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The more you get
the more you want
-it seems.
(Ferdinand Morton in 'Doctor Jazz', 1926)

Aan mijn ouders
Voor Marianne

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1. van Oosterhout AGM, van de Pol M, ten Velde G, Volovics A, Twijnstra A. Neurological disorders in 203 consecutive patients with small cell lung cancer: results of a longitudinal study. Submitted.

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3. Habets JM, Oosterhout van AGM, Velde ten GP, Wilmink JT, Twijnstra A. Diagnostic value of CT in the detection of brain metastases in small cell lung cancer patients. BTR 75: 179-181, 1992.

4. Twijnstra A, Oosterhout van AGM, Pol van de M, Wilmink JT, Velde ten GP. Diagnostic value of MR imaging in the detection of brain metastases at initial staging in small cell lung cancer. Neuroradiology (in press).

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6. Oosterhout van AGM, Boon PJ, Houx PJ, Velde ten GPM, Twijnstra A. Follow-up of cognitive functioning in patients with small cell lung cancer. Int J Radiat Oncol Biol Phys (in press).

7. Oosterhout van AGM, Ganzevles PGJ, Wilmink JT, Geus de BWJ, Vonderen van R, Twijnstra A. Central nervous system toxicity in long-term survivors of small cell lung cancer. Submitted.

Contents

1 General introduction

In the countries of north-western Europe, lung cancer is the most common cancer in males [1-3]. In the Netherlands, almost 8500 persons died of lung cancer in 1987 (about 7500 men and 1000 women) and another 261 had lung cancer as secondary cause of death, according to the Netherlands Central Bureau for Statistics [4]. Annually, lung cancer will be diagnosed presumably in about 9500 patients (8200 men and 1300 women) [4], in other words, 1 out of every 11 men will develop lung cancer before the age of 75 versus 1 out of every 60 women [5, 6]. The world standardised incidence rates were 81.3 for men and 10.1 / 100000 for women, for the two most southern areas of the Dutch provence of Limburg [7].

Since 1985 the high lung cancer incidence among males has gradually declined, whereas the low incidence for females rapidly increased since 1989 [5]. At the same time, the age-adjusted incidence and the proportional distribution of histological types showed a striking increase in adenocarcinoma for males, while a decline was observed in squamous and small cell carcinoma [4]. For females the incidence of all types, including undifferentiated cancer, increased [4]. Small cell lung cancer (SCLC) accounted for 17% of all lung cancer in males and 23% in females [4, 6]. The changes in lung cancer rates and distribution of histological types are probably related to changes in smoking behavior, as the number of male smokers declined and female smokers sharply rose [5, 6].

Small cell lung cancer distinguishes itself from other types of lung carcinomas by a remarkable propensity for early systemic spread and substantially greater initial sensitivity to chemotherapy and radiotherapy [8-13]. Nearly all patients have mediastinal or systemic metastases at the time of initial diagnosis, precluding therapy with surgery alone [14-16]. Combination chemotherapy will result in objective response rates in 85 to 95% for limited disease and in 65 to 85% in extensive disease patients [17]. Complete responses can be produced in about 50% of limited disease and in about 25% of extensive disease patients [17]. Depending on the addition of radiotherapy, in limited disease patients about a third will have disease free survival in excess of two years. Long term disease free survival in extensive disease patients is unusual. Despite constant refinements and changes of the therapy, long term survival remained stable at a 10 to 20% at two years [18, 19] and a poor 5% at five years [20], in the last decade.

A wide array of neurologic complications, diverging from brain metastases to paraneoplastic disorders, can complicate SCLC [21-24]. Neurologic complications of SCLC are mainly metastatic in nature; about 10% of the patients have brain metastases at initial diagnosis, about 30% subsequently develop brain metastases during treatment, and at autopsy the frequency is approximately 50% [25-27]. The actuarial risk of brain metastases increased with lengthening of survival to

50 to 80%, at two years from diagnosis [28-30]. Though the use of prophylactic cranial irradiation (PCI) effectively reduced the frequency of brain metastases [31-33], PCI became controversial as it did not provide any survival benefit and was associated with central nervous system (CNS) toxicity [34-35]. Manifestations of neurotoxicity and paraneoplastic syndromes may be confused with symptomatic CNS metastases. The pathogenesis of PCI related neurotoxicity is insufficiently understood as it is predominately described in small series of long term survivors, treated and analysed differently [36-50].

In this thesis, several aspects of brain metastasis in SCLC are investigated. The data used for most studies were yielded by a SCLC case register program, which began in October 1980. As part of this program patients with SCLC were seen by a neurologist at diagnosis and regular intervals thereafter. A CT-scan of the brain, MR-scan after 1991, was routinely performed at initial staging. More frequent neurologic consultations and other diagnostic tests were performed if required. Long term survivors were examined in different hospital troughout the Netherlands by a neurologist and neuropsychologist. The goals of the study thesis were:

- to describe the results of a neurologic follow-up of 203 consecutive patients with SCLC (chapter 1);
- to study the value of histopathologic subtyping of SCLC in predicting neurologic complications (chapter 2);
- to investigate the value of CT-scan (chapter 3) and MRI (chapter 4) for the detection of brain metastases, in context to the initial staging procedure;
- to describe the efficacy and safety of PCI in 203 consecutive patients with SCLC (chapter 5);
- to prospectively study the cognitive functioning of 32 consecutive patients with SCLC (chapter 6);
- to retrospectively investigate the neurologic outcome of 59 long-term survivors of SCLC (chapter 7).

Neurologic disorders are a frequent and enthralling problem in patients with SCLC. Some clinical aspects of brain metastasis in SCLC and its treatment are highlighted in this thesis.

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2 Neurologic disorders in 203 consecutive patients with small cell lung cancer: results of a longitudinal study

Introduction

Small cell lung cancer (SCLC) comprises about 25% of all lung cancers [1,2]. In patients SCLC is very aggressive and nearly always metastatic at the time of presentation, precluding therapy with surgery or chest irradiation alone [3]. The median survival of untreated patients is about 3 months from diagnosis, whereas combination chemotherapy, with or without radiotherapy, has provided improvements in median survival to almost a year, and 10% long-term, potentially cured survivors [4].

Neurologic disorders are a frequent and for the neurologist a fascinating problem in patients with SCLC. Central nervous system (CNS) metastases are diagnosed more frequently in SCLC than in other types of lung cancer [5]. Brain metastases are the most frequent sort of CNS metastases, and are an important cause of morbidity and mortality in patients with SCLC [6,7]. The actuarial probability of developing brain metastases increases with lengthening of survival to 50-80% at two years from diagnosis [6-9]. Because of its neuroendocrine properties, SCLC is associated with a wide array of paraneoplastic syndromes [10-14]. Treatment of SCLC, the combination of chemotherapy and cranial irradiation in particular, is potentially neurotoxic and can contribute to brain injury as well [14-21].

Neurologic disorders have been studied retrospectively, and mainly by pulmonologists and oncologists in previous reports [5-21]. In the present article, the results of a prospective neurologic follow-up study are presented. The present study was undertaken to investigate the clinical frequency and course of the neurologic complications of SCLC.

Patients and methods

Patients

From January 1983 to January 1993, 203 consecutive patients with microscopically proven SCLC were included in this prospective study. Till January 1994 minimal follow up was 1 year or until death. Initial staging of these patients by a pulmonologist, was based on physical examination, standard blood and chemistry profile, chest x-ray, CT-scan of the chest, ultrasound of the abdomen, radionuclide bone scan, fibre optic bronchoscopy, and bone marrow aspirate and biopsy. Limited disease (LD) was defined as tumor confined to the ipsilateral hemithorax, the mediastinum, and the ipsilateral and/or contralateral scalene and supraclavicular lymph nodes. In extensive disease (ED) tumor was found beyond these site.

Treatment

All patients were initially treated with a combination chemotherapy regimen, consisting of cyclophosphamide 1000 mg/m2, doxorubricin 45 or 50 mg/m2, and etoposide 100 mg/m2 on day 1,3, and 5 for at least five cycles. Chemotherapy was sometimes followed by radiotherapy to

Patients	Disease stage	
	limited	extensive
Total 79 129		
Men / Women	59 / 15	111 / 18
Median age at diagnosis (range)	64 (39-84) 65	(45-89)
Complete remission	37	30
Prophylactic cranial irradiation	17	5

Table 1. Patient characteristics.

the primary tumor site. Restaging was performed after five courses of chemotherapy and consisted of physical examination, and repetition of those examinations which were abnormal at the initial staging procedure; complete remission (CR) was defined as a total resolution of all detectable lesions.

Only patients who obtained CR were candidates for treatment with PCI. Till 1986 LD and ED patients could opt for PCI, after 1986 LD patients only, and in 1990 PCI was excluded from the treatment protocol. Between 1983 and 1988, two eligible LD patients refused PCI. Patient characteristics and treatment specifications are listed in *table 1*. PCI was administered to the entire cranial content following completion of chemotherapy. Patients were treated with a linear accelerator, usually 6 MV photons, using two lateral opposed fields. The dose was calculated in the mid plane, and delivered in daily fractions of 3 Gy, 4 times a week, up to a total dose of 30 Gy. During 1988 and 1990 the radiation technique was changed, the fraction dose being lowered to 2Gy, 5 fractions per week up to a total dose of 30 Gy.

Palliative treatment of manifest brain metastases consisted of daily treatment with fractions of 3 Gy, 4 times a week, up to a total dose of 30 Gy. Treatment of leptomeningeal metastases consisted of intrathecal methotrexate and systemic corticosteroid medication, which was sometimes combined with local radiotherapy at symptomatic sites. Therapy for spinal metastases comprised radiotherapy concurrent with corticosteroid medication. Radiotherapy was initiated a few hours after diagnosis was made if signs of spinal cord compression were present, otherwise within 48 hours. Dose and schedule were tailored to site and extent of metastasis.

Disorders	n	% of total
Total	174	100
Metastatic	118	67.8
brain metastases	79	45.4
leptomeningeal metastases	22	12.6
spinal metastases	17	9.8
• epidural	14	8.0
• spinal cord	3	1.7
Non Metastatic	55	31.6
peripheral neuropathy	23	13.2
• chemotherapy	12	6.9
• unknown cause	5	2.9
• diabetes mellitus	4	2.3
• alcohol	2	1.1
paraneoplastic syndromes	16	9.2
• SIADH	11	6.3
• Lambert-Eaton myasthenic syndrome	3	1.7
• subacute cerebellar degeneration	1	0.6
• limbic encephalitis	1	0.6
other	16	9,2
encephalopathy	12	6.9
• possible treatment-related	8	4.6
• metabolic	4	2.3
•steroid myopathy	2	1.1
•radiation plexopathy	1	0.6
•cerebrovascular accident	1	0.6

Table 2. Neurologic disorders in 203 consecutive patients with small cell lung cancer. SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

Neurologic follow-up

Patients were seen by a neurologist at diagnosis and at quarterly intervals (bi-annually after a year). Pretreatment a CT-scan of the brain was performed until 1989, thereafter a MRI. More frequent neurologic consultations and other auxiliary diagnostic tests took place if required. In patients with a long-term survival (defined as 2 years or longer from diagnosis) an additional CT-scan of the brain or MRI was performed. Abnormal brain functioning found in long-term survivors, was designated as possible treatment related encephalopathy unless otherwise clearly explainable.

Statistics

Overall survival was calculated from SCLC diagnosis to death or end of observation period, brain metastatic free survival from SCLC diagnosis to the diagnosis of brain metastases or end of observation period. Survival curves were estimated by the Kaplan-Meier method, differences tested by the Log-rank test. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total number of 174 neurologic disorders were diagnosed in 134 patients (66%); 23 patients had 2 neurologic disorders, and 9 patients had more than 2 different neurologic disorders. The diverse disorders are listed in *table 2*. The majority of the complications, 161 (93%), were directly related to SCLC or its treatment. Metastatic complications predominated. Brain metastases were found at initial diagnosis of SCLC in 27 patients, and during the course of disease in 52 patients. Histopathologic examination of the brain metastases after autopsy (n = 12) or neurosurgical intervention (n = 3) revealed a different diagnosis in 2 patients (another primary tumor n = 1, non-SCLC relapse after CR of SCLC n = 1). In the remaining patients the diagnosis SCLC was confirmed.

Brain metastatic free survival of LD and ED patients was significantly different ($p < .01$, Log-rank test). Two years from diagnosis, the cumulative risk of brain metastases reached 47% for LD and 69% for ED patients, see *figure 1*. The overall survival of patients with initial brain metastases did not differ significantly from the survival of ED patients without initial brain metastases ($p = .12$, Log-rank test). Survival following diagnosis of brain metastasis was significantly longer for patients with initial brain metastases than for LD and ED patients with delayed brain metastases ($p < .01$, Log-rank test), see *figure 2*. The median survival of 12 patients with initial CNS-limited disease was not better than the median survival of other patients with initial brain metastases, 2.1 months (range, 0.6 to 15.8) versus 5.1 months (range, 0.2 to 25.2). Eight out of 12 patients with initial CNS-limited disease died early due to various complications (sepsis n = 5, and haemorrhage in cerebral metastasis n = 1) or progressive disease (no response n = 1, and therapy refused n = 1).

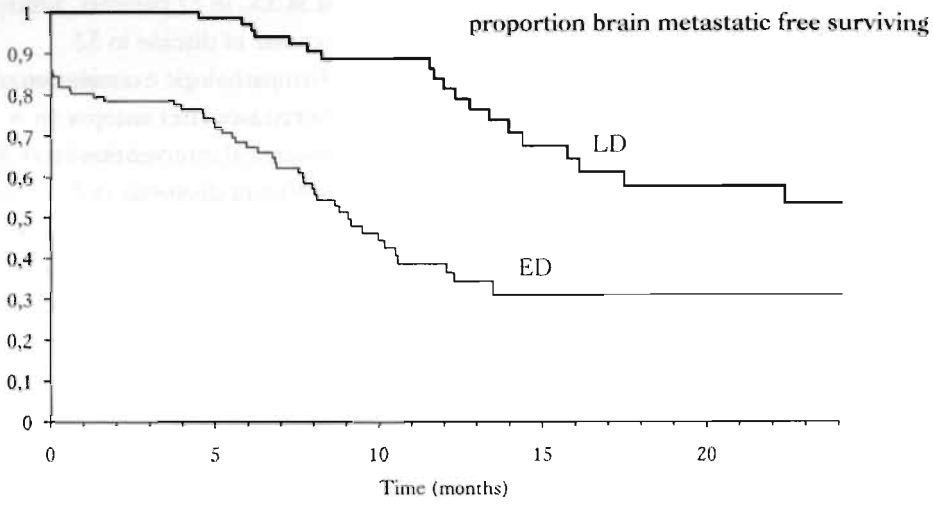

Figure 1. Cumulative risk of brain metastases in limited (LD) and extensive disease (ED) patients.

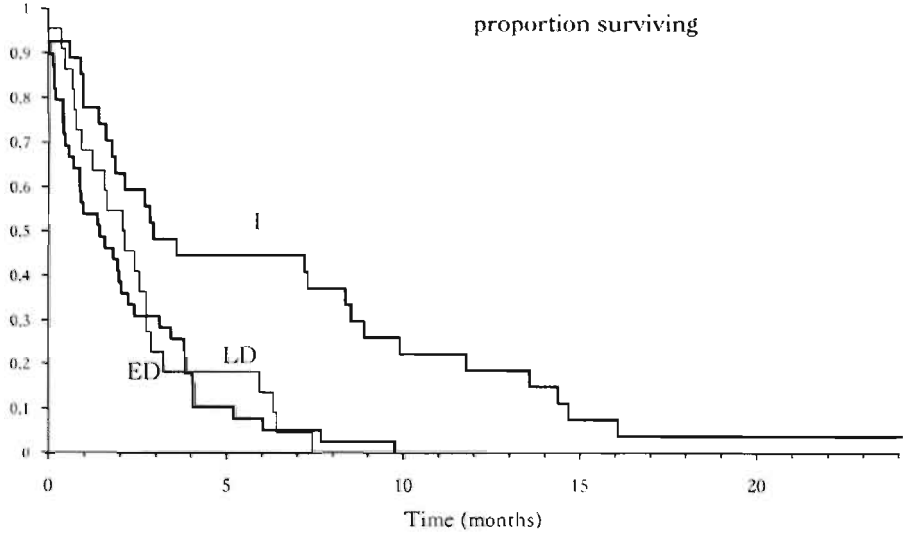

Figure 2. Survival following diagnosis of brain metastases for patients with initial brain metastases diagnosed prior to therapy (I), and limited (LD) and extensive disease (ED) patients with delayed brain metastases diagnosed during or after therapy.

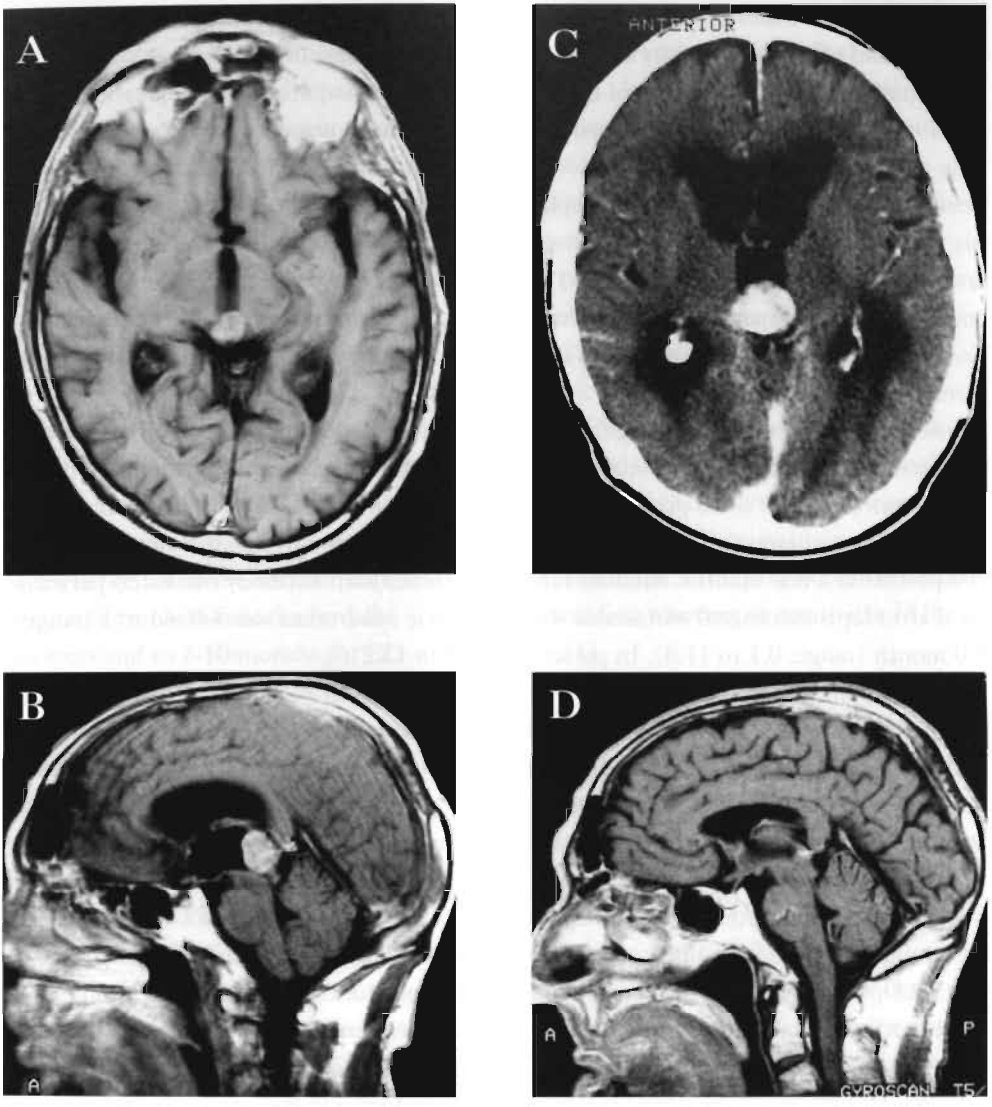

Figure 3. Staging MR scan with solitary metastasis in pineal gland (A). The volume of the metastasis remained unchanged for 13 months with chemotherapy alone (B). Secondary tumor growth and the hydrocephalus (C) were treated with vertriculair drainage and cranial irridation, which yielded complete radiologic and neurologic remission (D) for the remaining 6 months of the patient's life.

The volume of a solitary metastasis in the pineal gland of a neurologically asymptomatic patient with a CNS-limited disease remained the same for 13 months using only chemotherapy, see figure 3.
Secondary tumor growth and hydrocephalus were treated with ventricular drainage and cranial irradiation, which obtained complete radiologic and neurologic remission till death, 6 months later due to systemic relapse.
Clinical diagnosis of leptomeningeal metastases was confirmed by liquor cytology or autopsy in 13 of 22 patients. In most patients, therapy provided relief of symptoms for a few months. Median survival after leptomeningeal metastasis was 1.0 month (range, 0.1 to 11.8). In patients with back pain or signs of a spinal cord lesion, ancillary diagnostic tests for spinal metastases were carried out. The 14 patients with epidural metastases lived a median of 1.6 months (range, 0.2 to 14.7). Two patients with back pain only, lived 0.4 and 2.3 months afterwards. Spinal cord metastasis was found in 3 patients by MRI. All patients with spinal cord metastases suffered from back pain at diagnosis.

The most frequent paraneoplastic syndromes was SIADH (syndrome of inappropriate secretion of antidiuretic hormone), diagnosed in 11 patients (6.3%) who presented with a hyponatremia induced encephalopathy, at the time of diagnosis of SCLC or early during the course of the disease. In most patients SIADH subsided with chemotherapy of SCLC. Median survival of patients with SIADH was 6.8 months (range 0.1 to 13.6).
Antibody mediated paraneoplastic neurologic syndromes, were diagnosed in 5 patients (1.7%) only. Lambert-Eaton myasthenic syndrome was diagnosed in one patient 6.7 months before diagnosis of SCLC was made. The clinical manifestations of limbic encephalitis existed in one patient 3.5 months prior to diagnosis of SCLC. The course of the antibody mediated paraneoplastic syndromes was not influenced by the treatment of SCLC, and either remained stable or progressed slowly. Median survival of patients with antibody mediated paraneoplastic syndromes was 4.0 months (range 0.7 to 13.2).

Adverse effects of treatment were noticed in 23 patients (13%); peripheral neuropathy due to chemotherapy was reversible, whereas the other treatment-related complications were not. The number of sensory neuropathies was probably underestimated in the total number of polyneuropathies; during chemotherapy many patients complained of temporary numbness or tingling sensations over the distal parts of their extremities, mostly without further clinical evidence of a polyneuropathy or electromyographic abnormalities. Possible treatment-related encephalopathies were diagnosed in 8 of the 18 long-term survivors (7 with and 1 without PCI). Symptoms and signs had an insidious onset within 6 months following the termination of PCI, and comprised memory disturbances in 4 patients,

memory disturbances with temporary lethargy in 2 patients, and progressive memory disturbances with apathy in 2 patients. Except for the latter 2 patients, symptoms remained stable. Steroid myopathy was diagnosed in two patients with brain metastases and a protracted course of disease.

Discussion

The natural course of SCLC, known of as rapidly progressive and almost always fatal, has been protracted by the use of chemotherapy with or without the use of radiotherapy. The median survival has improved to 13-16 months for LD patients and to 7-10 months for ED patients [22,23]. A minority of patients with SCLC is cured, 10% of all patients, and 20% of patients with favourable prognostic factors [24]. With lengthened survival some clinical manifestations of SCLC have become more apparent and so has the risk of CNS spread. Approximately 10% (had brain metastases at diagnosis of SCLC [6,25], a further 20% developed brain metastases during therapy [6,25], and about 50% had brain metastases at autopsy [6,8,25]. At 2 years from diagnosis, the cumulative risk at brain metastases reached 50-80% for patients not treated with PCI and in CR [6-8], and nearly 100% for patients who did not achieve CR regardless of treatment with PCI [26].

In the present study, frequencies of brain metastases at diagnosis, during treatment, and at 2 years from diagnosis were in accordance with the data of other studes [6,8,25]. Autopsy rate was relatively low, revealing a different histology of brain metastases in 13% of patients. Explanations for the differences in histology may be found in alterations of cell morphology with therapy or time, and development of a second primary tumor [27-29]. Studies investigating the prognostic implications of histologic subtyping of SCLC were inconclusive as yet [30]. A relationship between histologic subtyping of SCLC and brain metastases was not found either, but hope existed that histologic subtyping could be useful in deciding whether or not to use PCI [30,31].

The prognosis of patients with initial presentation of brain metastases is not necessarily worse. If treated with cranial irradiation when brain metastases appeared, Hazel et al [32] found no differences in survival between LD patients and patients with the CNS as sole metastatic site. Because of the high frequency of intracranial metastases with the use of chemotherapy, it was assumed that the CNS was a relative chemotherapy sanctuary enclosed by the blood brain barrier. Reports of radiologically proven responses of cerebral metastases to systemic chemotherapy [33] encouraged several investigators to undertake trials with systemic chemotherapy for brain metastases [34].

Kristensen et al [35] compiled from data in the literature a cumulative response

rate of 75% and complete response rate of 44% for therapeutic cranial irradiation, and a cumulative cumulative response rate of 43% and complete response rate of 13% for delayed brain metastases. As the response of initial brain metastases to chemotherapy was almost as good as to cranial irradiation, it seems logical to wait for the effect of first line chemotherapy. In patients with delayed brain metastases who probably developed resistance to cytotoxic drugs and therefor have a shortened life expectancy, brain metastases should be treated with irradiation. Irradiation attains a slightly better response rate and is less toxic than chemotherapy [35].

In the present study, survival of patients with CNS-limited disease was poor because 8 of 12 patients (66%) died early from complications. Treatment of initial brain metastases generated a significantly better response than treatment of delayed brain metastases, in terms of survival. The better response could be caused by a greater sensitivity of the tumor or the more intense treatment given, during the initial stage of the disease. Only one patient was treated for brain metastases with chemotherapy alone; in this case, a solitary brain metastasis in the pineal gland remained clinically silent for a considerable time. When the pineal gland metastasis finally became symptomatic, radiotherapy yielded CR till death, neurologically and radiologically. Though the pineal gland is not a good example with its strong vascularisation and its relatively untight blood brain barrier, this case raises the question whether initial treatment of brain metastases with chemotherapy should be followed by consolidation radiotherapy. Whether or not chemotherapy treated patients with initial brain metastases should receive consolidation cranial irradiation remains to be seen [35].

In contrast to symptomatic treatment of brain metastases, PCI may contribute in curing patients. Rosenstein et al [36] found PCI effective in increasing survival of LD patients with durable thoracic control. The use of PCI is still under discussion; in randomised studies it reduced the frequency of brain metastases from 25 to 5%, but did not benefit survival and was associated with an increased risk of CNS toxicity [37]. In the present study, we found possible treatment-related impairment in 6 (33%) and disability in 2 (11%) of the 18 long-term survivors. Of the 8 patients with possible treatment-related brain injury 7 had received PCI. However, in individual patients it remains very difficult to identify retrospectively causal factors for the rather aspecific features of possible treatment-related brain injury. The most common anatomic abnormalities shown by CT scan or MRI following PCI treatment are white matter lesions and general brain atrophy. These abnormalities are linked to a wide range of clinical manifestations, and are indistinguishable from normal ageing processes as leucoaraiosis, by imaging techniques [38].

Paraneoplastic syndromes can be divided in hormone mediated and antibody mediated. Up to 54% of patients may have elevated hormone levels [39]. However, in the literature, the clinical frequency of a hormone mediated paraneoplastic syndromes as SIADH, varies from 9.5% to 12% [10]. In the present study, the frequency was lower as we were focused on neurologic abnormalities and not all patients with SIADH have a neurologic presentation. Antibody mediated neurologic paraneoplastic syndromes have a frequency of approximately 3% [40], coinciding with our results percentage wise. Therapy of SCLC was effective for the hormone mediated, but not for the antibody mediated paraneoplastic syndromes.

The longitudinal nature of the present study yielded a high frequency of neurologic disorders in SCLC patients, more so than in previous retrospective reports [5-21]. Brain metastases were the most common complication. The different concepts regarding the treatment of brain metastases need further investigation.

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3 The role of histopathologic subtyping in predicting neurologic complications in small cell lung cancer

Introduction

Many early studies have focused on the clinical implications of histologic subtyping of small cell lung cancer (SCLC) [1-11]. A few studies reported differences in metastatic CNS patterns for particular SCLC subtypes [1-3] and one of the authors [1] suggested that histologic subtyping could be useful in deciding whether or not to use prophylactic cranial irradiation (PCI). In SCLC cell lines, the classic small and variant subtypes show obvious differences in morphology, expression of neuroendocrine markers and oncogenes, and resistance to chemotherapy and radiotherapy [12-14]. However, initial studies investigating histologic subtyping of SCLC revealed conflicting data with respect to prognosis [1-8]. This was attributed to a lack of reproducible criteria, which is why the pathology panel of the International Association for the Study of Lung Cancer (IASLC) developed a new subclassification [15,16]. This classification system was correlated to cell culture work and recognizes three subtypes: small, mixed, and combined [15,16] and offers the best interobserver reproducibility thus far [9,10,16].

Relationships between this classification system and neurologic complications have hardly been investigated [11]. In an earlier analysis [11] our patient population was divided a priori into subgroups and half as large. The purpose of the present study was to reevaluate the prognostic relevance of the IASLC classification system with regard to propensity for neurologic complications, including CNS metastases. Therefore, the present retrospective study histologic subtyping of SCLC was related to the findings of prospective neurologic follow up.

Patients and methods

This study comprised 239 consecutive patients with a tissue diagnosis of SCLC, registered at the Department of Pulmonary Diseases of the University Hospital Maastricht from October 1980 to January 1992. Initial evaluation by the pulmonologist included physical examination, standard blood and chemistry profile, chest x-ray, bone scan, bone marrow aspirate and biopsy, ultrasound of the upper abdomen, and a CT -scan of the chest and brain. MRI (Magnetic Resonance Imaging) of the pelvis, spine, and brain was performed after 1990. Limited disease (LD) was defined as tumor confined to the ipsilateral hemithorax, the mediastinum, and the ipsilateral or contralateral scalene and supraclavicular lymph nodes. In extensive disease (ED) the tumor was found beyond these sites. Patients were initially treated with chemotherapy, consisting of cyclophosphamide 1000 mg/m2, doxorubicin 45 or 50 mg/m2, and etoposide 100 mg/m2 on days 1, 2, and 3 for at least five cycles. Radiotherapy to the primary tumor was applied to all patients until 1982, thereafter only if local tumor response was partial. Standard criteria of the World Health Organization were used in the definition

of responses. Patients who went into CR were non-randomly treated with PCI, at a total dose of 30 Gray for the entire cranial content in 10 fractions of 3 Gray over 2 to 3 weeks. PCI was not used after 1990. All patients were seen by a neurologist when diagnosed with SCLC and at quarterly intervals during the first year, biannually thereafter. Neurologic complications were documented using appropriate tests.

Pathology

One of the authors, unaware of the clinical outcome, reexamined the pretreatment histologic or cytologic specimens on which the original diagnosis was based. All cytologic specimens were Giesma stained. The SCLC subtyping of the histologic as well as the cytologic specimens was done according to the morphologic criteria proposed by the pathology panel of the IASLC [16]. In brief, "small cell carcinoma" is characterized by oval, round, or fusiform nuclei with diffusely distributed chromatin and small nucleoli, nuclear molding, and indistinct cell borders. The "mixed small cell carcinoma" is a small cell carcinoma that contains cells resembling those of large cell lung carcinomas with a prominent eosinophilic nucleolus with a paranucleolar halo. The "combined small cell carcinoma" is SCLC combined with a more or less prominent component of squamous or adenocarcinoma.

Statistical analysis

The following statistical procedures were used to analyze the data: chi-square tests for comparison of patient subgroups; logistic regression to investigate the prognostic significance of age, sex, histologic subtypes and disease stage with respect to developing brain metastases. The Cox proportional hazards model was used to investigate the prognostic value of the same factors with respect to brain metastatic free survival. Survival curves were estimated by the Kaplan-Meier method, differences tested by the log-rank test.

Results

Slides from 7 of the 239 patients slides were not retrievable, while only autopsy material was available for another 14 patients. In 8 cases the initial diagnosis of SCLC was changed to atypical carcinoid (n=2), Merckel cell tumor (n=1), squamous cell carcinoma (n=2), adenocarcinoma (n=2) or undifferentiated large cell carcinoma (n=1). These patients were not evaluated in the statistical analysis. Thus, 210 patients remained for morphologic subtyping. 187 patients (85%) were classified as having "small cell carcinoma" and 31 patients (15%) as having "mixed cell carcinoma". For the small cell type the diagnosis was based on 139 histologic slides and 39 cytologic slides. For the mixed cell type the basis was 26 histologic and 5 cytologic slides. Only one patient was classified as having "combined small cell carcinoma". In the further statistical analysis mixed and combined subtypes were grouped.

		Histologic subtype		
		small	mixed	no subtype
Age	median (range)	64 (41-83)	67 (48-83)	69 (49-81)
Gender	n (% subtype)			
	male	149 (84)	29 (91)	21 (100)
	female	29(16)	3 (9)	0 (0)
Disease stage n (% subtype)				
	LD	69 (39)	12 (38)	8 (38)
	ED	109 (61)	20 (62)	13 (62)

Table 1. Clinical data of 231 SCLC patients classifed by a histologic subtype; small (n=178), mixed (mixed small cell/large cell n=31 and combined n=1), and no subtype (no slides available n=7 and only autopsy material n=14); ED=extensive disease.

The clinical characteristics of the 231 patients with SCLC are shown in *table 1*. The frequencies of some of these characteristics fluctuated during the 11 years of follow up. Age, divided into subgroups (younger than 58, 58-65, 65-73, older than 73), changed with time; until 1982 there was a relatively high proportion of patients younger than 58; afterwards the number of patients younger than 58 and older than 73 decreased and the number of patients aged 58-73 increased. The percentage of female patients increased over these 11 years, from 0 to 15. The proportion of small versus mixed subtype (85/15), and LD versus ED (40/60) remained the same over the years. The response to therapy did not vary over these 11 years; about 20-30% of the patients went into CR. In time, PCI was increasingly reduced; it was used in 60% of the patients until 1982, in 15% between 1983 and 1990, and in none thereafter.

The neurologic complications evaluated at the time of diagnosis and during further follow up are listed in *table 2*. Metastatic complications predominated. Paraneoplastic complications with a neurologic presentation included pure neurologic paraneoplastic syndromes and neurologic syndromes caused by ectopic hormone production. In fact the number of paraneoplastic syndromes in the whole population was larger, but these patients had no neurologic symptoms and were therefore outside the scope of this study. The number of sensory neuropathies was probably underestimated in the total number of polyneuropathies; during chemotherapy many patients complained of temporary numbness or tingling sensations over the distal parts of their extremities,

Neulogic complications:	n (%total)
•total	144 (100)
Metastatic complications:	
•CNS total	91 (64)
•brain	61 (42)
•leptomeningial	18 (13)
•epidural	12 (8)
Paraneoplastic complications:	
•total	11 (7)
•SIADH	6 (14)
•Lambert eaton	1(.7)
•cerebellar degeneration	1 (.7)
•myelitis transversa	1 (.7)
•limbic encephalitis	2 (1.4)
Other complications:	
•total	41 (29)
•polyneuropathy	23 (29)
•encephalopathy	13 (9)
•cerebrovascular disease	4 (3)
•myopathy	1(.7)

Table 2. Number (n) and percentage of total (% total) of neurologic complications diagnosed in 210 small cell lung cancer patents; CNS=central nervous system; SIADH=syndrome of inappropiate ADH secretion.

mostly without further clinical evidence of a polyneuropathy or electromyographical abnormalities. Apart from 2 metabolic encephalopathies in relatively old and severely ill patients, 11 possibly PCI induced encephalopathies were diagnosed. The possibly PCI induced encephalopathies had an insidious onset within 6 months after termination of PCI. These involved memory disturbances (n=9), visual symptoms (n=1), ataxia (n=2), and dementia syndromes (n=2) and were irreversible, though not progressive for most of the patients. Myopathy, diagnosed in one patient, was induced by corticosteroid medication.

	Histologic subtype		
	Small cell	Mixed cell	p value
Complications:	n(% subtype)	n(% subtype)	n(% subtype)
•total CNS metastases	78 (44)	13 (41)	0.96
•brain metastases	52 (29)	9 (28)	0.90
•leptomeningeal metastases	17 (10)	1 (3)	0.19
•epidural metastases	9 (5)	3 (9)	0.33
•paraneoplastic syndromes	11 (6)	0 (0)	0.15
Time periods (range)		median (range)	median
•brain metastatic-free survival	532 (0-3748)	670 (0-891)	0.75
•overall survival	266 (1-3748)	208 (6-891)	-
•overall survival for patients with paraneoplastic syndrome	254 (8-745)	-	-

Table 3. Occurence of metastatic and parneoplastic complications, and survival data according to histologic subtype.

Clinical outcome according to histologic subtype is presented in *table 3*, brain metastatic free survival curves in *figure 1*. Statistical analysis yielded no significant differences in metastatic CNS patterns (chi-square tests). The percentage of brain metastases was similar for both histologic subtypes (about 30%). Brain metastases were diagnosed in 13 (26%) patients with LD and 49 (38%) with ED. Upon diagnosis of lung cancer, brain metastases were present in 9 patients with small cell type (5%) and 3 patients with mixed cell type (9%).

Prognostic relevance for developing brain metastases was investigated with regard to age, gender, histologic subtype, and disease stage (logistic regression). Brain metastases (upon diagnosis of lung cancer or developed during further follow up) were less common in older patients ($p=0.05$) and those with LD ($p=0.03$). The occurrence of brain metastases was not associated with histologic subtype ($p=0.68$) or gender ($p=0.25$).

The brain metastatic free survival was calculated from the moment of diagnosis of lung cancer. Histologic subtype, age, and gender were not significantly associated with the brain metastatic free survival; only disease stage was (Cox proportional hazards model). As expected, LD had a better prognosis than ED ($p=0.0001$). Analysis of the Kaplan-Meier curves with the log-rank test yielded no differences for histologic subtype ($p=0.75$) or brain metastatic free survival. Paraneoplastic syndromes with a neurologic presentation

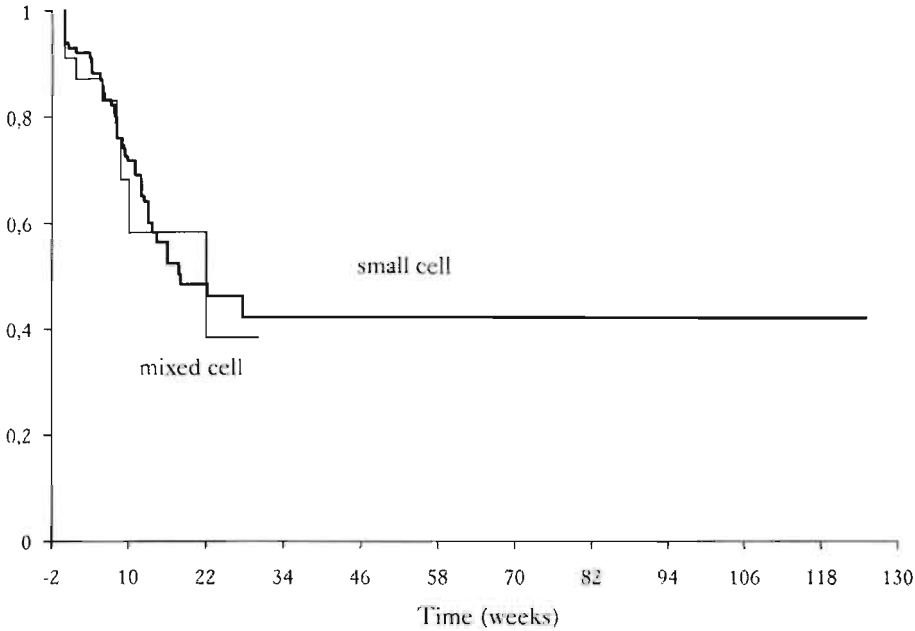

Figure 1. Kaplan-Meier curves of brain metastatic free survival for histologic subtypes.

were seen mostly in the small cell type, but this trend was not significant ($p=0.15$). The overall survival of patients with paraneoplastic syndromes was similar to that of other patients.

Discussion

Small cell carcinoma of the lung is a malignant neoplasm with a highly aggressive behavior, resulting in early metastasis [17-19]. The prognosis of patients with SCLC has been improved by combination chemotherapy [20]. The presence of brain metastases is the most frequent neurologic complication in SCLC and is associated with poor prognosis. With a longer survival time these metastases have become an increasingly important clinical problem [21-22]. The SCLC is delineated from other entities in the neuroendocrine spectrum of pulmonary neoplasms. At the other end of the spectrum, with a low malignant potential, is carcinoid. In the grey area between SCLC and carcinoid, several proposals for nomenclature have been made [23-26]. The most simple subdivision would be (1) carcinoid, for the classic cases, (2) neuroendocrine carcinoma instead of atypical carcinoid, in view of its more malignant nature, and (3) SCLC. As yet this subdivision is not implemented in the last WHO classification [26]. Since our purpose was to investigate the clinical usefulness of the subclassification of SCLC proposed in the consensus report by the Pathology Committee of the IASLC, we

restricted this study to SCLC and excluded the other entities of the neuroendocrine spectrum. The IASLC recommendations were intended to provide a reproducible histopathologic subclassification of SCLC [16]. Since the introduction of this classification, much research has been done in evaluating the clinical behavior and response to therapy of SCLC and its subtypes. The interobserver agreement with regard to the diagnosis of the histologic subtypes was reasonable well in the study of Fraire et al. [10].

The frequencies with which the different subtypes were diagnosed in this study is slightly larger than those reported by Bepler et al. [8], Aisner et al. [9], and Fraire et al. [10]. This may be due to possible differences in sampling and biopsy size. Their studies suggested that the mixed cell type is as rare as the combined cell type and has a frequency of less than 5%. The total number of mixed and combined cell types is not at variance with these studies. Tumor heterogeneity has been proposed to be common and to be more frequent in larger biopsy specimens and posttherapy or obduction tissues [2,27,28]. According to Yesner et al. [28], the mixed cell type is found more frequently in larger and less damaged biopsy specimens. In cases of tumor heterogeneity the use of small biopsies and cytologic specimens in this study may have led to differences in subtyping.

The results of this study do not show any statistically significant relationship between histologic subtyping and metastatic CNS pattern, developing brain metastases, or brain metastatic free survival. The number of neurologic paraneoplastic syndromes was similar to the 3% reported by Elrington et al. [29]. Because SCLC is delineated from other entities in the neuroendocrine spectrum of pulmonary neoplasms and the classic small cell lines are characterized by higher expression of neuroendocrine markers than the variant cell lines [12,14], the assumption arises that the classic small cell subtype more frequently predisposes to paraneoplastic complications than mixed and combined subtypes. A slight trend in line with this hypothesis was found in this study. Only the classic small cell subtype was encountered in patients with neurologic complications due to paraneoplastic syndromes. This tends to support the experimental research on SCLC. Other neurologic non-metastatic complications were not thought to be associated with histologic subtyping, but more likely to be treatment related or coincidental. Our neurologic data lack clinical significance with regard to histologic subtyping. This result supports the outcome of an earlier analysis of our patient population [11]. We conclude that histologic subtyping of SCLC has no implications for CNS metastases. However, the relationship with paraneoplastic syndromes deserves further study.

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4 Diagnostic value of CT in the detection of brain metastases in small cell lung cancer patients

Introduction

Small lung cell carcinoma (SCLC) constitutes 20% of all cases of lung cancer (1), and central nervous system (CNS) metastases are an important cause of morbidity and mortality among these patients (2). A simple two-stage division is customarily employed in SCLC. Limited disease (LD) is confined to the hemithorax of origin, the mediastinum and the supraclavicular nodes. In extensive disease (ED) tumor is found beyond these sites. Staging procedures to detect possible sites of distant metastases are important, because of different forms of treatment are given to patients with limited and extensive disease (3).

Current clinical methods of diagnosis of brain metastases include physical examination and cranial computed tomography (CT). Brain metastases are found in approximately 10% of newly diagnosed patients (4). Most of these patients are symptomatic, and indication for specific diagnostic methods is determined by the symptoms and signs (5,6).

CT carried out as a part of routine initial staging procedure in SCLC patients is not unanimously considered necessary, particularly when patients do not show neurological symptoms. Therefore, this study was undertaken to determine the value of a routine cerebral imaging in SCLC patients in comparison to neurological findings.

Patients and methods

Between January 1985 and April 1990, 57 patients with SCLC were treated with chemotherapy according to a prospective protocol (7). The diagnosis of SCLC was based on histological and cytological biopsy. The subjects, 47 (89%) males and 10 (11%) females, ranged in age from 45-80 (mean age 65). All patients underwent a neurological examination, a bedside mental status examination, a CT scan of the brain with and without contrast administration, and a bone scan. In the group of 57 patients 26 patients had LD, while 31 had ED. Three (5%) of the 57 patients were excluded from this study; two of them had previous cerebrovascular infarcts on CT and one had leptomeningeal metastases at the time of presentation. From January 1985 until February 1989, CT was performed with a Philips Tomoscan 350, and from February 1989 until April 1990 with a Siemens Somaton Plus scanner.

Technical data of the Philips machine were; 120 kV, scan time 4.8 sec, 180 mAs, slice thickness 9 mm and matrix 512x512. The images were recorded with a Philips multiformat camera. Technical data of the Siemens scanner were: 120 kV, scantime 2 sec, 420 mAs, slice thickness 10 mm and matrix 512x512. Imaging was performed with a 3M laser printer. All scans were at first performed without contrast, and repeated after intravenous contrast injection. 100 ml of Telebrix 350 mgI/ml was used mostly, while in cases with a history of allergy 100 ml of Hexabrix 320

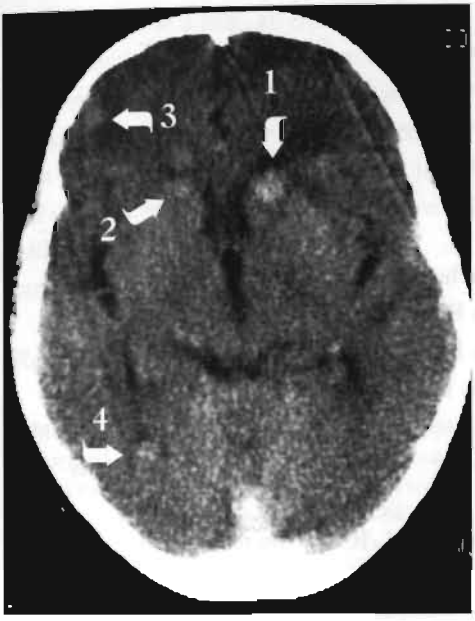

Figure 1. CT of the brain (third patient in table 1). Shows an enhancing lesion in the head of the left caudate nucleus (arrow 1), smaller lesions faintley visualized arround right frontal horn (arrow 2), right frontal lateral cortex and at the tip of the right occipital horn (arrow 3 and 4).

mgl/ml was injected. The window settings in which all scans were printed were: window width 100 Hounsfield Units (HU) and Center 40 HU. The CT findings were interpreted by a radiologist who had experience in cerebral CT scanning. Afterwards the CT scans were independently reviewed by neuroradiologist and a neurologist, and no discrepancies were found.

Results

Neurological symptoms and signs indicating metastasis were found in 4 patients out of 54 (7%), *see fig. 1*. Three of these patients met the CT criteria for cerebral metastasis, and the abnormalities found in the neurological examination were anatomically consistent with the abnormalities on the CT scan, see *table 1*.

Bone scans revealed no abnormalities of the skull. One patient with neurological symptoms and signs showed no evidence of brain metastasis on CT. However, six months later, this patient's CT scan indicated brain metastasis. In the remaining group of 50 neurologically asymptomatic SCLC patients no sign of cerebral metastasis was seen on CT.

Discussion

The value of routine cerebral cerebral scanning in SCLC patients is controversial. The literature presents conflicting data on the question whether patients without neurological symptoms should undergo CT of the brain. Levitan et al. (8) found that in 3 out of 44 (7%) SCLC patients with LD tumor, the stage was altered by the use of CT as a routine procedure. Crutz et al. (9) recommended routine CT scanning as part of the initial staging of patients with SCLC. He found that 6 neurologically asymptomatic patients out of 99 (6%) patients with LD had been upstaged to ED. Butler et al. and Johnson et al. studied neurologically

Patient nr, gender, age	Classification	Clinical presentation	Cranial CT
1. Male 75	ED	• headache • vertigo	single metastasis
2. Male 52	ED	• headache • vision R eye ⬇ • ptosis R eye • paresis R leg	multiple metastasis
3. Female 69	ED	• headache	multiple metastasis
4. Male, 59	ED	• papilledema L/R • vision L/R ⬇	no metastasis

Table 1. Symptomatic patiens with SCLC and frequences of brain metastasis; ED: extensive disease; L=left; R=right; SCLC= small cell lung cancer; CT=computer tomography.

intact SCLC patients and found brain metastases in three out of 55 (5.5%) and two out of 84 (2%), respectively. Both authors conclude that routine cerebral imaging is advisable in these patients.

Because of the low incidence of CNS metastases at the time of diagnosis in asymptomatic SCLC patients, we doubted the benefit of routine cranial CT. In our study 4 (7%) of the 54 SCLC patients showed evidence of neurological symptoms and signs, which was confirmed in 3 patients with CT. In one symptomatic patient no brain metastasis was found on the CT scan at the time of presentation. However, six months later CT indicated brain metastasis. We believe that CT was not sensitive enough in this patient to detect the initial small lesions. In such cases we would suggest MRI which is superior in detecting subtle lesions (10,11).

Although plain MRI carries the risk of false positive interpretation of non-neoplastic age-related parenchymal lesions in the elderly (10,11), contrast enhanced MRI using gadolinium DTPA can differentiate between areas of altered signal intensity due to widening of the perivascular spaces and areas containing metastases (12). It appears likely that contrast enhanced MRI will become the method of choice for detection of cerebral metastasis.

In our study, as a rule, all SCLC patients were examined by a neurologist, and no brain metastases were discovered in neurologically normal patients. We conclude that CT scanning of the brain at the initial stage of SCLC does not contribute additional diagnostic information to a careful neurological examination.

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5 Diagnostic value of MR imaging in the detection of brain metastases at initial staging in small cell lung cancer

Introduction

Small cell lung carcinoma (SCLC), which accounts for approximately 25 per cent of the cases of lung cancer, has a highly aggressive behavior, resulting in early metastasis [1]. The prognosis of patients with SCLC has improved with chemotherapy [2]. The occurrence of brain metastases is the most frequent neurological complication in SCLC, and is associated with a poor prognosis [3,4].

Prior to the advent of magnetic resonance (MR) imaging, neurological examination and cranial computed tomography (CT) were used as screening procedures for brain metastases [5-8]. More recently, the use of a contrast agent such as gadolinium DTPA has extended the role of MR imaging in the evaluation of brain metastasis and making MR imaging superior in sensitivity and specificity to the CT-scan for the detection of brain metastasis [9,10].

The value of MR imaging of the brain as a screening procedure in patients with SCLC has not been adequately studied. To assess the value of routine MR imaging in the staging work-up of patients with small cell lung cancer, we studied the correlation of MR findings with the neurological examination in 40 patients with small cell lung cancer.

Patients and methods

Subjects

Between May 1991 and March 1994, 40 patients with newly diagnosed SCLC were included in the study. The diagnosis of SCLC was based on histological or cytological biopsy. To detect areas of distant metastases, ultrasound and CT of the abdomen, radionuclide bone scan, MR bone scan and bone marrow aspirates were routinely performed. Limited disease (LD) was defined as tumor confined to one hemithorax with or without ipsilateral mediastinal or supraclavicular lymph node involvement. Patients with extrathoracic tumor spread beyond these sites were classified as having extensive disease (ED).

Treatment and clinical assessment

In the course of evaluation, all patients were routinely referred to the department of neurology for an assessment of possible neurological metastases. All patients underwent a neurological examination. Patients were prospectively evaluated by a neurologist every three months for the first year, and biannually thereafter. Follow-up cranial MR scans were performed on indication only. The patients were followed until death or for at least three months.

MR imaging

MR imaging of the brain was performed within one month (in 85% of the patients

within two weeks) after the pathological confirmation of SCLC. MR imaging was performed with a 0.5T system (Philips Gyroscan II). First a set of transverse T2-weighted images was obtained. In the first 38 examinations a conventional spin-echo sequence (TR 3-3.5 seconds, TE 120 msec FOV 230 mm, 5 mm slices 205x256 matrix, NSA1) was used. All later examinations featured a fast spin-echo sequence (TR 4.5-6.5 sec, TE 130 msec, FOV 230 mm, 241x256 matrix, NSA4, echo train length 16). T1-weighted spin-echo images were obtained (TR 600 msec, TE 18 msec FOV 230 mm, 10 mm slices 205x256 matrix, NSA4) before and after IV injection of the MR contrast medium gadolinium DTPA (MagnevistR) in a dosage of 0.1 mmol/kg.

MR findings were classified into four groups according to Elster [11] :1) normal scans; 2) scans with unequivocally benign lesions (infarctions, arachnoid cysts etc.) that harboured no suspicion of metastatic disease; 3) scans with at least one enhancing lesion compatible with a metastasis; and 4) scans with one or more hyperintensities of the deep and subcortical white matter and periventricular hyperintensities, none of which enhanced after contrast injection.
The MR findings were interpreted by a neuroradiologist (JTW) with extensive experience in cerebral MR and were later blindly reviewed by the same neuroradiologist together with a neurologist (AT) No discrepancies were found between the first and second assessments.

Results

Forty patients had both a neurological examination and an MR examination . Motion artefacts occurring in one agitated patient led to premature termination of the MR examination. This patient was excluded from the study population. Of the remaining 39 patients, 15 patients were staged by the pulmonologist as having limited disease, while 24 patients were staged as having extensive disease. The patients, 30 males and 9 females, ranged in age from 31-78 years (median age 62).

The MR findings are summarized in *table 1.* Of the 12 patients (31%) with normal MR examination (group 1), one patient with a history of chronic headache and transient ischemic attacks had recently developed difficulties with concentration. Clinical follow-up revealed no signs of brain metastases.

At the time of the MR imaging study, two patients (5%) with previously documented cerebrovascular diseases from group 2(benign lesions) had non-enhancing white matter lesions, which where confidently interpreted as non-metastatic.

Eleven patients (28%) had MR results which were interpreted as positive for tumor metastases (group 3). The neurologic deficits detected by neurologic examination were anatomically consistent with the MR findings. Three ED patients had asymptomatic brain metastases.

MRI		neurological examination	brain metastases
		abnormal / normal	within 6 months
group 1	12	1 / 11	0
group 2	2	2 / 0	0
group 3	11	8 / 3	11
group 4	14	4 / 10	2

Table 1. Magnetic resonance imaging and clinical findings in 39 patients with small cell lung cancer.Magnetic resonance imaging (MRI) findings were classified into four groups: group 1 = normal; group 2 = benign lesions (two patients with cerebral infarctions); group 3 = metastasases (three patients were asymptomatic); group 4 = non-enhancing white matter lesions (two of the four symptomatic patients developed brain metastases within six months, one patient after ten months).

Of the 8 neurologically symptomatic patients, 3 had no other signs of extrathoracic tumor activity and were initially classified by the pulmonologist as having limited disease. The classification was later changed to extensive disease on the basis of neurological consultation and MR findings.

Four of 14 patients (36%) from group 4 (non-enhancing white matter lesions) had neurologic symptoms and signs but showed no MR evidence of brain metastases. One patient with a brief history of frontal headache and atypical brachialgy at initial neurologic examination, did not develop brain metastases and turned out to have tension headache and a carpal tunnel syndrome. However, 3 of the 4 symptomatic patients were found to have developed brain metastases by follow-up MR imaging. The MR scan of the first patient demonstrated enhancing brain metastases two months later, with a rapidly progressive decline. The second patient, with left sided facial weakness and hyperreflexia of the left arm, developed an unstable gait and became progressively confused three months later. Then months after initial staging, the third patient, with a brief history of atypical pain, developed signs of raised intracranial pressure and cerebellar ataxia. As shown in *figure 1*, some of the initially non-enhancing white matter hyperintensities increased in volume and showed contrast-enhancement at follow-up examination.

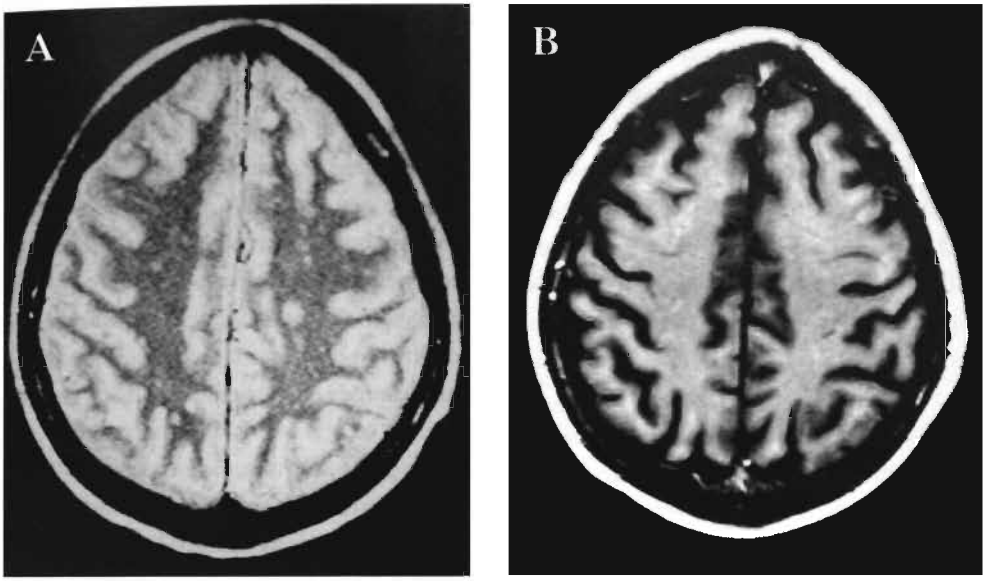
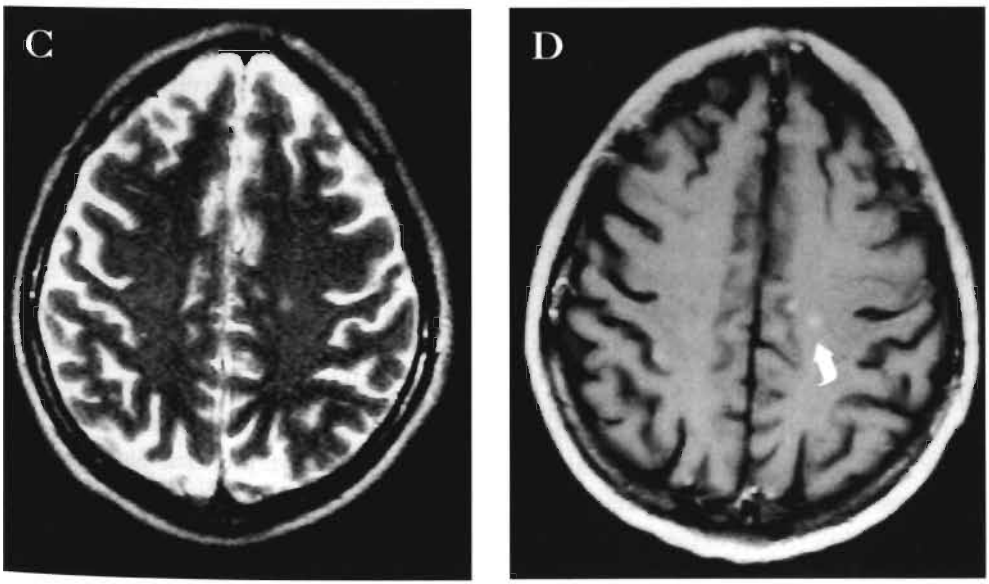


Figure 1. Magnetic resonance imaging of the brain in a 51-year old patient with neurological abnormalities at initial staging.

Figures A and B were obtained before treatment, figures C and D after neurological deterioration three months later; A T2-weighted image shows deep white matter hyperintensities; B T1-weighted image after Gd-DTPA injection do not show enhancement; C T2-weighted image once again shows deep white matter hyperintensities; D T1-weighted image after Gd-DTPA injection shows obvious contrast-enhancement.



Discussion

The major goals of staging patients with SCLC are to provide prognostic information and to select the best treatment. The value of routine cerebral imaging in SCLC patients is controversial, because CT has failed to detect some metastases, especially those which are in the posterior fossa. The literature presents conflicting data on the question whether patients without neurological symptoms and signs should undergo CT of the brain [6,7]. We have found that CT is not sensitive enough in asymptomatic patients and need therefore not be a part of the routine staging procedure in small cell lung cancer [8].

The advent of magnetic resonance imaging has had a profound effect on the evaluation of central nervous system (CNS) tumors; it offers marked advantages over CT and provides superior definition of a CNS tumor, particularly if a paramagnetic contrast agent is used. Contrast CT and non-contrast MR imaging are roughly comparable in the detection of brain metastases. Post-contrast MR imaging, however, have an increased accuracy, compared with contrast-enhanced CT, particularly in the detection of metastases in the posterior fossa and cortex (9,12). The value of contrast-enhanced MR imaging of the brain at initial staging in patients with SCLC has not been studied in the past. In the present study, brain metastases were found in 11 patients of the 39 patients (28%), depicted as contrast-enhancing lesions on initial MR imaging. Prior CT studies have demonstrated a 5 to 27% incidence of brain metastases at diagnosis of SCLC [5-8]. Magnetic resonance imaging revealed brain metastases in three neurologically asymptomatic patients in our study. However, these discrepancies did not affect the clinical staging, as the patients concerned were already known to have extensive disease on base of other extrathoracic metastases.

In the present study, non-enhancing white matter lesions were seen in 14 patients. Four of these patients were neurologically symptomatic and in three of them, the initially non-enhancing white matter lesions later changed into contrast-enhancing lesions, compatible with brain metastases. It therefore appears that contrast-enhanced MR imaging may under report some early metastases, which are obscured from view by high-signal white matter lesions on T2-weighted images and do not yet show contrast-enhancement on T1-weighted images.
Early investigators observed that MR imaging brings to light a high frequency of white matter abnormalities that cannot be related to clinical findings and could not previously be detected (13-15).These appear as bright areas on both proton density and T2-weighted images. Their sizes range from small foci to large confluent lesions, and they vary in extent and location. White matter hyperintensities in neurologically asymptomatic patients vary in frequency from 11% in the fourth decade to 65% in the seventh decade [14].

Fazekas et al found that deep white matter hyperintensities reflect increasing severity of ischemic tissue damage, the most likely substrate of white matter hyperintensities in elderly patients [15].

Some investigators have assumed that lesions of the subcortical, deep and periventricular white matter on T2-weighted images were not brain metastases if they did not enhance with contrast agent used in combination with T1-weighted images (9,10). Elster et al found that white matter lesions in cancer patients which not enhance with Gadolinium-DTPA at the time of the initial MR study had a low probability of representing metastatic disease and suggested that in questionable cases, follow-up scans should help to differentiate them from metastases (11). Our findings, however, showed that initially non-enhancing white matter lesions can develop into brain metastases. The earliest MR manifestation of metastatic disease in the brain is not known. It is unclear whether this earliest manifestation of metastatic disease is contrast enhancement or a high signal T2 abnormality, reflecting increased tissue water content rather than contrast accumulation.

In conclusion, MR imaging is a sensitive tool in the detection of brain metastases at initial staging of SCLC-patients, since brain metastases were visualized in three neurologically asymptomatic patients. The combination of MR imaging and clinical findings is of value in preventing false-negative diagnosis. When cerebral metastases are suspected on clinical grounds and MR imaging shows only non-enhancing white matter lesions, the best course of action would be to perform neurological and neuroradiological follow-up.

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6 Efficacy and safety of prophylactic cranial irradiation in 203 consecutive patients with small cell lung carcinoma

Introduction

Brain metastasis is a well recognised complication in small cell lung cancer (SCLC). Approximately 0-16% of the patients have brain metastases at initial diagnosis, 0-32% subsequently develop brain metastases during treatment, and 28-64% have brain metastases in various post-mortem studies [1]. The risk of brain metastasis increases with lengthening survival, to a cumulative risk of 80% in patients at 2 years after diagnosis [2]. Though combination chemotherapy with or without locoregional radiotherapy has yielded complete or partial responses in 80-90% of all patients, median survival is limited to 11-16 months depending on the initial tumor stage [3]. Prophylactic cranial irradiation (PCI) is effective in reducing the central nervous system (CNS) relapse rate [4].

However to date, no randomized trial showed any PCI survival benefit [4]. And its use has become controversial as PCI potentially contributed to CNS-toxicity in SCLC patients [4-10, 16]. PCI failure with regard to survival is probably explained in that CNS relapse in the majority of the patients is associated with recurrence or progression of systemic disease. The CNS as sole site of relapse is only seen in 3-4% of the patients [11]. However, PCI administration becomes interesting again with the development of new treatment protocols with increased median survival time and increased 2 year survival rate [12-14].

In this study, we present the results of a neurologic follow-up of a cohort of 203 consecutive patients with SCLC. The efficacy of PCI is analysed for limited stage patients who achieved complete remission, whereas all patients given PCI are evaluated for possible adverse effects of PCI. Furthermore the neurologic condition of 18 patients who survived the diagnosis of SCLC for more than 2 years is described in detail.

Patients and Methods

From January 1983 to January 1993, 203 consecutive patients with histologically proven SCLC were included in this prospective study. Minimal follow up was 1 year or until death, till January 1994. Initial staging of these patients by a pulmonologist, was based on physical examination, standard blood and chemistry profile, chest x-ray, CT-scan of the chest, ultra-sound of the abdomen, radionuclide bone scan, fibre optic bronchoscopy, and bone marrow aspirate and biopsy. Limited disease (LD) was defined as tumor confined to the ipsilateral hemithorax, the mediastinum, and the ipsilateral and/or contralateral scalene and supraclavicular lymph nodes. In extensive disease (ED) tumor was found beyond these site.

Patients were seen by a neurologist at diagnosis and at quarterly intervals (biannually after a year). A CT-scan of the brain, MR imaging after 1991, was performed before treatment.

More frequent neurologic consultations and other auxiliary diagnostic tests were done if required. In patients with a long-term survival (defined as 2 years or longer from diagnosis) an additional CT- or MR-scan of the brain was performed. Central nervous system abnormalities found in patients treated with PCI, were designated as possibly treatment related unless otherwise clearly explainable.

All patients were initially treated with a combination chemotherapy regimen, consisting of cyclophosphamide 1000 mg/m2, doxorubricin 45 or 50 mg/m2, and etoposide 100 mg/m2 on day 1,3, and 5 for at least five cycles. Chemotherapy was sometimes followed by radiotherapy to the primary tumor site. Restaging was performed after five courses of chemotherapy and consisted of physical and radiological examinations, fibre optic bronchoscopy, and those examinations which were abnormal at the initial staging procedure; complete remission (CR) was defined as a total resolution of all detectable lesions.

Only patients who obtained CR were candidates for treatment with PCI. Till 1986 LD and ED patients could opt for PCI, after 1986 LD patients only. Patients were treated with a linear accelerator, usually 6 MV photons, using two lateral opposed fields. The dose was calculated in the midline, and delivered in daily fractions of 3 Gy, 4 times a week up to a total dose of 30 Gy. During 1988 - 1990 the radiation technique was changed as the fraction dose was lowered to 2 Gy, 5 fractions a week up to a total dose of 30 Gy. In 1990 PCI was excluded from the treatment protocol. Between 1983 and 1990, two eligible LD patients refused PCI. Patient characteristics and treatment specifications are listed in table 1.

The efficacy of PCI was analyzed for LD patients with CR only. Statistical significance of the incidence of brain metastasis was calculated with the Fisher's exact test, of the survival curves with the log rank test. Overall survival was calculated from SCLC diagnosis to death or end of observation period, brain metastatic free survival from SCLC diagnosis to the diagnosis of brain metastases or end of observation period. The safety of PCI was evaluated for all patients who achieved CR and were treated with PCI. The neurological condition of the long-term survivors (defined as 2 years or longer from diagnosis) is described in detail, in particular with regard to adverse reactions of PCI.

Patients	Disease stage	
	limited	extensive
total	74	129
men / women	59 / 15	111 / 18
median age at diagnosis (range)	64 (39-84)	65 (45-89)
complete remission	37	30
prophylactic cranial irradiation	17	5

Table 1. Patient characteristics.

Results

Efficacy of PCI

Efficacy of PCI was assessed in 37 LD patients who achieved CR. Brain metastases were diagnosed in 3 of 17 patients treated with PCI versus 8 of 20 patients not treated with PCI. The number of brain metastases did not differ significantly ($p=0.26$). The brain metastatic free survival curves are shown in *figure 1*, and the overall survival curves in *figure 2*. For the analysis of the survival curves leptomeningeal metastases were considered as brain metastases for statistical reasons; two of the 5 patients with brain metastasis after PCI actually had leptomeningeal metastases. Log rank analysis of survival curves revealed significant differences between patients with and without PCI. Patients treated with PCI had a longer brain metastatic free survival ($p=0.012$) as well as a longer overall survival ($p=0.004$) than patients not treated with PCI.
The majority of the patients (30 patients or 81%) had an intrathoracic SCLC recurrence, see *table 2*. Brain metastases were diagnosed after systemic recurrence of the disease in 7 patients. Systemic recurrence was established within 1 month after the diagnosis of brain metastases in 3 other patients. The brain as sole site of relapse was seen in 1 patient who was treated with PCI. New malignancies [1 non-SCLC and 1 Non Hodgkin Lymphoma] were diagnosed in 2 patients. Only 3 patients (8%) had no relapse. The exact cause of death remained unknown in 1 patient.

Safety of PCI

Safety of PCI was assessed in 17 LD and 5 ED patients treated with PCI between 1983 and 1990. Early neurologic sequelae were seen till three months after PCI; 7 of the 22 patients experienced headache and nausea during PCI, another 5 patients reported with a brief period of increased tiredness.

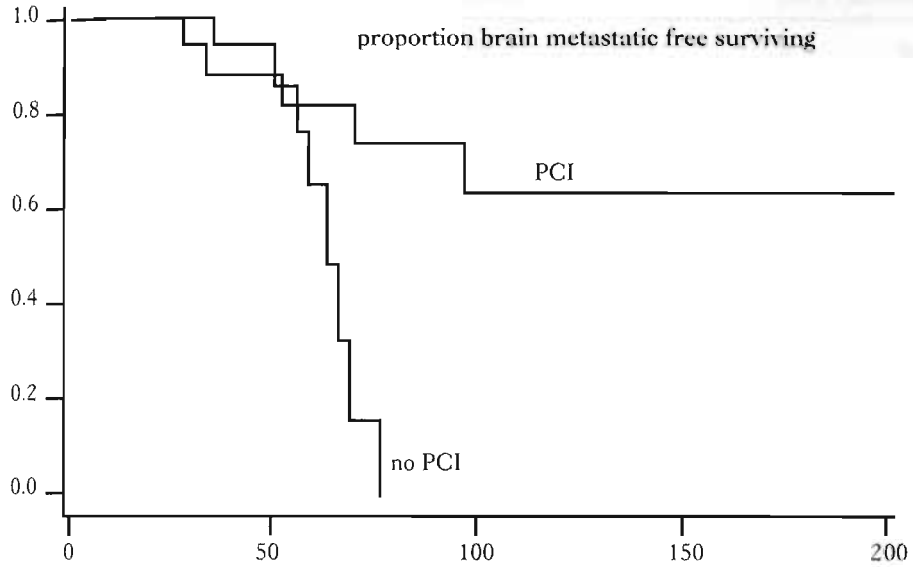

Figure 1. Brain metastatic free survival in weeks; 6 patiens in PCI group were still at risk past 200 weeks.

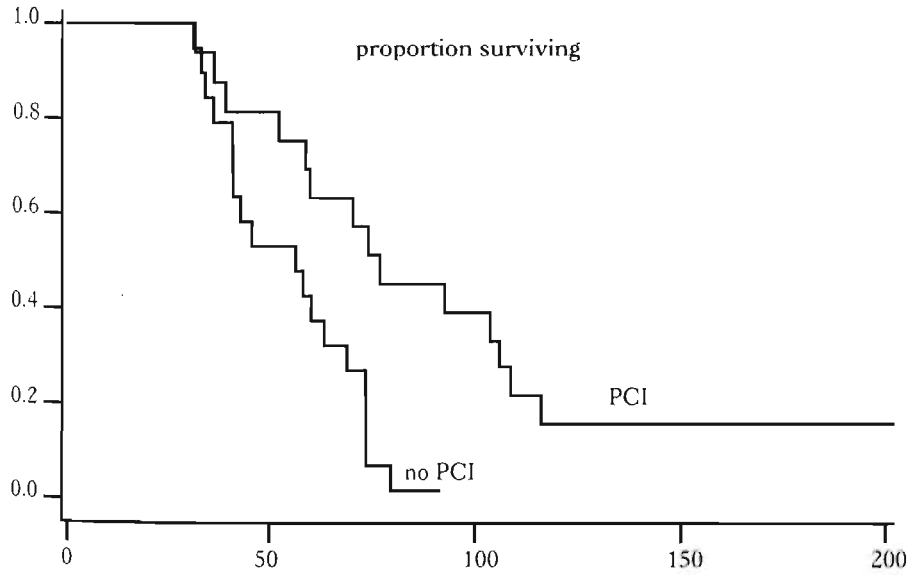

Figure 2. Overall survival in weeks; 1 patient in PCI group passed away at 417 weeks, 1 is still at risk.

Patients	PCI	no PCI
total	17	20
median age (range)	56 (42 - 78)	68 (48 - 84)
radiotherapy primary tumor	6	5
median survival (range)	18 (7 - 132)	13 (7 - 19)
Relapse		
lung	6	12
lung and CNS	4*	8
sole CNS	1	0
new malignity	2	0
none	3	0
unknown	1	0

Table 2.Outcome of 37 limited disease patients with complete remission.
Age is in years and survival in months; PCI = prophylactic cranial irradiation;
CNS = central nervous system; * 2 of these patients had leptomeningeal metastases.

Of the original group of 203 patients 18 patients (9%) survived for more than two years. Their neurologic outcome is presented in *table 3.* Four patients, all not treated with PCI remained without neurologic complications. Possible treatment related neurologic complications arose in 7 patients with PCI and 1 patient without PCI. Other, non treatment related, neurologic complications comprised brain metastases in 3 patients, cerebrovascular accident in 2 patients, and paraneoplastic subacute cerebellar degeneration in 1 patient.

Memory disturbances surfaced as the most frequent possible treatment related complication in 8 patients (7 with and 1 without PCI). Immediate recall was usually affected. The memory decline was insidious and started in 6 patients within 6 months after termination of therapy and in 2 other patients after 18 months. Once established the memory disturbances remained stable for months to years in most of the patients. Memory disturbances were accompanied by lethargy or a generalised lack of energy in 4 patients. Although the lethargy, in these patients, started simultaneously with the memory

Patients	PCI	no PCI
total	9	9
men/women	7/2	6/3
median age at diagnosis (range)	55 (52 -67)	60 (45 - 74)
median survival (range)	40 (25 - 120)	27 (24 - 56)
Neurologic complications		
none	0	4
possible	7	1
other	2	4
Radiologic abnormalities		
none	2	2
possible treatment related	5	3
other	2	4

Table 3. Neurologic outcome of long-term survivors.
Age is in years and survival in months; PCI = prophylactic cranial irradiation. Outcome is divided over three categories, with no, possible treatment related, and otherwise explainable neurologic complications or radiologic abnormalities, respectively.

disturbances, the course was more unpredictable; two patients improved and two patients developed a progressive apathy combined with drowsiness, in one of them resulting in a full blown dementia syndrome.

In 3 of 9 patients without PCI, possible treatment related radiologic abnormalities were manifest; 1 patient with memory disturbances had aspecific white matter lesions, and in 2 other patients though neurologically normal brain atrophy was present.

Of 9 patients receiving PCI treatment 5 had possible treatment related radiologic abnormalities. These 5 are broken down as follows: 1 patient suffering from memory disturbances, developed visual complaints 7 years post treatment. The complaints consisted of distortions and discolorations in her visual field.

Together with the visual complaints her walk became unstable. Brain MR scan showed aspecific white matter lesions right sided parieto-occipital but was otherwise normal. Two patients (one with memory disturbances and another with memory disturbances and non progressive lethargy) had brain atrophy, and finally 2 patients (with memory disturbances and progressive lethargy) manifested brain atrophy as well as periventricular white matter lesions. normal follow-up scans. Outside of these 5 patients, 2 PCI patients had possible treatment related neurologic complications (one with memory disturbances and another with memory disturbances and non progressive lethargy) and normal follow-up scans.

Of the 8 long-term survivors with possible treatment related neurologic abnormalities 5 (4 with and 1 without PCI) experienced minor neurologic deficits (memory disturbances), and 3 were seriously handicapped by these deficits (2 patients with a progressive lethargy, and 1 patient with visual complaints and an unstable gait). All other patients were capable of basic self care and resumed a lifestyle more or less similar to that before diagnosis of SCLC. Some patients concluded their working life earlier, because of impaired physical rather than neurological condition.

Discussion

An analysis of 9 randomized trials by Pedersen et al [4] revealed a reduction of the accumulated frequency of clinical brain metastases from 23% without PCI to 6% with PCI, but no improvement in overall survival. The total population of 716 patients in this analysis was rather heterogeneous as some studies included patients who did not achieve CR, and patients with ED. Furthermore these studies were, as far as reported, different with regard to the follow-up time. Rosen et al [15] demonstrated an increased survival with PCI in patients responding completely. Fleck et al [16] analysed 58 LD patients who went into CR and found significantly fewer overall CNS relapses in patients treated with PCI, though the difference between initial CNS relapses was small and the disease-free survival, and overall survival did not differ significantly. PCI appears to have been effective in increasing survival of LD patients who achieved durable thoracic control in a study by Rosenstein et al [17]. In the present neurologic follow-up study, PCI had no impact on the frequency of brain metastases whereas the brain metastatic free survival and overall survival improved significantly. However, these results should be interpreted carefully as the number of patients is small and it is a non-randomized study. Locoregional treatment differed slightly for patients treated with and without PCI. Radiotherapy to the primary tumor was administered to 6 of the 17 patients treated with PCI (35%) and 5

of the 20 patients not treated with PCI (25%).

Hirsch et al [18] showed that 33% of the patients had "silent" brain metastases, in a study in which clinical and autopsy findings were compared. In this study, the clinical diagnosis of brain metastases became more reliable by regular neurologic examinations and the use of modern imaging techniques, although it remained clinically difficult to establish the extent to which metastases are restricted to the CNS. Isolated CNS metastases can represent seeding from a previously undetected intrathoracic relapse. In the present study, a sole CNS relapse was seen in 1 patient treated with PCI only. The majority of the patients had a systemic recurrence of disease before or shortly after the diagnosis of brain metastases, which can represent new seeding as well as growth of already existing microscopic brain metastases. So rather than PCI treatment failure, brain metastasis may indicate the non-effectiveness of chemotherapy and locoreginal therapy. The same goes for the differences in brain metastatic free and overall survival, which are equally related to the recurrence of systemic disease.

The administration of PCI in combination with systemic chemotherapy is potentially neurotoxic; a wide range of neurologic abnormalities have been reported together with the occurrence of white matter changes and brain atrophy (displayed by ventricular dilatation as well as widening of sulci), particularly in long-term survivors [4-10, 16]. Pedersen et al [4] concluded from the combined data of 8 relatively small retrospective studies with a total of 123 long-term survivors of whom 102 patients received PCI that 45% had severe clinical CNS defects. The significance and frequency of the possible treatment related CNS abnormalities varied strongly in different studies. Most of the existing studies have attributed unexplained neurologic conditions following treatment to neurotoxicity of the chemotherapy and PCI combination, without clearly defining them. Johnson et al [9] studied 20 long-term survivors and found an increased CNS toxicity when PCI was administered in larger fraction doses or concurrent with chemotherapy. In the present study, PCI was delivered after termination of the systemic chemotherapy. Possible treatment-related neurologic complications and scan abnormalities were diagnosed more frequently in long-term survivors treated with PCI than long-term survivors not treated with PCI; 7/9 versus 1/9 neurologic complications and 5/9 versus 3/9 radiologic abnormalities respectively. In contrast with studies where chemotherapy has followed by or been concurrent with PCI [7-9, 16] and consistent with a study in which PCI was applied after chemotherapy [10], the neurologic complications were relatively mild for the majority of the patients.

Brain irradiation in combination with or without chemotherapy is hazardous for the CNS and white matter in particular

[19]. White matter changes are more sensitively imaged by MRI as focal hyperintensities of the central white matter [20, 21] than by CT. Some researchers have concluded that these white matter abnormalities are normal age related changes [22-25], while others suggested a marked relation with hypertension [26-29]. In a prospective study which was conducted to explore the value of routine cranial MR scanning as a pretreatment screening procedure in patients with SCLC, white matter hyperintensities were found in 14 (36%) of 39 patients who varied in age from 51 to 78 years [30]. As patients were primarily evaluated with CT-scan, the white matter abnormalities seen on MR scans of long-term survivors in this study cannot be attributed a priori to radiation damage. The higher frequency of possible treatment related radiologic abnormalities in long-term survivors treated with PCI is partially explained by the longer follow-up time, because radiation induced CNS changes tend to be irreversible and progressive over time [19]. Therefore, the possible treatment related radiologic abnormalities do not necessarily confirm the association of PCI, in the present study.

We conclude that the observed survival benefit in patients treated with PCI could be the result of PCI, but as the study was not randomized other treatment related factors may play a role as well. Randomized studies with more effective systemic treatment protocols would allow more definite conclusions. Possible treatment related adverse effects, though relatively mild, were seen more frequently in long-term survivors treated with PCI. The higher frequency of adverse effects might be explained by a longer follow up and differences in imaging technique. However, every adverse effect of PCI is valid as long as the efficacy of PCI is not clearly established. The results of this study confirm the general belief that PCI may be effective by increasing the brain metastatic free survival, and its use with systemic chemotherapy bears the risk of CNS toxicity.

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7 Follow-up of cognitive functioning in patients with small cell lung cancer

Introduction

The current treatment regimen of patients with small cell lung cancer (SCLC), including systemic chemotherapy with or without chest irradiation and prophylactic cranial irradiation (PCI), is potentially neurotoxic. Prophylactic cranial irradiation in particular has been blamed for adverse effects on the central nervous system (CNS) and its administration has become controversial (19,3,10,11,13,12,6,7,21).

The white matter of the CNS is especiallyvulnerable to radiation (1,2,18,14,4) Chemotherapy can by itself induce white matter injury, as well as enhance the toxic effects of radiation. Computed tomography and magnetic resonance studies have shown evidence of both white matter and cortical atrophy (18,14,4). Clinically, the neuroanatomic changes seen by computed tomography or magnetic resonance are associated with impairment of mental function, seizure disorders, and motor abnormalities. The most prominent clinical features, however, involve impairment of cognitive functioning (2,14).

In the present study, the results of a neurologic and neuropsychologic follow-up of a group of consecutive patients with SCLC are reported. The purpose of the current investigation was to establish early signs of cognitive dysfunction by a neuropsychologic follow-up. The neuropsychologic test battery was designed to allow group comparisons of neuropsychologic functioning on different domainsrather than the diagnosis of specific deficits in individual patients. The present study also compared patients in their pretherapeutic condition with matched controls in an attempt to distinguish between the impact of disease and treatment related factors.

Methods and materials

Thirty two consecutive SCLC patients were enrolled in a prospective study. All patients were initially treated with chemotherapy, consisting of cyclophosphamide 1000 mg/m2, doxorubicin 45 mg/m2, and etoposide 100 mg/m2 on days 1, 3, and 5 for five cycles. After chemotherapy, patients in complete remission received PCI, in a total dose of 30 Gy on the entire cranial content, in 15 fractions of 2 Gy over 2 to 3 weeks. Patients were seen by a neurologist upon diagnosis and at quarterly intervals thereafter (biannually after a year). A computed tomography scan of the brain was performed before treatment. More frequent neurologic consultations and other ancillary tests were done as required. Patients with brain metastases were excluded from the analysis.

Complete neuropsychologic evaluation included history, observation, and established procedures for testing intelligence, mental control, information processing speed, visuo-motor speed, verbal and visual memory, fine motor functions, and eye-hand coordination. Intelligence was tested pretherapeutically with the Groninger

Intelligentie Test (17), a Dutch-language standardized intelligence battery. Mean results on the Dutch version of the 15 Word auditory verbal learning test (15) the Stroop color-word test (15), and the Trailmaking test parts A and B (15) were analyzed, as for these tests, control data were available (9). Patients in pretherapeutic condition (session 1) were compared to controls, who were matched for age, gender, and educational level (16). Tests were repeated during chemotherapy (session 2), after chemotherapy (session 3), 1 month after PCI (session 4), and 5 months after PCI (session 5).

For the Trailmaking test, subjects are asked to connect successive numbers (part A), or alternating successive numbers and letters (part B) on a card (15). In the Stroop test subjects have to read color names (word), name colors (color), and read color names printed in a different color (color-word); during the color-word part of the test, subjects have to inhibit automatic reading responses, which causes a delay (interference effect) compared to the color part of the test (15) In the 15 word test, subjects are presented the same series of 15 words five times and are asked to reproduce these words after each presentation, as well as after 20 minutes. After the last spontaneous recall they are asked to recognize the 15 target items from a list of 30 words (15). Total recall capacity over five trials (total), difference between the worst and the best score over five trials (delta), the delayed recall, and the recognitionare analyzed. The relevant measure in the Trailmaking and Stroop tests is the performance speed.

Patient characteristics are listed in *Table 1*. None had a history of severe head injury or chronic intoxications (alcohol or psychoactive drugs). Brain metastases were diagnosed in 3 patients at the onset of SCLC and in 11 other patients during the course of the disease. Four other patients were excluded from further analysis, as they had not been neuropsychologically tested before the start of chemotherapy. Three patients with rapidly progressive SCLC died within the first 6 months. Therefore, the number of patients was reduced from 14 in the first two test sessions to 11 in the third test session. Only 5 patients were treated with PCI. The sample t-test was used for statistical analysis of the mean test results.

Results

Regular neurologic examination revealed no CNS abnormalities in patients without evidence of CNS metastases. All patients without evidence of rapidly progressive disease or CNS metastases remained ambulatory and capable of self care. Some patients complained about concentration problems, difficulties in recalling telephone numbers, slight word finding problems, and loss of libido. These complaints were heard at diagnosis, as well as during the course of the disease, when specifically asked.

	Total	Session1 and 2	Session3	Session 4 and 5
n	32	14	11	5
male	26	12	9	4
limited disease	12	4	1	3
age mean (range)	64 (45-78)	63 (51-73)	64 (54-73)	58 (52-62)
IQ mean (range)	103 (71-129)	103 (87-116)	103 (87-116)	101 (95-110)

Table 1. Patients charateristics: total=all patients enrolled; session 1 and 2=pretherapeutic and during chemotherapie; session3=after chemotherapy; session 4 and 5=one and five months after prophylactic cranial irridation; IQ=intelligence quotient.

The analysed neuropsychologic tests in the study measure aspecific effects of brain dysfunction, where perceptual-motor speed, attention span, flexibility, and memory are concerned. The mean results on the Dutch version of the 15-Word auditory verbal learning test (15) the Stroop color-word test (15) and parts A and B of the Trailmaking test (15) are shown in *Table 2*. The mean results scored on these tests by the patients in pretherapeutic condition were significantly worse than those of matched controls ($p < 0.001$). The test results did not show any significant deterioration during or after chemotherapy, nor after PCI ($0.1 < p < 0.8$). In the 5 patients taking part in all the test sessions, the changes of the various test items throughout time did not show a consistent pattern, yet were more indicative of improvement than of deterioration.

	Controls	Patients				
		session 1	session 2	session 3	session 4	session 5
		(n = 14)	(n = 14)	(n = 14)	(n = 11)	(n = 5)
Trailmaking Test						
part A	41.3 (16.1)	50.5 (23.3)	45.2 (16.6)	41.3 (14.6)	32.2 (10.0)	29.3 (5.3)
part B	62.6 (24.1)	77.0 (26.4)	75.4 (30.4)	72.5 (24.1)	78.8 (35.7)	88.7 (57.5)
Stroop Test						
word	40.6 (5.1)	50.4 (6.3)	47.9 (8.4)	49.8 (8.7)	47.4 (7.2)	48.5 (8.4)
color	55.4 (4.1)	63.0 (9.5)	57.1 (9.2)	63.3 (13.4)	64.4 (12.3)	59.3 (7.0)
color-word	93.7 (17.7)	134.1 (36.2)	110.9 (27.0)	127.7 (40.1)	138.4 (50.9)	120.0 (33.4)
interference	38.3 (12.0)	71.1 (32.2)	53.8 (23.3)	64.4 (30.9)	74 (39.2)	61.0 (31.0)
15 Word Test						
total	49.0 (5.5)	32.5 (9.3)	35.6 (11.6)	38.2 (8.6)	38.4 (12.4)	41 (15.6)
delta	6.9 (1.3)	4.9 (1.6)	5.0 (2.2)	5.0 (2.1)	4.2 (1.5)	4.5 (3.0)
delayed recall	10.3 (2.1)	6.4 (2.6)	6.6 (2.6)	7.6 (2.5)	7.2 (3.6)	7.0 (3.7)
recognition	29.4 (0.8)	27.0 (2.1)	26.1 (2.8)	26.4 (3.5)	28.6 (2.6)	27.5 (3.1)

Table 2. Mean Results (standard deviations) of Neuropsychologic Tests of Matched Controls and Patients, During Successive Test Sessions.

Statistical analysis (sample t-test) revealed significant differences between patients in session 1 versus matched controls ($p = < 0.001$), but no significant inter-session differences ($0.1 < p < 0.8$); session 1 = pretherapeutic; session 2 = during chemotherapy; session 3 = after chemotherapy; session 4 = 1 month after prophylactic cranial irradiation; session 5 = 5 months after prophylactic cranial irradiation.

Discussion

Follow-up assessments of cognitive function in patients with SCLC from diagnosis, or a comparison between their pretherapeutic performance and that of matched controls, have not been performed as yet. The neurotoxicity of the combination of chemotherapy and PCI, in the context of SCLC, is described mainly as late sequelae in long-term survivors. Theoretically speaking, nonmetastatic neurologic complications of SCLC or sequelae of its treatment can arise at any moment, starting from diagnosis. Chemotherapy related cerebral injury presents itself early, within weeks to months of treatment (14, 20). With the combination of cyclophosphamide, doxorubicin, and etoposide as used in our study, however, no CNS injury has been reported so far. Laukkanen et al. (12) identified headache and mild nausea during PCI, and concentration difficulties and a nonspecific lack of energy from 1 month after PCI as transient and early sequelae. Licciardello et al. (16) described 2 patients with progressive confusion 6 and 10 weeks after PCI. Irreversible adverse effects do occur usually 3 months after PCI (14, 20).

Pretherapeutic neuropsychologic test results of the group of patients as a whole were generally worse than those of the matched controls. Possible explanations could be that the patients were in suboptimal physical condition and were preoccupied with their future. The attending effective changes may have influenced their test performance. Although all patients remained motivated and none showed clinical evidence of significant depression, their general physical and mental condition cannot be ruled out. Microscopic brain metastases and paraneoplastic mechanisms may have further compromised the results (5). Moreover, we are unaware of the effects of chronic cigarette smoking, prior medication or brain traumas, and the interactions of these interindividually different data with the current treatment. Hill found that smoking may have a negative effect on performance speed in elderly adults (8).

An earlier study (21), performed by us, revealed no focal deficits such as aphasia, apraxia, or agnosia. None of the patients showed clinical signs of these specific disorders in the present study, although they were not specifically tested for. The present study also revealed no additional therapy effects on measures of aspecific effects of diffuse brain dysfunction; during and after treatment, some neuropsychologic test results even improved slightly. Standard neurologic examination revealed no serious neurotoxicity; specific history for cognitive dysfunction did not reveal more than a slight indication of brain dysfunction in some patients, objective CNS abnormalities were detected only in patients with brain metastases. This finding contrasts with several studies which have reported a considerable number of severe neurologic complications of therapy, especially in long-term

survivors (19,3,10,11,13,12,6,7,16). The fraction dose of PCI in these studies (3,10,11,13,12,6,7,16) was at least 3 Gy; this may have been more harmful than the 2 Gy used in our study.

The difference between the group of patients in pretreatment condition and the group of matched controls can not be interpreted a priori as clinically significant; although it could be meaningful for the individual patient in view of the standard deviations. The same goes for the therapy effects; although the mean group results remained relatively stable, the considerable standard deviations in combination with the small sample size makes it likely that the cognitive performance of individual patients were impaired. The number of patients is too small for definite conclusions; half of the study population developed brain metastases or died before neurotoxicity assessment could be performed, and we can not exclude long-term effects. However, the differences between patients in pretherapeutic condition and matched controls may very well have contributed to the short and long-term neurotoxicity reported in other studies (19,3,10,11,13,12,6,7,21,16). Our results confirm the importance of a pretherapeutic assessment in this field of research.

Conclusions

In patients with SCLC who were treated with chemotherapy and PCI, follow-up of cognitive functioning revealed no adverse treatment effects within 5 months after termination of PCI. However, when pretherapeutically compared to matched controls, patients performed significantly worse, suggesting that a nontreatment related cognitive impairment could exist in patients with SCLC.

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8 Central nervous system toxicity in long-term survivors of small cell lung cancer

Introduction

Central nervous system (CNS) metastases are an important cause of morbidity and mortality in patients with small cell lung cancer (SCLC) [1]. With lengthening survival the risk of CNS metastases increases to a cumulative risk of 58-80% in two-year survivors not treated with prophylactic cranial irradiation (PCI) [2]. For patients who did not achieve complete remission (CR), the actuarial likelihood of developing CNS metastases was nearly 100% at 2 years, irrespective of the administration of PCI [3]. PCI significantly reduced the frequency of brain metastases in a number of prospective, randomised clinical trials [4]. Though there was no evidence of improved survival, PCI became an optional part of the treatment program for patients with a CR to systemic chemotherapy, with or without chest radiation therapy [4].

It soon became evident, however, that the application of PCI involved the risk of serious CNS injury [5-9]. Both chemotherapy and cranial irradiation are potentially hazardous for the CNS and the white matter in particular [10]. Small cell lung cancer patients treated with chemotherapy alone showed less adverse effects than those who were treated with chemotherapy and PCI [4]. Administration of PCI in larger fraction doses, concurrent with or sandwiched by chemotherapy seemed to be associated with a higher frequency of CNS abnormalities [9]. However, exact frequency, severity, and etiology of these CNS abnormalities in long-term survivors of SCLC are unknown, at present. Studies on neurotoxicity in SCLC lack sufficient patient numbers and uniformity to allow definite conclusions on this topic [4, 11-14].

Using neurologic and neuropsychologic assessment, and computed tomography (CT) scanning or magnetic resonance (MR) imaging of the brain, the present study describes the neurologic outcome of 59 long-term survivors, defined as patients surviving the diagnosis of SCLC for more than two years. The purpose of the current investigation was to isolate residual effects of the treatment of SCLC. It was hypothesised that the treatment would affect mainly the cognitive performance of the patients. An attempt was made to asses the impact of different treatment-protocols on learning and memory, memory span, speed of information processing, and attention shifting. Specifically, the most sensitive neuropsychologic tasks to detect deficits in these cognitive domains were used to compare patients not treated with PCI, patients treated with PCI after chemotherapy, patients treated with PCI concurrent with or sandwiched by chemotherapy, and matched controls.

Patients and Methods

Patient population

Pulmonologists in the Netherlands were asked to request patients surviving the onset of SCLC more than two years to take part in the present study on a voluntary basis. They were visited by the authors for neurologic (AvO) and neuropsychologic assessment (BdG or RvV). Within two months after these assessments a CT or MR scan of the brain was performed in the different hospitals.

Between January 1991 and January 1993, 59 patients were enrolled. Six patients were excluded from further analysis; four patients with a cerebrovascular accident, one patient with a Korsakoff syndrome due to alcohol abuse, and one patient with a severe head injury prior to diagnosis of SCLC. For analysis of the neuropsychologic test results and for the determination of treatment effects four more patients were excluded, two because of insufficient command of the Dutch language, and two patients because they were not treated with chemotherapy or PCI.

Treatment

Fifty-one patients, were treated with chemotherapy, with or without chest irradiation. Thirty patients were treated with PCI, 23 patients did not receive PCI. Two patients were not treated with chemotherapy or PCI. These latter two patients underwent a lobectomy, in one followed by chest irradiation.

Patients were divided in three groups, according to the received treatment: group 1 chemotherapy alone (n = 21, including two patients with insufficient command of Dutch), group 2 PCI after termination of chemotherapy (n = 19), and group 3 PCI concurrent or sandwiched with chemotherapy (n = 11). Patient characteristics and treatment specifications are listed in *table 1*.

The group of controls comprised healthy subjects (n = 29), enrolled in a study on memory disturbances in the elderly [15]. They were matched on an individualised basis to the patients for age and educational level.

Patients	group 1 n = 19	group 2 n = 19	group 3 n = 11
Characteristics			
age	64.5 (7.2)	59.7 (9.1)	64.7 (9.9)
survival	5.4 (2.8)	4.1 (2.5)	7.8 (2.3)*
education level	3.0 (1.4)	3.4 (1.6)	3.9 (1.3)
Chemotherapy			
CTX,DOX,VCR	7	1	0
CTX,DOX,ETO	9	16	1
CTX,DOX,ETO/CTX,VCR,MTX	0	0	7
CTX,VCR,MTX	0	0	1
CTX,CIS,ETO	1	0	0
CTX,CIS,ETO/CCNU,ETO,MTX	2	0	0
CTX,CIS,ETO/CCNU,HMM	0	1	1
carboplatin and ifosfamide	0	1	0
carboplatin and VCR	0	0	1
Locoregional Radiotherapy	11	9	9
Prophylactic Cranial Irradiation			
15 x 2.0 Gy	0	3	1
12 x 2.5 Gy	0	10	5
10 x 3.0 Gy	0	6	5

Table 1. Patient characteristics and treatment specifications.
Group 1=chemotherapy alone; group 2=sequential prophylactic cranial irradiation; group 3=concurrent or sandwiched prophylactic cranial irradiation. Age, survival (*p=0.007, One Factor Anova), and education level of patients are displayed as mean and (standard deviation). Matched controls (n=29) had a mean age 61.4 (7.2) year and education level of 3.5 (1.2). Different treatment modalities are specified; CTX=cyclofosfamide; DOX=doxorubicin; ETO=etoposide; VCR=vincristine; CIS=cisplatin; MTX=methotrexate; HMM=hexamethylmelanine.

Neurologic assessment

The neurologic evaluation included history, assessment of functional status, and neurologic examination. We specifically concentrated on complaints or abnormal physical findings related to the CNS. Patients were screened for intoxications, head injuries, and cardiovascular risk factors as hypertension, diabetes mellitus, and coronary artery disease. The use of antihypertensive or antidiabetic medications was used to define hypertension or diabetes mellitus, respectively. The diagnosis of coronary artery disease required a documented history of myocardial infarction or an abnormal electrocardiogram for the presence of ischemic changes or arrhytmias. Functional status assessment included a clinical rating scale for the ability to perform self care and basic social maintenance using the Barthel score [16], the Karnofsky scale [17], and the score of Order, Hellman and von Essen [18].

Grading of ventricular enlargement, cortical atrophy, cerebellar atrophy, white matter lesions by CT and MR scan

All CT and MR scans were reviewed by a neuroradiologist (JW) who was unaware of the treatment and clinical condition of the patient. CT and MR scans were evaluated for ventricular enlargement, cortical atrophy, comparison of cerebral and cerebellar atrophy, and the extent of white matter lesions. Ventricular enlargement was rated according to the Evans index [19]. Cortical atrophy was judged as none if no sulcus was wider than 5 millimetres, light if a few sulci were wider than this value, moderate if more sulci but less than the half of them were wider than 5 millimetres, and severe if more than half of the sulci were wider than 5 millimetres. Visual assessment was used for the comparison of cerebral and cerebellar atrophy as less, the same, or greater. The extent of white matter lesions was judged as none if no such lesions were present, light if white matter lesions were restricted to a periventricular zone of no more than one ventricle width, moderate if white matter lesions were scattered throughout the white matter excepting the capsula interna, and severe if the total white matter was affected.

Neuropsychologic assessment

For the neuropsychologic testing battery five tests (two memory tests and three tests in which speed of performance was the main parameter) were chosen because of their sensitivity in distinguishing between chronic solvent exposed workers, intermittently exposed workers and healthy controls [20]: the Auditory Verbal Learning Test (AVLT) [21], the Digit Span [21], a paper and pencil Memory Scanning Test (MST) [22], Concept Shifting Test (CST) [15], and the Stroop Color-Word Test [21].

1) In the AVLT 15 one-syllable nouns, recorded with a cassette tape, were presented five times in the same order. The subjects were instructed to recall all nouns they could remember immediately

after the presentation (immediate recall). The measure parameters used in this test are the number of words recalled on the first trial, the sum of the differences between the scores of the successive trials (delta), the delayed recall and the delayed recognition. The later two were measured 30 minutes after trial 5.

2) In the Digit Span Forwards the largest number of digits of a sequence that was repeated in the right order by the subject was counted.

3) A paper and pencil MST tested the slowing caused by memory load, in a fashion similar to the Sternberg paradigm [23]. The test consisted of four different subtests, each on a separate sheet of A4 paper, containing a 12 x 12 matrix of letters. In each matrix, 24 letters were target letters and the other letters were distracters. For each subtest, the subject was requested to memorize 1-4 letters, the memory set, and to cross them out as quickly as possible, without making mistakes, each time they occurred on the test sheet. In subtest 1, the memory set consisted of 1 letter (all 24 target letters were the same). In subtest 2, 3, and 4, the memory set consisted of 2, 3, and 4 different target letters, respectively. The intercept and the slope of the time scores, calculated by means of linear regression, are the parameters used with this test.

4) In Stroop Color-Word Test the subject's performance was measured as time scores of the three subtests A, B, and C, and the interference induced by the 'Stroop' effect [21].

5) The CST consists of three subtests, analogous to the Revised Trail Making Test. Each subtest consists of 16 small circles (diameter 15mm), grouped in a larger circle (diameter 16mm), printed on a A4 paper. In the small circles the test items are randomly printed in the small circles: digits 1-16 in subtest A, letters A-P in subtest B and both digits 1-8 plus letters A-H in subtest C. The subjects are requested to cross out the items in the right order. The scores are time scores for each of the three subtest and the effect of interference induced by the digits/letters category switch.

The different test parameters were combined in four cognitive domains: learning and memory, memory span, speed of information processing, and attention shifting. Both the interference effect of the Stroop Test and the CST are viewed as a measure of aspects of arousal and alertness on executive functions [22], and were combined in a relative score, according the formula: $(C-A+B)/2)/(A+B)/2)*100$, in which A, B, and C represent the order of the three sub tasks of the Stroop and the CST.

Statistical analysis

Univariate F-tests and Kruskal-Wallis test were used to assess significance in the distribution of characteristics, performance scores, and radiologic findings between treatment groups. Differences in cognitive performance were assessed by univaria-

e F-tests and MANOVA's. Pearson correations were used

Results

Neurologic assessment

None of the patients was institutionalised. Three patients received some external domestic help. Of the 53 eligible patients 47 lived with their partner and 6 lived alone. Except for intermittent use of sleep medication, no psychoactive drugs were used. Three patients used more than four units alcohol on a regular daily basis. Cardiovascular risk factors have been recognised in 17 patients (32%); 9 patients group 1, 5 patients group 2, and 3 patients group 3 respectively.
All patients had optimal Barthel scores and were able to perform basic self care. Fifty percent of the patients had an optimal Karnofsky score, the lowest score on the Karnofsky scale was 60 (one patient in group 3). The rating on the Karnofsky scale was frequently more affected by the pulmonary condition than their neurologic condition. More than 50 percent of the patients had an optimal rating on the score of Order, Hellman, and von Essen [18]. Patients of group 1, 2, and 3 did not differ significantly with respect to their functional status, as measured by the Karnofsky score and the score of Order, Hellman, and von Essen.

Neurologic assessment revealed no abnormalities in 32 (60%), impairment in 13 (25%), and slight disability in 8 (15%) patients. Neurologic problems were seen in 5 patients in group 1 (24%), 8 patients in group 2 (42%), and 8 patients in group 3 (73%), *see table 2*. The two patients who were not treated with chemotherapy or PCI (age 74 and 80 years, and both with cardiovascular risk factors) suffered hearing loss but were otherwise neurologically normal.

Features of mental impairment included complaints of memory disturbances (n=14), concentration problems (n=3), slight word findings problems (n=2), and calculation problems (n=1). Though mental status and regular neurologic examination revealed no abnormalities, these complaints had quite a great impact on the social functioning of some patients; i.e. an accountant resigned because of memory and calculating problems, a busy executive ended his career because his inability to memorise agenda items, a housewife felt uncomfortable not being able to organise her domestic work as before and noticed memory disturbances and slight word finding problems when she argued with other people.

Motor abnormalities included discrete hemiparesis (n=1), unstable gait or ataxia (n=5), pyramidal tract signs in the legs in combination with incontinence of urine (n=2). The latter two patients were both treated with chest irradiation. One patient with memory disturbances developed visual complaints and an unstable gait; she noticed distortions and discolorations. MRI of her brain showed white matter lesions right sided parieto-occipital and a mild cortical atrophy.

Mental Complaints	
memory disturbances	14
concentration disturbances	3
slight dysfasia	2
dyscalculia	1
Motor Abnormalities	
discrete hemiparesis	1
unstable gait	5
pyramidal tract signs and urine incontinence	2
Other	
visual complaints	1
Total	
symptomatic patients	21
asymptomatic patients	32

Table 2. Results of neurologic assessment in 53 long-term small cell lung cancer survivors.

Neuroradiologic assessment

Cranial CT scanning was performed in 20 patients (7 patients group 1, 8 patients group 2, and 5 patients group 3) and MR imaging in 21 patients (7 patients group 1, 9 patients group 2, 4 patients group 3, and 1 patient not treated with chemotherapy or PCI). CT and MR scans were evaluated for ventricular enlargement (Evans index), cortical atrophy, comparison of cerebral and cerebellar atrophy, and presence and extent of white matter lesions.

The Evans index was pathologic in one patient only. The extent of cortical atrophy did not differ significantly between groups ($p=0.3$, Kruskal-Wallis test), see *table 3*. The atrophy of the cerebellum was in proportion with the rest of the cerebrum in most of the patients; judged as less in three and as more in one patient respectively. White matter lesions were localised as primarily periventricular; aspecific subcortical white matter lesions were seen in only one patient. The predominately periventricular localised white matter lesions were significantly more

Patients	group 1 n = 14	group 2 n = 17	group 3 n = 9
Cortical Atrophy			
none	2 (1/1)	1 (0/1)	0 (0/0)
mild	9 (4/5)	12 (5/7)	4 (3/1)
moderate/severe	3 (2/1)	4 (3/1)	5 (2/#)
White Matter Lesions			
none	9 (5/4)	6 (4/2)	1 (1/0)
mild	4 (1/3)	8 (2/6)	4 (3/1)
moderate/severe	1 (1/0)	3 (2/1)	4 (1/3)

Table 3. Degree of cortical atrophy and white matter lesions.
Degree of cortical atrophy ($p<0.3$, Kruskal-Wallis test) and white matter lesions ($p<0.02$, Kruskal-Wallis test) were established for different treatment groups; group 1=treated with chemotherapy alone; group 2=treated with prophylactic cranial irradiation after termination of chemotherapy; group 3=treated with prophylactic cranial irradiation concurrent or sandwiched with chemotherapy. Results are displayed as total numbers and specified for imaging technique numbers (CT/MR).

extensive in group 3 than in groups 1 and 2 ($p=0.02$, Kruskal-Wallis test), see table 3. A cerebral MR scan made in one of the two patients who were not treated with chemotherapy or PCI showed mild white matter lesions and moderate cortical atrophy.

Pearson correlations were studied between the extent of white matter lesions and type of brain imaging technique, age, survival, presence of cardiovascular risks factors, treatment group, number of chemotherapy courses, type of chemotherapy, as well as fraction dose of PCI. The Pearson correlation matrix ($r > 0.3$, $p < 0.05$) showed a positive correlation with treatment group 3 (0.423), large number of chemotherapy courses (0.301) and high fraction dose (0.300). There was no significant correlation found with the other factors.

Patients	group 1	group 2	group 3	controls	p-values
	n = 19	n = 19	n = 11	n = 29	F = 3.74
Learning and Memory					
AVLT delta	4.05	4.74	3.45	6.10	0.016
AVLT delayed recall	6.68	6.00	5.18	10.14	0.000
AVLT delayed recognition	13.05	12.84	12.81	14.10	0.057
Memory Span					
AVLT trial 1	4.31	3.73	3.27	5.50	0.000
MST slope score	13.29	10.36	12.20	9.80	0.337
Digit span	4.83	5.09	5.60	5.20	0.274
Speed Information Processing					
MST intercept score	51.61	39.23	36.51	34.66	0.000
CST subtest A	53.63	55.73	55.11	29.17	0.001
CST subtest B	62.88	66.94	53.11	32.82	0.000
Stroop subtest A	63.00	58.41	60.50	44.20	0.003
Stroop subtest B	76.00	68.64	69.30	57.36	0.013
Attention Shifting					
Stroop interference effect	111.08	96.97	194.06	93.57	0.001
CST interferrence effect	28.79	40.51	40.57	63.52	0.116

Table 4. Means of test parameters and p-values of univariate F-tests for different treatment groups and matched controls.

Group 1=treated with chemotherapy alone; group 2=treated with prophylactic cranial irradiation after termination of chemotherapy; group 3=treated with prophylactic cranial irradiation concurrent or sandwiched with chemotherapy. Test parameters were combined in four cognitive domains; AVLT= Auditory Verbal Learning Test; MST= Memory Scanning Test; Stroop= Stroop Color-Word Test; CST=Concept Shifting Test. High scores mean a good performance for the test parameters AVLT (delta, delayed recall, delayed recognition, and trial 1) and Digit span. Low scores mean a good performance for the other parmeters.

Neuropsychologic assessment

Separate MANOVA's per cognitive domain indicated that the mean results of different patient groups of patients were significantly worse than those of matched controls, for each cognitive domain; learning and memory: Wilks' Lambda = 0.634, $F(9.175) = 4.005$, $p < .000$; memory span: Wilks' Lambda = 0.685, $F(9.170) = 3.562$, $p < .000$; speed of information processing: Wilks' Lambda = 0.600, $F(15.174) = 2.289$, $p < .006$; and attention shifting: Wilks' Lambda = 0.735, $F(6.140) = 3.555$, $p < .003$. Comparisons of the three patient groups, using MANOVA, however, did not show differences within the four cognitive domains.

The mean scores of the single test parameters and the p-values of univariate F-tests are given in table 4. Univariate F-tests revealed significant differences between patients and controls for most test-parameters. No differences between patients and controls were seen with AVLT delayed recognition, Digit Span, the slope score of the MST and the interference score of the CST.

To evaluate whether treatment variables had an effect on individual cognitive performances, Pearson correlations ($r > 0.3$, $p < 0.05$) were calculated of test-parameters and type of chemotherapy, number of chemotherapy courses, fraction dose, and total dose of PCI. None of these correlations was significant above the 5% level.

Discussion

Long-term survivors are relatively scarce in neurotoxicity studies as a consequence of the severe prognosis of SCLC. From the results of several neurotoxicity studies, it becomes conceivable that PCI can induce very serious adverse reactions in combination with chemotherapy in individual SCLC patients [5-9, 13-14, 24-26]. Pedersen et al [4] concluded from the combined data of 8 relatively small retrospective studies with a total of 123 long-term survivors of whom 102 received PCI that 45% had severe clinical CNS defects. Clinical features of severe CNS injury comprised repeatedly progressive cognitive failure and ataxic gait disturbances [5-9, 13-14, 24-26]. Radiologic findings indicated loss of brain tissue [5-9, 13, 24-27], especially of the periventricular white matter [27-29].

In the present study, the long-term survivors were in relatively good condition, according to different rating scale scores. All patients were ambulatory and capable of self care. In contrast to previous neurotoxicity studies [5-9, 13-14, 24-26], we did not find seriously disabling CNS toxicity in long-term survivors, although some neurologic impairment was present. Neurologic impairment was found more frequently in more intensively treated patients. Abnormalities concerned predominately complaints about their cognitive functioning, with a considerable effect on the social functioning of some patients.

As the present study was retrospective, it could be argued that patients with a severe neurologic condition were not able to visit the hospital and therefore could not enter the study. On the other hand, 6 long-term survivors, patients on a regular basis and suffering from severe to less disabling CNS injury caused by cerebrovascular accident (n=4), trauma (n=1), and chronic alcoholism (n=1) participated in the present study. Survival of these 6 patients varied from 3 to 11.5 (mean 6.5) years.

The abnormalities seen on CT or MR scan did not differ significantly for the different patient groups, with the exception of the severity of white matter lesions. The periventricular white matter lesions have frequently been compared to 'leukoaraiosis' [33], which is commonly seen in the elderly population and presumed to be caused by arteriosclerosis. Leukoaraiosis is correlated with age and cardiovascular risk factors, hypertension in particular [34-35]. Zimmerman et al. [36] found that the radiation induced white matter lesions had the same aspect on MR scan as the white matter lesions seen in the normal elderly population, which makes the interpretation in our mainly older patient population difficult. However, no correlations were found with age or cardiovascular risk factors in the present study. The use of the same rating scale for the extent of the white matter lesions on CT scan and the for the detection of white matter lesions more sensitive MR technique [34-35], may have biased the results.

The white matter lesions are also compared to the 'leukoencephalopathy' described in children who were treated with systemic chemotherapy and a CNS profylaxe [30-31]. Leukoencephalopathy is thought to be the result of direct toxic effects of irradiation or chemotherapy to the neuroglia or indirect ischemic effects to the neuroglia caused by a irradiation or chemotherapy induced microangiopathy, and to be progressive over time [32]. Many risk factors for the development of neurotoxicity are combined in group 3: PCI concurrent or sandwiched by chemotherapy, large number of chemotherapy courses, higher fraction doses, and significant longer survival. Consequently, our CT and MR data do not allow definite conclusions with regard to the white matter toxicity of PCI. The use of PCI concurrent or sandwiched by chemotherapy has become obsolete at present.

Neuropsychologic assessment revealed no significant differences between the three groups of patients, whereas the cognitive performance of all patient groups was significantly worse when compared with the control group. The type of treatment had no effect on the cognitive impairment at group or individual level. The results suggest that the cognitive impairment of SCLC patients is more disease related than treatment related. We presumed that emotional distress caused by the knowledge of living with a malignant disease, and diminished physical condition compromised the cognitive performance of SCLC patients. The findings of the present study are in line with results of a

follow-up study of SCLC patients who underwent serial neuropsychometric testing, before and after various treatments [39].

As mean age and education level of patients are similar in both studies, a comparison of some results of the latter study [39] with present results was valid. It suggested that patients from the present study have slower information processing speeds. Speed of information processing appeared to be a crucial parameter of impairment in several neurologic as well as psychiatric diseases. As the mean survival of patients in the present study was greater than in the follow-up study [39], the lower information processing speed may be caused by additional long-term effects of SCLC or its treatment. We cannot exclude that secondary anxiety or mood disorders amplified the negative impact of the disturbed emotional condition. Neither are we able to determine the influence of progressive white matter lesions, which may represent a late adverse effect of chemotherapy or cranial irradiation [10,27-32]. Laukkanen et al [26] studied 12 long-term survivors, all treated with PCI, and found their performance limited by physical factors in three patients, mild depression in three patients, and significant emotional distress in two patients. Johnson et al [11], who performed a follow-up study of 15 long-term survivors, found a slow progressive decline in neuropsychologic function to be correlated to the extent of cranial CT or MR scan abnormalities.
The clinical finding that patients treated with PCI (group 2 and 3) complained more about their concentration and memory than patients not treated with PCI (group 1) was unsubstantiated by statistic significance of the psychometric results. The observation that the mean scores on trial 1 of the AVLT of group 2 and 3 were lower than the score of group 1, may account for this apparent inconsistency. Considering the first trial of the AVLT as a word-memory span under interference conditions, which are essential functions in everyday life, the group differences between PCI treated and not treated patients indicated a trend of interference sensitivity difference and may explain why the PCI groups complained more about their cognitive functions. A similar finding was seen in a study comparing cognitive profiles of intermittently solvent-exposed persons with healthy control subjects [20]. The exposed subjects who had strong complaints concerning concentration and attention only had lower scores on trial 1 of the AVLT. Further clarification for the apparent inconsistency between complaints and psychometric results can be found in the CST interference, which represents an aspect of divided attention. According to Stollery and Flindt [40], intermittently solvent-exposed workers without memory dysfunctions showed marked difficulties when attention had to be divided over two competing tasks. In concordance to those findings, scores of the CST interference showed a trend indicating that groups 2 and 3 were slower than group 1, in the present study.

Our study differs from previous studies in which CNS injury was heavily attributed to PCI treatment. Though we do not deny the potential hazardous possibilities of PCI, we consider PCI to be one of the factors capable of disturbing normal CNS functioning. We conclude that the diagnosis SCLC yielded measurable neuropsychologic effects compared to healthy subjects; that more intensively treated patients had relatively more neurologic complaints especially with regard to their cognitive functioning; that the significant longer surviving patients of group 3, who were treated with PCI concurrent or sandwiched by chemotherapy, large number of chemotherapy courses, and higher fraction doses, had more white matter abnormalities; that there was no statistical evidence for additional neurotoxicity of treatment with PCI.

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9 General discussion

This study deals with some clinical aspects of brain metastases and its treatment in small cell lung cancer. Brain metastases are the most frequent neurologic complication of small cell lung cancer (SCLC). In a longitudinal follow-up of 203 consecutive patients with SCLC, brain metastases were found in 27 patients (13%) during the initial staging procedure, and in 52 patients (21%) during the course of the disease. The cummulative risk of brain metastases reached 47% for LD and 69% for ED patients, at 2 years from diagnosis. Paraneoplastic syndromes, which are frequently associated with SCLC because of its high neuroendocrine expression, have a much lower occurance. The SIADH (syndrome of inappropriate secretion of antidiuretic hormone) was diagnosed in 11 patients (6.3%), antibody-medicated paraneoplastic syndromes in 5 patients (1.7%). The frequency of brain metastases was in accordance with data of previous studies; 10% (range, 0 to 16%) at diagnosis of SCLC, 20% (range, 7 to 30%) during therapy, and about 50% (range, 28 to 64%) at autopsy [1-2]. The frequency of paraneoplastic syndromes may be underestimated as only patients with a neurologic presentation were diagnosed and our attention was more or less fixed on central nervous system (CNS) abnormalities. Initial brain metastases responded significantly better than delayed brain metastases to symptomatic treatment, in terms of overall survival. Presently, symptomatic treatment of brain metastases consists of chemotherapy and/or radiotherapy. At first, it was believed that the CNS was a relative chemotherapy sanctuary as chemotherapy increased survival but brain metastases became more apparent. Later on, it was recognised that cytotoxic drugs can effectively penetrate into brain metastases. Response rates of 75 % were reported for chemotherapy as well as radiotherapy [4]. Brain metastases have, just as the primary tumor, a high initial response to therapy. In contrast the response of brain metastases to chemotherapy and/or radiotherapy following the first-line treatment of the primary tumor, is much lower and about 43 %. As symptomatic treatment of brain metastases is always palliative and when possible, toxicity should be kept to a minimum, it seems to make sense to treat initial brain metastases primarily with chemotherapy and delayed brain metastases primarily with radiotherapy. In case of initial brain metastases, the response to first-line treatment should be evaluated prior to using radiotherapy. The value of consolidation radiotherapy has yet to be thoroughly investigated. In view of the shortened life expectancy of patients with delayed brain metastases, these patients should primarily be treated with the slightly more effective and less toxic radiotherapy.

The histopathological subclassification system for SCLC of the International Association for the Study of Lung Cancer (IASLC) is based upon cell culture work and provided the best interobserver reproductibility thusfar [5-7]. In this study, subtyping was done of histologic as

well as cytologic material on which the original SCLC diagnosis was made. However, the frequences of the classic (85%) and variant subtypes (together 15%) were in line with the results of previous studies [5,6,8]. The results of the retrospectively done subtyping was correlated to the results of the longitudinal follow-up. Paraneoplastic syndromes were found exclusively in patients with the classic subtype. Statistically this finding represented a trend and needs further study. Nor were significant correlations found between subtypes and metastatic CNS pattern, developing brain metastases, or brain metastatic free survival. The disproportionate distribution of subtypes, and the possible presence of tumor heterogeneity limited the predictive value of the histopathologic subclassification of the IASLC.

The early detection of brain metastases can probably prevent sustained neurologic impairment as the effect of treatment seems to be primarily dependent on how advanced the neurologic symptoms have become when therapy is initiated [9]. In contrast to the use of CT-scan (computed tomography), MRI (magnetic resonance imaging) yielded important additional information to neurologic examination. With the use of MRI it appeared possible to detect brain metastases in neurologic asymptomatic patients as contrast-enhancing lesions. White matter lesions were also very sensitively demonstrated by MRI. Those focal or confluent, non contrast-enhancing hyperintensities on T2-weighted images represented benign lesions in most of the patients. However, in 2 of 4 neurologic symptomatic patients, those lesions covered brain metastases and part of them became contrast-enhancing in follow-up MRI. Consequently, in neurologic symptomatic patients with deep white matter on periventricular white matter hyperintensities on T2-weighted images, follow-up MRI is recommended as long as the usefulness of a double dose of contrast is unknown. Whether early detection of brain metastases yields a better response to therapy or just shortens the silent period, is open for discussion.

Delayed brain metastases can represent seeding from a relapse of the primary tumor, or represent secondary growth of initial micro brain metastases. Prophylactic cranial irradiation (PCI) was introduced to prevent the secondary growth of micro-metastases. In randomized studies, PCI proved to be effective in disminishing the frequency of brain metastases, from 25% to 6%, but failed to provide a consistent survival benefit [10]. Brain metastases were presumed to be a sole CNS relapse in up to 10 % of patients, while in the majority of patients the appearance of brain metastases was associated with a relapse of the primary tumor. The efficacy of PCI was studied in limited disease (LD) patients who achieved complete remission (CR) only, because this category of patients could benefit the most from PCI. Patients treated with PCI had a slightly lower number of brain

metastases, and a significantly longer brain metastatic free and overall survival than patients not treated with PCI. These results should be ionterpreted with caution. Only one patient, treated with PCI, had a sole CNS relapse. In all other patients, the appearance of brain metastases can reflect failure of PCI as well as failure of first-line treatment of the primary tumor. PCI was applied non-randomized. Patients treated with PCI had a longer follow-up and received more frequent loco-regional consolidation radiotherapy. Finally, the number of patients was relatively small. We concluded that because of the small patient numbers and the many biasing factors no conclusions should be drawn.

Adverse effects of PCI are normally related to as unexplained CNS abnormalities in long-term survivors of SCLC. Progressive anatomic changes are documented as white matter changes and brain atrophy by CT-scanning and MRI. Clinically, these anatomic abnormalities are associated with a wide range of manifestations, varying from mild cognitive deficits to rapid deteriorating dementia syndromes [10-14]. Although it is extremily difficult to attribute these changes to the use of PCI, it is conceivable from the abundant literature on this topic that PCI potentially contributes to the development of CNS toxicity. Many toxifying factors are involved in SCLC and its treatment. SCLC, the disease itself, can affect the cognitive performance by paraneoplastic mechanisms or microcoscopic brain metastases. Many of the drugs that are used during treatment of SCLC are potentially neurotoxic, cytotoxic drugs in particular. When cytotoxic drugs and PCI are used together they can enhance each others CNS toxicity. In SCLC, the use of PCI concurrent or sandwiched by chemotherapy is associated with more and intenser neurotoxicity [10-15].
Of the 18 long-term survivors in our longitudinal follow-up study, the 9 treated with PCI showed more possible treatment related neurologic and radiologic abnormalities than the remaining 9 not treated with PCI. The possible treatment related effects were relatively mild in most of the patients, probably as a result of treatment with PCI following completion of chemotherapy.

Neuropsychometric follow-up of 32 SCLC patients from diagnosis and during treatment revealed no cognitive deterioration. However, that group of patients scored significantly less than the control group of healthy subjects, who were matched age, gender, and education level. It is possible that the basic cognitive condition of SCLC patients is already compromised at diagnosis by psychologic factors and/or paraneoplastic mechanisms. A poor basic cognitive performance level may have be a contibuting factor to the late neurotoxicity, which is frequently associated solely to PCI. The clinical implications of these findings are diffficult to interpret as the tests used are rather aspecific measures of cognitive functioning and standard deviations varied widely.

An analysis of a large group of long-term survivors of SCLC revealed that the combination of chemotherapy and PCI generated mild neurologic disability and impairment only, in this group of patients which were retrospectively studied.
Complaints of cognitive dysfunction were heard more frequently from patients treated with PCI and the most of the patients treated with PCI concurrent with or sanwiched by chemotherapy. The differences in neurologic cognitive impairment were not substantiated by neuropsychometric tests. Neuropsychologically, no statistically significant difference were found between the treatment groups. Nor were correlations found betwen the individual cognitive performance and factors such as age, cardiovascular risk factors, and different treatment modalities. The apparent discrepancy between complaints and neuropsychologic findings was partly explained by a slightly worse score on trial 1 of the AVLT (auditory verbal learning task) and interference of the CST (concept shifting task). The trial 1 of the AVLT represent a memory span under interference conditions, which is an essential function for every day use of memory and concentration. The interference of the CST rewpresent an aspect of divided attention, which is necessary to perform two competing tasks in the same time.
Compared to the results of patients who were neuropsychologically tested at diagnosis and during treatment, long-term survivors had a lower information processing speed. As mean age and education level were similar in both studies the validity of this comparison is justified, and may be indicative of the long-term effects of SCLC or its treatment.
In the group of patients treated with PCI concurent with or sandwiched by chemotherapy, white matter lesions were more common. Leuco-encephalopathy is recognised as a late effect of the combination of chemotherapy and PCI in children, treated for acute leukaemia. The survival of the group of patients, treated with PCI concurent with or sandwiched by chemotherapy, was significantly longer than of the other groups. The longer survival may account for the difference in white matter lesions.
Another important observation was that all patient groups scored significantly less on the the different neuropsychologic tests than a control group of healthy subjects, who were matched for age, gender, and education level. Again supporting evidence was found for a disease rather than a treatment effect in CNS toxicity. This stresses the importance of a better understanding of the psychologic and copgnitive functioning of cancer patients. Gross disturbances are easily recognised but discrete disturbances are hardly understood. Nevertheless the fact that discrete cognitive disturbances can have a great impact on every day cognitive functioning. Our limited understanding of the cognitive functions impairs our ability to recognise dysfunctions.

Neurologic, neuropsychologic, psychologic, and radiologic study results have to be linked for a more concise understanding of cognitive functioning in cancer patients, and of CNS toxicity in SCLC patients in particular.
The clinician dealing with cancer patients needs to be better equiped to distinguish between normal and abnormal cognitive functioning in order to detect neurotoxicity earlier. In individual patients, SCLC and its tretment can generate serious side effects. For a better understanding of the CNS toxicity in SCLC we should not only deal with those serious side effects but be alert to the discrete CNS abnormalities which are manifest in patients but not immmediatly tied to the disease because of their subtility. This holds especiaaly true for SCLC in which the majority of patients already dealing with an extremily bad prognosis lack the disposition to notice subtle dysfunction.

In general,the prognosis, in terms of overall survival and appearance of metastatic neurologic complications, is mainly determined by the efficacy of the treatment of the primary tumor. Treatment of the peripheral neurologic complications is predominately symptomatic. The potential benefits and risks of PCI have been insufficiently researched. The small but not insignificant cure rate in patients with SCLC provide an incentive for further study in the area of long term neurologic complications.

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10 Summary

Small cell lung cancer (SCLC) is a relatively common lung malignancy and generally has a bad prognosis. This cancer can be accompanied by a wide range of neurologic diseases, ranging from paraneoplastic syndromes to brain metastases. This thesis focuses mainly on the brain metastases related to SCLC.

Chapter 1 comprises a brief general introduction and outlines this thesis' objectives.

Chapter 2 details the results of a longitudinal neurologic follow-up of 203 consecutive patients with SCLC. The most recurring neurologic complication was brain metastasis. A total of 79 patients were diagnosed as having brain metastases, of these 27 had been diagnosed prior to any treatment, and in the remaining 52 the diagnosis was made either during or after treatment of the lung carcinoma. The cumulative risk of developing brain metastasis was 47% in limited disease patients and 69% for extensive disease patients. Patients diagnosed with brain metastases prior to SCLC treatment had a significantly higher survival rate than patients diagnosed with brain metastases in later stages of the disease. Histopathologic examination of the brain metastases in 15 patients resulted in a different diagnosis for 2 patients (13%); other primary tumor n=1, no SCLC after having achieved complete remission for SCLC n=1. The discrepancy of the initial histologic diagnosis and that of the brain metastases might be explained by tumor heterogeneity, tumor changes influenced by treatment or time, and the development of an other primary tumor in the same patient. The other neurologic complications of SCLC are briefly described.

Using the guidelines provided by the Pathology Panel of the International Association for the Study of Lung Cancer the predictive value of the histologic subclassification for neurologic complications are discussed in chapter 3. A retrospective revision was made of the material used to establish the initial SCLC diagnosis of the 239 patients participating in a longitudinal neurologic follow-up study. The subclassification of the histologic as well as cytologic material of these patients resulted in the following: classic cell type n=178, variant cell type n=32 (mixed cell type n=31, combined cell type n=1), and non-classification n=29 (only autopsy material available n=14, initial diagnosis altered n=8, and slides missing n=7). The relationship between developing brain metastases or the duration of brain metastatic-free intervals and the histologic subtyping did not appear to be of any statistical significance. Those patients suffering neurologic complications of paraneoplastic syndromes all had classic small cell subtype. Not withstanding that this result coincides with the result of the experimental research where classic subtype was characterised by a greater manifestation of neuro-endocrine signs, this finding merely represents a trend. Other non-metastatic complications appeared not so much related to the subtype, but

more so dependant on treatment method or coincidence. The conclusion being that we find no clinical significance for histologic subclassification.

Chapter 4 and 5 continues with a discussion of the validity of using cranial computed- tomography (CT) scan and magnetic resonance (MR) imaging in staging patients with SCLC. As part of the initial staging research 57 consecutive patients underwent an examination by a neuro-oncologist and a cranial CT scan. These patients remained under the controlled supervision of the neuro-oncologist (during the first year quarterly, and biannually there after). A cranial CT scan was repeated if there was any suspicion of brain metastases. Three patients were excluded from the trial for various reasons (cerebrovascular accident n=2, leptomeningeal metastases n=1). Of the remaining 54 patients, 50 were neurologically asymptomatic and 4 were symptomatic. In 3 patients the use of CT scan showed aberrations symptomatic to brain metastases. The remaining patients showed no signs of possible metastases.
The same trial was carried out in 40 consecutive patients but this time using MR scan. Movement artefacts excluded 1 patient from this trial. Of the 11 patients in which the MR scan showed deviations similar to metastases 3 were neurologic asymptomatic. The clinical staging of these 3 patients did not change since they already had extensive disease. Of the 14 patients with deep hyperintensive non-Gadolinium enhanced white matter lesions, 4 were neurologic symptomatic. Two of these 4 developed brain metastases within 6 months. In the interim, part of the deep hyperintensive non-Gadolinium enhanced white matter lesions became contrast enhanced.
We concluded that the CT scan is not superior to neurologic examination for detection of brain metastases in SCLC patients. A MR scan, however, can contribute significantly to the early detection of brain metastases and contribute to the primary staging procedure. Deep white matter hyperintensities can make brain metastases undetectable in neurologically symptomatic patients.

Chapter 6 reports on the effectiveness and safety of prophylactic cranial irradiation (PCI) in a prospectively followed group of 203 consecutive SCLC patients. Of the 37 limited disease patients who had achieved complete remission, brain metastases developed in 3 of 17 treated with PCI, versus 8 of 20 non-PCI treated patients. The number of brain metastases did not differ significantly. Patients who underwent PCI treatment did have a considerably longer brain metastatic-free interval and survival rate. It should be noted that this was a non-randomized study, and that the remaining treatment course of the SCLC was not totally equal, as well as the fact that the patient population was too small to show any signs of the effects of PCI. Whether brain metastases developed or not seemed largely dependant on the behavior of the primary tumor.

The early as well as the later possible adverse effects of the treatment are covered in detail. Half of the 18 long-term surviving patients had undergone PCI. These patients had a marked increase in cognitive function associated complaints. There was also an increase in cranial CT scan or MR abnormalities, all of which maybe attributed to PCI treatment. When taken in conjunction with existing literature concerning the use and adverse effects of PCI, it becomes plausible that PCI treatment at least has a synergetic effect on the potential neurotoxic treatment of SCLC. The extent and severity of toxicity to the central nervous system as well as the effectiveness of PCI remains unknown.

Cognitive functioning of SCLC patients is the subject matter of chapter 7. In this study 32 consecutive patients underwent neuropsychologic testing, prior to, during, and after treatment with chemotherapy and/or PCI. During the same period these patients were examined neurologically. Patients with brain metastases were excluded from the neuropsychologic follow-up study. The pretreatment average results were compared to those of a control group with similar age, sex, and intelligence quotient. As a result of either brain metastases or premature death only 14 patients participated in the second trial session, 11 patients in the third and fourth trial session, and 5 patients in the last session. In patients with no indication of brain metastases neurologic deviations were not present. Less serious complaints of concentration and memory, word finding problems, and libido deficiency were indicated. When compared to the matched control group, the patient group clearly performed worse on the 15 Word Auditory Verbal Learning task, the Stroop color-word test and the Trailmaking test. No further treatment-related negative consequences were established.
We concluded that the disease itself can negatively the patients cognitive functioning abilities. Precluding a longitudinal follow-up the effects of the disease and those of the treatment are interchangeable.

Chapter 8 presents the results of research on 59 long-term SCLC survivors. Various long treatment centres in the Netherlands were approached and long-term survivors were asked to voluntarily take part in neurologic, neuropsychologic, and neurologic testing. Since the primary objective of the study was to determine the neurotoxicity of the treatment 8 patients were not able to take part for various reasons (cerebrovascular accidents n=4, no chemotherapy or PCI treatment n=2, Korsakov syndrome n=1, severe head trauma n=1). The neurologic findings are described in 21 patients treated solely with chemotherapy (group 1), 19 patients treated with PCI subsequent to chemotherapy (group 2), and 11 patients treated with concurrent or sandwiched PCI and chemotherapy (group 3). A statistical comparison is made of the quantifiable neuropsychologic and neuroradiologic data. The neuropsychologic test

results were compared between the study groups and also to the results of a healthy group matched for age, gender, and education level. Even though PCI treated patients complained more of cognitive dysfunction and though neurologic abnormalities were more often present in this group of patients (in group 3 more than in group 2), statistically these group differences could not or at best only partially be explained when neuropsychologic and neuroradiologic data were compared. Among the three patient groups there were no neuropsychologic differences. There was, however, a statistically significant difference with the control group. The statistics for the severity of cortical atrophy and the presence of ventricular enlargement and cerebellar atrophy between the three groups was not representative. Yet patients in group 3 did show meaningful statistic differences where white matter lesions are concerned. Namely they had more white matter lesions than the two other groups. Patients in group 3 had a significantly longer survival rate. The three patients groups did not differ in age, gender, education level, cardiovascular risk factors or research methods. The retrospective study of these long-term SCLC survivors concludes that no indications were found for serious PCI related toxicity. The neuropsychologic differences with the healthy control group and the lack of significant disparity among the three patient groups may be indicative of the fact that the patient groups were suffering from SCLC and/or chemotherapy related effects.

The general discussion once again examines the results of all the studies and draws the following conclusions:

- the most frequent neurologic complication of small cell lung cancer are brain metastases.
- the course of the disease when compounded by brain metastases is related to the point when the brain metastases are diagnosed.
- histologic subclassification of the International Association for the Study of Lung Cancer is of no significance in predicting neurologic complications.
- in contrast to computed tomography scanning, is magnetic resonance imaging clearly superior to neurologic examination in helping to establish an early diagnosis of brain metastases.
- hyperintensive white matter lesions impede the identification of brain metastases in neurologic symptomatic patients.
- a longitudinal study is necessary to adequately determine the neurotoxicity of the treatment in small cell lung cancer.
- the overall diminished condition of the patients, either due to the disease small cell lung cancer itself or chemotherapy must be taken into consideration when explaining the cognitive dysfunction in long-term survivors of small cell lung cancer
- retrospective study of 59 long-term survivors of small cell lung cancer could not establish indications of frequent and severe prophylactic cranial irradiation related toxicity.

• subtle cognitive impairment can have a huge impact on daily life functioning in long-term small cell lung cancer survivors.
• it is important to determine subtle changes in cognitive functioning in order to better understand and eventually prevent central nervous system toxicity associated with small cell lung cancer treatment.

11 Samenvatting

Het kleincellig longcarcinoom is een relatief veel voorkomende longmaligniteit met een over het algemeen slechte prognose. Een wijd spectrum van neurologische aandoeningen, varierend van paraneoplastische syndromen tot hersenmetastasen, kunnen de ziekte compliceren. Dit proefschrift richt zich met name op de hersenmetastasen van het kleincellig longcarcinoom.

In hoofdstuk 1 worden, na een korte algemene inleiding, de doelstelingen van dit proefstuk geformuleerd.

In hoofdstuk 2 worden de resultaten van een longitudinale neurologische follow-up van 203 opeenvolgende patienten met een kleincellig longcarcinoom beschreven. Hersenmetastasen waren de meest frequente neurologische complicatie van de ziekte. In het totaal werden bij 79 patienten hersenmetastasen vastgesteld, in 27 patienten voor behandeling en in de resterende 52 patienten gedurende of na behandeling van het longcarcinoom. Het cummulatieve risico op het krijgen van hersenmetastasen bedroeg 47% voor de limited disease patienten en 69% voor de extensive disease patienten. Na de diagnose van hersenmetastasen was de overleving significant langer van patienten bij wie de hersenmetastasen voor de behandeling van het kleincellig longcarcinoom werden vastgesteld dan van de patienten bij wie de hersenmetastasen pas later in het verloop van de ziekte werden gediagnostiseerd.
Histopathologisch onderzoek van de hersenmetastasen van 15 patienten leverde in 2 patienten (13%) een andere diagnose op (andere primaire tumor n=1, niet-kleincellig longcarcinoom nadat eerder complete remissie was bereikt van een kleincellig longcarcinoom n=1). Tumor heterogeniteit, veranderingen in de tumor onder invloed van behandeling of tijd en de ontwikkeling van een andere primaire tumor in dezelfde patient zouden de discrepantie tussen de initiele histologische diagnose en die van de hersenmetastasen kunnen verklaren.
Kort worden de overige neurologische complicaties van het kleincellig longcarcinoom beschreven.

In hoofdstuk 3 wordt de voorspellende waarde van het optreden van neurologische complicaties besproken van de histologische subclassificatie volgens de richtlijnen van het Pathology Panel van de International Association for the Study of Lung Cancer.
Het materiaal waarop de initiele diagnose kleincellig longcarcinoom was gesteld van de 239 opeenvolgende patienten, die deelnamen aan een longitudinale neurologische follow-up studie, werd retrospectief gereviseerd. De subclassificatie van zowel het histologische als het cytologische materiaal van deze patienten leverde de volgende resultaten op: classic cell type n=178, variant cell type n=32,(mixed cell type n=31, combined cell type n=1) en geen classificatie n=29 (alleen autopsie materiaal n=14, initiele diagnose veranderd n=8 en coupes verdwenen n=7). Het histologisch subtype

bleek niet statistisch significant gerelateerd te zijn aan het krijgen van hersenmetastasen of de duur van hersenmetastase-vrije interval.
Patienten met neurologische complicaties van paraneoplastische syndromen bleken allen het classic small cell subtype te hebben. Alhoewel deze bevinding aansluit bij de resultaten van experimenteel onderzoek waarin het classic subtype zich karakteriseerde door een hogere expressie van neuro-endocriene kenmerken, representeerde deze bevinding statistisch slechts een trend. Andere niet-metastatische complicaties leken niet subtype gerelateerd, doch eerder van de behandeling afhankelijk of op toeval berustend. Concluderend vonden wij geen klinische betekenis voor de histologische subclassificatie.

In hoofdstuk 4 en 5 wordt nader ingegaan op de waarde van respectievelijk computed tomography (CT) scan en magnetic resonance (MR) imaging van het cerebrum voor de vroeg detectie van hersen metastasen het stadieren van een patient met een kleincellig longcarcinoom. Als onderdeel van het initiele stadieringsonderzoek ondergingen 57 opeenvolgende patienten een onderzoek door een neuro-oncoloog en een craniele CT scan. Deze patienten bleven onder regelmatige controle van de neuro-oncoloog(eerste jaar elk kwartaal, daarna halfjaarlijks). Bij het vermoeden van hersenmetastasen werd de craniele CT scan herhaald. Drie patienten werden van het onderzoek uitgesloten om diverse redenen (cerebrovasculair accident n=2, leptomeningeale metastasen n=1). Neurologisch waren 50 van de overige 54 patienten asymptomatisch en 4 symptomatisch. CT scan leverde bij hersenmetastasen passende afwijkingen op in 3 patienten. In de overige patienten werden geen mogelijk op metastasen berustende afwijkingen gevonden. Met MR scan werd hetzelfde onderzoek herhaald in 40 andere opeenvolgende patienten. Een patient werd wegens bewegingsartefacten uitgesloten van het onderzoek. Van de 11 patienten met op metastasen lijkende afwijkingen op MR scan waren 3 patienten neurologisch asymptomatisch. De klinische stadiering van deze drie patienten veranderde niet omdat zij reeds een extensive disease hadden. Van de 14 patienten met diep in de witte stof gelegen, hyperintense, niet met Gadolineum aankleurende laesies waren 4 patienten neurologisch symptomatisch. Twee van deze 4 patienten kregen binnen 6 maanden hersenmetastasen. Een deel van de aanvankelijk niet aankleurende laesies bleek inmiddels veranderd te zijn in aankleurende laesies. Wij concluderen dat CT scan geen meerwaarde heeft boven het neurologisch onderzoek voor de detectie van hersenmetastasen bij patienten met een kleincellig longcarcinoom en derhalve van belang kan zijn voor het initiele stadierings onderzoek. MR scan daarentegen kan wel degelijk bijdragen aan de vroegdiagnostiek van hersenmetastasen. Dat de diepgelegen, hyperintense, niet met Gadolineum aankleurende witte stof laesies in neurologisch symptomatische patienten hersenmetastesen kunnen maskeren.

In hoofdstuk 6 wordt verslag gedaan van de effectiviteit en de veiligheid van profylactische schedel bestraling (PCI) in een groep van 203 opeenvolgende patienten met een kleincellig longcarcinoom, die prospectief werden vervolgd. Van de 37 limited disease patienten, die een complete remissie bereikten, kregen 3 van de 17 met PCI behandelde patienten hersenmetastasen versus 8 van de 20 niet met PCI behandelde patienten. Het aantal hersenmetastasen verschilde niet statistisch significant. De met PCI behandelde patienten hadden echter wel een significant langer hersenmetastase-vrij interval en een significant langere overall overleving. Hierbij moet worden aangetekend dat het een niet-gerandomiseerde studie betrof, de overige behandeling van het kleincellig longcarcinoom niet volledig gelijk was en dat de patientengroepen te klein zijn voor het aantonen van een PCI effect. Het wel of niet optreden van hersenmetastasen leek vooral bepaald door het gedrag van de primaire tumor. De vroeg en laat optredende mogelijke bijwerkingen van de behandeling worden in detail beschreven. Van de 18 langdurig overlevende patienten waren 9 met PCI behandeld. Mogelijk als gevolg van deze bestraling, presenteerden de met PCI behandelde patienten beduidend meer klachten aangaande hun cognitief functioneren en hadden zij vaker een afwijkende craniele CT of MR-scan.
Tesamen met gegevens uit de literatuur lijkt het aannemelijk dat PCI op zijn minst een synergistisch effect kan hebben op de potentieel neurotoxische behandeling van het kleincellig longcarcinoom. De exacte ernst en frequentie van de centraal zenuwstelsel toxiciteit zijn echter onbekend, evenals de effectiviteit van PCI.

Het cognitieve functioneren van patienten met een kleincellig longcarcinoom is het onderwerp van studie in hoofdstuk 7. Voor deze studie werden 32 opeenvolgende patienten neuropsychologisch onderzocht, voor, gedurende en na behandeling met chemotherapie en profylactische schedel bestraling (PCI). In dezelfde periode werden patienten ook neurologisch onderzocht. Patienten met hersenmetastasen werden van de neuropsychologische follow-up studie uitgesloten. Van de patienten groep werden de gemiddelde resultaten voor behandeling vergeleken met die van een voor leeftijd, geslacht en intelligentie quotient gematchte controle groep gezonde vrijwilligers. Door hersenmetastasen of vroegtijdig overlijden waren voor de tweede onderzoeks sessie 14, voor de derde en vierde onderzoeks sessie 11 en voor de vijfde onderzoeks sessie 5 patienten beschikbaar. Neurologisch werden geen afwijkingen gevonden in patienten zonder aanwijzingen voor hersenmetastasen. Zowel voor als tijdens behandeling werden lichte klachten over concentratie-, geheugen-, woordvindings- en libido stoornissen geuit. Gemeten met de 15-woorden test, de Stroop test en de Trailmaking test presteerden de patienten voor behandeling significant slechter dan de gematchte controle groep. Er werden geen additionele negatieve effecten van de behandeling op het cognitieve functioneren vastgesteld.

Wij concludeerden dat het cognitieve functioneren van patienten ook door de ziekte zelf negatief kan worden beinvloed. Zonder longitudinale follow-up kunnen de effecten van de ziekte met die van de behandeling verwisseld worden.

In hoofdstuk 8 worden de resultaten weergegeven van een onderzoek naar de centraal zenuwstelsel afwijkingen bij 59 langdurig overlevende patienten met een kleincellig longcarcinoom. In diverse longcentra in Nederland werden langdurig overlevende patienten gevraagd om zich op vrijwillige basis neurologisch, neuropsychologisch en neuroradiologisch te laten onderzoeken. Omdat de studie primair was ontworpen om de neurotoxiciteit van de behandeling van het kleincellig longcarcinoom vast te stellen, werden 8 patienten van het onderzoek uitgesloten om diverse redenen (cerebrovasculair accident n=4, geen behandeling met chemotherapie of PCI n=2, Korsakov syndroom n=1, ernstig schedeltrauma n=1). De neurologische bevindingen worden beschreven bij 21 alleen met chemotherapie behandelde patienten (groep 1), 19 met PCI na beeindiging van de chemotherapie behandelde patienten (groep 2) en 11 gelijktijdig of gesandwiched met PCI en chemotherapie behandelde patienten (groep 3). De gekwantificeerde neuropsychologische en neuroradiologische data worden statistisch vergeleken. De neuropsychologische testresultaten worden zowel onderling als met die van een groep voor leeftijd, geslacht en opleidingsniveau gematchte controlegroep gezonde personen vergeleken.

Alhoewel met PCI behandelde patienten meer klaagden over cognitief dysfunktioneren en bij hen meer neurologische afwijkingen werden geconstateerd (in groep 3 meer dan in groep 2), konden deze groepsverschillen niet of slechts gedeeltelijk statistisch worden bevestigd bij de vergelijking van de neuropsychologische en neuroradiologische data. Neuropsychologisch verschilden de patientengroepen onderling niet. Wel verschilden alle patientengroepen statistisch significant met de controle groep. De mate van corticale atrofie en het voorkomen van ventrikelverwijding en cerebellaire atrofie verschilden statistisch niet significant tussen de drie groepen patienten. Wel vertoonden patienten van groep 3 statistisch significant meer witte stof laesies dan de andere twee patientengroepen. Patienten van groep 3 hadden een significant langere overlevingsduur. De patientengroepen verschilden niet qua leeftijd, geslacht, opleidingsniveau, cardiovasculaire risicofaktoren of gebruikte onderzoekstechnieken.

Wij concludeerden dat in het retrospectieve onderzoek van deze langdurig overlevende patienten met een kleincellig longcarcinoom geen aanwijzingen werden gevonden voor het frequent voorkomen van een ernstige PCI gerelateerde toxiciteit. Het ontbreken van duidelijke groepsverschillen en het significante verschil met de controlegroep neuropsychologisch, doet eerder een ziekte- en/of chemotherapie effect vermoeden.

In de algemene discussie wordt nog eens

In de algemene discussie wordt nog eens ingegaan op de resultaten van alle onderzoeken en worden de volgende conclusies getrokken:

- hersenmetastasen zijn de meest frequente neurologische complicatie van het kleincellig longcarcinoom.
- het beloop van de door hersenmetastasen gecompliceerde ziekten is mede afhankelijk van het tijdstip waarop de hersenmetastasen worden gediagnosticeerd.
- voor het voorspellen van neurologische complicaties heeft de histologische subclassificatie van de International Association for the Study of Lung Cancer geen betekenis.
- voor de vroegdiagnostiek van hersenmetastasen heeft magnetic resonance imaging in tegenstelling tot computer tomography een meerwaarde boven neurologisch onderzoek.
- in neurologisch symptomatische patienten vormen de diep gelegen hyperintense witte stof laesies een beletsel voor de vroegdetectie van hersenmetastasen.
- voor het adequaat vaststellen van de neurotoxiciteit van de behandeling van het kleincellig longcarcinoom is een longitudinale studie noodzakelijk.
- bij de verklaring van de cognitieve problemen, die kunnen worden aangetroffem bij langdurig overlevende patienten, moet rekening worden gehouden met een door de ziekte en chemotherapie verminderde algehele conditie van de patient.
- retrospectief onderzoek van 59 langdurig overlevende patienten met een kleincellig longcarcinoom bracht geen aanwijzingen voor het bestaan van ernstige aan profylactische schedelbestraling gerelateerde toxiciteit.
- subtiele cognitieve problemen kunnen een grote impact hebben op het dagelijks funktioneren van langdurig overlevende patienten met een kleincellig longcarcinoom.
- voor een beter begrip en eventuele preventie van de centraal zenuwstelsel toxiciteit van de behandeling van het kleincellig longcarcinoom is het van belang om een achteruitgang in het cognitieve funktioneren vroeg vast te stellen.

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Curriculum vitae

Ansel van Oosterhout werd op 15 juni 1961 geboren in Delft. Zijn jeugd bracht hij door in Mook. In 1979 haade hij het eindexamen Atheneum-b aan het Elshofcollege in Nijmegen en in 1986 het arts-examen aan de Katholieke Universiteit in Nijmegen. Aansluitend vervulde hij zijn militaire dienstplicht als arts op de afdeling neurologie van het Militair Hospitaal in Utrecht onder supervisie van Dr. W.E. Vliegenthart. Van 1988 tot heden is hij als arts-assistent verbonden aan de afdeling neurologie van het De Wever Ziekenhuis in Heerlen (opleider Dr. C.L. Franke). In het Academisch Ziekenhuis Maastricht volgde hij een stage neuro-oncologie (Dr. A Twijnstra) en psychiatrie (Prof. Dr. H. van Praag en Prof Dr. G. van Leeuwen). In het De Wever Ziekenhuis in Heerlen werd in oktober 1994 de aantekening klinisch neurofysiologie behaald (opleider Dr. J.W. Vredeveld). Momenteel volgt hij een stage neurochirurgie in het Klinikum in Aken (Prof. Dr. J. Gilsbach).