North Clin Istanb 2023;10(2):172–180
doi: 10.14744/nci.2023.53896

Original Article RADIATION ONCOLOGY

Trimodality therapy of malignant pleural mesothelioma with helical tomotherapy

Hazan Ozyurt,[1] Sevim Ozdemir,[1] Bedriye Dogan,[2] Gun Gunalp,[1] Ayse Sevgi Ozden[1]

[1]Department of Radiation Oncology, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkiye
[2]Department of Radiation Oncology, Malatya Training and Research Hospital, Malatya, Turkiye

ABSTRACT

OBJECTIVE: The purpose of this study was to determine the efficacy and tolerability of hemithoracic radiotherapy implemented with helical tomotherapy (HTT) in malignant pleural mesothelioma (MPM) patients.

METHODS: Between October 2018 and December 2020, data from 11 MPM patients who received trimodality therapy, including lung-sparing surgery (pleurectomy-decortication, P/D), adjuvant chemotherapy (cisplatin+ pemetrexed), and radiotherapy, were retrospectively reviewed. HTT was used to deliver a total of 30 Gy, 50–54 Gy or 59.4–60 Gy to R2 disease with 1.8–2 Gy daily doses. Descriptive data are presented in number (percentage) or median (minimum– maximum). The Kaplan-Meier method was used to calculate survival data. In patients with toxicities, the risk organ doses were compared using the Mann-Whitney U test.

RESULTS: The median follow-up was 20.5 (12–30) months. Two-year local control, disease-free, and overall survival rates were 48.5%, 49%, and 77.9%, respectively. The median prescribed dose for planning target volume (PTV) was 50.4±8.7 (30–60) Gy. Mean dose (D_{mean}) of total lung was 19.9±6 (10.4–26) Gy; the V20 (%) of ipsilateral and contralateral lungs were 89.±11.2 (62.7–100) and 0.7±2.1 (0.49–5.9), respectively. Esophageal D_{mean} and maximum doses (D_{max}) were found as 21.7±8.4 (7.4–34) and 53.1±10.4 (25.4–64.4) Gy, respectively. V30 (%) and Dmean of heart were 22.3%±13.4% (3.9–47) and 21±5.7 (10.8–29.3) Gy, respectively. D_{max} of medulla spinalis (MS) was 38.6± 1.3 (13.7–48) Gy. Grade 1–2 radiation pneumonitis (RP) developed in 4 (36.4%) and esophagitis in 2 (18.2%) patients. RP was found to be associated with MS and esophageal doses ($p<0.05$). Myelitis was diagnosed in 1 (9.1%) patient (MS D_{max}: 29 Gy).

CONCLUSION: HTT can be used as part of trimodality therapy for MPM patients with acceptable toxicities. MS and esophageal doses should be considered for radiation pneumonitis risk, and new dose constraints for these organs should be defined.

Keywords: Helical tomotherapy; hemithoracic radiotherapy; malignant pleural mesothelioma; trimodality therapy.

Cite this article as: *Ozyurt H, Ozdemir S, Dogan B, Gunalp G, Ozden AS. Trimodality therapy of malignant pleural mesothelioma with helical tomotherapy. North Clin Istanb 2023;10(2):172–180.*

MPM is an aggressive tumor that originates from the pleural surfaces and associated with asbestos exposure [1]. In recent studies some tumor suppressor genes, such as BAF-1, have been identified as factors in mesothelioma carcinogenesis [2].

MPM is divided into 3 histopathological subgroups by WHO, which differ from each other in terms of prognosis: epithelioid, sarcomatoid, and biphasic. Epithelioid is the most common histopathological type with the best prognostic features, with a median survival of 14 months. Survival times of biphasic and sarcomatoid types were reported as 10 and 4 months, respectively [3].

MPM treatment includes different approaches such as surgery, radiotherapy, and chemotherapy. Two surgical approaches are available: gross tumor resection and radical removal of visible disease with tissues, or conservative approaches such as tissue sparing and debulking. Extra-pleural pneumonectomy (EPP) is a radical ap-

Received: February 05, 2023 *Revised:* March 08, 2023 *Accepted:* March 18, 2023 *Online:* March 28, 2023

Correspondence: Hazan OZYURT, MD. Kartal Dr. Lutfi Kirdar Sehir Hastanesi, Radyasyon Onkolojisi Klinigi, Istanbul, Turkiye.
Tel: +90 216 458 30 00 e-mail: hazanozyurt45@gmail.com

proach in which the ipsilateral lung, pericardium, pleura, and diaphragm are resected to clear macroscopically whole regions with disease risk. Pleurectomy/decortication is a lung-sparing surgery that removes only the visceral and parietal pleura, whereas extended pleurectomy removes the diaphragm and/or pericardium along with the visceral and parietal pleura. Both organ sparing procedures, pleurectomy/decortication (P/D) and extend-end pleurectomy, are commonly referred to as P/D [4]. Unlike EPP, it is not intended for complete tumor resection in P/D. Therefore, it is used in conjunction with multi-modality treatments [5]. The addition of EPP to the trimodal treatment increased the risk of death in a randomized study conducted by the Mesothelioma and Radical Surgery (MARS) group [6]. In a study comparing EPP and P/D, higher operative mortality was found with EPP. As a result, EPP has been replaced by less invasive surgical interventions [7].

Chemotherapy is the only treatment that has been shown to improve survival in MPM patients. Pemetrexed, an anti-folate, has been shown to have a survival advantage over cisplatin (8). Since 2003, the combination of cisplatin and pemetrexed has been the standard chemotherapy for MPM [5].

Radiotherapy is applied for palliative purposes for the treatment of symptoms in MPM or as an adjuvant to chemotherapy and surgery [9]. P/D and EPP alone are not sufficient for convincing local control and survival rates. Due to the intact lungs after P/D, it is not possible to protect the lungs, especially the ipsilateral lung, with conventional radiotherapy techniques. This situation poses a risk due to the possible cytotoxic effects of radiotherapy. For this reason, there is a need for precisely conformal techniques such as intensity modulated radiotherapy (IMRT), which can protect the lungs while irradiating entire ipsilateral pleura. [10]. After P/D and chemotherapy, hemithoracic radiotherapy with IMRT was found to be safe [11].

HTT is a sophisticated radiotherapy device designed for IMRT. By using HTT, highly conformal radiation application to the target volumes becomes possible as the patient moves longitudinally on the treatment couch, precisely protecting risk organs with the helical radiation paths created by a 6-MV linear accelerator containing binary moving ring-shaped collimators. In addition, it allows the creation of highly conformal treatment plans in irregular areas, the treatment of large areas, such as whole body irradiation, and the irradiation of many lesions in the same session [12]. Because all of these advanced features enable it to irradiate large hemitoracic volumes in MPM, the clinical outcomes and toxicity profiles of treatments performed with this device must be determined.

Highlight key points

- HTT can be administered as part of the trimodality therapy of MPM patients with acceptable toxicities.
- MS and esophageal doses should also be considered for radiation pneumonitis risk, and new dose constrains should be defined for these organs.

Therefore, in this study, we investigated the efficacy and toxicity of HTT as part of MPM trimodality treatment while implementing curative doses to target volume with maximal respect to risk organs.

MATERIALS AND METHODS

Treatments

Patients

The Kartal Dr. Lutfi Kirdar City Hospital Ethics Committee approved this study (2022/514/242/20; date: January 25, 2023). From October 2018 to December 2020, the data of 11 patients who were diagnosed with MPM and treated with a trimodality approach including P/D, adjuvant chemotherapy, and helical radiotherapy and had a 6-month follow-up period were retrospectively analyzed. Toxicities that occur during HTT were graded according to the RTOG/EORTC Radiation Toxicity Grading System [13].

Surgery

Patients underwent lung-sparing surgery. Tumors were removed with total or partial P/D with preservation of bilateral lung tissues. Patients with thoracic wall and/or lung wedge resection with pleurodectomy were also included in the study.

Chemotherapy

Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) were administered to the patients as adjuvant therapy after surgery at 21-day intervals.

Radiotherapy

Radiotherapy was applied by tomotherapy (HDA Precision, Accuray Inc., Sunnyvale, CA, USA). The Accuray iDMSTM version 1.1.1.1 system was used to create the

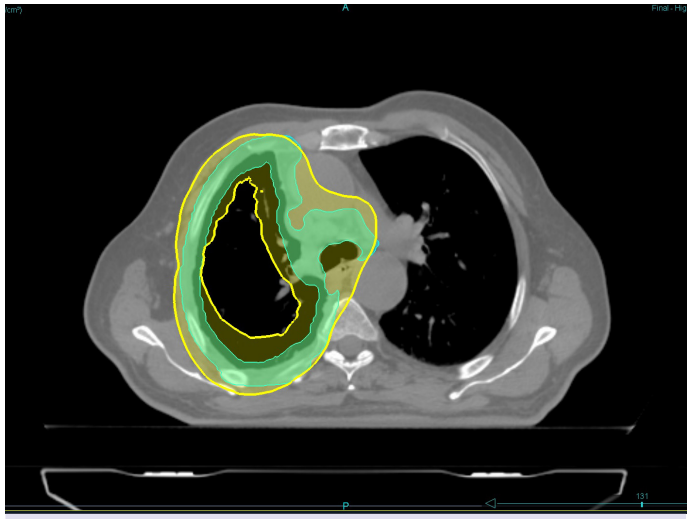

Figure 1. Dose distribution of right-sided MPM. Hemithoracic and mediastinal pleura treated with helical tomotherapy as a part of trimodality treatment. Planning targed volume (PTV, green) receiving 50.4 Gy (yellow).

plans. Images of the patients for planning were obtained by computed tomography (CT) in the supine position with hands above the head and sections of 0.25 mm thickness. Treatment volumes were determined by fusing CT and 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) images obtained before and after surgery. Gross tumor volume (GTV) included gross tumor tissue and/or surgical clips; clinical target volume (CTV) covered the entire ipsilateral parietal and visceral pleura, starting from the ipsilateral lung apex to the point where the diaphragm attaches to the L2 vertebral corpus. Ipsilateral hilum was included with the mediastinal pleura and pericardium. Mediastinal lymph nodes were included if FDG avidity and/or histopathological positivity were reported. Whole ipsilateral thoracic wall with adequate margins considering respiratory movements, and set-up errors were included in PTV. Organs at risk (OARs) were delineated as recommended by the Radiation Therapy Oncology Group Atlas [14], (Fig. 1).

Statistical Analysis

The IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL) was used for the analysis of the data. Descriptive data were presented in numbers (percentage) or median±standard deviation (minimum-maximum). Survival analyses were estimated with the Kaplan-Meier method. Dosimetric parameters of OARs were compared in patients with radiation toxicity by using Mann Whitney U test. A p value of <0.05 was considered an indication of statistical significance.

Table 1. Characteristics of patients, disease and treatments

Characteristics	n (%)
Age median (min-max)	57 (22-70)
Gender	
Female	3 (27.3)
Male	8 (72.7)
ECOG performance status	
0	5 (45.5%)
1	6 (55.5%)
Tumor localization	
Right hemithorax	6 (54.5)
Left hemithorax	5 (45.5)
Histopathological Type	
Sarcomatoid	1 (9.1)
Biphasic	2 (18.2)
Epitheloid	8 (72.7)
Surgery	
Extended P/D	9 (81.8)
P/D	2 (18.2)
Prescribed radiotherapy Dose (Gy)	
50-50.4 Gy/25-28 fr	3 (27.3)
50-60 Gy/30-33 fr (45-50+5-10 Gy boost)	7 (63.6)
30Gy/10 fr	1 (9.1)
Number of chemotherapy cycles	
3	1 (9.1)
4	2 (18.2)
6	7 (63.6)
9	1 (9.1)

ECOG: Eastern Cooperative Oncology Group; fr: fractions; P/D: Pleurodectomy and decortication.

RESULTS

Characteristics of Patients, Disease and Surgery

The median age of the patients was 57±9 (22-70) years. Three patients (27.3%) were female, while the remaining 8 (72.7%) were male. The ECOG performance score was 0 in 5 (45.5%) patients and 1 in 6 (55.5%) patients. Approximately half of the tumors (54.5%) were located on the right lung, and the other half (45.5%) were on the left lung. Histopathological types were: epithelioid (72.7%), biphasic (18.2%), and sarcomatoid (9.1%). The majority of patients (81.8%) underwent extended P/D as lung sparing surgery, with the remaining 18.2% undergoing P/D (Table 1). The median number of adjuvant chemotherapy cycles was 6, ranging from 3 to 9 cycles (Table 1).

TABLE 2. Dose parametrics of PTV

	Median	Minimum	Maximum	SD
Volume (mm^3)	1950	1220	2441.2	424.8
Prescribed dose	50.4	30	60	8.7
D_{max} (Gy)	57.9	33.5	68.9	9.9
D_{min} (Gy)	15.5	11.5	36.2	10
D_{95} (Gy)	49	25	59.2	10.1

PTV: Planning target volume; D_{mean}: Mean Dose; D_{min}:Minimum dose; D_{max}:Maximum dose; SD: Standart deviation; D_{max}:Maximum dose.

Dosimetric Parameters

Except for one patient who was administered 30 Gy in 10 fractions due to COVID-19 pandemia, all received ≥45 Gy with 1.8-2 Gy daily doses. Three patients (27.3%) received 50-50.4 Gy to whole hemithorax without boost doses and remaining 7 patients received 45-50 Gy to ipsilateral hemithorax with the dose of 5-10 Gy to boost volumes, totally 50-60 Gy (Table 1). The PTV was 1950±425 (1220-2441) mm3 and the median prescribed dose was 50.4±8.7 (30-60) Gy (Table 2). Total lung D_{mean} was 19.9±6 (10.4-26) Gy; ipsilateral and contralateral lung V20 (%) were 89.4±11.2 (62.7-100) and 0.7±2.1 (0-5.9) respectively (Table 3). Esophageal D_{mean} and D_{max} were 21.7±8.4 (7.4-34) and 53.1±10.4 (25.4-64.4) Gy, respectively. D_{max} of MS was 38.6± 1.3 (13.7-48) Gy. Dosimetric parameters of heart were as following; V30 (%) 22.3 ±13.4 (3.9-47) and D_{mean}: 21±5.7 (10.8-29.3) Gy. MS D_{max} was 38.1±1.3 (13.7-48) Gy (Table 4).

Toxicity

No patients had grade≥3 toxicity. RP developed in 4 (36.4%) patients within 6 months after the completion of radiotherapy. Esophagitis developed in 2 (18.2%) patients during radiotherapy. During post-radiotherapy follow-up, 1 patient complained of chest wall pain, and another patient experienced dyspnea without pneumonitis. MS and esophageal doses were found to be associated with RP. D_{max} (45.5±2 Gy vs 35.8±10.5 Gy) and D_{mean} (19.2±3.2 vs 10.7±5.9) of MS were significantly higher in patients with RP than in those without RP ($p<0.05$). Aside from MS doses, esophageal D_{max} was found to be significantly associated with RP (61 vs 51.6, $p=0.01$). Patients with RP also had higher

TABLE 3. Dosimetric parameters of lungs

	Total Lung V5 (%)	Contralat Lung V5 (%)	Ipsilat. Lung V5 (%)	Total Lung V10 (%)	Contralat Lung V10 (%)	Ipsilat. Lung V10 (%)	Total Lung V20 (%)	Contralat Lung V20 (%)	Ipsilat. Lung V20 (%)	Total Lung D_{mean} (Gy)	Contralat Lung D_{mean} (Gy)	Ipsilat. Lung D_{mean} (Gy)
Median	67.3	40.9	100	47.6	11.3	100	35.6	0.7	89.4	19.9	5.7	38.1
Minimum	41	8.7	99.6	23.1	0.1	98.4	18.1	0.0	62.7	10.4	3.1	25.6
Maximum	96	92.2	100	63.1	21.0	100	51.3	5.9	100	26	8.6	54.4
Std. D	17.7	25.4	0.1	12.3	7.2	0.5	11.9	2.1	11.2	6	1.7	8.8

Contralat:Contralateral; Ipsilat.:Ipsilateral; V5: Organ volume (%), receiving a dose of ≥ 5 Gy; V10: Organ volume (%), receiving a dose of ≥ 10 Gy; V20: Organ volume (%), receiving a dose of ≥ 20 Gy; Dmean: Mean Dose; Dmin: Minimum dose; Dmax: Maximum dose; Std.D: Standart deviation.

Table 4. Dose parameters of organ at risk organs

	Median±Std. D (min-max)
Esophagus D_{mean} Gy	21.7±8.4 (7.4-34)
Esophagus D_{max} Gy	53.1± 10.4 (25.4-64.4)
Heart V30 %	22.3 ±13.4 (3.9-47)
Heart D_{mean} Gy	21±5.7 (10.8-29.3)
MS D_{mean} Gy	15± 6.2 (2.9-21.9)
MS D_{max} Gy	38.6± 1.3 (13.7-48)

MS:Medulla spinalis; V30: Organ volume receiving a dose of ≥30 Gy; Dmean: Mean Dose; Dmin:Minimum dose; Dmax:Maximum dose; Std.D: Standart deviation.

V20 (%) of the heart (55.3 vs 26.6) but the difference was not statistically significant (p=0.067, Table 5). One patient was diagnosed with radiation myelitis within the first month of radiotherapy; MS D_{max} and D_{mean} were 29.1 and 19 Gy, respectively.

Survival Data

The overall survival time was 30±7.3 (95% CI: 15.7-44.3) months. Two-year local control, disease-free, and overall survival rates were 48.5%, 49%, and 77.9%, respectively (Fig. 2).

DISCUSSION

This study, which retrospectively examined the efficacy and toxicity of radiotherapy applied with HTT as part of trimodality treatment in patients who underwent P/D, reached high two-year local control (48.5%), disease-free (49%) and overall survival (77.9%) rates. Except for MS, it was safe in that it didn't cause any grade> 2 esophageal, heart, or lung toxicity. Transverse myelitis was diagnosed in 1 case. Even though MS doses were within the limits, radiation myelitis could not be excluded in this patient. RP developed in 4 patients, and higher doses of esophageal and MS were found in these patients.

The minimum standard for the radiotherapy of MPM is CT-planned, 3D conformal irradiation using photons and/or electron beams. In recent years, modern, safer, and more effective radiation therapy techniques have been used in the treatment of resectable MPM. Highly conformal radiotherapy techniques such as IMRT provide better coverage of the target volume while protecting the surrounding normal tissues and OARs (9). Over 5–6 weeks, the recommended dose is 45-60 Gy, 1.8-2 Gy/fraction. With regard to OAR constraints, a dose of 60 Gy for macroscopic residual disease can be delivered. The contralateral lung dose should be as low as possible, preferably D_{mean}<8.5 Gy. The dose administered to the ipsilateral lung should be limited as much as possible to reduce the risk of RP. Total lung D_{mean} and V20 are recommended to be<21 Gy and <40%, respectively [15]. In our study, the prescribed doses and dose constraints for OARs were within the recommended limits of NCCN guidelines. All of the patients received ≥ 45 Gy to the ipsilateral hemithorax with a dose of 5–10 Gy to boost volumes, except for one patient who was administered 30 Gy in 10 fractions during the COVID-19 pandemic period.

The two-year local control, disease-free, and overall survival rates (48.5%, 49%, and 77.9%, respectively) in our study were comparable to those reported in the literature. In a prospective study, patients who received IMRT after neoadjuvant chemotherapy and lung sparing surgery had a progression-free and overall survival rate of 12.4 and 23.7 months; in resectable disease, the 1- and 2-year overall survival rates were 80% and 59%, respectively. Hemithoracic IMRT was reported as safe with acceptable RP rates in patients with locally advanced MPM [11]. Since the incidence of microscopic disease is high with P/D, this provides a stronger rationale for radiotherapy after P/D [10]. However, with intact both lungs, a radiosensitive organ, it is difficult to irradiate the ipsilateral hemithoracic pleura safely while protecting lung parenchyma and other OARs [11]. The conventional radiotherapy after P/D was not found to be safe and effective, with 1.6% grade 5 radiation pneumonitis and local recurrence of 42% [16]. In a phase 2 study by Rimmer et al. [11] investigating the safety and feasibility of ipsilateral hemithoracic IMRT, 30% of patients developed grade≥2 radiation pneumonitis. In our study, the rate of grade 1–2 RP was 36.3% within the first 6 months of radiotherapy, and it was shown that trimodality treatment with HTT was safe in terms of lung toxicity. Grade 1-2 rates of esophagitis, dermatitis, fatigue, dyspnea, and pain in the thoracic wall were lower in our study group than in those treated with VMAT [11]. Dosimetric parameters may differ between IMRT techniques, and it is unknown whether this influences toxicity profiles. In a study comparing HTT and VMAT dosimetric

TABLE 5. Dosimetric parameters based on RP

Dosimetric parameters	RP positive* (n=4)	RP negative* (n=7)	p
Prescribed dose to PTV (Gy)	59.7±4.7 (50.4-60)	50.2±10.2 (30-60)	0.1
Total lung D_{mean} (Gy)	23.5±2.6 (20-26)	14.8±6.6 (10.4-26)	0.26
Total lung V20 (%)	41.6±6.5 (36.6-51.3)	28.3±6.5 (18.1-47.6)	0.26
Contralateral lung D_{mean} (Gy)	6.04±1 (5.17-7.41)	5.9±2.2 (3-8.6)	0.9
Contralateral lung V20 (%)	1.8±2.8 (0-5.9)	0.94±1.8 (0-4.8)	0.6
Heart V20 (%)	55.3±16 (28.6-63.7)	26.6±13.5 (14.5-44)	0.067
MS D_{max} (Gy)	45.5±2 (43.3-48.3)	35.8±10.5 (13.8-42.4)	0.01
MS D_{mea}n (Gy)	19.2±3.2 (15-21.8)	10.7±5.9 (3-17)	0.019
Esophagus D_{mean} (Gy)	29.5±5.3 (21.7-34)	18.1±8.6 (17.5-30.5)	0.067
Esophagus D_{max} (Gy)	61±3.5 (55.9-64.4)	51.6±10.9 (25.4-54.5)	0.01

PTV: Planning target volume; V20: Organ volume (%), receiving a dose of ≥20 Gy; D_{mean}: Mean Dose; D_{min}:Minimum dose; D_{max}: Maximum dose; Std. D: Standart deviation; MS: Medulla spinalis; *: median±Std.D, (min-max); RP: Radiation pneumonitis.

parameters, the PTV coverage of both techniques was similar, but the total lung V20 (26.7% vs. 31.1%) and D50 (24.8 vs. 22.9%) of HTT were better [17].

Although dose limits have been defined for the contralateral lung for IMRT applications in MPM treatment, there is no such definition for the ipsilateral lung. In our study, ipsilateral D_{mean} was found to be 38.1 Gy (25.6–54.4), and V20 was 89.4% (67.2–100). In a dosimetric study conducted by Leitzen et al., [18] ipsilateral lung tissue was also maximally preserved, with a D_{mean} for V20 of 80–81% (70.5–89.3). In this study, it was emphasized that the contralateral dose should be kept as low as possible, but the planning system of HTT does not allow protecting both lungs and then optimizing the plan for one side at the same time. It has also been stated that contralateral lung protection is achieved by accepting higher doses on the ipsilateral side.

In lung cancer patients, the predictive factors for any grade of radiation esophagitis were concomitant chemotherapy and the V20, V30, V40, V50, and V60 values of esophagus [19]. According to the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) analysis, the D_{mean} of esophagus should be kept at ≤34 Gy during lung IMRT [20]. Similarly, after lung sparing surgery, the esophageal D_{mean} in MPM patients was kept at ≤34 Gy (11). The esophageal D_{mean} of 21.7 Gy, below the suggested QUANTEC limits, explains the low rate (18.2%) of grade 1-2

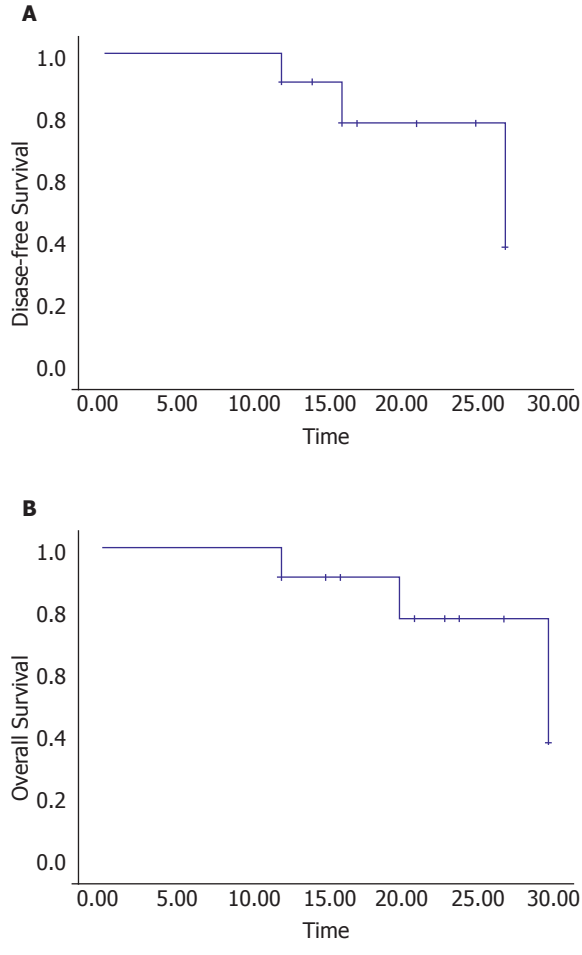

FIGURE 2. Disease free **(A)** and overal survival **(B)**.

and the absence of grade 3 esophagitis in our study group. Severe acute radiation esophagitis was reported to be a risk factor for symptomatic RP, and D_{mean} of esophagus and dosimetric factors of lung were correlated in patients with severe RP who received thoracic radiotherapy [21]. RP was also associated with MS parameters in addition to esophageal dosimetric parameters in our study. Patients with RP had higher D_{mean} and D_{max} of MS. In the literature, there was no evidence of a connection between MS D_{max} and RP. As a result, MS doses in MPM patients treated with trimodality should be kept as low as possible, with an emphasis on researching new MS dose parameters. In our study, one patient developed transverse myelitis within a month of completing HTT. For MS, the D_{max} and D_{mean} doses were 29 Gy and 19 Gy, respectively. These values were less than the median dose of 38.6 Gy (13.7-48.3 Gy) of the group. In a study in which HTT was applied after P/D, MS D_{max} was reported as 39.3±4.5 Gy, which is similar to the median dose of our group. After IMRT in MPM patients, no myelitis was reported in this study [22]. L'Hermitte's sign (LHs), a sign of radiation myelitis, was investigated in patients who underwent HTT with the diagnosis of head and neck tumor; 35.9% of the patients described LHs. In Binary Logistic Regression Analysis, the age and the V40 of MS had a borderline significant relationship with LHs. LHs are more likely to occur at younger ages and higher V40 ratios of MS. LHs risk was not associated with cisplatin in head-and-neck patients who underwent HTT [23]. Although cisplatin and pemetrexed combinations were well tolerated in MPM patients [8], the risk of myelitis or any other toxicities should be taken into account due to their radiosensitizing effects (24). Our patient who experienced myelitis was 67 years old, slightly older than the median age of the group. To the PTV of 1460 mm^3, 50 Gy in 25 fractions was applied. He was the only patient in the group with sarcomatoid histology, which was his most distinguishing feature. Although radiotherapy is not recommended for sarcomatoid histology [15], this patient received it due to positive surgical margins following lung wedge and chest wall partial resection. Although V20 of the heart was found to be higher in RP patients, the difference was not statistically significant when compared to patients without RP. Total lung V4 and heart V16 values were found to be the most predictive factors for grade 2 and higher RP after post-operative radiotherapy in non-small-cell lung cancer patients [25]. In MPM patients who received IMRT after lung-sparing surgery, there was a correlation between the heart V43 value and the risk of grade 2 RP. It has also been demonstrated that the risk of grade ≥3 RP is increased in relation to heart volumes receiving doses ranging from 31 to 45 Gy [26].

MPM treatment is determined by tumor histology and stage. Epithelioid histology is more common and has a better prognosis than biphasic and sarcomatoid types (1). Multimodality therapy is recommended for medically operable stages of 1-3 epithelioid and mixed-type histologies [3]. According to the NCCN, for sarcomatoid histology or medically inoperable tumors, only chemotherapy is recommended [15]. In consistent with the literature epithelioid histology had the most favorable prognosis.

Multimodality treatment protocols are often performed in the order of chemotherapy, surgery, and post-operativeradiotherapy. Chemotherapy is performed to eliminate microscopic disease after EPP or P/D [10]. Currently. cisplatin and pemetrexed combinations are the most commonly used neoadjuvant or adjuvant chemotherapy protocol [15].

No difference has been reported between neoadjuvant and adjuvant chemotherapy in terms of overall survival. In the literature, there are various studies with varying numbers of chemotherapy cycles [27]. The median number of cycles administered in a study that emphasized the superiority of the cisplatin-pemetrexed combination over cisplatin as a single medication was 8 cycles [8]. In a prospective study, cisplatin and pemetrexed were administered for 4 cycles or less as neoadjuvant treatments before the surgical procedure [11]. Chemotherapy is administered for 2 cycles as a neoadjuvant treatment and continued for 6 cycles after surgery in an ongoing study [28]. In our study, a median of 6 cycles (3–9) of cisplatin and pemetrexed combinations were administered as an adjuvant treatment before radiotherapy.

The major limitations of this study were that it was retrospective, and the small number of patients precluded subgroup analyses to investigate the relationship between dosimetric parameters and survival rates.

To summarize, while HTT is thought to be effective for MPM treatment, with higher local control and survival rates and lower toxicity, extra caution should be taken to keep MS and esophageal doses as low as possible. New dose contrains for OARs, particularly for MS, may be required.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar City Hospital Ethics Committee approved this study (2022/514/242/20; date: January 25, 2023).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – HO, SO, ASO, BD, GG; Design – HO, ASO, SO, GG, BD; Supervision – ASO, SO, HO, BD, GG; Resources – HO, SO; Materials – HO, ASO; Data Collection– HO, BD, GG; Analysis and/or Interpretation – HO, ASO; Literature Search – HO, SO, BD; Writing Manuscript – HO, SO, BD; Critical Review – HO, ASO, SO, BD.

REFERENCES

1. Moro J, Sobrero S, Cartia CF, Ceraolo S, Rapanà R, Vaisitti F, et al. Diagnostic and therapeutic challenges of malignant pleural mesothelioma. Diagnostics (Basel) 2022;12:3009.
2. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43:1022–5.
3. Meyerhoff RR, Yang CF, Speicher PJ, Gulack BC, Hartwig MG, D'Amico TA, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res 2015;196:23–32.
4. Rice D, Rusch V, Pass H, Asamura H, Nakano T, Edwards J, et al; International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. J Thorac Oncol 2011;6:1304–12.
5. Bibby AC, Tsim S, Kanellakis N, Ball H, Talbot DC, Blyth KG, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016;25:472–86.
6. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al; MARS trialists. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763–72.
7. Flores RM, Pass HI, Seshan VE, Dycoco J, Zakowski M, Carbone M, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008;135:620–6.
8. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636–44.
9. Gomez DR, Rimner A, Simone CB 2nd, Cho BCJ, de Perrot M, Adjei AA, et al. The use of radiation therapy for the treatment of malignant pleural mesothelioma: expert opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol 2019;14:1172–83.
10. Rimner A, Rosenzweig KE. Novel radiation therapy approaches in malignant pleural mesothelioma. Ann Cardiothorac Surg 2012;1:457–61.
11. Rimner A, Zauderer MG, Gomez DR, Adusumilli PS, Parhar PK, Wu AJ, et al. Phase II study of hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. J Clin Oncol 2016;34:2761–8.
12. Saw CB, Katz L, Gillette C, Koutcher L. 3D treatment planning on helical tomotherapy delivery system. Med Dosim 2018;43:159–67.
13. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.
14. Spring Kong FM, Quint L, Machtay M, Bradley J. Atlases for Organs at Risk (OARs) in Thoracic Radiation Therapy. Available at: https://www.eviq.org.au/getmedia/a4c012a8-d6a7-4d87-93f7-d3f465b49889/RTOG-lung-contouring-atlas.pdf.aspx?ext=.pdf. Accessed Mar 24, 2023.
15. NCCN. Recommendations of the National Comprehensive Cancer Network® (NCCN®) COVID-19 Vaccination Advisory Committee. Available at: https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed Mar 24, 2023.
16. Gupta V, Mychalczak B, Krug L, Flores R, Bains M, Rusch VW, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2005;63:1045–52.
17. Müdder T, Sarria GR, Henkenberens C, Holz J, Garbe S, Röhner F, et al. Dosimetric comparison between helical tomotherapy and volumetric modulated arc therapy in patients with malignant pleural mesothelioma. Clin Oncol (R Coll Radiol) 2022;34:164–71.
18. Leitzen C, Wilhelm-Buchstab T, Stumpf S, Heimann M, Koch D, Schmeel C, et al. Tomotherapy in malignant mesothelioma: a planning study to establish dose constraints. Strahlenther Onkol 2019;195:668–76.
19. Paximadis P, Schipper M, Matuszak M, Feng M, Jolly S, Boike T, et al; Michigan Radiation Oncology Quality Consortium. Dosimetric predictors for acute esophagitis during radiation therapy for lung cancer: results of a large statewide observational study. Pract Radiat Oncol 2018;8:167–73.
20. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76 Suppl 3:S10–9.
21. Tang W, Li X, Yu H, Yin X, Zou B, Zhang T, et al. A novel nomogram containing acute radiation esophagitis predicting radiation pneumonitis in thoracic cancer receiving radiotherapy. BMC Cancer 2021;21:585.
22. Nakanishi-Imai M, Murai T, Onishi M, Mouri A, Komiyama T, Omura M, et al. Survey of malignant pleural mesothelioma treatment in Japan: patterns of practice and clinical outcomes in tomotherapy facilities. J Radiat Res 2022;63:281–9.
23. Laidley HM, Noble DJ, Barnett GC, Forman JR, Bates AM, Benson RJ, et al. Identifying risk factors for L'Hermitte's sign after IMRT for head and neck cancer. Radiat Oncol 2018;13:84.
24. Yoshida D, Ebara T, Sato Y, Kaminuma T, Takahashi T, Asao T, et al. Interaction of radiation and pemetrexed on a human malignant mesothelioma cell line in vitro. Anticancer Res 2011;31:2847–51.
25. Shepherd AF, Iocolano M, Leeman J, Imber BS, Wild AT, Offin M, et al. Clinical and dosimetric predictors of radiation pneumonitis in patients with non-small cell lung cancer undergoing postoperative ra-

diation therapy. Pract Radiat Oncol 2021;11:e52–62.
26. Yorke ED, Jackson A, Kuo LC, Ojo A, Panchoo K, Adusumilli P, et al. Heart dosimetry is correlated with risk of radiation pneumonitis after lung-sparing hemithoracic pleural ıntensity modulated radiation therapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2017;99:61–9.
27. Sharkey AJ, O'Byrne KJ, Nakas A, Tenconi S, Fennell DA, Waller DA. How does the timing of chemotherapy affect outcome following radical surgery for malignant pleural mesothelioma? Lung Cancer 2016;100:5–13.
28. Lim E, Darlison L, Edwards J, Elliott D, Fennell DA, Popat S, et al; MARS 2 Trialists. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. BMJ Open 2020;10:e038892.