Hemithoracic Radiotherapy After Extrapleural Pneumonectomy for Malignant Pleural Mesothelioma

A Dosimetric Comparison of Two Well-Described Techniques

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Introduction: Extrapleural pneumonectomy (EPP) with adjuvant radiotherapy may be used to treat malignant pleural mesothelioma. Radiation pneumonitis, felt to be related to contralateral lung radiation dose, may affect patient mortality in this setting. Two standard therapeutic approaches currently used to deliver adjuvant radiotherapy were compared in this study: intensity modulation radiation treatment (IMRT) with a planned dose of 45 Gray (Gy) and a modified electron-photon technique delivering 54 Gy.

Methods: Treatment plans of 10 mesothelioma patients who underwent EPP and hemithoracic IMRT to a total dose of 45 Gy were analyzed. Plans using a combination of opposed anterior posterior radiation fields and electron supplementation (electron-photon technique [EPT]) to a total dose of 54 Gy were then generated and compared with IMRT plans.

Results: Dosimetric comparison revealed a significant reduction in contralateral lung dose with EPT versus IMRT, even with increased prescription dose used with EPT plans. Median heart and contralateral kidney doses were also significantly reduced with EPT versus IMRT. Dose coverage of planning target volume and doses to spinal cord, liver, and ipsilateral kidney were similar with use of the two techniques.

Conclusions: Our data suggest that hemithoracic radiotherapy delivered after EPP using EPT may minimize dose to contralateral lung and other structures when compared with IMRT, without compromise of planning target volume coverage.

Key Words: Hemithoracic IMRT, Radiotherapy after extrapleural pneumonectomy, Radiotherapy in treatment of mesothelioma, Radiation pneumonitis.

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Malignant pleural mesothelioma is a rare, aggressive tumor that arises from the pleural lining of the lung. It is associated with median survival rates of 4 to 12 months,[1] and death is nearly always due to local progression, with hematogenous spread usually occurring only very late in the disease course. Extrapleural pneumonectomy (EPP) is an aggressive surgical approach used by some centers as primary treatment for malignant pleural mesothelioma (MPM) but has not been demonstrated to increase overall survival (OS) when used alone.[2–4] The addition of radiation treatment (RT) and chemotherapy to EPP has potential to provide improvement in OS for patients with MPM; however, even after trimodality treatment, the ipsilateral hemithorax remains the most common site of first failure.[5] Additionally, local factors such as close or positive margins after EPP have been shown to impact survival.[6] For these reasons, attention to improved local control is particularly important.

Many centers make use of hemithoracic RT after EPP in attempt to improve local control rates, delivering RT through several described techniques, including intensity-modulated radiotherapy (IMRT), conventional use of photon and electron beams, and combinations of these.[7–10] Although in vitro work has demonstrated MPM cells to be radiosensitive[11] and higher RT doses have been demonstrated to improve local control rates,[12,13] RT dosing and delivery are complicated by the proximity of numerous vital organs and structures, including the contralateral lung, heart, kidneys, spinal cord, esophagus, and liver, to the regions at risk for residual disease. Recently, significant morbidity and mortality rates have been reported with use of IMRT after EPP, including a nearly 50% rate of fatal pneumonitis in one cohort of patients.[14] Contralateral lung dosing parameters, including volume of lung receiving 5 Gray (Gy) (V5), volume of lung receiving 20 Gy (V20), and mean contralateral lung dose have been demonstrated to be important factors in the development of pneumonitis and pulmonary-related death.[14,15]

In light of demonstrated local recurrence risk, which is likely affected by achievable RT dose after EPP, as well as morbidity and mortality risk associated with delivery of this RT, maximizing dose to structures at risk for recurrence while minimizing dose to contralateral lung and other organs would be expected to improve OS for patients with MPM.

This dosimetric study was undertaken to compare two different treatment delivery techniques that are currently being used to deliver postoperative hemithoracic RT after EPP for patients with MPM: hemithoracic IMRT and use of opposed anterior-posterior/posterior-anterior (AP-PA) photon fields with electron supplementation (electron-photon technique [EPT]).

METHODS

The purpose of this study was to compare two different treatment techniques that are currently being used to deliver hemithoracic RT after EPP. The EPT technique uses a combination of photon beam arrangements with matched electron beams to deliver a total prescription dose of 54 Gy in 1.8 Gy per fraction.[10] The IMRT technique used during the study period at our institution used multiple intensity modulated photon beams to deliver 45 Gy to the planning target volume (PTV).

Treatment plans were reviewed for 10 patients diagnosed with MPM and treated with EPP followed by hemithoracic IMRT at the Hospital of the University of Pennsylvania between 2003 and 2006. Five patients were treated for left-sided tumors and five for right-sided tumors; of these, three were women and seven were men. EPP consisted of resection of the entire ipsilateral lung and parietal pleura, ipsilateral pericardium, and ipsilateral hemidiaphragm with subsequent reconstruction of the hemidiaphragm with Gore-Tex, so that abdominal contents were maintained within the abdominal cavity. Resection margins were marked with radioopaque surgical clips. After postoperative recovery, patients underwent treatment planning computed tomographic simulation without intravenous contrast. Patients were positioned supine with arms above the head, and axial helical computed tomography images of 3 mm thickness were acquired. Wires were placed on scars and drain sites to facilitate radiation planning. In a multidisciplinary setting involving both the radiation oncologist and the thoracic surgeon, the PTV was delineated, encompassing the ipsilateral chest cavity and wall, as well as the adjacent abdomen, including the diaphragmatic insertion, crura, and pleural reflection (Figure 1). Surgical clips were included in the PTV and were used to facilitate PTV volume delineation. Skin was included in the PTV in the region of surgical scars, including drain sites, and 1 cm bolus was applied to scar regions to facilitate adequate dosing. PTV extended from the level of the thoracic inlet through the midabdomen or lowest level of diaphragmatic insertion as defined by surgical clip placement. Organs at risk (OAR), including contralateral lung, esophagus, heart, liver, spinal cord, and bilateral kidneys, were also delineated. The PTV was prescribed to receive 45 Gy in 1.8 Gy fractions delivered daily. Mean contralateral lung dose was constrained to be <9 Gy, with contralateral lung V5 and V20 (volume receiving 5 and 20 Gy, respectively) constrained to 60% and 20%, respectively. Dose and volume constraints consistent with standard allowances were imposed on other OAR (Table 1).

Treatment plans were generated using Oncentra Treatment Planning software, and treatment was delivered by Siemens linear accelerators using 6 MV photon beams. Several optimization iterations were required for each patient; the plan delivering the optimal PTV dose while best meeting the described organ constraints was ultimately chosen for each patient. Reduction of contralateral lung dose was given high priority during IMRT optimization with regard to beam angles; however, beam angles were not standardized due to anatomic variation requiring different beam arrangements to optimize dose delivery for each patient. Seven to nine beams were used depending on plan optimization (Figure 2). Of note, the first four patients in our study had been treated in an era when more relaxed organ constraints were used; these four cases were replanned using the above constraints for the purposes of this study. Two of 10 patients required a split-field IMRT single-isocenter technique with matched beams because the treatment length exceeded 40 cm in the craniocaudal axis, the maximal aperture available on our linear accelerators.

The same 10 cases were replanned using a EPT technique described previously[10] (Figure 3). Field borders for opposing AP-PA photon fields were placed at the upper border of T1 superiorly, the lower border of L2 inferiorly, the contralateral edge of the vertebral body medially, and flashing skin laterally. It should be noted that, in practice, no PTV is defined in the EPT technique; in this study, the dose to the PTV as defined for IMRT planning described earlier was assessed. A custom Cerrobend abdominal block was placed in each field to shield the stomach/liver and ipsilateral kidney from the outset of treatment. The total prescribed dose was 54

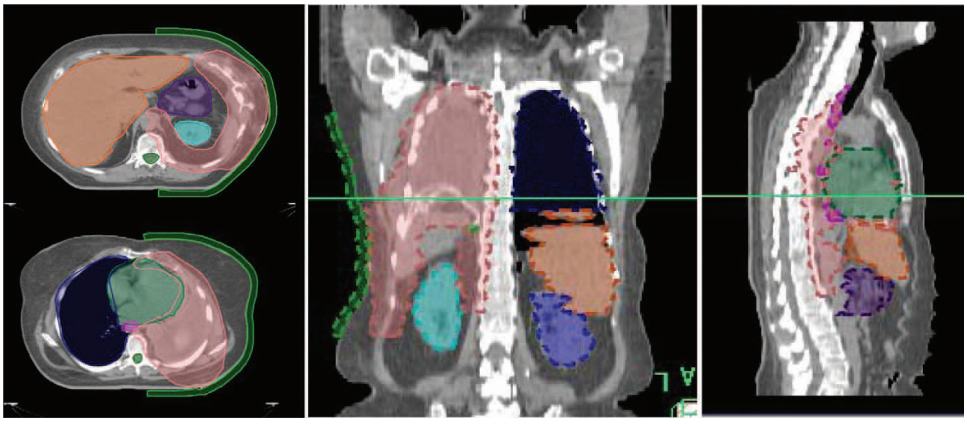

FIGURE 1. Planning target volume (PTV) used for intensity-modulated radiotherapy (IMRT) planning for hemithoracic radiotherapy after extrapleural pneumonectomy. PTV included the entire chest cavity and chest wall and adjacent abdomen from the level of the thoracic inlet to the diaphragmatic insertion as delineated by surgical clips. Treatment volumes were extended to encompass skin in regions of scar and drain sites.

TABLE 1. Constraints Applied for Organs at Risk During Intensity-Modulated Radiotherapy (IMRT) Planning

Organ at Risk	Constraint
Spinal cord	Maximum dose 50 Gy
	90% <45 Gy
Esophagus	Maximum dose 60 Gy
	70% <55 Gy
Contralateral lung	Mean dose <9 Gy
	V5* <60 Gy
	V20* <20 Gy
Heart	Maximum dose 60 Gy
	70% <45 Gy
	80% <50 Gy
Liver	50% <30 Gy
Kidney (each)	50% <18 Gy

*V5 and V20 refer to volume of lung receiving 5 and 20 Gy, respectively.
Gy, Gray.

Gy in 1.8 Gy fractions. This dose was chosen for this study as it is the dose that has been previously published and is used in current clinical practice.[10] The photon beam portion of the treatment was prescribed to midplane. The areas of the abdominal blocks were supplemented with *en face* electron fields. The daily electron dose was 1.53 Gy prescribed to the 90% isodose line, to a depth encompassing the chest wall; this dose was based on a previously published calculation of 15% scatter contribution under the blocks from the photon fields.[10] During treatment of the left hemithorax only, an anterior block was placed over the heart at a cumulative dose of 19.8 Gy, and the blocked area subsequently delivered 1.53 Gy daily through an *en face* electron field. At a dose of 41.4 Gy, anterior and posterior blocks were placed over the spinal cord.

Dose volume histograms and isodose lines were compared for the two techniques in the case of each patient. Dose and volume parameters for PTV, contralateral lung, heart, liver, spinal cord, and ipsilateral and contralateral kidneys were determined for each case. Values for all 10 patients were compared using a two-tailed Student's t test.[16] All values were considered significant if $p < 0.05$. Error bars were determined based on standard error of the mean.

RESULTS

Both techniques seemed to allow for similar and adequate PTV coverage: the average PTV volume receiving 95% of the prescribed dose was not significantly different between the two techniques (80% for EPT versus 81% for IMRT, $p = 0.8$). As described earlier, the PTV was prescribed to receive a total dose of 54 Gy in the EPT plans versus 45 Gy which was prescribed in the IMRT plans; this discrepancy was maintained to compare the technique with which our patients were actually treated with a different technique as described in the literature. Although prescribed doses were different for the two techniques, the percent of the prescribed dose received by 90%, 80%, 70%, and 50% of the PTV did not differ significantly between the two techniques (Figure 4). Absolute doses, of course, did differ: average median dose to PTV was 58.6 Gy (range, 55.5–61.8 Gy) with the EPT technique versus 48.2 Gy (range, 44.3 Gy–53.3 Gy) with IMRT ($p < 0.0001$). Similarly, average doses to 90%, 80%, and 70% of the PTV were 46.8 Gy (range, 40.3–56.8 Gy), 53.0 Gy (range, 47.7–56.4 Gy), and 56.4 Gy (range, 52.1–60.0 Gy) with EPT versus 41.8 Gy (range, 25.9–50.2), 43.6 Gy (range,

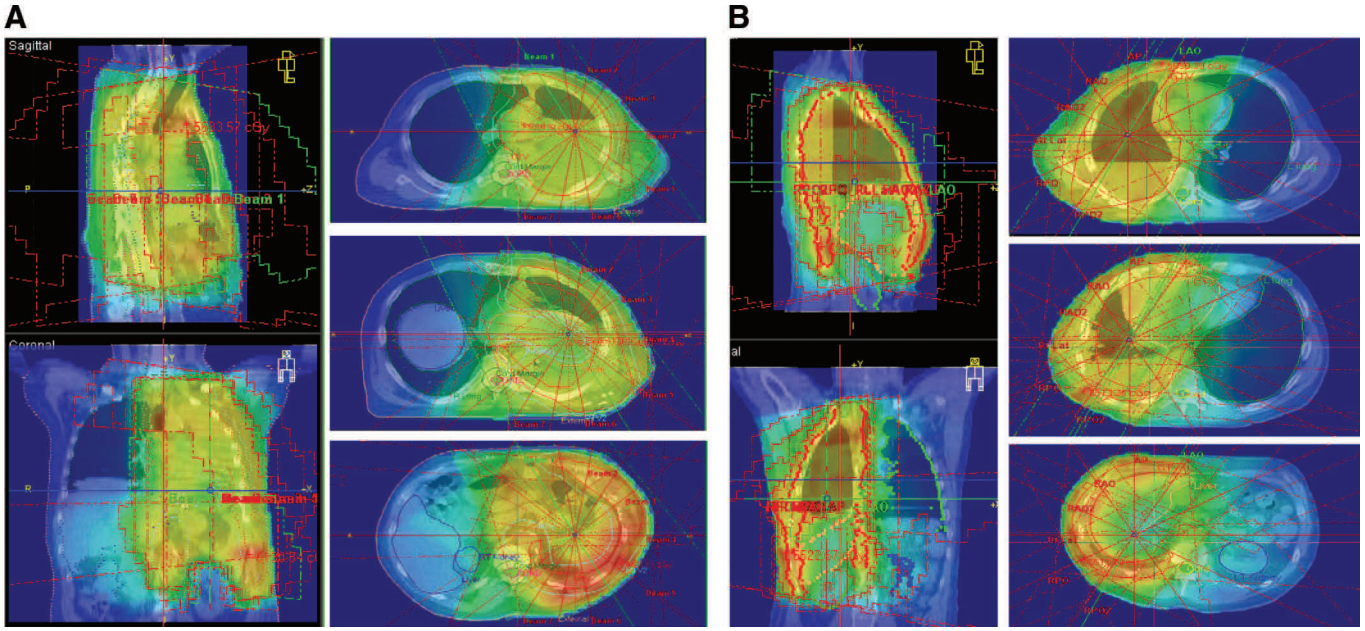

FIGURE 2. Sample beam arrangement and dose distribution for delivery of intensity-modulated radiation therapy (IMRT) to the (*A*) left and (*B*) right hemithorax after extrapleural pneumonectomy in treatment of malignant mesothelioma. Treatment consisted of delivery of 45 Gray (Gy) in daily fractions of 1.8 Gy to the planning target volume (PTV).

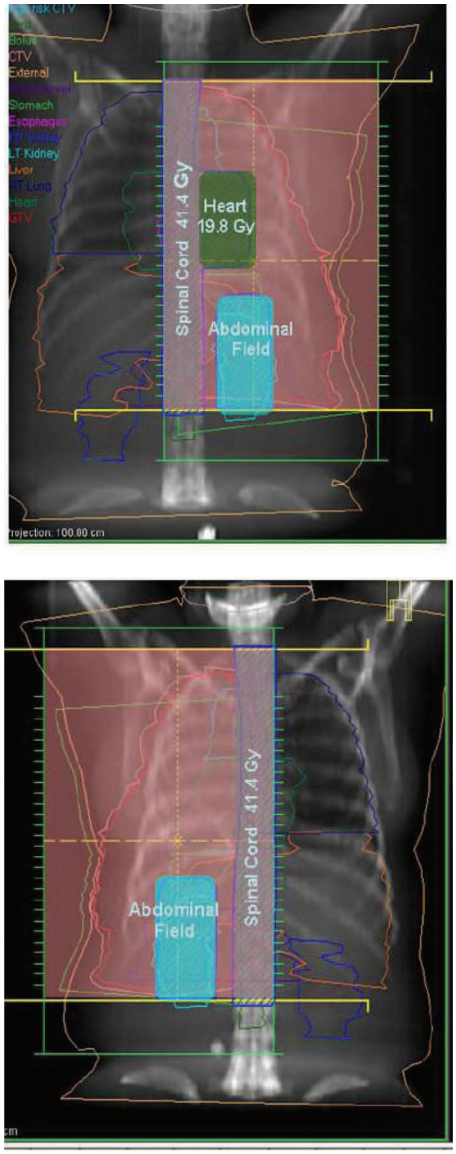

FIGURE 3. Field and block arrangements employed with use of combined electron-photon technique for hemithoracic radiotherapy after extrapleural pneumonectomy. The total prescribed dose from the anterior-posterior (AP-PA) photon fields and supplemental electron fields was 54 Gray (Gy) in 1.8 Gy fractions. At the initiation of treatment, blocks were placed in the region of the abdomen. During treatment of the left hemithorax, an anterior block was placed over the heart at 19.8 Gy. Blocked areas were subsequently delivered 1.53 Gy daily through an *en face* electron field. At 41.4 Gy, anterior and posterior blocks were placed over the spinal cord.

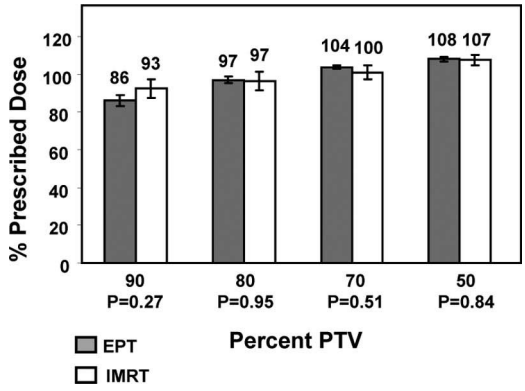

FIGURE 4. Average percent of prescribed dose to planning target volume with electron-photon technique (EPT) versus intensity-modulated radiotherapy (IMRT) during hemithoracic radiotherapy after extrapleural pneumonectomy.

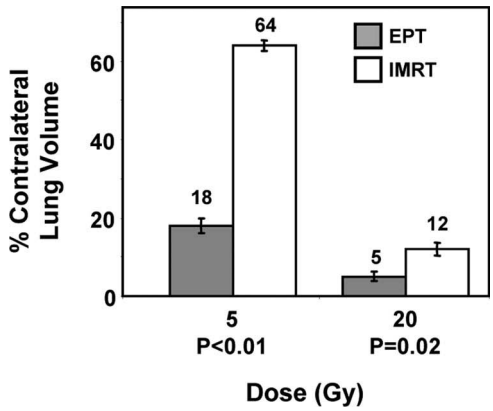

FIGURE 5. Average contralateral lung volume receiving dose of 5 Gray (Gy) and 20 Gy with electron-photon technique (EPT), prescribed to 54 Gy, versus intensity-modulated radiotherapy (IMRT), prescribed to 45 Gy, during hemithoracic radiotherapy after extrapleural pneumonectomy.

28.5–50.4 Gy), and 45.4 Gy (range, 35.9–52.0 Gy) with IMRT, respectively; as expected, differences in absolute PTV dose were statistically significant ($p = 0.03$, $p = 0.001$, and $p < 0.0001$ for average dose to 90%, 80%, and 70%, respectively). Significantly more inhomogeneity seemed to be present with use of the EPT technique, with a significantly higher volume receiving 105% of the planned dose with EPT versus IMRT (mean 56% [range, 31–73%] versus mean 36% [range, 18–69%] with EPT versus IMRT, respectively, $p = 0.01$).

The average contralateral lung V5 was 18% (range, 3–36%) with EPT versus 64% (range, 49–69%) with IMRT ($p < 0.0001$), and average contralateral lung V20 was 5% (range, 0.2–19%) versus 12% (range, 3–21%) with EPT versus IMRT, respectively ($p = 0.02$) (Figure 5). The average mean contralateral lung dose was 4.2 Gy with EPT (range, 2.2–7.3 Gy) versus 9.1 Gy with IMRT (range, 7.6–14.1 Gy) ($p = 0.001$) (Figure 6).

The average median dose to the contralateral kidney was 1.9 Gy with EPT (range, 1.4–3.1 Gy) versus 8.2 Gy (range, 4.1–11.9) with IMRT ($p < 0.0001$) (Figure 6). The average median dose to the ipsilateral kidney did not differ significantly between the two techniques (16.1 Gy, range 4.9–29.9 Gy, versus 21.3 Gy, range 6.6–43.9 Gy with EPT versus IMRT, respectively, $p = 0.37$) (Figure 6). Average maximum spinal cord dose did not differ significantly be-

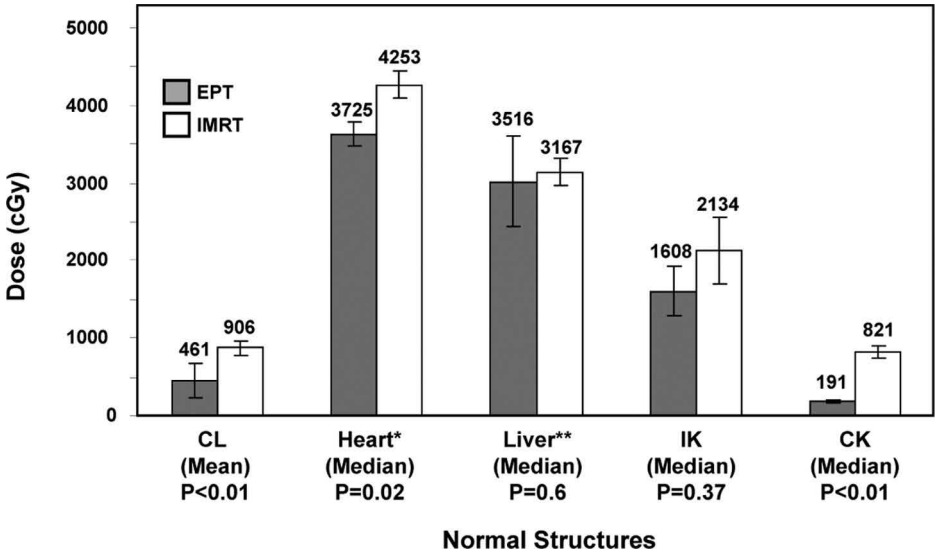

FIGURE 6. Dose to organs at risk with electron-photon technique (EPT) versus intensity-modulated radiotherapy (IMRT) for hemithoracic radiotherapy after extrapleural pneumonectomy. *Median heart dose for only patients receiving left-sided treatment ($n = 5$). **Median liver dose for only patients receiving right-sided treatment ($n = 5$). CL, contralateral lung; IK, ipsilateral kidney; and CK, contralateral kidney.

tween the two techniques (36.7 Gy with EPT versus 40.9 Gy with IMRT, $p = 0.17$).

For the five patients treated for left-sided tumors, average median dose to the heart was 37.2 Gy (range, 31.7–41.0 Gy) with EPT versus 42.5 Gy (range, 40.8–45.1 Gy) with IMRT ($p = 0.02$) (Figure 6). Average median dose to liver for the five patients treated for right-sided tumors was 35.2 Gy (range, 13.8–55.1 Gy) with EPT versus 31.7 Gy (range, 28.6–36.6 Gy) with IMRT ($p = 0.6$) (Figure 6).

DISCUSSION

This dosimetric analysis was performed to evaluate the potential for two different techniques to deliver tumoricidal radiation dose to the hemithorax after EPP in patients with MPM while reducing risk of life-threatening radiation-related complications resulting from increased dose to nearby vital organs. Our data suggest that both of the techniques evaluated, IMRT and EPT, likely allow adequate dosing of the PTV; however, doses to contralateral lung, contralateral kidney, and heart seem to be significantly reduced with the EPT technique when compared with IMRT, whereas dose to spinal cord, ipsilateral kidney, and liver remain similar.

MPM is a rare disease associated with a dismal prognosis. EPP is an aggressive surgical approach used by some centers as primary treatment for MPM that involves *en bloc* resection of the ipsilateral lung, pleura, hemidiaphragm, and pericardium and associated pericardial fat. The diffuse nature of MPM places the ipsilateral chest wall, diaphragmatic insertion, pericardium, mediastinum, and bronchial stump at risk for disease recurrence following this procedure. Likely as a result, EPP alone has not been shown to improve survival rates.[2–4] Death from MPM usually results from local progression, and the ipsilateral hemithorax remains the most common site of first failure after surgical resection with EPP. This risk is increased particularly for patients with close or positive surgical margins after EPP. For this reason, efforts by several centers have focused on developing RT techniques that allow delivery of tumoricidal radiation dose to address microscopic disease foci that remain after EPP. Recently, significant morbidity and mortality have been described due to radiation pneumonitis after hemithoracic RT, and the risk of severe pulmonary toxicity seems to be related to dose and volume parameters of the contralateral lung. Several other vital organs also remain at risk for severe, potentially life threatening, toxicity that may result from hemithoracic RT.

Our analysis demonstrates similar PTV coverage using either the EPT or the IMRT techniques. Although the prescribed PTV dose differed in this study for the two techniques used, the PTV volume receiving 95% of the prescribed dose, as well as the percent of the prescribed dose received by 90%, 80%, 70%, and 50% of the PTV, did not differ significantly between the two techniques. Several groups have published results with IMRT PTV prescription between 50 and 54 Gy[8,17,18] and have demonstrated that this dose prescription is possible with an IMRT technique and similar OAR constraints to those used in this study. Because there has historically been no PTV defined in the EPT technique, when it has been used clinically, this report represents the first to quantify the true dose delivered to the region of the hemithorax at greatest risk for local failure as defined by the PTV using EPT, and PTV coverage with EPT seems to be adequate.

Given that either technique may likely be used to deliver adequate PTV coverage, we must turn our attention to dose to the many OAR for damage from hemithoracic radiotherapy. Our study demonstrates that the mean contralateral lung dose, as well as the contralateral lung V5, and V20 can be significantly reduced with use of the EPT technique, and this finding has been documented by other groups.[18] Efforts to reduce contralateral lung dose using increasingly restricted IMRT techniques have resulted in decreases in V5, V20, and mean lung dose, but these values, most notably the V5, remain higher with IMRT than those demonstrated here and by other groups with use of the EPT technique.[17] Although the clinical impact of these differences remain uncertain, the V5, V20, and mean lung dose have been shown by several groups to contribute to risk of potentially fatal lung toxicity

and should be minimized as much as possible. After EPP, because no lung remains in the ipsilateral hemithorax, dose deposited in this region does not contribute to pneumonitis risk; rather, pushing dose into the ipsilateral hemithorax to minimize or eliminate dose to contralateral lung should in turn minimize or eliminate the risk of radiation-induced pneumonitis. This stands in contrast to treatment of patients who have not undergone EPP but instead more limited surgery such as pleurectomy/decortication. In these instances, when the ipsilateral lung remains present within the hemithorax, delivering dose to the underlying lung could potentially cause pneumonitis and IMRT offers clear benefit for delivering dose to the "rind" of the chest wall while minimizing dose to the chest cavity where lung tissue remains.

Our data also demonstrate significantly decreased cardiac dose with EPT versus IMRT in the patients treated for left-sided tumors. Although the clinical impact of reducing cardiac radiation dose in patients with mesothelioma has not been studied to our knowledge, increased cardiac morbidity and mortality attributable to radiation exposure has certainly been demonstrated in other disease sites.[19–21] Perhaps most importantly, decreasing cardiac dose during RT to the mediastinum has recently been demonstrated to reduce the risk of acute cardiac toxicity[21] and late cardiac effects. In patients with MPM, who have already undergone major surgical procedure and difficult RT, acute effects such as pericardial effusion may significantly detract from quality of life, and prevention or risk reduction seems particularly important. For this reason, reduction of cardiac dose will undoubtedly be in the best interests of our patients, and our data demonstrate lower cardiac dosing with EPT over IMRT.

In addition, significant reduction in contralateral kidney dose with EPT versus IMRT is evident and potentially clinically important. Although impact of renal radiation dose in treatment of mesothelioma has not been specifically studied, data in other disease sites demonstrate a relationship between total dose and incidence of late renal toxicity.[22] Contralateral kidney dose may be particularly important in the setting of mesothelioma, when radiation to the hemithorax may render the ipsilateral kidney unavoidably damaged. Furthermore, patients with MPM may receive any number of nephrotoxic drugs during the course of diagnosis, surgical treatment, and adjuvant treatment, including contrast dye, antibiotics, antifungals, and platinum-containing chemotherapeutics. All these factors underscore the importance of minimizing radiation dose to the contralateral kidney; our data demonstrate that this may be possible with use of EPT, when compared with IMRT.

Within our study, reduction of radiation dose to the contralateral lung, heart, and contralateral kidney seems to be possible with use of an EPT technique versus IMRT, even when EPT plans are prescribed to a higher dose than IMRT plans. These benefits seem to be feasible with neither reduction of PTV coverage nor increase in dose to other vital organs including liver, ipsilateral kidney, and spinal cord. Of course, the potential for further optimization with varied beam arrangements using IMRT may allow for decreased cardiac, contralateral lung, and contralateral kidney dose,[17] and further study of IMRT technique for MPM after EPP could certainly equalize this factor between IMRT and EPT. In addition, IMRT techniques may allow for simultaneous "boosting" or delivery of higher radiation dose to regions at particular risk for local failure after EPP (e.g., positive surgical margins), and this may contribute to improved local control. However, even in this setting, use of an EPT technique in combination with IMRT to deliver higher doses to at-risk regions may allow reduction of dose to the contralateral lung and other organs without sacrifice of PTV coverage.

Our study is limited by its very nature as a dosimetric analysis, in that clinical outcomes are not available from this data. Additionally, as described earlier, PTV dosing was different between the two techniques described. Our analysis was undertaken despite this difference in dosing to preserve the integrity of IMRT plans used for patient treatment and to compare them accurately to a previously described technique for EPT treatment. Finally, concerns regarding potential increased risk of set-up error with the EPT technique compared with IMRT are certainly valid and are not addressed in this study. The EPT technique is quite complicated to execute and use may increase risk of over and/or underdosing in regions of photon/electron match; these issues are evidenced in this study by the increased inhomogeneity and higher volumes of overdosing observed with the EPT technique. The complex nature of the EPT technique when compared with IMRT may well offset some of the potential benefit that it might provide. A clinical comparison in the form of a randomized, controlled, clinical trial would address these issues; however, given the significant differences in the two techniques, compounded by the relative rarity of MPM, such a trial is unlikely to be performed.

As radiotherapy techniques continue to evolve, our ability to treat large regions of tissue with improved conformality will undoubtedly improve. However, as we approach new technologies, the potential benefits of performing hemithoracic RT with an AP-PA technique should be kept in mind. This may prove to be particularly important as the potential use of proton beam therapy becomes available. For patients who have undergone EPP, protection, and in turn minimal RT exposure of the contralateral lung is of paramount importance. The use of an AP-PA technique may allow relative sparing of the contralateral lung and other structures when compared with other techniques. Potentially, use of proton beams could prevent the need for blocking of normal structures with this technique, eliminating the inherent risks of set-up error and under and overdosing in regions of matching photon and electron fields. The particulate nature of protons used for RT should allow even further reduction in cardiac, kidney, and liver dose as well.

Several different techniques exist for delivery of hemithoracic RT after EPP in patients with MPM. This dosimetric study demonstrates a decrease in dose to several OAR, particularly the contralateral lung, without sacrifice of PTV coverage, with an EPT technique over an IMRT technique. This improvement in dose distribution to vital organs would be expected to reduce morbidity and mortality associated with hemithoracic RT and to potentially improve out-

comes for patients with mesothelioma. Furthermore, this technique may be used with newer technologies, such as proton beams, as availability becomes more widespread.

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