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**Optimization of curative-intended multimodal therapy in patients
with limited (UICC I-III A-C 8th Ed.) disease small cell lung cancer
based on the analysis of treatment-related factors**

Habilitationsschrift
zur Erlangung der Venia legendi im
Fach

STRAHLENTHERAPIE

vorgelegt von

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Cumulative habilitation work is based on the following original publications:

Chemoradiotherapy duration correlates with overall survival in limited disease SCLC patients with poor initial performance status who successfully completed multimodality treatment.

Manapov F, Klöcking S, Niyazi M, Belka C, Hildebrandt G, Fietkau R, Klautke G.

Strahlenther Onkol. 2012 Jan;188(1):29-34. [IF 2.459]

Investigating a Correlation between Chemoradiotherapy Schedule Parameters and Overall Survival in a real-life LD SCLC Patient Cohort.

Manapov F, Eze C, Niyazi M, Roengvoraphoj O, Li M, Hegemann NS, Hildebrandt G,

Fietkau R, Belka C. J Cancer. 2016 Oct 17;7(14):2012-2017 [IF 3.249]

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

Manapov F, Niyazi M, Gerum S, Roengvoraphoj O, Eze C, Li M, Hildebrandt G, Fietkau R, Klautke G, Belka C.

BMC Cancer. 2016 Mar 14;16:216. [IF 3.288]

Timing of failure in limited disease (stage I-III) small-cell lung cancer patients treated with chemoradiotherapy: a retrospective analysis.

Manapov F, Klöcking S, Niyazi M, Oskan F, Niemöller OM, Belka C, Hildebrandt G, Fietkau R, Klautke G.

Tumori. 2013 Nov-Dec;99(6):656-60. [IF 1.304]

Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: a single institution experience.

Manapov F, Klautke G, Fietkau R. J Thorac Oncol. 2008 Jun;3(6):652-5. doi: 10.1097/JTO.0b013e3181757a76 [IF 10.336]

Central nervous system relapse continues to be a therapeutic challenge in extensive disease small-cell lung cancer patients with initial symptomatic brain metastases and good response to chemoradiotherapy.

Manapov F. J Neurooncol. 2010 Jul;98(3):349-55. doi: 10.1007/s11060-009-0079-y. Epub 2009 Dec 15 [IF 3.06]

Primary tumor response to chemoradiotherapy in limited-disease small-cell lung cancer correlates with duration of brain-metastasis free survival.

Manapov F, Klöcking S, Niyazi M, Levitskiy V, Belka C, Hildebrandt G, Fietkau R, Klautke G. J Neurooncol. 2012 Sep;109(2):309-14. doi: 10.1007/s11060-012-0894-4. Epub 2012 May 20 [IF 3.06]

Roengvoraphoj O, Eze C, Niyazi M, Li M, Hildebrandt G, Fietkau R, Belka C, **Manapov F**. Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. Strahlenther Onkol. 2017 Feb;193(2):150-155. [IF 2.459]

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.

Eze C, Roengvoraphoj O, Niyazi M, Hildebrandt G, Fietkau R, Belka C, **Manapov F**.

Clin Lung Cancer. 2017 Jul;18(4):e243-e249. doi: 10.1016/j.clcc.2016.11.005 [IF 4.204]

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INTRODUCTION

General aspects:

Small-cell lung cancer (SCLC) accounts for about 15% of all lung cancer cases and is associated with a history of heavy tobacco smoking (1). The incidence of SCLC has continuously declined in the last decades because of intensive onset of tobacco cessation programs. However, the prognosis of patients with SCLC remains very poor due to propensity for early dissemination, first of all to the brain (1, 2).

SCLC is typical for patients aged > 60 years. At initial presentation, symptomatic bulky tumor accompanying with extensive lymph node involvement is common. In 75 - 80% of patients at initial diagnosis, metastatic spread to different organs will be found. Multiple brain metastases (BM) are detected in up to 25% of patients at diagnosis; at least half of them will be occult and detected within the scope of initial tumor staging (2, 3).

Histology:

Morphologically rapidly proliferating small cells with a high nucleo-cytoplasmic ratio and neurosecretory granules are typical for SCLC (2, 4). There are several histological and immunohistochemical markers which were shown to be characteristic for this type of tumor. They include transcription thyroid factor-1 (positive in more than 85% of patients); cytokeratin 7; chromogranin A and synaptophysin. Additionally, *myc* amplification and *p53* mutation was described in approximately 75% of patients. Deletions of known tumor-suppressor genes (TP53 and RB1) are also typical. However, targeted driver mutations described for the non-small cell lung cancer (EGFR-, ALK-, ROS1-, BRAF-, RET- etc.) are extremely rare in SCLC (4).

Tumor Classification and Staging:

Since 2009 tumor-node-metastasis (TNM) classification has been proposed for SCLC (1, 2, 4, 5). Use of TNM classification is obligatory and will help clinicians to better assess the risk categories and prognostic factors of disease as well as personalize multimodal treatment. However, the absolute majority of institutions continuously use a simplified two-stage system which was developed by the Veterans Administration Lung Cancer Group. This old classification categorized SCLC tumor burden as limited (LD) or extensive (ED) disease. LD is defined as disease which is limited to one hemithorax with or without contralateral hilar and supraclavicular lymph node involvement. Pleural and pericardial effusion was excluded from LD.

An initial tumor staging in SCLC consists of contrast-enhanced computed tomographic (CT) scans of the neck, chest and abdomen, bone scintigraphy and a contrast-enhanced magnetic resonance image (MRI) or CT of the brain. The whole body 18F-FDG-PET/CT scan is also widely used as an initial staging tool. In this case a bone scan can be potentially omitted.

Treatment standards and prognosis

There are different treatment standards for LD and ED (1, 2, 4, 5). LD SCLC is a potentially curative disease. In general, treatment is always multimodal and depends on TNM Stage and patient performance status. In case of very limited disease (T1-2 tumors without mediastinal lymph node involvement) radical surgery consisting of lobectomy and regional lymph node dissection could be considered (6). For the absolute majority of patients platinum-based concurrent and/or sequential chemoradiotherapy (CRT) is an actual treatment standard. The landmark randomized

trials on this topic have shown that the best historical survival rates could be achieved with early (first chemotherapy cycle) concurrent hyperfractionated accelerated platinumbased CRT according to Turrisi et al. (7). After surgery and/or definitive CRT and in the case of intrathoracic treatment response, prophylactic cranial irradiation (PCI) should be delivered.

In case of ED, a platinum-based chemotherapy with 4 to maximal 6 cycles is a cornerstone of treatment. In the case of treatment response, consolidative thoracic irradiation and PCI are recommended to significantly reduce the rate of the loco-regional and intracranial failure.

In general practice, median overall survival and 5-year survival rates in metastatic (ED) and non-metastatic (LD) SCLC reached 9 to 12 and 15 to 25 months as well as 0-5 and 10-25%, respectively (1, 2, 4). In both non- and metastatic disease, there is a stagnation of real-life patient survival in the last two decades (2, 4). In spite of continuous clinical research, no significant improvement of patient prognosis could be achieved. According to prospective trials dedicated to primary multimodal treatment in SCLC, there is actually no benefit of chemotherapy intensification and consolidation. Also, the clinical results of targeted therapy remain disappointing.

RESEARCH BACKGROUND

In spite of progress in the development of new chemo- and targeted therapy agents as well as technical improvement of radiation delivery, the prognosis of patients with non-metastatic SCLC is still disappointing (2, 4). A marginal survival benefit achieved in the last decade is mostly due to significant improvement of the initial tumor staging: consecutive use of TNM classification and integration of comprehensive intra- and extracranial diagnostic procedures. However, there was no relevant progress, regarding the primary multimodal treatment itself. For many years, there has been ongoing debate concerning optimal patient-directed application of chemotherapy and thoracic as well as cranial irradiation.

According to the landmark randomized trials, primary CRT is a keystone treatment for LD SCLC (7 – 14). This multimodal treatment approach consists of the two primary modalities: chemotherapy and the loco-regional thoracic irradiation. Because of significant risk for the circulating tumor cells, micro-metastatic disease as well as early and rapid systemic dissemination, chemotherapy remains a cornerstone of treatment. However, an extremely high rate (50 to 90% in the first and second year after diagnosis, respectively) of post-chemotherapy intra-thoracic recurrences was a reason for the integration of the loco-regional radiotherapy as a consolidation treatment for primary thoracic disease (8 – 9). Three mostly considerable factors concerning thoracic irradiation in LD SCLC are application type (concurrent versus sequential), prescription of the radiation dose (hyperfractionated accelerated versus conventional) and timing (early versus late). All these factors have been the subject of randomized trials the last thirty years. Some of them have documented survival benefit for concurrent multimodal treatment (10 - 11), others have not (12 - 13). The results of the trials which directly

compared early versus late concurrent CRT were also diverse (14 – 18). Furthermore, relevant differences between trials regarding the initial tumor staging and the dose density of chemotherapy and thoracic irradiation are the most important critical points. Several meta-analyses have revealed a significant survival benefit for early platinum-based concurrent CRT with overall treatment time of thoracic irradiation less than 30 days (19 - 22). A short time between the first day of chemotherapy and the last day of thoracic irradiation was also associated with improved long-term outcome. The start of any treatment until the end of radiotherapy (SER) as a timing parameter was proposed as a prognostic parameter with a shorter SER (less than 30 days) as pre-requisite for 5-year survival rates greater than 20% (22). The latest meta-analysis on this topic consisted of nine randomized trials and individual data from 2305 LD SCLC patients (23). Moreover, only randomized trials comparing early vs. late timing schedules of curative thoracic irradiation together with chemotherapy were included. Importantly, early radiotherapy was defined as treatment starting before the third chemotherapy cycle or nine weeks after randomization. All patients were divided into two arms: “earlier or shorter” and “later or longer”. There were no significant differences regarding patient characteristics in both arms. Principally, the study could not find any positive survival effect of the “earlier or shorter” versus “later or longer” thoracic irradiation. However, subsequent subgroup analysis revealed a significant survival benefit in favour of “earlier or shorter” radiotherapy when similar and higher chemotherapy compliance was reached and in favour of “later or longer” radiotherapy when chemotherapy compliance was different and poor. This was the first time a significant association of treatment and/or patient compliance and treatment effect was documented in LD SCLC.

Another relevant treatment-related aspect in this field is universal adoption of early concurrent platinum-based hyperfractionated accelerated CRT analogue Turrisi et al in clinical routine (24, 25). Although best historical survival rates have been achieved with Turrisi protocol, the adoption rate of this early concurrent treatment, unfortunately, remains low and depends significantly on geographic region and treatment center (academic vs non-academic). Additionally, the highly-awaited phase III trial (CONVERT) was published last year and demonstrated non-significant differences in outcomes with hyperfractionated accelerated versus conventional concurrent CRT, starting both with the second chemotherapy cycle (median overall survival of 30 versus 25 months (HR 1.18, 95% CI 0.95–1.45; $p=0.14$) and 5-year survival rate of 34% versus 31%, respectively) (26).

Hence, conventionally fractionated platinum-based concurrent CRT starting within the first nine weeks after initial diagnosis (up to the third chemotherapy cycle) remains a mostly acceptable primary multimodal treatment protocol. Therefore, there is a clear interest of the multidisciplinary clinical community to optimize this multimodal concept regarding treatment efficacy and tolerability.

OWN WORK

- Treatment-related factors and optimization of the definitive chemoradiotherapy in LD SCLC**
- Comprehensive brain imaging and prophylactic cranial irradiation in LD SCLC**

Treatment-related factors and optimization of the definitive chemoradiotherapy in LD SCLC

Manapov F, Klöcking S, Niyazi M, Belka C, Hildebrandt G, Fietkau R, Klautke G. Chemoradiotherapy duration correlates with overall survival in limited disease SCLC patients with poor initial performance status who successfully completed multimodality treatment. *Strahlenther Onkol.* 2012 Jan;188(1):29-34. [IF 2.459]

Manapov F, Eze C, Niyazi M, Roengvoraphoj O, Li M, Hegemann NS, Hildebrandt G, Fietkau R, Belka C. Investigating a Correlation between Chemoradiotherapy Schedule Parameters and Overall Survival in a real-life LD SCLC Patient Cohort. *J Cancer.* 2016 Oct 17;7(14):2012-2017. [IF 3.249]

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Manapov F, Klöcking S, Niyazi M, Oskan F, Niemöller OM, Belka C, Hildebrandt G, Fietkau R, Klautke G. Timing of failure in limited disease (stage I-III) small-cell lung cancer patients treated with chemoradiotherapy: a retrospective analysis. *Tumori.* 2013 Nov-Dec;99(6):656-60. [IF 1.304]

Since a randomized phase III study from Turrisi et al. was published in 1999, early concurrent hyperfractionated accelerated platinum-based CRT was established as a preferential treatment standard for LD SCLC (5, 7). The early start of thoracic irradiation with the first chemotherapy cycle was considered as an important pre-requisite. Almost 20 years later, a randomized phase III study (CONVERT) demonstrated non-significant differences in long-term patient outcome (median overall survival of 30 versus 25 months (HR 1.18, 95% CI 0.95–1.45; $p=0.14$) and 5-year survival of 34% versus 31%) with hyperfractionated accelerated (analog Turrisi et al) versus conventional fractionated (once daily) concurrent CRT, starting with the second cycle of chemotherapy and reported historically best overall survival rates in both arms (26). However, the relevant difference between both landmark trials was a total dose of the thoracic irradiation in the once daily group (45 a 1.8 Gy versus 66 a 2.0 Gy in the Turrisi and CONVERT trials, respectively). Importantly, along the time period between these important studies, adoption of the Turrisi protocol in clinical practice has remained very low, especially in Europe (between 5-21% of cancer centers) (24, 25). The reasons for this was because of the significantly higher rates of acute severe toxicity (especially esophagitis) and higher logistic effort for the treating radiation oncology department. Hence, continuous optimization of conventionally fractionated CRT protocols was mostly a way to improve patient prognosis in non-metastatic SCLC.

In the first work published in 2011, impact of treatment course of primary CRT on outcome in LD SCLC patients with poor initial performance status was analyzed (27). 149 patients with initial performance status WHO 2-3, histologically confirmed SCLC and comprehensively staged disease were allocated to primary multimodal therapy. In 24/149 (16%) patients, definitive CRT could not be completed because of treatment-

related toxicity and further deterioration of patients' general condition. The successful completion of primary multimodal treatment was the first factor significantly influencing patient prognosis (see **Figure 1**).

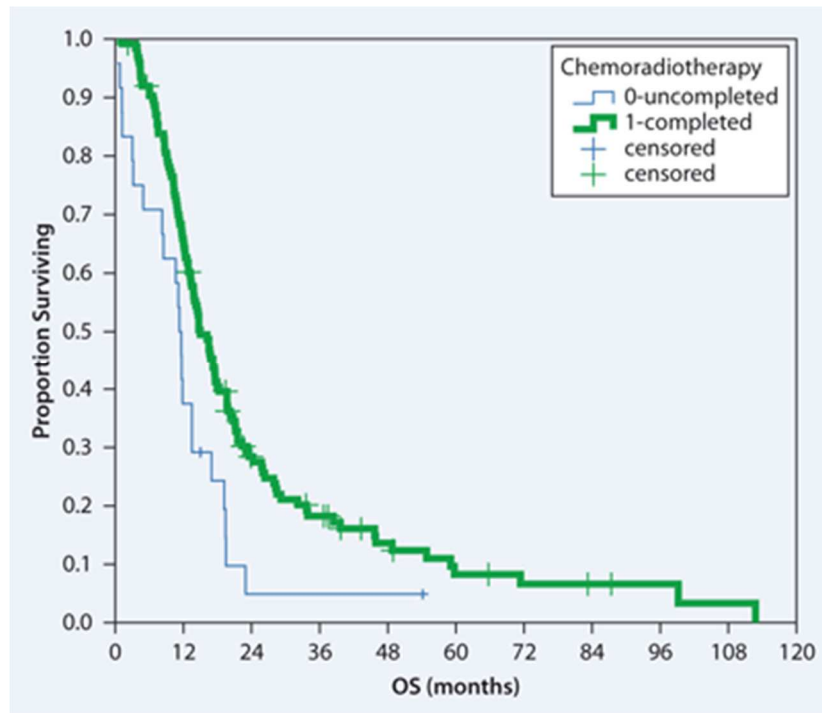


Figure 1: Overall survival in LD SCLC patients with poor initial performance status according to the completion of primary multimodal treatment ($p < 0.005$, log-rank test)

In patients who could not complete CRT, the median survival time of 11.3 months was very disappointing and comparable with metastatic stage. Hence, further analysis of treatment-related factors was focused exclusively on the patient cohort who successfully completed initial therapy. 125/149 (84%) patients were identified. Importantly, the conventionally fractionated thoracic irradiation with a total dose of at least 50.0 Gy was delivered in all patients, whereas 13/125 (10%) patients were treated with less than four cycles of chemotherapy. Sequential and concurrent CRT, was applied in 74 (59%) and

51 (41%) patients, respectively. PCI was delivered only in complete responders to primary treatment. There was no difference in the objective response rate, progression-free and overall survival in patients treated in the sequential or concurrent setting. However, the study identified an overall duration of CRT itself as a prognostic treatment-related factor for both sequential and concurrent patient subgroups. Overall duration of CRT was the sole factor correlating with overall survival on uni- ($p < 0.014$) and multivariate ($p < 0.025$) analyses, respectively. Patients with short and dose-dense primary multimodal treatment achieved a significantly improved long-term outcome. Additionally, a trend to prolonged overall survival in patients who completed concurrent CRT was documented on the multivariate analysis ($p = 0.072$). Therefore, this study was the first reporting a prognostic role of the overall duration of primary multimodal treatment in LD SCLC patients with poor initial performance status.

Four years later, a new investigation with the aim of exact evaluation of the impact of CRT schedule parameters on outcome in a real-life LD SCLC patient cohort from two university hospitals was conducted (28). In total, schedule parameters of the primary multimodal treatment were analyzed in 182 patients. Only 4% of patients were treated with early hyperfractionated accelerated concurrent CRT according to Turrisi et al (7). PCI was performed in patients with complete and partial remission after CRT. To better define the role of the concurrent treatment phase, a new parameter IST (interval of simultaneous treatment) was established. IST was assessed as a time interval, measured in days, when radiotherapy and chemotherapy for the primary thoracic disease were applied concurrently, including weekends and time between chemotherapy cycles. Definition of this parameter and its possible variations in the primary multimodal treatment course is illustrated in the **Figure 2**.

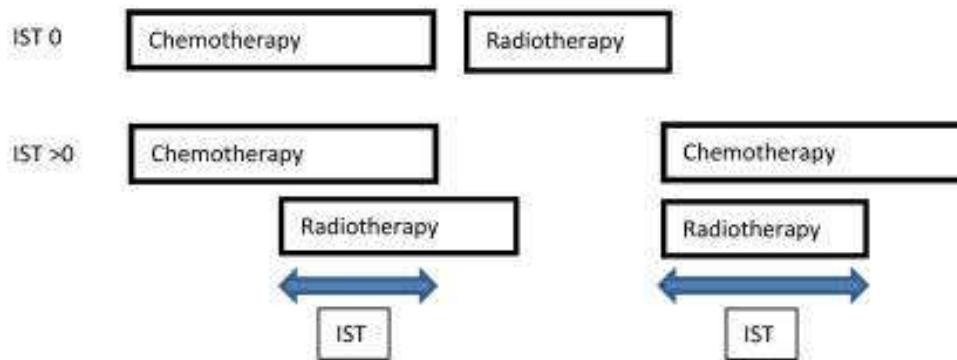


Figure 2: Definition of interval of simultaneous treatment (IST)

All 182 patients completed primary CRT: an absolute majority (96%) of patients were treated according to the conventional CRT protocol with total radiation dose of at least 50 Gy (range: 50 – 66). Median duration of chemotherapy was 128 and 93 days in patients treated concurrently and sequentially, respectively; median duration of thoracic irradiation was 43 days. Several IST values (30, 35, 42 and 49 days) were reviewed. IST 35 was supposed to be an optimal cut off for further analysis because this interval included at least two completed chemotherapy cycles and considered both the patients treated with accelerated (analogue Turrisi et al.) and conventional thoracic irradiation. According to the IST definition, 182 patients were divided as follows: IST 0 (sequential CRT) 111/182 (61%), IST > 0 and < 35 (short dose dense concurrent phase) 20/182 (11%) and IST > 35 51/182 (28%) (prolonged concurrent phase) subgroups, respectively. Median survival of the entire cohort reached 534 days and did not differ significantly between patients treated in the concurrent or sequential setting (589 and 533 days, respectively). Nevertheless, in the analysis according to the IST values, the IST > 0 and < 35 subgroup showed a trend to prolonged overall survival with 1169 (95CI: 800 – 1538) days vs. 533 (95CI: 446 – 620) and 448 (95CI: 361 – 535) days in the IST 0 and IST > 35 subgroups, respectively (p = 0.109) (see **Figure 3**).

Almost a doubling of the overall survival time compared with the rest of cohort was reached in patients treated with short dose dense concurrent CRT corresponding to the IST > 0 and > 35 days. In a further analysis of 71/182 (39%) patients treated exclusively with concurrent CRT, the overall survival benefit in the IST > 0 and < 35 subgroup reached significance on uni- ($p = 0.021$) and multivariate ($p = 0.039$, HR 0.38) analyses, respectively. Importantly, there was no registered survival benefit between patients who completed sequential (IST = 0) and prolonged concurrent phase CRT (IST > 35 days).

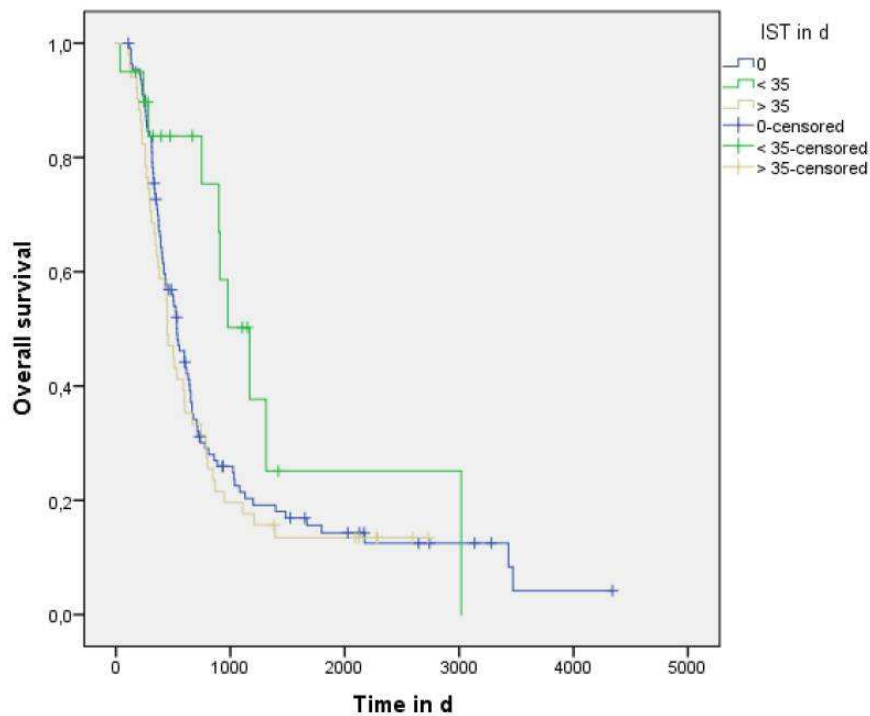


Figure 3: Overall survival in patient subgroups defined by IST

Taken together, the present study determined that duration of the concurrent phase of primary multimodal treatment, namely IST, was associated with patient outcome and revealed a short dose-dense concurrent phase (IST > 0 and < 35 days) as an optimal value for the planning of definitive CRT.

Subsequently, the next analysis evaluated an impact of the primary tumor response

after completion of CRT on patient outcome (29). The patient subgroups were defined according to the achieved remission status after primary multimodal treatment, e.g. complete vs. partial response vs. non-response (defined as stable and progressive disease) and compared with each other referring to the different survival parameters. Again, all 184 patients completed primary multimodal treatment and PCI was performed exclusively in the complete and partial responders. From the 184 analyzed patients who successfully completed primary multimodal treatment, 65 (35%), 77 (42%) and 37 (20%) demonstrated complete, partial remission and non-response, respectively. In 5 (3%) patients, remission status could not be validated. Median overall survival was 21.8 (95CI: 18.6-25) vs. 14.9 (95CI: 11.7-18.2) vs. 11.5 (95CI: 8.9-15) months in the complete, partial and non-responders, respectively ($p < 0.001$) (see **Figure 4**).

The same effect was observed for the time to progression and distant-metastasis-free survival. On multivariate analysis (after adjustment for other prognostic factors), patients who achieved a complete remission to primary multimodal treatment showed a significantly improved overall survival in comparison to non-responders and demonstrated a trend to improved time to progression ($p = 0.1$, HR 1.48) and distant-metastasis-free survival ($p = 0.06$, HR 1.63) compared to partial responders.

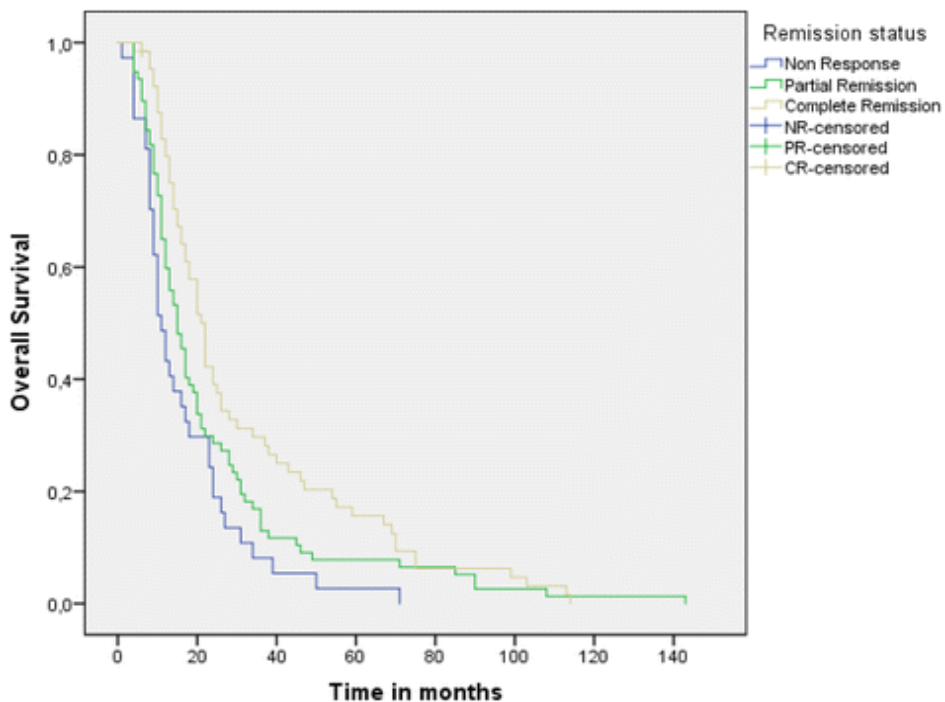


Figure 4: Overall survival in patient subgroups defined by remission status after primary multimodal treatment

Thus, this study revealed a significant correlation of achieved remission status of primary thoracic disease after CRT with patient survival and control of distant systemic disease. Especially important was the overall survival and distant control advantage documented in the complete compared to partial responders.

Finally, an extensive retrospective follow-up analysis for the exact assessment of the timing of treatment failure (temporal distribution of recurrent disease) in LD SCLC patients after completion of CRT was carried out (30).

The medical charts of LD SCLC patients who successfully completed primary multimodal treatment were reviewed. This temporal analysis of treatment failure demonstrated that disease recurrence including local, distant and intracranial relapse will occur in the first year after initial diagnosis in more than half of the treated patients.

Based on this finding, the study recommended an intensified follow-up at least in the first year after diagnosis with the possibility of early salvage treatment, also in asymptomatic patients.

Comprehensive brain imaging and prophylactic cranial irradiation in LD SCLC

Manapov F, Klautke G, Fietkau R. Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: a single institution experience. *J Thorac Oncol.* 2008 Jun;3(6):652-5. [IF 10.336]

Manapov F. Central nervous system relapse continues to be a therapeutic challenge in extensive disease small-cell lung cancer patients with initial symptomatic brain metastases and good response to chemoradiotherapy. *J Neurooncol.* 2010 Jul;98(3):349-55. [IF 3.060]

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Roengvoraphoj O, Eze C, Niyazi M, Li M, Hildebrandt G, Fietkau R, Belka C, **Manapov F**. Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. *Strahlenther Onkol.* 2017 Feb;193(2):150-155. [IF 2.459]

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Staged With Cranial Magnetic Resonance Imaging. Clin Lung Cancer. 2017
Jul;18(4):e243-e249. [IF 4.204]

Because of the biology of SCLC as a highly aggressive tumor characterized by rapid growth and early metastatic dissemination, a special attention of clinicians must be focused on the incidence of intracranial metastases (1, 2, 4). At least 10% of subjects will be present with symptomatic BM at initial evaluation with the cumulative risk rising to more than 50% in the second year after initial diagnosis and up to 80% of subjects at autopsy. The reported rate of asymptomatic (occult) BM at initial diagnosis is considered higher and could rise to 24% of all patients evaluated by contrast-enhanced cranial magnetic resonance imaging (MRI) (3, 4). The brain is considered as a sanctuary site because the blood-brain barrier can serve as potential protection of intracranial metastases from cytotoxic agents. The aim of PCI in LD SCLC was proposed to overcome this protection effect.

In 1999, a key meta-analysis from Aupérin et al. first demonstrated a significant decrease in the cumulative incidence of BM in SCLC complete responders after PCI (31). Importantly, the absolute majority of patients included in the study presented initially with LD. Moderate overall survival benefit (3-year survival rate: 20.7 versus 15.3% with and without PCI, respectively) was reported in the complete responders, regardless of whether they were treated with sequential CRT or chemotherapy alone.

This meta-analysis included seven randomized trials with enrollment period from 1977 to 1994. According to the enrollment time, comprehensive brain imaging based on contrast-enhanced cranial MRI at initial diagnosis as well as after completion of primary multimodal treatment was not consecutively performed. The tumor re-staging after primary treatment also varied significantly between the trials.

Respecting these relevant clinical uncertainties, a single-center study on the role of comprehensive brain imaging (serial contrast-enhanced cranial MRIs) in patients with

LD SCLC was conducted (32). We analyzed 105 consecutive LD SCLC patients treated with sequential and/or concurrent CRT. 40/105 (38%) patients achieved complete remission to primary multimodal treatment and were considered for PCI. Importantly, first contrast-enhanced cranial MRI was performed in all patients at initial diagnosis. A second MRI was scheduled exclusively in the forty complete responders immediately before PCI to exclude occult intracranial relapse (see Figure 1).

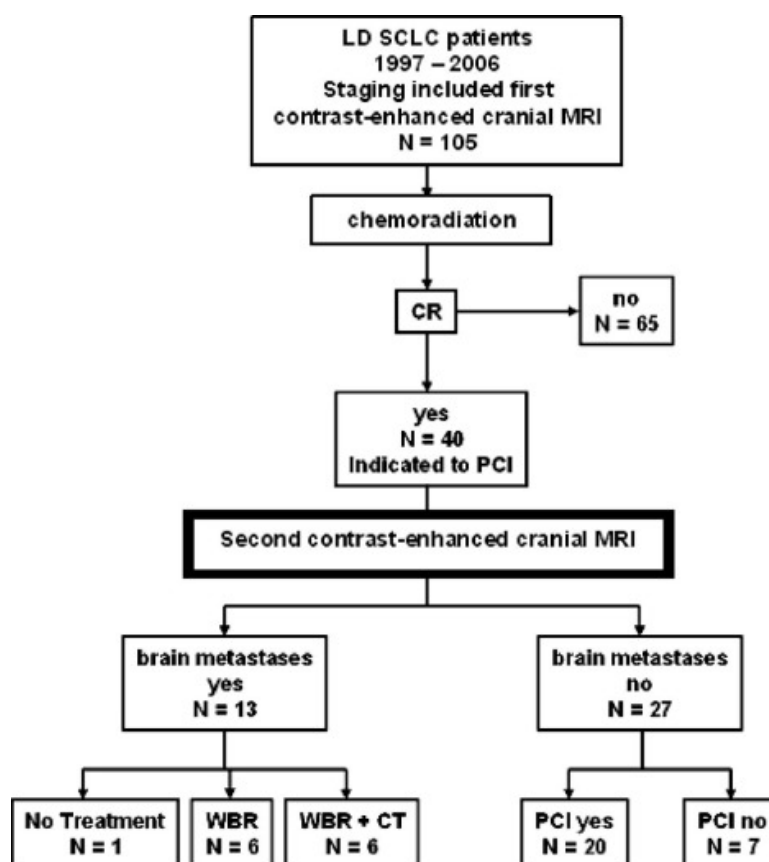


Figure 5: Patient selection according to the outcome of chemoradiotherapy

All forty complete responders were neurologically asymptomatic at that time. Surprisingly, the study revealed asymptomatic BM in 13/40 (32.5%; 95% CI: 18-47%) asymptomatic patients. Furthermore, complete responders with occult BM demonstrated a significantly

worse long-term outcome compared with patients without pre-PCI detected BM (median overall survival and 1-year survival rate: 14 versus 26 months and 58.7 versus 92%, $p = 0.0001$, respectively). The highly negative prognostic impact of intracranial involvement in SCLC also in spite of intensive multimodal treatment with cranial and thoracic CRT was confirmed in another small study (33).

Taken together, this single-center study investigating the role of second contrast-enhanced cranial MRI was the first demonstrating a significant prevalence of asymptomatic BM in LD SCLC complete responders immediately before PCI and providing evidence that a comprehensive brain imaging program, including first and second cranial MRI before and after primary treatment and immediately before PCI, could be an optimal detection tool for the exclusion of occult intracranial disease.

Subsequently, a correlation between response of primary thoracic disease to applied CRT and duration of brain-metastasis-free survival in LD SCLC was investigated (34). 125 LD SCLC patients who successfully completed multimodal treatment were analyzed. There was a significant difference in the incidence of metachronous intracranial relapse according to the achieved primary treatment response in the thorax. 50% (15/30 patients) of the metachronous BM occurred in the thoracic non-responders (stable disease and/or local progression) compared to 33 and 17% in the patients with complete and partial remission, respectively ($p < 0.0001$). Importantly, the duration of brain-metastasis-free survival was also significantly different in the patient subgroups according to the remission status of thoracic disease. The median time interval to development of BM was 252, 298 and 567 days in the non-, partial and complete responders, respectively ($p < 0.0001$). In the complete responders, application of PCI led to further prolongation of brain-metastasis-free survival (640 compared to 482 days in patients with and without

PCI, respectively ($p = 0.047$)). The study has also confirmed a dismal prognosis of SCLC patients with metachronous intracranial failure with only 2.6 months median survival time from diagnosis of brain relapse. Altogether, the main finding was a direct correlation between achieved primary intrathoracic tumor response and duration of brain-metastasis-free survival as well as incidence of metachronous intracranial recurrence. Present results suggested that achieved response of primary tumor can further influence the course of SCLC disease and must be respected in clinical trials considering PCI and different consolidation protocols. Additionally, another study assessing the prognostic impact of the patient gender in LD SCLC, found a higher prevalence of metachronous BM in the male subgroup compared to females (36 vs 26%, respectively, $p=0.03$), although a small but significant difference in the rate of achieved partial remission to CRT was detected in women compared to men (48 versus 42%, $p = 0.05$) (35). Importantly, no difference in overall survival between male and female patients treated with PCI was found.

To extend research on the potential mutual effect of achieved intra-thoracic treatment response and PCI on the patient prognosis in LD SCLC, clinical data were updated and a new study investigating the prognostic role of both factors in a real-life LD SCLC patient cohort comprehensively staged with contrast-enhanced cranial MRI was conducted (36).

The flow-chart of this study is illustrated in the **Figure 2**.

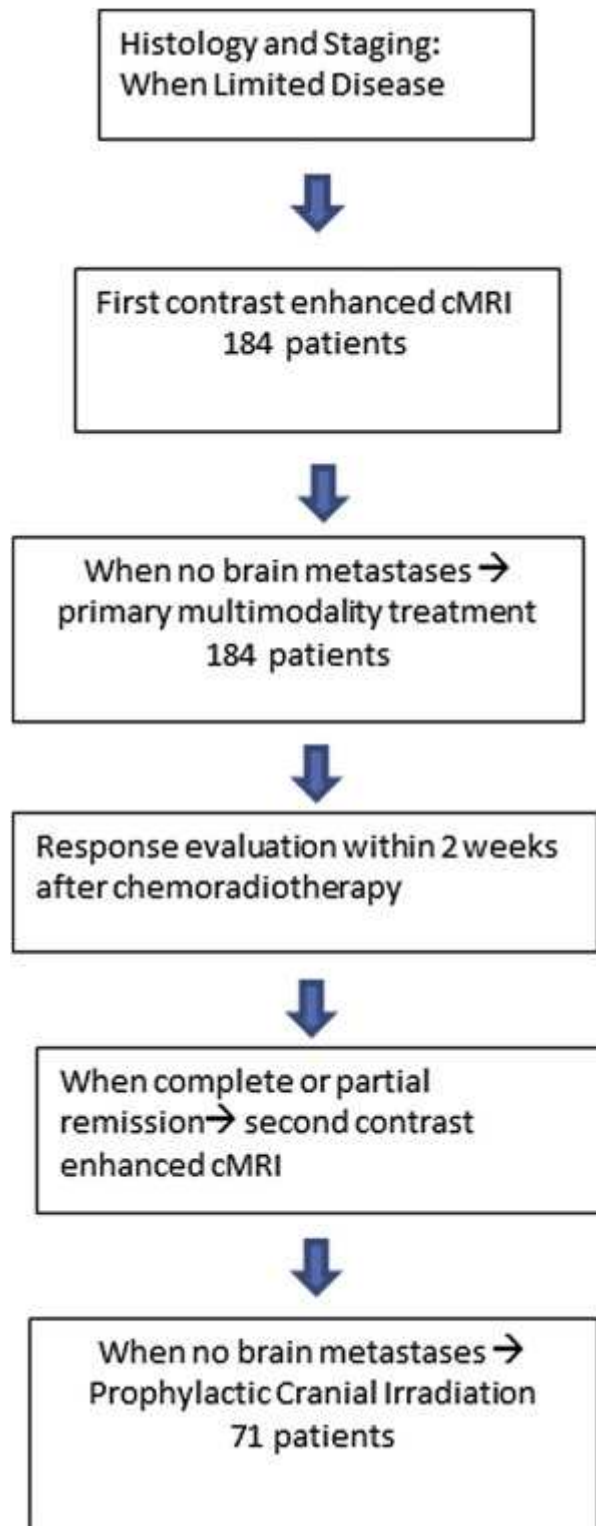


Figure 6: Study design

From 184 consecutive LD SCLC patients treated in two university centers, 60% were men. Importantly, in 60 and 55% of patients involved, mediastinal lymph nodes and

clinical T3/T4-stage were found at initial diagnosis. Concurrent or sequential CRT was applied in 39% and 61% of patients, respectively. 71/184 (39%) patients with partial and complete remission after primary multimodal treatment did not demonstrate occult BM on second contrast-enhanced cranial MRI and were referred for PCI. Different survival parameters were compared between the PCI (71 patients) and non-PCI (113 patients) subgroups also according to the achieved remission status of the primary thoracic disease. There was moderate imbalance between the subgroups regarding patient gender, CRT mode and dose-intensity of the chemotherapy. Especially, different dose-intensity of systemic treatment (8 versus 27% of patients treated with less than four chemotherapy cycles in the PCI- and non-PCI subgroups, respectively) could potentially have an impact on the long-term outcome. As expected, the incidence of metachronous BM was lower in the PCI (23%) compared to non-PCI (37%) subgroup. Furthermore, partial and complete responders treated with PCI demonstrated a significantly longer time to progression and overall survival compared to the therapy-responders without PCI and non-responders (see **Table 1**).

	Partial and complete responders with PCI, months	Partial and complete responders without PCI, months	Non-responders, months
Overall survival	26 (range 19.4 - 32.6)	14 (range 11.4 - 16.6)	9
Time to progression	27	14.5 (range 9 - 19.9)	8.8 (range 7.7 - 9.9)

Table 1: OS and PFS according to remission status and PCI

The overall survival plot demonstrated a remarkable long-term survival benefit of CRT responders treated with PCI, beginning early after completion of the primary multimodal treatment and sustained for more than 60 months (**Figure 3**).

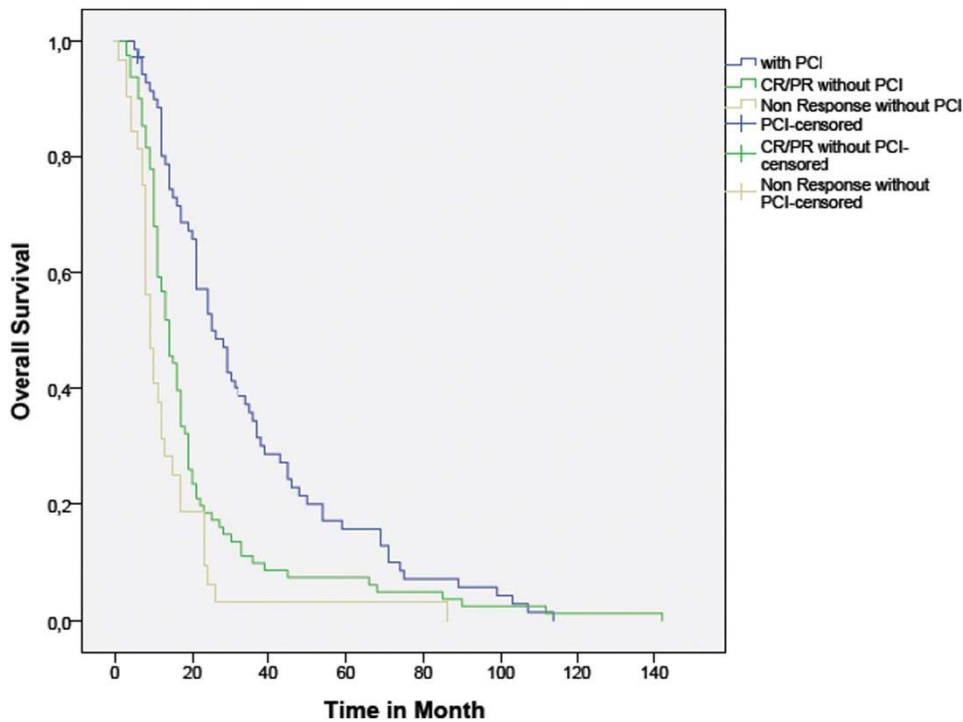


Figure 3: Overall survival in patient subgroups defined by application of PCI and treatment response after CRT

Importantly, the overall survival benefit was also confirmed on multivariate analysis after adjustment of other prognostic factors. In all, this study assessed an authentic prophylactic effect of PCI and confirmed a strong impact of the PCI versus non-PCI on patient long-term outcome in treatment responders to CRT. Additionally, the study pointed out a potential mutual effect of achieved remission of primary disease and PCI in the LD SCLC.

SUMMARY

In summary, several consecutive studies in the field of definitive CRT in LD SCLC have resulted in the identification and characterization of the important treatment-related factors with significant impact on patient prognosis:

The completeness of primary multimodal treatment in LD SCLC is of special importance. The patients who could not successfully complete CRT demonstrated very disappointing outcome which was comparable to metastatic disease.

When considering primary multimodal treatment of thoracic disease, extra attention must be paid to the overall duration of the CRT itself. Short and dose-dense multimodal treatment was associated with significantly improved patient survival independent of CRT mode (concurrent and/or sequential).

In patients treated with simultaneous CRT, a special focus must be made on the concurrent phase of multimodal treatment. An IST > 0 and < 35 days, as an optimal value to achieve the best long-term outcome, was recommended.

An achievement of complete remission of primary thoracic disease after multimodal treatment is a relevant factor for patient prognosis because of improved time to progression and overall survival in complete versus partial responders.

As a result of continuous research in this field, further treatment-related factors regarding application of PCI after completion of primary multimodal treatment in LD SCLC were described:

Second contrast-enhanced cranial MRI after completion of CRT and immediately before PCI was established as a diagnostic tool and demonstrated significant prevalence of occult intracranial disease in LD SCLC complete responders. After exclusion of the

occult BM, a real authentic role of PCI on patient prognosis could be evaluated. This study has resulted in the incorporation of second contrast-enhanced cranial MRI immediately before PCI in the current international guidelines for SCLC (NCCN, ESMO).

Subsequently, correlation between response of primary thoracic disease to multimodal treatment and duration of brain-metastasis-free survival was described. The study showed that incidence and temporal distribution of the metachronous intracranial relapse depended on the achieved thoracic remission status. Hence, remission of primary thoracic disease after CRT must be taken into consideration prior to planning of PCI and further consolidation treatment.

The mutual prognostic role of both achieved intra-thoracic treatment response and PCI was confirmed in a real-life LD SCLC patient cohort comprehensively staged with contrast-enhanced cranial MRI. This data is of special importance because a significant survival advantage was confirmed in the partial and complete responders treated with PCI.

In conclusion, an intensive follow-up, at least, in the first year after initial diagnosis was recommended because of the results of a retrospective study on temporal distribution of disease recurrence in LD SCLC. Also, the results of this follow-up study were included as a recommendation for patient surveillance in the current NCCN guidelines.

ABBREVIATIONS

ALK	Anaplastic lymphoma kinase
BM	Brain metastases
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
ED	Extensive disease
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
PET/CT	Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D glucose integrated with computed tomography
HR	Hazard ratio
IST	interval of simultaneous treatment
LD	Limited disease
MRI	magnetic resonance imaging
NCCN	National comprehensive cancer network
PCI	Prophylactic cranial irradiation
SCLC	Small-cell lung cancer
SER	The start of any treatment until the end of radiotherapy
TNM	Tumor, Node, Metastases
UICC	Union international contre le cancer

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BIOGRAPHY

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Cancer, Thorax, Radiation, Chemotherapy, Immunotherapy, Multimodal, Concurrent, Radiosurgery, Pneumonitis

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Dr. Manapov has teaching responsibilities that include formal teaching to the students and residents on the topics of thoracic malignancies and radiosurgery.

Dr. Manapov attends several weekly Thoracic Oncology Tumor Boards.

In addition, Dr. Manapov has an active laboratory-based research program in which he investigates predictive markers for the optimization of concurrent multimodal treatment, especially radioimmuno- and chemoradioimmunotherapy.

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European Society for radiotherapy and Oncology

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Service to Professional Publications

Journal Reviewer: Ann Oncol, IJROBP, Lung Cancer, Clin Epidemiol, Radiat Oncol

AUTHOR'S PUBLICATIONS

- 26 Original Research thereof 16 as first/last author (cumulative IF 102.279, JCR 2018)
- 10 Correspondence/Letter to Editor, thereof 10 as first/last author (cumulative IF 165.591, JCR 2018)
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STRAHLENTHERAPIE UND ONKOLOGIE (Vol. 187, pp. 66-66)

**RESPONSE OF PRIMARY THORACIC DISEASE TO CHEMORADIOTHERAPY
CORRELATES WITH BRAIN-METASTASIS FREE SURVIVAL IN LIMITED-DISEASE
SMALL-CELL LUNG CANCER PATIENTS WITH POOR INITIAL PERFORMANCE
STATUS WHO SUCCESSFULLY COMPLETED MULTIMODALITY TREATMENT**

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EIDESSTATTLICHE ERKLÄRUNG

Hiermit versichere ich an Eides statt, dass ich meine schriftliche Habilitationsleistung selbständig und ohne andere als die angegebenen Hilfsmittel angefertigt habe, zudem die Herkunft des verwendeten und zitierten Materials ordnungsgemäß kenntlich gemacht habe.

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Dr. med. Farkhad Manapov

Übersicht der eingebrachten Publikationsleistungen

-Als Volltext im Anhang