The Use of Radiation Therapy for the Treatment of Malignant Pleural Mesothelioma: Expert Opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation

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ABSTRACT

Introduction: Detailed guidelines regarding the use of radiation therapy for malignant pleural mesothelioma (MPM) are currently lacking because of the rarity of the disease, the wide spectrum of clinical presentations, and the paucity of high-level data on individual treatment approaches.

Methods: In March 2017, a multidisciplinary meeting of mesothelioma experts was cosponsored by the U.S. National Cancer Institute, International Association for the Study of Lung Cancer Research, and Mesothelioma Applied Research Foundation. Among the outcomes of this conference was the foundation of detailed, multidisciplinary consensus guidelines.

Results: Here we present consensus recommendations on the use of radiation therapy for MPM in three discrete scenarios: (1) hemithoracic radiation therapy to be used before or after extrapleural pneumonectomy; (2) hemithoracic radiation to be used as an adjuvant to lung-sparing procedures (i.e., without pneumonectomy); and (3) palliative radiation therapy for focal symptoms caused by the disease. We discuss appropriate simulation techniques, treatment volumes, dose fractionation regimens, and normal tissue constraints. We also assess the role of particle beam therapy, specifically, proton beam therapy, for MPM.

Conclusion: The recommendations provided in this consensus statement should serve as important guidelines for developing future clinical trials of treatment approaches for MPM.

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Keywords: Mesothelioma; Radiation therapy; Consensus guidelines; Treatment recommendations

Indications for Radiation Therapy in MPM

Radiation therapy has had an evolving role with regard to its role in the multidisciplinary treatment for malignant pleural mesothelioma (MPM). In this article, we discuss four specific radiation paradigms, each with varying levels of evidence and some of which are considered largely experimental in nature: (1) hemithoracic radiation to be used before or after extrapleural pneumonectomy (EPP); (2) procedure tract radiation therapy; (3) hemithoracic radiation as an adjuvant treatment after lung-sparing procedures, such as pleurectomy/decortication (P/D); and (4) palliative radiation for focal symptoms caused by the disease. Each of these scenarios is discussed in this article, as is the use of proton therapy for MPM. We will be discussing each recommendation in the context of the 2018 American Society of Clinical Oncology (ASCO) expert panel, and it is important to note that the current proposal is aligned with that consensus panel.

Guidelines for Radiation Simulation and Image Guidance During Treatment

For patients receiving treatment to the entire or inferior hemithorax, a nuclear perfusion renal scan is recommended before treatment simulation to assess relative urinary flow in each kidney, because the ipsilateral kidney typically receives a moderate dose of radiation that approaches tolerance limits.

Patients undergoing treatment simulation should be immobilized with a customized mold, with the arms over the head when possible, to maximize the beam angles that can be used in treatment planning. Placement of a wire marker and bolus over scars and drain sites to increase surface dose is optional. If a bolus is to be used, we recommend that it be 0.5 cm thick with a 3.0- to 3.5-cm diameter around these regions.

For patients receiving hemithoracic radiation, either free-breathing or four-dimensional (4D) computed tomography (CT) scans are recommended, with a slice spacing of 2.5 to 3 mm depending on the scanner. The free-breathing and 4D CT scans should include the entire thorax extending from the lung apex to at least the L3 vertebra to cover the lowest insertion point of the diaphragm with margin inferiorly. Obtaining a positron emission tomography (PET) scan before contouring can be considered for restaging and for optimal target delineation. In addition, magnetic resonance imaging (MRI) scans have been demonstrated to be the superior imaging modality for the detection of T3 to T4 disease, as well as in definition of the pleural gross tumor volume (GTV) and thus should also be incorporated into the imaging regimen when appropriate and available. We particularly recommend obtaining an MRI scan when a lung-sparing approach is used in the context of gross disease, in which case the T1, T2, fat-suppressing sequences, and diffusion-weighted MRI can greatly aid in the target delineation.

The isocenter should be placed at the center of a field that encompasses the top of T1, the bottom of the L2 vertebra, the contralateral edge of the vertebral bodies, and a 2-cm margin on the lateral edge of the thoracic chest wall. The GTV and clinical target volume (CTV) are to be contoured on the PET/CT treatment planning scan and adjusted for the internal target volume (ITV) established with 4D CT. In patients with completely resected disease after pleurectomy, only a CTV is to be defined. Elective nodal radiation is not typically used, except in the surgery for mesothelioma after radiation.
therapy (SMART) approach, which is described later in this article. Motion management techniques such as deep inspiration breath hold, abdominal compression, or gating may be used as alternatives to 4D CT scanning for patients who can tolerate and cooperate with these techniques.

All patients receiving hemithoracic treatment should undergo daily image guidance with onboard kilovoltage (kV) orthogonal paired images or with cone-beam CT scans. If necessary, orthogonal megavoltage (MV) imaging can also be used. Patients should also undergo regularly scheduled verification CT scans throughout the course of treatment, generally every week or every other week, to assess potential dosimetric changes in the treatment plan. Adaptive planning should be considered as clinically indicated to ensure optimal preservation of the radiation dose distribution throughout the course of treatment.

Treatment simulation for palliative, focal (i.e., nonhemithoracic) radiation should be tailored to the site receiving radiation and the planning techniques being used, which will vary on an individual basis.

### Adjuvant Hemithoracic Radiation Therapy after EPP

Hemithoracic radiation therapy after EPP has evolved substantially over the past 15 to 20 years. Historically, this treatment was delivered by using conventional anteroposterior/posteroanterior fields, with blocks placed over critical anatomic structures (heart, abdomen) and electron supplementation to achieve adequate dose to the pleura. Unsurprisingly, this technique led to suboptimal dosimetry, with heterogeneous dosing and inevitable exposure of several intrathoracic and upper abdominal structures. Approximately 15 years ago, intensity-modulated radiation therapy (IMRT) was expanded for this purpose. The initial results were promising with regard to disease control and toxicity, but implementation was hindered by a 2006 report of fatal pneumonitis in nearly 50% of patients so treated. Several factors have been considered potential causes of these high-grade adverse events, but the primary etiology was likely excessive dose to the remaining lung within the low-dose bath.

As a result, dose constraints have been modified to substantially reduce the remaining lung dose, and toxicity results have greatly improved since that time. Most centers now report rates of high-grade pneumonitis less than 10%, with similarly low rates of grade 3 or higher esophagitis, fatigue, and dermatitis.

The efficacy of EPP followed by hemithoracic radiation therapy has been promising, with in-field failure rates of approximately 15% to 35%. However, one recent trial has brought the use of comprehensive radiation therapy after EPP into question. In the SAKK 17/04 study, patients at institutions in Switzerland, Belgium, and Germany received three cycles of neoadjuvant chemotherapy followed by EPP. Patients with an R0 or R1 resection (R2 resection excluded) were then randomized to receive either hemithoracic radiation with a variety of dose/fractionation schedules allowed versus no hemithoracic radiation. The primary end point was locoregional control. From 2005 through 2012, 54 patients were randomized, 27 to each group. Overall, no significant differences were seen in locoregional control between the two treatment groups, with one grade 5 pneumonitis event in the radiation group. The authors concluded that these findings “did not support the routine use of hemithoracic radiotherapy for [MPM] after neoadjuvant chemotherapy and EPP.” In an accompanying editorial by both radiation oncologists and surgeons, several limitations of this trial were discussed, including its lack of statistical power (the study closed owing to poor accrual), substantial patient dropout from registration to randomization, lack of details on radiotherapy guidelines (including the correlation of dosimetric variables and toxic events), and lack of central review of target and normal structures despite the highly complex radiation treatment.

The substantial limitations of the SAKK trial led many in the radiation oncology community to continue to advocate the use of hemithoracic radiation after EPP on the basis of data from individual institutions, and in fact, given the current limitations of data either supporting or contradicting its utility, hemithoracic radiation therapy remains the standard of care after EPP for stage I to III medically operable disease in the most recent version of the National Comprehensive Cancer Center guidelines (version 2.2018). Indeed, this recommendation is consistent with that given by the 2018 ASCO expert panel, which states that “[h]emithoracic adjuvant radiation therapy may be offered to patients who undergo non-lung-sparing cytoreductive surgery (EPP), preferably in centers of excellence with experience in this modality for mesothelioma.”

### Contouring Guidelines

Contouring of normal tissue should be done according to the Radiation Therapy Oncology Group (RTOG) atlas guidelines. Notably, a planning-at-risk volume of 3 to 5 mm is typically defined for the spinal cord to account for positioning uncertainties. Table 1 provides a reference to pertinent target volumes that will be discussed in this article.

The postoperative field should encompass the entire ipsilateral pleural bed. A CTV can encompass this region inclusive of the ribs laterally and with a margin at the mediastinal/pleural interface of 0.5 to
Efforts should be made to minimize the dose to the heart, particularly for left-sided tumors, and the mediastinal lymph nodes should not be electively encompassed. Anteromedially, the volume should extend to the sternum and include coverage of the anterior pericardium and pleura. Posteriorly, the volume should extend to the vertebral body, and inferiorly the volume should cover the diaphragmatic insertion until the emergence of the psoas muscle (Fig. 1). Extension to the skin in the setting of bolus has questionable utility and should be considered optional. Attention should also be paid to the kidneys and the liver (for right-sided disease), such that dose constraints are met for these structures.

After the CTV is delineated, a PTV expansion should be constructed. We recommend a 0.5-cm PTV expansion and use of daily image-guided radiation therapy.

### Treatment Planning Guidelines

For hemithoracic radiation to be given after EPP, we recommend a total dose of 45–54 Gy, to be given in 1.8- to 2.0-Gy fractions, with respect for dose constraints for organs at risk (Table 2). For patients with an R1 or R2 resection, a boost to 54 to 60 Gy can be used, and a simultaneous integrated boost can be considered if IMRT is being used. Treatment is given to the PTV with IMRT (by using a “step-and-shoot” or sliding-window technique) or arc therapy.

### Table 1. Description of Target Volumes Described in the Article

<table>
<thead>
<tr>
<th>Target Volume</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Gross disease</td>
</tr>
<tr>
<td>CTV</td>
<td>Gross disease plus margin for microscopic areas at risk for unresectable patients or microscopic areas at risk in the postoperative tumor bed in patients having undergone a macroscopic complete resection</td>
</tr>
<tr>
<td>PTV</td>
<td>CTV plus margin for patient setup variations/error</td>
</tr>
<tr>
<td>iGTV</td>
<td>GTV plus margin for internal respiratory motion</td>
</tr>
<tr>
<td>iCTV</td>
<td>iGTV plus margin for microscopic areas at risk</td>
</tr>
<tr>
<td>PTV outer</td>
<td>Planning target volume for outer pleura is the target volume for the outer pleura, typically within the setting of the IMPRINT technique</td>
</tr>
<tr>
<td>PTV inner</td>
<td>Planning target volume for inner pleura is the target volume for the inner pleura, typically within the context of the IMPRINT technique; the rind between the PTV outer and PTV inner constitutes the final PTV for IMPRINT</td>
</tr>
</tbody>
</table>

GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; iGTV, internal gross tumor volume; iCTV, internal clinical target volume; PTV outer, planning target volume for the outer pleura, typically within the context of the IMPRINT technique; PTV inner, planning target volume for the inner pleura, typically within the context of the IMPRINT technique; IMPRINT, intensity-modulated pleural radiation therapy.

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Figure 1. Considerations for planning adjuvant radiation therapy to be delivered after extrapleural pneumonectomy for patients with malignant pleural mesothelioma.
difference was observed between immediate and deferred radiation. In addition, a systematic review and meta-analysis evaluating the role of procedure tract radiotherapy, which evaluated five prospective randomized controlled trials assessing this technique, demonstrated again that prophylactic radiotherapy did not result in a statistically significant reduction of the risk of procedure site recurrence. The review thus confirmed that there is no role for radiation to prevent PTMs in the setting of MPM, and we thus do not recommend this treatment. However, we do want to distinguish prophylactic radiation from procedure tract radiation for patients who have histologically positive resection of intervention tracts. We would not recommend radiation in the prophylactic scenario but would indeed do so in the latter situation. This recommendation is also consistent with those published by the 2018 ASCO expert panel.

Neoadjuvant Radiation Therapy Followed by EPP (the SMART Approach)

The recently reported Surgery for Mesothelioma After Radiation Therapy (SMART) study involves a novel treatment paradigm in which neoadjuvant hemithoracic accelerated radiation therapy is followed by EPP. We acknowledge that there are no randomized or multi-institutional prospective data supporting this approach. Indeed, we concur with the recommendation by the 2018 ASCO expert panel in that the technique should be performed only in highly experienced centers and within the context of a clinical trial. Emphasizing this context, we will discuss the general strategy here. The rationale for this protocol is based on the observation that when radiation is given after EPP (i.e., as adjuvant therapy), the recurrences often involve the contralateral lung and peritoneum, suggesting that tumor spillage during EPP may be contributing to these recurrences. The hypothesis for the SMART study was that giving radiation as neoadjuvant therapy, before EPP, would impair the ability of tumor clonogens to reimplant and recur at distant sites in the coelomic cavity. However, delivering the typical doses needed to ensure microscopic control (usually 45–50 Gy in 25 daily fractions over 5 weeks) to an intact whole lung would be exceedingly toxic and likely lethal. Thus, to deliver neoadjuvant radiation safely, an accelerated fractionation regimen of 25 to 30 Gy in five daily fractions over 1 week was developed on the basis of a similar neoadjuvant radiation regimen used for rectal cancer. The potential toxicity of the radiation therapy mandates that patients be selected carefully to ensure that they will be able to proceed to surgery. Figure 2 depicts a typical SMART radiation field.

### Table 2. Treatment Planning Dosimetric Guidelines for Conventionally Fractionated Hemithoracic Radiation after Extrapleural Pneumonectomy

<table>
<thead>
<tr>
<th>Target/Normal Organ</th>
<th>Criteria Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed dose</td>
<td>45–54 Gy in 1.8 Gy/fraction</td>
</tr>
<tr>
<td>GTV</td>
<td>D95 &lt; 95%</td>
</tr>
<tr>
<td>PTV</td>
<td>D95 ≥ 94% (make sure hot spots are inside the PTV)</td>
</tr>
<tr>
<td>Contralateral/remaining lung (defined as lung, not GTV)</td>
<td>Lung V20 Gy &lt; 7%</td>
</tr>
<tr>
<td>Esophagus (defined as the entire esophagus from the cricoid cartilage to the gastroesophageal junction)</td>
<td>Mean dose ≤ 34 Gy</td>
</tr>
<tr>
<td>Spinal cord (defined as spinal canal)</td>
<td>Dmax &lt; 50 Gy</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>Dmax &lt; 65 Gy</td>
</tr>
<tr>
<td>Heart (defined as the pericardial sac)</td>
<td>Right-sided meso: V40 Gy ≤ 25%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>V18 Gy ≤ 33%</td>
</tr>
<tr>
<td></td>
<td>(V18 Gy ≤ 50% if V18 Gy ≤ 33% cannot be achieved)</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose ≤ 30 Gy</td>
</tr>
<tr>
<td></td>
<td>V10 Gy ≤ 50%</td>
</tr>
</tbody>
</table>

GTV, gross tumor volume; PTV, planning tumor volume; meso, mesothelioma.

Radiation Therapy for the Prophylaxis of PTMs

One approach to reducing the risk of local recurrence in MPM has been solely targeting procedure tract metastases (PTMs). The rationale for this technique is that many patients undergo needle biopsy of the pleura, with the theoretical risk of spread. In addition, a potential benefit is that only a modest amount of lung tissue is radiated, thus minimizing the risk of morbidity compared with the risk of morbidity with more extensive fields, such as when hemithoracic approaches are used. Indeed, select single-institution analyses have demonstrated promising results with this technique. However, a multicenter phase III randomized study that did not demonstrate a benefit with this regimen was recently published. Specifically, the Prophylactic Radiotherapy for the Prevention of Procedure Tract Metastases after Surgical and Large-Bore Pleural Procedures in Malignant Pleural Mesothelioma study (note that the acronym SMART was used for this trial, which should be differentiated from the SMART approach described later in this article in relation to surgery for mesothelioma after radiation therapy) enrolled 203 patients at 22 hospitals in the United Kingdom between 2011 and 2014 to receive either immediate prophylactic procedure tract radiotherapy to 21 Gy in three fractions or deferred radiation given within 35 days of PTM diagnosis. Although toxicity was modest in the radiation arm, no significant...
After the completion of radiation therapy (usually 10 days after the initial dose), patients then proceed to undergo a planned EPP to remove the irradiated lung, thereby avoiding the risk of severe radiation pneumonitis. The intent is to deliver a neoadjuvant dose to the entire ipsilateral hemithorax, from the thoracic inlet down to the thoracic outlet, including diaphragmatic attachments, as well as the ipsilateral mediastinal nodal stations, upper retroperitoneal nodes, and any biopsy/chest tube tract sites.

Contouring Guidelines
For this procedure, the CTV consists of the union of several subvolumes: the entire thoracic cavity, ipsilateral mediastinal nodal stations, upper retroperitoneal nodes, and tract sites. The thoracic cavity and retroperitoneal nodes are defined as follows: superiorly from the top of the ipsilateral first rib; inferiorly down to the twelfth floating rib; laterally to include the lung and chest wall interface; and medially to include the mediastinal pleura (including retrosternal fat), the ipsilateral pericardium (when above the diaphragm), the ipsilateral crus of the diaphragm, and anterior preaortic space down to renal vessels (when below the diaphragm). Elective mediastinal nodes are defined to include ipsilateral stations 2 (upper), 4 (lower), and 7 (subcarinal), as well as 5 (aortic window) and 6 (paraaortic) if a left-sided case. The tract site is defined by contouring the incision and the tract through the chest wall with a 3-cm isotropic margin (excluding air and the thoracic cavity), creating a cylindrically shaped squat chest wall volume.

A boost dose CTV is defined to cover areas at high risk or with gross disease such as pleural plaques or PET-avid disease and tract site to reduce risk of tract site recurrences. These subvolumes are joined in a Boolean union to create a final CTV. CTVs are defined for both the inhale and exhale conditions and fused to create ITVs (i.e., the ITV and the ITV boost). Usually, respiratory motion is quite limited, and the inhale and exhale volumes are within 5 mm of each other; therefore, the ITV is often almost identical to the CTV exhale plus CTV inhale.

The PTV is defined as the ITV plus a uniform 5-mm margin. For the purposes of IMRT optimization, a PTV evaluation (the PTV excluding 5 mm superficially) should be defined to avoid difficulties with dosimetric buildup.

The normal tissues outlined should include the heart, liver, spinal cord, contralateral lung, ipsilateral and contralateral kidneys, and esophagus as per the RTOG contouring atlas guidelines. A planning-at-risk-volume with an appropriate margin (3-5 mm) is defined for the spinal cord to account for positioning uncertainties.

Treatment Planning Guidelines
A multifield IMRT technique should be selected, with the radiation delivered with a 6- to 18-MV linear accelerator. Five to ten nonopposed gantry angles should be used, depending on patient geometry. Treatment is to be given to the PTV by using step-and-shoot IMRT segments or arc therapy. Premedications are to be prescribed (ondansetron 1 hour before radiation, pantoprazole once daily) to be taken each day. Because of the risk of severe radiation pneumonitis, patients are committed to completing EPP after they have finished radiation therapy. Treatment planning dosimetric guidelines in the SMART protocol are depicted in Table 3.

Adjuvant Radiation Therapy with Two Intact Lungs
Since the controversial MARS 1 trial, the use of EPP has gradually declined in recent years in favor of less radical lung-sparing approaches such as P/D, leaving many patients with two intact lungs that need to be spared when they receive radiation therapy, especially high-dose IMRT, to avoid severe radiation toxicity. The feasibility of delivering IMRT to the entire pleura after P/D to a median dose of 46.8 Gy was first demonstrated in a series of 36 patients showing acceptable side effects. A prospective phase II study of the feasibility of this hemithoracic intensity-modulated pleural radiation
therapy (IMPRINT) technique in conjunction with chemotherapy and P/D demonstrated that a planned dose of 50.4 Gy in 28 fractions can be administered safely, with no grade 4 or 5 pneumonitis observed.20

The high precision of IMRT requires detailed knowledge of the anatomy of the thorax and the diaphragm, state-of-the-art diagnostic imaging tools, information on the pathologic findings at the time of surgery, a 4D CT scan to assess the respiratory tumor motion, and image-guided radiation delivery. We thus concur with the recommendation by the 2018 ASCO expert panel that this technique should be performed only in highly experienced centers, and preferably within the context of a clinical trial.1 The use of fludeoxyglucose F 18 PET for treatment planning has been shown to improve target delineation and thereby improve local control.21,22 The IMPRINT technique is delivered with a static gantry, fixed-angle beam IMRT, or arc therapy, as depicted in Figure 3. Although the standard dose is 50.4 Gy in 28 fractions, the total prescription dose may need to be adjusted to avoid exceeding normal tissue constraints, as noted later in this article. A dose-painting simultaneous integrated boost to gross residual disease up to 60 Gy may be possible if normal tissue constraints can be respected. Ideally, treatment should start within 4 to 8 weeks after completion of P/D or the last dose of chemotherapy. Additional details are described later in this article.

Given the complexity and operator dependence of the IMPRINT technique, an ongoing phase II study is testing its safety and exportability to several other treatment centers with experienced radiation therapy departments and a high volume of patients with mesothelioma (ClinicalTrials.gov identifier NCT00715611). This study was developed to include strict radiation planning criteria, central contouring and plan review for every patient, and clear toxicity end points with a Simon two-stage design.

**Target Delineation**

Normal tissue contouring is consistent with that described in the previous section on radiation therapy after EPP and should follow the RTOG contouring atlas.

**Table 3. Treatment Planning Dosimetric Guidelines for the SMART Protocol**

*ITV, internal target volume; PTV, planning target volume; meso, mesothelioma.*

<table>
<thead>
<tr>
<th>Target/Normal Organ</th>
<th>Criteria Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed dose</td>
<td>25 Gy in 5 Gy/fraction with an optional simultaneous integrated boost to 30 Gy in 6 Gy/fraction over 5-8 d</td>
</tr>
<tr>
<td>ITV D100% ≥24.8 Gy; D95% ≥23 Gy acceptable</td>
<td></td>
</tr>
<tr>
<td>ITV boost D95% ≥28.5 Gy</td>
<td></td>
</tr>
<tr>
<td>PTV D95% ≥23.7 Gy; D92% ≥23 Gy acceptable; no hot spot &gt;33 Gy; ideally V10S% ≤2 cm²</td>
<td></td>
</tr>
<tr>
<td>Lungs contralateral lung mean dose &lt;3.5 Gy; contralateral V7Gy &lt;20%</td>
<td></td>
</tr>
<tr>
<td>Esophagus Dmax &lt;30 Gy</td>
<td></td>
</tr>
<tr>
<td>Spinal cord Dmax &lt;22 Gy</td>
<td></td>
</tr>
<tr>
<td>Brachial plexus No hot spots &gt;30 Gy</td>
<td></td>
</tr>
<tr>
<td>Heart Right-sided meso: V15Gy &lt;40%; mean dose &lt;15 Gy</td>
<td></td>
</tr>
<tr>
<td>Left-sided meso: V15Gy &lt;70%; mean dose &lt;18 Gy</td>
<td></td>
</tr>
<tr>
<td>Kidneys Ideally, both kidneys (but at least 1 kidney) mean dose &lt;5 Gy; V7Gy &lt;33%</td>
<td></td>
</tr>
<tr>
<td>Liver Right-sided meso: V15Gy &lt;60%; mean dose &lt;17 Gy</td>
<td></td>
</tr>
<tr>
<td>Left sided meso: V15Gy &lt;30%; mean dose &lt;8 Gy</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Considerations for planning adjuvant hemithoracic radiation therapy to be delivered after lung-sparing surgery for malignant pleural mesothelioma (the Intensity-Modulated Pleural Radiation Therapy technique). Note that the “rind” is created to minimize the high dose to the ipsilateral lung, with further dose limitations on the heart, esophagus, spinal cord, and relevant abdominal structures (based on laterality).
guidelines. On slices containing GTV, the outer and inner CTVs are defined by 3-mm margins surrounding the GTV. On slices containing only normal lung, typically after a complete macroscopic resection, the outer and inner CTVs are collapsed to a virtual space at the lung–chest wall interface. Below the level of the diaphragm, the CTV is typically only a single crescent-shaped contour that requires expansion to cover the pleura toward the sternum, the diaphragm, and the diaphragmatic crura to the midline anteriorly and the paravertebral space posteriorly. An ITV is delineated as an expansion of the CTV to account for respiratory motion seen on the 4D CT scans. The ITV takes into account exterior movement of the CTV outer as well as interior movement of the CTV inner. It should especially capture the diaphragmatic region including the lower hemithorax and upper abdomen, where respiratory movement is typically most pronounced. However, in many patients who have undergone lung-sparing surgery, diaphragmatic motion is restricted because of postsurgical fibrosis, intraoperative sacrifice of the phrenic nerve, or resection and reconstruction of the diaphragm. In patients who are well enough and can cooperate, motion management techniques such as deep inspiration breath hold or gating may be helpful and should be used on an individualized basis. The PTV is a rind-like structure, with PTV outer defined as the CTV outer plus a 1-cm external expansion into the chest wall. After this uniform expansion, the PTV outer needs to be adjusted to cover the entire thickness of the chest wall, including the ribs and intercostal muscles, to the lateral edge of the sternum, the costovertebral joint and the lateral edge of the vertebral body, the costodiaphragmatic and costomediastinal recess, and the crus of the diaphragm. The PTV inner is the CTV inner with a 6-mm expansion into the lung parenchyma. The final PTV is the volume between PTV inner and PTV outer. Below the level of the diaphragm, only the PTV outer will exist as a crescent-shaped structure with a 6-mm margin interiorly and a 10-mm margin exteriorly to the CTV outer. Typically, the volumes extend inferiorly to the insertion point of the diaphragm, usually near the bottom of the L2 vertebral body.

**Treatment Delivery**

Treatment is delivered with 6-MV photon beams, either as static-field IMRT with the dynamic multileaf collimator or sliding window technique or as arc therapy (volumetric modulated arc therapy or tomotherapy). Suggested beam angles for static-field IMRT are six to nine beam directions approximately equally spaced over a range of 190 to 200 degrees (which was chosen to avoid the contralateral lung as much as possible). Suggested beam angles for arc therapy are four arcs going between 180 degrees posteroanteriorly and 20 degrees to the other side anteriorly, with collimator angles between 0 and 10 degrees, or with two arcs covering the “lung limit” (arc length determined by shape of the lungs). Daily kV imaging matching on bones should be used for setup verification.

The prescribed dose per fraction is 1.8 Gy, and the total prescribed dose is 50.4 Gy. An optional concomitant boost to 60 Gy for gross residual disease may be incorporated if normal tissue constraints can be met. An optional bolus to the scar may be applied. The total prescribed dose may be reduced to a minimum of 45 Gy as required to satisfy the normal tissue constraints noted in Table 4. Daily two-dimensional imaging matched on the spine is recommended. Weekly cone-beam CT scans may be obtained. Patients with left-sided MPM should be offered a pneumococcal polyvalent vaccine if they have not had one during the previous 5 years.

Typical side effects from IMPRINT include profound fatigue, anorexia or weight loss, dermatitis, dysphagia, dehydration, esophagitis, cough, dyspnea, and radiation

<table>
<thead>
<tr>
<th>Target/Normal Organ</th>
<th>Criteria Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed dose</td>
<td>50.4 Gy in 1.8 Gy/fraction</td>
</tr>
<tr>
<td>GTV</td>
<td>GTV D95 ≥95%</td>
</tr>
<tr>
<td>PTV</td>
<td>PTV D95 ≥94%</td>
</tr>
<tr>
<td>PTV V95 ≥94%</td>
<td></td>
</tr>
<tr>
<td>D95 ≤115% of prescribed dose</td>
<td></td>
</tr>
<tr>
<td>Dmax ≤130% of prescribed dose</td>
<td></td>
</tr>
<tr>
<td>Make sure that any hot spots are inside the PTV</td>
<td></td>
</tr>
<tr>
<td>Total lungs (defined as lungs, not GTV)</td>
<td>Total lung V20Gy ≤37%</td>
</tr>
<tr>
<td></td>
<td>Mean lung dose ≤20.5 Gy</td>
</tr>
<tr>
<td></td>
<td>Contralateral mean lung ≤8 Gy</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral lung V40 ≤67%</td>
</tr>
<tr>
<td>Esophagus (defined as the entire esophagus from the cricoid cartilage to the gastroesophageal junction)</td>
<td>Mean dose ≤34 Gy</td>
</tr>
<tr>
<td>Spinal cord (defined as spinal canal)</td>
<td>Dmax ≤50 Gy</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>Dmax ≤65 Gy</td>
</tr>
<tr>
<td>Heart (defined as the pericardial sac)</td>
<td>Right-sided meso: V40Gy ≤25%</td>
</tr>
<tr>
<td></td>
<td>Left-sided meso: V30Gy ≤35%</td>
</tr>
<tr>
<td>Left and right kidneys (evaluated separately)</td>
<td>V18Gy ≤33% (V18Gy ≤50% if V18Gy ≤33% cannot be achieved)</td>
</tr>
<tr>
<td>Liver (defined as liver, not GTV)</td>
<td>Mean dose ≤30 Gy</td>
</tr>
<tr>
<td>Stomach, not PTV</td>
<td>V30Gy ≤45%</td>
</tr>
<tr>
<td>Bowel</td>
<td>Mean dose ≤30 Gy</td>
</tr>
<tr>
<td>Bowel</td>
<td>Dmax ≤PTVmax ≤55 Gy</td>
</tr>
<tr>
<td>Bowel</td>
<td>D5cm3 ≤50 Gy</td>
</tr>
</tbody>
</table>

GTV, gross tumor volume; PTV, planning tumor volume; meso, mesothelioma.
Proton Beam Therapy

Because delivery of definitive or adjuvant radiation therapy after lung-sparing surgery for MPM is associated with significant risks of toxic events, additional advanced modalities other than IMRT, such as proton therapy, are emerging. Proton therapy allows energy deposition at a specific depth, termed the Bragg peak, with rapid energy falloff beyond that point, allowing reduced dose to adjacent organs at risk.

The dosimetric rationale for proton therapy for MPM is compelling, and proton therapy has been reported to optimally preserve quality of life\(^\text{27}\), while minimizing toxicity or resulting in improved outcomes in prospective studies and large series for adjuvant,\(^\text{28}\) definitive,\(^\text{26,29,30}\) or repeat\(^\text{31}\) therapy for locally advanced NSCLC, SCLC,\(^\text{32}\) and thymic malignancies;\(^\text{33}\) however, its use for MPM has to date been limited to small institutional series. Investigators from the M. D. Anderson Cancer Center compared PBS with IMRT plans for seven patients with lung-intact MPM, four of whom had been treated with PBS and three of whom had been treated with IMRT. They found that PBS plans led to lower mean doses to the contralateral lung, esophagus, liver, heart, and ipsilateral kidney and that all four patients who received PBS tolerated it well without requiring treatment breaks.\(^\text{34}\) In a report on proton therapy for MPM from investigators at the University of Pennsylvania, 16 patients with MPM received 17 courses of proton therapy as adjuvant therapy after lung-sparing radical pleurectomy (n = 8), to sites of gross disease after progression on prior chemotherapy (n = 8), or as initial definitive therapy concurrently with chemotherapy (n = 1). The median proton dose was 51.75 Gy (relative biological effectiveness [RBE]) in 2.0-Gy (RBE) daily fractions (range 50.0–75.0 Gy [RBE] in 1.8- to 2.5-Gy fractions). All patients achieved durable local control, and no patient experienced development of acute or late grade 3 or higher toxicity; acute grade 2 toxic events included radiation dermatitis (n = 8), esophagitis (n = 4), anorexia (n = 3), fatigue (n = 2), and cough (n = 1). Clinical late radiation pneumonitis (grade 2) occurred in only one patient.\(^\text{35}\) In the first prospective study on proton therapy for MPM by those same investigators, 10 patients with stage III to IV (nonmetastatic) disease were treated to a median of 55.0 cobalt gray equivalent/1.8 to 2.0 cobalt gray equivalent adjuvantly (n = 8) or as salvage therapy (n = 2) after extended P/D. The 2-year local control rate was 90%, and the median survival time from radiotherapy completion was 19.5 months (30.3 months from diagnosis). No patient experienced Common Terminology Criteria for Adverse Events, version 4, grade 2 or higher acute or late toxicity.\(^\text{25}\)

Investigators from the University of Washington School of Medicine reported outcomes for three patients with MPM treated with PBS to 54 to 66 Gy (RBE) after EPP in contrast with the outcomes of to proton therapy delivered to intact lungs. Compared with volumetric-modulated arc therapy photon plans, PBS produced lower doses to organs at risk. None of the three patients experienced development of radiation pneumonitis; acute grade 2 toxic events included dermatitis (n = 2) and nausea (n = 1).\(^\text{36}\)

Treatment Planning, Optimization, and Delivery

For patients to be treated with passive scattering proton therapy, motion (as assessed by 4D CT) should be limited to 10 mm or less; for patients to be treated with PBS, motion should ideally be 5 mm or less.\(^\text{26,37}\) Use of a compression belt or other means of motion mitigation should be used when necessary, and repainting can be considered for PBS plans. The target contours for GTV, internal GTV, and internal CTV are the same as those described for photon contouring. For passive scattering proton therapy, an expansion for the PTV to account for proton beam properties and range uncertainties should be applied.\(^\text{38}\) For PBS, a beam-specific PTV\(^\text{39}\) should be created to account for setup and proton range

Rapid side effects include the need for oxygen, life-threatening pneumonitis, pericarditis, and arrhythmias. Patients with grade 2 pneumonitis should quickly begin a course of corticosteroids, starting at a minimum dose of 40 mg of prednisone daily and tapered over 8 to 10 weeks.

Proton Beam Therapy

Because delivery of definitive or adjuvant radiation therapy after lung-sparing surgery for MPM is associated with significant risks of toxic events, additional advanced modalities other than IMRT, such as proton therapy, are emerging. Proton therapy allows energy deposition at a specific depth, termed the Bragg peak, with rapid energy falloff beyond that point, allowing reduced dose to adjacent organs at risk.\(^\text{21,24}\) We agree with the 2018 ASCO expert panel that this modality should be considered only in centers with significant experience, and preferably within the context of a clinical trial.\(^\text{1}\) Here we present general guidelines for this approach.\(^\text{25}\)

Penet beam scanning (PBS) proton therapy may be the optimal proton delivery choice for MPM. PBS involves the use of steering magnets to “paint” proton beam “spots” layer by layer over the target volume, which can provide better dose coverage than passive scattering proton therapy for volumes of complex shape and also allows the delivery of intensity-modulated proton therapy (IMPT),\(^\text{26}\) which is especially useful for treating the large, irregularly shaped volumes involved in hemithoracic radiotherapy after EPP or whole pleural radiotherapy after extended P/D.

Although clinical outcomes data for proton therapy in the setting of MPM are sparse, several dosimetric studies have demonstrated that IMPT provides superior sparing of normal tissue of the ipsilateral and contralateral kidneys, liver, heart, esophagus, and contralateral lung than is possible with IMRT after EPP, while also significantly improving PTV coverage.

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uncertainties; it is both patient specific and beam specific but often approximates 5 mm. Treatment plans should be created on the basis of the averaged CT image data set and should also be evaluated on the 0% and 50% phases of the 4D CT to ensure adequate coverage.

At least two treatment fields should be used in all cases. IMPT should be used for delivering hemithoracic or whole pleural therapy, delivered with an anteroposterior/posteroanterior opposed beam arrangement or with beams that are slightly oblique from the ipsilateral side. Multiple-field optimization treatment planning may be needed to optimally spare normal tissues.

Plan robustness should be assessed for all PBS plans. This can be accomplished by creating dose perturbances for multiple scenarios, including isocenter offsets (up to 5 mm in each of six primary anatomic directions) and at least one range variation (e.g., 3.5% positive and negative), and the dose delivered to the tumor volume should be evaluated on the nominal plan and the plan with the perturbed doses.

In all cases, daily image guidance should be used. Verification CT scans should also be regularly scheduled throughout treatment, generally once a week or every other week, to assess for dosimetric changes in the treatment plan. Significant anatomic changes identified on cone-beam CT scans should also prompt a verification CT scan. Adaptive planning should be considered as clinically indicated to ensure optimal preservation of the radiation dose distribution throughout treatment.

Palliative Radiation Therapy

Most patients with MPM present with advanced disease, and chest wall pain, a common presenting symptom at the time of diagnosis, can be difficult to manage medically. Hence, radiation is often used for palliative treatment of MPM. Palliative radiation can be used to resolve hemoptysis, improve cough or dyspnea symptoms, prevent spinal cord compromise, or most commonly, to improve pain in patients with MPM. Radiation therapy can also be effective for treating a localized area of pain corresponding to a site of cancer, such as chest wall invasion of tumor. Notably, pain relief may not appear for 10 to 14 days after palliative radiation therapy is begun.

We concur with the ASCO expert panel in recommending standard palliative dosing regimens for most patients with symptomatic disease, such as 8 Gy once, 4 Gy five times, or 3 Gy 10 times. Higher total doses and higher doses per fraction can be considered for some patients to optimize symptomatic response rates. Symptomatic relief in one study was greater for patients treated to doses higher than 40 Gy than for those treated to lower doses. In a retrospective study of 227 courses of radiotherapy to 189 patients with MPM, the local response rate was higher among patients treated with a 4-Gy-per-fraction regimen (to a median dose of 36 Gy) than among those receiving less than 4 Gy/d (50% versus 39%), with pain recurrence appearing predominantly within the previous radiotherapy field, most commonly within 3 months of irradiation.

Thus, the evidence to date suggests that rather than the common palliative regimen of ten 3-Gy fractions used for other thoracic malignancies, daily doses of 4 Gy or more may be more effective in providing chest wall pain relief than are lower daily irradiation doses. Other dose fractionation schemes that should be considered include one 8-Gy fraction, total doses of 30 to 39 Gy in 3-Gy daily fractions, or total doses of 20 to 40 Gy in 4-Gy or larger daily fractions. Stereotactic radiation techniques may allow the safe delivery of even higher doses per fraction with high rates of long-term local control, which may be useful for treating localized or isolated recurrences.

Conclusions

Comprehensive radiation treatment of the entire hemithoracic cavity at risk for recurrence has become feasible and reasonably safe only in recent years, thanks to technical improvements such as IMRT and image-guided radiation therapy. Two approaches for early-stage MPM that are particularly promising from a radiation oncology perspective are the delivery of IMRT preoperatively (SMART) and postoperatively (IMPRINT). IMPRINT is currently being investigated in a phase II study exploring the exportability, reproducibility, safety, and feasibility of this complex technique being delivered by multiple centers. A thorough central review platform for contouring and treatment planning was developed for that study. If IMPRINT proves to be feasible for multiple investigators at multiple centers, a subsequent randomized study to demonstrate the efficacy of adding IMPRINT to P/D and chemotherapy has been prioritized by the recent National Cancer Institute—International Association for the Study of Lung Cancer—Mesothelioma Applied Research Foundation Clinical Trials Planning Meeting as warranting further study. This consensus statement, created by radiation oncology experts in pleural mesothelioma in North America, will serve as an important guideline for future National Cancer Institute–sponsored trials in mesothelioma for the foreseeable future, whether those trials focus on IMPRINT, SMART, proton therapy, palliative radiotherapy, or other as-yet undiscovered approaches.

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