker die met PCI werden behandeld samengevat. Om ervoor te zorgen dat de conclusies betrouwbaar zijn, concentreerde ik me op prospectieve klinische onderzoeken met voldoende steekproef grootte. De belangrijkste boodschap is dat data van hoge kwaliteit ontbreekt. Leeftijd, PCI-dosis, regime en timing kunnen in verband worden gebracht met cognitieve stoornissen na PCI, maar verder onderzoek is nodig.

Met een overzicht van de status en de beperkingen van huidige neurocognitieve functie gerelateerde onderzoeken, onderzocht ik het zelfgerapporteerde cognitieve functioneren (self-reported cognitive functioning, SRCF) en de QOL bij SCLC-patiënten die werden behandeld met PCI of HA-PCI in de fase III Nederlands-Vlaamse gerandomiseerde klinische studie

(randomized controlled trial, RCT), NCT01780675 (**Hoofdstuk 6**). De conclusie is: HA-PCI of PCI leiden niet tot een verschil in SRCF en QOL.

Vervolgens heb ik de twee vergelijkbare fase III RCT's, de Nederlands-Vlaamse NCT01780675 trial en de Spaanse PREMER/NCT02397733 trial, samengevoegd om de impact van HA-PCI op SRCF en BM te onderzoeken, inclusief BM incidentie en locatie (**Hoofdstuk 7**). Het toonde aan dat HA-PCI geen invloed heeft op SRCF, het sparen van de hippocampus leidde niet tot een hogere incidentie van geïsoleerd ontwikkelen van BM binnen of buiten de vermijdingszone van de hippocampus.

Ondertussen heb ik ook de risicofactoren voor cognitieve stoornissen onderzocht bij patiënten met radicaal behandeld stadium III NSCLC op basis van de longitudinale data van de fase III NVALT-11 studie (**Hoofdstuk 8**). Ik ontdekte dat cognitieve stoornissen dynamisch zijn bij individuen en kunnen worden ingedeeld in vier typen op basis van veranderingen in de tijd: aanhoudend, reversibel, terugkerend, en alternerend, wat ook werd bevestigd bij patiënten met SCLC (**Hoofdstuk 7**). Een cognitieve stoornis op baseline is de belangrijkste risicofactor voor later cognitief functioneren.

Het laatste deel van het proefschrift (**Hoofdstuk 9**) bevat de belangrijkste bevindingen van elk project en een algemene discussie over de bevindingen, inclusief de waarde van de bevindingen, samen met sterke punten en bijdragen van onze studies, uitdagingen die we zijn tegengekomen bij het uitvoeren van de studies, beperkingen die in elk onderzoek aandacht behoeven, wat we hebben gedaan om de overeenkomstige vertekening te verminderen, hoe we dit in toekomstig werk kunnen verbeteren, en toekomstperspectieven.

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第十章

论文小结

曾海燕

肺癌是癌症相关死亡的主要原因。 脑转移 (brain metastases, BM) 在肺癌患者中非常常见，并且明显降低生存质量 (quality of life, QOL) 和总生存期 (overall survival， OS)。明确脑转移的风险因素有助于临床医师识别出病程中容易出现脑转移的高危患者，并提出相应策略降低脑转移的风险， 例如进行预防性颅脑照射 (prophylactic cranial irradiation, PCI)。预防性脑照射能有效降低肺癌患者的脑转移发生率。然而，这也与神经认知功能下降相关。因此，理想情况下，预防性脑照射应选择性地仅应用于更容易出现脑转移的患者。不过，预防性脑照射并不是可能导致神经认知功能障碍的唯一原因。因此，明确神经认知功能障碍的危险因素也非常重要，因为这有助于通过改进治疗方案来减少神经认知功能的损害，从而改善生活质量，例如进行海马保护预防性脑照射(hippocampal avoidance - prophylactic cranial irradiation, HA-PCI)。基于上述原因，本人为这篇博士论文开展了一系列研究以优化肺癌患者的预防性脑照射治疗。

第一章作为论文的第一部分，详细介绍了本论文的背景，包括肺癌及其两种主要的病理类型小细胞肺癌 (small cell lung cancer, SCLC) 和非小细胞肺癌(non-small cell lung cancer, NSCLC)，以及这两种疾病之间的主要区别。 描述了肺癌脑转移及其预后，以及目前已知的危险因素及进一步研究的必要性。总结了如何通过预防性脑照射降低脑转移的发生率，预防性脑照射的优缺点以及如何通过海马保护预防性脑照射降低神经系统毒性。详细阐述了神经认知功能障碍的定义以及如何对神经认知功能和生存质量进行评估。后续章节将围绕本章所述问题展开课题研究。

第二部分探索了小细胞肺癌患者和非小细胞肺癌患者的脑转移危险因素：

第二章是一项国内开展的多中心回顾性研究，以明确胸部常规分割放疗 (once-daily radiotherapy, ODRT) 和加速超分割放疗 (twice-daily radiotherapy TDRT) 对小细胞肺癌预防性脑照射后脑转移发生率的影响。采用了倾向性评分匹配法控制两组之间的混杂因素。本研究表明：胸部加速超分割放疗会增加脑转移的风险，但不影响总生存期。

第三章系统地回顾了当前文献中报道过的所有关于小细胞肺癌脑转移的危险因素，并在数据满足质量控制条件时进行了荟萃分析。本研究发现较小的年龄、较高的 T 分期和广泛期 (Extensive disease, ED) 是最重要的风险因素。共有六项研究探讨过胸部放疗分割方案 (ODRT/TDRT) 与发生脑转移的相关性，但结论相互矛盾。可惜该因素缺乏合格的数据进行荟萃分析。因此，胸部加速超分割放疗是否增加脑转移风险尚有待进一步研究加以明确。

第四章探索了根治性治疗后的 III 期非小细胞肺癌患者脑转移的危险因素，包括胸部放疗定位 CT 扫描中的大体肿瘤体积 (Gross tumor volume, GTV)及其影像组学特征。本研究开发了一个临床模型、三个影像组学模型（GTV、受累淋巴结 GTV [GTV of lymph nodes, GTVn]、原发肿瘤 GTV [GTV of primary tumor, GTVp]）及一个综合模型，并对各个模型的性能和临床实用性进行了比较。结果表明 GTVn 的影像组学模型是最好的预测模型。年龄较小、非鳞状细胞癌和较大的 GTVn 是脑转移的危险因素。 GTVn 体积和 GTVn 影像组学特征最具预测价值。因此，在临床工作中，GTVp 和 GTVn 应分别勾画，以便更好地判断预后。

第三部分探讨了小细胞肺癌患者和非小细胞肺癌患者的神经认知功能障碍及生存质量：

第五章系统地回顾了接受过预防性脑照射治疗的肺癌患者神经认知能力下降的危险因素。 为确保结论可靠，该系统综述仅纳入样本量充足的前瞻性临床试验。研究的主要结论是：当前文献中尚缺乏高质量的研究数据。年龄、预防性脑照射的剂量、方案和时间可能与预防性脑照射后的认知障碍有关，但有待进一步明确。

通过系统评价掌握了对当前神经认知功能相关研究的现状和缺陷后，论文第六章采用荷兰-佛兰芒 III 期随机对照临床试验 (NCT01780675) 的数据研究分析了预防性脑照射组及海马保护预防性脑照射组的小细胞肺癌患者的主观报告神经认知功能 (self-reported cognitive functioning, SRCF) 和生存质量(quality of life, QoL)。研究显示：预防性脑照射伴或不伴海马保护不会导致主观报告神经认知功能及生存质量的显著差异。

接下来，第七章汇集了最近发表的全球仅有的两项大型 III 期随机对照临床试验，即荷兰-佛兰 NCT01780675 试验和西班牙 PREMER/NCT02397733 试验，以明确海马保护预防性脑照射对主观报告神经认知功能和脑转移发生率及脑转移部位的影响。研究表明 ： 相较于常规的预防性脑照射， 海马保护预防性脑照射对主观报告神经认知功能没有显著的保护作用，海马保护预防性脑照射不增加海马保护区内外的脑转移发生率。

同时，第八章采用 III 期随机对照临床试验 NVALT-11 试验的长期随访数据探索了接受根治性治疗后的 III 期非小细胞肺癌患者主观报告神经认知障碍的危险因素。研究发现：神经认知功能障碍在个体中是动态变化的，根据其变化特点可分为四种类型：持续型、可逆型、复发型和交替型。这在小细胞肺癌患者中也得到了证实(第 七章)。基线时就出现神经认知障碍是后续神经认知功能最重要的影响因素。

最后一部分(第九章)展示了每项课题的主要发现及讨论，包括发现的价值，本研究的优势、亮点和研究结论的贡献，课题开展过程中遇到的难题及挑战，每项研究中需要注意的局限性及我们为减少相应误差所做的努力，以及如何在以后的研究中加以改善，还有未来的研究方向和前景。

Addendum I

Impact

Haiyan Zeng

Scientific contribution

In **Chapter 2**, I revealed that TDRT is a risk factor for developing BM after PCI in patients with SCLC in China. This is an inspiring finding that might motivate more in vitro and in vivo studies to further investigate the underlying mechanisms, as well as more prospective studies in China or Asia to further confirm it and in the end, probably change the clinical practice.

In **Chapter 3**, I systematically reviewed all the risk factors that have been reported in the literature and made a comprehensive summary, which can support the design of future studies evaluating BM prevention strategies for patients with SCLC. I raised to the community that it is of foremost importance to assess the quality of data before pooling everything together to perform a meta-analysis. I proposed a simple and effective method to evaluate the quality of data: only studies of the same type using the same method with proper statistical analysis should be pooled together under the premise that the patients belonged to the same category. This will avoid misleading conclusions from heterogeneous data.

In **Chapter 4**, I used the planning CT of thoracic radiotherapy, which is a part of clinical care and no additional contouring is necessary, and therefore extracting radiomics features from GTVs is feasible in clinical application for all patients with a radiotherapy treatment plan. I was the first one to separate GTVp and GTVn to analyze their associations with BM development. I found that GTVn radiomics features provided higher predictive value for BM development than GTVp and GTV. Therefore, I proposed to separate GTVp and GTVn in clinical and research practice and to further validate these findings in the ongoing NVALT28 trial.

The association of GTVs with BM should also be investigated in patients with SCLC, for which I have set up an international collaboration platform with multiple centers and collected 400 patients (South Korea, China, Barcelona, Zuyderland, Viecuri, Laurentius, MUMC, Rotterdam, Eindhoven, Utrecht, Amsterdam). In addition, I have obtained a research grant from BeiGene. Furthermore, we have designed a prospective clinical trial on this project to participate in the Eighth Multidisciplinary Collaborative Clinical Trial Workshop in Shenzhen, China (Joined online because of the COVID-19 pandemic), with such a relevant reach out to win the Outstanding Clinical Trial Concept Award.

In **Chapter 5**, I found that until now not enough validated data has been published to evaluated risk factors associated with neurocognitive decline after PCI in patients with lung cancer. None of the included clinical trials were judged to be at low risk of bias. This systematic review has relevance for the clinical community, since neurocognitive decline is common after PCI, both in SCLC and NSCLC. I also provided an overview on areas where future PCI-neurocognition research should focus on, which would be very helpful to improve future clinical trials and studies.

In **Chapter 6**, I found that there was no significant difference in cognitive decline and QOL between PCI and HA-PCI arms in patients with SCLC. As a result, the benefit of sparing the hippocampus in the context of PCI is still subject of debate.

𝒜 𝕀

In **Chapter 7**, I pooled the two most recent comparable clinical trials and provided the most robust evidence thus far that HA-PCI is safe in terms of reducing BM incidence and that HA-PCI has no impact on SRCF. Additional neuroprotective agents such as memantine should be investigated to further preserve the neurocognitive function.

In **Chapter 8**, I quantitatively showed that cognitive impairment at baseline is the most important risk factor for subsequent cognitive impairment, irrespective of having received PCI or not. These findings could identify patients who may benefit from interventions that are increasingly investigated. I also found that cognitive impairment is dynamic in individuals. I was the first one to propose that the cognitive impairment can be classified into four types based on changes over time: sustained, reversible, recurring, and alternating. The classification in the four types of impairment is very innovative and prompt for further clinical trials which may in the future lead to the early recognition, selection of patients for neuroprotective strategies and therefore mitigation of problems.

Patient care impact

1. If validated in the NVALT28 trial, patients with NSCLC, especially those at higher risk for developing BM (adenocarcinoma, larger GTVn), shall periodically undergo brain MRI to detect BM earlier, with hopefully better survival and quality of life. Furthermore, if also validated in

SCLC, my data could also select patients that do not have to undergo potentially neurotoxic PCI.

2. Patients with lung cancer, even in the absence of PCI, can have neurocognitive impairment. Therefore, patients shall periodically perform neurocognitive assessments, including neuropsychological tests and self-reported questionnaires, to better evaluate their cognitive function and to make individualized treatment strategies accordingly to reduce the risk of neurocognitive impairment.

3. Clinicians shall avoid prescribing twice-daily PCI or concurrent PCI with chemoradiotherapy to reduce the neurotoxicity.

𝔄 I

4. Radiation oncologists shall delineate GTVn and GTVp separately in radiotherapy practice for better prognostic value.

Societal impact

1. If confirmed in a future trial, thoracic TDRT can be replaced by ODRT for patients with SCLC in China or Asia, especially where too many patients are waiting for radiotherapy within limited radiotherapy accelerators.

2. More financial and logistic investments are needed to conduct high quality clinical trials, such as encouraging participants to come back for brain MRI scanning and neurocognitive functioning assessments by offering reimbursements.

3. Suggestions on how to improve BM and cognitive function related trials will help the society conduct better studies with more reliable conclusions, therefore improve the daily care for patients with cancer.

4. Highly selective PCI can avoid unnecessary irradiation and subsequent neurotoxicities for patients who are not likely to develop BM, and consequently reduce the economy and health care burden for society and the family.

5. Optimizing PCI will reduce the risk of neurotoxicity and improve the QOL for patients with lung cancer.

Industrial impact

1. The findings of this thesis could result in several subsequent studies, both in the laboratory for mechanism research and in the clinical setting for clinical trials, which might further improve healthcare. For example, if HA-PCI plus memantine will be found to preserve neurocognitive function significantly, memantine will result a higher need in the market. And facilities and technicians that enables the application of HA-PCI techniques will also have a higher market share.

2. The series of projects in this thesis show that we are a very professional and productive team capable of conducting multiple studies and clinical trials. Based in Maastro, a nationally and internationally renowned radiotherapy center that explicitly wants to make the connection between patient care, education and effective scientific research, and Maastricht University Medical Centre+ (MUMC), distinguished nationally and internationally top clinical patient care, research, and education, our team has made great contributions in patients care and academy.

3.The radiomics findings will stimulate more related studies, not only in patients with NSCLC, but also in SCLC, esophageal cancer, breast cancer, and for any solid tumors at any sites of the body that need radiotherapy during the whole disease course; not only in radiomics field, but also can be extended to other fields of computer science and data science that dealing with big data, such as deep learning, machine learning, and artificial intelligence.

4. The neurocognitive findings will inspire more cognition related trials in clinical settings, encourage neuropsychologists to develop and improve neuropsychology tests, promote the

using of patient-reported EORTC questionnaires, and stimulate the medicine industry to develop related agents.

5. The findings on the pitfalls of risk of bias assessment tool will help the Cochrane improve the assessment tools for systematic review and meta-analysis.

Cultural impact

1. The series of projects in this thesis involves patients and international collaborators from multiple centers worldwide. I developed a broad network worldwide with different culture backgrounds, such as Chinese, Belgium, Dutch, Italian, American, Spanish, and Iranian. By working closely together, I learned about each other's' culture and I connected multiple centers. This is very helpful for global networks and collaborations in the future.

2. The projects in this thesis involve experts from multiple disciplines, such as radiation oncologists, oncologists, radiologists, computer scientists, data scientists, neuropsychologists, statisticians, and epidemiologists. A diverse interdisciplinary collaboration enables us to broaden our knowledge and bridge professional gaps between disciplines.

3. In addition, I also have learnt a third language, Dutch, and have improved my English level. This benefits me a lot to improve my 4-years life abroad.

Dissemination

Three oral presentation at ESTRO annual conferences (2021, 2023).

One poster at WCLC 2021.

One ePoster at WCLC 2022.

One poster at ESMO 2022.

Multiple presentations within MAASTRO.

Multiple peer-reviewed publications, including some high-impact journals.

Addendum II

Acknowledgements

Haiyan Zeng

A II

Time is flying. It is surprising to realize that I almost came to the end of the 4-years PhD journey now. At this moment, all sorts of feelings well up in my heart, both exciting and sentimental. It is exciting that after 4-years working and living abroad alone, I finally will achieve my goal soon. It is sentimental to realize that I will leave here soon after enjoying the PhD and Dutch life for four years. I want to thank so many people and institutions for accompanying me and helping me along the way. Dear all, I am always grateful to have you in my life. You lighten my world and warm my heart. I feel so lucky and so blessed. Dear all, thank you so much! I hope I will be able to help others like you in the near future.

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楚晴师妹、王南南师妹、安宁师弟的牵挂和惦念。感谢郑雅文师姐、孙枫淏师弟的支持和帮助。

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最后，衷心感谢祖国的培养和厚爱，使我有这么宝贵的机会出国留学，安心科研，顺利完成学业。希望能早日回国，安居乐业，报效祖国。

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Addendum III

Curriculum Vitae

Haiyan Zeng

$\mathcal{A}$ III

Haiyan Zeng was born in Ganzhou, Jiangxi, China on Sep 21st, 1988. In September 2007, she started studying at Nanchang University, majoring in Clinical Medicine. She obtained her Bachelor's Degree of Medicine in July 2012 as an "Outstanding graduate of Nanchang University". Afterwards she worked for two years as a doctor in Fujian (The First Affiliated Hospital of Fuzhou General Hospital, Fujian Medical University Union Hospital). She obtained her Identification of Physician's Qualification in 2013. From September 2014, she studied in the University of Jinan, majoring in Oncology. In June 2017, she obtained her Master's Degree of Clinical Medicine with her thesis "High Risks for Brain Metastases after Prophylactic Cranial Irradiation in Small Cell Lung Cancer". For her thesis she was awarded the "Outstanding Master's Thesis of University of Jinan" and "Outstanding Master's Thesis of Shandong Province". Then she worked at Shandong Cancer Hospital Affiliated to Shandong University for two years as a radiation oncologist in the department of thoracic cancer and continued doing research on lung cancer. For her research she was awarded the "Scientific innovative awards of Jinming Yu (2017)".

In 2019 she came to Maastricht University for PhD training under the supervision of Prof. Dirk De Ruysscher, Dr. Lizza Hendriks, and Dr. Alberto Traverso with the financial support of the China Scholarship Council (Grant No. : CSC 201909370087). Her research focused on brain metastases and neurocognitive impairment in patients with lung cancer. She completed the basic course for Regulatory Organization for Clinical researchers in December, 2020. During her stay in Maastricht, she established a global multicenter network with international colleagues, and she collaborated with hospitals such as the Seoul National University Hospital, Zhejiang Cancer Hospital, Maastricht University Medical Centre+, Zuyderland Medical Centre Heerlen, VieCuri Medical Centre, Laurentius Hospital, Catharina Hospital, National Cancer Institute, Erasmus University Medical Center Rotterdam, Hospital Clínic de Barcelona, University Medical Center Groningen, the Christie Hospital NHS Foundation Trust, Fondazione Policlinico Universitario Campus Bio-Medico, and Hospital del Mar. During her stay, she obtained several grants and awards, such as a BeiGene Charitable Donation Grant, a

René Vogels Stichting Travel Grant, and the Outstanding Clinical Trial Concept Award for her trial proposal at the Shenzhen Eighth Multidisciplinary Collaborative Clinical Trial Workshop. Furthermore, her research resulted in several abstract presentations at international conferences, such as three oral presentations at ESTRO (2021, 2023), a poster presentation at ESMO 2022, one ePoster at WCLC 2022 and one poster at WCLC 2021. She has also given multiple presentations within MAASTRO. She has published articles and correspondences in peer-reviewed journals, including some high-impact journals (such as *Journal of Clinical Oncology*, *Lancet Oncology*) and open access journals (Such as *JAMA Network Open*). In addition, she was an active PhD-representative of the GROW School PhD students from 2020-2022 to help PhD students adapt better to the PhD.

Addendum IV

Publication list

Haiyan Zeng

𝒜 IV

Part I. Peer-reviewed publications

1. First author

1. **Zeng H**, Li R, Hu C, Qiu G, Ge H, Yu H, Zhang K, Hu M, Zeng P, Xiao D, Miao C, Wei C, Ni M, Shen J, Li H, Yue J, Lu H, Fan B, Zhu H, Hu X, Kong FM, Yu J, Yuan S: Association of Twice-Daily Radiotherapy With Subsequent Brain Metastases in Adults With Small Cell Lung Cancer. JAMA Network Open 2:e190103, 2019. doi:10.1001/jamanetworkopen.2019.0103 (**IF 13.353**).

2. **Zeng H**, Hendriks LEL, van Geffen WH, Witlox WJA, Eekers DBP, De Ruysscher DKM: Risk factors for neurocognitive decline in lung cancer patients treated with prophylactic cranial irradiation: A systematic review. Cancer Treatment Review 88:102025, 2020. doi:10.1016/j.ctrv.2020.102025 (**IF 13.608**).

3. **Zeng H**, Hendriks LEL, Witlox WJA, Groen HJM, Dingemans AC, Praag J, et al Belderbos J, Houben R, van der Noort V, De Ruysscher DKM: Risk factors for cognitive functioning in radically treated stage III NSCLC: Secondary findings of the NVALT-11 study. Radiotherapy and Oncology:109627, 2023. doi:10.1016/j.radonc.2023.109627 (**IF 6.901**).

4. **Zeng H**, Tohidinezhad F, De Ruysscher DKM, Willems Y, Degens JHRJ, van Kampen-van den Boogaart VEM, Pitz C, Cortiula F, Brandts L, Hendriks LEL, Traverso A: The association of gross tumor volume and its radiomics features with brain metastases development in patients with radically treated stage III non-small cell lung cancer. Cancers. 15:3010, 2023. https://doi.org/10.3390/cancers15113010 (**IF 6.575**).

5. **Zeng H,** Yuan S, Yu J: Prophylactic Cranial Irradiation in Non-Small-Cell Lung Cancer: Hope or Hype? J Clin Oncol, 2018:Jco1800617. doi:10.1200/jco.18.00617 (**IF 50.717**).

6. **Zeng H**, Yu J, Yuan S: Is it time to convert the frequency of radiotherapy in small-cell lung cancer? Lancet Oncol 2017; 18(10): e553. doi:10.1016/s1470-2045(17)30580-6 (**IF 54.433**).

7. **Zeng H,** Zheng D, Witlox W, Levy A, Traverso A, Kong FM, Houben R, De Ruysscher DKM, Hendriks LEL: risk factors for brain metastases in patients with small cell lung

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cancer: a systematic review and meta-analysis. Frontiers in Oncology, 2022; **12**: 889161. doi:10.3389/fonc.2022.889161 (**IF 5.738**).

8. **Zeng H,** De Ruysscher DKM, Hu X, Zheng D, Yang L, Kong FM, Hendriks LEL: Radiotherapy for small cell lung cancer in current clinical practice guidelines. Journal of the National Cancer Center, 2022; **2**(2): 113-25. https://doi.org/10.1016/j.jncc.2022.02.003 (New journal)

9. **Zeng H**, Xie P, Meng X, Yuan S, Sun X, Li W, Fan B, Li X, Yu J : Risk factors for brain metastases after prophylactic cranial irradiation in small cell lung cancer. Sci Rep 7:42743, 2017. doi: 10.1038/srep42743.doi:10.1038/srep42743 (IF **4.996**).

10. **Zeng H**, Li R, Sun X, Xie P, Meng X, Fan B, Li W, Yuan S: Hazard model for brain metastases after prophylactic cranial irradiation in local disease small cell lung cancer. Journal of Shandong University (Health science) 2017; 55(7): 61-6 (Chinese journal).

11. **Zeng H**, Yuan S, Meng X, Yu J: Prevention and treatments of esophageal perforation during or after radiotherapy in esophageal carcinoma: a review of literature. Chinese Journal of Cancer Prevention and Treatment 2017; 24(7): 501-6 (Chinese journal).

12. **Zeng H**, Schagen SB, Hendriks LEL, Sánchez-Benavides G, Jaspers JPM, Manero RM, Lievens Y, Mejía MM, Kuenen M, Rico-Oses M, Albers EAC, Samper P, Houben R, de Ruiter MB, Dieleman EMT, López-Guerra JL, de Jaeger K, Couñago F, Lambrecht M, Calvo-Crespo P, Belderbos JSA, De Ruysscher DKM, Rodríguez de Dios N: Impact of hippocampal avoidance-prophylactic cranial irradiation on brain metastases and self-reported cognitive functioning: pooled findings of NCT01780675 and PREMER. Submitted. 2023.

13. **Zeng H,** Hendriks LEL, Schagen SB, Belderbos JSA, Dubois L, Zhang X, Houben R, Brandts L, Compter I, Holt M, Liston A, Prezzemolo T. De Ruysscher DKM: Association of serum biomarkers with neurocognitive decline after PCI in small cell lung cancer: exploratory study of the phase III NCT01780675 trial. In preparation. 2023.

2. Co-author

14. Albers EAC**, Zeng H,** De Ruysscher DKM, Kuenen MA, Kessels R, Hendriks LEL,Belderbos JSA, Schagen SB: Self-reported cognitive function and quality of life in small cell lung cancer patients in the hippocampal avoidance prophylactic cranial irradiation (HA-PCI) vs. PCI in randomized phase III trial (NCT01780675). JTO Clinical and Research Reports, 2023. doi:https://doi.org/10.1016/j.jtocrr.2023.100506

15. Keek SA, Kayan E, Chatterjee A, Belderbos JSA, Bootsma G, van den Borne B, Dingemans AC, Gietema HA, Groen HJM, Herder J, Pitz C, Praag J, De Ruysscher D, Schoenmaekers J, Smit HJM, Stigt J, Westenend M, **Zeng H,** Woodruff HC, Lambin P, Hendriks L. Investigation of the added value of CT-based radiomics in predicting the development of brain metastases in patients with radically treated stage III NSCLC. Ther Adv Med Oncol. 2022 Aug 22;14:17588359221116605. doi: 10.1177/17588359221116605 (**IF 5.485**).

16. Chen J, **Zeng H,** Zhang C, Shi Z, Dekker A, Wee L, Bermejo I: Lung Cancer Diagnosis Using Deep Attention Based Multiple Instance Learning and Radiomics. Med Phys. 2022; **49**(5): 3134-43.doi: 10.1002/mp.15539 (IF **4.506**).

17. Wang Y, Song J, Li W, **Zeng H,** Liu N, Zhu S, Yuan S, Hu X. Effectivity of involved-field radiotherapy for recurrent brain metastasis in patients with small-cell lung cancer. J Cancer Res Ther. 2022 Sep;18(5):1276-1285. doi: 10.4103/jcrt.jcrt_185_22. PMID: 36204873 (IF **1.331**).

18. Ni M, Liu W, Jiang A, Wang Y, Sheng Y, **Zeng H,** Liu N, Li L, Qi Y, Wang Y, Yu J, Yuan S: Whole Brain Radiation Therapy Plus Focal Radiation Boost May Generate Better Survival Benefit for Brain Metastases From Non-small Cell Lung Cancer. Front Oncol 10:576700, 2020. doi:10.3389/fonc.2020.576700 (IF **5.738**).

19. Ni M, Jiang A, Liu W, Sheng Y, **Zeng H,** Liu N, Gao Q, Wang Y, Yu J, Yuan S: Whole brain radiation therapy plus focal boost may be a suitable strategy for brain metastases in SCLC patients: a multi-center study. Radiat Oncol 15:70, 2020. doi:10.1186/s13014-020-01509-3 (IF **4.309**).

20. Li X, Li B, **Zeng H**, Wang S, Sun X, Yu Y, Wang L, Yu J: Prognostic value of dynamic albumin-to-alkaline phosphatase ratio in limited stage small-cell lung cancer. Future Oncol. 2019. doi:10.2217/fon-2018-0818 (IF **3.674**).

21. Cao X, Li X, Wang X, Duan J, Zhu S, **Zeng H,** Yin Y, Yuan S, Hu X: Use CT Imaging to Predict the Short-Term Outcome of Concurrent Chemoradiotherapy in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma. Dose Response 17:1559325819897175, 2019. doi:10.1177/1559325819897175 (IF **2.603**).

22. Liu Y, Liu X, Xu L, Liu L, Sun Y, Li M, **Zeng H**, Yuan S, Yu J: Magnetic resonance imaging evaluation of treatment efficacy and prognosis for brain metastases in lung cancer patients after radiotherapy: A preliminary study. Thorac Cancer 2018;9: 865-873. doi:10.1111/1759-7714.12763 (IF **3.223**).

23. Su L, Hou W, **Zeng H,** Zhao W, Ni M, Yu S: Comparison of the efficacy and safety of recombinant human endostatin combined with chemotherapy in the treatment of lung squamous cell carcinoma and non-squamous cell carcinoma. Chinese Journal of Cancer Prevention and Treatment 2019; 26(07): 489-493 (Chinese journal).

24. Chen Z, Li X, Sheng X, **Zeng H**, Ding F, Li X, Xu P: Clinical comparison of IMRT versus 3D-CRT for patients with cervical cancer after radical hysterectomy. Chinese Journal of Cancer Prevention and Treatment 2017; 24(11): 759-65 (Chinese journal).

Part II. Abstract publications at international conferences

1. Oral presentation
1.1.ESTRO 2023 (Vienna, Austria; May 12 - 16, 2023)
1. Zeng H, Schagen SB, Hendriks LEL, Sánchez-Benavides G, Jaspers JPM, Manero RM, Lievens Y, Murcia-Mejía M, Kuenen M, Rico-Oses M, de Ruiter M, Couñago F, Dieleman EMT, de Jaeger K, Calvo-Crespo P, Lambrecht M, Samper P, Belderbos JSA, De Ruysscher DKM, Rodríguez de Dios N: Pattern of brain metastases after HA-PCI and SRCF in SCLC: pooled findings of NCT01780675 and PREMER (OC-0607).

2. Zeng H, Tohidinezhad F, De Ruysscher DKM, Degens JHRJ, van Kampen-van den Boogaart VEM, Pitz C, Hendriks LEL, Traverso A. Radiomics models from chest CT scan to predict brain metastases in radically treated stage III NSCLC (OC-0089).

3. Nürnberg L, Bontempi D, Verhoeven K, **Zeng H,** Canters R, Quesada E, Giglioli F, Ricardi U, Levis M, De Ruysscher D, Traverso A. Deep Learning Segmentation of Cardiac Substructures in Radiotherapy Planning (OC-0122).

<div style="text-align: right">𝒜 IV</div>

1.2. ESTRO 2021 (Madrid, Spain; Aug 27-31, 2021: OC-0176)
4. Zeng H, Hendriks L, Witlox W, Groen H, Dingemans A, Praag J, Belderbos J, Houben R, van der Noort V, De Ruysscher D: OC-0176 Risk factors for cognitive impairment in NSCLC: Secondary findings of the NVALT-11 study. Radiotherapy and Oncology 161:S107-S108, 2021. doi:https://doi.org/10.1016/S0167-8140(21)06791-8

2. Poster presentation
2.1. ESMO 2022 (Paris, France; Sept 9 - 13, 2022: 959P)
Zeng H, Willems Y, Cortiula F, Bootsma G, Traverso A, De Ruysscher DKM, Hendriks LEL: 959P The association of GTV and brain metastasis development in patients with stage III NSCLC.   Annals   of   Oncology   33:S985-S986,   2022. doi:https://doi.org/10.1016/j.annonc.2022.07.1085

2.2. WCLC 2021 (Virtual online; Sept 8 - 14, 2021: P63.12)
Zeng H, De Ruysscher DKM, Hu X, Zheng D, Yang L, Kong FM, Hendriks LEL: P63.12 Radiotherapy for Small Cell Lung Cancer in Current Clinical Practice Guidelines. Journal of Thoracic Oncology 16:S1187, 2021. doi:https://doi.org/10.1016/j.jtho.2021.08.668

2.3. ASCO 2019 (Chicago, USA; May 31 - June 4, 2019: 8560)
Zeng H, Li R, Hu C, Qiu G, Ge H, Yu H, Zhang K, Hu M, Zeng P, Xiao D, Miao C, Wei C, Ni M, Shen J, Li H, Hu X, Kong FM, Yuan S, Yu J: Thoracic twice-daily radiotherapy and brain metastasis in patients with small cell lung cancer. Journal of Clinical Oncology 37:8560-8560, 2019. doi:10.1200/JCO.2019.37.15_suppl.8560

2.4. ASTRO 2017 (San Diego, USA; Sept 24–27, 2017: 3204).

Zeng H, Li R, Yuan S, Xie P, Sun X, Meng X, Fan B, Li W, Yu J: 3204: Hazard model for brain metastases after prophylactic cranial irradiation in local disease small cell lung cancer. E508, 2017. doi:10.1016/j.ijrobp.2017.06.1818

2.5. ASTRO Thoracic Symposium (Multidisciplinary thoracic cancers symposium) (San Francisco, USA; Mar 16 - 18, 2017: 148).

Zeng H, Li R, Hu C, Meng X, Xie P, Yuan S, Zhu H, Sun X, Li W, Fan B, Kong FM, Yu J: 148: Hyperfractionated Accelerated Radiotherapy May Increase Risk for Brain Metastases in Small Cell Lung Cancer, Int J Radiat Oncol Biol Phys, 2017, 98(1): 244.

2.6. ELCC 2022 (Virtual online; Mar 30 - Apr 2, 2022: 127P)

Hendriks L, Keek SA, Kayan E, Chatterjee A, Belderbos JSA, Bootsma G, van den Borne B, Dingemans AC, Gietema HA, Groen HJM, Herder J, Pitz C, Praag J, De Ruysscher D, Schoenmaekers J, Smit HJM, Stigt J, Westenend M, **Zeng H,** Woodruff HC, Lambin P: 127P Does radiomics have added value in predicting the development of brain metastases in patients with radically treated stage III non-small cell lung cancer (NSCLC)? Annals of Oncology 33:S91, 2022. doi:https://doi.org/10.1016/j.annonc.2022.02.156

2.7. ESTRO 2021 (Madrid, Spain; Aug 27-31, 2021: PO-1164)

Trimpl M, Charlton P, Teoh S, **Zeng H,** Vallis K, Stride E, Gooding M: PO-1164 Clinical evaluation of an interactive deep-learning assisted contouring method for target contouring. Radiotherapy and Oncology 161:S966-S967, 2021. doi:https://doi.org/10.1016/S0167-8140(21)07615-5

3. ePoster presentation
3.1. WCLC 2022 (Vienna, Austria; Aug 6 – 9, 2022: EP14.01-014)

Zeng H, Zheng D, Witlox W, Levy A, Traverso A, Kong F, Houben R, De Ruysscher D, Hendriks L: EP14.01-014 Risk Factors for Brain Metastasis in Patients with Small Cell Lung Cancer: A Systematic Review and Meta-analysis. Journal of Thoracic Oncology 17:S532, 2022. doi:https://doi.org/10.1016/j.jtho.2022.07.950

4. Publication only
4.1. ASCO 2016 (Chicago, USA; June 3 - 7, 2016)

1. Zeng H, Xie P, Meng X, Yuan S, Sun X, Li W, Yu J: Risk factors for brain metastases after prophylactic cranial irradiation in small cell lung cancer, J Clin Oncol 34, 2016 (suppl; abstr e20095).

2. Li X, Sun X, **Zeng H**, Li W, Xie P, Yu J: Sequential Serum Let-7 Is a Novel Biomarker to Predict Accelerated Reproliferation During Fractional Radiotherapy in Lung Cancer, J Clin Oncol 34, 2016 (suppl; abstr e23098)

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