Radiation Therapy for Malignant Pleural Mesothelioma

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KEYWORDS

• Radiation therapy • Radiotherapy • Intensity-modulated radiation therapy • Mesothelioma
• Pleural IMRT • IMPRINT

KEY POINTS

- Malignant pleural mesothelioma typically presents with disease localized to the hemithorax. Therefore, although distant disease is still a risk, local control is of primary importance after surgical resection.
- Radiation therapy after surgery can reduce the rate of local failure in mesothelioma.
- In most postoperative situations in oncology, the region needing treatment is well-defined, such as a lymph node region or a surgical bed. However, in mesothelioma, the entire pleura is at risk, and this requires a large radiation field that increases the risks of toxicity.
- When administering post-operative radiation therapy after extra-pleural pneumonectomy, the dose to the remaining lung must be minimized.
- After pleurectomy/decortication, because the ipsilateral lung is intact, delivering radiation while sparing the normal lung is technically challenging.

INTRODUCTION

Malignant pleural mesothelioma (MPM) typically presents with disease localized to the hemithorax. Therefore, although distant disease is still a risk, local control is of primary importance after surgical resection. Radiation therapy is a standard adjuvant therapy that is used to improve the rate of local control in a variety of malignancies. In most postoperative situations in oncology, the region needing treatment is well defined, such as a lymph node region or a surgical bed. However, in mesothelioma, the entire pleura is at risk and this requires a large radiation field that increases the risks of toxicity.

Two types of surgery are commonly performed for malignant pleural mesothelioma: extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). EPP involves en bloc resection of the entire pleura, lung and diaphragm, and ipsilateral half of the pericardium. P/D involves resection of all gross tumor without resecting the lung. Although it still has significant toxicity, radiation therapy after EPP is facilitated by the removal of the lung.[1] In fact, part of the rationale for EPP was to allow for the use of high doses of postoperative radiation therapy. In P/D, because the ipsilateral lung is intact, delivering radiation while sparing the normal lung is technically challenging.

Radiation Therapy Techniques

Initially, when administering radiotherapy (RT) as adjuvant therapy following EPP or P/D, patients were treated with conventional radiation techniques using anterior/posterior fields with matching electrons. Local failure with this technique has been reported to be greater than 50% by some centers.[2] Eventually 3-dimensional conformal radiation therapy (3D-CRT) replaced conventional techniques as the standard of care.

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Over the past 20 years, intensity-modulated radiation therapy (IMRT) has become a common radiation technique used in many different cancers. IMRT is a highly conformal radiation technique that allows more effective sparing of normal tissues, providing an opportunity for safer, less toxic treatments and increased efficacy by enabling higher radiation doses to the tumor target. It comes with a much higher level of dosimetric control and certainty leads to better target coverage than conventional techniques[3] (Fig. 1). A potential disadvantage of IMRT in mesothelioma is dose inhomogeneity and the dose of radiation delivered to the contralateral lung, which potentially leads to a higher risk of pneumonitis.

The National Cancer Database (NCDB) is a large population-based database. An NCDB study compared 3D-CRT and IMRT. It was more likely for IMRT to be used since 2004 and IMRT was also more likely to be delivered at academic centers. However, there did not seem to be a difference in outcome for patients between the 2 techniques.[4]

Another form of radiation therapy is proton beam radiation. Unlike IMRT, which involves the use of photons, protons deposit their radiation energy at the end of their range, known as the Bragg peak. There is a lower entrance dose of radiation and less radiation delivered along the beam path. Protons have been investigated as a potential treatment of MPM and have favorable dosimetric characteristics. However, because of their high cost of construction, there are currently only 35 proton treatment centers in the United States, and only preliminary work on its utility in MPM has been performed.[5] Protons can be especially useful for patients who have had a local recurrence after prior photon radiation and are in need of reirradiation (Fig. 2).

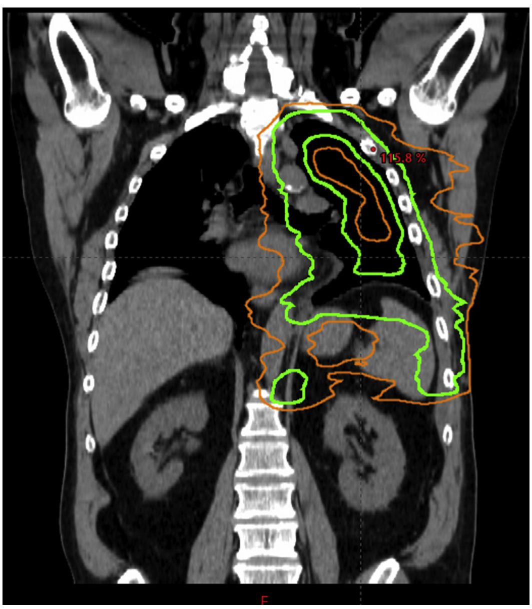

Fig. 1. Patient with malignant pleural mesothelioma after pleurectomy/decortication. Isodose distributions from an intensity-modulated radiation therapy treatment plan in the coronal plane. The 5040 and 2000 cGy isodose curves are represented by the bold green and orange curves respectively. The goal of the plan was to adequate dose to the periphery of the lung while limiting dose to the central portions.

The Role of Radiation Therapy After Surgical Resection

There are limited data with regard to the use of radiation therapy as a standard treatment modality in mesothelioma. A retrospective review of 663 patients from 3 institutions demonstrated improved survival with the use of multimodality therapy as compared with surgery alone.[6]

The role of radiation therapy has been questioned in an analysis of the Surveillance, Epidemiology, and End Result (SEER) database of 14,228 patients with mesothelioma.[7] On multivariable analysis, female gender, younger age, early stage, and treatment with surgery were independent predictors of longer survival. In comparison to no treatment, surgery alone was associated with significant improvement in survival. However, surgery and radiation combined was associated with similar survival as surgery alone. The adjusted hazard ratio for radiation was 1.14 suggesting radiation may not improve outcome in patients with MPM.

There have been multiple analyses of patients in NCDB who underwent definitive surgery for mesothelioma followed by radiation. Nelson and colleagues reported that patients with stage I and II disease who received adjuvant RT had an improved survival. However, this was not demonstrated in patients with stage III or IV disease.[8] A similar analysis by Ohri and colleagues found that younger age, lower comorbidity score, private insurance, surgical resection, and receipt of chemotherapy were associated with increased RT utilization. In addition, patients who received adjuvant RT had higher overall survival at 2 and 5 years.[9] All large database studies, such as SEER and NCDB, must be interpreted with caution due to the lack of detail in a large deidentified database. This is especially relevant in mesothelioma where there is wide variation in the nature of surgical resection and there is no standardization for the RT procedures.

Radiation After Extrapleural Pneumonectomy

Rusch and colleagues[1] at Memorial Sloan-Kettering Cancer Center completed a phase 2 trial

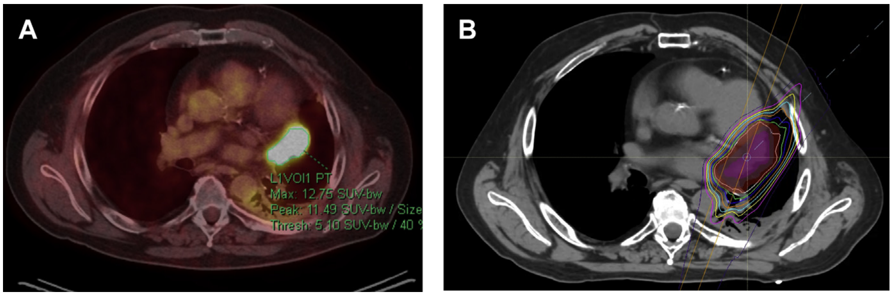

Fig. 2. Patient with recurrent malignant pleural mesothelioma after pleurectomy/decortication and postoperative radiation. Four and a half years after the completion of his initial course of therapy the patient in **Fig. 1** developed a recurrent paramediastinal lesion (*A*). He subsequently received 4 cycles of carboplatin, pemetrexed, and durvalumab with a good response and received 5940 CGE of proton radiation (*B*). One year after the completion of proton radiation he remains disease free.

of EPP followed by postoperative radiation delivered via conventional techniques. Most of the patients (n = 62) underwent an EPP followed by 54 Gy. There were 7 postoperative deaths, all primarily related to pulmonary complications in patients who had undergone an EPP. A total of 33 patients had some complications, including atrial arrhythmias, respiratory failure, pneumonia, and empyema. The median survival was 17 months, with an overall survival of 27% at 3 years. Only 13% had locoregional recurrence, with most of the patients who recurred having distant metastases. The investigators concluded that their approach of aggressive surgery with EPP followed by high-dose radiation to the entire hemithorax provided a favorable outcome for those patients who were able to complete the therapy.

Allen and colleagues,[10] from Dana-Farber Cancer Institute, investigated the use of IMRT after EPP and reported a 46% risk of fatal toxicity from radiation pneumonitis. This led many to question the use of this form of radiation therapy. A higher mean lung dose and the volume of lung receiving 5, 10, or 20 Gy have been associated with a greater risk for lung toxicity.[11–13] In the advent of the Dana-Farber experience, further work was done by multiple investigators to establish dosimetric guidelines for the use of IMRT in mesothelioma. Clearly, the dose of radiation to the contralateral (remaining) lung was of primary importance. In the traditional photon-electron technique, the dose of radiation to the remaining lung was minimal because none of the radiation beams were delivered at an angle, which is standard practice for IMRT.

MD Anderson Cancer Center updated their experience in treating MPM with IMRT after EPP.[14] Gomez and colleagues retrospectively analyzed 86 patients who underwent hemithoracic IMRT after EPP. Grade 3 or worse pulmonary toxicity occurred in 11.6% of patients. Almost all patients had gastrointestinal symptoms, consisting primarily of nausea and esophagitis. There were 5 fatal cases of pulmonary toxicity, 3 from radiation pneumonitis and 2 bronchopleural fistulas. At 2 years, the rates of overall survival, local control, and distant control were 32%, 55%, and 40%, respectively. Fourteen patients (16%) experienced local failure and only 2 of these patients had local failure alone. Fifty-one patients (59%) had distant metastases, which included failures in the contralateral hemithorax and the abdomen.

A review from the University of North Carolina group also examined whether increased experience with received IMRT following EPP led to improvements in outcome.[15] They compared the first 15 patients treated with the second consecutive group of 15 patients. Target coverage (a measure of how well the treatment plan is adequately targeting the tumor) improved in the second group. In addition, the mean dose to the normal structures of the heart and lung also improved in the second group of patients, which suggests that increased experience with this rare disease for the physicians, physics, and therapy staff is of great value in producing high-quality treatment delivery.

A study from the Curie Institute and the Rene Gauducheau Cancer Center, both in France, examined the use of helical tomotherapy (a specialized type of IMRT) after EPP.[16] The investigators used a dose of 50 to 54 Gy with a potential boost to 60 Gy to positive margins. Treatment planning was done to limit the radiation dose to the lung. Twenty-four patients were treated and 4 (16%) had grade 3 or worse radiation pneumonitis within 6 months, including two deaths (8%). There was one case of grade 3 esophagitis. There were only 3 cases of local failure. The remaining patients had distant failure.

An analysis of local failure from the SAKK multimodality trial revealed that only one patient of 18 eligible patients (5%) had an isolated local failure. Five patients in total had local failure (24%), but the other 4 patients also had a component of distant failure outside of the radiation field. All local failures were in regions that received underdosing of radiation, highlighting the need for consistent and advanced treatment techniques.[17,18]

Radiation Before Extrapleural Pneumonectomy

de Perrot and colleagues[18] from Princess Margaret Hospital reported on an innovative technique to combine radiation therapy and extrapleural pneumonectomy. Patients received 25 to 30 Gy to the entire hemithorax using IMRT 1 week before extrapleural pneumonectomy. Patients with pathologically involved mediastinal lymph nodes received adjuvant chemotherapy. Out of 62 patients, there was only one patient who died in the hospital after EPP and 2 patients who died after discharge for a treatment-related mortality of 5%. Twenty-four patients (39%) developed grade 3 or higher toxicity, which was mostly atrial fibrillation or empyema. No patient underwent radiation therapy without subsequently having surgical resection. The median survival for all patients as an intention-to-treat analysis was an encouraging 36 months. An accompanying editorial suggested that a bold approach such as SMART should only be attempted in centers with significant surgical and radiation oncology expertise.[19]

Most recently, the Princess Margaret group has found that the presence of CD8+ tumor infiltrating lymphocytes was an independent factor for improved survival after SMART, suggesting that the tumor microenvironmental response to radiation may be an important component of tumor control.[20]

Radiation After Pleurectomy/Decortication

With the growing use and potential benefit of P/D instead of EPP,[5] it became an increasing challenge to develop techniques to deliver therapeutic doses of radiation therapy to the entire pleura in the setting of an intact lung. Using conventional treatment planning techniques yielded a 1-year local control rate of 42% and a median survival of 13.5 months.[21] Possible explanations for the poor outcomes include a median radiation dose being only 42.5 Gy and the dose uncertainties with this technique. In addition, the treatment was quite toxic, with 28% grade 3 to 4 toxicity and 2 patients with grade 5 (fatal) toxicity.

Therefore, IMRT was considered to be a potential technique to improve the therapeutic index in these patients. Hemithoracic pleural IMRT (also known as *I*ntensity *M*odulated *P*leural *R*ad*I*atio*N* *T*herapy [*IMPRINT*]) has been explored. In this situation, the dose of radiation to the lung as a paired organ would be of dosimetric interest, similar to the challenges seen in the treatment of lung cancer.

Rosenzweig and colleagues[22] from Memorial Sloan-Kettering Cancer Center (MSKCC) reviewed 36 patients treated with pleural IMRT who underwent P/D or biopsy alone. The purpose of the study was to establish the feasibility of pleural IMRT and assess its toxicity. A median dose of 4680 cGy was delivered to the pleural surface and almost 90% of the patients had received chemotherapy, although none received it concurrently. There were 7 patients (20%) with grade 3 or worse toxicity, including one fatality. Five patients (16%) had persistent pneumonitis as a long-term toxicity. The investigators concluded that pleural IMRT is a safe and feasible treatment technique for patients with MPM who have an intact lung on the affected side.

An update of the MSKCC experience evaluated 67 patients with MPM treated with definitive or adjuvant hemithoracic pleural IMRT.[23] Pretreatment imaging, treatment plans, and posttreatment imaging were retrospectively reviewed to determine failure location. Failures were categorized as in-field, marginal, out-of-field, or distant depending on the failures' relation to the 90% and 50% isodose lines. The median follow-up was 24 months from diagnosis, and the median time to in-field local failure from the end of RT was 10 months. Forty-three in-field local failures (64%) were found with a 1- and 2-year actuarial failure rate of 56% and 74%, respectively. For patients who underwent P/D versus those who received a partial pleurectomy or were deemed unresectable (ie, patients who had residual disease), the median time to in-field local failure was 14 months versus 6 months, respectively ($P<.03$). The investigators concluded that local failure remains the dominant form of failure pattern and that patients treated with adjuvant hemithoracic pleural IMRT after P/D experience a significantly longer time to local and distant failure than patients treated with definitive pleural IMRT.

A retrospective review of all patients who received P/D followed by adjuvant RT was also performed by the investigators at MSKCC. Adjuvant RT was either given conventionally or via IMPRINT. The patients receiving IMPRINT, not surprisingly, had higher rates of chemotherapy treatment. Despite that, on multivariable analysis, the use of IMPRINT had significantly higher overall survival. There was also significant reduction in the rate of grade 2 or higher esophagitis.[24]

Investigators in Aviano, Italy reported on 28 patients who were treated with HT after pleurectomy/decortication or biopsy alone.[25] All patients had FDG-PET scans after surgery for staging and were treated to an intended dose of 50 Gy. Areas that were hypermetabolic on PET were boosted with an additional 10 Gy. The primary pulmonary dosimetric constraint was the contralateral lung to a mean dose of less than 7 Gy. The ipsilateral lung and the total lung did not have specific constraints. Five patients (18%) had respiratory toxicity, but only 2 were grade 3 (7%) and none were grade 5. The percent of contralateral lung receiving 5 Gy was strongly correlated with the risk of pneumonitis. This is especially interesting considering that theoretically there should be some function in the intact lung that might be susceptible to radiation toxicity.

Combined modality therapy

Radiation therapy as part of a multimodality treatment of MPM has been explored. A typical treatment approach has been the use of induction chemotherapy followed by surgical resection and adjuvant radiation therapy. In some of the earlier trials, cisplatin and gemcitabine were used as induction therapy.[26] After a randomized phase III trial established the effectiveness of pemetrexed in combination with cisplatin,[27] subsequent trials explored that chemotherapy regimen before surgery. One multiinstitutional phase II study evaluated 77 patients who received induction pemetrexed and cisplatin.[28] Fifty-four patients subsequently underwent EPP and 40 completed hemithoracic radiation. Median survival in the overall population was 16.8 months. Patients completing all therapy had a median survival of 29.1 months and a 2-year survival rate of 61.2%.

Stahel and colleagues published the results of SAKK 17/04, a multicentered phase II randomized trial. In this trial, patients received 3 cycles of induction chemotherapy with cisplatin and pemetrexed.[29] Patients then received extrapleural pneumonectomy and were subsequently randomized to either hemithoracic radiation therapy or no further treatment. One hundred fifty-three patients were enrolled in the study and 113 underwent surgery. However, only 54 patients went on to randomization. There was no significant difference in local-regional progression-free survival and overall survival between the 2 randomized groups. Although the investigators concluded that there is no role for postoperative radiation therapy after extrapleural pneumonectomy for mesothelioma, it is more likely that this trial was too severely underpowered to detect any difference between the groups.

The use of P/D as the surgical intervention has also been investigated. A multiinstitutional phase II trial of neoadjuvant cisplatin/pemetrexed followed by P/D and IMPRINT is ongoing (ClinicalTrials.gov identifier NCT00715611). The main purpose of this study is to test the feasibility of performing a trial using IMPRINT at various centers, given the complexity of the treatment technique. The NRG cooperative study group has recently opened LU-006. In this trial, patients receive induction chemotherapy followed by P/D. Patients are subsequently randomized to either IMPRINT or no further treatment. This is first phase III randomized trial evaluating radiation therapy in the definitive setting.

Skin boost

Patients with MPM who undergo instrumentation in the chest wall can develop tumor seeding and tumor development at the incision sites. In an effort to reduce the risk of this, prophylactic radiation has frequently been used. It typically consists of a single electron field with a dose of 2100 cGy in 3 fractions. This dose of radiation is not associated with significant side effects.

Boutin and colleagues[30] reported that the use of prophylactic radiation to intervention tracts decreased the risk of subcutaneous tumor development from 40% to 0%. However, a systematic review of the literature showed conflicting results in the multiple trials that had been done.[31] They also reported that there was wide variation in clinical practice in the United Kingdom for this technique.

The group subsequently performed a large multicentered randomized trial of prophylactic radiation versus no radiation. Three hundred seventy-five patients were randomized, and no significant difference was seen in the incidence of chest wall metastases at 6 months between the 2 groups (6% vs 10%). There was a 10% rate of grade 2 and a 0.5% rate of grade 3+ skin toxicity associated with the radiation.[32]

Radiation treatment planning

The determination of the planning target volume and the organs at risk to be avoided is the basis of radiation treatment planning. Given the relative rarity of this disease and the unique aspects of the tumor region, tumor definition can be challenging. An excellent atlas and guide to radiation treatment planning was developed by a joint effort of National Cancer Institute Thoracic Malignancy Steering Committee, the International Association for the Study of Lung Cancer, and the Mesothelioma Applied Research Foundation and should be referenced for physicians who need guidance in caring for mesothelioma patients with radiation therapy.[33]

Similarly to lung cancer, the key organs at risk in treatment planning for mesothelioma are the lungs and the heart. Dose constraints should be developed at each institution due to the individual characteristics of their treatment machines and dose calculation algorithms but should be based on published experience. In general, for treatment after pneumonectomy, the dose to remaining contralateral lung should be kept as low as possible, such as a mean lung dose of 8 Gy or the percentage of lung receiving 20 Gy (V20) less than 7%. These constraints are much lower than typical lung cancer dose recommendations and reflect the fact that there is a single lung and that even a mild radiation pneumonitis can be a fatal complication. For patients with 2 intact lungs, either after P/D or no surgery, a typical constraint is to keep the mean lung dose less than 20 Gy the V20 to 37%. Heart dose may be a significant component of patients diagnosed with radiation pneumonitis. For left-sided tumors a constraint of V40 less than 35% is appropriate. For right-sided tumors, a V40 less than 25% should be used.

SUMMARY

Many aspects of treatment of patients with malignant pleural mesothelioma are still not standardized. There is still variation in the surgical technique used and the role of radiation therapy. The use of pemetrexed chemotherapy is standard, but there is still no clinically effective second-line systemic treatment.

The use of radiation therapy has changed radically since the advent of advanced radiation treatment planning techniques, especially IMRT. IMRT is now part of the care for almost all patients when radiation therapy is used. The publication of the Dana-Farber experience over 10 years ago was a sobering reminder of the potential dangers of new technologies for our patients. Patients with mesothelioma represent an especially difficult population with which to work with because their disease is related to environmental exposures that often leave them prone to other medical comorbidities.

Many thoracic surgeons have decreased their use of EPP in favor of pleurectomy/decortication in an effort to decrease operative morbidity and mortality, especially considering the possibility that there is no clear difference in clinical outcome. Therefore, radiation oncologists will be evaluating patients with 2 intact lungs in need of adjuvant radiation therapy. IMRT, with its ability to deliver concave doses of radiation therapy to complex geometries, is a logical solution to this problem.

The clinical issues for these patients, including contouring, treatment planning, and delivery are not inconsiderable, and it is important to receive care at a center with significant experience in caring for patients with mesothelioma. In addition, although the toxicity for these treatments has decreased, it is not insignificant and must be taken into consideration when treating our patients.

CLINICS CARE POINTS

- Delivering radiation therapy for patients with malignant pleural mesothelioma is technically challenging due to the large anatomic area at risk and the poor health of the typical patient.
- Advanced radiation treatment techniques, such as IMRT or proton beam therapy must radiation must be used to minimize side effects from treatment.
- Special care must be given to minimize radiation dose to the heart and lung(s).
- Prophylactic radiation to sites on the skin where ports had been placed is not routinely recommended.

DISCLOSURE

The author has nothing to disclose.

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