PET-Guided Dose Escalation Tomotherapy in Malignant Pleural Mesothelioma

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Purpose: To test the feasibility of salvage radiotherapy using PET-guided helical tomotherapy in patients with progressive malignant pleural mesothelioma (MPM).
Patients and Methods: A group of 12 consecutive MPM patients was treated with 56 Gy/25 fractions to the planning target volume (PTV); FDG-PET/CT simulation was always performed to include all positive lymph nodes and MPM infiltrations. Subsequently, a second group of 12 consecutive patients was treated with the same dose to the whole pleura adding a simultaneous integrated boost of 62.5 Gy to the FDG-PET/CT positive areas (BTV).
Results: Good dosimetric results were obtained in both groups. No grade 3 (RTOG/EORTC) acute or late toxicities were reported in the first group, while 3 cases of grade 3 late pneumonitis were registered in the second group: the duration of symptoms was 2–10 weeks. Median overall survival was 8 months (1.2–50.5 months) and 20 months (4.3–33.8 months) from the beginning of radiotherapy, for groups I and II, respectively ($p = 0.19$). A significant impact on local relapse from radiotherapy was seen (median time to local relapse: 8 vs 17 months; 1-year local relapse-free rate: 16% vs 81%, $p = 0.003$).
Conclusions: The results of this pilot study support the planning of a phase III study of combined sequential chemoradiotherapy with dose escalation to BTV in patients not able to undergo resection.

Key words: **Helical tomotherapy · Malignant pleural mesothelioma · IGRT · PET imaging**

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PET-geführte Dosiseskalationsstudie mit Tomotherapie bei malignen Pleuramesotheliomen

Zweck: Prüfung der Machbarkeit von Salvage-Strahlentherapie mit der Hilfe PET-geführter helikaler Tomotherapie bei Patienten mit progredientem malignem Pleuramesotheliom (MPM).
Patienten und Methoden: Die erste Gruppe von 12 aufeinanderfolgenden MPM-Patienten wurde mit 56 Gy/25 Fraktionen im Planungszielvolumen behandelt. Eine FDG-PET/CT-Simulation wurde stets durchgeführt, um alle positiven Lymphknoten und MPM-Infiltrationen einzuschließen. Danach wurde eine zweite Gruppe von 12 aufeinanderfolgenden Patienten mit der gleichen Dosis auf der gesamten Pleura behandelt mit gleichzeitigem integriertem Boost von 62,5 Gy auf die FDG–PET/CT-positiven Bereiche (BTV).
Ergebnisse: Gute dosimetrische Ergebnisse wurden in beiden Gruppen erzielt. In der ersten Gruppe wurde keine akute oder späte Grad-3-Toxizität (RTOG / EORTC) berichtet, während drei Fälle von später Grad-3-Pneumonitis in der zweiten Gruppe auftraten. Die Symptome hielten 2 bis 10 Wochen an. Das mediane Gesamtüberleben betrug 8 Monate (1,2–50,5 Monate) und 20 Monate (4,3–33,8 Monate) ab Therapiebeginn in Gruppe I und II ($p = 0,19$). Es wurde signifikanter Einfluss der Strahlentherapie auf Lokalrezidive beobachtet (mediane Zeit bis zum Lokalrezidiv: 8 vs 17 Monate; Rate 1-jähriger Lokalrezidivfreiheit: 16% vs 81%, $p = 0,003$).
Schlussfolgerungen: Die Ergebnisse dieser Pilotstudie sprechen für die Planung einer Phase-III-Studie der kombinierten sequentiellen Radiochemotherapie mit Dosiseskalation auf BTV bei inoperablen Patienten.

Schlüsselwörter: **Helikale Tomotherapie · Maligne Pleuramesotheliome · IGRT · PET-Bildgebung**

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Introduction

There is no clear consensus on the optimal treatment of malignant pleural mesothelioma (MPM), a multifocal or extensive disease on the pleural surface at the time of detection. Despite the lack of controlled/randomized trials using combined treatments, the so-called trimodality therapy (extrapleural pneumonectomy + adjuvant chemotherapy + radiotherapy) has been adopted as the standard of care, based on a number of institutional experiences claiming improved outcome compared to the surgery alone approach [18, 30, 32, 36]. However, due to advanced disease at the time of diagnosis, most patients are considered to be unresectable [29, 36, 39] and are generally candidates for chemotherapy or palliative treatment.

The role of radiotherapy has not yet been clearly assessed but its impact has been claimed for the trimodality therapy [8, 25, 27, 28, 38], suggesting that more aggressive local treatment with high radiation doses could provide some benefit. Recent developments in the field of intensity-modulated and image-guided radiotherapy have led radiation oncologists to reconsider the role of radiotherapy, also for unresectable patients [1], thanks to the greatly improved possibility of closely tailoring the dose distribution around the target [26, 34, 35].

Based on these considerations, a feasibility study using high-dose image-guided tomotherapy was conducted at our institute in unresectable patients.

Materials and Methods

Study Design

A two-step nonrandomized, dose escalation pilot study was performed with the aim of achieving good palliation in progressive disease (PD) patients. The patients included were not previously irradiated on the ipsilateral pleura/lung and showed CT/PET progression/relapse after the previous treatments (surgery and/or chemotherapy). Written informed consent was obtained from all treated patients.

In the first step (May 2006–November 2007), 12 consecutive MPM patients with PD were treated. The optimal total dose, dose per fraction, and timing have not yet been defined for MPM patients, although there is some hope of improving local control by treatment acceleration. MPM cell line radiosensitivity presents α/β values varying from 4–28 Gy [19] with some evidence of a very high proliferation rate especially in the most aggressive tumors. For this reason, and in order to reduce the hospitalization time, a moderately hypofractionated regimen was chosen; the median prescribed dose to the planning target volume (PTV) was 56 Gy in 25 fractions (2.24 Gy/fraction) [13], approximately equivalent to a 2 Gy equivalent dose (EQD2) around 60 Gy, which is generally considered appropriate in many institutions.

Subsequently, 12 additional consecutive patients were treated with simultaneous integrated boost (SIB) dose escalation during the period March 2008–April 2009. The dose prescription was 56 Gy in 25 fractions to the PTV, while concomitantly delivering 62.5 Gy to the PET-positive subvolumes (named biological target volume, BTV). Thus, the BTV could receive an EQD2 up to approximately 70 Gy.

Patients' Characteristics

The main patients' characteristics are shown in Table 1; the two groups (no-SIB and SIB) were quite homogeneous. The following surgeries were performed: 1 extrapleural pneumonectomy, 4 pleurectomy/decortications, and 7 biopsy/talc pleurodesis in the no-SIB group, and 7 pleurectomy/decortication and 5 biopsy/talc pleurodesis in the SIB group. In the no-SIB group, 10 patients received permetrexed-based chemotherapy, 1 patient received gemcitabine–cisplatin, and 1 patient with a previous gastrointestinal stromal tumor (GIST), in treatment for

Table 1. Patients' characteristics.

Tabelle 1. Patientencharakteristika.

	Group I (no boost)	Group II (boost)
No. of patients	12	12
Gender: M	8	10
F	4	2
Median age, years (range)	65 (41–73)	66 (47–75)
Site: Right	6	7
Left	6	5
Histology: Epithelial	10	10
Biphasic	2	2
Stage at diagnosis (IMIG):		
I	5	3
II	4	5
III	3	3
IV	0	1
Type of surgery:		
-Extrapleural pneumonectomy (EPP)	1	0
-Pleurectomy/decortication	4	7
-Biopsy/talc pleurodhesis	7	5
Chemotherapy:		
-Permetrexed based	10[a]	10
-Cisplatin–gemcitabin	1	–
-Glivec	1[b]	–
-No chemotherapy	–	2[c]
Median time from diagnosis to radiotherapy, months (range)	11 (6–20)	14 (2–43)
Treatment median dose (range)	56 Gy/25 fractions (31.2–58.24 Gy)[d]	56 Gy/25 fractions with 62.5 Gy SIB[e]

[a]The extrapleural pneumonectomy (EPP) patient received intraoperatory intrapleural heated cisplatin; [b]the patient with gastrointestinal stromal tumor continued imatinib with which she was being treated, at MPM diagnosis; [c]one patient was in renal failure; [d]the EPP patient radiotherapy was interrupted at 31.2 Gy; one patient received an extra fraction to compensate for an interruption caused by machine failure; [e]one patient received 54 Gy to PTV and 60 Gy SIB to BTV to reduce the kidney dose because of a previous irradiation, in 2006, for seminoma

1 year with imatinib, continued imatinib treatment. Two of the patients of the SIB group, 1 patient with talc pleurodesis and the other with biopsy only, did not receive chemotherapy, one of them due to renal failure. All patients were in progressive disease without other therapeutic options.

Imaging, Contouring, and Planning Procedures

The role of FDG-PET/CT in the definition of the target volume in the radiotherapy of MPM is not mentioned even in the most recent papers [22], although some publications have shown that PET could play an important role in MPM diagnosis [4, 16] and its prognostic value has been demonstrated [5, 33]. Recent studies have shown that FDG-PET allows the stratification of the patients for surgical treatment [14, 37] and permits the early prediction of chemotherapy response and survival [15].

It was upon this evidence that we based the delineation of the clinical target volume (CTV) on FDG-PET/CT images taken for planning purposes with the patient in the same treatment position. Patients were treated in the supine position, with their arms up on a wing-board and were asked to breathe normally during CT/PET acquisition and treatment. The acquisition of FDG-PET positive areas (biological target volume: BTV) takes several minutes and consequently includes the (minor) effects of breathing movements.

The CTV was defined as the whole pleura including BTV and the PET/CT positive mediastinal lymph nodes and infiltrations in thoracic muscles or in the lung. BTV was contoured based on the experience of the nuclear physician (i.e., no fixed threshold levels were applied). An isotropic margin of 10 mm in all directions was added to CTV to create the PTV.

In the SIB group, the CTV to PTV margin was reduced to 0.5 cm in all directions except the craniocaudal, where 0.8 cm was added, due to the improved confidence in applying daily set-up correction with megavoltage CT (MVCT) image guidance, performed for every patient. PTV-OAR overlaps for esophagus, heart, or spinal cord were used to limit the dose to 56 Gy, 56 Gy, and 50 Gy, respectively.

Inverse planning optimization was performed on the tomotherapy planning station; field widths of 2.5–5 cm, modulation factor of 2.5–3.5, and pitch of 0.25–0.3 were used. 95% of the PTV volume received at least 95% of the prescribed dose. Normal tissue constraints from published intensity-modulated radiotherapy (IMRT) studies [1, 2, 21] were adopted; in addition, planning optimization was always stressed to obtain the lowest dose possible for every OAR without compromising target coverage, an approach that we usually follow during tomotherapy optimization [7, 11, 12].

Assessing Treatment Outcome

Patients were examined every week during treatment. A follow-up schedule with PET/CT at 4 months after radiotherapy was planned in order to limit the influence of inflammatory phenomena; then, contrast-enhanced thoracic CT (CT) and PET/CT were alternated every 4 months. Toxicities were defined according to Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) criteria [9]; the Student's t test and X^2 test were used for comparing the characteristics of the two groups and the rates of different toxicities.

Overall, cancer-specific and relapse-free survival curves were calculated from the first day of radiotherapy until either the date of death/relapse or the date of last follow-up with the Kaplan–Meyer method. The impact of a number of variables, including dose (no-SIB group vs SIB group), gender, location (left–right), stage (I–II vs III–IV), chemotherapy, type of surgery (radical vs nonradical), age, and treatment duration, was assessed using log-rank tests. The SPSS (v. 17) software was used for the analyses.

Results

The last update refers to March 2011. All patients of the first group were dead at the last follow-up, while 3 patients of the second group were still alive. Median time between diagnosis and radiotherapy was 11 months (range, 6–20 months) for the no-SIB group and 14 months (range, 2–43 months) for the SIB group. Median follow-up from the start of tomotherapy was 13 months (range, 1.2–50.5 months): 8 months (1.2–50.5 months) and 20 months (4.3–33.8 months) for the no-SIB and the SIB groups, respectively. Apart from follow-up duration, no other characteristics of the two subgroups reported in Table 1 significantly differ.

Planning Data

A summary of the relevant dosimetric data is reported in Table 2. The sparing of the main organs at risk was excellent in both groups; in particular, the mean contralateral lung dose was very low (< 8 Gy).

Toxicities

The no-SIB group showed acceptable acute and late toxicity (Table 3). Two patients died within 1 month of the end of radiotherapy. Based on clinical statements, treatment was not considered to be the cause.

Three patients of the SIB group needed hospitalization due to actinic pneumonitis 2–6 weeks after the end of radiotherapy; all three recovered. One patient died 4 months after the end of the treatment due to rapid abdominal PD. Another patient, with local SD, died 5 months after radiotherapy with pulmonary artery thrombosis, which he developed after the surgery, despite anticoagulant treatment. The long surviving patients (> 12 months) of the SIB group presented hemithoracic fibrosis at CT; 3 of these patients also presented a deviation from the axis in the direction of the disease.

When comparing the two groups, acute grade 2 dermatitis and late grade 3 pneumonitis were increased in the SIB group ($p = 0.07$): considering all pulmonary symptoms, 6 of 12 experienced late grade 2–3 toxicity. The mean ipsilateral lung (outside CTV) dose in the SIB group was found to be 4 Gy higher

Table 2. Mean doses and standard deviation (in parentheses) of main organs at risk; for the spinal cord (serial organ) the maximum dose was reported. Median volume of lung receiving more than X Gy (VX) and range (in parentheses). All values were reported to one decimal place without rounding.

Tabelle 2. Mittlere Dosen und Standardabweichungen der wichtigsten gefährdeten Organe; für Rückenmark wurde die maximale Dosis dokumentiert. Mittlere Volumen der Lunge, die mehr als X Gy (VX) erhalten haben, und Range (in Klammern). Alle Werte auf eine Dezimalstelle, ohne Rundung der Werte.

Mean doses (in Gy)	**Group I (no boost)**		**Group II (boost)**	
Laterality	**Left-sided MPM (6 patients)**	**Right-sided MPM (6 patients)**	**Left-sided MPM (5 patients)**	**Right-sided MPM (7 patients)**
Heart	29.4 (± 6.5)	23.5 (± 4.0)	27.5 (± 2.7)	22.4 (± 2.0)
Liver	7.0 (± 2.4)	20.6 (± 4.0)	8.6 (± 2.0)	25.0 (± 2.3)
Ipsilateral kidney	22.0 (± 8.6)	13.9 (± 7.8)	14.6 (± 6.7)	10.7 (± 5.4)
Contralateral kidney	3.7 (± 2.1)	2.8 (± 3.1)	6.0 (± 2.5)	4.8 (± 1.1)
Spinal cord (D_{max})	39.1 (± 3.1)	37.4 (± 1.9)	46.0 (± 4.6)	40.2 (± 5.7)
Ipsilateral lung outside CTV	48.5 (± 4.6)	46.4 (± 5.6)	51.7 (± 5.1)	49.0 (± 3.8)
Contralateral lung	7.6 (± 2.7)	7.9 (± 2.6)	6.8 (± 0.5)	7.5 (± 0.7)
V5 (%)	57.5 (39.0–96.0)	69.0 (53.0–92.0)	66.0 (53.0–86.4)	75.3 (52.3–87.3)
V10 (%)	16.0 (0.0–40.0)	13.5 (2.0–28.0)	12.2 (6.5–15.1)	16.1 (9.4–33.2)
V20 (%)	4.0 (0.0–10.0)	0 (0.0–5.0)	0.1 (0.0–0.4)	0.9 (0.2–1.5)

Table 3. Acute and early late toxicities.

Tabelle 3. Akute und frühe Spättoxizitäten.

Symptom	**Grade toxicity**	**Acute toxicity**		**Late toxicity**	
		Group I, no boost (12 patients)	**Group II, boost (12 patients)**	**Group I, no boost (9 patients)**	**Group II, boost (12 patients)**
Dysphagia	G1	3	3	–	1
	G2	3	3	–	1
Odynophagia	G1	1	2	–	–
Stomach pain/ gastritis	G1	1	–	–	–
	G2	2	–	1	–
Vomiting	G1	–	–	–	–
	G2	1	–	–	–
Radiodermatitis	G1	2	3	–	–
	G2	–	3	–	1
Asthenia	G1	2	2	1	–
	G2	–	–	2	2
Thoracic pain	G1	1		1	
	G2	–		1	
Dyspnea	G1	0	–	–	2
	G2	–	1	4	3
	G3		–	–	1
Cough	G1	0	1	1	2
	G2	–	–	–	–
Radiation pneumonitis	G1	–	–	–	–
	G2	–	2	–	1
	G3	–	–	–	3[a]

[a]The radiation pneumonitis symptoms began 2–6 weeks after the end of radiotherapy

than that of the no-SIB group (p = 0.01), which could explain the increase in lung toxicity.

The largest BTV at FDG-PET/CT was registered in the second group; it was 900 ml in a patient with a 43-month interval between diagnosis and radiotherapy. If trying to correlate the toxicity with the volume of BTV, surprisingly, the risk of toxicity was higher for smaller BTV (see Figure 1): the incidence was 5/6 and 1/6, respectively, for BTV < 180 ml and > 180 ml (p = 0.04). This result is probably due to the fact that patients with smaller tumor volumes show some functioning of the lung, while the lung of the patients with a large BTV had already been compromised.

Control and Survival Analysis

In the no-SIB group, the response was assessed with PET/CT in 7 patients and with contrast enhanced CT in 2 patients (3 died prior to the first follow-up). The median overall survival was 8 months. One patient had complete response (CR), 4 had partial response (PR), and the other 4 had PD. All early responses were followed by PD after the first or second control (at 3–6 months). The patient with CR had a local relapse 6 months later. She responded to successive salvage chemotherapies and died with bilateral PD 50.5 months after the end of the treatment.

In the SIB group, all patients underwent PET/CT evaluation. The median overall survival was 20 months. One CR, in a third stage unoperated, chemonaive patient, 5 PR, and 2 SD were obtained. The CR patient had a contralateral relapse

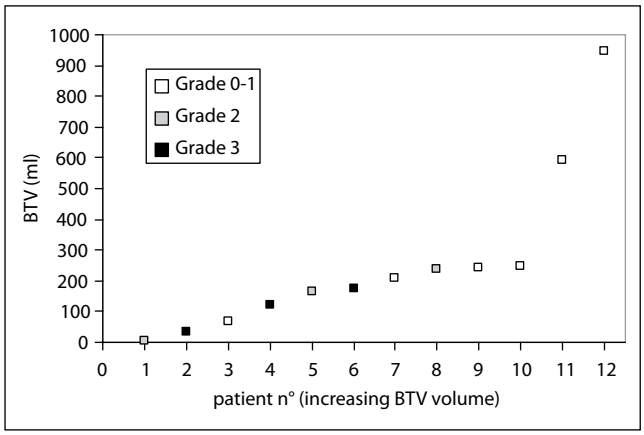

Figure 1. Late pulmonary toxicities in the SIB group are plotted according to the PET positive volume (BTV) for the subgroup with dose escalation on BTV (n=12): lower volumes are correlated with an increased risk of toxicity.

Abbildung 1. Späte pulmonale Toxizitäten entsprechend PET-positiven Volumen (BTV) in der Untergruppe mit Dosiserhöhung auf BTV (n = 12): Niedrigere Volumen gehen mit einem erhöhten Toxizitätsrisiko einher.

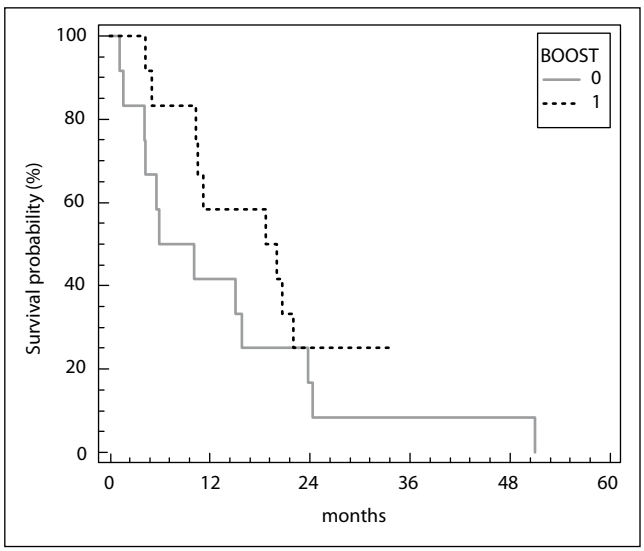

Figure 2. Overall survival curves: the two groups with (*dotted line*) and without (*continuous line*) dose escalation on PET-positive volumes are compared (boost vs no boost). Median survival 8 vs. 20 months (p = 0.19).

Abbildung 2. Gesamtüberlebensraten in den Gruppen mit (*gestrichelte Linie*) und ohne (*durchgezogene Linie*) Dosiseskalation auf PET-positive Volumen (Boost vs kein Boost).

12 months later. Four patients were in PD at the first evaluation: 1 was in local PR with PD in the contralateral lung, 2 were in SD and abdominal PD, and 1 was in local and distant progression.

When comparing the two groups, the largely improved overall survival was not statistically significant (1-year survival: 41% vs 59%, log-rank p = 0.19, Figure 2). The median time to relapse (including both local and distant) was longer for the

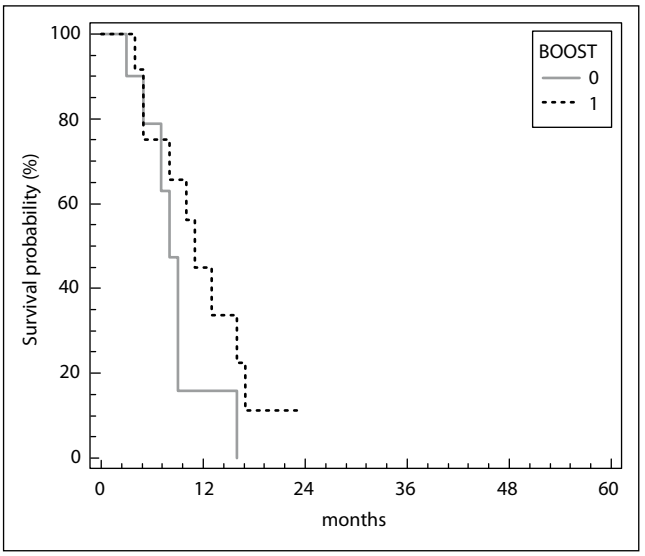

Figure 3. Relapse-free survival curves (including both local and distant): the two groups with (*dotted line*) and without (*continuous line*) dose escalation on PET-positive volumes are compared (boost vs no boost). Median time to relapse (distant + local) 8 vs. 11 months (p = 0.19).

Abbildung 3. Rezidivfreies Überleben (einschließlich lokaler wie auch Fernmetastasen) in den Gruppen mit (*gestrichelte Linie*) und ohne (*durchgezogene Linie*) Dosiseskalation auf PET-positive Volumen (Boost vs kein Boost).

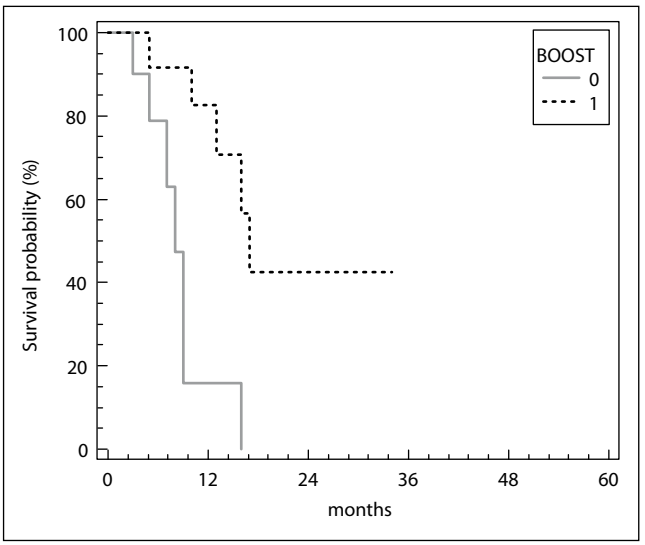

Figure 4. Local relapse-free survival curves: the two groups with (*dotted line*) and without (*continuous line*) dose escalation on PET-positive volumes are compared (boost vs no boost). Median time to local relapse: 8 vs. 17 months (p = 0.003).

Abbildung 4. Lokalrezidivfreies Überleben in den Gruppen mit (*gestrichelte Linie*) und ohne (*durchgezogene Linie*) Dosiseskalation auf PET-positive Volumen (Boost vs kein Boost).

SIB group, although not significantly (11 vs 8 months, log-rank p = 0.19, Figure 3). The median time to local relapse for no-SIB and SIB groups was 8 and 17 months, respectively; of note, the 1-year local relapse-free rate was 16% vs 81% for the two groups (log-rank p = 0.003, Figure 4). A slightly larger difference, compared to overall survival, was found when considering cancer-specific survival (1-year survival: 46% vs 71%, p = 0.12, Figure 5). No other variables were found to be correlated with overall and/or relapse-free survival.

Discussion

Several works failed to find an impact of radiotherapy on survival of unresectable MPM patients compared to best supportive care [17, 24]. A potential role of radiotherapy in MPM emerged from a number of studies in an adjuvant to surgery context [8, 25, 27, 28, 38], while the feasibility of dose escalation with IMRT for unresectable, recurrent MPM has only recently been suggested [26]; on the other hand, several experiences have shown the role of the low dose received by the contralateral lung on fatal pneumonitis [2, 25, 31, 40], quite consistent with reported rates of fatal pneumonitis during whole lung irradiation in TBI [10]. When lung doses are low, for pleural localization of disease or in TBI, the toxicity is acceptable [20, 23].

In our tomotherapy experience, we have been able to reduce the dose to the contralateral lung to safe levels, with average values of MLD below 8 Gy in both groups of patients; as a result, no fatal radiotherapy-induced pneumonitis have been found to date.

Because of the presence of the ipsilateral lung, one could expect a higher rate of actinic pneumonitis compared to the most studied EPP series. However, as in other published series, the toxicity was acceptable [18, 25], although increased in the SIB group where 3 patients experienced grade 3 pneumonitis. The duration of the symptoms, treated with antibiotics, dexamethasone, and oxygen was between 2 and 10 weeks.

A higher dose of hemithoracic radiotherapy improved 1-year relapse-free survival. A Memorial Sloan Kettering Cancer Center (MSKCC) study has already shown that external beam radiotherapy doses ≥ 40 Gy were associated with an improvement in survival with 1-year local control of 42% [18].

After EPP the results demonstrated that a dose of 54 Gy is necessary for microscopic and residual disease. In a MSKCC phase II trial, the investigators delivered 54 Gy in 30 fractions to the ipsilateral hemithorax postoperatively and

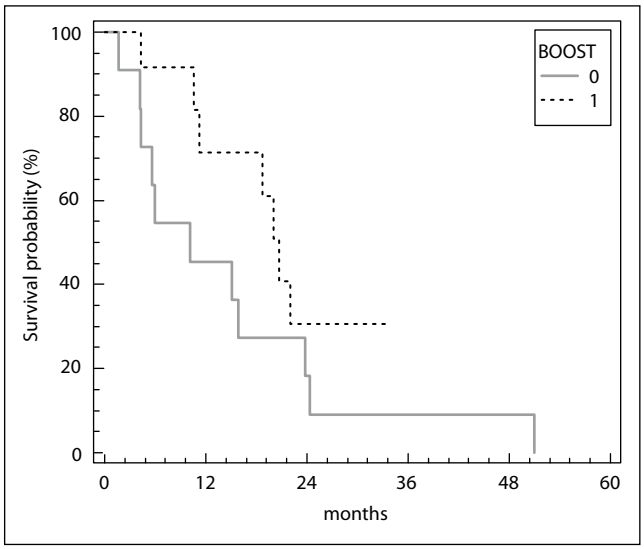

Figure 5. Cancer-specific survival curves: the two groups with (*dotted line*) and without (*continuous line*) dose escalation on PET-positive volumes are compared (boost vs no boost). Median cancer-specific survival: 8 vs 20 months (p = 0.12).

Abbildung 5. Krankheitsspezifisches Überleben in den Gruppen mit (*gestrichelte Linie*) und ohne (*durchgezogene Linie*) Dosiseskalation auf PET-positive Volumen (Boost vs kein Boost).

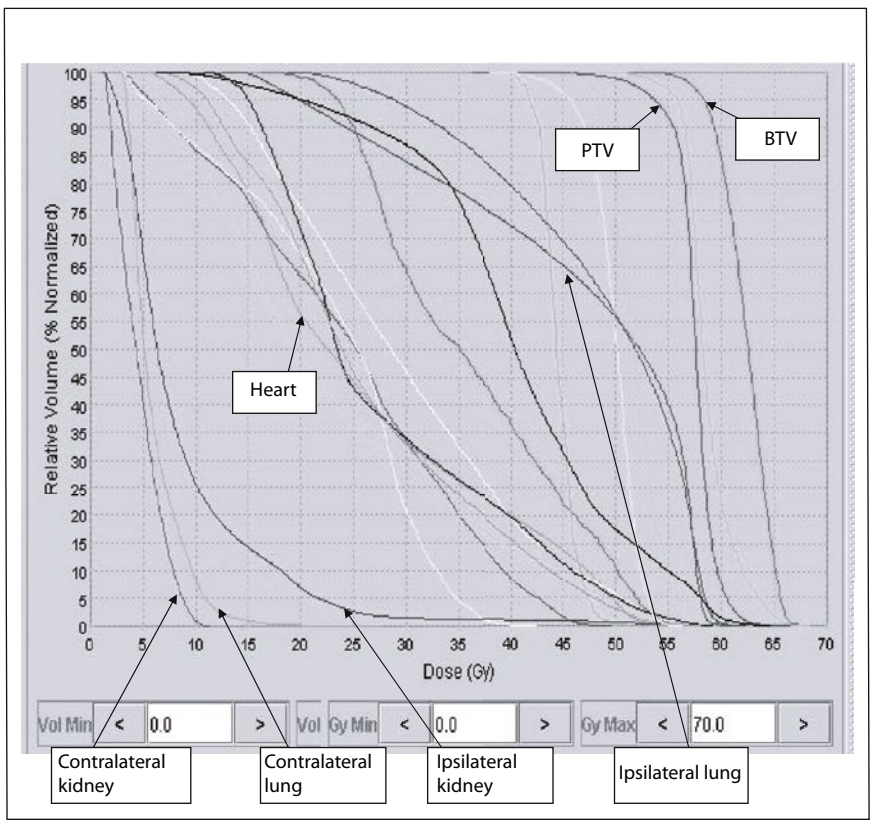

Figure 6. Dose–volume histogram of a representative patient (left lung) of the boost group.

Abbildung 6. Dosis-Volumen-Histogramm eines repräsentativen Patienten der Boost-Gruppe.

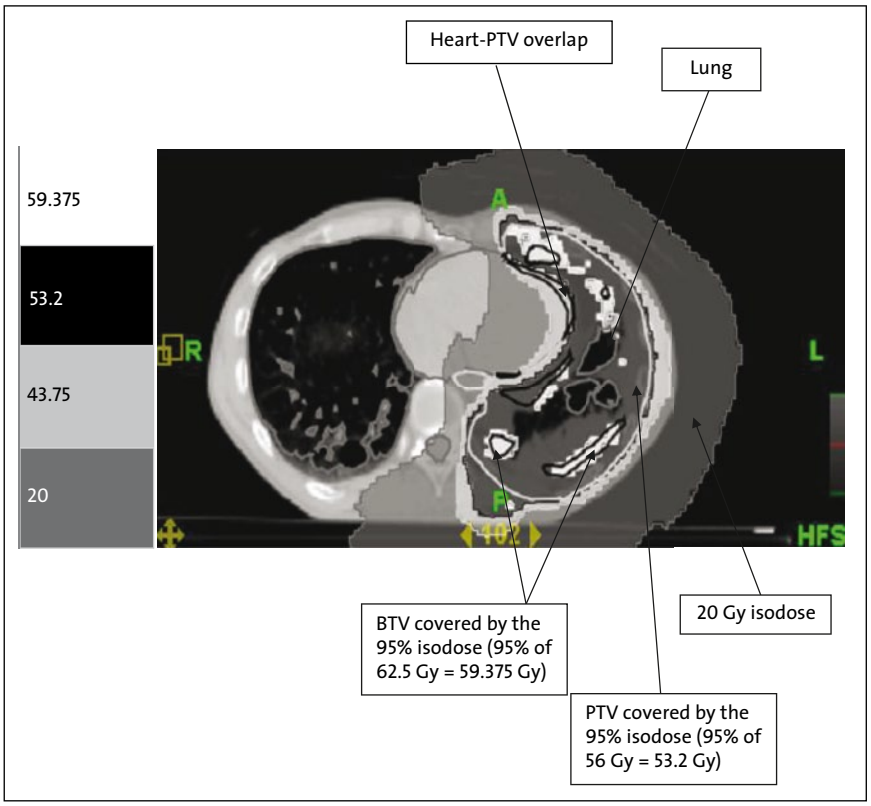

Figure 7. Dose distribution of a representative patient (left lung) of the boost group.

Abbildung 7. Dosisverteilung (linke Lunge) eines repräsentativen Patienten der Boost-Gruppe.

observed a low locoregional recurrence rate. When updating their follow-up, it was observed that not all local recurrences were within the field [41]. In addition, Allen et al. [3] demonstrated the influence of radiotherapy technique and dose in limiting in-field local failures, which makes distant relapse the most significant challenge; this is, after decades of struggle, a remarkable result. IMRT has the potential to further improve the uncomplicated local control rate [1, 2, 21, 31, 35]. Hypofractionation in MPM radiotherapy has been less studied [6].

There are some discrepancies with the results of Sterzing et al. [35], who reported a mean dose to the ipsilateral kidney of 7.7 Gy (Figure 6). The differences are probably due to the CTV definition. The Sterzing et al. paper published the results of a prophylactic treatment, after an EPP, of the theoretical pleural space. We treated the effective pleura and MPM infiltration in tissues, in patients in PD. Some patients had a significant volume of BTV in the diaphragmatic region of the pleura (Figure 7).

With our scheme using helical tomotherapy, in a consecutive, nonselected series of PD patients, one CR and several PR were obtained in the no-SIB group; all subsequently experienced PD, but the CR patient lived for 50.5 months after the radiotherapy, with grade 1 dyspnea until bilateral progression. Similarly, in the dose-escalated SIB group, only one CR was obtained in a non-operated, chemonaive patient, but more PR and SD were found compared to the first group. Toxicity was higher, but manageable. A statistically significant difference in local control, in favor of dose escalation, was observed. In this group distant relapses were dominant, reproducing to some extent the result found in postextrapleural pneumonectomy radiotherapy with high-dose IMRT. The improved overall survival with dose escalation could not be demonstrated, probably due to the limited number of patients.

Conclusion

Despite the study limitations, a statistically significant improvement in local control was obtained in consecutive, nonselected patients, when the dose was escalated on the PET-positive volumes in a SIB approach with tomotherapy.

A multi-institutional phase III study comparing no-SIB vs SIB dose escalation image-guided IMRT after permetrexed/cisplatin chemotherapy for unresectable MPM patients may be suggested because the confirmation of the impact of moderate dose escalation on BTV in a controlled trial could open new perspectives in the treatment of this poor prognosis cancer.

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