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Moderately Hypofractionated Helical IMRT, FDG–PET/CT-guided, for Progressive Malignant Pleural Mesothelioma in Patients With Intact Lungs

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Abstract

Fifty-one patients with malignant pleural mesothelioma treated with helical intensity-modulated radiation therapy in presence of intact lungs were analyzed. A positron emission tomography positive volume ≥ 473 cc was found predictive of early death. A positron emission tomography positive volume < 205 cc was associated with longer survival in stage III to IV patients treated with simultaneous integrated boost, and also with higher late pulmonary ≥ grade 2 toxicity.

Introduction: The objective of this study was to present the outcomes of moderately hypofractionated helical intensity-modulated radiation therapy (HT) with/without simultaneous integrated boost (SIB) on fluorodeoxyglucose-positron emission tomography (FDG-PET) positive areas (gross tumor volume [GTV]-PET) for patients with progressive malignant pleural mesothelioma (MPM) after previous treatments. **Methods and Materials:** From May 2006 to April 2014, 51 patients with a median age of 68.8 years (range, 38.6-82 years) were treated. There were 41 men and 10 women; 43 epithelioid MPM and 8 sarcomatoid, involving the left pleura in 25 patients and the right pleura in 26 patients. The initial stage was: I, 11 patients; II, 14 patients; III, 17 patients; and IV, 9 patients. Chemotherapy was prescribed for 46 patients, for 6 cycles (range, 0-18 cycles). Eighteen patients had pleurectomy/decortication, and 33 had talc pleurodesis. FDG-PET was used for target identification. A median dose of 56 Gy/25 fractions was prescribed to the involved pleura, and SIB to 62.5 Gy to GTV-PET was added in 38 patients. **Results:** The median survival from diagnosis was 25.8 months (range, 8.4-99.0 months). One patient, treated with SIB, was alive at the October 2017 follow-up. Two cases of grade 5 radiation pneumonitis were registered. A GTV-PET ≤ 205 cc was predictive of late ≥ grade 2 lung toxicity, but also of better survival in stage III and IV disease: 5.9 versus 11.7 months ($P = .04$). A GTV-PET ≥ 473 cc was predictive of early death ($P = .001$). **Conclusions:** Moderately hypofractionated, FDG-PET guided salvage HT in patients with progressive MPM after previous treatments showed acceptable toxicity and outcome results similar to adjuvant radiotherapy after pleurectomy/decortication, suggesting that the delay of radiotherapy is not detrimental to survival, and has the associated benefit of postponing inherent toxicity.

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Introduction

Malignant pleural mesothelioma (MPM) has a low incidence, but because of the low median survival of about 9 months,[1] MPM represents an important health problem.

Except for a randomized phase III trial demonstrating a modest increase of the median time to progression and overall survival (OS) with the addition of permetrexed-based chemotherapy,[2] there has been no major progress in recent decades.[3]

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The results of MARS (Mesothelioma and Radical Surgery)[4] and SAKK 17/04 (Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemitoracic radiotherapy)[5] trials have led to a reduction in the use of extrapleural pneumonectomy (EPP) and a questioning of the role of radiotherapy after an unnecessarily extended surgery, adding confusion in the field owing to questionable methodology.[6,7]

Moreover, a survival meta-analysis on almost 3000 patients showed that EPP gives higher short-term mortality rates than pleurectomy/decortication (P/D) (4.5% vs. 1.7%), and similar 2-year OS.[8]

Intensity modulated radiotherapy (IMRT) has allowed better normal tissue sparing and homogeneous dose distribution; thus adjuvant radiotherapy was offered to patients treated with less extensive surgery, in presence of both intact lungs.[9]

Here, we report our results of high-dose hypofractionated helical IMRT (HT) (TomoTherapy, Accuray Inc, Sunnyvale, CA) in patients with MPM with both lungs intact and progressive disease (PD) after chemotherapy and limited surgery.

Patients and Methods

Patient Selection and Characteristics

First, a 2-step nonrandomized, dose-escalation pilot study was performed on 24 consecutive patients with MPM in our institution.[10] In the absence of other therapeutic options, the patients, all of whom presented with PD after previous chemotherapy + EPP or P/D, or biopsy/talc pleurodesis (B/TP) ± chemotherapy, received salvage HT. A total dose of 56 Gy/25 fractions (2.24 Gy/fraction) to the hemithorax/whole pleura with simultaneous integrated boost (SIB) of 62.5 Gy (2.5 Gy/fraction) to fluorodeoxyglucose-positron emission tomography (FDG-PET) positive areas (gross tumor volume [GTV]-PET) was identified as sufficiently safe.[10] Subsequently, 56 Gy/25 fractions without SIB (non-SIB) were prescribed only for 2 patients, for whom the organ at risk (OAR) constraints (owing to GTV-PET position) exceeded the limits. A retrospective analysis was performed on patients with both lungs intact treated according to this protocol.

The institutional ethics committee approved the study. All patients initially signed an informed consent to therapy and permission for publication of disease-related information in accordance with the Declaration of Helsinki.

From May 2006 to April 2014, 51 patients were treated with HT. Patient characteristics are summarized in Table 1.

Chemotherapy was not prescribed in 5 patients, owing to comorbidities (renal insufficiency, myasthenia gravis, cardiomyopathy with 28%-35% ejection fraction). One patient with gastrointestinal stromal tumor, continued imatinib (Glivec), with which she was being treated, at MPM diagnosis, and another patient was treated with cisplatin + gemcitabine. Four patients received different dose prescriptions: 50.6 Gy/23 fractions, 54.5 Gy/25 fractions, 53.76 Gy/25 fractions, and 58.24 Gy/26 fractions, having asked to stop the therapy at the end of the 23rd fraction (the first), for dosimetric reasons (second and third), and tumor burden (the fourth). One patient received 54 Gy on the planning target volume (PTV) and 60 Gy SIB on GTV-PET volume to reduce dose to the kidney owing to previous irradiation in 2006 for a seminoma.

Table 1 Patient Characteristics

Characteristics	n
No. patients: total	51
Group with no SIB	13
Group with SIB	38
Median age, y (range)	
All patients	68.8 (38.6-82.0)
Group with no SIB	69.7 (41.2-79.0)
Group with SIB	68.5 (38.6-82.0)
Gender, M:F	
All patients	41:10
Group with no SIB	9:4
Group with SIB	32:6
Site, right:left	
All patients	26:25
Group with no SIB	6:7
Group with SIB	20:18
Histology, epithelial versus sarcomatoid	
All patients	43:8
Group with no SIB	11:2
Group with SIB	32:6
Stage at diagnosis	
All patients	I = 11; II = 14; III = 17; IV = 9
Group with no SIB	I = 4; II = 3; III = 5; IV = 1
Group with SIB	I = 7; II = 11; III = 12; IV = 8
Surgery, yes (P/D):no (B/TP)	
All patients	18:33
Group with no SIB	4:9
Group with SIB	14:24
Chemotherapy, PMX-based: other: no ChT	
All patients	44:2:5
Group with no SIB	11:2:0
Group with SIB	33:0:5
Chemotherapy > 6 cycles: ≤ 6 cycles	13:38
Median dose prescription (range)	
Group with no SIB	56 Gy/25 fr (50.6 Gy/23 fr to 58.24 Gy/26 fr)
Group with SIB	56 Gy/25 fr whole pleura; 62.5 Gy SIB BTV
Interval from diagnosis to salvage RT, mos (range)	
All patients	10.3 (2.7-45.7)
Group with no SIB	12.8 (5.3-24.0)
Group with SIB	10.1 (2.7-45.7)

Abbreviations: B/TP = Biopsy/talc pleudrodesis; ChT = chemotherapy; P/D = pleurectomy/decortication; PMX = permetrexed; RT = radiotherapy; SIB = simultaneous integrated boost.

Imaging, Contouring, Planning Procedures, Dose Prescription, and Treatment Delivery

Technical aspects of the treatment are reported in a previous work.[10] FDG-PET/computed tomography (CT) was chosen for target definition because of its prognostic value and role in the stratification of patients for surgical treatment.[11,12]

Table 2 Dose Constraints

Organ	Constraint
Spine	D max < 40 ± 5 Gy (No portion > 50 Gy)
Heart	D max < 56 Gy
Heart left-sided MPM	D mean < 28.5 ± 5 Gy
Heart right-sided MPM	D mean < 23.2 ± 2.9 Gy
Heart	V60 Gy EQD2 < 5%
Liver (left-sided MPM)	D mean < 7.7 ± 2.3 Gy
Liver (right-sided MPM)	D mean < 23 ± 4 Gy
Kidney ipsilateral	V29 Gy < 50%
Kidney ipsilateral	V48 Gy < 20%
Kidney ipsilateral	D 80% < 16 Gy
Kidney contralateral	As low as possible
Stomach	D max < 42 Gy
Lung, contralateral	D mean < 8 Gy, as low as possible
Lung, contralateral	V20 Gy < 20%
Esophagus	D max < 56 Gy

Abbreviations: D max = Maximum dosage; D mean = mean dosage; EQD2 = equivalent 2 Gy dosage; MPM = malignant pleural mesothelioma.

MPM is, apparently, a radio-resistant tumor, and studies published to date have demonstrated better local control with high doses in the adjuvant setting[13] and better palliation with hypofractionation.[14] There is a lack of radiobiological studies from which to estimate the α/β ratio for MPM, which is probably low, owing to its non-squamous histology. Consequently, in order to reduce hospitalization time without significantly increasing lung toxicity risk, a moderately hypofractionated regimen was chosen,[10] prescribing 56 Gy/25 fractions to the PTV, and SIB on GTV-PET to 62.5 Gy (Table 1).

The clinical target volume (CTV) was defined as the whole pleura including GTV-PET and the PET/CT positive mediastinal lymph nodes and infiltrations in thoracic muscles or in the lung. 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 5 mm in all directions except the cranio-caudal, where 8 mm was added, owing to the improved confidence in applying daily set-up correction with megavoltage CT image guidance, performed for every patient. GTV-PET was contoured based on the experience of the nuclear physician (ie, no fixed threshold levels were applied). Inverse planning optimization was performed on the TomoTherapy planning station; field widths of 2.5 to 5 cm, modulation factor of 2.5 to 3.5, and pitch of 0.25 to 0.3 were used. Ninety-five percent of the PTV volume received at least 95% of the prescribed dose. Normal tissue constraints from published IMRT studies were adopted[15]; in particular, esophagus, heart, and spinal cord were constrained to limit the maximum dose to 56 Gy, 56 Gy, and 50 Gy, respectively. In addition, planning optimization was always stressed to obtain the lowest dose possible for every OAR without compromising target coverage. In 2010, based on the experience with the first 24 patients, a set of constraints was generated (Table 2). The heart dose constraints will be revised, owing to the results of this analysis, to keep the mean dose (D-mean) to the heart < 21.2 Gy.

Daily IGRT was performed (megavoltage CT).

Assessing Treatment Outcome

During the treatment, patients were seen weekly by their radiation oncologist, and at the conclusion of the treatment, follow-up with imaging (FDG-PET or contrast-enhanced CT) was scheduled every 4 months.[10] Toxicities were scored according to Common Terminology Criteria for Adverse Events, v 4.0

The Kaplan-Meier method was used to calculate OS, local relapse-free survival (LRFS), and cancer-specific overall survival (CSS). All statistical analyses (Cox and logistic regression) were estimated from the start of radiotherapy; some additional (OS) data were reported from the date of initial diagnosis.

A Cox univariate analysis and log-rank tests were used to verify the impact of some selected variables on the considered survival endpoints. Histology, stage (I vs. II vs. III vs. IV), chemotherapy (yes vs. no), and number of chemotherapy cycles (>6 or ≤ 6 cycles, considering salvage second to third lines as more than the 6 cycles of the first-line chemotherapy), surgery (P/D vs. TP), SIB versus no SIB, age at diagnosis, and GTV-PET volume were considered. A receiver operator characteristic analysis was performed to determine the best GTV-PET cutoff; the median value of GTV-PET was also considered as the cutoff value in a discrete analysis. A logistic regression analysis was similarly used to investigate the impact of the selected variables on the worst prognosis, considered as death/cancer death within 3 months from the start of the radiotherapy. Given the increasing evidence that the dose received by the heart in thoracic radiotherapy may impact on survival, the association between mean dose to the heart and OS was tested. A Mann-Whitney U test was used to examine whether patients in the SIB and non-SIB groups differ with respect to the following: GTV-PET volume, PTV, and mean doses of ipsilateral/contralateral lung and heart. MedCalc (v.12.14) software was used for the analyses.

Results

All patients were referred to radiotherapy when in PD after previous treatments (Table 1), when no other reasonable therapies were available, except for 5 patients, with no chemotherapy prescription for comorbidities. The median interval between diagnosis and radiotherapy was 10.3 months (range, 2.7-45.7 months). The median follow-up, from the end of treatment to October 2017, was 9.3 months (range, 0.0-77.5 months).

The median GTV-PET and PTV volumes were respectively 204.6 cc (range, 2.4-1727.7 cc) and 3201.3 cc (range, 1326.9-5421.9 cc). The median mean contralateral lung dose (MLD) was 6.86 Gy (7.83 Gy no SIB vs. 6.45 Gy SIB), whereas the median V20, V10, and V5 were equal to 0% (range, 0%-10%), 14% (range, 0%-40%), and 65.5% (range, 18%-100%), respectively. The median mean ipsilateral lung dose was 54.09 Gy (range, 52.22-55.97 Gy). The median doses to ipsilateral kidney, contra-lateral kidney, liver, and heart were 6.83 Gy (range, 2.12-32.1 Gy), 3.76 Gy (range, 0-9.38 Gy), 24.41 Gy (range, 3.52-28.66 Gy), and 21.2 Gy (range, 17.35-38.7 Gy), respectively. The median value of the maximum dose to spinal cord was 41.00 Gy (range, 30.49-52.43 Gy).

The mean contralateral lung dose was higher in the non-SIB group, but the difference was not statistically significant. The experience and the lower CTV-PTV margins probably contributed to a lower MLD.

Table 3 Acute Toxicity, Subdivided Between the 2 Dose Levels: 13 Patients Treated With 56 Gy/25 Fr on Whole Pleura and 38 Patients Treated With SIB to 62.5 Gy on GTV-PET

Group	Non-SIB (56 Gy/25 Fr), n (%)			SIB (62.5 Gy/25 Fr), n (%)			
Grading	**G1**	**G2**	**G3**	**G1**	**G2**	**G3**	**G5**
Dysphagia	4 (30.8)	3 (23)	1 (7.7)	10 (26.3)	13 (34.2)	0	0
Odynophagia	1 7.7	0	0	6 (15.8)	0	0	0
Stomach pain/gastritis	2 (15.4)	2 (15.4)	0	6 (15.8)	1 (2.6)	0	0
Vomiting	1 (7.7)	1 (7.7)	0	5 (13.2)	4 (10.5)	0	0
Lost appetite	1 (7.7)	0	0	2 (5.3)	1 (2.6)	0	0
Fever	0	0	0	3 (7.9)	0	0	0
Radiodermatitis	3 (23.1)	1 (7.7)	0	10 (26.3)	5 (13.2)	0	0
Asthenia	3 (23.1)	0	0	10 (26.3)	2 (5.3)	0	0
Thoracic pain	0	1 (7.7)	0	7 (18.4)	2 (5.3)	0	0
Dyspnea	2 (15.4)	0	0	6 (15.8)	4 (10.5)	0	0
Cough	0	0	0	11 (28.9)	0	0	0
Dysphonia	0	0	0	3 (7.9)	0	0	0
Radiation pneumonitis	0	0	0	0	3 (7.9)	1 (2.6)	1 (2.6)

Abbreviations: Fr = Fraction; G = grade; GTV-PET = Positron emission tomography positive gross tumor volume; SIB = simultaneous integrated boost.

Acute Toxicity

All but 2 patients tolerated the treatment without interruption. One patient needed a 4-day treatment interruption and parenteral nutrition owing to grade 3 dysphagia. Another patient, with grade 2 vomiting, had treatment interruptions and asked to end the treatment after 23 fractions (at 50.6 Gy). Acute side effects are summarized in Table 3.

Ten patients died within 3 months of the end of radiotherapy; the majority with evidence of PD or infectious episodes.

Of the 4 patients of the non-SIB group with an early death, 1 with a previous gastro-intestinal stromal tumor, in treatment with Glivec, died owing to a pulmonary embolism on the last day of treatment. A second patient had metastases before starting the radiotherapy. A third patient with a poor baseline Eastern Cooperative Oncology Group performance status, died almost 3 months after the end of treatment. A fourth patient died exactly 3 months after the end of the treatment with evidence of contralateral and abdominal progression. The treatment was not the cause of death for any of these 4 patients.

There were 6 patients in the SIB group with early death. One patient, with grade 2 dysphagia, and grade 1 odinophagia, dyspnea, and thoracic pain, presented 3 weeks later with fever (>38° C) and severe dyspnea, followed by sudden death the next morning, despite the antibiotics and oxygen therapy prescribed by the ambulance doctor. In the absence of any clear demonstration of the cause of death, we could not exclude the possibility that it was because of radiotherapy, and it was registered as grade 5 radiation pneumonitis despite a "safe" contralateral lung D-mean of 7.09 Gy.

The second patient had a sudden death at home, almost 2 months after the end of radiotherapy. The third patient died owing to abdominal progression.

A fourth patient died because of cardiac arrest during hospitalization. He previously presented with grade 2 radiation pneumonitis; he was eupnoic, not needing oxygen support, and his conditions improved after the treatment.

A fifth patient, with metastases before starting the radiotherapy, died (during the hospitalization in medical oncology for poor

Table 4 Late Toxicity in 9 Patients Treated With 56 Gy/25 Fr on Whole Pleura and 33 Patients Treated With SIB to 62.5 Gy on GTV-PET

Group	Non-SIB (56 Gy/25 Fr), n (%)		SIB (62.5 Gy/25 Fr), n (%)			
Grading	**G1**	**G2**	**G1**	**G2**	**G3**	**G5**
Dysphagia	0	0	1 (3.0)	3 (9.1)	0	0
Stomac pain/gastritis	0	1 (11.1)	2 (6.1)	0	0	0
Lost appetite	0	0	1 (3.0)	0	0	0
Radiodermatitis	0	0	1 (3.0)	1 (3.0)	0	0
Asthenia	1 (11.1)	2 (22.2)	3 (9.1)	1 (3.0)	0	0
Thoracic pain	1 (11.1)	1 (11.1)	4 (12.1)	2 (6.1)	0	0
Dyspnea	0	5 (55.6)	8 (24.2)	6 (18.2)	3 (9.1)	0
Cough	0	0	6 (18.2)	1 (3.0)	0	0
Dysphonia	0	0	1 (3.0)	0	0	0
Radiation pneumonitis	0	0	0	2 (6.1)	7 (21.2)	1 (3.0)

Abbreviations: Fr = Fraction; G = grade; GTV-PET = Positron emission tomography positive gross tumor volume; SIB = simultaneous integrated boost.

performance status) owing to local and bone disease progression and without evidence of pneumonitis at chest x-ray.

Finally, the sixth patient died 2 months after the end of radiotherapy, during hospitalization in our institution. He presented with an actinic pneumonitis of right medium and lower lobe and a pneumocystis carinii pneumonia of the left lung. He was previously treated with 5 cycles of pemetrexed-based chemotherapy (4 with cisplatin, the fifth with carboplatin owing to subsequent renal insufficiency), and then, for progressive disease, with 11 cycles with gemcitabine and an experimental drug, up to the progression with the invasion of the nervous root of T1 vertebra, when he was referred to radiotherapy. He also presented with local PD at the contrast-enhanced CT performed during the hospitalization.

Radiotherapy could have played a role in the death of this patient, but it was not, in our opinion, the decisive factor. He was registered with grade 3 radiation pneumonitis, even though the pneumocystis carinii pneumonitis, secondary to the immunosuppression determined by the long chemotherapy, determined the necessity for oxygen therapy, and eventually death. He also had evidence of local progression.

Late Toxicity

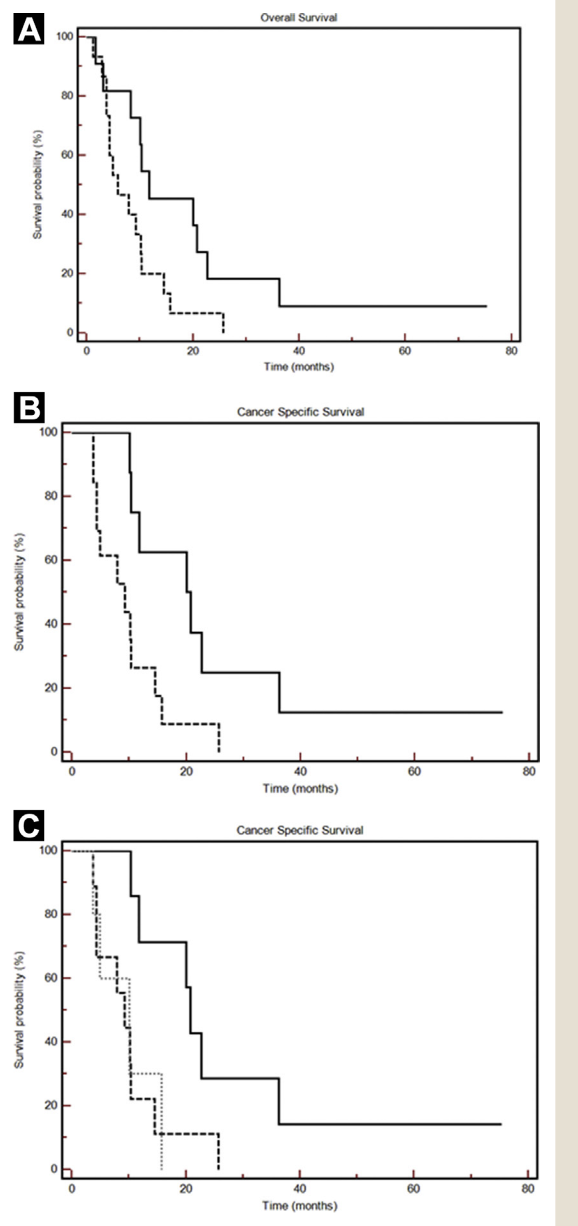
In 42 patients (9 non-SIB, 33 SIB), late toxicity was assessed: results are summarized in Table 4.

Late toxicities regarding dysphagia, gastritis, asthenia, thoracic pain, cough, dysphonia, lost appetite, and radiodermatitis were low, $\leq$ grade 2. Grade 3 dyspnea was 9.1%, an acceptable value, taking into account the irradiated volume. Grade 3 radiation pneumonitis was 21.2%, and 2 cases of grade 5 radiation pneumonitis were registered, 1 acute and 1 late—results in line with other studies reporting MPM radiotherapy on underlying lung. Actuarial late respiratory toxicity (dyspnea and pneumonitis $\geq$ grade 2) was 39.5% (37% in the SIB group and 42% in the non-SIB group). The longest registered persistence of actinic pneumonitis, without evidence of disease progression, was 2.5 months. For 1 patient with pericardial diffusion of MPM, disease progression was considered the cause of dyspnea.

One patient, who presented with partial response (PR) at the contrast-enhanced CT and was, importantly, diabetic, died from recurrent bilateral pneumonitis, despite the cortisone and antibiotic treatment, 6.7 months after the end of radiotherapy, although mean contralateral lung dose (5.56 Gy), V20, V10, and V5 constraints were respected. As CT revealed bilateral actinic pneumonitis, the patient was registered as grade 5 radiation pneumonitis. The risk of late radiation pneumonitis with grade $\geq$ 2 was higher for smaller GTV-PET; a volume < 204.6 cc (median value) was found to be predictive of late pulmonary toxicity. (P = .028; odds ratio [OR], 0.089; 95% confidence interval [CI], 0.010-0.775), possibly owing to the presence of a more significant remnant lung function.[9,10]

Long-term survival patients presented with ipsilateral lung fibrosis and chest wall asymmetry, with hyper-expansion of the healthy lung.

Figure 1 A, Overall Survival Probability in Patients With Stage III to IV MPM With GTV-PET < 204.6 cc (Continuous Line) Versus > 204.6 cc (Dashed Line); B, Cancer-specific Survival Probability in Patients With Stage III to IV MPM With GTV-PET < 204.6 cc (Continuous Line) Versus > 204.6 cc (Dashed Line); C, Cancer-specific Survival Probability in Patients With Stage III to IV MPM Without SIB (Dashed Line), With SIB and GTV-PET > 204.6 cc (Dotted Line), and SIB and GTV-PET < 204.6 cc (Continuous Line)



Abbreviations: GTV-PET = Positron Emission Tomography Positive Gross Tumor volume; MPM = malignant pleural mesothelioma; SIB = simultaneous integrated boost.

Outcome

The median survival from diagnosis was 25.8 months (range, 8.4-99.0 months). Kaplan-Meier estimated OS from the diagnosis at 1, 2, and 3 years was 89%, 51%, and 20.6%, respectively.

Crude median survival for all patients, from the start of radiotherapy (chosen as a reference point for possible fatal toxicity caused by irradiation) was 10.4 months (range, 1.2-78.8 months): 5.9

Table 5 Results of Cox Univariate and Multivariate Analysis for Local Progression, Overall Survival, and Cancer-specific Survival

	Univariate		Multivariate	
	P Value	HR (95% CI)	*P* Value	HR (95% CI)
Local progression				
Histology (epithelial vs. sarcomatoid)	.17	1.95 (0.76-5.03)	.10	3.03 (0.82-11.18)
Stage (I & II vs. III & IV)	.32	1.51 (0.67-3.45)	.13	2.26 (0.79-6.43)
Chemotherapy (yes vs. no)	.56	1.55 (0.36-6.62)	.92	0.91 (1.14-5.81)
No. chemotherapy cycles (>6 vs. ≤ 6)	.73	0.84 (0.31-2.28)	.21	2.39 (0.62-9.26)
Surgery (pleurectomy/decortication vs. biopsy-talc pleurodesis)	.13	1.89 (0.83-4.30)	.13	2.36 (0.77-7.20)
SIB (yes vs. no)	.50	0.70 (0.25-1.94)	.16	3.1 (0.06 -1.55)
Age at diagnosis (continuous)	.42	0.98 (0.93-1.02)	.55	1.017 (0.96-1.08)
GTV-PET (continuous)	.45	1.01 (0.99-1.002)	.35	1.001 (1.00-1.003)
Contralateral lung D mean	.60	0.92 (0.67-1.26)	.92	1.009 (0.85-1.19)
Ipsilateral lung D mean	.53	1.04 (0.94 -1.13)	.28	0.79 (0.52 -1.21)
Heart D mean (continuous)	.89	0.99 (0.89-1.11)	.53	1.04 (0.92-1.19)
Overall survival				
Histology (epithelial vs. sarcomatoid)	.96	1.02 (0.48-2.17)	.23	1.85 (0.69-5.01)
Stage (I & II vs. III & IV)	.16	1.50 (0.86-2.62)	.08	2.01 (0.93-4.33)
Chemotherapy (yes vs. no)	.38	1.52 (0.60-3.84)	.19	2.20 (0.68-7.17)
No. chemotherapy cycles (>6 vs. ≤ 6)	.70	1.13 (0.60-2.13)	.22	1.72 (0.72-4.08)
Surgery (pleurectomy/decortication vs. biopsy-talc pleurodesis)	.64	0.87 (0.48-1.56)	.37	0.68 (0.30-1.56)
SIB (yes vs. no)	.42	0.77 (0.41-1.45)	.31	0.58 (0.20-1.66)
Age at diagnosis (continuous)	.99	1 (0.997-1.03)	.75	1.01 (0.97-1.05)
GTV-PET (continuous)	**.001**	**1.001 (1.00 - 1.002)**	**.02**	**1.001 (1.00 -1.003)**
Contralateral lung D mean	.36	0.92 (0.75-1.11)	.95	1.00 (0.90-1.11)
Ipsilateral lung D mean	.34	1.04 (0.96 -1.1)	.68	0.95 (0.73-1.23)
Heart D mean (continuous)	.95	0.99 (0.92-1.08)	.98	1.00 (0.91-1.09)
Cancer-specific survival				
Histology (epithelial vs. sarcomatoid)	.86	0.92 (0.38-2.21)	.08	3.42 (0.89-13.17)
Stage (I & II vs. III & IV)	.19	1.53 (0.82-2.88)	**.04**	**2.95 (1.06-8.16)**
Chemotherapy (yes vs. no)	.71	1.20 (0.47-3.08)	.36	1.84 (0.50-6.78)
N chemotherapy cycles (>6 vs. ≤ 6)	.77	1.11 (0.54-2.29)	.07	3.07 (0.92- 10.19)
Surgery (pleurectomy/decortication vs. biopsy-talc pleurodesis)	.37	0.73 (0.37-1.44)	.29	0.56 (0.19-1.63)
SIB (yes vs. no)	.50	0.78 (0.38-1.61)	.23	0.45 (0.12 -1.64)
Age at diagnosis (continuous)	.79	1.006 (0.96-1.05)	.53	1.02 (0.97-1.07)
GTV-PET (continuous)	**.001**	**1.001 (1.00 -1.003)**	**.004**	**1.002 (1.00-1.004)**
Contralateral lung D mean	.35	0.90 (0.72-1.12)	.53	0.907 (0.67-1.23)
Ipsilateral lung D mean	.12	1.07 (0.98 -1.17)	.62	1.03 (0.92 -1.16)
Heart D mean (continuous)	.48	1.03 (0.95-1.12)	.30	1.07 (0.94-1.23)

Bold text indicates a statistically significant difference with a *P* value <.05.
Abbreviations: CI = Confidence interval; D mean = mean dosage; GTV-PET = Positron emission tomography positive gross tumor volume; HR = hazard ratio; SIB = simultaneous integrated boost.

months (range, 1.2-50.5 months) in the non-SIB group and 10.9 months (range, 1.7-78.8 months) in the SIB group. CSS was 14.5 months. Interestingly, the time to local relapse (16.8 months) was longer than the time to distant progression (13.5 months), indicating that radiotherapy probably influenced the history of the disease.

Only 1 patient was alive at the last follow-up, in October 2017, 78.8 months after the start of radiotherapy. The GTV-PET volume was significantly correlated with OS ($P = .001$) and CSS ($P = .001$). In particular, a best cutoff value of 473.3 cc was found to be significantly predictive (OR, 18.9; 95% CI, 3.27-108.63; $P = .001$) of patients with a worse prognosis (death within 3 months). No other clinical variable was significantly associated with outcome.

When restricting the analysis to stage III to IV patients, an OS of 11.7 months was found for patients with GTV-PET volume < 204.6 cc, compared with 5.9 months for GTV-PET volume > 204.6 cc (hazard ratio [HR], 0.47; 95% CI, 0.184-0.977; $P = .044$) (Figure 1A). Similarly, CRFS of 9.2 and 20.4 months were found,

Table 6 Mann-Whitney *U* Test for GTV-PET Volume, PTV, and Mean Doses of Ipsilateral Lung, Contralateral Lung, and Heart

	SIB	Non-SIB	*P*
GTV-PET vol (cc)	180.58 (2.74-1218.46)	576.98 (2.43-1727.71)	.0973
PTV vol (cc)	3166.69 (1326.93-5421.96)	3250.21 (2050.65-4037.58)	.897
D mean, ipsilateral lung (median value)	50.62 (41.57-58.27)	46.3 (39.2-55.97)	.178
D mean, contralateral lung (median value)	6.45 (4.62-9.02)	7.83 (4.1-11.9)	.1672
D mean heart (median value) (continuous)	24.34 (17.35-33.32)	24.2 (20-38.7)	.4969

Abbreviations: D mean = Mean dosage; GTV-PET = Positron emission tomography positive gross tumor volume; PTV = planning target volume.

respectively, for patients with GTV-PET volume higher or lower than 204.6 cc (HR, 0.349; 95% CI, 0.113-0.79; $P = .015$) (Figure 1B).

Interestingly, in stage III to IV patients, a median CSS of 10.1 months was found for patients without SIB, compared with 9.2 months with SIB and GTV-PET volume > 204.6 cc and 20.7 months with SIB and GTV-PET volume < 204.6 cc (Figure 1C). Therefore, SIB had no longer effect in high-volume disease.

Concerning the other considered clinical variables, for stage III to IV patients, a slight correlation was found between OS and number of chemotherapy cycles (>6 and $\leq$ 6) (HR, 2.85; 95% CI, 0.99-8.21; $P = .054$).

For the heart, the cutoff value of 21.2 Gy (median value), for the D-mean was considered to transform this continuous variable into a binary variable. Median OS was 5.6 months for patients with higher dose compared with 10.5 months for patients with lower dose. When including the obtained binary variable as predictor in a Cox regression model to predict OS, we found that patients treated with the higher dose had a significantly increased risk of dying than those treated with the lower dose (HR, 2.068; 95% CI, 1.053 -7.30; $P = .039$).

Multivariate analyses confirmed the findings of univariate analyses and detected the role of stage (I-II vs. III-IV) for CSS, which was not observed, and thus not reported in our previous paper[10] (Table 5). To test whether the 2 patient groups (SIB vs. non-SIB) were different with respect to the target volumes and mean dose to the lungs and heart, a Mann-Whitney *U* test was performed. No significant difference was found (Table 6).

Discussion

Of 51 patients treated with moderate hypofractionation to the whole pleura (56 Gy/25 fraction/5 weeks), and SIB, up to 62.5 Gy, to GTV-PET, revealed by FDG PET/CT, was prescribed for 38 patients. Statistically significant higher OS and CSS were obtained in stage III to IV patients with SIB, when GTV-PET volume was below 204.6 cc.

Salvage radiotherapy was performed at a median of 10.3 months after diagnosis; we may consider our results as promising in the context of a salvage treatment: in fact, the relatively high median survival from diagnosis (25.8 months) is similar to data reported by adjuvant radiotherapy studies.[9]

Toxicity was the subject of greatest concern, especially because of deaths from contralateral lung radiation pneumonitis after EPP.[15] Once the constraints of median lung dose and volume of contralateral lung receiving 20, 10, and 5 Gy were defined, mortality after radiotherapy dramatically decreased, and radiotherapy was performed even in patients with both lungs intact[9,16,17] with better local control and acceptable toxicity results.

Recently, de Perrot and coworkers published the results of their SMART (Surgery for Mesothelioma After Radiation Therapy) protocol, on 62 patients, treated with neoadjuvant extremely hypofractionated IMRT, of 25 Gy/5 fractions to the entire hemithorax, with a 5 Gy SIB to the tract sites and GTV, identified with CT and FDG-PET.[18] One week later, an EPP was performed, and ypN2 patients received adjuvant chemotherapy. The median OS (51 months) was very high. The timing of surgery was considered critical, with the necessity of removing the lung before the appearance of any potentially fatal radiation pneumonitis. Despite the encouraging results of the de Perrot study, initial enthusiasm for trimodal therapy has largely vanished, especially in Europe, as recognized in the most recent systematic reviews,[19,20] which emphasized on both sides of the Atlantic the interest in radiotherapy with intact lungs.

To enhance the probability of local control, which remains the primary issue after P/D, some institutions have performed pleural RT on limited groups of patients with promising local control and acceptable toxicity results. In 36 patients treated at Memorial Sloan Kettering Cancer Center, Rosenzweig et al reported a median survival of 26 months with surgery and 17 months without surgery, with 5 patients of the 30 evaluable for late toxicity experiencing continuous grade 3 pneumonitis, 1 experiencing grade 4, and 1 experiencing grade 5 acute pneumonitis.[9] The global median survival for this study of 25.8 months was very similar despite the postponed radiotherapy (the patients were referred to radiotherapy only when in progression after chemotherapy/surgery).

Rimner et al, analyzing the experience of the same institution with adjuvant radiotherapy in 67 patients, confirmed the better outcome of patients with P/D versus unresectable patients.[16] The median survival of the cohort was 24 months from diagnosis, median time to in-field failure 10 months, and median time to distant failure, which occurred in 48% of patients, was 17 months. In both studies, patients were treated with lower, conventionally fractionated doses.

Chance et al[17] published an MD Anderson Cancer Center experience comparing 24 patients who underwent P/D with 22 patients who underwent EPP treated with 45 Gy adjuvant IMRT to the involved hemithorax. The median OS was 28.4 months after P/D and 14.2 months after EPP. Two grade 3 pneumonitis were registered in the P/D-IMRT arm, but 2 radiation-induced deaths were reported in the EPP-IMRT arm.

Other researchers have published their experience of patients with MPM with underlying lung present, treated with HT in the adjuvant setting. In a recent publication, Harrabi et al described the adjuvant treatment performed at University Hospital of Heidelberg.[21] Ten patients treated with P/D and 4 to 6 cycles of pemetrexed-cisplatin chemotherapy (2 patients neoadjuvant, 8 patients adjuvant chemotherapy), were treated with HT on the pleural cavity to a median dose of 52.2 Gy, with conventional fractionation (2 Gy/fraction). In 4 patients with gross residual disease, a simultaneous integrated boost up to 60 Gy was delivered to the macroscopic residual disease defined on the contrast-enhanced CT. Similarly to our later patients, 5 mm CTV-PTV margins were used in all directions except caudal (where a margin of 10 mm was used inferior to diaphragm to account for breathing motion). No additional breathing motion management was applied. With a median follow-up of 17 months, the median OS was 19 months; the median PFS was 13 months, and 2 in-field recurrences were registered, with 1 of the patients being treated with SIB. Four patients presented distant progression. Two patients developed radiogenic pneumonitis. Based on Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) data, the authors calculated that limiting V20 of the ipsilateral lung to less than 30% to 35% and the MLD to 20 to 23 Gy would reduce the risk for higher-grade radiation pneumonitis to 20%. However, they underlined that, despite their MLD of 32.8 Gy (±6.8) and V20 of 71.7% (range, 45%-100%), treatment-related lung toxicity occurred in only 2 patients, owing to the good sparing of the contralateral lung (MLD, 8.3 Gy; V20, 2.3%).

Minatel et al described the experience of "Centro di Riferimento Oncologico di Aviano" in 3 consecutive papers: on 28 patients with a median follow-up of 19 months,[22] on 20 patients with a median follow-up of 27 months,[23] and finally on 69 patients with a median follow-up of 19 months.[24] The surgery consisted of extended P/D or partial pleurectomy. The patients received 1 to 6 cycles (median, 4 cycles) of pemetrexed-platinum chemotherapy (neoadjuvant, adjuvant, or both). Then, 6 to 8 weeks after surgery (if treated with neoadjuvant chemotherapy) or 4 weeks after completion of adjuvant chemotherapy, the patients underwent HT on whole pleura at 50 Gy/25 fractions (2 Gy/fraction) with an SIB up to 60 Gy to the residual disease or FDG−PET-positive areas. The median boost volume was 180 cc (range, 30-480 cc). In contrast to our study, only favorable prognostic patients were treated; those who experienced tumor progression during and after chemotherapy, or who had metastatic disease, were not referred to radiation therapy. Interestingly, a dummy structure, representing the central part of the treated lung, located more than 2 cm internal to the pleural surface, was also delineated to improve the optimization of planning, and a mean dose of less than 36 Gy was the constraint defined for this structure, in the absence of a constraint for ipsilateral lung or total lung. Owing to the high peripheral lung dose and, in any case, high central lung dummy structure constraint, its role in limiting toxicity is questionable. In fact, after treating the first 28 patients, the authors identified the V5 of contralateral lung correlated with the risk of severe pneumonitis and established a constraint of < 17%. The 2- and 3-year OS was 65% versus 58% and 44% versus 36% for extended P/D versus partial pleurectomy, a statistically non-significant difference. Locoregional control at 2 years was 65% versus 64%. As in our study, a change in the illness pattern of failure was observed, with distant failure exceeding the local relapse. One fatal pneumonitis was reported, and 20% of patients presented grade 2 to 3 severe respiratory symptoms.

In another recent publication, Parisi et al described the "Istituto Scientifico Romagnolo per lo studio e la cura dei tumori" experience.[25] Between 2008 and 2012, 36 patients with MPM underwent accelerated hypofractionated radiotherapy with HT on the hemithorax, after P/D (19 patients) or biopsy (17 patients). The dose prescription was 25 Gy/5 fractions at the reference isodose of 60% to 70%, over 5 consecutive days with an inhomogeneous dose escalation to 37.5 Gy to the GTV. The mean equivalent 2 Gy (EQD2) doses were 39 Gy (range, 30-43 Gy) for the GTV and 35 Gy (range, 33-38 Gy) for CTV. Eighty percent of patients also received neoadjuvant or adjuvant pemetrexed−platinum-based chemotherapy. Acute and late toxicity were lower than expected with a high dose per fraction, with only 3% acute and 6% late grade 3 pneumonitis, probably owing to the lower total dose (toxicity depends on dose/fraction and total dose). The median follow-up was 37 months in living patients at the time of the study, and the median OS was 21.6 months.

In order to reduce the ipsilateral lung dose and thus the inherent toxicity, further technical progress has been made, and the first case series of patients with MPM with underlying lung present treated with proton therapy were reported.[26,27] For its superior physical characteristics, the role of proton therapy in limiting the dose to the underlying lung and thus respiratory toxicity is undeniable, but further data are awaited to understand whether the high precision of protons, correlated with respiratory movement, may result in a loss in local control.[28]

A future direction could be a change of treatment strategy, irradiating only the volumes involved, and not the whole pleura, thus allowing a real sparing of the underlying lung, with a subsequent toxicity reduction. This approach was proposed by Botticella et al to allow dose escalation.[29] In our opinion, a selective irradiation of bulk tumor only, together with the novel therapies with immune checkpoint inhibitors,[30] may provide additional options for those affected by this disease.

The main limitation of this study is its retrospective nature and the limited number of patients, although limited cohorts are usual for radiotherapy studies on MPM (including the MARS and SAKK 17/04 trials). Despite these limitations, it is worth underlining that this is the first study reporting the results of hypofractionated image-guided IMRT with simultaneous integrated boost dose escalation with PET/CT guidance in patients with MPM with both lungs intact, with PD after previous treatments. Our experience of moderate hypofractionation is unique in patients with intact lungs and worse prognosis. An independent study, evaluating the Normal Tissue Complication Probability (NTCP) in accordance with QUANTEC constraints for the OARs, concluded that dose escalation to 62.5 Gy is feasible.[31] The SIB dose escalation in our feasibility study was stopped at 62.5 Gy because 3 (25%) of the 12 patients presented with grade 3 pneumonitis without any grade 5 event.[10] In patients treated after the adoption of this protocol, the rate of ≥ grade 3 late pneumonitis was 24%. Late toxicity was, generally, a persistence of acute toxicity, started 4 to 8 weeks after the end of radiotherapy (median, 2 months; range, 1-7 months); thus it started early enough to be observed, if present, in high-volume GTV-PET patients. For 2 deaths, the cause was assumed to be primarily, although not solely, radiation pneumonitis. One patient experienced a dramatic worsening from evening to morning, 3 weeks after the end of radiotherapy, with fever and dyspnea requiring oxygen therapy; the other, a patient with type II diabetes, a disease known to increase morbidity and pneumonia-related mortality,[32] died in hospital 6.7 months after the end of RT, from bilateral pneumonitis. Moreover, we observed that the mean heart dose is significantly correlated with OS. As already demonstrated for patients with pneumonectomy for lung cancer, a leading (nearly 15%) cause of death is pneumonia in the remaining lung.[33] Moreover, it was demonstrated that pneumonia is associated with an increased risk of cardiovascular disease[34] and heart failure.[35] It must be considered that these patients experienced an extended period (months to years) of impairment of 1 lung function.

A GTV-PET $<$ 204.6 cc was found to be statistically significant for late $\geq$ grade 2 lung toxicity, but also for better survival in stage III to IV patients treated with SIB. A GTV-PET $\geq$ 473.3 cc was predictive of early death. The inverse relationship between risk of pneumonitis and GTV-PET volume is likely owing to a better-conserved initial pulmonary functionality in patients with smaller GTV-PET.

Conclusion

The results of our study suggest that radiotherapy at the time of progression is a feasible option with acceptable toxicity. This is an alternate approach to offering adjuvant radiation therapy at the time of initial diagnosis. A good survival could be obtained in selected patients, based on the GTV-PET volume. The precise benefit regarding the timing of radiation therapy, however, should be a subject for future studies.

Clinical Practice Points

- The results of MARS and SAKK 17/04 trials have led to a reduction in the use of EPP and have questioned the role of radiotherapy.
- IMRT has allowed better normal tissue sparing and homogeneous dose distribution; thus adjuvant radiotherapy was offered by various institutions to patients treated with less extensive surgery, in presence of both intact lungs.
- In this retrospective analysis conducted in a mono-institutional experience, we report the outcome of patients with progressive MPM with intact lungs after previous treatments. The included patients were treated with moderate hypofractionation, FDG-PET/CT guided HT, with daily image-guided radiotherapy.
- A PET positive volume $\geq$ 473 cc was predictive of early death, with disease progression despite high-dose radiotherapy, whereas a volume $<$ 205 cc was associated with longer survival in patients with stage III to IV disease treated with SIB, but also was associated with higher late pulmonary $\geq$ grade 2 toxicity.
- A GTV-PET volume has been found to be essential in identifying patients who will benefit from the treatment, those who will not respond, presenting a rapid progression to death even after high doses of radiotherapy, and those who will present significant toxicity. The volume criteria therefore can help in the selection of patients with MPM with intact lungs to be irradiated resulting in the exclusion of patients with GTV-PET volumes $\geq$ 473 cc.

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Disclosure

The authors have stated that they have no conflicts of interest.

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