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Clinical experience of volumetric modulated arc therapy for malignant pleural mesothelioma after extrapleural pneumonectomy

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The purpose of this study was to evaluate the efficacy and safety of volumetric modulated arc therapy (VMAT) after extrapleural pneumonectomy (EPP) in patients with malignant pleural mesothelioma (MPM). A total of 15 patients who received VMAT after EPP were enrolled. All patients were males, and the median age was 67 years (Stage IB in two, II in six, and III in seven patients). The clinical target volume (CTV) included the entire preoperative ipsilateral hemithorax and involved nodal stations. The CTV was generally expanded by 10–15 mm beyond the planning target volume (PTV). The dose prescription was designed to cover 95% of the PTV with 54 Gy in 30 fractions. The median follow-up period was 11 months. Treatment-related toxicities were evaluated by Common Terminology Criteria for Adverse Events (CTCAE) ver. 4. One-year local control, disease-free survival, and overall survival rates were 55.7% [95% confidence interval (CI): 25.6–85.8%], 29.3% (95% CI: 5.3–53.3%), and 43.1% (95% CI: 17.1–69.0%), respectively. According to the histological analysis, the one-year LC rate was significantly worse in patients with non-epithelial type (biphasic and sarcomatoid types) than in patients with epithelial type [epithelial type: 83.3% (95% CI, 53.5–100%), non-epithelial type: 0% (95% CI, 0%), $P = 0.0011$]. Grade 3 pneumonitis after VMAT was observed in three patients (20.0%); however, no patients died of pulmonary toxicity. VMAT appears to be relatively safe for patients with MPM after EPP because of the low pulmonary dose.

Keywords: volumetric modulated arc therapy (VMAT); malignant pleural mesothelioma (MPM); extrapleural pneumonectomy (EPP); radiation pneumonitis

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare cancer and is most commonly caused by asbestos exposure. According to the latest Japanese survey of MPM conducted in 2009, asbestos imports peaked in 1990 and were banned in 2000; therefore, the number of deaths from MPM has begun to increase following the 40-year latent period, and is expected to peak in 2030 [1]. Improved treatments are needed, and optimal treatment for MPM remains under investigation, delayed by the absence of Phase III randomized trials. 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 [2 –6]. Adjuvant radiotherapy after EPP has contributed to the reduction in local recurrence [7, 8]. The recommended dose of adjuvant radiotherapy is 50–54 Gy in 1.8–2-Gy fractions according to the guidelines of the National Comprehensive Cancer Network, the European Respiratory Society, and the European Society of Thoracic Surgeons [9, 10]; however, delivery of the recommended

doses and fractions to the hemithorax (which has a complex shape) using the 3D conformal radiotherapy (3D-CRT) technique has been difficult. Therefore, intensity-modulated radiotherapy (IMRT), which is a highly conformal technique, was designed to allow more effective sparing of normal tissues and to provide conformal high-dose irradiation for improved coverage of the hemithorax compared with the 3D-CRT technique [11]. Recently, several reports using IMRT in the adjuvant setting after EPP have demonstrated good local control (LC) [12–14]. However, the higher percentages of the contralateral lung volume receiving ≥5 Gy (V5), or the mean lung dose (MLD), have been associated with severe pulmonary toxicity [15–18]. Volumetric modulated arc therapy (VMAT), a form of intensity-modulated arc therapy, is a promising new method using the regular linear accelerator and, compared with conventional static IMRT, it has the potential to improve target coverage and dose sparing to the organs at risk (OARs) [19, 20]. However, there are limited reports of VMAT.

The aims of this study were to evaluate the treatment results and pulmonary toxicity in patients with MPM using VMAT in an adjuvant setting after EPP.

METHODS

Patient eligibility

From December 2009 to January 2014, 17 patients received VMAT at Hiroshima University Hospital in the setting of a trimodality therapy, which included neoadjuvant chemotherapy (cisplatin and pemetrexed in 2–5 cycles), EPP, and adjuvant radiotherapy using VMAT. The inclusion criteria for curative adjuvant VMAT included the following: (i) age > 20 years; (ii) an Eastern Cooperative Oncology Group Performance Status of 0–1; (iii) a diagnosis of pathological Stage I–III by the International Mesothelioma Interest Group (IMIG) criteria after EPP; (iv) adequate post-EPP pulmonary function (forced expiratory volume in 1 s > 1000 ml; (v) adequate bone marrow reserve, and normal liver and renal function; (vi) no severe complications after EPP (e.g. severe heart disease, active infection, or pneumonia). All patients submitted written informed consent to participate in this study. If patients did not satisfy these inclusion criteria, they underwent 3D conformal radiotherapy.

Simulation and target delineation

For treatment planning, all patients were immobilized in the supine position with their arms overhead using a Vac-Lok positioning cushion (Civco Medical Solutions, Kalona, IA, USA). All incision or drain sites were covered with a 5-mm-thick tissue-equivalent bolus extending 2–3 cm beyond the site margins. Simulation computed tomography (CT) scans (Lightspeed QX/I; GE Medical Systems Inc., Waukesha, WI, USA) were performed after the injection of non-ionic iodinated contrast material (100 ml at a rate of 1 ml/s) under free breathing. CT volume data was acquired with 2.5-mm-thick slices at 2.5-mm intervals and transferred to the Eclipse treatment planning system (ver. 11.0; Varian Medical System Inc., Palo Alto, CA, USA). A gross tumor volume (GTV) was defined if the macroscopic residual tumors were identified on contrast-enhanced planning CT. The clinical target volume (CTV) included the entire preoperative ipsilateral hemithorax, scars, drain sites and involved nodal stations. In general, the upper border of the CTV was 10 mm superior to the apex of the ipsilateral hemithorax, and the lower border was the posterior diaphragmatic sulcus, which may reach as far posteriorly as the L2 vertebra. The anterior, posterior and lateral margins of the CTV were 5 mm beyond the ipsilateral hemithorax. If nodal metastasis was positive, the ipsilateral mediastinum was also included in the CTV. The PTV was delineated by uniform margins of 10 mm around CTV1 and CTV2, respectively, and bound by the external body surface. The OARs were also delineated, including the contralateral lung, liver, heart, kidney, spinal cord, esophagus, stomach and intestine.

Treatment planning of volumetric modulated arc therapy

For clinical treatment, VMAT plans were generated using three coplanar arcs with gantry rotation angles of 220° (to avoid the contralateral lung) on the Eclipse treatment-planning system. The collimator angles of each arc were set to 10° or 80° to avoid the tongue-and-groove effect. In VMAT plans, beams were delivered with 6–10-MV photons from a linear accelerator (CLINAC iX; Varian Medical Systems Inc., Palo Alto, CA). The maximum dose rate was set to 600 monitor units (MU)/min. Dose calculation was performed with the Eclipse AAA algorithm using a grid of 2/5 mm.

In principle, the dose prescription was designed to cover 95% of the PTV with 54 Gy in 30 fractions. If dose constraints to the OARs were not satisfied, especially to the contralateral lung, the dose prescription for the PTV was decreased to 50.4 Gy in 28 fractions or 45 Gy in 25 fractions. If the GTV was observed at the planning CT, it was boosted using a simultaneously integrated boost technique. Table 1 lists the dose constraints to the OARs. In previous reports, a high incidence of fatal pulmonary toxicity was observed when the mean lung dose (MLD), V5 and V20 to the contralateral lung were high [15–18]. In the present study, dose constraints to the contralateral lung were more strictly monitored because of the uncertainties in using VMAT (Table 1).

Evaluation

In this study, we evaluated preliminary treatment results and toxicities, especially pulmonary toxicity, in actual treatment settings using VMAT. All patients were examined monthly. Follow-up chest X-ray and hematological examinations were performed every month and CT scans every 3–6 months after completion of VMAT. Treatment-related toxicities were

Table 1. Dose constraints of organs at risk (OARs)

OARs	Index	Dose constraints	
		Deviation	
		None	Minor
Contralateral lung	**V5**[a]	<60%	<65%
	V20[a]	<10%	<15%
	mean dose	<8 Gy	<8.5 Gy
Liver	**V30**[b]	<30%	<45%
	mean dose	<30 Gy	<35 Gy
Heart	**V45**[c]	< 30%	<45%
	max dose	<60 Gy	<65 Gy
Contralateral kidney	**V15**[d]	<20%	<25%
Stomach/Bowel	**max dose**	<50 Gy	<54 Gy
Spinal cord	**max dose**	<50 Gy	<54 Gy

[a]V5 and V20 = the percentages of the contralateral lung volume receiving ≥5 and ≥20 Gy, respectively, [b]V30 = the percentage of the liver volume receiving ≥30 Gy, [c]V45 = the percentage of the heart volume receiving ≥45 Gy, [d]V15 = the percentage of the contralateral kidney volume receiving ≥45 Gy.

evaluated using the Common Terminology Criteria for Adverse Events ver. 4.0.

Statistical methods

The overall survival (OS), progression-free survival (PFS) and LC rates were calculated using the Kaplan–Meier method. The OS, PFS and LC were calculated from the beginning date of VMAT. Log-rank testing was used to compare outcomes between the subsets of patients analyzed. All statistical analyses were performed using StatMate for Windows statistical software (ver. 4.01; ATMS, Tokyo, Japan). A probability (P) < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Of the 17 patients who underwent VMAT, two were excluded after leaving the study (at 18 Gy in a patient with biphasic type and at 37.8 Gy in patient with sarcomatoid type) because of progressive disease during VMAT: therefore, 15 patients received the prescribed doses and included in the analysis. The patients' clinical characteristics are summarized in Table 2. The median PTV prescription dose was 54 Gy (range, 45–54 Gy). One patient received up to

Table 2. Patients' background

Median Age (Range)		67 years (56–78 years)	**Pathological T stage (IMIG[a])**	1b	2 patients
Gender	male	15 patients		T2	8 patients
	female	0 patients		T3	5 patients
Performance status (PS)	0	3 patients	**Pathological N stage (IMIG[a])**	N0	11 patients
	1	12 patients		N1	1 patients
Side	Right	8 patients		N0	3 patients
	Left	7 patients	**Pathological Stage (IMIG[a])**	IB	2 patients
Histology	Epithelial	10 patients		II	6 patients
	Sarcomatoid	2 patients		III	7 patients
	Biphasic	3 patients	**Treatment paradigm**		
Postoperative pulmonary function			ChT[c]→EPP[d]→VMAT[e]		14 patients
Median FEV1.0[b] (range)		1.32 l (1.0–1.81 l)	EPP[$]→VMAT[&]→ChT[#]		1 patient
Chemotherapy cycles	2	2 patients	**Total dose and fractionations (PTV[f]1)-**		
	3	8 patients	54 Gy in 30 fractions		9 patients
	4	4 patients	50.4 Gy in 28 fractions[g]		5 patients
	5	1 patient	45 Gy in 25 fractions		1 patient

[a]IMIG = International Mesothelioma Interest Group, [b]FEV1.0 = the forced expiratory volume in 1 s, [c]ChT = chemotherapy, [d]EPP = extrapleural pneumonectomy, [e]VMAT = volumetric modulated arc therapy, [f]PTV = planning target volume, [g]one patient received up to 61.6 Gy in 28 fractions as simultaneously integrated boost to the PTV2.

Table 3. Dosimetric parameters in VMAT[a]

Target or Organs at risk (*n* = 15)	Parameters	VMAT Mean ± SD[b] (range)
Planning target volume	mean dose (Gy)	55.0 ± 3.3 (44.7–55.7)
(PTV)	D2[c] (Gy)	58.9 ± 3.8 (48.1–64.2)
	D95[c] (Gy)	50.5 ± 3.8 (40.4–54.0)
	Homogeniety Index[d]	1.23 ± 0.07 (1.12–1.36)
	Conformity Index$^{e}_{95\%}$	1.35 ± 0.50 (1.12–1.37)
Contralateral lung	mean dose (Gy)	6.5 ± 1.0 (5.2–8.2)
	V5[f] (%)	45.4 ± 10.0 (29.3–57.7)
	V20[f] (%)	2.7 ± 2.3 (0.1–6.6)
Liver	mean dose (Gy)	21.0 ± 9.6 (9.0–34.2)
	V30[f] (%)	26.9 ± 17.9 (3.2–53.3)
Liver (right[g])	mean dose (Gy)	29.4 ± 2.8 (25.9–34.2)
(*n* = 8)	V30[f] (%)	42.1 ± 7.2 (31.9–53.3)
Liver (left[h])	mean dose (Gy)	11.5 ± 2.3 (9.0–15.0)
(*n* = 7)	V30[f] (%)	9.6 ± 5.5 (3.2–18.2)
Heart	max dose (Gy)	60.3 ± 4.7 (48.8–66.2)
	V45[f] (%)	38.2 ± 17.6 (12.9–90.8)
Heart (right[g])	max dose (Gy)	59.8 ± 4.7 (48.8–64.5)
(*n* = 8)	V45[f] (%)	30.9 ± 11.3 (12.9–48.6)
Heart (left[h])	max dose (Gy)	60.7 ± 5.0 (52.4–66.2)
(*n* = 7)	V45[f] (%)	46.6 ± 20.4 (32.6–90.8)
Contralateral kidney	V15[f] (%)	2.6 ± 5.1 (0–16.0)
Stomach/Bowel	max dose (Gy)	50.4 ± 10.8 (26.7–60.7)
Spinal cord	max dose (Gy)	42.8 ± 5.1 (33.1–49.8)
Monitor unit		685.9 ± 162.4 (483–1066)

[a]VMAT = volumetric modulated arc therapy, [b]SD = standard deviation, [c]Dx (Gy) = dose receiving ≥*x*% of volume, [d]Homogeniety Index = Dmax (max dose of PTV)/prescribed dose, [e]Conformity Index$_{95\%}$ = ratio between patient volume and the PTV volume receiving ≥95% of prescribed dose, [f]V*x* (%) = volume receiving ≥*x*% of prescribed dose, [g]right = indicates that primary tumor is located in right hemithorax, [h]left = indicates that primary tumor is located in left hemithorax.

61.6 Gy in 28 fractions as a simultaneously integrated boost to the macroscopic residual tumors. The median duration between surgery and the start of VMAT was 90 days (range, 48–252 days). The median follow-up period was 11 months (range, 4–30 months).

Dosimetric parameters in volumetric modulated arc therapy

Dosimetric parameters of VMAT are shown in Table 3. Dose coverage of the PTV was adequate, with acceptable conformity and homogeneity. Although dose constraints for the contralateral lung were maintained in all patients, it was difficult to achieve a liver V30 < 30% in patients who underwent right-sided treatment, or a heart V45 < 30% in patients who underwent left-sided treatment.

Figure 3 illustrates the typical dose distributions of a patient who underwent right-sided treatment (**A**) and of a patient who underwent left-sided treatment (**B**).

Preliminary treatment results and toxicities in an actual treatment setting using volumetric modulated arc therapy

Figure 1A–C indicates OS, PFS and LC rates. Although the follow-up periods were relatively short, the 1-year OS, PFS and LC rates were 43.1% [95% confidence interval (CI), 17.1–69.0%], 29.3% (95% CI, 5.3–53.3%) and 55.7% (95% CI, 25.6–85.8%), respectively. The histological analyses of the epithelial type vs the non-epithelial type (biphasic and sarcomatoid types) revealed significant differences in the 1-year LC rate [epithelial type: 83.3% (95% CI, 53.5–100%),

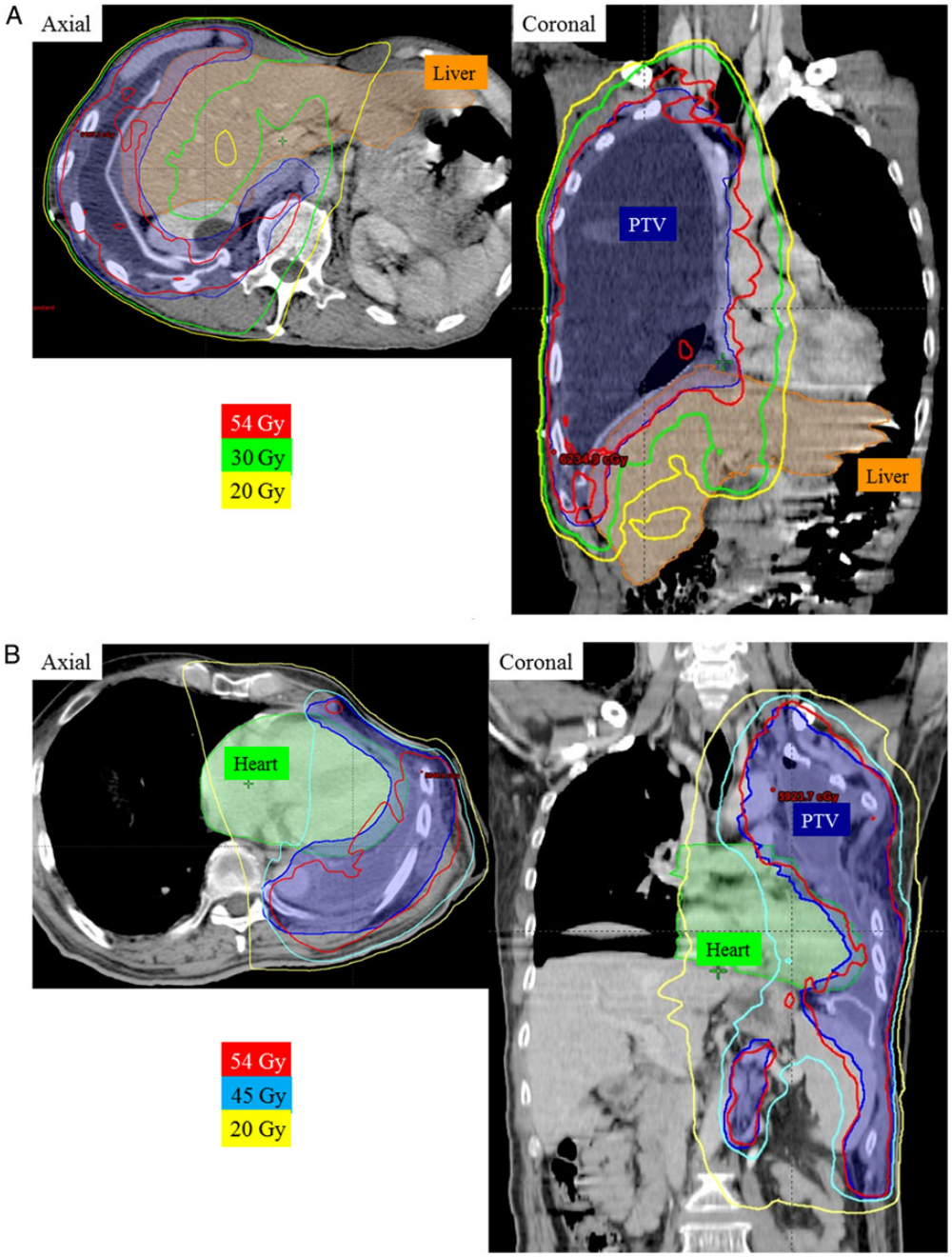

Fig. 1. Typical dose distributions for a patient who underwent right-sided treatment (A) and a patient who underwent left-sided treatment (B). (**A**) A patient who underwent right-sided treatment (pT1bN0M0). This patient was 68 years old and received VMAT at 54 Gy in 30 fractions. Usually, it was difficult to achieve a liver V30 < 30% in patients who underwent right-sided treatment (mean dose to liver; 29.4 Gy, V30 = 40.6% in this patient). This patient died from locoregional recurrence at 11 months from the beginning of VMAT. Liver dysfunction was not observed during the follow-up period. (**B**) A patient who underwent left-sided treatment (pT3N0M0). This patient was 64 years old and received VMAT at 54 Gy in 30 fractions. Usually, it was difficult to achieve a heart V45 < 30% in patients who underwent left-sided treatment (max dose of heart; 57.1 Gy, V45 = 50.0% in this patient). This patient died of distant metastasis at 8 months from the beginning of VMAT. Cardiac dysfunction was not observed during the follow-up period.

non-epithelial type: 0% (95% CI, 0%), $P = 0.0011$] (Fig. 2); however, there was no significant difference in either OS [epithelial type: 56.3% (95% CI, 23.9–88.6%), non-epithelial type: 20.0% (95% CI, 0–55.1%), $P = 0.0865$] or PFS rates [epithelial type: 46.7% (95% CI, 14.2–79.2%), non-epithelial type: 0% (95% CI, 0%), $P = 0.0513$]. Table 4 indicates the

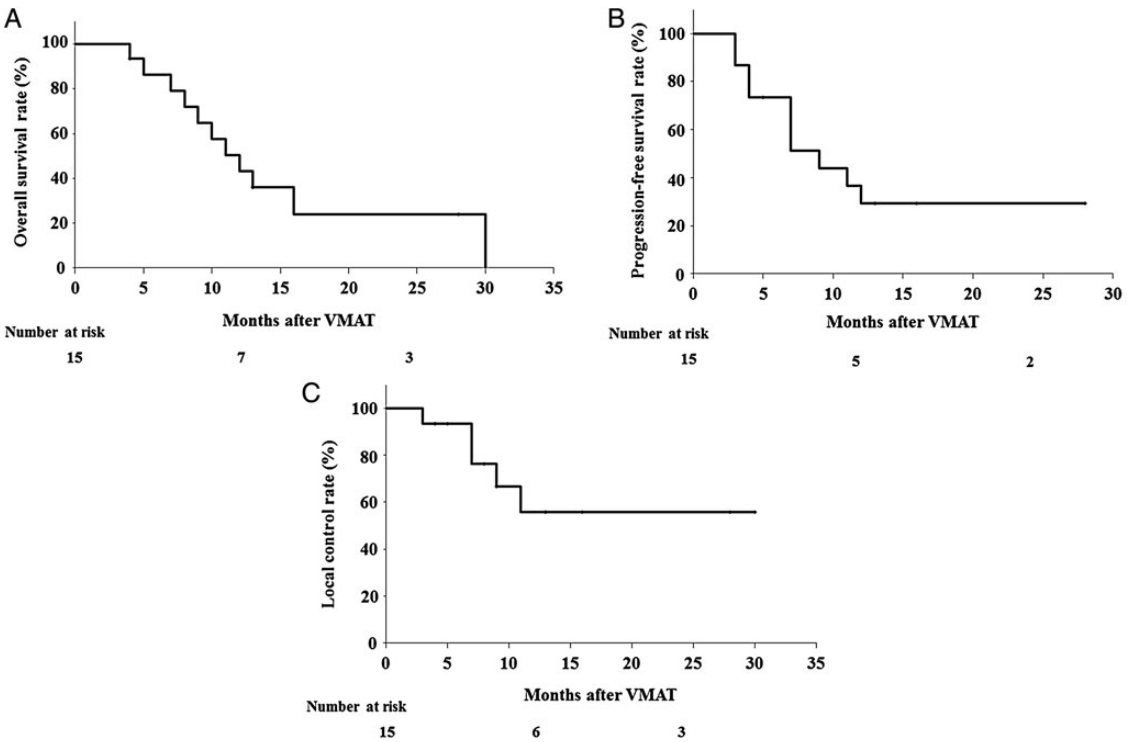

Fig. 2. Treatment results in patients with malignant pleural mesothelioma (MPM) using volumetric modulated arc therapy (VMAT) after extrapleural pneumonectomy (EPP). (**A**) OS rate. The 1-year OS rate was 43.1%. (**B**) PFS rate. The 1-year PFS rate was 29.3%. (**C**) LC rate. The 1-year LC rate was 55.7%.

Table 4. Patterns of failure

	Patterns of failure					Number of patients
	Local					2
	Local	+	Regional			1
	Local	+			Distant	2
	Local	+	Regional	+	Distant	0
			Regional	+		0
			Regional	+	Distant	0
					Distant	5
Total	5		1		7	10

Table 5. Treatment-related toxicities

Toxicity ($n = 15$)	Grade					
	0	**1**	**2**	**3**	**4**	**5**
Pneumonitis	10	0	2	3	0	0
Esophagitis	1	7	7	0	0	0
Dermatitis	0	10	5	0	0	0
Anemia	0	13	2	0	0	0
Decreased platelet count	3	11	1	0	0	0
Pericarditis	15	0	0	0	0	0
Fatigue	0	7	8	0	0	0
Nausea	3	3	9	0	0	0
Appetite loss	3	4	6	2	0	0

patterns of treatment failure. Local, regional and distant failure were observed in five (33.3%), one (6.7%) and seven (46.7%) patients, respectively. Of the five patients with local failure, four patients were the non-epithelial type.

Table 5 lists treatment-related toxicities. Three patients (20.0%) developed Grade 3 pulmonary toxicity within 3 months after completion of VMAT; however, none developed fatal pulmonary toxicity (Grade 4 or 5). In the other toxicities, two patients (13.3%) exhibited Grade 3 appetite loss; however, no patient developed >Grade 3 toxicities.

Regarding the correlations between pulmonary toxicity and dosimetric parameters for the contralateral lung, the median 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. There were no significant differences in MLD, V5 or V20 between Grade 0–2 and Grade 3 pneumonitis (MLD = 6.5 Gy vs 6.5 Gy, $P = 0.4518$; V5 = 46.6% vs 40.6%, $P = 0.1846$; V20: 2.4% vs 3.7%,

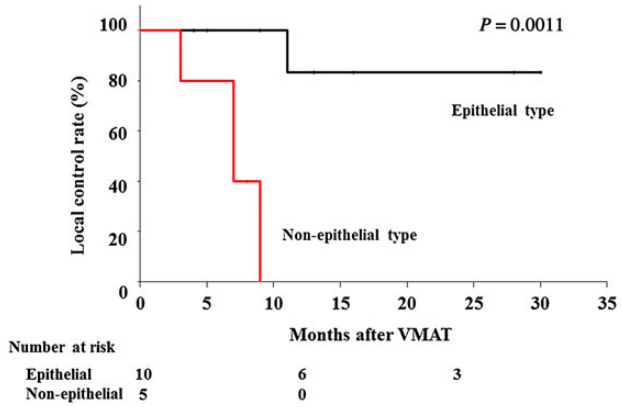

Fig. 3. Local control (LC) rates according to histological type in patients with MPM using VMAT after EPP. Between epithelial and non-epithelial types (biphasic and sarcomatoid types), there was a significant difference in the 1-year LC rate (83.3% vs 0%, respectively; $P = 0.0011$).

$P = 0.4518$, respectively). A scan of a 66-year-old patient who received VMAT of 54 Gy in 30 fractions (MLD = 7.9 Gy, V5 = 53.1%) and developed Grade 3 pneumonitis is shown in Fig. 4. He developed a cough, a high fever and dyspnea, requiring oxygen at 2 weeks after completion of VMAT. CT revealed pneumonitis not only in the low-dose area but also in the area that received 20 Gy. Steroid pulse therapy was administered immediately, and the pneumonitis improved.

DISCUSSION

This is the first report of VMAT for MPM after EPP in a clinical setting. VMAT is a recently developed arc-delivery radiotherapy technique using a regular linear accelerator. Several authors have reported the dosimetric advantages of VMAT compared with static (conventional) IMRT in planning studies. Scorsetti *et al*. conducted a planning study that included six MPM patients to compare the dosimetric parameters of VMAT and IMRT [19]. They concluded that VMAT had a similar target coverage but better dose sparing to the OARs, including the contralateral lung, than conventional IMRT. Krayenbuehi *et al.* also reported a similar study in six MPM patients with significant postoperative intrathoracic air cavities. They concluded that VMAT allowed a lower lung dose and was less affected by air cavity variation than IMRT [20]. Helical tomotherapy is a rotational delivery method. Sterzing *et al*. simulated and compared target homogeneity, conformity, and normal tissue dose between helical tomotherapy and conventional IMRT in 10 MPM patients [21]. They reported that both achieved excellent target coverage, while sparing the OARs; however, the conformity and homogeneity of the target volume were improved in the helical tomotherapy group. Table 6 summarizes a comparison of the dosimetric factors in these reports. The dose coverage of the PTV and the dose to the contralateral lung and kidney were similar in all reports, including our study; however, that of liver and heart was not satisfied in our results compared with the other reports. We need to decrease the irradiation dose to the liver and heart.

IMRT, including VMAT and helical tomotherapy, can potentially improve the LC rate because of its good coverage to the target volume. Buduhan *et al.* compared 3D-DRT with IMRT ($n = 24$ and 14 patients, respectively) after EPP and found a lower incidence of local recurrence of 14.3% in the MRT group compared with 41.7% for the 3D-DRT group ($P = 0.03$) [13]. Patel *et al*. reported 2-year LC and OS rates of 47% and 50%, respectively, in their experience of 30 patients who underwent IMRT with a median dose of 45 Gy following EPP [14]. Sylvestre *et al.* used helical tomotherapy for hemithorax irradiation (median dose, 50 Gy) after EPP in a cohort of 24 patients and reported a 2-year DFS rate of 51.8%, and that only two patients (8.3%) experienced local relapse [22]. In our study, the 1-year LC and OS rates were 55.7% and 43.1%, respectively. Although the dose coverage to the PTV was >50 Gy using VMAT, these results were worse than those of representative studies. One of the reasons for this difference was the significantly lower LC rate of patients with non-epithelial-type disease. Despite the relatively good 1-year LC rate in patients with epithelial-type disease, that in patients with non-epithelial type was significantly worse (83.3% vs 0%, respectively, $P = 0.0011$). In addition, four of five patients who experienced local failure had non-epithelial type disease. The rate of non-epithelial-type disease in our study was slightly higher than the rates reported by Patel *et al*. and Sylvestre *et al*. (33.3% in our study vs 21% and 26.7%, respectively). Rice *et al*. performed multivariate analysis of predictive factors of OS among 63 patients who underwent EPP and IMRT and found that significant factors for improved survival included epithelial histology and the absence of nodal metastasis [12]. To improve the LC rate among patients with the non-epithelial type, other modalities should be considered, such as particle therapies [23] or boron neutron capture therapy [24].

On the other hand, fatal pulmonary toxicity should be resolved by adjuvant IMRT after EPP. Previous reports describing the incidence of fatal pulmonary toxicity and the dosimetric factors of the contralateral lung in adjuvant IMRT after EPP are listed in Table 7 [14, 15, 17, 18, 25]. In general, the incidence of fatal pulmonary toxicity seemed to occur in patients who received relatively higher doses to the contralateral lung. Chi *et al.* recommended limiting the MLD to <8.5 Gy, V5 to <60%, and V20 to <20% in the contralateral lung to decrease the incidence of severe pulmonary toxicity [26]. Despite concerns of exposure to low-dose irradiation to a large area of the contralateral lung, we maintained a low dose to the contralateral lung (i.e. V5, V20 and MLD) without decreasing the dose to the PTV

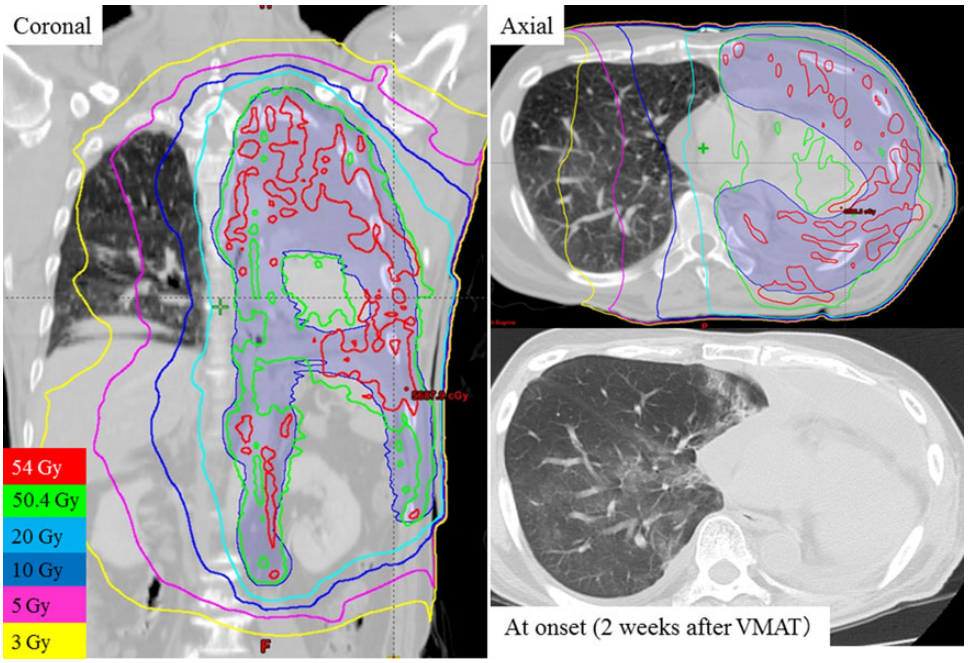

Fig. 4. A patient with Grade 3 pneumonitis. This patient was 66 years old and received VMAT at 50.4 Gy in 28 fractions (MLD = 7.9 Gy; V5 = 53.1%). He developed a cough, high fever and dyspnea, requiring oxygen at 2 weeks after the completion of VMAT. CT confirmed pneumonitis not only in the low-dose area but also in the area that received 20 Gy. Steroid pulse therapy was commenced immediately and the pneumonitis improved.

Table 6. Comparison of dosimetric factors in VMAT[a] and tomotherapy

Organs at risk	Parameters	Current study Mean ± SD[b]	Scorsetti *et al.* [19] Mean ± SD[b]	Krayenbuehl *et al.* [20] Mean ± SD[b]	Sterzing *et al.* [21] Mean ± SD[b]
	Modality	VMAT	VMAT	VMAT	Tomotherapy
	Number of patients	15	6[c]	6[c]	10[c]
	Prescribed dose (Gy)	54	54	45.5	54
PTV	**Mean dose (Gy)**	55.0 ± 3.3	54.4 ± 0.2		53.66 ± 0.14
	V95[d] (%)	96.3 ± 4.3	93.5 ± 3.4	94.2 ± 1.3	96.42 ± 0.76
	Conformity Index[e]$_{95\%}$	1.35 ± 0.50	1.1 ± 0.1		
Contralateral lung	**Mean dose (Gy)**	6.5 ± 1.0	5.6 ± 0.7	4.6 ± 1.5	4.85 ± 0.33
	V5[d] (%)	45.4 ± 10.0	47.9 ± 7.4	40.8 ± 13.6	37.6 ± 6.92
	V20[d] (%)	2.7 ± 2.3	0.4 ± 0.4	0.9 ± 1.1	0.09 ± 0.13
Liver	**Mean dose (Gy)**	21.0 ± 9.6	14.7 ± 8.1	14.6 ± 7.9	17.21 ± 7.48
	V30[d] (%)	26.9 ± 17.9	12.8 ± 14.0		
Heart	**Mean dose (Gy)**	35.0 ± 7.5	24.6 ± 8.5		21.49 ± 4.37
	V45[d] (%)	38.2 ± 17.6	19.2 ± 11.5		
Contralateral kidney	**V15[d] (%)**	2.6 ± 5.1	0.0 ± 0.0	0.0 ± 0.0	3.44 ± 1.91

[a]VMAT = volumetric modulated arc therapy, [b]SD = standard deviations. [c]All six patients were evaluated for simulation study. [d]Vx (%) = volume receiving ≥x% of prescrived dose, [e]Conformity Index$_{95\%}$ = ratio between patient volume and the PTV volume receiving ≥95% of prescribed dose.

Table 7. FPT[a] of adjuvant IMRT after EPP

Author year, country	*n*	Type of IMRT	Prescribed dose (median)	FPT (%)	Patients with no FPT			Patients with FPT		
					Lung V5 (mean)	Lung V20 (mean)	Mean lung dose (mean)	Lung V5 (mean)	Lung V20 (mean)	Mean lung dose (mean)
Allen 2006, USA [15]	13	static IMRT	54 Gy	6 (46%)	90	10.9	12.9	98.6	17.6	15.2
Rice 2007, USA [17]	63	static IMRT	45 Gy	6 (9.5%)	70	3.9	7	92.5	9.8*	10.2
Kristensen 2009, Denmark [18]	26	static IMRT	50 Gy	4 (15.3%)	94.1 (median)	13.2 (median)	12.4 (median)	97.7 (median)	20.3 (median)	13.9 (median)
Patel 2012, USA [14]	30	static IMRT	45 Gy	1 (3.3%)	55	3.9	7	92.4	6.9	11.4
Giraud 2011, Feance [22]	24	tomotherapy	50 Gy	2 (8.3%)	99[b] (median)	4[b] (median)	11[b] (median)	99[c] (median)	7[c] (median)	11[c] (median)
Current study Japan	15	RA	54 Gy	0 (0%)	45.4	2.7	6.5			

[a]FPT = fatal pulmonary toxicity, [b]Including all patients. [c]Including two patients with Grade 3 and two patients with fatal pneumonitis (Grade 5), *statistically significant compared with patient without toxicity.

using VMAT (Table 3). No deaths due to pulmonary toxicity occurred among our patient cohort. Grade 3 pulmonary toxicity was observed in three patients but there were no significant differences in dosimetric parameters.

No other fatal treatment-related toxicities were observed. However, a longer follow-up period is needed, especially to monitor liver function in patients with right-sided primary lesions and cardiac function of patients with left-sided primary lesions because of exceeding the dose constraints to these organs. If severe toxicities are observed, strict dose constraints to the liver and heart should be considered.

Because of its retrospective nature, we are aware that this study has certain limitations, such as the single-institutional design, small number of patients, and short follow-up periods. Moreover, VMAT for MPM after EPP is still under investigation. Therefore, studies with a greater number of participants and with longer follow-up periods are warranted.

CONCLUSION

VMAT can effectively decrease the treatment time while maintaining a similar dose coverage to that of static IMRT. It appears to be feasible and relatively safe for patients with MPM after EPP because of the low pulmonary dose combined with excellent dose coverage to the PTV. VMAT should be considered for improved locoregional control and OS.

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