



Dosimetric evaluation of helical tomotherapy and volumetric-modulated arc therapy for malignant pleural mesothelioma: a planning study for dose escalation

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Background: To compare the dosimetric differences between helical tomotherapy (HT) and volumetric-modulated arc therapy (VMAT) treatment plans for inoperable malignant pleural mesothelioma (MPM).

Methods: Ten patients with inoperable MPM were retrospectively planned with the HT and VMAT techniques, and the dose-volume histogram (DVH)-based parameters of the planning target volume (PTV) and organs at risk (OARs) were compared.

Results: Compared with the VMAT plans, the target homogeneity index (HI) and conformity index (CI) of the HT plans were significantly better (HI: 1.04 ± 0.01 vs. 1.11 ± 0.03 , CI: 0.80 ± 0.07 vs. 0.71 ± 0.12 , respectively) ($P < 0.001$, $P = 0.013$, respectively). Regarding the OARs, including the ipsilateral lung, contralateral lung, heart, and spinal cord, the differences among the V30 (Vx: fraction of volume receiving >5 , 10, 20, and 30 Gy, respectively) of the ipsilateral lung and V5, V10, and V20 of the contralateral lung were statistically significant ($P = 0.031$, $P = 0.030$, $P = 0.021$, $P = 0.003$, respectively). However, there was no significant differences between HT plans and VMAT plans, regarding the V5, V10 and V20 of the ipsilateral lung, V3 of the contralateral lung, V5 and Dmean of the heart, and Dmax of the cord. The treatment delivery time of the VMAT was significantly shorter than that of the HT (mean delivery time: 3.27 ± 1.65 vs. 11.11 ± 3.75 min, respectively) ($P < 0.001$).

Conclusions: Compared to the VMAT plans, the HT plans not only demonstrated more optimal target coverage and conformity but also considerably reduced the dose-volume parameters of the OARs in both low-dose areas in contralateral lung and high-dose areas in ipsilateral lung and contralateral lung, which is correlated to radiation injury. However, the treatment delivery time of the HT plans was longer.

Keywords: Helical tomotherapy (HT); volumetric-modulated arc therapy (VMAT); organs at risk (OARs); dosimetric evaluation; malignant pleural mesothelioma (MPM)

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Introduction

Although the incidence of malignant pleural mesothelioma (MPM) is low, most lesions are extensive, with obvious symptoms and a poor prognosis. Trimodality therapy including chemotherapy, extrapleural pneumonectomy

(EPP), and hemithorax radiotherapy, has shown promising results in patients with medically operable MPM, with a median survival period of 19–33.5 months in prospective studies (1-5). Findings from a contemporary cohort demonstrated that lung-sparing extended pleurectomy/

decortication (P/D) comprised most surgical procedures for MPM compared with EPP (6). However, most cases in China are inoperable at the time of diagnosis; hence, palliative high-dose hemithoracic radiotherapy to the entire ipsilateral pleura with conventional fractionation is used in the management of MPM in the adjuvant, neoadjuvant, and palliative settings (7).

As external beam radiotherapy evolved from three-dimensional conformal radiation therapy (3DCRT) to intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and helical tomotherapy (HT), treatment planning and delivery improved greatly. And IMRT/VMAT/HT therapy are being used more commonly now than historically (8). For instance, several studies have shown that conventional static IMRT achieves better dose coverage and improved local control compared with 3DCRT (6-13) for MPM, while other studies have demonstrated that VMAT allows for even better dose conformity in a shorter delivery time compared with static IMRT, sparing potential organs at risk (OARs) during MPM radiotherapy (14-16). Moreover, several studies exploring the feasibility of prescription dose escalation using HT and VMAT have also been reported (17-21). However, little research has been published comparing the differences between HT and VMAT from a dosimetric escalation perspective. Therefore, in this study, we retrospectively analyzed the dosimetric and technical differences between VMAT and HT for MPM in 10 patients previously treated with static IMRT. We quantitatively compared the quality of the treatment plans according to dose uniformity and target volume and dose conformity to the surrounding normal tissue of the ipsilateral lung, contralateral lung, heart, and spinal cord. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2452>).

Methods

Patients selection, positioning, and computerized tomography (CT) scanning

Ten patients diagnosed with MPM from September 2006 to May 2013 who were unable to undergo surgery for various reasons were randomly selected as the study subjects. The median age was 48.5 years. All cases were diagnosed as MPM via puncture biopsy combined with immunohistochemistry. Staging was implemented according to the American Joint Committee on Cancer (AJCC)

and the Union for International Cancer Control (UICC) seventh edition TNM classification (22), with two patients in stage II, six in stage III, and two in stage IV. For the CT scan, the patients were fixed with a body fixator, placed in a supine position, with both arms raised above their head, and scanned from the level of the larynx to the upper abdomen on a CT simulator (Brilliance Big Bore CT, Philips Medical Systems, Cleveland, USA) with a 5-mm slice thickness and slice separations.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of The Seventh Medical Center of Chinese PLA General Hospital (No. 2020-022) and informed consent was taken from all the patients.

Contouring of target volume and OARs

The contouring of the target volume and OARs for all patients was performed by a single radiation oncologist with extensive experience in MPM treatment according to the International Commission on Radiation Units and Measurements Report No. 62 (23). The gross target volume (GTV) included the tumors observed in clinical and radiological data, while the planning target volume (PTV) was obtained by expanding the GTV 10 mm in the direction of the pleura and 5 mm in the direction of the lungs. The OARs included the ipsilateral lung, contralateral lung, heart, and spinal cord.

Treatment planning

The HT planning was conducted on the Hi-Art[®] (version 4.1.2, Madison, USA) treatment planning system using field widths of 2.5 cm, a modulation factor of 2.5-3.0, and a pitch of 0.287 or 0.43. The VMAT planning was completed on the Monaco system (version 5.11, Elekta AB, Stockholm, Sweden) using 6-MV photon beams from an Elekta linac (Synergy, Elekta AB, Stockholm, Sweden) and two partial arcs of 220°. The prescribed dose to the PTV was 60 Gy in 2-Gy daily fractions. The dose-volume constraints used for the OARs are listed in *Table 1*.

Plan comparison

The dosimetric comparison of the plans was performed based on the following parameters extracted from the dose-volume histogram (DVH): the homogeneity index (HI) (24), conformity index (CI) (24), the maximum dose (D_{max}),

the minimum dose (D_{min}), and the mean dose (D_{mean}) of the PTV (D_{max} : dose received by 2% volume of the PTV, D_{min} : dose received by 98% volume of the PTV) (25), V_5 , V_{10} , V_{20} , and V_{30} (V_x : fraction of volume receiving >5 , 10, 20, and 30 Gy, respectively) of the ipsilateral lung, V_3 , V_5 , V_{10} , and V_{20} of the contralateral lung, V_5 and D_{mean} of the heart, and D_{max} of the spinal cord. *Figure 1* displays the isodose distributions of the HT and VMAT radiotherapy plans for a typical patient.

Statistical analysis

The Wilcoxon signed rank test was used to compare the results of the two types of plans using the SPSS 20 software (SPSS Inc., Chicago, USA). The quantitative data were

Table 1 Dose-volume constraint for OARs

OARs	Dose (Gy)	Volume (%)
Ipsilateral lung	10	<70
	20	<50
Contralateral lung	10	<40
Heart	5	<60
Cord	45	<1

OARs, organs at risk.

expressed in the form of the mean \pm standard deviation ($\bar{x} \pm s$). A value of $P < 0.05$ was considered statistically significant.

Results

Comparison of the HI, CI, D_{max} , D_{min} , and D_{mean} for the HT and VMAT

The DVH plots of the PTV of the HT and VMAT plans of a typical patient were exported into the Computational Environment for Radiological Research software and are illustrated in *Figure 2*. The HI, CI, D_{max} , D_{min} , and D_{mean} of the plans are presented for comparison in *Table 2*. Significant differences were found in the D_{max} , D_{min} , D_{mean} , HI, and CI values between the HT and VMAT plans ($P=0.002$, $P=0.010$, $P=0.002$, $P=0.002$, $P=0.004$, respectively). Overall, the HT plans provided significantly better uniformity and conformity than the VMAT plans.

The DVH plots of the OARs of the HT and VMAT plans of a typical patient are illustrated in *Figure 3*. The doses and irradiated volume parameters of the ipsilateral lung, contralateral lung, heart, and spinal cord are listed in *Table 3*. The V_{30} of the ipsilateral lung and V_3 , V_{10} , and V_{20} of the contralateral lung all demonstrated significant differences ($P=0.037$, $P=0.043$, $P=0.039$, $P=0.004$,

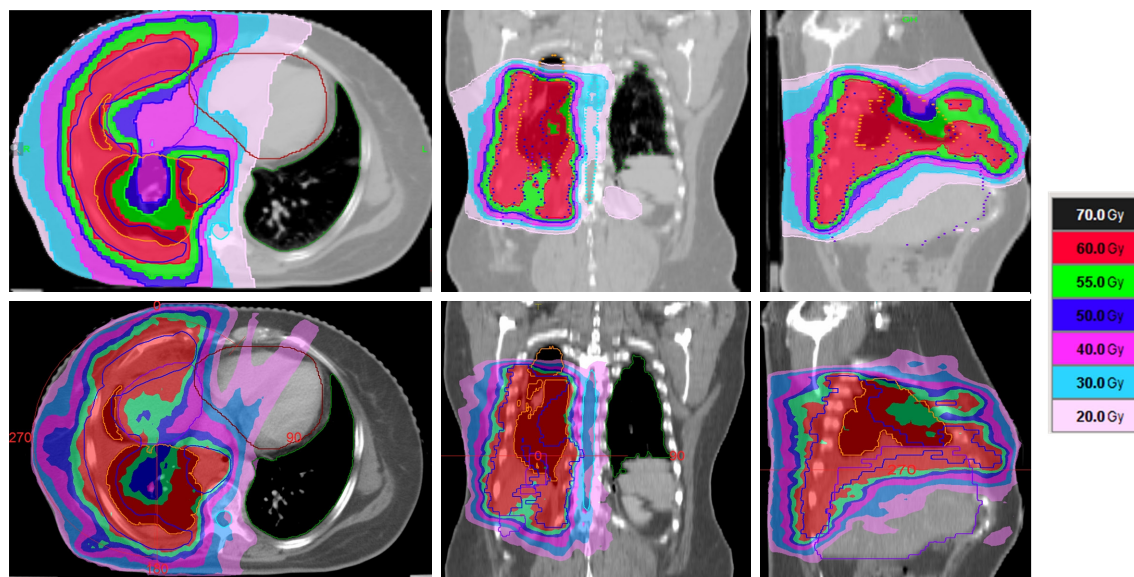


Figure 1 The isodose distributions of HT and VMAT radiotherapy plans for a typical patient in transverse, coronal, sagittal view (upper: HT, lower: VMAT). HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

respectively). However, there was no significant differences between HT plans and VMAT plans, regarding the V5, V10 and V20 of the ipsilateral lung, V5 of the contralateral lung, V5 and Dmean of the heart, and Dmax of the cord (P=0.098, P=0.846, P=0.084, P=0.064, P=0.313, P=0.131, P=0.105, respectively).

Treatment delivery efficiency

The efficiency of the two plan types was evaluated by the

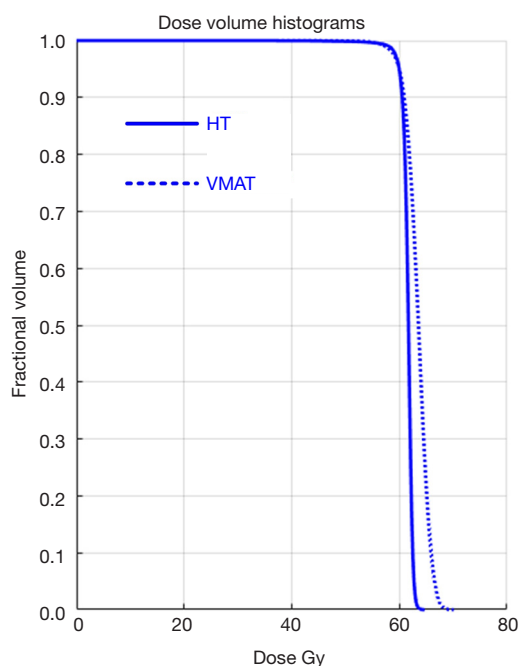


Figure 2 DVH plots of PTV of the HT and VMAT plans of a typical patient. DVH, dose-volume histogram; PTV, planning target volume; HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

number of monitor units (MUs) and the delivery time (Table 4). The number of MUs in the HT plan was much higher than that in the VMAT plan, and the former’s treatment delivery time was 239.8% longer than that of the latter. The treatment delivery time of the VMAT was significantly shorter than that of the HT (mean delivery time: 3.27±1.65 vs. 11.11±3.75 min, respectively) (P=0.002).

Discussion

A novel IMRT system that integrates spiral CT technology with linear accelerator technology, HT implements delivery in a 360° range at all angles. In the irradiation process, the gantry rotation, table motion, accelerator pulse, and opening and closing of the binary multileaf collimator (MLC) are synchronized (26). Meanwhile, VMAT is based on the development of fixed-field IMRT and image-guided radiation therapy technology and differs from conventional static IMRT in that it can simultaneously change the rotation speed of the gantry, the MLC position, and the dose rate to achieve a highly conformal dose distribution.

In previous research, Helou *et al.* used HT to treat 29 patients with MPM with a median prescription dose of 50 Gy and 2 Gy per fraction. The V2, V5, V10, V13, and V20 of the lungs in the treatment plan were 100%, 98%, 52 %, 36%, 19%, and 5%, respectively. They found that when V10 of the contralateral lung was greater than 50%, the risk of radiation pneumonia tended to increase (27). Minatel *et al.* treated 28 MPM patients with HT, delivering a prescribed dose of 50 Gy to the PTV. Any fluorodeoxyglucose-avid areas or regions of particular concern for residual disease were given a simultaneous boost of radiotherapy up to 60 Gy. Three patients had grade 2 radiation pneumonitis, and two had grade 3 radiation pneumonitis. The V5 of the contralateral lung was 32%—far higher than those who did not develop radiation

Table 2 Comparison of HI, CI, Dmax, Dmin, Dmean for HT and VMAT ($\bar{x}\pm s$)

Parameters	HT	VMAT	Z value	P value
Dmax	63.15±0.99	67.22±2.21	-2.803	0.002
Dmin	59.26±0.46	58.61±0.72	-2.497	0.010
Dmean	61.82±0.68	63.27±1.04	-2.803	0.002
HI	1.04±0.01	1.11±0.03	-2.814	0.002
CI	0.80±0.07	0.71±0.12	-2.703	0.004

HI, homogeneity index; CI, conformity index; Dmax, dimension maximum; Dmin, dimension minimum; Dmean, dimension mean; HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

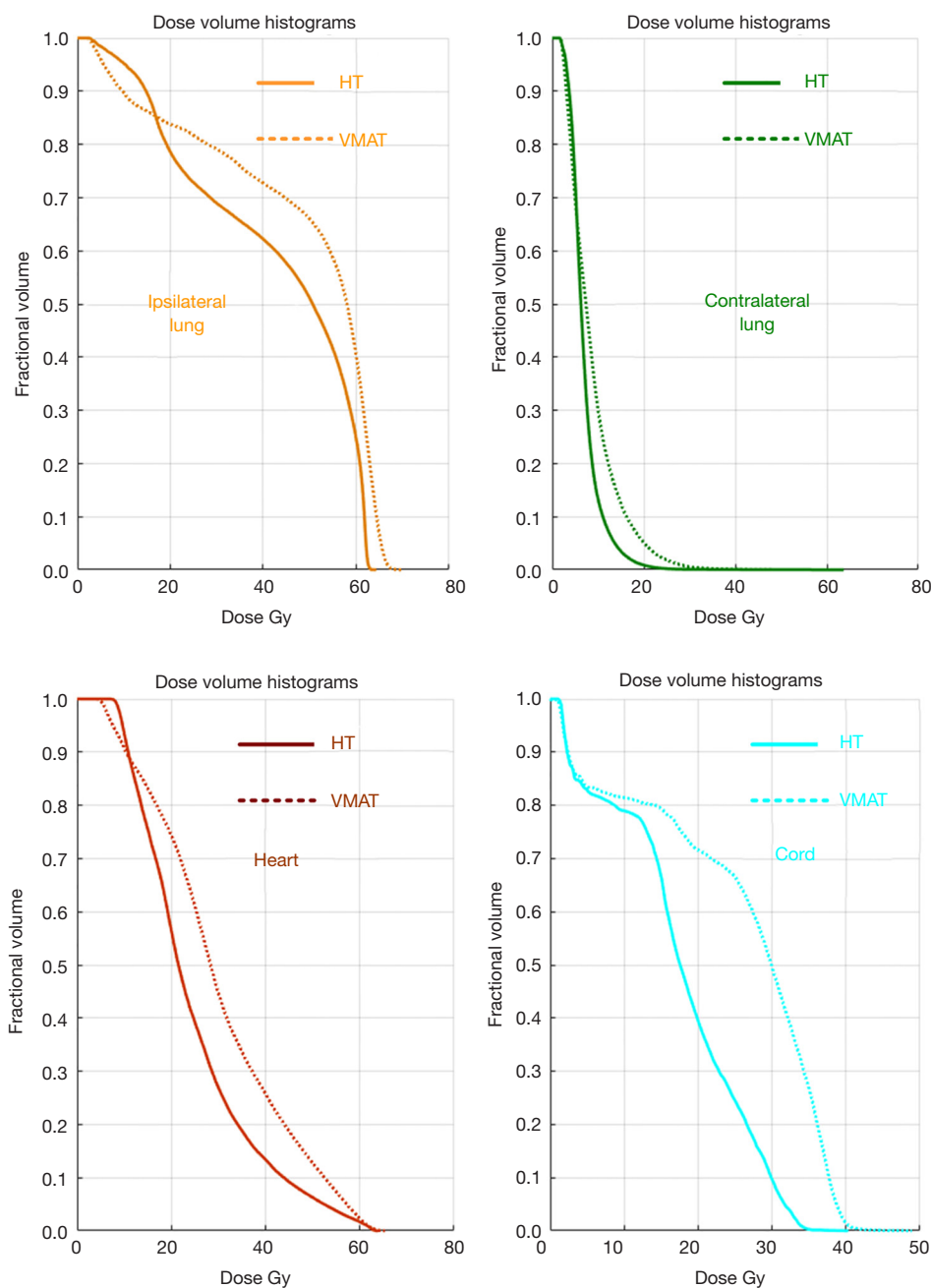


Figure 3 DVH plots of OARs of the HT and VMAT plans of a typical patient. DVH, dose-volume histogram; OARs, organs at risk; HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

pneumonitis ($V_5 = 17\%$) (28). Harrabi *et al.* used HT in 10 patients with MPM who had undergone pleurectomy/decortication (P/D), with a median prescription dose of 52.2 Gy. The minimum lethal dose (MLD) and V_{20} of the ipsilateral lung were 32.8 Gy and 71.7%, respectively. No

treatment-related toxicity exceeding grade III according to the common toxicity criteria was observed (29). Hong *et al.* treated 11 patients who had received neoadjuvant chemotherapy after surgery with HT at a prescription dose of 25 Gy in five fractions to the entire ipsilateral hemithorax.

Table 3 Comparison of dosimetric parameters of OARs for HT and VMAT ($\bar{x}\pm s$)

OARs	Parameter	HT	VMAT	Z value	P value
Ipsilateral lung	V5	79.64±21.80	83.37±21.08	-1.718	0.098
	V10	73.32±25.14	75.41±25.24	-0.255	0.846
	V20	51.23±26.72	57.13±29.44	-1.784	0.084
	V30	37.38±23.58	44.68±30.77	-2.090	0.037
	Dmean	27.19±12.16	28.68±15.39	-0.357	0.770
	V(cc) <20 Gy	603.02±412.31	619.27±461.91	-0.459	0.695
	V(cc) <30 Gy	447.95±340.68	500.36±457.97	-0.968	0.375
Contralateral lung	V3	72.87±30.64	79.93±26.09	-2.016	0.043
	V5	63.19±34.60	73.89±29.72	-1.886	0.064
	V10	29.89±29.88	46.69±24.54	-2.073	0.039
	V20	4.45±6.47	12.94±11.40	-2.666	0.004
	Dmean	7.26±4.32	7.89±4.52	-1.274	0.232
Total lung	Dmean	14.65±5.73	16.97±8.56	-1.070	0.322
	V20	24.32±11.17	26.88±14.55	-1.478	0.160
Heart	V5	65.62±45.96	71.93±44.88	-1.214	0.313
	Dmean	17.76±13.69	22.15±16.44	-1.580	0.131
Cord	Dmax	32.45±12.93	36.16±10.45	-1.682	0.105
Liver	V30	13.87±21.76	15.77±26.15	-0.944	0.438
	Dmean	11.31±12.91	11.71±14.69	-0.255	0.826
Ipsilateral kidney	V15	8.40±17.99	9.52±20.21	-1.342	0.500
Contralateral kidney	V15	0.16±0.47	0.25±0.74	-1.000	1.000
Esophagus	Dmean	21.74±12.53	24.85±13.40	-2.803	0.002

OARs, organs at risk; HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

Table 4 Comparison of MU and treatment delivery time ($\bar{x}\pm s$)

Parameter	HT	VMAT	Z value	P value
MUs	9,776.8±3,301.6	907.6±378.9	-2.803	0.002
Treatment time (min)	11.11±3.75	3.27±1.65	-2.803	0.002

MUs, monitor units; HT, helical tomotherapy; VMAT, volumetric-modulated arc therapy.

The MLD and V7 of the contralateral lung were lower than 3.5 Gy and 20%, respectively, and only one patient developed acute grade 3 radiation pneumonitis (30). Leitzen *et al.* performed an HT planning study on the datasets of 13 patients who received radiotherapy after pleurectomy, with an applied dose to the PTV of 50.4 Gy and single doses of 1.8 Gy per fraction. For the PTV (left-sided/right-sided),

the Dmin was 49.37/49.71 Gy (98.0%/98.6%), and the Dmax was 54.19/54.61 Gy (107.5%/108.3%). The beam-on time was kept below 15 min. The MLD of the contralateral lung was below 4 Gy, and the Dmean of the heart was 22.23 Gy (31). Kimura *et al.* treated a total of 15 patients after EPP with VMAT. The dose prescription was designed to cover 95% of the PTV with 54 Gy in 30 fractions. The

MLD, V5 and V20 of the contralateral lung were 6.4 Gy (range, 5.2–8.2 Gy), 45.9% (range, 29.3–57.7%) and 2.1% (range, 0.1–6.6%), respectively. Grade 3 pneumonitis after the treatment was observed in three patients (20.0%) (14). A recent study compared HT and VMAT in terms of dosimetric parameters in positron emission tomography-CT-based radiation therapy in unresectable MPM. The PTV1 and PTV2 prescription doses were 45.0 and 54 Gy, respectively, in 1.8 Gy per fraction. For the HT plan, the V5, V10, and V20 of the ipsilateral lung were 99.7%, 95.1%, and 80.2%, respectively, while the V5, V10, and V20 of the contralateral lung reached 30.6%, 29.6%, and 0.5%, respectively. The Dmean of the heart was 25.8 Gy, and the Dmax of the cord was 33.2 Gy. For the VMAT plan, the V5, V10, and V20 of the ipsilateral lung were 100%, 100%, and 92%, respectively, while the V5, V10, and V20 were 67.8%, 51.4%, and 3.5%, respectively. The Dmean of the heart was 33.3 Gy, and the Dmax of the cord was 39.3 Gy (31). Both the Dmax and Dmean of the PTV1 and PTV2 favored the HT plan over the VMAT plan. Additionally, the HT also provided more homogeneous dose distribution and numerically lower doses received by most OARs. The primary disadvantage of the HT technique was the requirement for longer treatment times (7.4 vs. 2.5 minutes/fraction).

In this retrospective dosimetric study, to explore the feasibility of escalating the prescription radiotherapy dose for patients suffering inoperable MPM, the prescribed PTV dose was determined to be 60 Gy in all cases, which has not yet been applied in clinical work. When 95% of the PTV received the prescribed dose of 60 Gy, the dose-volume parameters of some patients' lungs significantly exceeded the tolerated dose limits of today's clinic routine, so some plans could not be used for clinical implementation. This is a limitation of the study.

Herein, the target area conformity and dose uniformity of the HT treatment plan were better than those of the VMAT plan, and the dose-volume parameters of the OARs of the former were slightly lower than those of the latter. Regarding the HT plans, the V5, V10, and V20 of the ipsilateral lung, Dmean of the heart, and Dmax of the cord were 79.6%, 73.3%, 51.23%, 17.8 Gy, and 32.5 Gy, respectively, all of which were lower than the corresponding values in Pehlivan's study (32). The V5 and V20 of the contralateral lung were 63.2% and 4.5%, respectively, higher than the corresponding values in Pehlivan's study, while the V10 was similar in both studies. Regarding the VMAT plans, the V5, V10, and V20 of the ipsilateral

lung, Dmean of the heart, and Dmax of the cord were 83.4%, 75.4%, 57.1%, 22.2 Gy, and 36.2 Gy, respectively, all of which were lower than the corresponding values in Pehlivan's study. The V5 and V20 of the contralateral lung were 73.9% and 12.9%, respectively, higher than the corresponding values in Pehlivan's study, while the V10 was again similar in both. However, HT technology still has deficiencies in clinical treatment operation, as the segment number in an HT plan significantly lengthens the treatment time, making it difficult to fully ensure the patient's comfort and setup repeatability throughout.

Conclusions

This dosimetric study demonstrated the possibility of precise hemithoracic irradiation of medically/technically inoperable MPM patients with either HT or VMAT. These novel radiotherapy techniques have great potential to transform technological advantages into therapeutic benefits in future clinical work.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-2452>

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of The Seventh Medical Center of Chinese PLA General Hospital (No. 2020-022) and informed consent was taken from all the patients.

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