

Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review

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Complications of Treatment

Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review



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ABSTRACT

Recently, non-small cell lung cancer (NSCLC) has been partly subclassified into molecularly-defined oncogene “addicted” tumors for which targeted agents are available. Tyrosine kinase inhibitors (TKI) are currently approved for patients with an activating epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) rearrangement. In these patients, brain metastases are often the first site of progression while on TKI treatment. The TKI may however still be active on extra-cranial sites and clinicians are thus faced with the question if the TKI may be continued during cranial radiotherapy. Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up. A disadvantage is the possibly increased risk of (neuro)toxicity. The present systematic review addresses the toxicity of combining TKI with cranial radiotherapy in NSCLC patients.

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Introduction

Increasingly, new molecular features of non-small cell lung cancer (NSCLC) are being discovered, leading to an unprecedented growth of targeted agents. These are often tyrosine kinase inhibitors (TKI) [1]. Currently, TKI are approved for metastasized NSCLC patients with an activating epidermal growth factor receptor (*EGFR*) mutation or an anaplastic lymphoma kinase (*ALK*) rearrangement, either as first line or beyond [2,3]. Examples are erlotinib, gefitinib, afatinib and icotinib (China only) for *EGFR*-mutations, and crizotinib and ceritinib (USA only) for *ALK*-rearrangements. Approximately 20–35% of these patients are diagnosed with brain metastasis at initial diagnosis and these patients are often amenable for initial treatment with TKI [4–8]. However, a substantial part will develop new brain metastasis or progression of brain metastasis during treatment. On erlotinib

and gefitinib treatment 14–33% of patients develop (progression of) brain metastasis [9–15]. In patients with a survival beyond five years, this percentage increases to 52.9% [6]. On crizotinib treatment 70% of patients experience progression of brain metastases after an initial cerebral disease control rate of 60% (median time to intracranial progression: 7 months). 20% of patients without brain metastasis at initial NSCLC diagnosis develop brain metastasis during crizotinib treatment and this increases to about 58% in patients with a survival beyond three years [6,8]. In these patients, the brain is often the first and/or only site of progression (oligo-progression) [8,12,14,16].

The TKI may however still be active on extra-cranial sites and clinicians are thus faced with the question if the TKI may be continued during cranial radiotherapy. Although there are pre-clinical studies suggesting that TKIs enhance radiation effects, the effects on normal tissues are unclear [17–20]. Data show that some molecular features of the tumor are not only related to response to TKI but also to radiation susceptibility of the tumor. As an example, tumors with activating *EGFR*-mutations not only show a high probability to respond to *EGFR*-TKI but also to radiation [21]. In current guidelines (ESMO 2014, NCCN 2014, ASTRO 2012) no recommendations are made regarding the concurrent use of TKI's and cranial radiotherapy in NSCLC patients with an activating

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mutation [2,3,22,23]. Frequently, TKI's are discontinued during cranial radiation because of (neuro)toxicity concerns. However, toxicity (e.g., radiation pneumonitis) does not seem to increase when EGFR-TKI are combined with thoracic radiotherapy in the majority of studies although some did report a higher incidence of grade 3–5 radiation pneumonitis [24–27]. Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up. The latter has been described in both EGFR-mutated patients (23% of patients, median time to disease flare-up 8 days, range 3–21 days) and in an ALK-translocated patient (time to disease flare-up 15 days) [28,29]. Among the factors associated with an increased risk for a disease flare-up was the presence of central nervous system (CNS) disease [28].

The aim of the present systematic review is to address the toxicity of combining TKI with cranial radiotherapy in NSCLC patients as, to the best of our knowledge, there is no systematic review on this topic. The focus will be on neurotoxicity. When possible, a daily practice advice will be formulated.

Methods

Search strategy and selection criteria

The literature search was performed following the PICO method [30] and is shown in Appendix 1. This search was used to identify studies in Pub Med, EMBASE, Web of Science and the Cochrane Library from 2001 until the search date in November 2014. Additionally, clinicaltrials.gov was searched to identify unpublished or ongoing clinical trials.

Selection criteria were established prior to the search and selection of articles. These included human only studies, including a minimum of 5 NSCLC patients treated with concurrent cranial radiotherapy and TKI's (EGFR: erlotinib, gefitinib, afatinib, icotinib, ALK: crizotinib, ceritinib and alectinib). As safety was the primary endpoint there was no restriction on the presence of a targetable mutation. Studies with whole brain radiotherapy (WBRT) as well as stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT) were included. Language was restricted to English, German and Dutch. Original articles and conference proceedings were included, reviews were excluded. Additionally, references of eligible articles were manually searched to find other relevant studies. All inclusion and exclusion criteria are summarized in Table 1.

Outcomes

One researcher (LH) conducted the search and selection of eligible studies. All articles were then evaluated by another independent reviewer (JS). When available, the following data were

Table 1
Inclusion criteria for this review.

Subjects included	Human only
Language	English, German, Dutch
Article type	Original article, conference proceeding
Number of patients	≥ 5
Site of primary tumor	NSCLC
Tumor stage	IV
Treatment	WBRT and/or SRS/SRT concurrent with TKI (EGFR- or ALK-TKI)
Follow up period	All
Outcome	Safety/adverse events one of the outcomes measured

Abbreviations: NSCLC: non-small cell lung cancer; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; TKI: tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

extracted from eligible studies by one researcher (LH) and independently by another researcher (JS): author, year of publication, original article or conference proceeding only, type of study, duration of study, number of included patients, EGFR mutation/ALK-translocation status available (yes/no) and results of mutation testing, dose cranial radiotherapy (WBRT and/or SRS/SRT), description of TKI used (including dosing and timing), safety and efficacy outcomes.

Data were extracted and tabulated independently (Appendix 2). Consensus was reached by discussion between reviewers when outcomes differed.

Results

Search results

The initial search in the four databases included 710 articles in total. Using Endnote and manual screening, 179 duplicate articles were excluded. Another 461 articles were excluded based on not relevant titles for this study, 70 articles were further screened. After reading of the abstracts, another 43 articles were excluded based on the exclusion criteria. Of the 27 remaining articles and conference proceedings, the whole article was read (not possible for conference proceeding). Based on the exclusion criteria, 11 articles and 3 conference proceedings were eligible to include in this review. With a manual search of the reference list of the included articles one other relevant article was found (flowchart in Fig. 1).

Description and quality of the studies

Of the 12 original articles and 3 conference proceedings that matched the selection criteria and were included in this review, 6 evaluated erlotinib concurrent with WBRT (one study combined WBRT with SRS) [31–36], 4 evaluated gefitinib concurrent with WBRT [37–40] and in 3 studies both drugs were studied [41–43]. In 2 studies icotinib concurrent with WBRT was studied [44,45]. For afatinib, crizotinib, ceritinib and alectinib no studies were found concurrent with cranial radiotherapy.

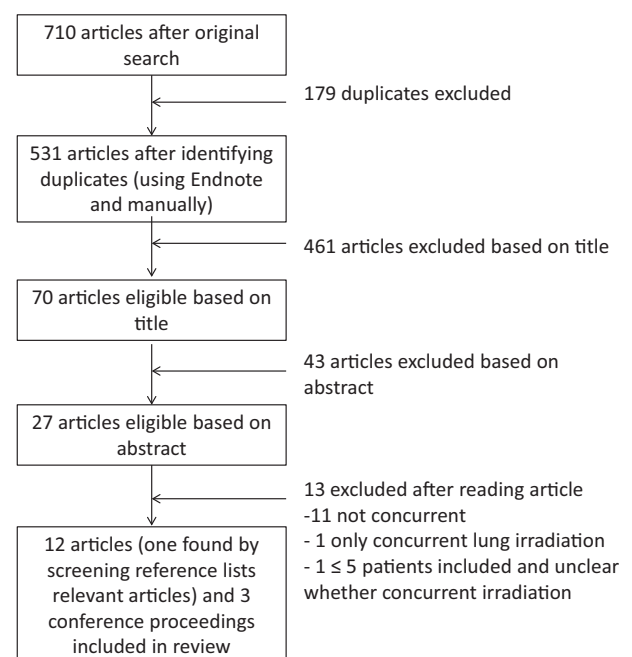


Fig. 1. Flowchart article selection.

Five studies were retrospective [33,40–43]. 2 studies were phase I [32,45], 7 were phase II [31,35–39,44], and there was only one phase III trial [34]. The phase III trial was a randomized, but not placebo controlled study [34]. 4 out of 7 phase II studies consisted of 2 arms [31,36,38,39]. In one of these studies patients were not randomized to one of the arms, but treatment allocation was based on whether *EGFR*-mutation status was determined. These patients (irrespective of *EGFR*-testing results) were allocated within the concurrent arm, the patients in which mutation analysis was not performed were allocated within the WBRT only arm [36]. Of the 4 phase II, 2 arm-studies only one study was a double blind, placebo controlled study [31].

There was one study in which only patients with an activating *EGFR* mutation were included [45] and there were 8 other studies in which at least part of the included patients were tested for activating *EGFR* mutations [31,35,36,39–41,43,44]. In these studies, percentage of *EGFR*-mutated patients (computed as number *EGFR*-mutated/total number of patients included) varied between 1.3% and 69.8%.

For WBRT, the total radiation dose varied between 20 and 50 Gy in 4 (20 Gy) to 25 (50 Gy) fractions. *EGFR*-TKI were initiated from one week before the onset of cranial radiation to the first day of radiotherapy. In most studies, after WBRT, investigators could continue the *EGFR*-TKI at their own discretion [31–35,37–45]. Only in one study the *EGFR*-TKI was discontinued one month after completion of WBRT [36]. In the two-arm studies, the treatments that were compared varied between WBRT only (or combined with temozolomide or chemotherapy) and WBRT concurrent with *EGFR*-TKI, and *EGFR*-TKI only compared to WBRT concurrent with *EGFR*-TKI [31,34,36,38–41]. Primary outcomes ranged between overall survival (OS), (neurological) progression free survival ((n)PFS), local PFS (LPFS), intracranial response rate, toxicity and quality of life (QoL). All studies are summarized in Table 2. For the retrospective studies, all outcomes are listed as primary.

Frequency and methods of toxicity evaluation

In 3 out of 10 (30%) prospective studies, toxicity was the primary objective [32,39,45]. In the study of Lind et al., neurotoxicity was not an end point of the trial; neurological examination was performed at baseline and was not specified during the follow-up although adverse events were recorded according to the Common Terminology Criteria of Adverse Events (CTCAE) criteria [32]. Wang et al. did not include specific neurocognitive functioning tests [39]. Zhou et al. (abstract only) only performed Mini Mental State Examinations (MMSE) up to 20 weeks after WBRT [45]. In the study of Lee et al., toxicity itself was not a primary objective, however nPFS was. This consisted of a clinical (MMSE, assessment of motor strength, visual acuity and gait) and radiological assessment. Adverse events according to the Common Terminology Criteria of Adverse Events (CTCAE) criteria were only recorded up to 28 days after finalizing the treatment [31].

From the other 6 prospective studies, Welsh et al. did the most extensive neurotoxicity evaluation. Neurological examination and MMSE were performed at baseline, at 6 months and at 12 months after treatment. Patients had also formal cognitive testing (neurological examination, Hopkins Verbal Learning Test-Revised, Trail Making Test Part A and B, Multilingual Aphasia Examination Controlled Oral Word Association) before enrollment, within 14 days of WBRT completion and at each follow-up visit (at 1 month and then every 3 months) [35]. In the study of Pesce et al., cognitive function (MMSE, Trail Making Test part B, EORTC QLQ-C30 cognitive function subscale) was assessed prior to start and on day one of cycles 2, 3 and 5 [38]. In the study of Ma et al., neurological examination was performed weekly during concurrent treatment [37]. In the other studies, neurotoxicity was not

a specific item and toxicity was scored according to the CTCAE criteria [34,36,37,44]. Methods and frequency of toxicity assessment are summarized in Table 3. Only prospective studies are summarized, as in the retrospective studies there was no specified protocol for follow-up.

Toxicity outcomes

All outcomes are summarized in Table 4. 9 trials (3 retrospective) specifically mentioned neurotoxicity [32–35,37,40,41,45] of which 5 reported that there was no increased neurotoxicity of the concurrent treatment [32,35,40,41,45]. However, in one of these studies 2 questionable late neurotoxicity events were reported: one 74-year old male developed dementia two years after study completion and one 56-year old female had 5 months after study completion intracranial progression for which she received SRS, she developed brain necrosis thereafter. Other contributing factors for these events were older age (possibly unrecognized cognitive impairment) in the first patient and the use of SRS in the second [35]. In one study 5% grade 3 dizziness for both the WBRT only and the WBRT + erlotinib group was reported but no late neurotoxicity. Duration of dizziness was not mentioned [36]. In one retrospective study ($N=8$) 3 patients had mental status change. Two of these patients also had grade 3 hyponatremia and an intercurrent infection as a possible contributing factor for the mental status change [33]. In a prospective randomized study of WBRT together with SRS and combined with erlotinib, temozolomide or no systemic treatment, grade 4 brain necrosis and grade 5 hemorrhagic stroke both occurred in 1/41 patients in the erlotinib arm. Grade 3 confusion and ataxia were also found, but number of patients was not specifically mentioned [34]. In a single arm prospective study ($N=21$) 14% grade 3 headache was reported, but grade 4–5 toxicities did not occur [37]. In the other 6 studies neurotoxicities were not specifically described. However, all grade/grade 3–5 toxicities were mentioned and these did not include grade 3–5 neurotoxicities. Time to resolution of toxicities was not mentioned [31,38,39,42–44].

Discussion

A relatively high percentage of *EGFR*-mutated and *ALK*-rearranged patients will develop brain metastases during the course of their disease, often while on TKI treatment [9–15,46]. A possible explanation for this high percentage is that the first generation TKI's do not achieve therapeutic concentrations in the brain due to (relative) inability to cross the blood–brain barrier [47–49]. In this situation, extra cranially located cancer cells are often still dependent on *EGFR*- or *ALK*-signaling and are responding to TKI's [12]. In patients with brain metastases both WBRT and SRS/SRT can be considered, mainly dependent on the number/volume of brain metastases and the performance status of the patient [3]. In current guidelines, no advice regarding TKI use during cranial radiotherapy is given [2,3,22,23]. To our knowledge, the present study was the first to systematically review the literature in order to evaluate the safety of concurrent cranial radiotherapy and TKI. For *ALK*-TKI, no studies were found. For *EGFR*-TKI, 15 studies were found of which 5 were retrospective [31–45]. In only 9 studies, presence of an activating *EGFR*-mutation was evaluated with varying percentages (1.3–100%) [31,35,36,39–41,43–45]. Only one study was a phase III study [34] and only 3 out of 7 phase II studies were randomized 2 arm studies [31,38,39]. In the identified papers, treatments studied varied between WBRT only, WBRT concurrent with *EGFR*-TKI (in one study also combined with SRS) and *EGFR*-TKI only. No studies were found for SRS without WBRT concurrently with TKI. No studies were identified in which patients with

Table 2
Trial characteristics of the included studies.

Trial, year	Trial type	N	EGFR mutation analysis	WBRT/SRS treatment	TKI treatment (± comparator)	Primary study objective	Secondary study objectives
<i>Erlotinib and WBRT + SRS</i>							
Sperduto et al. (2013) [34]	Phase III, multicenter, 3 arms, randomized, not placebo controlled, 2004–2009	126 (planned 381)	Not tested	WBRT 35 Gy (15f/2.5 Gy) combined with SRS to brain mets: 18–24 Gy	Arm A: WBRT/SRS Arm B: WBRT/SRS + temozolomide 75 mg/m ² /day Arm C: WBRT/SRS + erlotinib 150 mg/day, start day 1 of RT, continuation after WBRT on discretion of investigator	OS	PFS intracranial PS at 6 months Steroid dependence Cause of death Toxicity mentioned in results, not in objectives
<i>Erlotinib and WBRT</i>							
Lind et al. 2009 [32]	Phase I, single arm, 2006–2007	11	Not tested	30 Gy (10f/3 Gy)	4 patients: erlotinib 100 mg/d, 7 patients 150 mg/day, started one week before, concurrent with WBRT, then maintenance 150 mg/day	Toxicity (CTCAE v 3.0)	PFS (intra- and extracranial) OS
Olmez et al. (2010)[33]	Retrospective, single center, 2007–2009	8	Not tested	35 (15f/2.5 Gy)–40 Gy (20f/2 Gy)	Erlotinib 150 mg/day, started within 5 days of RT	Outcome (response rate intra- and extracranial) Toxicity (CTCAE v 3.0)	None
Welsh et al. (2013) [35]	Phase II, 2 centers, single arm, 2006–2010	40	17/40 tested 9/17 EGFR+	First 10 patients 30 Gy (10f/3 Gy), others 35 Gy (14f/2.5 Gy)	Erlotinib 150 mg/day, started one week before, concurrent with WBRT, then maintenance 150 mg/day	OS	Radiologic response Toxicity (CTCAE v 3.0 AND neurological evaluation)
Zhuang et al. (2013) [36]	Phase II, single center, 2 arms, not randomized, not placebo controlled, 2009–2011	54	23/54 tested 11/23 EGFR+	30 Gy (10f/3 Gy)	Arm A: EGFR mutation status tested (not necessarily activation mutation) erlotinib 150 mg/day from first day of WBRT to month after end of WBRT Arm B: only WBRT	Intracranial response rate LPFS	Toxicity (CTCAE v unknown) PFS OS
Lee et al. (2014) [31]	Phase II, multicenter, two-stage, randomized, double blind, placebo controlled, 2009–2010	80	35/80 tested 1/35 EGFR+	20 Gy (5f/4 Gy)	Arm A: erlotinib 100 mg/day started 1st day of WBRT, after completing WBRT increased to 150 mg/day maintenance Arm B: placebo starting on 1st day of WBRT	2-Month nPFS	Toxicity (CTCAE v 3.0) QoL
<i>Gefitinib and WBRT</i>							
Zeng et al. (2012) [40]	Retrospective, single center, 2005–2009	90	20/90 tested 12/20 EGFR+	40 Gy (20f/2 Gy)	Arm A Gefitinib 250 mg/day with concurrent WBRT, afterwards 250 mg/day continued Arm B: gefitinib 250 mg/day	"Efficacy and toxicity of gefitinib alone compared to concurrent with WBRT"	
Pesce et al. (2012) [38]	Open label, randomized, 2 stage, Phase II, multicenter, 2005–2009	59	Not tested	30 Gy (10f/3 Gy)	Arm A: gefitinib 250 mg/day concurrent with WBRT, afterwards 250 mg/day continued Arm B: temozolomide 75 mg/m ² concurrent with WBRT, afterwards 75 mg/m ² continued	OS	PFS (intra- and extracranial) QoL (including cognitive function, toxicity, tolerability)
Wang et al. (2014) [39]	Prospective, randomized, phase II, number of centers unknown, no placebo, 2010–2013	73	Number tested unknown, in gefitinib group 9/37 EGFR+	50 Gy (25f/2 Gy)	Arm A: gefitinib 250 mg/day start first day of WBRT Arm B: VM-26 100 mg/day iv dag 1–3, cisplatin 25 mg/m ² iv dag 1–3, 2 cycles, every cycle 21 days. Start first day of WBRT	Intracranial response rate OS Toxicity (CTCAE v 3.0)	
Ma et al. (2009) [37]	Phase II, single arm, single center, 2005–2007	21	Not tested	40 Gy (20f/2 Gy)	Gefitinib 250 mg/day concurrent with WBRT, afterwards 250 mg/day continued	Intracranial response rate QoL	Toxicity (CTCAE) PFS OS

(continued on next page)

Table 2 (continued)

Trial, year	Trial type	N	EGFR mutation analysis	WBRT/SRS treatment	TKI treatment (± comparator)	Primary study objective	Secondary study objectives
<i>Erlotinib or gefitinib and WBRT</i>							
Cai et al. (2013) [41]	Retrospective, single center, 2009–2012	157	All tested, 43 EGFR+	30–42 Gy (10–14f/3 Gy)	Arm A: erlotinib 150 mg/day or gefitinib 250 mg/day concurrent with WBRT. Startdate TKI not mentioned Arm B: only WBRT	Intracranial response rate PFS OS Toxicity (CTCAE and RTOG)	
Lee et al. (2012) [43]	Retrospective, 2 centers, 2003–2011	43	All tested, 30 EGFR+	30 (10f/3 Gy)–40 Gy (20f/2 Gy), with/without boost 50–60 Gy on metastases	44% EGFR–TKI concurrent with WBRT, in EGFR + group 50%, dose erlotinib or gefitinib not mentioned	“impact of EGFR mutations on RT” (intracranial response rate, toxicity (CTCAE v 3.0), OS) Toxicity	Effect of concurrent chemo or EGFR–TKI
Inamasu (conf abstract) (2012) [42]	Retrospective, single center, 2005–2011	18	Not mentioned	Not mentioned	Erlotinib or gefitinib concurrent with WBRT, dose not mentioned	Toxicity	
<i>Icotinib and WBRT</i>							
Zhou et al. (conf abstract) (2014) [45]	Phase I, single center, open label, dose finding, 2011–2013	15	All tested, all EGFR+	37.5 Gy (15f/2.5 Gy)	3 + 3 design, icotinib 125, 250, 375, 500 mg TID. Start 7 days before WBRT, concurrent with WBRT, continuation after WBRT	Toxicity Neurocognitive functioning (MMSE) within 20 weeks of WBRT	ORR, DCR, PFS
Yun et al. (conf abstract) (2013) [44]	Phase II, single arm, open label, 2012–2013	20	All tested, number of EGFR + not mentioned	30 Gy (10f/3 Gy)	Icotinib 125 mg TID concurrent with WBRT	Response rate intracranial	PFS, OS, QoL Toxicity Relationship response and EGFR-mutation CSF concentration of icotinib

Abbreviations: EGFR: epidermal growth factor receptor; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; TKI: tyrosine kinase inhibitor; RT: radiotherapy; OS: overall survival; PFS: progression free survival; PS: performance score; CTCAE: Common Terminology Criteria of Adverse Events; LPFS: locoregional progression free survival; nPFS: neurological progression free survival; QoL: quality of life; mg: milligram; iv: intravenous; TID: three times a day; MMSE: mini mental state examination; ORR: overall response rate; DCR: disease control rate; CSF: cerebrospinal fluid.

Table 3
Methods of toxicity evaluation in the included studies.

Trial, year	Toxicity primary endpoint	Frequency of toxicity assessment	Method of general toxicity assessment	Method of neurocognitive toxicity assessment
<i>Erlotinib and WBRT + SRS</i> Sperduto et al. (2013) [34]	No	Monthly during protocol therapy	CTCAE v 3.0	Not specifically assessed
<i>Erlotinib and WBRT</i> Lind et al. (2009) [32]	Yes	Week 1 and 2 of WBRT Then at 2 weeks, 4 weeks, 2 months Then every 2 months until disease progression and/or death	CTCAE v 3.0	Baseline assessment: neurological examination Otherwise only CTCAE
Olmez et al. (2010) [33] Welsh et al. (2013) [35]	No	Retrospective study, not specified Baseline, within 14 days of WBRT completion Afterwards at 1 month, then every 3 months	CTCAE v 3.0	Neurological examination, MMSE (at 0, 6 and 12 months) Formal cognitive testing (thorough neurological examination, Hopkins Verbal Learning Test-Revised, Trail Making Test Part A and B, Multilingual Aphasia Examination Controlled Oral Word Association)
Zhuang et al. (2013) [36]	No	Baseline, 1 month after WBRT Afterwards every 2–3 months	CTCAE v 3.0	None
Lee et al. (2014) [31]	No	CTCAE evaluation only the first 28 days. Neurological exam: before randomisation first 8 weeks 2-weekly Then monthly the first 12 months, afterwards 2-monthly	CTCAE v 3.0	MMSE Clinical assessment of motor strength, visual acuity and gait
<i>Gefitinib and WBRT</i> Zeng et al. (2012) [40] Pesce et al. (2012) [38]	No	Retrospective study, not specified Baseline Day 1 of cycle 2, 3 and 5	CTCAE v 3.0	MMSE, Trail Making Test part B and EORTC QLQ-C30 cognitive function subscale
Wang et al. (2014) [39]	Yes	Weekly during concurrent treatment Then 3-monthly interval for the first year Afterwards every 3–6 months	CTCAE v 3.0	None
Ma et al. (2009) [37]	No	Weekly during concurrent treatment Afterwards not very well specified, presumably every month	CTCAE, version not mentioned	Neurological examination
<i>Erlotinib or gefitinib and WBRT</i> Cai et al. (2013) [41] Lee et al. (2012) [43] Inamasu (conf abstract) (2012) [42]		Retrospective study, not specified Retrospective study, not specified Retrospective study, not specified		
<i>Icotinib and WBRT</i> Zhou et al. (conf abstract) (2014) [45]	Yes	Not mentioned in abstract	CTCAE, version not mentioned	MMSE up to 20 weeks after WBRT
Yun et al. (conf abstract) (2013) [44]	No	Not mentioned in abstract	Not mentioned in abstract	Not mentioned in abstract

Abbreviations: WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; CTCAE: Common Terminology Criteria of Adverse Events; MMSE: mini mental state examination.

an activating mutation/translocation developed brain metastases while on TKI treatment and were subsequently randomized to cranial radiotherapy with concurrent TKI or cranial radiotherapy with temporarily discontinuation of the TKI. Primary outcomes varied and outcome data were measured and reported in a non-uniform way. Based on these data, WBRT concurrent with EGFR-TKI does not seem to increase neurotoxicity, although no firm conclusions can be made. However, one should be cautious in interpreting the neurological toxicity data from most of these studies, as in only two studies extensive neurocognitive tests were performed [35,38]. In both of these studies neurotoxicity was not the primary endpoint; one study was a single arm study and the other was not powered to detect neurotoxicity differences. Moreover, in the two arm study there was no comparator arm without an active systemic drug (one arm gefitinib concurrently with WBRT, the other temozolomide concurrently with WBRT) [38]. As such, subtle changes in neurocognitive functioning due to concurrent TKI and cranial radiotherapy cannot be excluded. Furthermore, WBRT combined with SRS, concurrent with EGFR-TKI does seem to increase neurotoxicity when compared to historical data for WBRT and

SRS without concurrent systemic treatment. In the study arm with concurrent EGFR-TKI, grade 3 confusion and ataxia (percentage not mentioned), grade 4 brain necrosis (2.4%) and grade 5 stroke (2.4%) were reported [34]. In a previous study without systemic treatment, acute toxicities were grade 3 in 2% of patients, grade 4 in 1% and none had grade 5 toxicities [50]. Non-neurological toxicities seem to increase with the concurrent use of EGFR-TKI when compared to monotherapy EGFR-TKI or WBRT. EGFR-TKI's are known to cause grade ≥ 3 toxicities, like rash (3–13%), diarrhea (0–25%), fatigue (0–19%), nausea (3–6%), vomiting (3–5%) and interstitial lung disease (1.2%, all grades) [51–53]. When compared to the 3–13% grade ≥ 3 rash encountered with monotherapy EGFR-TKI, this percentage is slightly higher in the concurrent treated patients in this review (9–20%) [31–35,43]. Grade ≥ 3 rash was more often encountered with erlotinib than with gefitinib as is also known from literature, possibly because erlotinib is given at the maximum tolerated dose (MTD) and gefitinib is given at approximately one third of the MTD [54]. Although location of rash was not described, it is possible that this occurred on the scalp due to the concurrent WBRT. The same holds true for grade ≥ 3 mucositis,

Table 4
Trial results of the included studies.

Trial, year	Retrospective (R) or prospective (P)	N	Arms specified when necessary	Neurological safety outcome	All other grade 3–5 toxicities	Efficacy outcome
<i>Erlotinib and WBRT + SRS</i> Sperduto et al. (2013)	P	126 (planned 381)	A: WBRT/SRS B: WBRT/SRS + temozolomide C: WBRT/SRS + erlotinib	Arm C: grade 3 confusion and ataxia (% not mentioned), grade 4 brain necrosis (2.4%), grade 5 stroke (2.4%)	Grade 3–5 toxicities arm A, B, C 11%, 41% and 49%, respectively Arm C: fatigue, acne, diarrhea, pneumonia, hyperkalemia, muscle weakness	Median OS Arm A, B, C resp 13.4, 6.3 and 6.1 m (NS)
<i>Erlotinib and WBRT</i> Lind et al. (2009) [32]	P	11	Single arm	No treatment related neurotoxicity	ILD 18%, rash 9%, fatigue 9%	7 patients FU imaging; 5/7 PR, 2/7 SD
Olmez et al. (2010) [33]	R	8	Single arm	Mental status change (37.5%)	Rash, diarrhea, mucositis, oral trush (all 12.5%), fatigue (37.5%), hepatotoxicity (25%), hyponatremia (50%)	7 patients evaluable, 75% DCR (25% PR, 50% SD)
Welsh et al. (2013) [35]	P	40	Single arm	No direct neurotoxicity (measurements including neurocognitive testing) 2.5% gr 3 headache 2 patients questionable late neurotoxicity (1 male, aged 74 developed dementia 2 years after study completion, one patient developed radiation necrosis after intracranial PD for which she received SRS)	(all grade 3) 15% rash, 12.5% fatigue, 10% diarrhea, 2.5% nausea, 5% vomiting, 10% dehydration, 5% liver test abnormalities, 2.5% pleural effusion	ORR CNS 86% Overall median OS 11.8 m EGFRwt 9.3 m EGFR + 19.1 m
Zhuang et al. (2013) [36]	P	54	A: WBRT + erlotinib B: only WBRT	5% grade 3 dizziness in both arms No difference in late neurotoxicity between arm A and B (not specified)	Grade 3 toxicities arm A: 10% anorexia, arm B: none No grade 4–5 toxicities	ORR arm A and B resp 96 and 55% 1 year OS arm A and B resp 35 vs 6%
Lee et al. (2014) [31]	P	80	A: WBRT + erlotinib B: WBRT + placebo	Arm A: grade 3/4 somnolence 2.5% Arm B: grade 3/4 headache 10%, seizure 5%, somnolence 2.5%,	Grade 3/4 toxicities similar in both arms (70%), except for rash (erlotinib 20%, placebo 5%) and fatigue (erlotinib 17.5%, placebo 35%) QoL similar	Neurological PFS both arms 1.6 m Median OS arm A and B resp 3.4 and 2.9 m
<i>Gefitinib and WBRT</i> Zeng et al. (2012) [40]	R	90	A: WBRT + gefitinib B: gefitinib only	“no significant differences although headache and vomiting occurred more often in the WBRT arm”	Alopecia significantly more in WBRT + TKI arm compared to TKI alone (73% vs 4%)	ORR of brain mets arm A and B resp 64% vs 27% DCR of brain mets 71% vs 42% Median PFS 10.6 vs 6.6 m Median OS 23.4 vs 14.8 m
Pesce et al. (2012) [38]	P	59	A: WBRT + gefitinib B: WBRT + temozolomide	None	Grade 3–4 toxicities arm A: fatigue 18.8%, dyspnea 6.3%, mucositis 6.3%, diarrhea 6.3% Arm B: lymphopenia 9.3%, low CD4 2.3%, liver test abnormalities 9.3%, fatigue 18.6%	Arm A closed prematurely due to futility Median OS arm A and B resp 6.3 and 4.9 m
Wang et al. (2014) [39]	P	73	A: WBRT + gefitinib B: WBRT + VMP	None	For arm A (gefitinib) not well defined: 70% rash, grade not mentioned Arm B: grade 3–4 hematological toxicities 41%	RR arm A vs B 54% vs 47% Median OS arm A vs B 13.3 vs 12.7 m

Table 4 (continued)

Trial, year	Retrospective (R) or prospective (P)	N	Arms specified when necessary	Neurological safety outcome	All other grade 3–5 toxicities	Efficacy outcome
Ma et al. (2009) [37]	P	21	Single arm	14% grade 3 headache, 86% grade 3 alopecia No grade 4–5 toxicities	All domains of QoL improved during treatment Grade 3 toxicities: 14.3% diarrhea, 14% nausea, 14% vomiting, 14% fatigue No grade 4–5 toxicities	ORR 81% Median PFS 10.0 m Median OS 13 m
<i>Erlotinib or gefitinib and WBRT</i>						
Cai et al. (2013) [41]	R	157	A: WBRT + TKI B: WBRT only	No significant neurotoxicity differences between arm A and B. grade not mentioned.	Arm A: (grade not mentioned) rash 47.7%, interstitial pneumonia 7.7%, diarrhea 7.7%,	Arm A RR 76.9% DCR 96.9% Arm B RR 70.7% DCR 89.1% Arm A PFS 6.0 m, OS 10.6 m Arm B PFS 3.4 m, OS 7.7 m
Lee et al. (2012) [43]	R	43	A: WBRT only B: WBRT + TKI	None	No ≥grade 3 toxicities in arm A. In arm B: 11% grade 3 rash, 5% grade 3 oral mucositis, 5% grade 3 otitis media	RR EGFR + vs EGFRwt 80% vs 46%, EGFR + only predictor for treatment response
Inamasu (conf abstract) (2012) [42]	R	18	Single arm	None	No grade ≥3 toxicities	100% intracranial DCR
<i>Icotinib and WBRT</i>						
Zhou et al. (conf abstract) (2014) [45]	P	15	Single arm	Compared to baseline no changes in neurocognitive functioning at 20 weeks, low dose vs high dose no differences	500 mg TID = DLT (1 pt grade 3 ALAT increase, 2 pts grade 3 nausea)	ORR 80%, DCR 100%, median PFS 46 weeks (intracranial 78 weeks)
Yun et al. (conf abstract) (2013) [44]	P	20	Single arm	No grade > 3 toxicities, all grades: headache 35%	No grade >3 toxicities, all grades: rash 40%, diarrhea 15%, nausea 45%, vomiting 20%, fatigue 45%	ORR 80% Median PFS EGFR + vs EGFRwt: NR vs 4.2 months

Abbreviations: R: retrospective; P: prospective; N: number; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; OS: overall survival; resp: respectively; NS: non-significant; ILD: interstitial lung disease; FU: follow-up; PR: partial response; SD: stable disease; DCR: disease control rate; PD: progressive disease; (O)RR: (overall) response rate; CNS: central nervous system; EGFR: epidermal factor growth receptor; wt: wild type; QoL: quality of life; PFS: progression free survival; TKI: tyrosine kinase inhibitor; TID: three times a day; DLT: dose limiting toxicity; ALAT: alanine-aminotransferase; NR: not reached.

Table 5
Ongoing or unpublished trials of TKI concurrent with cranial radiation.

Trial, number	Trial type	N (to be included)	EGFR mutation analysis	WBRT/SRS treatment	TKI treatment (\pm comparator)	Primary study objective	Secondary study objectives	Estimated primary completion date
<i>Erlotinib and WBRT</i>								
NCT00871923	Phase II, single center, open label, single arm	20	Not mandatory	WBRT 35 Gy (14f/2.5 Gy)	Erlotinib 150 mg once daily, start 5 days before WBRT, continue during WBRT, continuation after WBRT at investigators discretion	Median OS (designated as safety issue)	Not provided	March 2016
NCT01887795	Phase III, multicenter, open label, randomized	224	Mandatory, unclear in description whether only EGFR + patients are included	WBRT 40 Gy (20f/2 Gy)	Arm A: Erlotinib 150 mg once daily, start 5 days before WBRT, continue during WBRT Afterwards erlotinib treatment not specified Arm B: WBRT only	Time to neurological progression (designated as safety issue)	OS Response QoL	August 2016
NCT01518621	Phase II, open label, randomized	150	Not mandatory	WBRT 30 Gy (10f/3 Gy)	Arm A: Erlotinib 150 mg once daily, start 1 day before WBRT, continue during WBRT Arm B: WBRT only	Median OS	Safety, local control rate, time to neurological progression (neuropsychological testing), QoL, effect of mutation status	Not provided
NCT01130779	Phase II, open label, single arm, enrolling by invitation	23	Not mandatory, however only patients included on EGFR-TKI treatment with good extracranial control	WBRT, SRS or surgery Dose radiotherapy not specified	Patients on EGFR-TKI treatment and brain only PD: local treatment with continuation of EGFR-TKI	PFS (not designated as safety issue)	OS Response rate Time to treatment failure Toxicity profiles	August 2010 (study information not updated)
<i>Gefitinib and WBRT</i>								
NCT01363557	Phase II, open label, multicenter, randomized	Only 1 enrolled	Mandatory, only EGFR + patients included	WBRT 30 Gy (10f/3 Gy)	Arm A: gefitinib 250 mg once daily concurrent with WBRT Arm B: gefitinib 250 mg once daily only	Response rate brain metastases (designated as safety issue)	Neurological adverse events PFS OS	Closed prematurely due to poor accrual
NCT02338011	Phase II/III, open label, 2 arm, randomized, single center	210	Mandatory, only EGFR + patients included	WBRT 30 Gy (10f/3 Gy)	Arm A: gefitinib 250 mg once daily concurrent with WBRT Arm B: gefitinib 250 mg once daily only Gefitinib in both arms until progression	PFS: intracranial, extracranial and overall (designated as safety issue)	OS Site of first progression QoL Mental status (MMSE)	November 2017
<i>Icotinib and WBRT</i>								
NCT01926171	Phase IV, single arm, open label	80	Not mandatory	WBRT 40 Gy (20f/2 Gy)	Icotinib (dose?) TID concurrent with WBRT	Response rate brain metastases (not designated as safety issue)	PFS All cause progress/mortality Safety	September 2014

Abbreviations: N: number; EGFR: epidermal growth factor receptor; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; TKI: tyrosine kinase inhibitor; OS: overall survival; QoL: quality of life; PD: progressive disease; PFS: progression free survival; MMSE: mini mental state examination; TID: three times a day.

as this is seldom encountered with first generation EGFR-TKI [53], and was observed in 5–12.5% in the studies described in this review [33,38,43]. However, only one of these studies was randomized and in this trial, in both arms a systemic agent was given (temozolomide or gefitinib) [38]. Moreover, the technique of WBRT was very simple, thus including some mucosa in the irradiated volumes. Percentages of grade ≥ 3 fatigue, nausea and vomiting do not seem to increase with EGFR-TKI concurrent with WBRT compared to monotherapy EGFR-TKI, although WBRT itself also can also cause fatigue, nausea and vomiting (usually \leq grade 2) [55].

As safety was the focus of our review there was no restriction on the presence of a targetable mutation. As such, the question whether the potential increase in local CNS response rate and the prevention of tumor flare when the TKI is continued during cranial radiation outweighs the potential risk of clinically significant side effects is not answered. To date, there are no studies addressing this specific question in patients with an activating mutation. In two out of four studies that compare WBRT to concurrent EGFR-TKI and WBRT, the response rate and OS were higher in patients that were treated with the combined treatment. However, in these trials *EGFR* mutation status was not tested or known only for a subset of patients. It was also unclear whether *EGFR*-mutated patients treated with WBRT only were afterwards treated with EGFR-TKI (i.e., possible undertreatment of these WBRT only patients) [31,34,36,41].

As mentioned above, no studies were identified in which patients with an activating mutation/translocation developed brain metastases while on TKI treatment and were subsequently randomized to cranial radiotherapy with/without concurrent TKI. In current guidelines, no advice regarding TKI use during cranial radiotherapy is given [2,3,22,23]. In daily practice, the TKI is often discontinued for 4–5 times the half-life ($T_{1/2}$) of the drug before start of cranial radiotherapy and is reinitiated a couple of days after cranial radiotherapy because of (neuro)toxicity concerns. For the first generation TKI's, $T_{1/2}$ is 36 h (erlotinib) to 40–42 h (gefitinib–crizotinib) [56–58]. $T_{1/2}$ of icotinib is only six to eight hours [58]. As a result, TKI's are discontinued approximately two to three weeks because of cranial radiotherapy with the risk of a systemic disease flare-up. The 4–5 times the $T_{1/2}$ is based on the finding that after this time drugs are eliminated from the blood. However, it is unclear whether there are still remaining biological effects of the drug. Moreover, it is also unknown whether there is a dose-dependent effect for radiosensitisation. Furthermore, for other drugs like monoclonal antibodies $T_{1/2}$ is often more than one week (e.g., ipilimumab $T_{1/2}$ 15 days) which makes it impossible due to the need for systemic disease control to discontinue these drugs for 4–5 times the $T_{1/2}$ [59]. As there is a lack of pre-clinical data for e.g., radiosensitisation and dose-dependency as well as remaining biological effects after discontinuation of the drug (TKI as well as monoclonal antibodies), this should be subjected to further research. Another question that is not evaluated in this review is what the best treatment sequence is for patients with an activating *EGFR* mutation or *ALK*-rearrangement with already a diagnosis of asymptomatic brain metastasis before commencement of a TKI. Based on available literature, patients with an activating *EGFR* mutation can start directly with an EGFR-TKI, as, despite the poor blood–brain-barrier penetration of first generation EGFR-TKIs, the cerebral response rate is more than 80% [7]. For *ALK*-rearranged patients, data are less clear. In the retrospective pooled analysis of the subgroup of patients with previously untreated brain metastases included in the PROFILE 1005 and 1007 studies, cerebral response and disease control rate were only 18% and 53%, respectively, and the CNS was the initial site of progression in 70% of patients [8]. One can argue that in this patient population, cranial radiotherapy can be considered first.

Also, the place of the second and third generation TKI's (EGFR: afatinib, AZD9291, CO-1686, ALK: ceritinib, alectinib) should be determined as these agents have a better penetration in the CSF compared to first generation TKI's and cranial responses are found with these agents in patients who develop brain metastases when they have already been treated with first generation TKI [15,60–62]. Another option that could be explored in this patient population is the use of SRS without WBRT, even for multiple (five to ten) brain metastases. This because recently it was found that results for SRS alone did not differ between patients with two to four brain metastases compared to five to ten metastases [63]. The advantages for SRS/SRT without WBRT are that both cognition and quality of life are superior with SRS/SRT alone [64]. Moreover, local control rates are durable (12-month local control rate between 50% and more than 80% dependent on radiation dose and volume of brain metastases) and complication rate is low (grade ≥ 3 adverse events less than 5%) [63,65,66]. However, because of number and/or volume of brain metastases, not all patients are suitable for SRS/SRT and WBRT still is an option in this patient population. Although there are some studies investigating WBRT concurrently with an EGFR-TKI (overview in Table 5), there are currently no ongoing studies in patients with an activating *EGFR*-mutation oligoprogressive in the brain while on EGFR-TKI treatment.

In summary, although there are arguments that EGFR-TKI can be safely applied concurrent with WBRT, there is no high-level evidence to support this. With the addition of SRS/SRT to WBRT, severe (grade 3–5) toxicities may increase, although further studies are needed [34]. For *ALK*-rearranged patients no data are available. This review stresses the need for high quality studies evaluating the use of TKI with concurrent radiotherapy in patients with an activating *EGFR*-mutation and/or *ALK*-rearrangement as well as for the further evaluation of the place of second and third generation TKI's and SRS/SRT in this selected patient population.

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No conflict of interest.

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Contributions

L. Hendriks: conception and design of study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of article.

J. Schoenmaekers: acquisition of data, analysis and interpretation of data, critically revising the article, final approval of article.

J. Zindler: analysis and interpretation of data, critically revising the article, final approval of article.

D. Eekers: analysis and interpretation of data, critically revising the article, final approval of article.

A. Hoeben: analysis and interpretation of data, critically revising the article, final approval of article.

D. De Ruyscher: analysis and interpretation of data, drafting and critically revising the article, final approval of article.

A.-M. Dingemans: Conception and design of study, analysis and interpretation of data, drafting and critically revising the article, final approval of article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ctrv.2015.05.005>.

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