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Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged with Cranial Magnetic Resonance Imaging

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Munich, 27.02.2018
Place, date

Chukwuka Eze
Signature doctoral candidate

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Abbreviations

AJCC – American Joint Committee on Cancer

APUD – Amine Precursor Uptake Decarboxylase

BID – twice a day

BM – Brain metastases

CAV – Cyclophosphamide, doxorubicin and vincristine

CRT – Chemoradiotherapy

EORTC – European Organisation for Research and Treatment of Cancer

EP – Etoposide and cisplatin

ES – extensive stage

Gy - Gray

IARC – International Agency for Research on Cancer

IASLC – International Association for the Study of Lung Cancer

IPD – individual patient data

LS – Limited stage

MRI – Magnetic resonance imaging

NCCN – National Comprehensive Cancer Network

NCDB – National Cancer Data Base

OID – once a day

OR – Odds ratio

OS – Overall survival

PCI – Prophylactic cranial irradiation

SEER – Surveillance, Epidemiology, and End Results

SCLC – Small Cell Lung Cancer

SRS – Stereotactic radiosurgery

TRT – Thoracic radiotherapy

UICC – Union for International Cancer Control

VA – Veterans Administration

Publication list

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Introduction

Based on the IARC world cancer report 2014, lung cancer is the most frequent cancer worldwide with in excess of 1.8 million new cases (13% of cancer incidence) and approximately 1.6 million deaths (20% of cancer mortality), as estimated in 2012.[1] In 2018, an estimated 234,030 people in the United States will be diagnosed with lung cancer of which an estimated 154,050 deaths will occur.[2] In addition to increasing age, other factors associated with increased risk for lung cancer include prior history or current tobacco use, passive smoking, occupational exposure to arsenic, asbestos, chromium, beryllium, nickel and other agents, increased air pollution, family history of cancer and radiation exposure.[3–11] Tumours of neuroendocrine origin account for approximately 20% of lung cancers with the absolute majority in the order of 14% constituting SCLC which is also called oat cell cancer.[12] Small cell lung cancer is thought to stem from neuroendocrine cells (APUD cells) in the bronchus called Feyrter cells.[13] Thus, these cells express multiple neuroendocrine markers and are associated with paraneoplastic syndromes and Cushing's syndrome. SCLC is a highly aggressive, recalcitrant and lethal tumour with TP53 mutation in 70-90% of cases. At initial diagnosis about 30% of patients will present with SCLC restricted to the ipsilateral hemithorax, which can be safely encompassed within a radiation field. Historically, the Veterans Administration Lung Cancer Study Group defined a 2-stage classification and designated the above-mentioned group of patients as having limited stage (LS) disease. In contrast, patients with tumour dissemination beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous are said to have extensive stage (ES) disease.[14,15] However, the AJCC/UICC and IASLC revised the TNM staging for lung malignancies (8th edition) which became effective on January 1, 2018 and in comparing both systems, LS disease is defined as stage I-III (T any, N any, M0).[16,17]

Chemotherapy is an essential pillar for treatment of SCLC regardless of disease stage. Since the mid 1980s, EP is considered standard chemotherapy regimen.[18] This regimen displaced

alkylator/anthracycline-based regimens e.g. CAV regimen based on its favourable efficacy and toxicity profile.[19–21]

Initially, early stage disease was treated with surgery; however, a Medical Research Council comparative trial randomised 144 patients with SCLC, diagnosed by biopsy and deemed operable (71/49%) vs. primary radical radiotherapy (73/51%) of cases. A complete resection was achieved in 48% of patients in the surgical arm and radiotherapy delivered in 85% of patients in the radiotherapy arm. The survival rates in the surgery vs. radiotherapy arm were 4% and 10% at 24 months, 3% and 7% at 48 months, and 1% and 4% at 60 months, respectively.[22] A 10-year follow-up demonstrated improved survival in favour of the radiotherapy arm. The authors concluded that radical radiotherapy conferred favourable survival outcomes in comparison to surgery in operable patients.[23] Another trial published in 1994 enrolled 328 patients with LS-SCLC with histologically confirmed small cell histology and who were deemed eligible for thoracotomy to either undergo pulmonary resection vs. observation for patients responding to induction chemotherapy with CAV for five cycles administered every 21 days. All randomised patients received radiotherapy to the chest (50 Gy in 25 fractions) and PCI (30 Gy in 15 fractions). Sixty-six percent (217 patients) demonstrated good response. Sixty-six percent of responders (146 patients) were thus randomised to surgery (70 patients) vs. observation (76 patients). In the surgical series, a resection rate of 83% was achieved. No statistical significance was achieved between both arms. Median survival for all enrolled patients and randomised patients was 12 and 16 months, respectively. The results of the trial did not endorse inclusion of pulmonary resection to multimodality treatment of SCLC.[24] Currently, there is some data supporting the use of surgery in patients with stage I disease under the premise that patients are comprehensively staged prior to surgical treatment. Following surgery, based on current guidelines, adjuvant chemotherapy is recommended in this setting based on a NCDB analysis by Yang et al.[25]

SCLC is highly radiosensitive and TRT improves survival of patients. In 1992, two meta-analyses demonstrated that the addition of TRT to chemotherapy was associated with improved

survival outcome in LS-SCLC. The first meta-analysis by Pignon et al. collected the individual patient data on all patients enrolled before December 1988 in randomised trials comparing chemotherapy alone with chemotherapy combined with TRT. A total of 13 trials and 2140 patients of which 2103 patients were evaluated. The overall relative risk of death in the multimodal therapy arm vs. chemotherapy arm was 14% lower.[26] Moreover, the meta-analysis by Warde et al. included 11 randomised trials and demonstrated an overall OR for benefit of TRT on 2-year survival of 1.53 (95% CI 1.3-1.76; $p < 0.001$). Intrathoracic tumour control was improved by 25.3% and TRT improved two-year survival by 5.4 %.[27] Chemoradiotherapy was established as standard of treatment for LS-SCLC with the burden of evidence supporting early concurrent CRT endorsed by various studies and meta-analyses which have reported that early concurrent CRT is associated with favourable survival outcome in comparison to late concurrent/sequential CRT.[28–34] The Japan Clinical Oncology Group Study 9104 study from Takada and colleagues strongly suggested that concurrent CRT with EP is more effective for the treatment of LS-SCLC than sequential CRT.[31] De Ruysscher et al. defined a short time interval between the first day of any treatment and the last day of TRT as SER which correlated with OS.[35] More recently, De Ruysscher published another meta-analysis of IPD from 12 trials (2668 patients) reporting improved 5-year survival in the early concurrent CRT vs. late concurrent CRT arm.[36] In LS-SCLC, previous randomised trials have reported median survivals of 18-24 months and 40%-50% 2-year survival rates.[28,31,37–39] Previously, the preponderance of evidence has reported no consistent survival benefit from administration of supplementary chemotherapeutic agents or other platinum-based combination regimens, increased dose density and intensity and maintenance chemotherapy.[29,40–46] Regarding the fractionation schedule of TRT, the landmark intergroup 0096 trial endorsed twice-daily CRT commencing with the first chemotherapy cycle for patients with limited stage disease as significantly improved survival was conferred compared to once-daily CRT. In the study, patients were randomised to receive 45/1.8 Gy once-daily concurrent CRT or 45 Gy twice-daily concurrent CRT (1.5 Gy per fraction). Median survival was 19 and 23 months for the once- and the twice-

daily group, respectively. Two- and five-year survival rates were 41% and 16% in the once-daily radiotherapy vs. 47% and 26% for patients receiving twice-daily radiotherapy. However, this was at the cost of significantly increased treatment related toxicity e.g. significantly higher incidence of grade 3 oesophagitis occurred in the twice-daily vs. once-daily group (27% vs. 11%).[39] However critics have argued whether the improved survival outcome was due to the higher biologically effective dose of TRT or the shorter start of any treatment until the end of radiotherapy. As such twice-daily CRT was not universally adopted for the above-mentioned reasons as well as operational issues pertaining to delivery of TRT twice per day. Consequently, the CONVERT trial by Faivre-Finn et al. was designed as a non-inferiority trial comparing higher dose once-daily radiotherapy with concurrent EP vs. the twice-daily regimen in the intergroup 0096 trial.[47] In that study, the authors demonstrated non-significant differences in survival outcomes with once- vs. twice-daily CRT (median OS of 25 vs. 30 months in the once- vs. twice-daily group), 2-year and 5-year OS of 51% vs. 56%, and 31% vs. 34% in favour of the twice-daily group. Interestingly, toxicity was comparable and below the estimated threshold. However, increased grade 4 neutropenia with twice-daily CRT was detected. Moreover, no difference in grade 3-4 oesophagitis and grade 3-4 radiation pneumonitis was determined. As the trial had a non-inferiority design, the authors concluded that twice-daily CRT remain standard practice in this setting. However, once-daily CRT is a feasible option.

Prophylactic cranial irradiation in LS-SCLC

Approximately 10% of SCLC patients present at diagnosis with BM with the cumulative risk rising to ≥ 50% and an incidence of BM in up to 80% of subjects at autopsy.[48,49] The brain is considered a sanctuary and the blood-brain barrier considered to protect the CNS from cytotoxic agents. The incapability of multiple systemic chemotherapeutic agents to penetrate the blood-brain-barrier has hampered their use. Prophylactic cranial irradiation (PCI) was initially proposed for SCLC in 1973 due to the high incidence of BM in these patients and insufficient control with whole brain radiotherapy. Two meta-analyses showed benefit in terms of development of BM and survival.[50,51] The first meta-analysis by Aupérin and colleagues demonstrated a modest but significant overall survival improvement from administration of PCI in complete responders which led to a 5.4% increase in 3-year survival. Moreover, PCI increased the rate of disease-free survival and decreased the cumulative incidence of BM.[50] The second meta-analysis from Meert and colleagues incorporated 12 randomised trials with 1547 patients. PCI significantly decreased the incidence of BM and conferred favourable survival outcome in complete responders. However, long-term neurologic sequelae was not sufficiently described.[51]

However, the criticism levelled against both meta-analyses was they included studies in an era in which consequent neuroimaging was not mandated (pre-MRI era) and hence the role of PCI in the current age of ubiquitous availability of brain imaging might be subject to re-evaluation. Manapov et al. ascertained the role of a repeat cranial MRI before PCI. In a small retrospective study, BM were detected in 13/40 LS-SCLC patients who initially showed no evidence of BM on the first cranial MRI before primary treatment but developed brain failure on repeat MRI prior to PCI.[52] Furthermore, Ozawa et al. deemed that PCI might be less effective in LS-SCLC provided extended management with cranial MRI and SRS were readily accessible.[53] PCI has thus been the topic of recurring discussion as experts have serially debated its pros and cons in particular in relation to potential neurologic sequelae. Historically, prior to the publication by Aupérin et al., Cmelak and colleagues published a large survey with a total of 1231 responders,

including 628 (51%) radiation oncologists, 587 (48%) medical oncologists. Seventy-four percent of respondents recommended PCI in LS-SCLC (82% of radiation oncologists and 65% of medical oncologists). Only 30% of respondents recommended PCI for ES-SCLC. Medical oncologists believed more often than radiation oncologists that PCI causes late neurological sequelae (95% vs. 84%, $p<0.05$).[54]

The NCCN guidelines recommend PCI in patients with LS-SCLC who demonstrate a good response to initial therapy based on the above-mentioned meta-analyses, which as stated included trials which did not incorporate routine brain imaging.[55] The role of PCI in the small subset of patients with resected pathological stage I disease has previously been extensively discussed with the paucity of data suggesting a relatively low incidence of BM.[56,57] Thus omission of PCI in this subgroup of patients may be a viable option.

PCI in Elderly (≥70 yr.)

The proportion of elderly among all cases of SCLC has increased over the past 40 years.[58] The number of elderly patients (>70 years) among all cases of SCLC increased as per the Surveillance, epidemiology, and end results database from 23% in 1975 to 44% in 2010. In general, elderly could be characterised by a lower performance status and higher comorbidity index. Earlier studies have shown that elderly fair significantly worse in comparison to younger SCLC patients.[59,60] Also, a large cohort study regarding therapeutic whole brain irradiation reported significant toxicity such as neurocognitive dysfunction with memory loss in patients older than 70 years.[61] In this context, elderly patients are the focus of research to reduce treatment-related toxicity of cranial irradiation and improve prognosis.

There are no previous prospective randomised studies addressing the issue of PCI in elderly, however in the meta-analysis by Aupérin et al., patients ≥65 yr. had a relative risk of death of 0.79 (95% CI 0.60-1.03) and RR of BM of 0.37 (95% CI 0.24-0.59) which in both cases was lower than in patients <65 yr.[50] Additionally, various retrospective studies have shown a significant improvement in survival in elderly patients[62,63]. In a study by Rule et al., PCI

resulted in a median survival of 12.0 months vs. 7.6 months in the non-PCI group as well as 3yr. OS 13.2% vs. 3.1%.[62] Similarly, Eaton et al. demonstrated using the SEER database that PCI conferred favourable survival outcome.[63] The recent phase III CONVERT-Study included patients with LS-SCLC with 83 patients (15%) ≥70 yr. and this data was presented at the 2016 World Conference of Lung Cancer in Vienna, Austria and the final publication is still pending.[47] In the first publication, we defined an association between treatment response to multimodal therapy and survival parameters in LS-SCLC and compared survival parameters based on treatment response e.g. complete vs. partial remission. As previously extensively stated, the preponderance of evidence suggests that chemoradiotherapy with thoracic radiotherapy starting with the first or second cycle of CRT represents the standard treatment for LS-SCLC. In contrast, Sun et al. demonstrated that a delayed start of TRT (late TRT arm) to a total dose of 52.5 Gy in 2.1 Gy daily fractions starting with the third cycle of chemotherapy (day 43) is statistically non-inferior to early TRT beginning on day 1 of the first cycle of chemotherapy (early TRT arm) [median OS 26.8 months vs. 24.1; HR 0.90; 95% CI 0.18–1.62 and median progression-free survival 11.2 months vs. 12.4; HR 1.10; 95% CI 0.37-1.84] and is associated with significantly favourable haematological toxicity profile, including neutropenic fever (10.2% vs. 21.6%;p= 0.02).[64] In addition, no differences in remission rates and early vs. late irradiation arms were detected. However, favourable OS outcome was significantly associated with achievement of complete remission. Furthermore, Manapov et al. demonstrated in a previous publication that the duration of BM-free survival correlated with long-term outcome. Moreover, the response of the primary tumour to CRT correlated with the duration of BM-free survival in LS-SCLC.[65]

The second publication sought to characterise the role of PCI in an actual heterogeneous LS-SCLC cohort. Based on a previous publication by Manapov et al. published in 2008 which detected a significant incidence of BM in LS-SCLC patients who initially showed no signs of BM prior to primary treatment but showed evidence of BM on repeat MRI before PCI.[52] Thus repeat MRI is recommended for LS-SCLC patients prior to PCI. Ozawa and colleagues

postulated that PCI may be less effective in LS-SCLC provided extended management with brain MRI and SRS was readily accessible.[53] As previously extensively discussed, the landmark meta-analyses of PCI included trials in the pre-MRI era. Thus, critics have argued that its modest survival benefit might dissipate in the presence of comprehensive brain imaging as some have suggested that the improved survival outcome conferred by PCI may be attributed to treatment response of subclinical BM to cranial irradiation and not per se "PCI".

This conclusion was highlighted by a recent Japanese trial by Takahashi et al. in patients with extensive stage SCLC which has sparked renewed debate within the thoracic oncology community. Since the EORTC trial by Slotman et al. in 2007 which demonstrated a reduction in risk of BM, 1-year cumulative risk of BM of 14.6% and 40.4%, 1-year survival rate of 27.1% vs. 13.3% in the PCI vs. control group and an association of PCI with improved median disease-free survival from 12.0 weeks to 14.7 weeks and median OS from 5.4 months to 6.7 months from randomisation, PCI was established as treatment standard in ES-SCLC.[66]

The Japanese study by Takahashi et al. randomised 224 patients between 2009- 2013 to PCI vs. observation. On interim analysis of the first 163 enrolled patients, Bayesian predictive probability of PCI being superior to observation was 0.011%, resulting in early termination of the study due to futility. In the final analysis, median OS from randomisation was 11.6 and 13.7 months in the PCI and observation arm, respectively. The authors concluded that PCI could be omitted in therapy responders provided these patients were followed comprehensively by serial brain imaging and radiotherapy be deferred till onset of BM.[67]

The purpose of the second study was to demonstrate favourable survival outcome conferred by PCI in an actual heterogeneous cohort prodigiously staged with brain MRI.

Summary

Based on the results of our retrospective analyses, we defined the role of remission status in LS-SCLC solely treated with CRT and compared survival outcome in patients based on remission status. In the first study, remission status was significantly associated with tumour

control. Subsequently showing a clear association with overall survival. Furthermore, complete remission led to improved time to progression, distant metastasis-free survival and overall survival compared to patients with stable or progressive disease and especially patients with partial remission.

The second study on assessing the efficacy of PCI in an actual LS-SCLC cohort continuously staged with cranial MRI. PCI was delivered exclusively in patients who demonstrated good response to primary treatment and no signs of BM on repeat MRI. Thus, we sought out to define the authentic preventative role of PCI in comparison to the landmark meta-analyses which included trials prior to the MRI era. Our results demonstrated a significant association between delivery of PCI in therapy responders and time to progression, brain metastasis-free survival and overall survival.

Zusammenfassung

Basierend auf den Ergebnissen unserer retrospektiven Analysen haben wir die Rolle des Remissionsstatus bei LS-SCLC Patienten, die mit primärer Radiochemotherapie behandelt wurden. Wir verglichen die Überlebensparameter in den verschiedenen Untergruppen von Patienten, die nach dem Remissionsstatus definiert wurden. Die erste Studie zeigte einen klaren Zusammenhang zwischen Remissionsstatus und Tumorkontrolle. Zudem konnte ein klarer Zusammenhang mit dem Gesamtüberleben nachgewiesen werden. Darüber hinaus führte eine vollständige Remission zu einer verbesserten Zeit bis zum Fortschreiten der Erkrankung, zu einem verbesserten Fernmetastasenfreien Überleben und letztendlich zu einem besseren Gesamtüberleben im Vergleich zu Patienten mit stabiler oder fortschreitender Erkrankung und insbesondere zu Patienten mit partieller Remission.

Die zweite Studie zielte darauf ab, die Rolle der PCI in einer realen heterogenen LS-SCLC-Patientenkohorte, die mit kranialer MRT umfassend untersucht wurde, zu untersuchen. PCI wurde ausschließlich bei Patienten eingesetzt, die auf die primäre Behandlung gut ansprachen und keine Anzeichen von BM bei wiederholter MRT zeigten. Daher haben wir versucht, die

authentische präventive Rolle der PCI im Vergleich zu den wegweisenden Meta-Analysen zu definieren, die Studien vor der MRI-Ära inkludierten. Unsere Ergebnisse zeigten einen signifikanten Zusammenhang zwischen der Verabreichung von PCI in Therapie-Respondern und der Zeit bis zur Progression, dem Überleben ohne Hirnmetastasen und dem Gesamtüberleben.

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Evaluation of the role of remission status in a heterogeneous limited disease small-cell lung cancer patient cohort treated with definitive chemoradiotherapy

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Abstract

Background: The role of remission status in limited disease (LD) small-cell lung cancer (SCLC) patients treated with definitive chemoradiotherapy (CRT) remains to be finally clarified.

Methods: Individual data from 184 patients treated with definitive CRT concurrently or sequentially were retrospectively reviewed. Kaplan-Meier analysis as well as univariate and multivariate Cox regression models were used to describe survival within patient subgroups defined by remission status.

Results: 71 (39 %) patients were treated in the concurrent, 113 (61 %) in the sequential CRT mode. Prophylactic cranial irradiation (PCI) was applied in 71 (39 %) patients. 37 (20 %) patients developed local, while 89 (48 %) distant recurrence. 58 (32 %) patients developed metachronous brain metastases. Complete, partial remission and non-response (defined as stable and progressive disease) were documented in 65 (35 %), 77 (42 %), and 37 (20 %) patients, respectively. In complete responders median overall survival was 21.8 months (95CI: 18.6 – 25) versus 14.9 (95 % CI: 11.7 – 18.2) ($p = 0.041$, log-rank test) and 11.5 months (95 % CI: 8.9 – 15.0) ($p < 0.001$, log-rank test) in partial and non-responders, respectively. The same effect was documented for the time to progression and distant metastasis-free survival. In the multivariate analysis achievement of complete remission as a variable shows a trend for the prolonged time to progression ($p = 0.1$, HR 1.48) and distant metastasis-free survival ($p = 0.06$, HR 1.63) compared to partial responders and was highly significant compared to non-responders.

Conclusion: In this treated heterogeneous LD SCLC patient cohort complete remission was associated with longer time to progression, distant metastasis-free and overall survival compared to the non- and especially partial responders.

Keywords: Remission, Chemoradiotherapy, Limited disease, Small-cell, Lung cancer

Background

SCLC accounts for about 13 % of all lung cancer cases with one third of the patients presenting with LD [1]. Due to the early tendency to systemic dissemination, LD SCLC has a relatively rapid course with a median survival for treated patients of approximately one and half a years [1]. Multimodality treatment consisting of chemotherapy and thoracic radiation therapy (TRT) represents a key treatment stone. Additionally, PCI has shown to improve overall survival due to prevention of brain metastasis (BM) [2, 3]. Consecutive meta-analyses for LD SCLC reported better long-term outcome when platinum-based chemotherapy and early concurrent TRT are applied [4, 5]. De Ruysscher et al. found that a short time interval between the first day of any treatment and the last day of TRT is associated with improved overall survival (OS) [6]. Another retrospective study demonstrated that duration of CRT, itself, correlates with OS in

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LD SCLC patients with poor initial performance status (PS) successfully treated with multimodality therapy [7].

In 2013 Sun et al. published a phase III study investigating the timing of TRT in the course of chemotherapy in LD SCLC [8]. No differences were found in the remission rate and survival between early and late irradiation groups. However, complete response was significantly associated with better OS. A 1997 published trial on the timing of TRT has already described significantly higher complete remission rates associated with better long-term outcome in the early versus late irradiation group [9]. Correlation between remission status after CRT and brain-metastasis free survival in LD SCLC has also been previously documented [10].

The aim of the present study was firstly to establish a correlation between response to multimodality treatment and survival in a heterogeneous LD SCLC patient cohort and secondly to compare different survival parameters in the subgroups of treatment responders, e.g. complete versus partial remission.

Methods

Patients

One hundred eighty-four patients from two institutions with initial PS score of WHO 0–3 were diagnosed with LD (UICC Stage I-III) SCLC and successfully treated with definitive CRT in concurrent or sequential modes from 1998 to 2011. Diagnosis was histologically proven in all patients. LD was defined as disease confined to one hemithorax with or without contralateral mediastinal and ipsilateral supraclavicular lymph node involvement, according to Murray et al. [11]. Evidence of pleural effusion and involvement of the contralateral supraclavicular and/or hilar lymph nodes was considered as an exclusion criterion [12]. In all patients initial staging included bronchoscopy with biopsy, CT scans of the chest and abdomen, bone scintigraphy and contrast-enhanced cranial MRI. All patients provided written informed consent before they started treatment. Retrospective study was approved by the University of Munich Ethic Committee.

Chemoradiotherapy

Concurrent CRT mode was conducted in 71 (39 %) patients and consisted of TRT starting with the first or second cycle of chemotherapy followed by two to four consolidation cycles. The sequential mode of treatment was applied in 113 (61 %) patients consisting of four to six chemotherapy cycles followed by TRT. The most common chemotherapy regimen was a combination of cisplatin either with etoposide or irinotecan. Chemotherapy was given in a 28-day cycle in patients treated with concurrent CRT and in a 21-day cycle in patients treated with sequential CRT according to Takada et al. [13]. TRT was delivered on the linac with megavoltage equipment (8–15 MV) using a coplanar multiple field technique. Three-dimensional CT-simulated treatment planning was performed. Planning target volume was defined as a primary tumour bulk including involved lymph nodes visualised on the pre-therapeutic CT with 1.0 cm margin. 96 % patients were treated 5 days a week with daily fractions of 1.8/2.0 Gy to a total dose of at least 54 Gy (range: 54 – 66Gy). 4 % of patients were treated with hyperfractionated accelerated TRT according to Turrisi AT et al. [14]. After completion of CRT 71 patients (39 %) with good partial and complete remission were treated with PCI (daily 2 Gy to a total dose of 30–36 Gy).

Response assessment

Response evaluation was done within two weeks after completion of CRT and based on CT scanning of thorax and abdomen as well as bone scintigraphy. Contrast-enhanced cranial MRI was routinely performed before commencing PCI to exclude BM (Brain metastasis). Follow-up care was performed every 3 months during the first two years and every 6 months from the third year onwards. Response evaluation was based on the CT scans and performed by radiologist. Tumor response was defined according to Response Evaluation Criteria in Solid Tumors criteria [15]. Complete remission was defined in cases where staging did not demonstrate any signs of tumor and bronchoscopy revealed a tumor-free biopsy.

Statistics

All patients were recorded until death. There is no median follow-up due to the fact that the majority of patients died; therefore follow-up was as complete as possible. Survival rates were analysed according to Kaplan-Meier method and were measured from the date of initial diagnosis using SPSS 16.0 software. Kaplan-Meier analyses (pair-wise comparisons) were used to compare survival curves for the complete remission, partial remission and non-response (stable and progressive disease) subgroups. Remission status was also analysed for its association with time to progression (TTP), distant metastasis-free survival (DMFS) and overall survival (OS) by univariate and multivariate Cox regression models after adjustment for other prognostic factors (borderline significant factors in the univariate analysis).

Results

Patient and treatment characteristics

Patient characteristics are described in Table 1. Of 184 patients treated, 111 (60 %) were men and 73 (40 %) were women. Median age at diagnosis was 63 years (range: 34–83). 34 (19 %) patients were older than 70 years. Median PS according to WHO for the entire cohort was 1 (range: 0 to 3). 71 (39 %) patients were treated

Table 1 Patient- and treatment characteristics

Characteristics	Number of Patients (*N* = 184)	%
Age at diagnosis		
Median 63 (range 34–83)		
>70 years	34	19
Sex		
M	111	60
F	73	40
CRT mode		
Sequential	113	61
Concurrent	71	39
Chemotherapy		
Platinum based	164	89
Non platinum based	20	11
Chemotherapy Cycles		
> = 4	148	80
<4	36	20
PCI		
yes	71	39
no	113	61

with concurrent and 113 (61 %) sequential treatment modes. T3/4-Stage disease was diagnosed in 101 (55 %) patients. 110 (60 %) patients presented with N-Stage 2 or 3. T1-T2 (<5 cm) primary tumors without lymph node involvement were only detected in five (3 %) patients. Sufficient data on T- and N-stage were missing in 26 (14 %) and 35 (19 %) cases, respectively. There were no significant differences in regard to age, sex, PS and TNM-stage between patients treated in the concurrent and sequential groups. Platinum-based chemotherapy was applied in 164 (89 %) patients. 36 (20 %) patients were treated with less than four cycles of chemotherapy. PCI was applied in 71 (39 %) patients with good partial or complete remission. Median duration of multimodality treatment was 165 (range: 16–327) days. Median duration of TRT was 43 (range: 16–76) and of chemotherapy 108 (range: 5–233) days, respectively.

Treatment response

Treatment response to definitive CRT is described in Table 2. Objective response was found in 142 (77 %) patients. Complete remission was documented in 65 (35 %) patients and was confirmed with bronchoscopy. 77 (42 %) patients had a partial remission. 37 (20 %) patients had non-response (stable or progressive disease). A lack of data on remission status was documented in 5 (3 %) cases. Local recurrence was found in 37 (20 %) patients. 89 (48 %) patients developed distant metastases. Metachronous BMs were detected in 58 (32 %) patients. Median OS, DMFS and TTP for the entire cohort were 16.8 (95 CI: 14.8 – 18.9), 18.2 (95 CI: 14.1 – 22.2) and 14.5 months (95 CI: 11.9 – 17.1), respectively. No difference in survival parameters could be found in patients treated with the concurrent versus sequential modes.

Table 2 Distribution of treatment response to definitive chemoradiotherapy

Treatment Response	Number of Patients (*N* = 184)	%
Complete remission	65	35
Partial remission	77	42
Non-Response (stable/progressive disease)	37	20
Not validated	5	3
Metachronous brain failure	58	32
Distant failure	89	48
Local failure	37	20

Remission status and survival

Pair-wise comparisons for OS, DMFS and TTP within the patient subgroups defined by remission status were performed. Median OS in complete responders was 21.8 (95 % CI: 18.6 – 25) versus 14.9 (95 % CI: 11.7 – 18.2) ($p = 0.041$, log-rank test) and 11.5 months (95 % CI: 8.9 – 15) ($p < 0.001$, log-rank test) in partial and non-responders, respectively (Fig. 1). Considering the control of systemic disease, median DMFS in patients with complete remission was not reached (Fig. 2: see Plateau was over 50 %) whereas in partial and non-responders, it was only 16.6 (95 % CI: 11.9 – 21.2) ($p = 0.009$, log-rank test) and 11.9 (95 % CI: 8.9 – 15) ($p = 0.001$, log-rank test) months, respectively. The same effect was also shown for the TTP: in complete responders it was 23.6 versus 13.5 (range: 9.2 – 17.7) ($p = 0.027$, log-rank test) and 10 (range: 6.1 – 13.9) ($p < 0.0001$, log-rank test) months in patients with partial remission and stable/progressive disease, respectively (Fig. 3: see Plateau).

In the multivariate analysis, comparing survival in complete and partial responders, the trend for prolonged TTP ($p = 0.1$, HR 1.48) and DMFS ($p = 0.06$, HR 1.63) was demonstrated (Table 3). Significantly longer OS, DMFS and TTP in complete responders compared to non-responders were confirmed.

Discussion

The aim of this retrospective analysis was to establish the role of remission status in LD SCLC patients treated with chemotherapy and TRT without surgery and to compare survival parameters in the different subgroups defined by remission status. This study demonstrates a clear correlation between achieved remission after primary multimodality treatment and systemic disease control as well as overall survival. Especially our results show that complete response following CRT was associated with

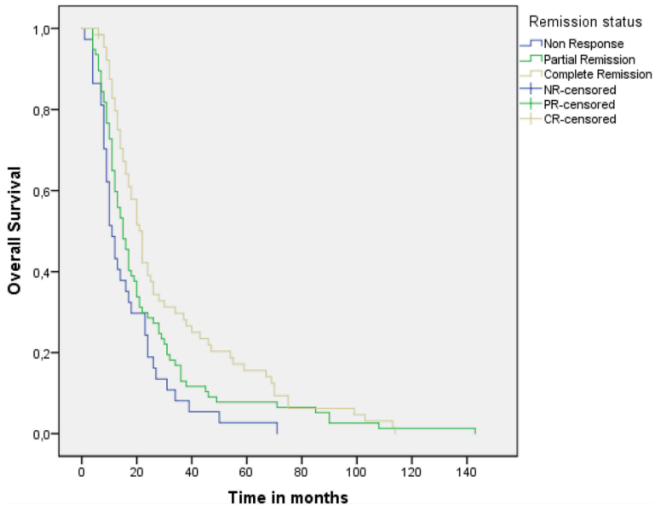

Fig. 1 Overall survival in patient subgroups defined by remission status after CRT

prolonged TTP, DMFS and OS when compared to partial remission.

Disease control becomes of prime importance in the treated LD SCLC due to the early onset of metastases. A number of studies have reported that the absolute majority of patients with LD SCLC will develop a recurrence [1, 12, 16, 17]. Our analysis on the timing of treatment failure in LD SCLC has demonstrated that in more than half of the patients with distant relapse, failure occurred in the first year from initial diagnosis [18]. Hence previous clinical trials have addressed the question of the correlation between treatment response, disease control and outcome after CRT. A phase III trial published in 1997 by Jeremic et al. firstly showed higher complete remission rates in patients treated with early compared to late concurrent CRT correlated with better long-term survival [9]. However, remission status itself was not analyzed as a prognostic factor. Sixteen years later Sun et al. conducted a phase III study

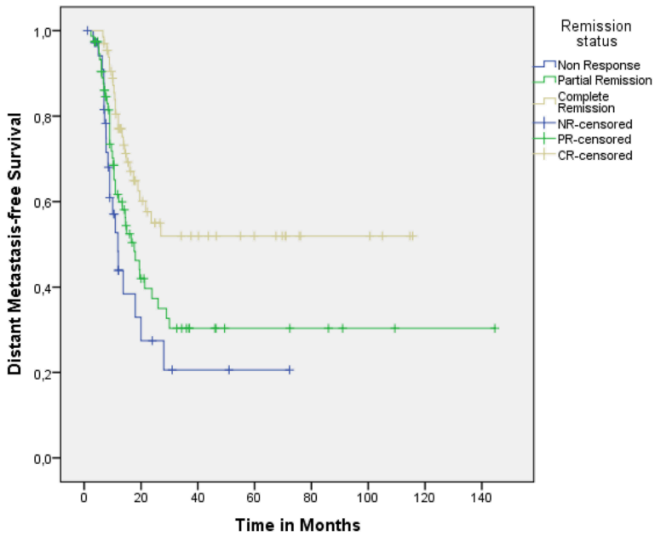

Fig. 2 Distant metastasis-free survival in patient subgroups defined by remission status after CRT

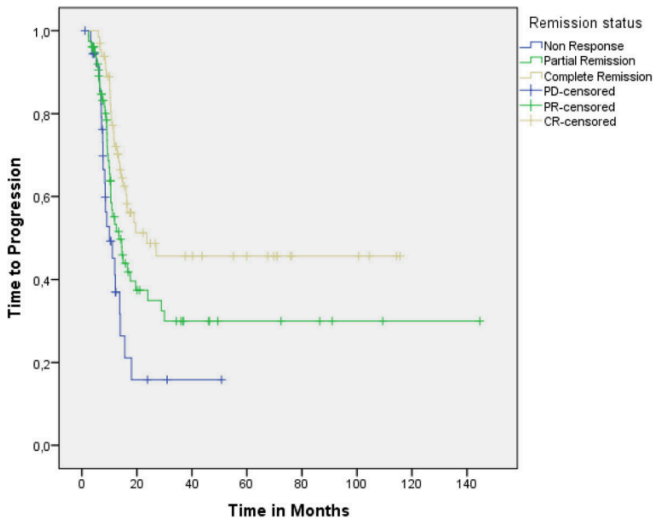

Fig. 3 Time to progression in patient subgroups defined by remission status after CRT

on the timing of TRT concurrent with chemotherapy with complete remission rate as the primary endpoint. Early and late TRT arms were found to be identical concerning remission status and survival rates. The trial demonstrated that complete responders independent of the timing of TRT have significantly better prognosis compared to the rest of the treated patients [8]. In contrast to the above mentioned studies, the present analysis was conducted in a heterogeneous patient cohort and aimed to compare survival parameters between complete, partial and non-responders. The importance of the achievement of complete remission for the TTP, DMFS and OS was emphasized. This fact may be considered in the planning and assessment of future multimodality trials for LD SCLC.

The relevance of tumor shrinkage or downstaging during the course of CRT was already investigated in several smaller studies [19–21]. A correlation between early metabolic (before start of TRT) and CT changes of the tumor volume and survival in LD SCLC was described by van Loon et al. [19]. Go et al. revealed that downstaging during CRT can be considered as an independent prognostic factor [20]. Also Fujii et al. reported that the achievement of remission after the first cycle of chemotherapy applied simultaneously with TRT was associated with significantly better 2-year survival rate [21].

Table 3 Survival parameters in the multivariate analysis after adjustment for other prognostic factors

Survival	Complete versus partial remission (HR and *p* value)	Complete remission versus non-response (HR and *p* value)
Median OS	1.267 (95CI: 0.899 – 1.787) $p = 0.177$	2.135 (95CI: 1.392 – 3.275) $p = 0.001$
Median DMFS	1.632 (95CI: 0.978 – 2.724) $p = 0.061$	3.276 (95CI: 1.771 –6.057) $p < 0.001$
Median TTP	1.486 (95CI: 0.912 – 2.422) $p = 0.1$	3.144 (95CI: 1.776 –5.595) $p < 0.0001$

A major limitation of the present study is its retrospective nature. However, described treatment response rates and survival correlated well with reported historical data. Another important critical point is the heterogeneity of the analyzed cohort but only 3 % of patients presented with primary tumors <5 cm without lymph-node involvement (UICC Stage I). Comprehensive retrospective acquisition of the treatment toxicity was not possible and we decided to analyze only medical charts of the patients who completed definitive CRT without interruptions. Moreover an integration of the PET-CT (Positron emission tomography–computed tomography) could not be exactly evaluated, because fewer than 20 % percent of patients received PET-CTs at initial staging. Nevertheless, present results point out a clinical relevance of the complete remission after definitive CRT and suggest that remission status may be considered as an additional factor in the planning and assessment of multimodality clinical trials for LD SCLC.

Conclusion

In our retrospective analysis of heterogeneous LD SCLC patient cohort, achievement of complete remission after definitive CRT was associated with a relevant survival

advantage compared to the patients with stable/progressive disease and especially partial responders.

Abbreviations
BM: brain metastasis; CRT: chemoradiotherapy; CT: computed tomography; DMFS: distant metastasis-free survival; LD: limited disease; OS: overall survival; PCI: prophylactic cranial irradiation; PET-CT: Positron emission tomography–computed tomography; PS: performance status; SCLC: small-cell lung cancer; TRT: thoracic radiation therapy; TTP: time to progression.

Competing interests
The authors declare that they have no competing interests.

Authors' contribution
All persons listed as authors have read the manuscript and given their approval for the submission. FM collected data, participated in the study design, performed the statistical analysis, wrote the manuscript. MN performed the statistical analysis. SG participated in the study design, performed the statistical analysis. OR collected data, wrote the manuscript. CE collected data, wrote the manuscript. ML participated in the study design, edited the manuscript. GH collected data, participated in the study design. RF collected data, participated in the study design. GK collected data, participated in the study design. CB participated in the study design, edited the manuscript.

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Publication II

Original Study

Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging

Chukwuka Eze,[1] Olarn Roengvoraphoj,[1] Maximilian Niyazi,[1] Guido Hildebrandt,[2] Rainer Fietkau,[3] Claus Belka,[1,4] Farkhad Manapov[1]

Abstract

To evaluate the effect of prophylactic cranial irradiation (PCI) in patients with disease that responded to therapy, we reviewed 184 limited-disease small-cell lung cancer patients comprehensively staged by contrast-enhanced cranial magnetic resonance imaging. Treatment response and PCI strongly correlated with prolonged overall survival, time to progression, and brain metastasis–free survival.

Introduction: Prophylactic cranial irradiation (PCI) has proven to decrease the incidence of brain metastases (BMs), with a modest improvement in survival. **Patients and Methods:** The impact of PCI was evaluated in 184 patients treated with chemoradiotherapy. PCI was applied to patients with disease with partial and complete response only when cranial magnetic resonance imaging before and after primary treatment revealed no BMs. Correlation between PCI and overall survival (OS), BM-free survival (BMFS), and time to progression (TTP) was analyzed to describe survival within subgroups. **Results:** Concurrent and sequential chemoradiotherapy was applied in 71 patients (39%) and 113 patients (61%), respectively. Seventy-one patients (39%) with partial and complete response were treated with PCI. Metachronous BMs were detected in 16 (23%) of 71 patients in the PCI group compared to 42 (37%) of 113 patients in the non-PCI group. Median BMFS in the PCI group was not reached; it was 23.6 months in the non-PCI group. Median OS and TTP were 26 months (range, 19.4-32.6 months) in the PCI group versus 14 months (range, 11.4-16.6 months) in patients without PCI whose disease responded to therapy versus 9 months in patients with disease that did not respond to therapy ($P < .0001$), and 27 versus 14.5 months (range, 9.0-19.9 months) versus 8.8 months (range, 7.7-9.9 months) ($P < .0001$) in the PCI group versus those with response without PCI versus those with nonresponse. The effect of PCI was independent of gender. On multivariate analysis, PCI was a variable correlating with OS (hazard ratio = 1.899; 95% confidence interval, 1.370-2.632; $P < .0001$) and TTP (hazard ratio = 2.164; 95% confidence interval, 1.371-3.415; $P = .001$) after adjustment for other prognostic factors. **Conclusion:** In real-life patients comprehensively staged with cranial magnetic resonance imaging, treatment response and PCI strongly correlated with prolonged OS, TTP, and BMFS.

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Keywords: Brain metastasis, Chemoradiotherapy, PCI, SCLC, Survival

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Introduction

Small-cell lung cancer (SCLC) accounts for about 13% of all lung cancer cases[1] and is characterized by early dissemination and high sensitivity to chemotherapy and radiotherapy.[2-4] SCLC has a strong tendency to metastasize to the brain. About 10% of the patients initially present with brain metastases (BMs). The 2-year cumulative risk rises to $\geq$ 50%,[5] and BMs are found in up to 80% of SCLC patients at autopsy.[6]

Because the blood–brain barrier has been considered to protect the central nervous system from cytotoxic agents, the role of prophylactic cranial irradiation (PCI) has been extensively studied.[7-10] Schild et al[8] demonstrated that PCI was associated with a significant survival benefit for both limited-disease (LD) and extensive-disease SCLC patients who had stable disease or better response to chemotherapy with or without thoracic radiotherapy (TRT). In addition, a study by Rule et al[10] using the same pooled data demonstrated that PCI was associated with a significant improvement in survival for the entire elderly SCLC patient cohort on univariate analysis.

A review of retrospective data on PCI suggested that prolongation of OS would be restricted to the patients in complete remission because those with residual extracranial disease die promptly from systemic cancer progression.[11] Another retrospective analysis suggested that the gain in survival was restricted to patients with locally advanced disease stage (International Union Against Cancer [UICC] II-IIIB).[12] In 1999, Aupérin et al[9] showed in a meta-analysis of PCI for SCLC patients with complete remission after induction therapy that the relative risk of death in the PCI group versus the control group was 0.84 (95% confidence interval [CI], 0.73-0.97; $P = .01$), which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the control group vs. 20.7% in the treatment group). PCI also increased the rate of disease-free survival (relative risk of recurrence or death, 0.75; 95% CI, 0.65-0.86; $P < .001$) and decreased the cumulative incidence of BM (relative risk, 0.46; 95% CI, 0.38-0.57; $P < .001$). Previously we found a significant prevalence of BMs in LD SCLC patients with complete response immediately after completion of primary treatment and recommended a second cranial magnetic resonance imaging (cMRI) study as a routine diagnostic tool before application of PCI.[13] A recently published retrospective study from Ozawa et al[14] suggested that PCI may be less beneficial in patients with LD SCLC when continuous management with cMRI and stereotactic radiosurgery as a treatment option are permanently available.

To evaluate the exact impact of PCI on survival in a real-life patient cohort treated with chemoradiotherapy (CRT), we retrospectively analyzed the medical charts of 184 LD SCLC patients who were comprehensively staged with cMRI at initial diagnosis and immediately before application of PCI.

Patients and Methods

From 1998 to 2012, 184 patients from 2 institutions in Germany were diagnosed with LD (UICC stage I-III) SCLC. Diagnosis was confirmed histologically. LD consisted of patients with disease confined to a single hemithorax with or without contralateral mediastinal and ipsilateral supraclavicular lymph node involvement.[15] Patients with pleural effusion and involvement of the contralateral supraclavicular and/or hilar lymph nodes were excluded from the analysis.[16] Initial staging consisted of computed tomographic (CT) scans of the chest and abdomen, bone scintigraphy, bronchoscopy with biopsy, and first cMRI. All patients received definitive CRT concomitantly or sequentially. Before treatment, all patients provided written informed consent. The university's ethics committee approved this retrospective study.

Before 2005, sequential CRT was provided as per institutional policy. Seventy-one patients (39%) received concomitant CRT consisting of TRT starting with the first or second cycle of chemotherapy followed by 2 to 4 consolidation cycles, while 113 patients (61%) received sequential CRT, defined as 4 to 6 cycles of chemotherapy followed by TRT. TRT was delivered on LINAC with multiple coplanar 6 to 15 MV beams. Three-dimensional CT-simulated treatment planning was performed. Planning target volume was defined as initial primary tumor and involved lymph nodes (short axis > 1 cm on pretherapeutic CT) with a 1.0 cm margin. A total of 96% patients were treated 5 days a week with 1.8 to 2.0 Gy daily fractions to a total dose of at least 54.0 Gy (range, 54.0-66.0 Gy). Four percent of patients were treated with hyperfractionated accelerated TRT according to Turrisi et al.[17] On completion of CRT, response evaluation was performed within 2 weeks based on CT scans (thorax and abdomen) and bone scintigraphy. A second cMRI was routinely performed in patients with disease that partially or completely responded to therapy before commencing PCI to exclude BM. A total of 71 patients (39%) were treated with PCI (2 simulated opposite fields with daily fraction of 2.0 Gy to a total dose of 30.0 Gy). Thereafter, patients were followed every 3 months during the first 2 years and every 6 months for the third year from the end of multimodal therapy until death.

All patients were registered until death or loss to follow-up. Survival rates were analyzed according to the Kaplan-Meier method and were measured from the date of initial diagnosis by SPSS 16.0 software (IBM SPSS). Kaplan-Meier analyses were used to compare survival curves for the PCI and non-PCI subgroups. Application of PCI to those with disease that responded to therapy was analyzed for its association with overall survival (OS) and time to progression (TTP) by univariate and multivariate Cox regression. A 2-sided error level of $P < .05$ was considered statistically significant. Variables significantly associated with OS in the univariate analysis were entered into a multivariate analysis. TTP was defined as the length of time from the date of diagnosis until the disease worsened or spread to other parts of the body. Hence, TTP theoretically differed from progression-free survival in that the event of interest was only disease progression.[18]

Results

One hundred eighty-four patients were treated with definitive CRT. Patient and treatment characteristics are listed in Table 1. One hundred eleven (60%) were men and 73 (40%) were women. Median age at diagnosis was 63 years (range, 34-83 years). Median performance status according to the World Health Organization classification for the entire cohort was 1 (range, 0-3). Mediastinal lymph node involvement was documented in 110 patients (60%). A total of 101 patients (55%) had stage T3/4 disease. Seventy-one patients (39%) were treated in the concurrent and 113 (61%) in the sequential setting. There were no significant differences with in regard to age, sex, performance status, and tumor, node, metastasis

Table 1 Patient and Treatment Characteristics

Characteristic	PCI (n = 71)	No PCI (n = 113)
Sex		
Male	36 (51%)	75 (66%)
Female	35 (49%)	38 (34%)
WHO performance status	1 (0-3)	1 (0-3)
Chemoradiotherapy		
Concurrent	34 (48%)	35 (31%)
Sequential	37 (52%)	78 (69%)
Chemotherapy		
Platinum based	68 (96%)	96 (85%)
Not platinum based	3 (4%)	17 (15%)
≥4 cycles	65 (92%)	83 (73%)
<4 cycles	6 (8%)	30 (27%)
Metachronous BM	16 (23%)	42 (37%)

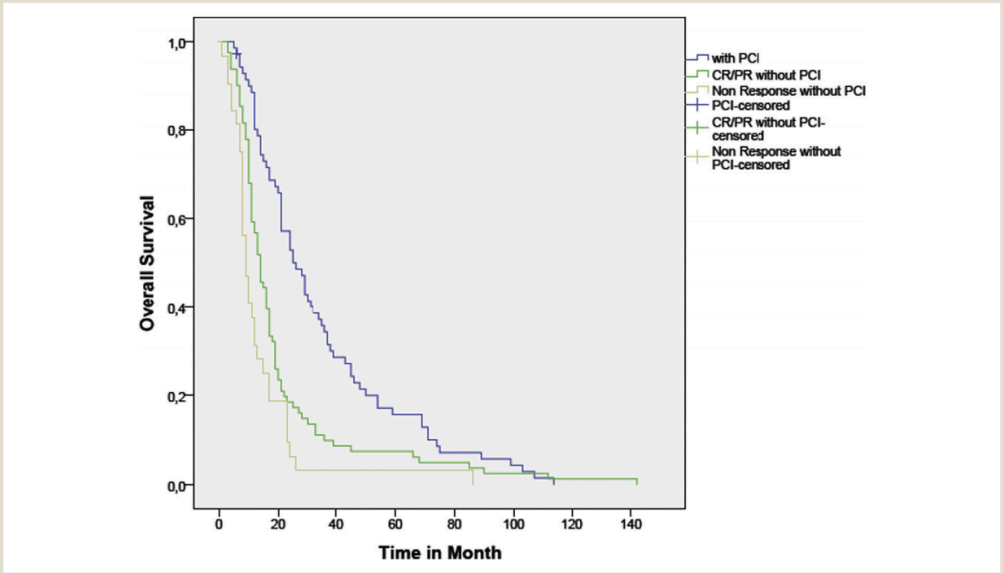
Abbreviations: BM = brain metastases; PCI = prophylactic cranial irradiation; WHO = World Health Organization.

classification system disease stage between patients treated with concurrent or sequential CRT. Platinum-based doublet chemotherapy with predominantly etoposide or irinotecan was applied in 164 patients (89%), while the rest of the patient cohort received predominantly CAV (cyclophosphamide, doxorubicin, vincristine) chemotherapy. Fewer than 4 cycles of chemotherapy were applied in 20% of patients. No interruptions of chemo- and radiotherapy were documented in the medical charts. Response evaluation was done in all patients about 2 weeks after the completion of primary multimodal treatment. One hundred fifty-two patients (83%) experienced complete or partial response; of patients whose disease responded to therapy, 71 patients (39%) showed no signs of BM in the second cMRI after primary treatment and were treated with PCI approximately 3 weeks after completion of CRT.

Patients whose disease responded to therapy treated with PCI survived significantly longer than those with responsive disease who did not receive PCI and those without responsive disease. The median OS was 26 months (range, 19.4-32.6 months) in the PCI group versus 14 months (range, 11.4-16.6 months) for patients with responsive disease without PCI versus 9 months in patients whose disease did not respond to therapy ($P < .0001$, log-rank test) (Figure 1). The same effect was observed for the TTP: 27 months versus 14.5 months (range, 9.0-19.9 months) versus 8.8 months (range, 7.7-9.9 months) ($P < .0001$, log-rank test) in the PCI group versus patients with responsive disease without PCI versus patients with nonresponsive disease, respectively (Figure 2). The effect of PCI on OS was independent from patient sex and remained highly significant in both female and male subgroups ($P < .0001$, log-rank test), respectively. Median BM-free survival (BMFS) in the PCI group was not reached, whereas it was 23.6 months in the non-PCI group ($P < .0001$, log-rank test). Figure 3 illustrates metastasis-free survival.

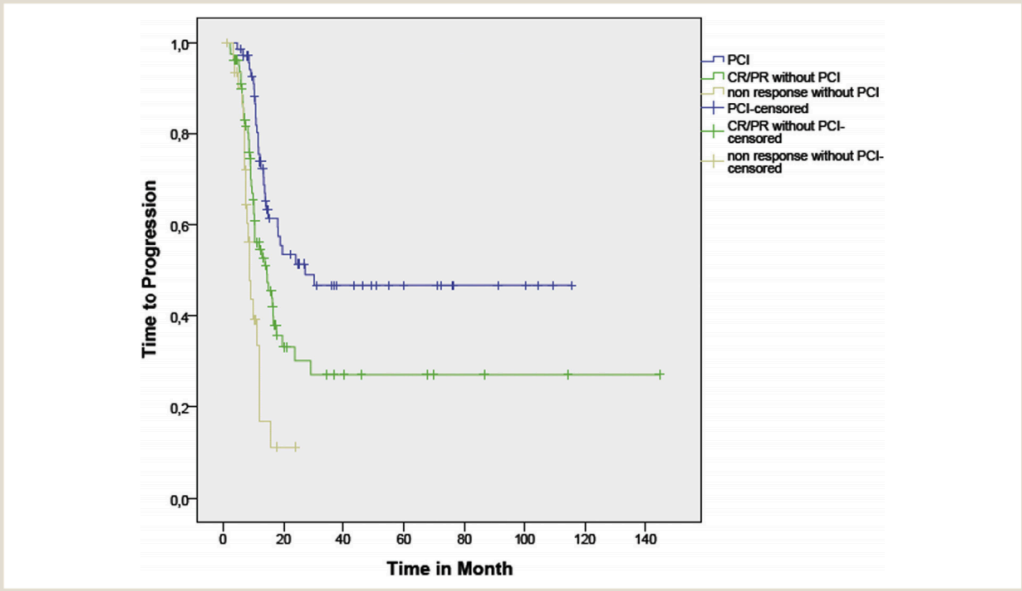
Factors that were significant or borderline significant in the univariate analysis were included in the multivariate analysis (Table 2). On multivariate analysis, PCI was a variable significantly correlating with OS (hazard ratio = 1.899; 95% CI, 1.370-2.632;

Figure 1 Overall Survival in Patient Subgroups Defined by Application of PCI and Treatment Response After CRT



Abbreviations: CRT = chemoradiotherapy; PCI = prophylactic cranial irradiation.

Figure 2 Time to Progression in Patient Subgroups Defined by Application of PCI and Treatment Response After CRT



Abbreviations: CRT = chemoradiotherapy; PCI = prophylactic cranial irradiation.

$P < .0001$) and TTP (hazard ratio = 2.164; 95% CI 1.371-3.415; $P = .001$).

Discussion

The aim of this retrospective study was to evaluate the exact impact of PCI in an unselected real-life LD SCLC patient cohort comprehensively staged with cMRI and treated with definitive CRT. The treatment flowchart is provided in Figure 4. PCI was applied exclusively in patients with disease in partial or complete remission when the first and second contrast-enhanced cMRI before and after the definitive CRT showed no signs of BMs. This is an important aspect of the study; it refers to the assessment of the authentic preventative role of PCI in LD SCLC patients with disease that responded to therapy.

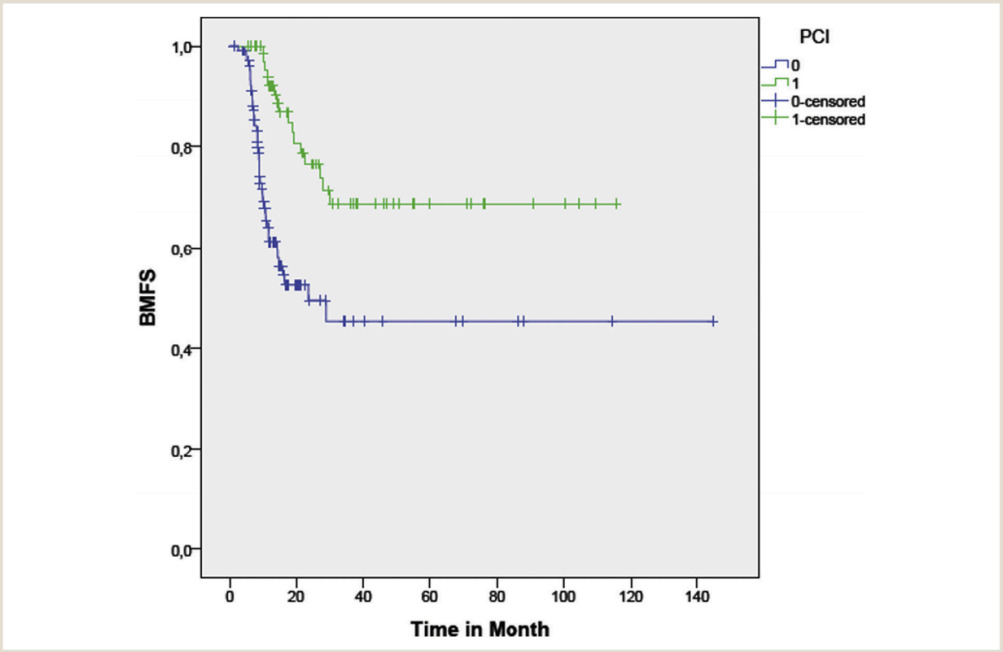
Our results revealed a significantly positive effect of PCI with approximately a doubling of the TTP and OS as well as consequential improvement in BMFS. Importantly, we applied PCI to patients whose disease partially and completely responded to therapy. A study from Tai et al[11] found a significant low incidence of BMs after PCI in LD SCLC patients with incomplete response after CRT, but there was no correlation with a cause-specific and OS. Moreover, a retrospective analysis from Aarhus University confirmed a benefit of PCI in LD SCLC, although it was offered to all patients with good performance status and no signs of progression after primary multimodal treatment. However, contrast-enhanced cMRI was not obligatory and was performed only if clinically indicated.[19] Furthermore, our group has already reported that a maximum tumor response (complete vs. partial remission vs. nonresponse) to applied CRT itself can affect BMFS and OS in LD SCLC.[20] This phenomenon could be a plausible explanation for potentially improved survival benefit after PCI in LD SCLC patients with complete response. This is in accordance with the results of a meta-analysis from Aupérin et al,[9] which included data from 7 randomized prospective studies and compared the PCI and no-PCI groups after complete remission to primary treatment.

Another important point of the present analysis is that the majority of patients presented with locally advanced disease. Previously published studies on surgery in LD SCLC could not demonstrate a relevant risk of developing BMs in patients with pathologic stage I disease.[12,21] However, a National Cancer Data Base (NCDB) analysis demonstrated that patients with early-stage (pT1-2N0M0) SCLC treated with surgical resection alone have worse outcomes than those who undergo resection with adjuvant chemotherapy alone or chemotherapy with cranial irradiation.[22]

Another relevant point is the fact that PCI was applied exclusively to patients with responsive disease when second contrast-enhanced cMRI immediately before showed no signs of BMs. The significance of a second cMRI before PCI has previously been described.[13] A previous study of patients with complete response after CRT found in 13 (32.5%) of 40 patients (95% CI, 18-47) asymptomatic BMs by cMRI after completion of multimodal treatment and immediately before PCI.[13] Hence, patients developing asymptomatic BMs in the course of primary treatment were excluded from our analysis.

We have also observed that the effect of PCI was independent from patient gender. This is in accordance with the results of an analysis of the Surveillance, Epidemiology, and End Results

Figure 3 Brain Metastasis–free Survival in Patient Subgroups Defined by Application of PCI After CRT



Abbreviations: CRT = chemoradiotherapy; PCI = prophylactic cranial irradiation.

database by Patel et al,[23] which supported a prognostic role of PCI in LD SCLC and described a similarly significant magnitude of this benefit regardless of sex.

The major limitations of the present study are its retrospective nature and the absence of acute toxicity analysis owing to insufficient documentation of toxicity events.

Another relevant point is due to institutional policy before 2005; the majority of patients (61%) were treated with sequential CRT. Nevertheless, the uniqueness of the present study is due to consequential cMRI staging of the treated cohort, we believe that the achieved significant OS benefit of PCI in patients whose disease responded to therapy can be reproduced in a future prospective study.

Table 2 Multivariate Analysis of Overall Survival

Characteristic	Hazard Ratio	95% Confidence Interval	*P*
Sex	1.4	1.029-1.921	.032
≥4 cycles	1.123	0.765-1.648	.554
Platinum-based chemotherapy	1.489	0.911-2.433	.112
PCI	1.899	1.370-2.632	<.0001
Complete vs. partial remission	1.267	0.899-1.787	.177
Complete remission vs. nonresponse	2.135	1.392-3.275	.001

Abbreviation: PCI = prophylactic cranial irradiation.

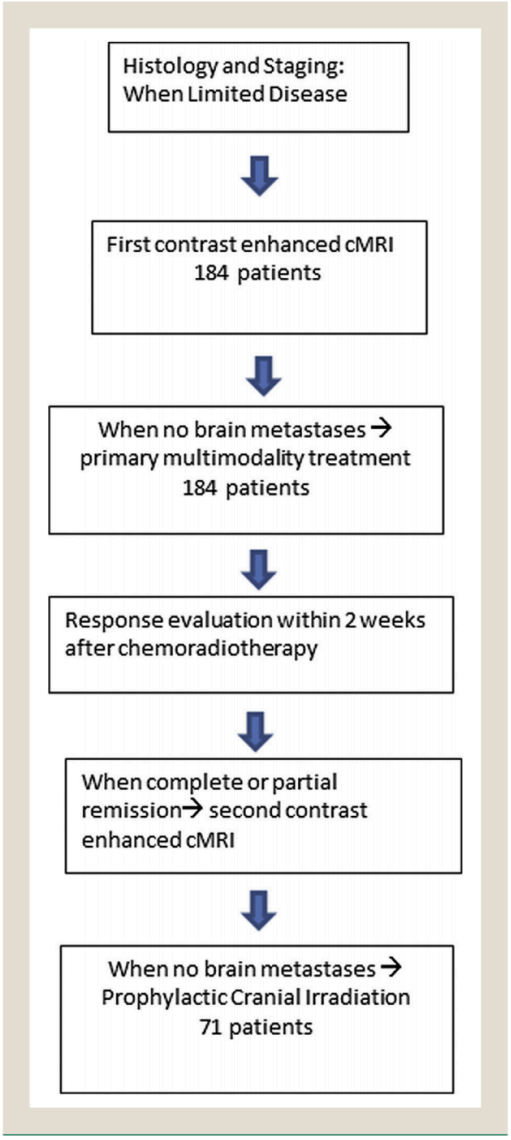
Conclusion

The present analysis found a highly positive effect of PCI applied to patients with responsive disease on OS in a real-life LD SCLC patient cohort comprehensively staged with contrast-enhanced cMRI before and more importantly after definitive CRT, and strongly endorses its role in patients with responsive disease. Our data provide a basis for prospective analysis of the authentic preventative role of PCI in LD SCLC patients whose disease responded to therapy. Such a study is currently being planned.

Clinical Practice Points

- SCLC accounts for about 13% of all lung cancer cases and is characterized by early dissemination and high sensitivity to chemo- and radiotherapy.
- In 1999, Aupérin et al[9] published a meta-analysis in which PCI for SCLC patients with complete remission after induction therapy had a 5.4% improvement in 3-year survival versus the control group. Previously, our group demonstrated a significant prevalence of BMs in LD SCLC patients whose disease completely responded to therapy immediately after completion of primary treatment and recommended a second cMRI as a

Figure 4 Treatment Flowchart



routine diagnostic tool before application of PCI. A retrospective study from Ozawa et al[14] suggested that PCI may be less beneficial in patients with LD SCLC when continuous management with cMRI and radiosurgery as a treatment option are permanently available.

- To evaluate the exact impact of PCI on survival in a real-life patient cohort treated with CRT, we retrospectively analyzed the data of 184 LD SCLC patients who were comprehensively staged with cMRI at initial diagnosis and immediately before application of PCI.
- We found a highly positive effect of PCI on OS, time to progression, and BMFS in LD SCLC patients whose disease responded to therapy, comprehensively staged with contrast-enhanced cMRI before and, more importantly, after primary multimodal treatment. Our findings strongly endorse the application of PCI in this group of patients. Our data provide a basis for prospective analysis of the authentic preventative role of PCI in LD SCLC patients with responsive disease.

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