Patterns of Local and Nodal Failure in Malignant Pleural Mesothelioma After Extrapleural Pneumonectomy and Photon-Electron Radiotherapy

Vishal Gupta, MD,* Lee M. Krug, MD,† Benjamin Laser, MD,* Kiran Hudka, CMD,‡ Raja Flores, MD,§ Valerie W. Rusch, MD,§ and Kenneth E. Rosenzweig, MD*

Introduction: Multimodality therapy including extrapleural pneumonectomy (EPP), chemotherapy, and radiotherapy (RT) is often recommended for fit patients with early stage malignant pleural mesothelioma. Planning RT after an EPP is difficult due to the large target area, the high doses required to prevent recurrence, and the proximity of critical structures. We studied patterns of local and nodal recurrence in patients treated at our institution with EPP and RT, and whether advanced treatment planning techniques, such as intensity modulated radiotherapy (IMRT), could have been of potential benefit.

Methods: From 1993 to 2008, 86 patients with malignant pleural mesothelioma underwent EPP followed by hemithoracic RT (median dose: 54 Gy). The RT technique included a combination of photons and electrons to maximize dose to the target, whereas minimizing dose to normal tissues. After treatment, patients were followed with serial imaging and patterns of local and nodal failure were studied.

Results: Median follow-up time for 78 analyzed patients was 17 months. Eight percent were in stage I, 35% stage II, 55% stage III, and 2% stage IV. Ten percent of all patients developed late grade 3 pulmonary toxicity and no patient died of RT. Fifteen patients failed in local and/or nodal sites and did not have a distant component to their failure pattern. Of these 15 patients, 10 failed in regions of dose inhomogeneity and could have possibly benefited from IMRT.

Conclusions: The photon-electron technique was tolerable, but IMRT may provide better target coverage in some patients. IMRT’s advantages must be balanced against the increased risk of fatal pulmonary toxicity.

Key Words: Mesothelioma, Radiation therapy, Extrapleural pneumonectomy, Patterns of failure, Intensity modulated radiation therapy.

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Malignant pleural mesothelioma (MPM) affects nearly 3000 Americans annually and remains a therapeutic challenge. Most patients present with disease confined to the ipsilateral hemithorax, and as a result, surgical resection has historically been a mainstay of treatment. The debate regarding the ideal surgical procedure lingers, but generally the more aggressive extrapleural pneumonectomy (EPP) has been felt to yield a more complete resection than pleurectomy/decortication, which is typically reserved for either stage IA or palliative disease.1 With either of these techniques, however, residual disease typically remains. Aggressive multimodality therapy attempts to control local, regional, and distant disease. Adjuvant chemotherapy and radiotherapy (RT) are usually recommended to improve survival. Trimi- dality therapy combining EPP with chemotherapy and RT has resulted in median survival rates of 19 to 29 months.2,3

Planning RT for MPM is difficult due to the large irregularly shaped area at risk, the high doses required to prevent local recurrence, and the proximity of critical structures such as the spinal cord, liver, heart, kidney, and contralateral lung. The optimal RT technique is a subject of controversy. The technique at Memorial Sloan-Kettering Cancer Center (MSKCC), which has been previously described,4,5 uses a combination of photons and electrons. With this technique, photons treat most of the hemithoracic field, but blocks are needed to spare critical structures. Electron beams are used to supplement the photon-blocked regions. Electrons treat the superficial tissues and spare the deeper critical organs. Although this technique respects the tolerance doses for organs at risk, it may potentially underdose regions deep to the electron field. For example, the paraspinal area and costophrenic sulcus are regions that are blocked from the photon beams and treated superficially with electrons to spare the spinal cord and abdomen yet are also areas of concern for local failure. These regions of dose inhomogeneity may have a higher likelihood for local recurrence.

Alternatively, other institutions have used intensity modulated radiotherapy (IMRT) to overcome the difficulties of treating such a complex target.6–9 IMRT may result in better dose distributions by delivering higher doses to the target while sparing critical tissues.10 The dose to the contralateral lung is a major drawback to IMRT for thoracic malignancies. In fact, Allen et al.8 reported that six of 13
patients treated with EPP, IMRT, and chemotherapy for MPM died of contralateral pneumonitis. This is an unacceptable rate of pulmonary toxicity and argues against the use of IMRT in MPM.

Thus, the best RT technique for post-EPP patients is still unclear. To help determine which technique is most appropriate, we studied the patterns of local and nodal recurrence in patients treated at our institution with EPP and the photon-electron combination technique. If tumors were found to recur in regions of dose inhomogeneity (i.e., deep to the electron field) then IMRT may prove to be more appropriate.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board at MSKCC. We retrospectively reviewed MPM cases treated with EPP followed by photon-electron RT. EPP entailed en bloc resection of the entire pleura, lung, diaphragm, and pericardium, if necessary. The diaphragm was reconstructed to prevent herniation of the abdominal contents into the thorax and to facilitate postoperative RT.

The RT technique has been previously described in detail. Briefly, radiation to the ipsilateral hemithorax began 3 to 6 weeks after EPP and was prescribed to 45 to 54 Gy in 1.8 Gy fractions. The typical field borders were the top of T1 superiorly, the bottom of L2 inferiorly, and the skin laterally. The medial border was at the contralateral edge of the vertebral bodies if there was no mediastinal lymph node involvement and 1.5 to 2.0 cm beyond the vertebral bodies if there was mediastinal lymph node involvement. Skin bolus to prevent scar recurrence was typically not used.

An abdominal block was placed at the start of treatment to shield the liver or stomach from photon irradiation. For left-sided tumors, a heart block was placed at 19.8 Gy. The blocked abdominal and cardiac regions were treated with electron irradiation (1.53 Gy daily). After 41.4 Gy, the medial field border was moved to the ipsilateral edge of the vertebral bodies to block the spinal cord; the superior, inferior, and lateral field borders did not change.

For further analysis of the failures in our patient population, a clinical target volume (CTV) and planning target volume were identified retrospectively. The CTV included the ipsilateral chest wall including ribs and intercostal muscles. The planning target volume was a 1 to 2 cm expansion around the CTV. Although these target volumes were identified on the computed tomography (CT) simulation scan, the field borders were typically set according to the anatomic landmarks specified above. Spinal cord dose was limited to <45 Gy.

Figure 1A shows an axial slice of the isodose distribution of the photon-electron technique for a patient with right-sided MPM. Patients were excluded if they had IMRT, brachytherapy, or intraoperative RT.

After completing therapy, all patients underwent close surveillance with serial imaging (CT and/or positron emission tomography scans) approximately every 3 months. Local failure was defined as recurrent disease noted on imaging in the ipsilateral hemithorax. Nodal failures included recurrent disease in mediastinal lymph nodes. Hematogenous metastases and disease in the contralateral hemithorax or abdominal peritoneum were considered distant failures.

The CT and/or positron emission tomography images of patients with local failures were reviewed in detail to identify the specific location(s) of failure. These sites of failure were then correlated to the radiation field to assess their relationship to the photon blocks/electron fields. The goal was to analyze the patterns of local failure and determine whether IMRT could potentially have provided better target coverage and improved local and nodal control. This study includes patients included in previous reports from MSKCC and provides an update of our experience on MPM. Only those patients who underwent RT at our institution with appropriate follow-up are included in this analysis.

RESULTS

From 1993 to 2008, 86 patients underwent EPP followed by photon-electron RT for MPM at MSKCC. Eight of the 86 patients terminated RT early because of progressive disease during RT (six patients) or extreme nausea/dehydration (two patients) and were excluded from this study. Seventy-eight patients received a median dose of 54 Gy (range, 45–54 Gy) and 30 (38%) of these received preoperative chemotherapy as well. Median follow-up time was 17 months for all patients and 30 months for survivors. Demographic and staging information is listed in Table 1. RT was tolerable with appropriate medical support, with the exception of the two patients who stopped RT early due to dehydration. Eight of the 78 patients (10%) who completed RT developed late grade 3 pulmonary toxicity and no patient died of RT (grade 5).

The failure pattern for all 78 patients is reported in Table 2. Of the 78 patients who completed EPP and hemithoracic RT, 43 (55%) failed distantly, 26 without and 17 with local and/or nodal recurrence. These patients were unlikely to benefit from improved RT techniques. Twenty patients were without evidence of disease at their last follow-up. The fifteen remaining patients (19% of the series, 43% of the 35 patients without distant recurrence) developed local and/or nodal failures (without distant failures) and are the focus of this study.

Table 3 details the specific sites of the 15 patients who had only local and/or nodal failures. Twelve patients (15% of all 78 patients) failed only in local sites, two patients (3%) failed in local and nodal sites only, and one (1%) failed in nodal sites only. Only one patient had a scar recurrence in the lateral chest wall despite not using bolus during RT routinely. After identifying patients with local and nodal failures, their follow-up images were thoroughly reviewed to determine the exact site(s) of failure, which were then correlated with the RT field. An example is provided in Figure 1. Figure 1A demonstrates the dose distribution with the photon-electron technique. Tumor recurrence in the posterior chest wall is seen in Figure 1A, which corresponds to the heterogeneous dose distribution in Figure 1A. Because of the retrospective nature of this analysis, it is impossible to estimate the exact dose to these regions or the effect of variations in radiation therapy technique among different treating physicians. Figure 1C demonstrates a potential improvement in target coverage.

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in the area of local recurrence using a proposed seven-field IMRT plan.

Fifteen patients had local and/or nodal failures (i.e., did not fail distantly). Ten of these 15 patients had local or nodal recurrences in regions of high dose inhomogeneity and could have possibly benefited from IMRT. Five patients failed in one or more sites that were all in high dose, homogeneous areas, and it is not likely that IMRT would have offered an advantage over the photon-electron technique. Of these 15 patients, one received 45 Gy, four received 50.4 Gy, and 10 received 54 Gy.

**DISCUSSION**

Local recurrences continue to be a challenge in MPM. Fifteen (19%) of the 78 patients (43% of the 35 patients without distant recurrence) developed only local and/or nodal failures (without distant failures). Fourteen of these 15 patients received at least 50 Gy. Of the 15 patients with only local or nodal failures, 10 failed in sites of dose heterogeneity. Therefore, only 10 (13%) of 78 patients in this study may have benefited from the improved target coverage that IMRT can deliver. Improved surgical techniques may also increase local control.

Indeed, it is difficult to determine whether our patients would have benefited from IMRT. IMRT may have prevented recurrences in the 10 patients with local and nodal recurrences in regions of high-dose inhomogeneity because it would have provided better target coverage. However, in some patients, MPM has shown resistance to the current doses of RT and locoregional recurrence may be inevitable regardless of RT technique. In addition, the improvement in dose distribution with IMRT may be offset by increased fatal pneumonitis.

IMRT has the potential to improve locoregional control rates in MPM as it has shown to have better dose distributions when compared with conventional techniques in other disease sites.\(^{12-14}\) Table 4 displays the results of selected institutions’ experience with conventional RT after EPP,\(^ {11,15-17}\) and results

![Figure 1](image-url)
of four institutions’ experience with IMRT after EPP.6,8,18–20 Rice et al.20 reported a 13% locoregional failure rate, whereas Miles et al.6 found a 46% failure rate. Even if control rates are improved with IMRT, the fatality rate is concerning. The rate of fatal radiation pneumonitis ranged from 8 to 46% with IMRT versus 0% in patients treated with conventional RT techniques. The radiation dose to the remaining lung has been implicated as the cause of this unacceptably high rate of pneumonitis. These studies have hypothesized restrictions on contralateral lung dose to keep treatment safe, but these parameters need to be tested in the clinical setting. Helical tomotherapy may yield lower lung doses than step-and-shoot IMRT.9 The patients in our study tolerated photon-electron RT with the appropriate medical support and none died due to RT-related pulmonary toxicity.

In conclusion, our study has shown that the local and nodal failure rate of MPM after EPP and photon-electron radiation therapy is approximately 40%. There was acceptable toxicity and there were no treatment-related deaths. IMRT may have improved the target coverage in a subset of patients (13% of the 78 patients), but it may potentially cause increased toxicity. Therefore, if physicians use IMRT in these patients they must be extremely cautious to prevent fatal pneumonitis.

REFERENCES


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