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Dosimetric Correlates of Pulmonary Toxicity in Patients with Malignant Pleural Mesothelioma Receiving Radiation Therapy to the Intact Lungs.

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Abstract

Introduction: We aimed to determine dose-volume constraints that correlate with severe (grade 3) radiation pneumonitis (RP) in patients diagnosed with malignant pleural mesothelioma (MPM), treated using volumetric modulated arc therapy (VMAT).

Methods: Data from 40 patients with MPM who underwent pleurectomy decortication (P/D) and adjuvant radiation therapy at our institution between December 2010 and October 2016 were retrospectively analyzed. Dosimetric variables for the absolute volume as well as percentage volume of the ipsilateral lung, contralateral lung and heart were recorded. Events of RP were assessed using the Common Terminology Criteria for Toxicity and Adverse Events v4.0. Statistical analysis with Wilcoxon rank-sum, Spearman rank correlation and Receiver operating characteristic curves was computed using MATLAB V9.1, RV3.4 and SAS V9.4.

Results: Of 40 patients, 26 patients were male (65%). The median age at diagnosis was 66.5 years (range 44-84). The median prescription dose was 45 Gy (30 Gy – 54 Gy). Five patients (12.5%) had grade 3 RP. Incidence of grade 3 RP showed significant correlation ($P < 0.05$) with the absolute volume and percentage volume of the ipsilateral lung spared of 20 Gy and higher (55cc; 7%) as well as spared of 30 Gy and higher (200cc; 23%). Dosimetric variables of the contralateral lung, total lung and heart did not show correlation with incidence of grade 3 RP.

Conclusions: In our cohort, sparing ipsilateral lung of at least 55cc of 20Gy and 200cc of 30Gy correlated with a reduced incidence of severe (grade 3) radiation pneumonitis.

Keywords

IMRT; VMAT; mesothelioma; pneumonitis; correlation; toxicity; radiation

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive disease of the lung pleura. Surgical options for these patients include pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP). P/D involves removal of the pleural lining of the lung while sparing the lung parenchyma and is a less morbid procedure than EPP¹. Although surgery aims for macroscopic complete resection of the tumor, it alone does not offer adequate long-term local control and survival. The role of multimodality therapy; involving surgery with adjuvant radiation and/or chemotherapy, has been established to improve clinical outcomes for patients who have received EPP² or P/D²⁻⁴. As P/D leaves both lungs intact, the target volume encompasses and is proximal to critical organs, thus presenting the planner with a unique challenge.

The use of static field Intensity Modulated Radiation Therapy (IMRT) for the pleura (IMPRINT) has been demonstrated as a safe technique for radiotherapy planning and delivery for this site⁵⁻⁸. This technique typically utilizes 8-9 static fields uniformly arranged over a 200° angular range. Dose distribution conforms to the target volume while sparing the underlying lung. However, treatment fields tend to be large and the planning process often requires splitting the fields, increasing the treatment time and monitor units (MU). In a dosimetric comparison of volumetric modulated arc therapy (VMAT) with static field IMPRINT for MPM after P/D⁹, it was shown that VMAT produces comparable dose distributions as static field IMRT with respect to target coverage and sparing of all critical organs. VMAT additionally reduced the MU and treatment time, thereby making it a more favorable choice for radiotherapy treatment planning and delivery for these patients. At our institution, VMAT has been used routinely since 2010 to plan and treat these cases with radiation. Although these techniques aim at maximizing target coverage while minimizing dose to critical organs, the predicted risk of radiation pneumonitis (RP) limits the prescription dose that can be chosen safely. In this article we analyze the dosimetric predictors of RP in patients treated at our institution with VMAT. Based on our experience, we assess our dosimetric planning constraints.

Materials and Methods

A total of 49 patients with pathologically proven MPM treated between December 2010 and October 2016 were evaluated for this study. Eligibility criteria included patients who underwent P/D and received adjuvant hemithoracic radiation therapy at our institution. All patients were treated by the same radiation oncologist. Of the 49 patients identified, 40 met these eligibility criteria and were included in the current analysis. Excluded patients underwent EPP (n=5), had incomplete surgical data from an outside institution (n=2), experienced progression of disease while on treatment (n=1) or were unable to tolerate the prescribed treatment (n=1).

Simulation and Target Delineation

Patients were immobilized in the supine position with a custom alpha-cradle mold and arms raised above their head. A computed-tomography (CT) scan with free-breathing was acquired for treatment planning. The clinical target volume (CTV) was defined as the entire

hemithoracic parietal and visceral pleura including the entire diaphragm and involved lymph node stations but without inclusion of the fissures. The CTV spanned the thoracic inlet superiorly (approximately the top of the T1 vertebral body) to the insertion of the diaphragm inferiorly (approximately the bottom of the L2 vertebral body). Laterally, the parietal pleura was covered along the ribs. Medially, the mediastinal pleura and the ipsilateral hilum were included. A planning target volume (PTV) was generated using a 4 to 5 mm internal margin and a 10-mm outer margin followed by modification to cover the entire thickness of the chest wall of the involved ipsilateral hemithorax where necessary.

Treatment planning and dosimetric parameters

Treatment planning utilized two partial arcs and 6 MV photons with VMAT. Details on the arc range and jaw settings for this field arrangement have been explained previously¹⁰. Constraints for the total lung and heart were similar to those used during planning non-small cell lung cancer (NSCLC) cases with conventional fractionation, while constraints for the kidney, liver, stomach, esophagus and bowel were similar to those used during planning abdominal tumors with conventional fractionation (Table 1). Dose constraints were classified either as limits or as guidelines. While guidelines could be violated at the discretion of the treating physician, limiting constraints could not be violated. The treatment planning system used was Eclipse (Varian Medical Systems, Palo Alto, CA) and the dose calculation algorithm was AAA (Analytical Anisotropic Algorithm). Example of a dose distribution has been shown in Figure 1. Dose volume histogram parameters recorded were absolute volume and percentage volume of the ipsilateral lung spared of 20 Gy, 30 Gy and 40 Gy, of the contralateral lung spared of 5 Gy and 10 Gy and of the total lung spared of 5 Gy, 10 Gy, 13 Gy, 20 Gy and 30 Gy. Mean dose to the total lung and total lung V20 Gy were also noted. Mean heart dose, heart V5 Gy, V10 Gy, V15 Gy, V30 Gy, V35 Gy, V40 Gy and V45 Gy as well as the absolute volume and percentage volume of the heart in the PTV were recorded.

Toxicity parameters

Common Terminology Criteria for Toxicity and Adverse Event Reporting (CTCAE) V 4.03 from the NCI for pulmonary toxicity were graded. Grade 3 radiation pneumonitis is defined as “severe symptoms; limiting self-care ADL; oxygen indicated.”¹¹. Patients who required oxygen supplementation were graded as grade 3, while those who were prescribed steroids were graded as grade 2. Patients were followed with physical exam weekly during treatment, 2-4 weeks following treatment and every 3-6 months thereafter. Further evaluation was performed by chest CT or contrast-enhanced CT for thrombus protocol as warranted.

Statistical methods

The Wilcoxon rank-sum test was used to test the significance of the difference between the median values of the dosimetric variables of patients who developed grade 3 or higher radiation pneumonitis (RP) versus those who did not. Significance of correlation between dosimetric variables and the development of grade 3 or higher RP was tested using the Spearman rank correlation method. For each variable showing significant correlation with the incidence of RP, the optimal threshold value that differentiated between the incidence of RP versus no RP was calculated using the receiver operating characteristic (ROC) curve¹². The area under the ROC curve (AUC) is a measure of the ability of the parameter to

correctly discriminate those with and without a condition, such as RP¹³. For each dosimetric parameter, the curve was calculated using the logistic regression model. All computation was done in MATLAB V9.1, R V3.4.0 and Statistical Analysis Software (SAS) V9.4. The AUC values for the different dosimetric variables were compared to see whether the difference in the ability to differentiate RP versus no RP was statistically significant using DeLong's test with Bonferroni correction.

Results

Patient and Treatment Characteristics

The median follow-up was 12.5 months (range, 3-38). Characteristics of the 40 evaluable patients are listed in Table 2. 26 patients were male (65%) and 14 female (35%). The median age at diagnosis was 66.5 years (range, 44-84). Asbestos exposure was recorded for 36 (90%) patients; 13 reported known asbestos exposure, 11 possible exposure, 9 denied exposure and 4 did not know if they had been exposed. 29 patients had epithelioid histology, 1 (3%) sarcomatoid, 9 (23%) mixed histology and one patient (3%) had pleomorphic/anaplastic histology. At diagnosis, 23% stage I disease, 33% stage II, 38% stage III, and 8% had stage IV disease.

Surgery

37 patients underwent pulmonary function testing prior to surgery. All patients underwent P/D and 1 patient who received their surgery at an outside institution underwent an additional partial lung resection. 28 patients (70%) were reported as R1 resection and 12 patients (30%) were reported as R2 resection.

Chemotherapy

28 patients (70%) had chemotherapy as part of their treatment. Eight received neoadjuvant, 6 adjuvant (before radiation), 10 adjuvant (after radiation) and 4 palliative following a recurrence.

Radiation

Treatment was delivered to a median dose of 4,500 cGy. Twenty-two patients (55%) received a total dose of 4,500 cGy. 37 patients (93%) were treated with total hemithoracic treatments (range, 3000 – 5,040 cGy). Of those, 3 patients received a cone down to a reduced volume; 2 received a total dose of 45 Gy and 1 a total dose of 54 Gy. Three patients (7%) received partial hemithoracic treatments to areas of residual disease or concern (range 3,960 – 5,400 cGy).

Toxicity

Seven patients (17.5%) experienced grade 2 or worse RP; four with grade 3 pneumonitis treated with prednisone and/or supplemental oxygen and one presumed fatal pneumonitis (grade 5). The median time to radiation pneumonitis was 2 months. The patient with grade 5 toxicity received 4,500 cGy to the right total hemithorax and was hospitalized during treatment for radiation induced pericarditis. Mild radiation pneumonitis was noted at two-

week follow up interval and steroids were prescribed. The patient was again hospitalized 4 months after treatment where chest X-ray showed complete right lung opacification with left sided pleural effusion. Although, there was a reported concern for pulmonary and peritoneal carcinomatosis, the patient was graded as a fatal toxicity, because he expired 4 months following the completion of treatment and pathologic recurrence was never confirmed.

Correlation of dosimetric parameters with radiation pneumonitis

Median values of the dosimetric parameters for patients that developed grade 3 RP versus those that did not (Table 3) revealed a statistically significant difference in the absolute and percentage volume of the ipsilateral lung spared of 20Gy and 30Gy but not 40Gy. No differences were seen in the dosimetric parameters for the contralateral lung, total lung, mean lung dose, mean heart dose or amount of heart overlapping the PTV.

The optimal threshold absolute volume to be spared of 20Gy and 30 Gy was computed to be 55cc ($p = 0.02$) and 200cc ($p = 0.04$) respectively. The statistical validation of these findings can be found in supplemental tables S1-S4 and figure S1.

Analysis of the incidence of radiation pneumonitis using the computed threshold values demonstrated an increased likelihood of radiation pneumonitis if the threshold absolute or percentage of volume of ipsilateral lung spared was not met (Figure 2). Of 11 patients who had less than 55cc of ipsilateral lung spared of 20Gy, 4 developed radiation pneumonitis (36.4%). In contrast, of the 29 patients who had at least 55cc of ipsilateral lung spared, only one developed RP (3.4%). The rates of radiation pneumonitis for those spared of less than or greater than 200 cc of ipsilateral lung were 50% and 3.4% respectively. Additionally, the patient with grade 5 RP had 0cc spared of 20Gy and 174 cc spared of 30Gy.

Discussion

Adjuvant radiation treatment with IMRT for mesothelioma following pleurectomy/decortication has previously been associated with a high rate (up to 46%) of grade 5 pneumonitis.¹⁴ More recently, reports have indicated decreased toxicity with this treatment. Shaikh et al reported a rate of 26% of grade 2 or greater radiation pneumonitis following IMRT.³ The rate of RP in the current study, using VMAT, was similar at 17.5%.

This retrospective study of 40 patients treated with VMAT following P/D demonstrates a correlation between volume of ipsilateral lung spared and the incidence of RP. Our analysis demonstrates that sparing 7% or 23% of ipsilateral lung of 20 Gy or 30 Gy respectively correlates with a reduced incidence of severe RP. Percentage of lung may be variable based on contouring and so absolute volume may be a more translatable parameter for plan evaluation. We have established that sparing of an absolute volume of 55cc or 200cc of ipsilateral lung of 20 Gy or 30 Gy respectively correlates with a reduced incidence of severe RP. To our knowledge, this is the first study to show such a correlation.

We did not find any correlation between RP and contralateral lung dose, in contrast to other reports.^{15,16} MD Anderson reported a correlation between contralateral V20 >7% and an increased risk of pulmonary-related death from their experience using IMRT for

mesothelioma after EPP.¹⁷ Others have recommended limiting contralateral lung V20 < 4-10% following EPP.^{14,18} In the current study, all patients received pleurectomy/decortication and planning protocols dictated limiting the contralateral lung as much as possible. It is possible that a correlation between RP and contralateral lung dose was not seen because the dose to the contralateral lung in all patients was too low to see a difference.

There is significant variability in the anatomy of the thorax and lung after pleurectomy/decortication for MPM. Many patients, due to “lung trapping” from the disease have a relatively small remaining ipsilateral lung or a short distance between the mediastinum and lateral chest wall. In these situations, the typical dose constraints of V20 and mean lung dose may be misleading since there isn’t much useful lung remaining to be spared and the dosimetric parameters may be encouraging. However, it is possible that the amount of lung spared in this study may be an indicator of how useful the “trapped lung” may be, and that contralateral lung dose may contribute less to toxicity outcomes in this setting.

Therefore, we attempted to identify a different approach to evaluating DVHs in order to minimize the risk of pneumonitis or chronic dyspnea. Although both sparing >55cc of 20Gy and >200 cc of 30 Gy were statistically significant, the authors find >200cc of ipsilateral lung spared of 30Gy a more clinically useful constraint, and have incorporated into our treatment planning process.

Our analysis did not find any dosimetric correlation to heart dose and RP. This is in contrast to a retrospective analysis by Yorke, et al. of 103 patients treated with IMPRINT, which showed a correlation between percentage volume of the heart receiving 41Gy and the highest dose encompassing 25% of the heart volume with the incidence of grade 3 RP¹⁶. As a result, the authors recommended dosimetric constraints of V_{40Gy} <35% to the left and V_{40Gy} <25% to the right sides of the heart. Average heart doses in our study, 18% to the left and 10.4% to the right, fall well below these proposed constraints, which may explain the lack of heart dose correlation seen in our cohort. However, both studies had similar rates of 3 RP; Yorke, et al. 13.6% versus 12.5% in our experience. Perhaps this provides further credence that the volume of ipsilateral lung spared of 20 or 30Gy, rather than the heart dose, may provide better reduction RP rates.

Conclusions

Total hemithoracic adjuvant radiation therapy following pleurectomy/decortication for malignant mesothelioma can be a challenging to plan due to the presence of the ipsilateral lung. We have established that sparing the ipsilateral lung at least 55cc of 20Gy and 200cc of 30Gy correlates with a reduced incidence of severe (grade 3) radiation pneumonitis. This parameter can be helpful in determining safe lung dose in the setting of varied patient anatomy after pleurectomy/decortication. This may provide a new perspective when planning the treatment volume to the ipsilateral lung. However, prospective studies are needed for validation of this proposed constraint.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Example of treatment plan in a) Coronal, b) Sagittal and c) Axial views.
The 95% isodose (yellow) line 'doughnut' shape outlines the volume receiving the treatment dose; sparing the lung within.

Figure 2:
Incidence of radiation pneumonitis compared by computed threshold values.

Table 1.

Summary of dosimetric criteria

Structure	Parameter	Objective
PTV	D95 (%)	94% *
	V95 (%)	94% *
	D05 (%)	120% *
Total Lung	Mean dose	20 Gy *
	V20 Gy	37% –40%
Contralateral Lung	Mean dose	8 Gy *
	V20 Gy	7% *
	V5 Gy	< 25%
Cord	max	50 Gy *
Heart	Mean (Gy)	30 Gy *
	V30 Gy	50% *
Ipsilateral Kidney	V18 Gy	33% (50% *)
Liver	Mean (Gy)	30Gy (31Gy *)
	V30 Gy	50% *
Stomach not PTV	Mean (Gy)	30 Gy *
Esophagus	Mean (Gy)	34 Gy *
Bowel	$D_{05\%}$	50 Gy *

Abbreviation: PTV, planning target volume.

* Used as limiting constraints. Others are used as guidelines.

Table 2.

Characteristics of the 40 evaluable study patients

Patient Characteristics	Value (%)
	n=40
Age at diagnosis	
Median	66.5
Range	44-84
Gender	
Male	26 (65)
Female	14 (35)
Histologic Subtype	
Epithelial	29 (73)
Sarcomatoid	1 (3)
Mixed	9 (23)
Pleomorphic/Anaplastic	1 (3)
Laterality	
Right	18 (45)
Left	22 (55)
Clinical Stage	
I	9 (23)
II	13 (33)
III	15 (38)
IV	3 (8)
Race	
White	32 (80)
Hispanic	6 (15)
Black	1 (3)
Asian	1 (3)

Table 3.

Dosimetric parameters (median values) for patients who did and did not develop grade 3 RP

Structure	Parameter	Grade 3 RP (n = 5)	Non-RP (n = 35)	p value
Ipsilateral	V(cc)<20Gy	1.5	97.7	<0.01 *
Lung	V(cc)<30Gy	174	276	0.01 *
	V(cc)<40Gy	447	552	NS
	V(%)<20Gy	0.2	11.8	<0.01 *
	V(%)<30Gy	17	30.2	0.01 *
	V(%)<40Gy	37.4	54	NS
Contralateral	V(cc)<5Gy	802.8	831	NS
Lung	V(cc)<10Gy	1314.9	1430	NS
	V(%)<5Gy	49.9	54.3	NS
	V(%)<10Gy	87.8	88.8	NS
Total Lung	V(cc)<5Gy	806.4	823	NS
	V(cc)<10Gy	1317.6	1434	NS
	V(cc)<13Gy	1443.3	1580	NS
	V(cc)<20Gy	1494	1701	NS
	V(cc)<30Gy	1633.7	1906.2	NS
	V(%)<5Gy	32.1	32.4	NS
	V(%)<10Gy	55.5	55.6	NS
	V(%)<13Gy	57	60.3	NS
	V(%)<20Gy	61	65.3	NS
	V(%)<30Gy	68	71.7	NS
	Mean lung dose (Gy) (MLD)	19.5	17.5	NS
	V20Gy (%)	39	34.8	NS
	V5Gy (%)	96	99.9	NS
	V10Gy (%)	72	81	NS
	V15Gy (%)	54.5	61.4	NS
Heart	V30Gy (%)	30.3	27.7	NS
	V35Gy (%)	22.4	21.2	NS
	V40Gy (%)	15.8	14	NS
	V45Gy (%)	10.1	8.8	NS
	Vol in PTV (cc)	40	24.9	NS
	Vol in PTV (%)	7.4	4.5	NS
	Mean heart dose (Gy) (MHD)	21.1	22.9	NS

* = statistically significant.

NS = non-significant.