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Optimization of curative-intended multimodal therapy in patients with limited (UICC I-IIIA-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

Dr. med. Farkhad Manapov

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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.cllc.2016.11.005 [IF 4.204]

CONTENT

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 analogueTurrisi 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]

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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**).

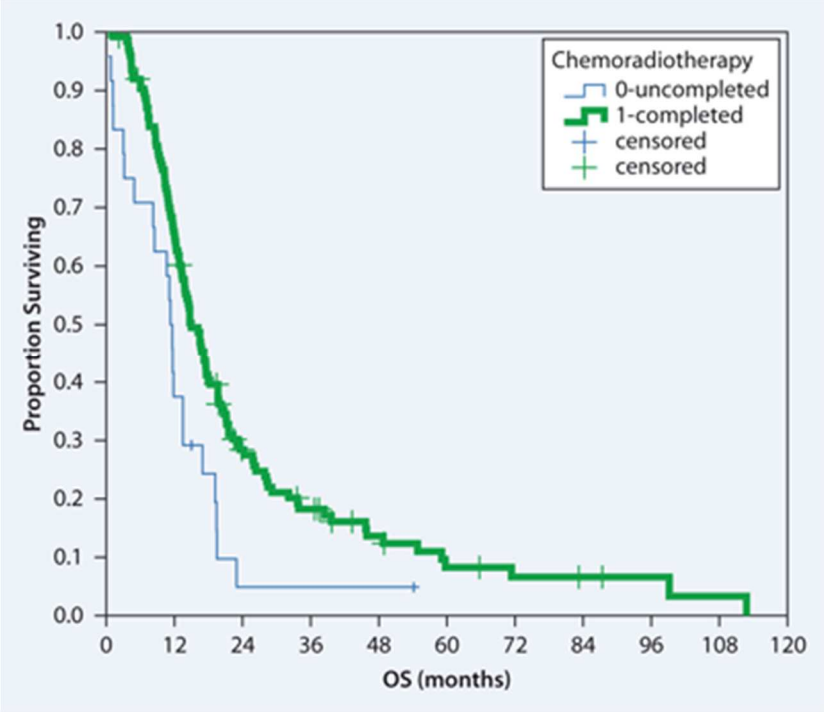

Figure 1: Overall survival in LD SCLC patients with poor initial performance status according to the completion of primary multimodal treatment (p< 0.005, log-rank test)

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**.

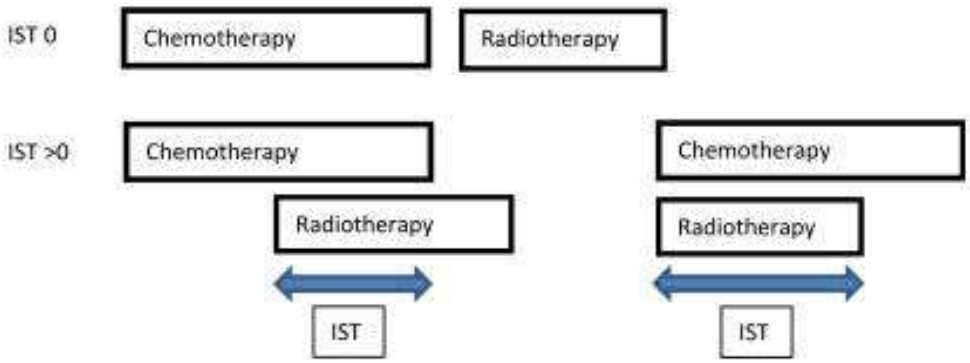

Figure 2: Definition of interval of simultaneous treatment (IST)

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).

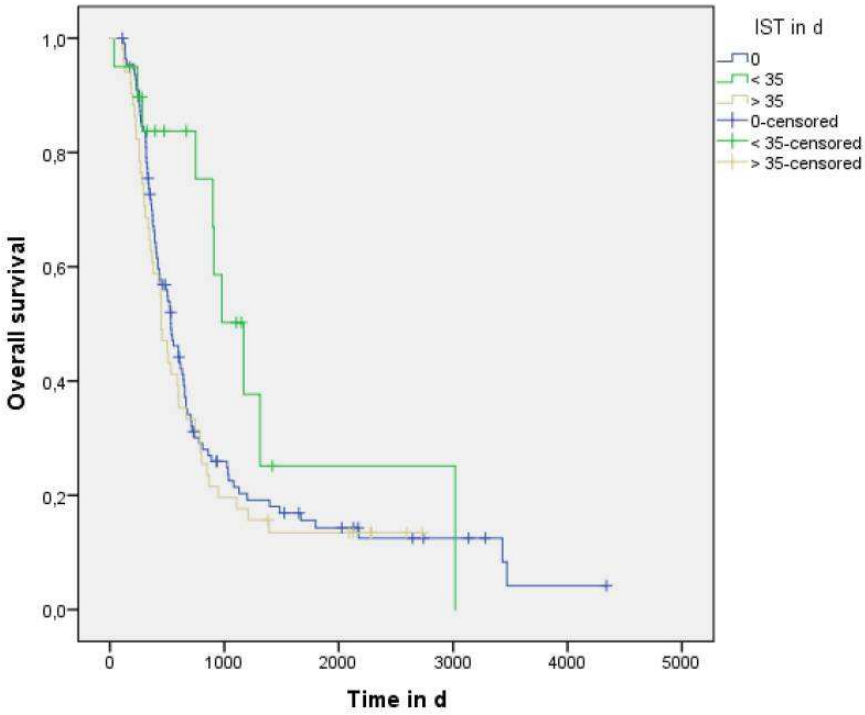

Figure 3: Overall survival in patient subgroups defined by IST

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.

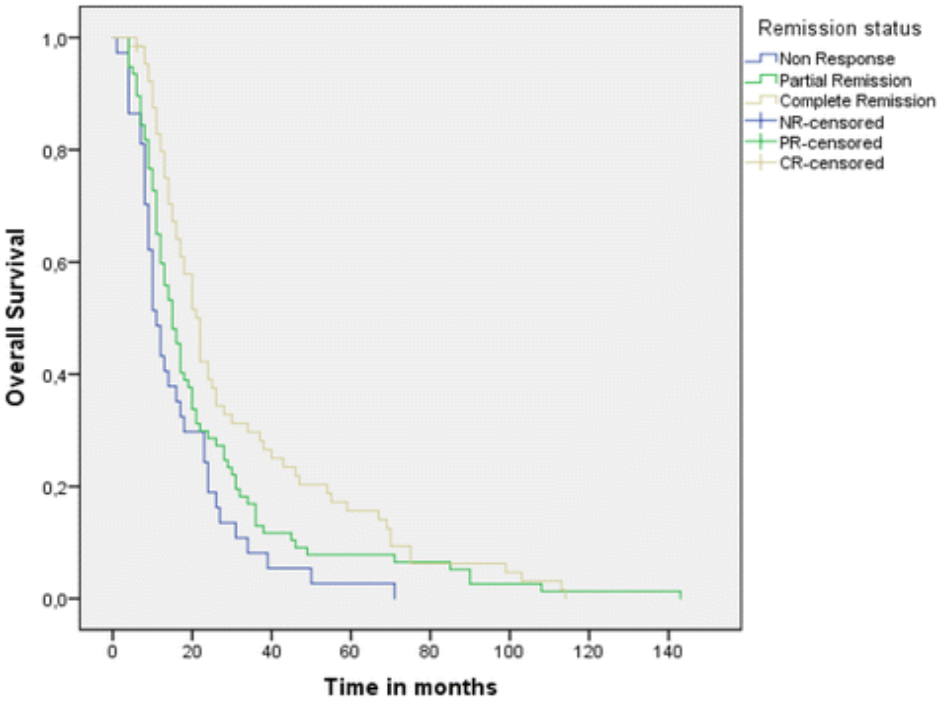

Figure 4: Overall survival in patient subgroups defined by remission status after primary multimodal treatment

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]

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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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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**).

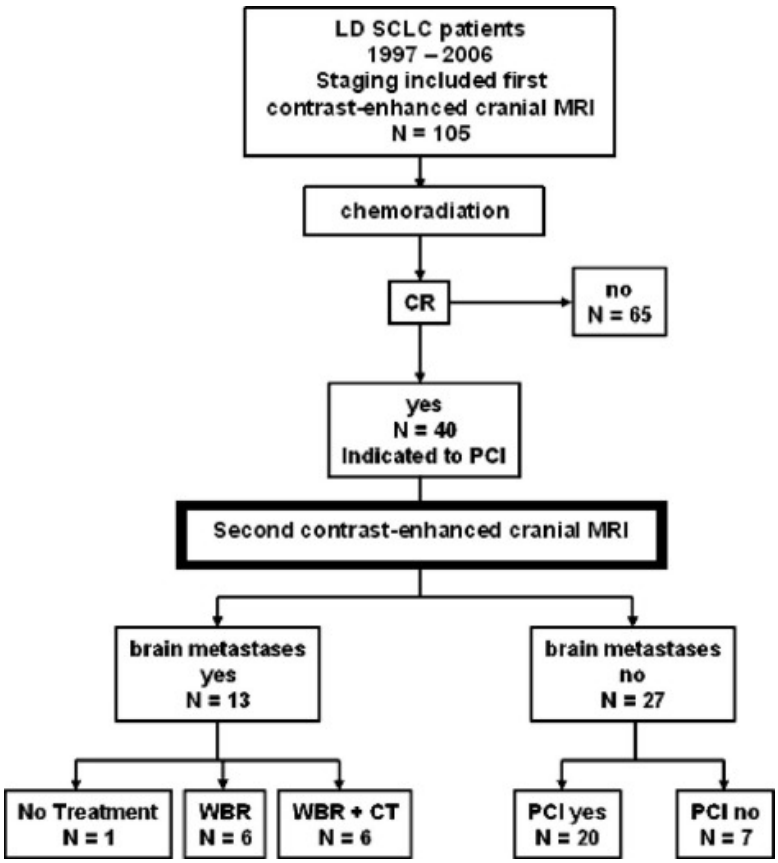

Figure 5: Patient selection according to the outcome of chemoradiotherapy

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**.

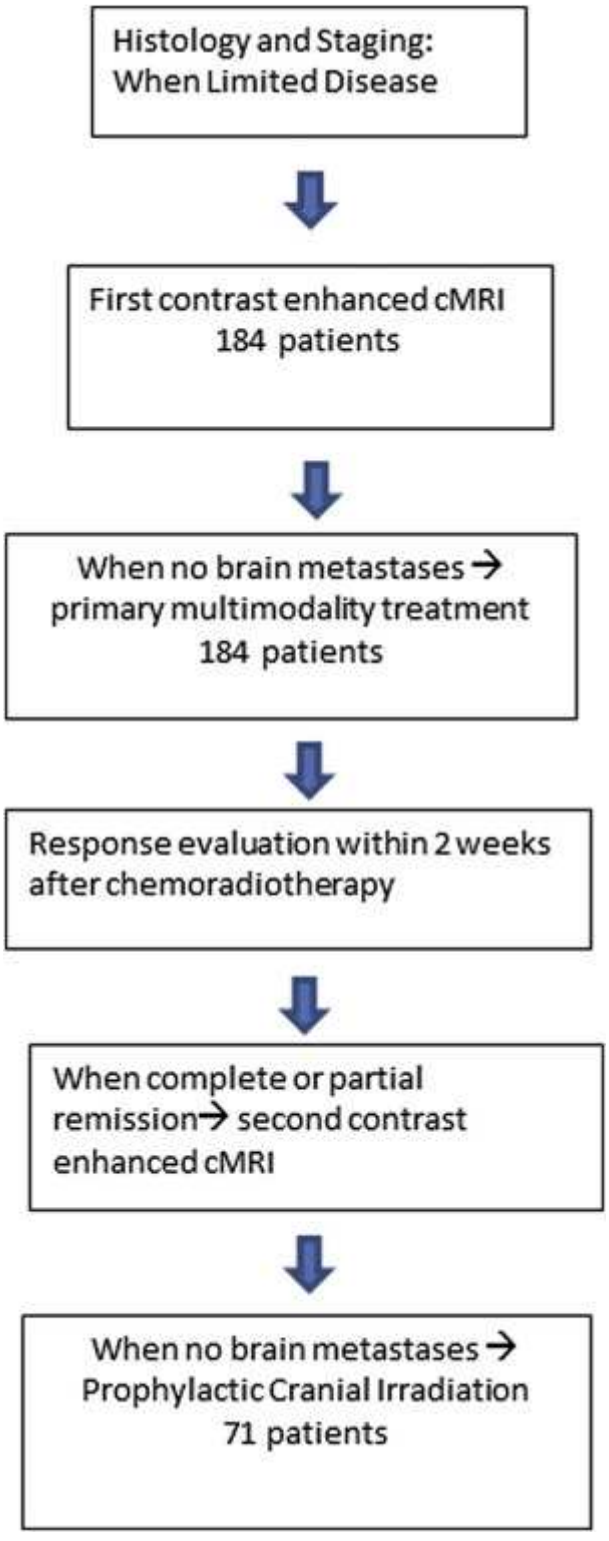

Figure 6: Study design

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**).

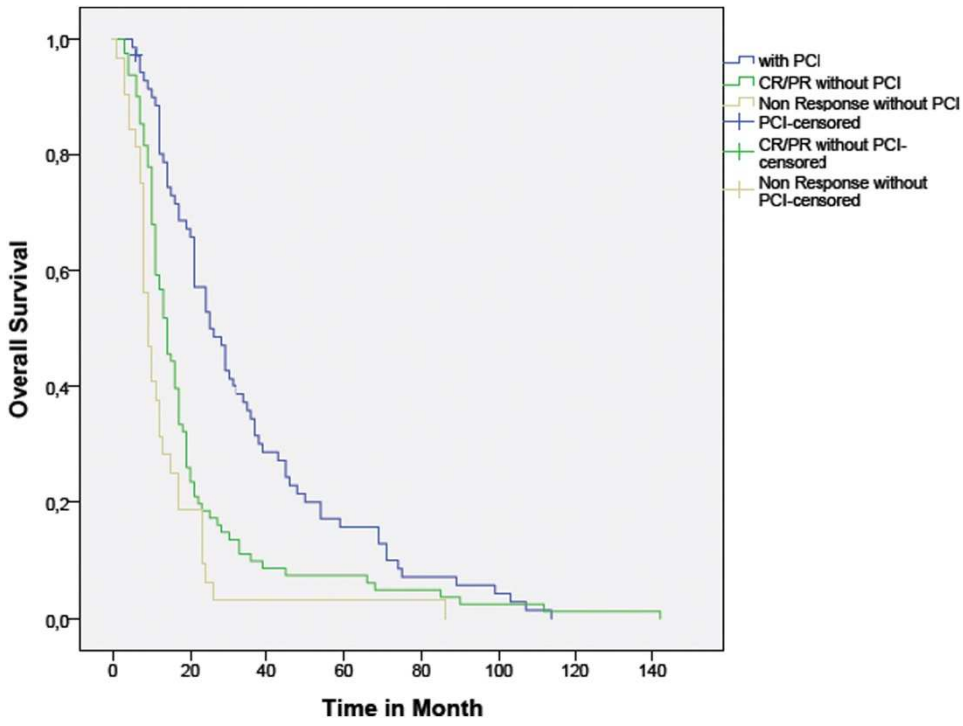

Figure 3: Overall survival in patient subgroups defined by application of PCI and treatment response after CRT

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

REFERENCES

1. Govindan R, Page N, Morgensztern D, Read W, Tierney R, Vlahiotis A, Spitznagel EL, Piccirillo J. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the Surveillance, Epidemiologic, and End Results database. J ClinOncol. 2006;24:4539–4544. doi: 10.1200/JCO.2005.04.4859.

2. Jackman DM, Johnson B. Small-cell lung cancer. Lancet. 2005;366:1385–1396. doi: 10.1016/S0140-6736(05)67569-1.

3. Hochstenbag, MMH, Twijnstra, A, and Wilmink, JT. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. J Neurooncol. 2000;48:243–248.

4. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017 Dec;17(12):725-737. doi: 10.1038/nrc.2017.87.

5. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 S):400-19. doi: 10.1378/chest.12-2363.

6. Low M, Ben-Or S. Thoracic Surgery in Early-Stage Small Cell Lung Cancer. Thorac Surg Clin. 2018 Feb;28(1):9-14. doi: 10.1016/j.thorsurg.2017.08.003.

7. Turrisi AT 3rd, Kim K, Blum R, et al.: Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340 (4): 265-71, 1999. doi: 10.1056/NEJM199901283400403.
8. Pignon JP, Ariagada R, Ihde DC et al. A meta-analysis of thoracic radiotherapy for small cell lung cancer. N Engl J Med 1992; 327(23): 1618-24. doi: 10.1056/NEJM199212033272302.
9. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited stage small cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992; 10(6): 890-5. doi: 10.1200/JCO.1992.10.6.890.
10. Takada M, Fukuoka M, Kawahara M et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: Results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002; 20: 3054-60. doi: 10.1200/JCO.2002.12.071.
11. Turrisi AT III. Platinum combined with radiation therapy in small cell lung cancer: Focusing like a laser beam on crucial issues. Semin Oncol 1994; 21: 36-42. Review. PubMed PMID: 8052872.
12. Gregor A, Drings P, Burghouts J et al. Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: A European Organisation for Research and Treatment of Cancer Lung Cancer Cooperative Group study. J Clin Oncol 1997; 15: 2840-47. doi: 10.1200/JCO.1997.15.8.2840.

13. Gregor A, Drings P, Rinaldi M et al. Acute toxicity of alternating schedule of chemotherapy and irradiation in limited small-cell lung cancer in a pilot study (08877) of the EORTC Lung Cancer Cooperative Group. Ann Oncol 1995; 6: 403-5 (letter).

14. Murray N, Coy P, Pater JL et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited stage small-cell lung cancer. J Clin Oncol 1993; 11: 336-4. doi: 10.1200/JCO.1993.11.2.336.

15. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small cell lung cancer. J Clin Oncol 1997; 15: 893-0. doi: 10.1200/JCO.1997.15.3.893.

16. Work E, Nielsen OS, Bentzen SM, Fode K, Palshof T. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. J Clin Oncol 1997; 15: 3030-37. doi: 10.1200/JCO.1997.15.9.3030.

17. Skarlos DV, Samantas E, Briassoulis E et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: A randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). Ann Oncol 2001; 12: 1231-38.

18. Spiro SG, James LE, Rudd RM et al. Early compared with late radiotherapy in combined modality treatment for limited disease cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol 2006; 24: 3823-29. doi: 10.1200/JCO.2005.05.3181.

19. Fried DB, Morris DE, Poole C et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004; 22: 4837-45. doi: 10.1200/JCO.2004.01.178.

20. Pijls –Johannesma MCG, De Ruysscher D, Lambin P et al. Early versus late chest radiotherapy for limited stage small-cell lung cancer. Cochrane Database Syst. Rev. 2004; 4, CD004700. doi: 10.1002/14651858.CD004700.pub2.

21. De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J et al. Systematic review and meta-analysis of randomized, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. Ann Oncol 2006; 17(4): 543-2. doi: 10.1093/annonc/mdj094.

22. De Ruysscher D, Pijls-Johannesma M, Bentzen SM et al. Time between the first day of chemotherapy and last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. J Clin Oncol 2006; 24(7): 1057-63. doi: 10.1200/JCO.2005.02.9793.

23. De Ruysscher D, Lueza B, Le Péchoux C, Johnson DH, O'Brien M, Murray N, Spiro S, Wang X, Takada M, Lebeau B, Blackstock W, Skarlos D, Baas P, Choy H, Price A, Seymour L, Arriagada R, Pignon JP; RTT-SCLC Collaborative Group. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. Ann Oncol. 2016 Oct;27(10):1818-28. doi: 10.1093/annonc/mdw263.

24. Movsas B, Moughan J, Komaki R et al. Radiotherapy patterns of care study in lung carcinoma. J Clin Oncol 2003; 21: 4553-59. doi: 10.1200/JCO.2003.04.018.

25. Komaki R, Khalid N, Langer CJ, Kong FM, Owen JB, Crozier CL, Wilson JF, Wei X, Movsas B. Penetration of recommended procedures for lung cancer staging and management in the United States over 10 years: a quality research in radiation oncology survey. Int J Radiat Oncol Biol Phys. 2013 Mar 15;85(4):1082-9. doi: 10.1016/j.ijrobp.2012.10.016.

26. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18(8):1116-1125. doi:10.1016/S1470-2045(17)30318-2.

27. 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. doi:10.1007/s00066-011-0016-9.

28. 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. doi: 10.7150/jca.16741.

29. Manapov F, Niyazi M, Gerum S, Roengvoraphoj O, Eze C, Li M, Hildebrandt G, Fietkau R, Klautke G, Belka C. Evaluation of the role of remission status in a heterogeneous limited disease small-cell lung cancer patient cohort treated with definitive chemoradiotherapy. BMC Cancer. 2016 Mar 14;16:216. doi: 10.1186/s12885-016-2245-x.

30. 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. doi: 10.1700/1390.15452.

31. Auperin A, Arriagada R, Pignon JP et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic cranial irradiation overview collaborative group. N Engl J Med 1999; 12: 476-4. doi: 10.1056/NEJM199908123410703.

32. 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. doi: 10.1097/JTO.0b013e3181757a76.

33. 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. doi: 10.1007/s11060-009-0079-y.

34. Manapov F, Klöcking S, Niyazi M, Levitskiy V, Belka C, Hildebrandt G, Fietkau R, Klautke G. Primary tumor response to chemoradiotherapy in limited-disease small-cell lung cancer correlates with duration of brain-metastasis free survival. J Neurooncol. 2012 Sep;109(2):309-14. doi: 10.1007/s11060-012-0894-4.

35. 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. doi: 10.1007/s00066-016-1073-x.

36. Eze C, Roengvoraphoj O, Niyazi M, Hildebrandt G, Fietkau R, Belka C, Manapov F. 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. Clin Lung Cancer. 2017 Jul;18(4):e243-e249. doi: 10.1016/j.cllc.2016.11.005.

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

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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)
- ➔ 7 Case Report, thereof 4 as first/last author (cumulative IF 18.589, JCR 2018)
- ➔ 2 Reviews
- ➔ 22 most relevant Abstracts

Original research (first/last authorship):

How much primary tumor metabolic volume reduction is required to improve outcome in stage III NSCLC after chemoradiotherapy? A single-centre experience.
Roengvoraphoj O, Eze C, Wijaya C, Dantes M, Taugner J, Tufman A, Huber RM, Bartenstein P, Belka C, **Manapov F**.
Eur J Nucl Med Mol Imaging. 2018 Jun 6. doi: 10.1007/s00259-018-4063-7. [IF 7.704]

Pneumonitis in Irradiated Lungs After Nivolumab: A Brief Communication and Review of the Literature.
Manapov F, Roengvoraphoj O, Dantes M, Marschner S, Li M, Eze C.
J Immunother. 2018 Feb/Mar;41(2):96-99. doi: 10.1097/CJI.0000000000000198. [IF 3.826]

Analysis of primary tumor metabolic volume during chemoradiotherapy in locally advanced non-small cell lung cancer.
Roengvoraphoj O, Wijaya C, Eze C, Li M, Dantes M, Taugner J, Tufman A, Huber RM, Belka C, **Manapov F**.
Strahlenther Onkol. 2018 Feb;194(2):107-115. doi: 10.1007/s00066-017-1229-3. Epub 2017 Nov 7. [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.cllc.2016.11.005 [IF 4.204]

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]

Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy.
Roengvoraphoj O, Eze C, Niyazi M, Li M, Hildebrandt G, Fietkau R, Belka C, **Manapov F**.
Strahlenther Onkol. 2017 Feb;193(2):150-155. doi: 10.1007/s00066-016-1073-x [IF 2.459]

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. doi: 10.1186/s12885-016-2245-x. [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. doi: 10.1700/1390.15452. [IF 1.304]

Dose-volumetric parameters and prediction of severe acute esophagitis in patients with locally-advanced non small-cell lung cancer treated with neoadjuvant concurrent hyperfractionated-accelerated chemoradiotherapy.
Manapov F, Sepe S, Niyazi M, Belka C, Friedel G, Budach W.
Radiat Oncol. 2013 May 17;8:122. doi: 10.1186/1748-717X-8-122. [IF 2.862]

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. [IF 3.060]

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. doi: 10.1007/s00066-011-0016-9. Epub 2011 Dec 23. [IF 2.459]

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. [IF 3.060]

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]

Translocation of p21(Cip1/WAF1) from the nucleus to the cytoplasm correlates with pancreatic myofibroblast to fibroblast cell conversion.
Manapov F, Muller P, Rychly J.
Gut. 2005 Jun;54(6):814-22. [IF 17.016]

Original research (co-authorship):

ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer.
Nestle U, De Ruysscher D, Ricardi U, Geets X, Belderbos J, Pöttgen C, Dziadiuszko R, Peeters S, Lievens Y, Hurkmans C, Slotman B, Ramella S, Faivre-Finn C, McDonald F, **Manapov F**, Putora PM, LePéchoux C, Van Houtte P.
Radiother Oncol. 2018 Apr;127(1):1-5. doi: 10.1016/j.radonc.2018.02.023. [IF 4.942]

Clinical relevance of the M1b and M1c descriptors from the proposed TNM 8 classification of lung cancer.
Tufman A, Kahnert K, Kauffmann-Guerrero D, **Manapov F**, Milger K, Müller-Lisse U, Winter H, Huber RM, Schneider C.
Strahlenther Onkol. 2017 May;193(5):392-401. doi: 10.1007/s00066-017-1118-9. [IF 2.459]

Prefraction displacement and intrafraction drift of the prostate due to perineal ultrasound probe pressure.
Li M, Hegemann NS, **Manapov F**, Kolberg A, Thum PD, Ganswindt U, Belka C, Ballhausen H.
Strahlenther Onkol. 2017 Jun;193(6):459-465. doi: 10.1007/s00066-017-1105-1. [IF 2.459]

Comparison of prostate positioning guided by three-dimensional transperineal ultrasound and cone beam CT.
Li M, Ballhausen H, Hegemann NS, Reiner M, Tritschler S, Gratzke C, **Manapov F**, Corradini S, Ganswindt U, Belka C.
Strahlenther Onkol. 2017 Mar;193(3):221-228. doi: 10.1007/s00066-016-1084-7 [IF 2.459]

Stereoscopic X-ray imaging, cone beam CT, and couch positioning in stereotactic radiotherapy of intracranial tumors: preliminary results from a cross-modality pilot installation.
Zollner B, Heinz C, Pitzler S, **Manapov F**, Kantz S, Rottler MC, Niyazi M, Ganswindt U, Belka C, Ballhausen H.
Radiat Oncol. 2016 Dec 7;11(1):158. [IF 2.862]

A comparative assessment of prostate positioning guided by three-dimensional ultrasound and cone beam CT.
Li M, Ballhausen H, Hegemann NS, Ganswindt U, **Manapov F**, Tritschler S, Roosen A, Gratzke C, Reiner M, Belka C.
Radiat Oncol. 2015 Apr 9;10:82. doi: 10.1186/s13014-015-0380-1. [IF 2.862]

Stereotactic radiotherapy of intrapulmonary lesions: comparison of different dose calculation algorithms for Oncentra MasterPlan®.
Troeller A, Garny S, Pachmann S, Kantz S, Gerum S, **Manapov F**, Ganswindt U, Belka C, Söhn M.
Radiat Oncol. 2015 Feb 22;10:51. doi: 10.1186/s13014-015-0354-3. [IF 2.862]

Prognostic factors for survival and radiation necrosis after stereotactic radiosurgery alone or in combination with whole brain radiation therapy for 1-3 cerebral metastases.
Schüttrumpf LH, Niyazi M, Nachbichler SB, **Manapov F,** Jansen N, Siefert A, Belka C.
Radiat Oncol. 2014 May 2;9:105. doi: 10.1186/1748-717X-9-105. [IF 2.862]

Timing of radiotherapy following breast-conserving surgery: outcome of 1393 patients at a single institution.
Corradini S, Niemoeller OM, Niyazi M, **Manapov F**, Haerting M, Harbeck N, Belka C, Kahlert S.
Strahlenther Onkol. 2014 Apr;190(4):352-7. doi: 10.1007/s00066-013-0540-x. [IF 2.459]

Automated biological target volume delineation for radiotherapy treatment planning using FDG-PET/CT.
Niyazi M, Landrock S, Elsner A, **Manapov F**, Hacker M, Belka C, Ganswindt U.
Radiat Oncol. 2013 Jul 12;8:180. doi: 10.1186/1748-717X-8-180. [IF 2.862]

Mature results of a randomized trial comparing two fractionation schedules of high dose rate endoluminal brachytherapy for the treatment of endobronchial tumors.
Niemoeller OM, Pöllinger B, Niyazi M, Corradini S, **Manapov F**, Belka C, Huber RM.
Radiat Oncol. 2013 Jan 7;8:8. doi: 10.1186/1748-717X-8-8. [IF 2.862]

Case reports:

Concurrent radiotherapy and nivolumab in metachronous metastatic primary adenosquamous-cell carcinoma of the prostate.
Eze C, **Manapov F**, Gratzke C, Schmidt-Hegemann NS, Jung A, Kirchner T, Heinemann V, Stief CG, Belka C, Boeck S.
Eur J Cancer. 2018 May;95:109-111. doi: 10.1016/j.ejca.2018.01.086. [IF 7.191]

Moderate hypofractionated image-guided thoracic radiotherapy for locally advanced node-positive non-small cell lung cancer patients with very limited lung function: a case report.
Manapov F, Roengvoraphoj O, Li M, Eze C.
Radiat Oncol J. 2017 Jun;35(2):180-184. doi: 10.3857/roj.2017.00129. [IF 0.76]

Concurrent Afatinib and Whole-Brain Radiotherapy in Exon 19-del-EGFR Mutant Lung Adenocarcinoma: A Case Report and Mini Review of the Literature.
Eze C, Hegemann NS, Roengvoraphoj O, Dantes M, **Manapov F**.
Front Oncol. 2017 May 10;7:88. doi: 10.3389/fonc.2017.00088. [IF 4.416]

Concomitant trimodality therapy of re-irradiation, chemotherapy and regional hyperthermia for a pretreated inoperable sarcoma recurrence.
LI M, Andrä C, Niyazi M, Issels RD, Abdel-Rahman S, Oskan F, **Manapov F**.
Tumori. 2015 Mar-Apr;101(2):e54-6. [IF 1.304]

Primary non-small cell lung cancer in a transplanted lung treated with stereotactic body radiation therapy. A case study.
Oskan F, Ganswindt U, Belka C, **Manapov F**.
Strahlenther Onkol. 2014 Apr;190(4):411-5. doi: 10.1007/s00066-013-0511-2 [IF 2.459]

Primary non-small cell lung cancer in a transplanted lung treated with hypofractionated stereotactic body radiation therapy: case report
Oskan, F., Gerum, S., Ganswindt, U., Belka, C., **Manapov, F**.
STRAHLENTHERAPIE UND ONKOLOGIE (Vol. 189, pp. 61-61) [IF 2.459]

Reviews:

Hypofractionated radiotherapy for prostate cancer.
Hegemann NS, Guckenberger M, Belka C, Ganswindt U, **Manapov F**, Li M.
Radiat Oncol. 2014 Dec 6;9:275. doi: 10.1186/s13014-014-0275-6. [IF 2.862]

Hippocampus sparing in whole-brain radiotherapy. A review.
Oskan F, Ganswindt U, Schwarz SB, **Manapov F**, Belka C, Niyazi M.
Strahlenther Onkol. 2014 Apr;190(4):337-41. doi: 10.1007/s00066-013-0518-8. [IF 2.459]

Correspondence/Letter to Editor:

Mediastinal lymph node clearance and anti-PD-1 induction in resected NSCLC.
Manapov F, Eze C, Käsmann L, Dantes M, Roengvoraphoj O.
Ann Oncol. 2018 Jun 4. doi: 10.1093/annonc/mdy200. [IF 13.926]

18FDG-PET/CT for the Visualization of Inflammatory Component of Radiation-Induced Lung Injury After Stereotactic Radiotherapy.
Roengvoraphoj O, Pazos-Escudero M, Eze C, Dantes M, **Manapov F.**
Clin Nucl Med. 2018 Mar;43(3):e87-e88. doi: 10.1097/RLU.0000000000001932. [IF 6.281]

Is it time to convert the frequency of radiotherapy in small-cell lung cancer?
Eze C, Roengvoraphoj O, Dantes M, **Manapov F**.
Lancet Oncol. 2017 Oct;18(10):e555. doi: 10.1016/S1470-2045(17)30620-4. [IF 36.418]

Survival advantage for etoposide/cisplatin over paclitaxel/carboplatin concurrent chemoradiation in patients with inoperable stage III NSCLC: a subgroup analysis for ECOG 2 patients would be of great interest.
Manapov F, Eze C.
Ann Oncol. 2017 Sep 1;28(9):2319-2320. doi: 10.1093/annonc/mdx254. [IF 13.926]

Why is survival after pembrolizumab affected by previous radiotherapy?
Manapov F, Roengvoraphoj O, Eze C.
Lancet Oncol. 2017 Sep;18(9):e504. doi: 10.1016/S1470-2045(17)30472-2 [IF 36.418]

Prophylactic Cranial Irradiation in Resected Small Cell Lung Cancer: Comprehensive Staging, Adjuvant Chemotherapy, and Strict Stratification of Pathological Stage Play a Role.
Eze C, Roengvoraphoj O, **Manapov F**.
J Thorac Oncol. 2017 Sep;12(9):e137-e138. doi: 10.1016/j.jtho.2017.03.021. [IF 10.336]

Prophylactic cranial irradiation in small-cell lung cancer.

Manapov F, Eze C.

Lancet Oncol. 2017 Jul;18(7):e366. doi: 10.1016/S1470-2045(17)30402-3. [IF 36.418]

Prophylactic Cranial Irradiation in Resected Early-Stage Small Cell Lung Cancer.

Eze C, Roengvoraphoj O, **Manapov F**.

Int J Radiat Oncol Biol Phys. 2017 Jul 1;98(3):612-614.

doi:10.1016/j.ijrobp.2017.03.002. [IF 5.554]

Timing of thoracic irradiation in limited stage small-cell lung cancer: is it still a star on the rise?

Manapov F, Niyazi M, Li M.

Radiat Oncol J. 2013 Sep;31(3):175-6. doi: 10.3857/roj.2013.31.3.175. [IF 0.76]

Is cetuximab-induced rash conclusion really a remnant of the skin erythema dose?

Oskan F, Belka C, **Manapov F**.

Int J Radiat Oncol Biol Phys. 2013 Nov 1;87(3):462-3. doi:

10.1016/j.ijrobp.2013.06.2058. [IF 5.554]

Most relevant cited Abstracts:

Response to checkpoint inhibition in lung cancer with molecular driver alterations.

Amanda Tufman, Kathrin Kahnert, Diego Kauffmann-Guerrero, Benjamin-Alexander Bollmann, Simone Reu, Zulfiya Syunyaeva, Christian Schneider, **Farkhad Manapov**, Thomas Wehler, Rudolf M. Huber, Heiko Golpon
Journal of Clinical Oncology 36, no. 15_supp. DOI: 10.1200/JCO.2018.36.15_suppl.e21071 [IF 26.303]

Evaluation of pulmonary function parameters after moderate hypofractionated image-guided thoracic irradiation in locally advanced node-positive non-small cell lung cancer patients with very limited lung function

F.Manapov, O.Roengvoraphoj, J.Taugner, M.Dantes, C.Wijaya, C.Belka, C.Eze
Journal of Thoracic Oncology 13.4 (2018): S63. [IF 10.336]

Feasibility of moderate hypofractionated image-guided thoracic irradiation for locally advanced node-positive non-small cell lung cancer patients with very limited lung function

F.Manapov, O.Roengvoraphoj, J.Taugner, M.Dantes, C.Wijaya, C.Belka, C.Eze
Journal of Thoracic Oncology 13.4 (2018): S65. [IF 10.336]

Prophylactic cranial irradiation in SCLC: A survey of German radiation oncology institutions on recommendations for brain imaging

C.Eze, O.Roengvoraphoj, M.Dantes, R.Abdo, N-S.Schmidt-Hegemann, C.Belka, **F.Manapov**
Journal of Thoracic Oncology 13.4 (2018): S47. [IF 10.336]

Patterns of care for patients with small cell lung cancer: A survey of German radiation oncology institutions on recommendations for prophylactic cranial irradiation

C.Eze, O.Roengvoraphoj, M.Dantes, R.Abdo, N-S.Schmidt-Hegemann, C.Belka, **F.Manapov**

Journal of Thoracic Oncology 13.4 (2018): S46. [IF 10.336]

Symptomatic pneumonitis in the irradiated lung after nivolumab: Three case studies

O. Roengvoraphoj , C. Eze, M. Li, **F. Manapov**

Annals of Oncology, Volume 28, Issue suppl_2, 1 April 2017 [IF 13.926]

Treatment Response and Prophylactic Cranial Irradiation Are Important Prognostic Factors in LD SCLC Patients Staged with cMRI

Chukwuka Eze, Olarn Roengvoraphoj, Maximilian Niyazi, Guido Hildebrandt, Rainer Fietkau, Claus Belka, **Farkhad Manapov**

Journal of Thoracic Oncology, 12(1), S1470-S1471[IF 10.336]

Symptomatic pneumonitis in the irradiated lung after nivolumab: case study.

Roengvoraphoj, O.; Eze, C.; Li, M.; **Manapov, F**.

Strahlentherapie und Onkologie, Vol. 193: S143-S143 [IF 2.459]

Prognostic value of pre- to posttreatment primary tumor metabolic volume reduction on 18F-FDG-PET/CT in a homogeneous patient cohort with inoperable locally-advanced non-small cell lung cancer treated with definitive chemoradiotherapy

Roengvoraphoj, O.; Eze, C.; Wijaya, C.; Fendler, W.; Belka, C.; **Manapov, F.**

Strahlentherapie und Onkologie, Vol. 193: S144-S144 [IF 2.459]

Prognostic value of pre- to post-treatment primary tumor metabolic volume reduction on 18F-FDG-PET/CT in a patient cohort with inoperable locally-advanced NSCLC treated with definitive chemoradiotherapy
O. Roengvoraphoj, C. Eze, W. Fendler, M. Dantes, C. Belka, **F. Manapov**
Annals of Oncology 28. suppl_2 (2017) [IF 13.926]

A comparative analyse of prostate positioning guided by transperineal 3D ultrasound and cone beam CT
M. Li, H. Ballhausen, N.S. Hegemann, M. Reiner, S. Tritschler, F. **Manapov**, U. Ganswindt, C. Belka

Maximum treatment response and prophylactic cranial irradiation are important prognostic factors in limited disease small-cell lung cancer patients comprehensively staged with cranial magnetic resonance imaging.
Eze C, Roengvoraphoj O, Gerum S, Belka C, **Manapov F**.
J Thorac Oncol. 2016 Apr;11(4 Suppl): S111. doi: 10.1016/S1556-0864(16)30240-4. [IF 10.336]

Maximum response and PCI are important prognostic factors in LD SCLC patients staged with cMRI
C. Eze, O. Roengvoraphoj, M. Niyazi, S. Gerum, G. Hildebrandt, R. Fietkau, C. Belka, **F. Manapov**
Radiotherapy and Oncology 119 (2016): S65-S66 [IF 4.942]

Pre-fraction shift and intra-fraction drift of the prostate due to perineal ultrasound probe pressure
H. Ballhausen, **F. Manapov**, A. Kolberg, P.D. Thum, U. Ganswindt, C. Belka, M. Li
Radiotherapy and Oncology 119 (2016): S839 [IF 4.942]

Impact of the primary tumor metabolic volume (PT-MV) changes in the course of multimodality treatment on overall survival in patients with locally-advanced non-small cell lung cancer.
Roengvoraphoi O, Wijaya C, Eze C, Fendler W, Gerum S, Belka C, **Manapov F**.
J Thorac Oncol. 2016 Apr;11(4 Suppl): S109. doi: 10.1016/S1556-0864(16)30236-2 [IF 10.336]

Subgroup analysis of overall survival according to the duration of chemoradiotherapy in limited disease small-cell lung cancer patients who responded to multimodality treatment
Manapov, F., Kloecking, S., Niyazi, M., Belka, C., Levitskiy, V., Hildebrandt, G., ... & Klautke, G.
STRAHLENTHERAPIE UND ONKOLOGIE (Vol. 188, pp. 97-97) [IF 2.459]

The Response of the Primary tumor to Chemoradiotherapy correlates with brain metastasis-free Survival in Patients with small cell Lung cancer in Stage" Limited disease" with initially poor Performance Status after successful completion of multimodal Therapy
Manapov, F., Kloecking, S., Niyazi, M., Levitskiy, V., Belka, C., Hildebrandt, G., ... & Klautke, G.
STRAHLENTHERAPIE UND ONKOLOGIE (Vol. 187, pp. 67-67) [IF 2.459]

The Duration of Chemoradiotherapy correlates with the overall survival of patients with small cell lung cancer in Stage" Limited Disease" with initially poor Performance Status after successful completion of multimodal Therapy.
Manapov, F., Kloecking, S., Niyazi, M., Belka, C., Hildebrandt, G., Fietkau, R., & Klautke, G.
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

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

Lung Cancer 71 (2011): S35. [IF 4.486]

CHEMORADIOTHERAPY DURATION CORRELATES WITH OVERALL SURVIVAL IN LIMITED-DISEASE SMALL-CELL LUNG CANCER PATIENTS WITH POOR INITIAL PERFORMANCE STATUS WHO SUCCESSFULLY COMPLETED MULTIMODALITY TREATMENT

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

Lung Cancer 71 (2011): S35 [IF 4.486]

Translocation of p21Cip1/WAF1 from nucleus into cytoplasm is involved in pancreatic myofibroblast to fibroblast cell conversion

Farkhat Manapov; Mueller, Petra; Rychly, Joachim

European Journal of Cell Biology 83 (2004): 32 [IF 2.936]

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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