Consensus Statement on Proton Therapy in Mesothelioma

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Abstract

Radiation therapy for mesothelioma remains challenging, as normal tissue toxicity limits the amount of radiation that can be safely delivered to the pleural surfaces, especially radiation dose to the contralateral lung. The physical properties of proton therapy result in better sparing of normal tissues when treating the pleura, both in the post-pneumonectomy setting and the lung-intact setting. Compared to photon radiation, there are dramatic reductions in dose to the contralateral lung, heart, liver, kidneys, and stomach. However, the tissue heterogeneity in the thorax, organ motion, and potential for changing anatomy during the treatment course all present challenges to optimal irradiation with protons. The clinical data underlying proton therapy in mesothelioma are reviewed here, including indications, advantages, and limitations. The Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee task group provides specific guidelines for the use of proton therapy for mesothelioma. This consensus report can be used to guide clinical practice, insurance approval, and future research.

Introduction

Mesothelioma is an uncommon malignancy with approximately 2,500 cases per year in the United States,[1] and around 10,000 cases in North America, Western Europe, Japan, and Australia combined.[2] Generally, prognosis is poor, with a median survival of about one year.[3] The most commonly used treatment options include chemotherapy and/or immunotherapy, surgery, and radiation therapy, either alone or in combination. Treatment is dependent on several clinical factors, including extent of disease, performance status, baseline pulmonary function, and tumor histology. Significant toxicities are associated with the currently available treatment options, and optimal management is controversial. The two main surgical options for mesothelioma are extrapleural pneumonectomy (EPP) and extended pleurectomy and decortication (P/D). Resection carries substantial risk, with perioperative mortality of 12.5% in a randomized trial of EPP, and at least 3.4-7% even in high volume centers.[4-7] P/D is generally better tolerated than EPP but is still associated with a 3.1% postoperative mortality in the Society of Thoracic Surgeons Database and 4% in a separate large series from Memorial Sloan Kettering Cancer Center (MSKCC).[6,7] EPP was considered standard of care for patients with resectable disease, but the MARS trial called into question the role of EPP versus chemotherapy alone, and retrospective series have suggested that P/D may lead to superior survival than EPP.[5,7,8]

Radiation therapy for mesothelioma also carries substantial risks of toxicity. Radiation can be given in several scenarios: 1) hemithoracic radiation post-EPP; 2) hemithoracic radiation with an intact ipsilateral lung, either as definitive radiation, post-P/D adjuvant radiation, or neoadjuvant radiation prior to planned resection; 3) palliative radiation to focal areas as needed; and 4) as prophylactic irradiation of surgical tract sites.[9,10] Regardless of whether patients have an intact ipsilateral lung or are post-EPP, radiation dose to the lung is one of the most critical

determinants of toxicity from radiation treatment. Early clinical experience with intensity-modulated radiation therapy (IMRT) in the post-EPP setting resulted in a 46% fatal pneumonitis rate, highlighting the need for stringent dose constraints to be applied to the remaining contralateral lung, resulting in much lower rates of high-grade radiation pneumonitis.[11,12] These findings led to an increasing awareness of the need to minimize radiation exposure to the contralateral lung. One approach to minimize radiation to the contralateral lung is through the use of opposing anterior-posterior (AP/PA) photon beams with supplemental electrons to treat the medial and inferior regions of the hemithorax. This strategy has been shown to provide greater lung sparing than IMRT[13]. However, the complex dosimetry of the electron-photon technique as well as concerns for inadequate dose delivery to the medial and inferior regions supplemented with electrons have limited clinical use of this approach. Hemithoracic radiation with an intact ipsilateral lung has been feasible in small series, but pneumonitis remains a major concern.[14,15] Increasing use of P/D over EPP further increases the challenge of delivering safe and effective radiation therapy for mesothelioma treatment.[16] The role of radiation therapy in the management of mesothelioma was recently reviewed by the U.S. National Cancer Institute (NCI), International Association for the Study of Lung Cancer Research (IASLC), and Mesothelioma Applied Research Foundation (MARF)[17].

The unique dosimetric characteristics of proton radiation compared with photon radiation can decrease radiation dose to critical structures such as the lungs and heart, while delivering the prescribed dose to the target volume. There are little data published on proton therapy for mesothelioma, and technical challenges unique to proton therapy. This summary is the Particle Therapy Co-operative Group (PTCOG) Thoracic Subcommittee task group's review of proton therapy for malignant pleural mesothelioma.

Photon Therapy for Mesothelioma

Radiation therapy for pleural mesothelioma has evolved over the last several decades.[18] Because this cancer is uncommon, very few randomized trials have been conducted with radiotherapy as the primary focus. Single institution studies or retrospective reviews have led to the current treatment paradigms for patients with mesothelioma. Aggressive therapies (surgery and adjuvant or neoadjuvant radiation therapy) are typically reserved for fit patients with Stage I-III and epithelioid subtype of mesothelioma.[19]

Conventional radiation therapy for mesothelioma began with 2D or 3D fields and evolved at specialized centers to include AP/PA photon fields and matching electrons fields with blocks to protect the spinal cord, liver, stomach, kidneys and heart.[13,20,21] Most initial reports included patients who had undergone EPP. While acceptable, this technique was felt to be lacking in terms of coverage and dose homogeneity. As technology improved, so did radiation techniques. IMRT allows more conformal coverage of large and complex treatment volumes with the possibility of dose escalation, and as such its use to treat mesothelioma is increasingly significantly, but it results in a large volume of uninvolved tissues receiving a "low dose radiation bath."[22,23] After initial reports with unacceptably high rates of severe and fatal pneumonitis, dose constraints to the uninvolved lung emerged, with most centers applying a mean dose less than 8 Gy to the contralateral lung to enhance safety.[11,24-28] SAKK17/04 was an international multicenter randomized phase 2 trial conducted with radiation as the primary question. This study enrolled patients who had undergone R0 or R1 resection after EPP and neoadjuvant chemotherapy (cisplatin and pemetrexed) and randomized 54 patients to radiation or observation. The investigators found no difference in locoregional relapse-free survival and

increased toxicity in those who received radiation.[29] Their controversial conclusion to not recommend radiation therapy following EPP has been questioned due to the small numbers of patients enrolled resulting in low power (the trial was closed early due to poor accrual) as well as lack of central review and shared dosimetric results.[30] There was no apparent advantage to the radiotherapy, but the trial was both underpowered and incomplete. However, EPP is being performed less frequently since many centers are increasingly performing P/D, with EPP now more commonly reserved only for select patients.[31]

Many centers have been reluctant to provide adjuvant radiation therapy to patients who have undergone P/D, as they have an intact lung underlying the radiation portal that is susceptible to radiation-induced lung injury. Treating the entire pleural surface of a lung safely is quite challenging. A pioneer in this area has been MSKCC. Their approach consists of comprehensive pleural IMRT and is known as Intensity Modulated Pleural RadIatioN Therapy (IMPRINT) after P/D.[32] Their single institution, single arm studies have shown that this approach is safe (20% incidence of grade 3 pneumonitis with one treatment related death), with median survival rates range from 17 to 26 months.[33] They also found that heart dose correlated strongly with symptomatic radiation pneumonitis; therefore, both lung and heart doses must be considered to minimize pneumonitis risk[34]. With a 2-year local failure rate of 74%, they stress the need for adequate initial surgery.[14] MSKCC also conducted a phase II study with MD Anderson Cancer Center utilizing neoadjuvant chemotherapy followed by P/D and adjuvant IMRT and reported median PFS of 12.4 months and OS of 23.7 months.[32] This technique will be applied in an upcoming NRG Oncology cooperative group study randomizing patients to receive or not receive adjuvant IMPRINT (NRG LU006). A recent randomized study presented at the European Society for Radiotherapy and Oncology 2019 meeting showed that for patients

with incompletely resected mesothelioma after lung sparing surgery, radical hemithoracic radiotherapy (50 Gy hemithorax with 60 Gy to gross disease) improved 2-year overall survival from 28% to 58%, compared to palliative dose radiation, providing strong, high level evidence that "definitive" dose radiation is beneficial in this patient population [35].

For patients with unresectable disease, the role of radiation is frequently palliative. The National Comprehensive Cancer Network (NCCN) recommends palliation with doses of 20-40 Gy and with preference for a larger fraction size of 4 Gy.[19] Dr. MacLeod and his colleagues from the University of Edinburgh conducted a multicenter, single arm Phase 2 study looking at pain relief following 20 Gy in 5 fractions.[36] They found that 14 out of the 40 patients treated had a clinically meaningful improvement in their pain at 5 weeks following treatment. One typical palliative regimen is 25-30 Gy in 5 fractions for chest wall disease.[9]

Finally, de Perrot and colleagues from the Princess Margaret Hospital are investigating the use of high doses of radiation therapy to the entire intact lung followed by EPP within 7 days for select patients with clinically node-negative disease; they call this protocol SMART (Surgery for Mesothelioma After Radiation Therapy).[37] In this single arm Phase 2 study, patients who were fit for surgery underwent radiation therapy to 25 Gy to the entire lung and a simultaneous integrated boost of 5 Gy to gross disease. Patients who were found at surgery to have positive nodes went on to receive chemotherapy. The investigators reported a very promising median survival of 36 months. This study has not yet been replicated by other centers.

Conclusions

Toxicity from radiation treatment for mesothelioma remains a major challenge. Heart, lung and often esophagus doses are high and predispose patients to life-threatening complications. Local

control and survival remain poor. This leaves much room for improvement in therapy to both mitigate toxicity and increase efficacy.

Rationale for Proton Therapy in Mesothelioma

The physical properties of proton beam therapy are particularly advantageous for sparing of large radiosensitive thoracic organs-at-risk (lungs, heart, spinal cord, esophagus) when treating pleural mesothelioma. Proton therapy has the potential to both decrease toxicity and to dose escalation to the target to improve local control and survival. The ability to modulate the shape and intensity of the proton beam with intensity-modulated proton therapy (IMPT) using scanning beam technology provides further advantages over passive scattering proton therapy. Lin et al demonstrated that scanning beam proton therapy achieved better tumor coverage and conformity of radiation dose with reduced dose to the lungs, esophagus, heart, and spinal cord compared with first generation proton therapy using double scattering technique.[38]

Figures 1 through 4 provide dosimetric comparisons between photon IMRT plans and IMPT plans for two patients treated at MD Anderson Cancer Center. Figure 1 shows the three-field IMPT plan for a patient post-EPP. The prescription dose was 50 Gy in 2 Gy fractions. Figure 2 shows the dosimetric comparison between the IMPT plan in Figure 1 and an IMRT plan for the same patient. Although both IMRT and IMPT plans had similar target coverage, the IMPT plan produced lower doses to the contralateral lung, heart, esophagus, liver, and kidneys. Importantly, mean dose to the contralateral lung was 4.8 Gy with IMRT and only 1.4 Gy with IMPT. The higher doses with IMRT mainly resulted from the low-dose bath, as the two plans had similar contralateral lung V20 and V10 values, but V5 was higher with IMRT (34.2% vs. 8.0%). IMPT further led to a lower mean heart dose (12.6 Gy vs. 28.2 Gy for IMRT), mean liver

dose (12.6 Gy vs. 29.1 Gy), and mean doses for the ipsilateral and contralateral kidneys (11.3 Gy vs. 32.8 Gy, and 0.2 Gy vs. 3.9 Gy, respectively). These are clinically meaningful decreases to these organs.[39,40]

Other groups have also found a clear dosimetric advantage to proton therapy over IMRT in the post-EPP setting. Krayenbuehl et al performed a dosimetric comparison of IMPT versus IMRT in 8 patients with mesothelioma treated by EPP followed by IMRT. They found significant improvements in target coverage (V95) and reduced mean doses to kidneys, contralateral lung, heart, spinal cord, and liver with IMPT compared to IMRT.[41] A similar dosimetric comparison of IMRT to IMPT was performed by Lorentini et al in 7 patients treated with EPP and IMRT. The authors confirmed the findings of the previous analysis, noting significant reductions in several organs at risk with IMPT. In addition, using normal tissue complication probability modeling, they predicted significantly reduced risks of toxicities to the liver, kidneys, and esophagus with IMPT compared with IMRT. Likewise, a series from investigators at the University of Washington showed that in the post-EPP setting for hemithoracic radiation, IMPT radiation plans can deliver up to 66 Gy to the target volume while meeting normal tissue dose constraints with contralateral mean lung doses of $\leq$1.5 Gy.[42] This is compared with photon VMAT plans that would either have to exceed normal tissue dose limits to achieve similar target volume coverage or sacrifice target volume coverage to meet normal tissue constraints. A comparison of various spot sizes with IMPT found that larger spot sizes (sigma of 9 mm) are generally more robust compared to a small spot size (sigma of 3 mm), but resulted in slightly reduced target coverage while still meeting target coverage goals and dose constraints of OARs.[43] Robustness of smaller spot sizes may be mitigated through 4D robust optimization.

Less has been published on proton therapy in the post-P/D setting (with an intact ipsilateral lung). Figure 3 shows a proton IMPT plan for a patient post-P/D. The prescription dose was 50 Gy with 2 Gy per fraction. Due to the large PTV volume (3276.4 cc), a two isocenter technique with four beams was used in this case to design a multi-field optimization (MFO) plan, although some of the newer proton machines can treat this volume without needing to split the fields, and 2 beams could be used to treat the volume. Figure 4 shows the dosimetric comparison between the IMPT plan in Figure 3 and a VMAT plan for the same patient. The most challenging normal tissue constraint in this setting remains the ipsilateral lung dose. IMPT produced lower mean doses to the contralateral lung (0.1 vs. 2.9 Gy), heart (7.4 vs. 21.4 Gy), liver (14.8 vs. 29.0 Gy), ipsilateral kidney (2.6 vs. 11.2 Gy), and contralateral kidney (0.07 vs. 5.8 Gy). However, the mean dose for ipsilateral lung is slightly higher for the IMPT plan (48.7 vs. 46.3 Gy), largely due to a slight increase in PTV coverage for the IMPT plan. In post-P/D hemithoracic radiation, proton radiation can decrease dose to organs outside the target volume (contralateral lung, heart, liver, kidneys, etc.) but not to the ipsilateral lung.

Conclusions:

Compared with photon-based radiation techniques, proton therapy for mesothelioma can substantially reduce radiation dose to the contralateral lung (mean dose to contralateral lung often <1.5 Gy, V5Gy <10%), which is associated with mortality and morbidity in mesothelioma treatment. Proton therapy also decreases mean heart, mean liver, and kidney doses by more than half. This is true both in the post-EPP setting as well as the post-P/D setting. Proton therapy does not appear to reduce ipsilateral lung dose compared to photon therapy in the post-P/D setting. Although there is no high-level comparative clinical data on proton therapy versus photon therapy for mesothelioma, the clear dosimetric advantages of proton therapy in this

setting, especially IMPT, and the high mortality/morbidity risk associated with normal tissue dose in mesothelioma radiation therapy, means that IMPT should be strongly considered in this setting, when available, and delivered by experienced multi-disciplinary management teams.

Challenges with Proton Therapy for Mesothelioma

Range Uncertainty in Protons

Proton beams have a characteristic Bragg Peak with a distinctive sharp dose fall-off at the distal end. This makes proton beam therapy sensitive to range uncertainties. The proton range in tissue is associated with considerable uncertainties in inherent CT uncertainties, patient setup, anatomical variation and dose calculation. In addition, while dose calculations use a constant relative biological effectiveness (RBE) of 1.1 for protons, the RBE is potentially higher toward the distal end of the proton beam. The variable RBE effect can potentially extend the range up to 3 mm.[44] The use of a constant RBE of 1.1 is clinically employed because of the uncertainties in RBE and lack of RBE modeling in existing commercially available treatment planning systems.[45]

To address the range uncertainties caused by CT imaging and patient setup, different proton centers have individual margin recipes to account for range uncertainties ranging from 2.5% of the range + 1.5 mm to 5% of the range + 5 mm.[45] For IMPT, ±3% in range and ±3-5 mm in patient setup uncertainties are often used for clinical target volume-based robust optimization and/or robustness analysis.

For treatment delivery, range shifters are generally needed to cover the target volume in the shallow region and a larger air gap may be used for treatment setup clearance. However, the analytical pencil beam dose calculation algorithm implemented in most proton treatment

planning systems does not accurately account for the lateral inhomogeneity for each of the ray traces and the dose scattered from ranger shifters. Therefore, the use of a Monte Carlo dose calculation algorithm is preferred to ensure dose calculation accuracy.[46,47]

Organ Motion

Proton beams are sensitive to the volume and density of tissue that is traversed on the way to the target. The potential dosimetric impact of respiratory motion, cardiac motion, and tissue density variation need to be addressed carefully.

IMPT is more sensitive to tumor motion as compared to a compensator-based/passive-scattering techniques. Dose to the moving target can be affected by interference between the dynamic spot-by-spot scanning beam delivery and tumor motion, commonly known as the interplay effect[48]. While the averaging effect over many fractions in a conventional fractionation scheme can reduce the interplay effect, 4D robust planning, increased spot sizes, layered re-scanning, volumetric re-scanning, breath holding/assisted breathing, and gating techniques have been used as mitigation strategies.[48-51] These strategies can effectively mitigate the interplay effect depending on the magnitude of tumor motion, tumor volume and proton beam spot size.[50] In addition to 4D robust treatment planning, 4D robustness evaluation should be employed to assess the combined effect of possible uncertainties impacting IMPT treatments[52]. A detailed discussion of IMPT in the treatment of thoracic malignancies can be found in the recent consensus statement by PTCOG.[53]

For patients with malignant pleural mesothelioma after pleurectomy/decortication, tumor and normal tissue motion in the ipsilateral lung is typically minimal due to limited diaphragmatic excursion or in the definitive setting due to tumor restricting respiratory excursion.[33]

Nevertheless, target motion should be assessed with 4D CT, and appropriate tumor motion mitigation strategies should be used, as needed.

IGRT and Anatomy Change

On-board cone-beam CT is ideal for on-line IGRT and can allow for deformable registration for ease of adaptive proton therapy, but it is not available at every proton center.[54] On-board KV orthogonal imaging is acceptable for IGRT, as bony anatomy can be used as surrogates. However, the potential of anatomy change, including air volume and changes in pleural effusions in the hemithorax for mesothelioma patients receiving radiotherapy can be significant. In patients who undergo EPP, the hemithorax will gradually fill with fluid in the post-operative period, especially in the first 8 weeks after surgery. This needs to be monitored during radiotherapy and can impact target coverage and doses to OARs.[41] The impact of this volume change has a greater impact with protons than photons. Therefore, volumetric imaging either using on-board cone-beam and/or regularly scheduled quality assurance CT scans should be used during the treatment course to monitor for anatomy changes. Adaptive re-planning may be needed to adjust to the anatomy changes to ensure proper dose delivery.

Conclusions:

When using proton therapy for mesothelioma, close attention must be paid to range uncertainty, organ motion, changes in anatomy and beam path tissue composition, as well as limitations in image guidance. Proton therapy for mesothelioma should preferentially be delivered at high volume centers with specialized expertise.

Clinical Data on Proton Therapy for Mesothelioma

Although clinical data on mesothelioma patient outcomes after proton beam therapy are limited, early reports have demonstrated very promising treatment toxicity and disease control outcomes. University of Washington reported a 3-case series of patients with mesothelioma receiving hemithoracic proton radiation post-EPP.[42] All three patients received neoadjuvant cisplatin/pemetrexed prior to EPP. Even with boost doses up to 66 Gy, treatment was well tolerated, and radiation pneumonitis was not observed. Mean dose to the contralateral lung was 0.3 Gy, 0.7 Gy, and 1.5 Gy for the three patients treated to 54 Gy to the hemithorax, with one patient receiving a 60 Gy boost and another patient receiving a 66 Gy boost.

University of Pennsylvania reported their experience of 16 patients with unresectable mesothelioma treated with 17 proton therapy courses. Patients were predominantly male (81%) with epithelial histological subtype (82%) and stage III-IV disease (94%). Patients were a median of 69.8 years old at the time of PT, which was delivered a median of 11.1 months after mesothelioma diagnosis (range 3.5-69.3 months). All patients received pemetrexed plus cisplatin or carboplatin prior to (n=15) or concurrently with (n=1) proton therapy. Proton therapy was administered as adjuvant therapy following lung-sparing radical pleurectomy (n=8), to sites of gross disease (but excluding the entire pleural surface) following progression on systemic therapy (n=8), or as initial definitive therapy with concurrent chemotherapy (n=1). Patients were treated to a median dose of 51.75 Gy (CGE) in 2.0 Gy (CGE) daily fractions (range 50.0-75.0Gy/1.8-2.5Gy). All patients had durable local control throughout the follow-up period at a median follow-up of >5 months from proton therapy completion. At the time of reporting at International Association for the Study of Lung Cancer 16th World Conference on Lung Cancer, the median overall survival for the cohort had not yet been reached, and no patient developed any acute or late grade ≥3 toxicity. Across the 17 proton therapy courses, acute grade

2 toxicity included radiation dermatitis (n=8), dysphagia/esophagitis (n=4), anorexia (n=3), fatigue (n=2), and cough (n=1). Late grade 2 toxicity included radiation pneumonitis in just one patient (6%). Overall, patients' ECOG performance score improved from proton therapy beginning to end (mean 1.2 to 0.9).[55] In a subsequent report, the same investigators prospectively treated 10 patients with proton therapy to a median of 55.0 CGE/1.8-2.0 CGE (range 50-75 CGE) adjuvantly (n=8) or as salvage therapy (n=2) following P/D. Patients were predominantly male (90%) with epithelioid histology (100%) and stage III-IV disease (100%). Two-year local control was 90%, with distant and regional failure rates of 50% and 30%, respectively. Median survival from proton therapy completion was 19.5 months (30.3 months from diagnosis), and no patient experienced CTCAEv4 grade ≥2 acute or late toxicity.[56] The lack of severe toxicity is unique and important.

MD Anderson Cancer Center also reported on their experience using IMPT to treat 3 mesothelioma patients with intact lungs, showing that the technique is safe and feasible.[57] IMPT plans produced lower doses to normal tissues compared to IMRT plans for the same patients. The dose reduction to the heart and contralateral lung were particularly notable. The University of Maryland reported on the first 10 consecutive patients treated with whole pleural (WP) IMPT for lung-intact MPM[58]. Median prescribed WP dose was 45Gy (range 45.0-50.4 Gy/1.8-2.0 Gy) and median total dose was 54Gy (range 50.0-60.0 Gy/1.8-2.4 Gy). At a median follow-up of 6.5 months, treatment was well tolerated, with only two patients suffering grade 3 pneumonitis (20%) and no other severe (grade ≥3) toxicities. Six month local control was 87.5% (95% CI: 76 – 99), progression free survival 31% (95% CI: 14 - 48) and overall survival 64.3% (95% CI 48 – 81).

Best Practice Recommendations for the Treatment of Mesothelioma with Proton Therapy

Based on the data presented above, for patients undergoing radiation treatment for mesothelioma in the non-palliative setting, we recommend intensity-modulated proton therapy (IMPT) with scanning beam proton technology as the preferred proton delivery method. Although there are no high-level comparative clinical data on proton therapy versus photon therapy for mesothelioma, there are clear dosimetric advantages for proton therapy. The high mortality/morbidity risks associated with photon therapy strongly suggests that IMPT should be considered in this setting, when available, and delivered by experienced multi-disciplinary management teams. Specific recommendations for steps of the treatment process follow. We also encourage readers to review the recent consensus guidelines on radiation therapy for mesothelioma by the U.S. NCI, IASLC, and MARF[17], and the NRG Oncology contouring atlases for lung cancer.

Simulation

All patients should undergo 4-D CT-based simulation with motion evaluation with slice thickness ≤3mm, scanning from at least C3 to below both kidneys (top of iliac crest). Patients are treated supine with their arms up with immobilization devices. For target volumes that exhibit more than a threshold of motion (typically >5 mm maximum), motion mitigation strategies should be employed, such as abdominal compression, breath hold, respiratory gating, and dose repainting techniques. The combined effect of possible uncertainties should be assed via 4D evaluation of the interplay effect for every patient.

Contouring

Gross disease should be contoured as gross tumor volume (GTV). The pleural surface is included in the clinical target volume (CTV), which typically includes a 5 mm rind of tissue from lung apex/thoracic inlet down to the insertion of the diaphragm posteriorly down to the

T12-L1 vertebral body.[59] Pleura covering interlobar fissures, however, is not typically included unless grossly involved. Resection tracks and involved nodes are also included, but elective nodal irradiation is not recommended. Motion management of target volumes (IGTV/ICTV) should be contoured per PTCOG consensus guideline on implementing scanning beam proton therapy[53].

Treatment Planning

Treatment planning is typically performed on the average CT scan but reviewed on additional phases (typically at least maximal inhalation and exhalation) to ensure coverage throughout the respiratory cycle, ideally with 4D robust optimization[60]. IMPT is highly recommended for mesothelioma treatment due to the complicated target shape. Two to four fields are typically used in planning, most optimally with MFO, with beam angles ranging from anterior to posterior, laterally around the ipsilateral chest (i.e. left sided beams for treating a left sided tumor). The use of a Monte Carlo dose calculation algorithm for improved dose calculation accuracy is also preferred.

Target dose should be at least 45 Gy for microscopic disease and 60 Gy for gross disease. With proton therapy, dose escalation beyond 60 Gy is possible while still staying well below normal tissue dose constraints[42,61]. Relevant OARs include normal lungs, heart, liver, kidneys, esophagus, spinal cord, stomach, brachial plexus, and skin. Proton therapy can typically achieve contralateral mean lung dose <1.5 Gy with V20Gy <5%, mean heart dose <15 Gy, mean liver dose <25 Gy (for right sided tumors), ipsilateral kidney mean dose <18 Gy, contralateral kidney mean dose <1 Gy, mean esophagus dose <34 Gy, and spinal cord max 45 Gy. While there are no specific dose constraints for the skin, plans should be optimized to minimize hot spots and dose to the skin rind. For patients being treated with two intact lungs in the post-P/D setting, the

ipsilateral lung will receive almost the entire prescription dose, and this treatment should only be performed at high volume centers or on a clinical trial. Total lung mean dose should be <20 Gy, when feasible.

Onboard Imaging/Adaptive Replanning

Daily cone-beam CT is ideal for treatment of mesothelioma due to the potential for anatomic changes in the thoracic cavity during the several week-long treatment course. Since many proton centers do not have this technology, daily kV-kV orthogonal pairs is also acceptable, with repeat verification quality assurance CT simulation at least once every 5 (ideal, especially in the first half of treatment) to 10 fractions to confirm stability in anatomy[54,62]. Since weeks can pass between simulation and treatment start, the first quality assurance scan should happen early in the treatment course (first week). When a re-scan is done for quality assurance, the treatment plan should be run on the new re-scan to ensure target coverage and normal tissue dose limits are still met. If there is a clinically meaningful decrease in coverage or increase in normal tissue dose, adaptive replanning should be performed.

Overall Recommendations:

For patients receiving non-palliative radiation therapy for mesothelioma, proton therapy is likely to be beneficial in terms of its ability to decrease radiation dose to the contralateral lung (the greatest potentially life-threatening toxicity risk in radiation therapy for mesothelioma), as well as other organs such as heart, liver, and kidneys. Proton therapy has clear dosimetric advantages over photon therapy. There are significant expertise requirements to delivering hemithoracic radiation with proton therapy due to the large volume that needs to be treated, complex shape of the target, organ motion, as well as possible changes in tissue density during treatment. Proton

therapy for mesothelioma, therefore, should preferentially be delivered at high volume centers with specialized expertise in delivering this treatment. IMPT is better suited for the complex tumor volume anatomy, but motion management strategies must be applied and adequate image guidance utilized. Dose reduction to normal tissues opens up possibilities of treatment intensification to improve outcomes, such as radiation dose escalation, or combination with concurrent systemic therapy. The limited but growing clinical data reported to date on proton therapy for mesothelioma is promising, and more publications on the clinical experience of proton therapy for mesothelioma treatment are needed. The currently poor prognosis for patients with mesothelioma makes it imperative that strategies are explored to increase treatment efficacy, as well as decrease treatment toxicity to improve quality of life.

FIGURE LEGENDS

Figure 1. IMPT plan for a patient with mesothelioma post-EPP. Axial, coronal and sagittal images show the dose distribution for each of the three proton fields: ALAPB (a), BPAPB (b), CRAPB (c), and composite dose (d). Multi-field optimization (MFO) was required to cover this complex volume. At least two beams contributed to dose at every voxel to maximize target uniformity and organ sparing. ALAPB and CRAPB beams provided most of the dose to the anterior region; BPAPB and CRAPB beams provided most of the posterior coverage; and all three beams contributed to coverage superiorly. Although the dose from each beam is not uniform, the composite plan provides uniform dose coverage across the target.

Figure 2. Dosimetric comparison in post-EPP setting. IMPT plan (top panel left) and IMRT plan (top panel right) for a patient post-EPP are shown, with corresponding DVHs of the IMPT plan (solid line, bottom panel) and IMRT plan (dashed line, bottom panel). The IMRT plan used 8 co-planar 6-MV beams (0°, 30°, 165°, 190°, 215°, 240°, 265°, 290°). Normal tissue constraints used included: mean contralateral lung dose <5 Gy, maximum cord dose <45 Gy, mean esophagus dose <34 Gy, mean heart dose <26 Gy, and heart V30Gy <45%. Goal planning target volume (PTV) coverage was >95% of PTV receives at least the prescription dose.

Figure 3. IMPT plan for a patient with mesothelioma post-P/D. Axial, coronal and sagittal images show the dose distribution for each of the four proton fields: AAPPB (a), BRPPB (b), CRAPB (c), DPAPB (d) and composite dose (e). Due to the large PTV volume (3276 cc), a two isocenter technique with four beams was used to design a MFO plan. The two isocenters were

5cm apart to achieve maximum overlap and efficient daily set-up. The posterior beams, BRPPB (gantry angle 220) and DPAPB (gantry angle 180), were assigned to the lower isocenter and covered the superior and posterior portion of the target volume. Two anterior beams (AAPPB at gantry angle 0, CRAPB at gantry angle 320) were assigned to the upper isocenter and covered the superior and anterior portion of the target volume. MFO was utilized to ensure uniform dose over the overlapping regions. Each beam was delivered in 4–7 minutes, for a total of 25 minutes of beam-on time for the 4-beam plan. Robust evaluation tools were used to analyze the IMPT plan against 3-mm setup and 3.5% range uncertainties.

Figure 4. Dosimetric comparison in the post-P/D setting. An IMPT plan (top panel left) and IMRT plan (top panel right) are shown for a patient post-P/D, with corresponding DVHs of the IMPT plan (solid line, bottom panel) and IMRT plan (dashed line, bottom panel). The IMRT plan used volumetric arc therapy (VMAT) with two arcs (181° to 37° clockwise with 10° collimator rotation and 35° to 183° count clockwise with 350° collimator rotation).

Figure 1.

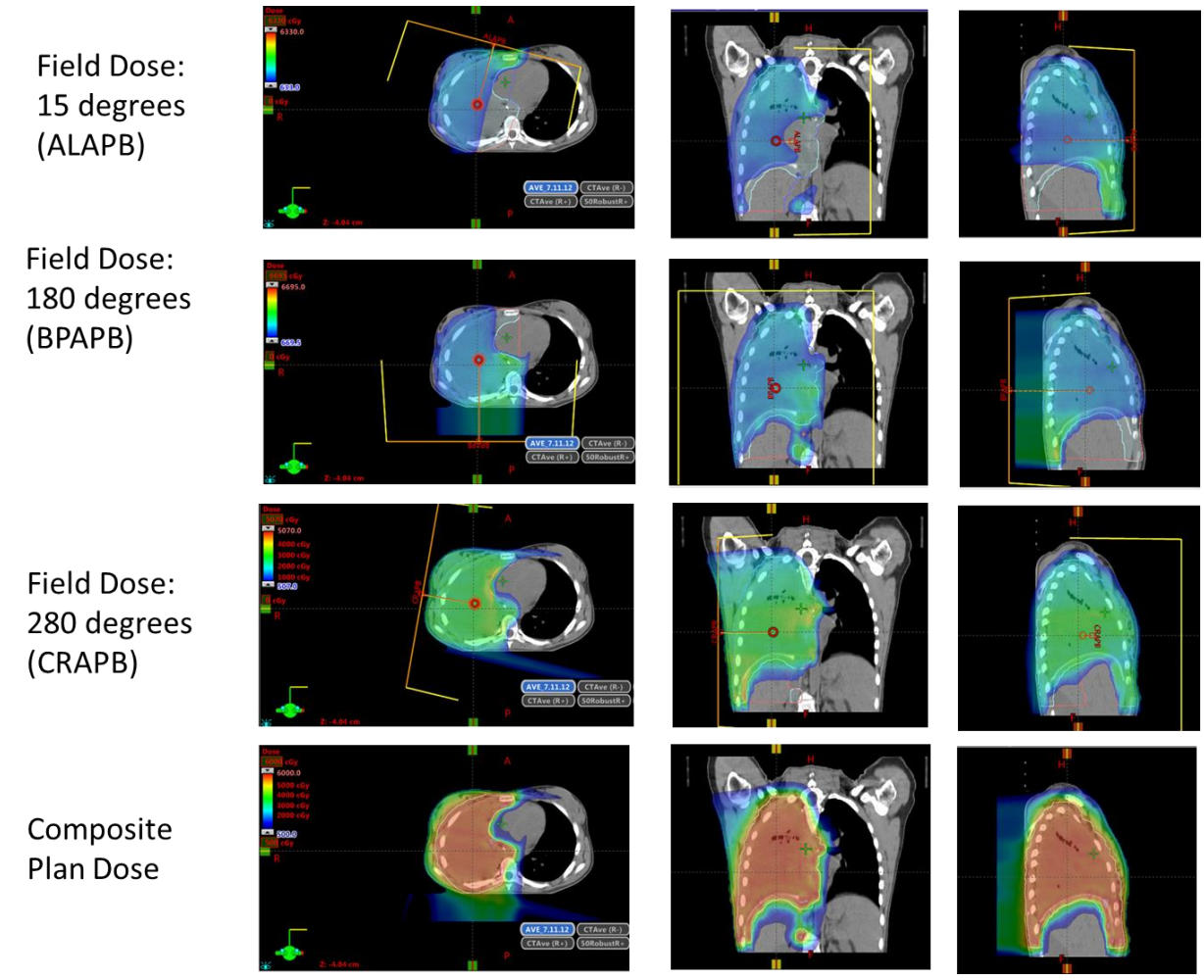
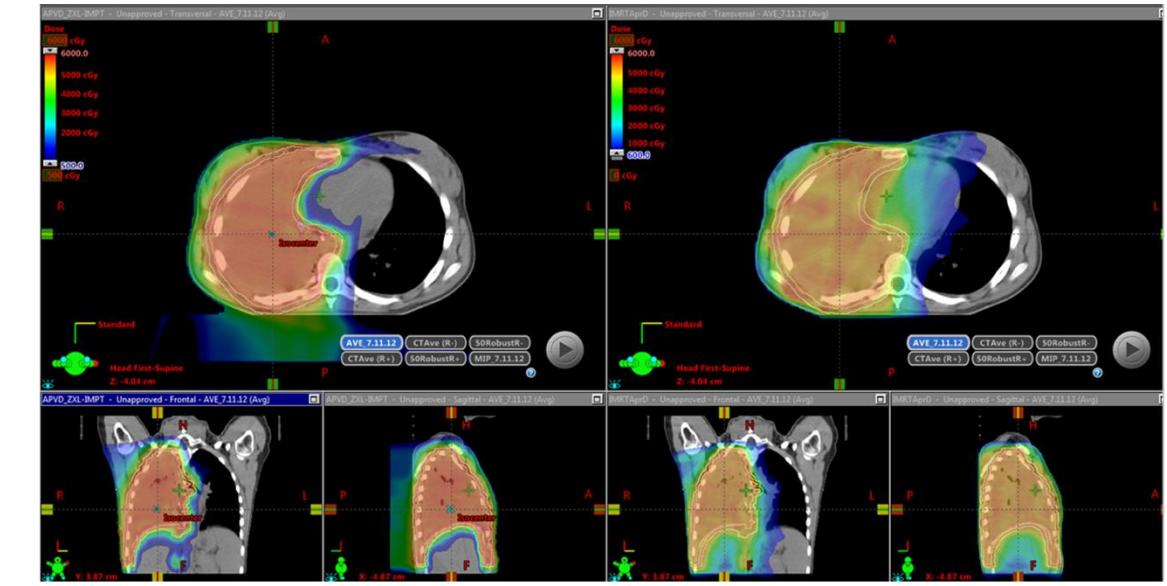
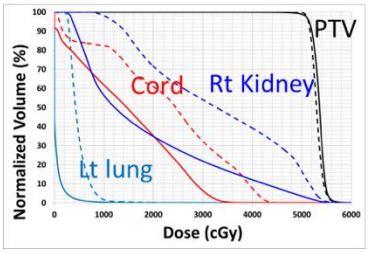
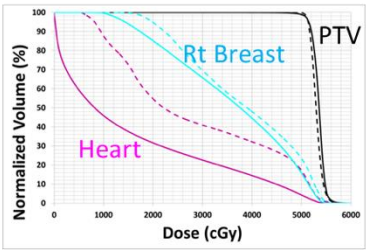

Field Dose:
15 degrees
(ALAPB)
Field Dose:
180 degrees
(BPAPB)
Field Dose:
280 degrees
(CRAPB)
Composite
Plan Dose

Figure 2.




PTV
Cord
Rt Kidney
Lt lung
Normalized Volume (%)
Dose (cGy)


PTV
Rt Breast
Heart
Normalized Volume (%)
Dose (cGy)

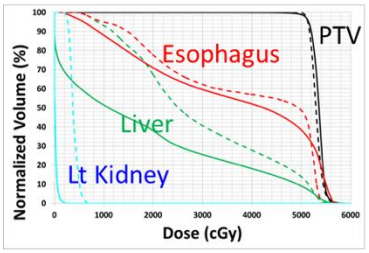

PTV
Esophagus
Liver
Lt Kidney
Normalized Volume (%)
Dose (cGy)

Figure 3.

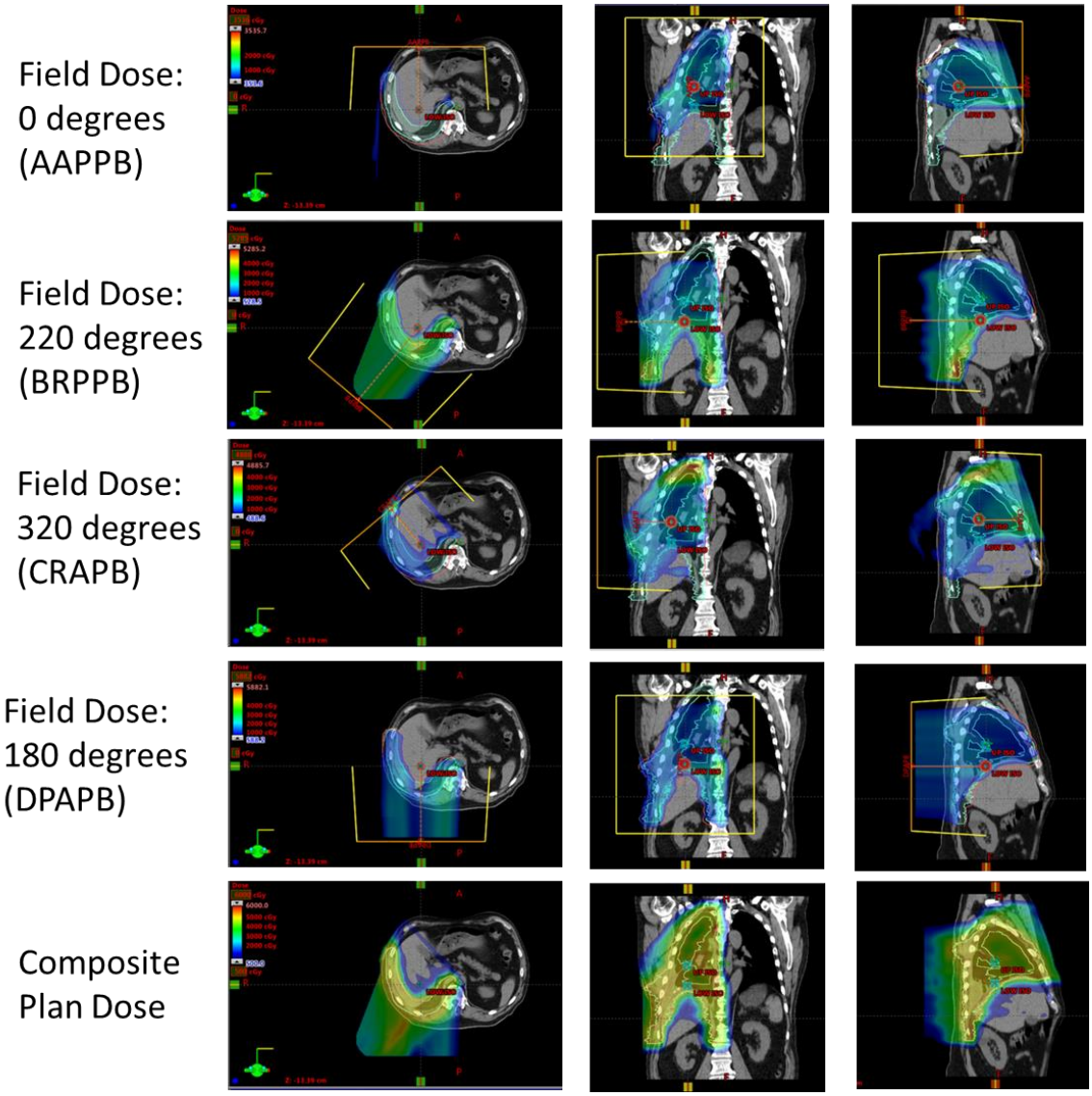
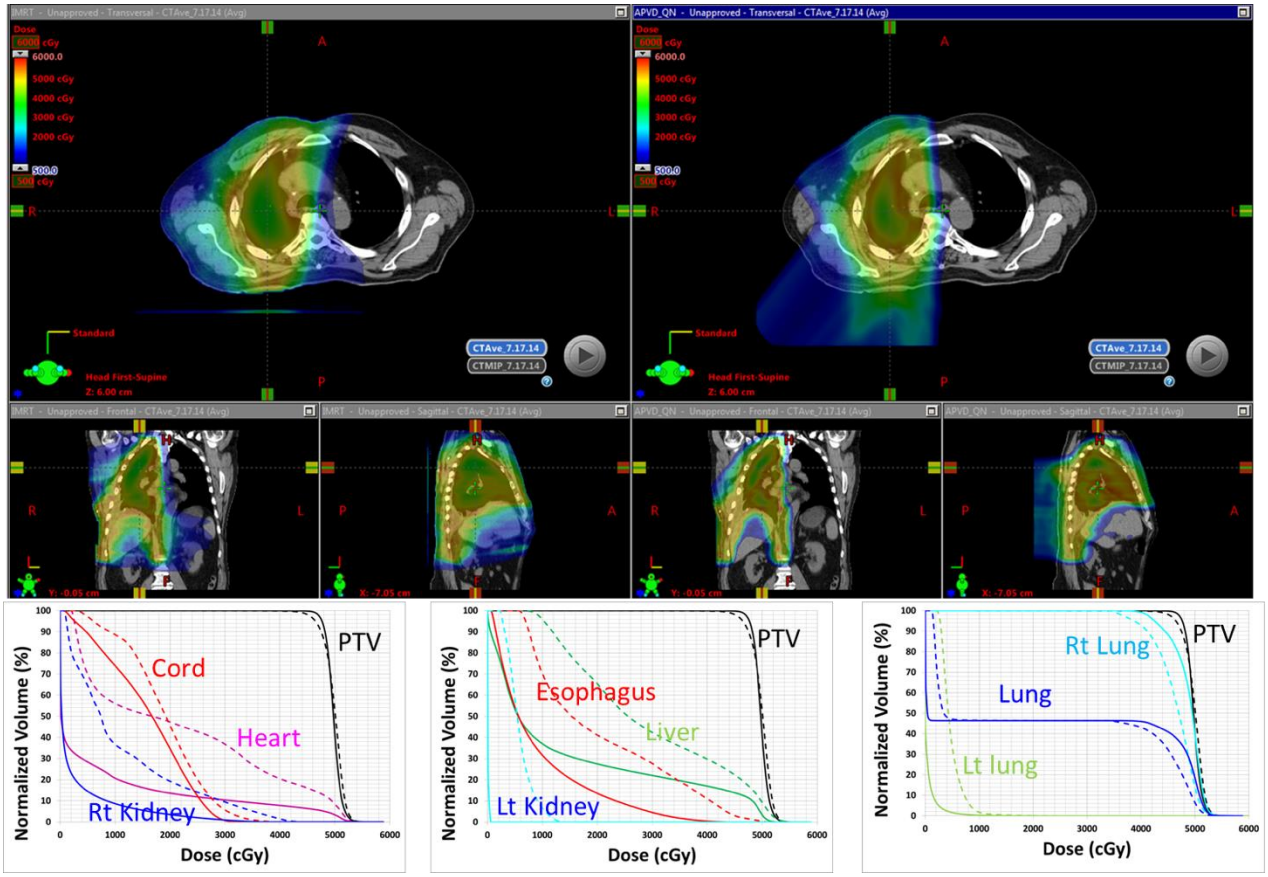

Field Dose:
0 degrees
(AAPPB)
Field Dose:
220 degrees
(BRPPB)
Field Dose:
320 degrees
(CRAPB)
Field Dose:
180 degrees
(DPAPB)
Composite
Plan Dose

Figure 4.


IMRT - Unapproved - Transversal - CTAve_7.17.14 (Avg)
APVD_QN - Unapproved - Transversal - CTAve_7.17.14 (Avg)
Dose
6000 cGy
5000 cGy
4000 cGy
3000 cGy
2000 cGy
500 cGy
Standard
Head First-Supine
Z: 6.00 cm
CTAve_7.17.14
CTMIP_7.17.14
IMRT - Unapproved - Frontal - CTAve_7.17.14 (Avg)
IMRT - Unapproved - Sagittal - CTAve_7.17.14 (Avg)
APVD_QN - Unapproved - Frontal - CTAve_7.17.14 (Avg)
APVD_QN - Unapproved - Sagittal - CTAve_7.17.14 (Avg)
Normalized Volume (%)
Dose (cGy)
PTV
Cord
Heart
Rt Kidney
Esophagus
Liver
Lt Kidney
Rt Lung
Lung
Lt lung

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