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A Novel Prospective Study Assessing the Combination of Photodynamic Therapy and Proton Radiation Therapy: Safety and Outcomes When Treating Malignant Pleural Mesothelioma†

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Abstract

Malignant pleural mesothelioma remains difficult to treat, with high failure rates despite optimal therapy. We present a novel prospective trial combining proton therapy (PT) and photodynamic therapy (PDT) and the largest-ever mesothelioma PT experience ($n = 10$). PDT photosensitizers included porfimer sodium ($2 \text{ mg} \cdot \text{kg}^{-1}$; 24 h drug-light interval) or 2-[1-hexylox-yethyl]-2-devinyl pyropheophorbide-a (HPPH) (4 mg m^{-2} ; 48 h) with wavelengths of 630 nm to 60 Jcm^{-2} and 665 nm to $15\text{--}45 \text{ Jcm}^{-2}$, respectively. With a median age of 69 years, patients were predominantly male (90%) with epithelioid histology (100%) and stage III-IV disease (100%). PT was delivered to a median of $55.0 \text{ CGE}/1.8\text{--}2.0 \text{ CGE}$ (range $50\text{--}75 \text{ CGE}$) adjuvantly ($n = 8$) or as salvage therapy ($n = 2$) following extended pleurectomy/decortication (ePD)/PDT. Two-year local control was 90%, with distant and regional failure rates of 50% and 30%, respectively. All patients received chemotherapy, and four received immunotherapy. Surgical complications included atrial fibrillation ($n = 3$), pneumonia ($n = 2$), and deep vein thrombosis ($n = 2$). Median survival from PT completion was 19.5 months (30.3 months from diagnosis), and 1-and 2-year survival rates were 58% and 29%. No patient experienced CTCAEv4 grade ≥ 2 acute or late toxicity. Our prolonged survival in very advanced-stage patients compares favorably to survival for PT without PDT and photon therapy with PDT, suggesting possible spatial or systemic cooperativity and immune effect.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a tumor that arises from the mesothelial surfaces of the lung pleura that is more often seen in men and diagnosed most typically in the 5th to 7th decade of life (1). Approximately 2500 cases occur per year in the United States, and MPM is linked with asbestos exposure (2,3). Survival remains poor, with stage III-IV

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patients having estimated median overall survivals ranging from 10 to 14 months (4). Multiple studies have shown that patients with epithelial subtype have a more favorable prognosis than biphasic and sarcomatous subtypes of mesothelioma across treatment approaches (5–14).

Combined chemotherapy, most commonly with cisplatin or carboplatin and pemetrexed, remains a mainstay of treatment (15–18). In well-selected patients, surgical resection can improve survival and is recommended on the basis of consensus guidelines by the International Mesothelioma Interest Group Congress (19,20). For patients who are surgically resectable, two options of surgical excision exist: extrapleural pneumonectomy (EPP) in which the lung, pleura, pericardium and diaphragm are removed en bloc, or extended pleurectomy/decortication (ePD), a lung-sparing surgery that removes macroscopic disease with the parietal/visceral pleura but that generally allows for preservation of the diaphragm and phrenic nerve (21). EPP can leave less residual tumor cells compared with ePD; however, it often results in high morbidity and even mortality rates, severe depression of cardiorespiratory function, and poor quality of life (22). In a systematic review and meta-analysis of seven studies with comparative data on EPP and ePD, perioperative mortality and morbidity was found to be 2.9% and 27.9% in the ePD group compared to 6.8% and 62.0% in the EPP arm, respectively (22).

Photodynamic therapy (PDT) can be utilized for the treatment of malignant and non-malignant causes (23–27). It is composed of three components that include a photosensitizing chemical, a light source with a wavelength appropriate to cause excitation, and oxygen within a tissue that is exposed. The wavelength of light is specific to the photosensitizer and is responsible for producing free radical and/or reactive oxygen species. Energy is transferred mainly from the triplet sensitizer to ground state oxygen to produce a highly reactive form of oxygen known as singlet oxygen. Singlet oxygen is highly cytotoxic with a very short duration in tissue on the order of microseconds (28,29). PDT has been used in conjunction with both EPP and ePD (30–32).

An older phase III trial performed from 1993 to 1996 to compare maximal debulking surgery with postoperative cisplatin, interferon alpha-2b and tamoxifen $\pm$ intraoperative PDT failed to influence the patterns of recurrence or improve median survival in 63 patients with malignant pleural mesothelioma (14.1 vs 14.4 months) (33). All underwent maximum debulking surgery and were randomized to either PDT or no PDT intra-operatively with photophrin II and 630-nm laser light. While there were no differences between surgical or immunochemotherapeutic toxicities in the PDT and no PDT arms, the toxicity was notable with 11 postoperative complications in 10 patients, most commonly medically reversible arrhythmia ($n = 4$), bronchopleural fistula ($n = 4$), and cardiac herniation requiring pericardial patching ($n = 1$). The bronchopleural fistulas were evenly split between the PDT and no PDT arm. One intraoperative death occurred in the PDT arm due to avulsion of the IVC after a right-sided pleuropneumonectomy. While this trial did not employ real-time PDT dosimetry and included patients with gross residual disease for which PDT would not be expected to be treated effectively with the limited penetration of PDT, a number of additional studies including some that employed real-time dosimetry (34), showed that PDT

is well-tolerated, improves local control (35) and may offer a survival advantage in the Phase I and Phase II settings (32,36–38).

Mesothelioma has intrinsic sensitivity to radiation as evidenced by *in vitro* analysis of mesothelioma and non-small cell lung cancer cells (39,40). Radiation has been used for palliation with a notable dose-response to higher doses and dose-per-fraction, as well as prophylaxis for biopsy sites and drain sites (41–45). Phase II data for preoperative radiation from Princess Margaret Hospital delivering 25 Gy in 5 fractions to the entire affected lung and pleura with a simultaneous integrated boost to 30 Gy to gross disease followed by EPP within 7 days and adjuvant chemotherapy for lymph node positive patients showed excellent results with a median overall survival of 36 months (46). The use of external beam radiotherapy given adjuvantly for mesothelioma has historically been limited by significant morbidities and risk of fatal pneumonitis when treating large pleural volumes (47–49). A Dana-Farber Cancer Institute-Brigham and Women's Hospital study showed fatal pneumonitis in 46% when delivering radiotherapy after EPP (48). Factors associated with development of pneumonitis in this series included the dosimetric parameters of mean lung dose (MLD), volume of lung receiving at least 5 Gy (V5) and volume of lung receiving at least 20 Gy (V20).

While there has been a trend toward increased utilization of intensity-modulated radiation therapy (IMRT) for malignant pleural mesothelioma (50), proton therapy (PT) may more optimally treat this challenging disease than IMRT (51–53). PT is an emerging modality that reduces irradiation to normal tissues compared with photon therapy, which has been shown to improve outcomes and/or reduce toxicities in other thoracic tumors like non-small cell lung cancer (54,55), small cell lung cancer (56), thymic tumors (57,58) and thoracic reirradiation (59). As such, it may be more safely delivered to large pleural surfaces and more safely combined with chemotherapy and surgery/PDT.

The abscopal effect has been described dating back to 1953 and refers to the effects of ionizing radiation at a distance from the irradiated volume but within the same organism (60,61). Immune modulation and recognition is responsible for this event, and an *in vitro* study of multiple cancer cell lines evaluating the up-regulation of surface molecules involved in immune recognition showed that there is upregulation of these molecules and also increased sensitivity to cytotoxic T-lymphocyte killing of tumor cells (62). Additionally, the use of PDT has been shown to be immunogenic in multiple studies (63–65). We, therefore, hypothesized that the use of ePD with PDT and adjuvant PT would offer immunogenic stimulation through multiple mechanisms and enhance tumor kill in mesothelioma patients.

We present a novel prospective experience of patients treated with chemotherapy, ePD/PDT and PT, as well as the largest PT mesothelioma experience reported to date. As there currently are no clinical data combining PDT and PT, we analyze our prospective cohort receiving both modalities to assess for toxicities, local control, and overall survival.

MATERIALS AND METHODS

Patient characteristics and workup.

After IRB approval and patient consent, patients were prospectively enrolled on one of two trials in the Department of Radiation Oncology at the Hospital of University of Pennsylvania between 2011 and 2015. A mesothelioma multidisciplinary team evaluated all patients before enrollment. Criteria for enrollment included epithelial subtype, being deemed medically “fit” for surgery, disease confined to one hemithorax, and informed consent. Patients were selected for this study if they received PT as adjuvant therapy following lung-sparing ePD/PDT or as salvage therapy after ePD/PDT as a part of multi-modality therapy. Ten consecutive patients treated with both PDT and PT were evaluated for this analysis.

Patient characteristics.

A total of 10 patients were enrolled in this trial. Table 1 depicts the patient and treatment characteristics. Patients were predominantly male (90%), and all patients were Caucasian with epithelial histologic subtype and AJCC 7th Edition stage III-IV disease.

Radiotherapy.

PT was delivered to a median dose of 5500 centi-Cobalt Grey Equivalent (cCGE) in 180–200 cCGE daily fractions adjuvantly following lung-sparing ePD/PDT ($n = 8$) or as salvage therapy for progression after surgery/PDT ($n = 2$) at a median of 7.5 months (range 3.5–68.3 months) after ePD/PDT and 10.9 months (range 3.5–69.3 months) after mesothelioma diagnosis. All patients previously underwent ePD and all achieved a macroscopically complete resection of all gross disease. Definitive PT was delivered using 70–235 MV Proton Uniform or Double Scattering therapy. Target volumes for patients receiving adjuvant PT included any areas of surgical concern, any areas of chest wall invasion, and all high risk hilar and mediastinal lymph node stations, including the ipsilateral lower paratracheal, upper and lower hilar, and subcarinal lymph nodes, as well as any other lymph nodes that were sampled preoperatively or resected intraoperatively and pathologically positive for metastatic disease, inclusive of posterior intercostal lymph nodes when applicable. Target volumes for patients receiving salvage PT included all areas of gross disease as assessed on CT and PET/CT imaging. Using 4D-CT, an internal gross tumor volume (iGTV) was created and expanded 5–8 mm to create a clinical target volume that accounts for microscopic disease spread. A 5 mm expansion was added for a planning target volume (PTV) to account for daily setup errors and proton beam uncertainties. Owing to the already large irradiation volumes and potential risks of additional elective treatment, elective whole pleural irradiation was not administered. Daily image guidance, inclusive of cone-beam CT scans as previously reported (66), was conducted for verification prior to treatment delivery.

Photodynamic therapy (PDT).

Each patient received intravenous porfimer sodium (Photofrin) $2 \text{ mg} \cdot \text{kg}^{-1}$ with a 24-hour drug-light interval or 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH) $4 \text{ mg} \cdot \text{m}^{-2}$ with a 48 h drug-light interval based on which of two prospective studies they enrolled on. Laser light at a wavelength of 630 nm for porfimer sodium or 665 nm for HPPH was then

delivered to a measured dose of 60 and 15 to 45 J·cm⁻² (per the dose escalation HPPH trial), respectively, as registered on eight strategically placed isotropic light detectors using a custom-built dosimetry system (67–71). The chest was filled with 0.01% dilute intralipid solution to facilitate light dispersion. Light delivery was administered generally over 60–100 min intraoperatively through optical fibers through spinal needles. This lengthened the operating room time 90–120 min per case for diode placement and PDT delivery.

Statistics and follow-up outcomes.

Patients were followed with a PET/CT or chest CT every 3 months following PT completion. Patient demographics and treatment variables were described by frequencies and percentages. Response evaluation criteria in solid tumors (RECIST) v1.1 criteria were used to define disease progression or stability. Local control was defined as resolution or arrested progression of intrathoracic disease, time to progression was defined as the time interval from the end of PT to any failure (local, regional [nodal] or distant), and overall survival was defined as the time interval from PT completion to death from any cause or last follow-up. Biopsies were performed to confirm disease prior to initiating salvage therapy in the recurrent setting. Acute and late toxicities were recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.0. Statistical analysis was performed using the software package SPSS (SPSS Inc., Chicago, IL).

RESULTS

Systemic therapy

Systemic therapy was given before PT in 70% of patients, consisting of cisplatin and pemetrexed ($n = 4$) or carboplatin and pemetrexed ($n = 3$). One patient received concurrent pemetrexed with PT. Adjuvant and/or salvage chemotherapy was delivered in four patients consisting of gemcitabine alone ($n = 1$), gemcitabine with carboplatin ($n = 1$), carboplatin and pemetrexed ($n = 1$), and cisplatin and pemetrexed ($n = 1$). Two patients received neoadjuvant immunotherapy and one received adjuvant therapy with interferon alpha, while an additional patient underwent PD1 treatment adjuvantly. The details of systemic therapy are depicted in Table 2.

Failure patterns

One patient suffered a local recurrence 3.2 months after the completion of PT. Local control at 1 and 2 years was 90% and 90%, respectively. Three patients had regional recurrences at a median of 2.5 months (range 1.8–6.3 months) after PT. Half of the patients ($n = 5$) suffered a distant failure, with the initial site of metastases in the liver ($n = 2$), peritoneum ($n = 1$), contralateral lung ($n = 1$), and bone ($n = 1$) at a median of 2.2 months (range 0.5–8.8 months) after the completion of PT. Individual patient data and failure patterns are depicted in Table 3.

Survival

At a median follow-up of 7.1 months (range 2.0–33.2 months) from completion of PT and 20.2 months (range 12.4–71.6 months) from diagnosis, the median survival from the end of

PT was 19.5 months (Fig. 1), and 1-year and 2-year survival rates were 58% and 29%, respectively. When measured from diagnosis, median survival was 30.3 months.

Toxicity

In general, treatment was well tolerated amongst patients. There was no diaphragmatic rupture, pericardial effusion requiring drainage or prolonged hospitalizations as the result of surgery. Three patients developed transient atrial fibrillation, while two patients developed a deep vein thrombosis and two developed pneumonia. No external phototoxicities were seen from PDT. The most common adverse effects definitely, probably, or possibly related to PT were grade 1 fatigue, experienced by all patients who underwent treatment. Seven patients (70%) developed grade 1 cough, while one patient (10%) had a grade 2 cough. Dyspnea during treatment was grade 1 in 6 (60%) and grade 2 in 2 patients (20%), respectively. One patient developed grade 2 radiation pneumonitis (10%), and no grade 3 pneumonitis was observed. Radiation dermatitis was grade 1 in 50% of patients ($n = 5$) and grade 2 in an additional 50% ($n = 5$). Half of the patients (50%) developed grade 1 pruritis during their PT treatment course. Two patients (20%) each had grade 1 and grade 2 dysphagia. No patient experienced CTCAEv4 grade 3 acute or late toxicities.

DISCUSSION

In the largest report of proton therapy for MPM to date, and the only study to combine PT with PDT, we have shown excellent local control (90%) in a disease typically hard to achieve long-term local control, as well as excellent overall survival values of 56% at 1 year and 29% at 2 years for patients undergoing ePD with PDT followed by PT. With a median survival of 19.5 months from PT completion and 30.3 months from diagnosis, this far exceeds prior median survival reports for patients with Stage III and IV MPM, which per the updated staging guidelines range from 10 to 14 months (4). The authors do note that our histology of epithelial subtype may have contributed, in part, to the prolonged survival achieved in this study, although the present results far exceed what would be expected for stage-matched epithelial patients reported in other surgical series. Survival in this series exceeds the median survival in a phase II study evaluating outcomes in MPM in patients undergoing surgery and adjuvant radiation therapy despite our current study having generally more advanced-stage patients and including salvage patients progressing after pre-PT treatment (72). When measured from the time of diagnosis, the median survival in this cohort exceeded 30 months, in line with a prior study of RP and PDT from our institution despite our current study having no stage I-II patients (31). Furthermore, this survival time far exceeds the median survival of our institutional experience of PT without PDT for malignant pleural mesothelioma (73). This may suggest potential synergistic effects with the combination of PDT and PT.

There are theoretical reasons to think that PDT and PT may be synergistic. PDT promotes the microenvironment to be more conducive to immunologic effect, can lead to an inflammatory reaction that can evoke a host anti-tumor immune response, and can lead to immunogenic cell death (74–76). Recent reports have suggested that proton and heavy ion therapy may stimulate the immune system to a greater degree than photon therapy (62,77).

As such, we hypothesized that priming the immune system with intraoperative PDT at the time of lung-sparing surgery for mesothelioma may have allowed for more indolent recurrences and a preferential potentiation of a radiation vaccination effect on the immune system. This may be more prominent for proton therapy than photon therapy and may allow for especially prolonged overall survival in patients sequentially treated with PDT and proton therapy. Additionally, PDT may be synergistic with RT, and it may do so with non-overlapping toxicity.

When microscopic disease remains after surgical resection, even when intraoperative PDT is delivered, pleural and nodal recurrence rates are high for mesothelioma. Fortunately, mesothelioma is known to be radioresponsive tumor (39,40). Since the majority of mesothelioma patients have significant symptoms related to local disease, quality of life, in addition to local control and potentially even overall survival, can be improved if radiation is able to be safely delivered. As it is known that lung irradiation dose correlates with the risk of pulmonary or non-cancer related death (47), PT may be the most ideal radiotherapy delivery modality for mesothelioma, as studies have shown significant reductions in dose of radiation to organs at risk like lung (51,52). As rates of radiation pneumonitis are compounded in patients undergoing surgery and chemotherapy due to the added inflammation to lung parenchyma in these multi-modality patients (78), concerns for toxicity are heightened when adding another inducer of acute inflammation like PDT. PT, therefore, can mitigate these compounding risks and allow for the safe sequential delivery of PDT and radiotherapy.

In fact, the toxicities related to treatment observed in this study were notably low, and the acute toxicities noted were attributable to what would typically be seen in a patient undergoing PT alone without the addition of PDT. The fact that no Grade 3 or higher acute or chronic toxicities occurred speaks to the safety of this multi-modality regimen, and while studies with larger patient numbers would be helpful to confirm our findings, our study should serve as a baseline to encourage further studies of PDT-PT combinatory therapy in mesothelioma.

This work is hypothesis generating, and future prospective trial design at mesothelioma centers of excellence and high-volume mesothelioma centers (79) should consider incorporation of PDT with lung-sparing surgery along with PT to reduce the volume of contralateral lung and other critical organs that are damaged, as this contributes to non-cancer related toxicities and death. It would be a mistake not to mention the need for continued improvements and evaluation of chemotherapy and immunotherapy, as 50% of our patients did fail distantly in this series, and therapies after failure of first-line chemotherapy are limited with low response rates. As the efficacy of both PT (80) and PDT (81) may be impacted by the immune system and immunotherapy, outcomes of this study might have been impacted if more of the current patient cohort received immunotherapy. As such, we look forward to the mature results of the Phase II MAPS-2 trial of immunotherapy consisting of nivolumab monotherapy or nivolumab combined with ipilimumab in the second or third line treatment of mesothelioma. Initial results in the combination arm are promising, with the median survival not yet reached at 15-month follow-up (82). Thus, these

results strengthen the argument for an aggressive, multi-modality approach to the treatment of well selected operable MPM patients.

CONCLUSION

This is the first reported study combining chemotherapy, ePD/PDT and PT. It is also the largest ever study of PT for malignant pleural mesothelioma. This study shows the sequential combination to be well tolerated and also shows that PT may reduce toxicities of radiotherapy when delivered after ePD/PDT. Our median survival of over 30 months from mesothelioma diagnosis in a very advanced-stage population compares favorably to previously published reports and to our own mesothelioma institutional survival for PT without PDT and for photon therapy with PDT. This may suggest the possibility of spatial or systemic cooperativity and immune effect with the combination of these two immunogenic therapies of PDT and PT.

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Figure 1.

Overall survival (OS). OS of all malignant pleural mesothelioma (MPM) patients who were treated with a combination of extended pleurectomy/decortication with photodynamic therapy (PDT) followed by adjuvant ($n = 8$) or salvage ($n = 2$) proton therapy (PT). PT was given to a median dose of 55 Cobalt Grey Equivalents (CGE) in 1.8–2.0 CGE per fraction. Survival was measured as time from completion of PT until date of death or last follow-up (censored). Median survival was 19.5 months, with 1- and 2-year OS of 58% and 29%, respectively.

Table 1.

Patient and tumor characteristics.

Characteristic		N (%)
Median age at diagnosis in year (range, years)		69 years (51–80 years)
Sex	Male	9 (90)
	Female	1 (10)
Tumor location	Right	9 (90)
	Left	1 (10)
Median Radiation dose Gy (range, CGE)		55 CGE (50–75 CGE)
Surgery	ePD	10 (100)
Race	Caucasian	10 (100)
Smoking history	Yes	2 (20)
	No	8 (80)
Known asbestos exposure	Yes	8 (80)
	No	2 (20)
Histologic Subtype	Epithelioid	10 (100)
	Biphasic	0 (0)
	Sarcomatoid	0 (0)
ECOG Performance Status	0	4 (40)
	1	4 (40)
	2	2 (20)
T stage	T1	0 (0)
	T2	1 (10)
	T3	5 (50)
	T4	4 (40)
N Stage	N0	1 (10)
	N1	0 (0)
	N2	9 (90)
Overall Clinical Stage	I	0 (0)
	II	0 (0)
	III	7 (70)
	IV	3 (30)
Photosensitizer	Photofrin	7 (70)
	HPPH	3 (30)
Chemotherapy timing	Before PT	7 (70)
	Concurrent with PT	1 (10)
	After PT	4 (40)
Chemotherapy Type Pre-PT	Cisplatin/pemetrexed	4 (40)
	Carboplatin/pemetrexed	3 (30)
Concurrent Chemotherapy Type	Pemetrexed	1 (10)

Characteristic		N (%)
Chemotherapy Type Post-PT	Gemcitabine	1 (10)
	Gemcitabine/carboplatin	1 (10)
	Carboplatin/pemetrexed	1 (10)
	Cisplatin/pemetrexed	1 (10)
Immunotherapy	Yes	3 (30)
	No	7 (70)
Immunotherapy Type	Interferon alpha	3 (30)

ePD, extended pleurectomy/decortication; HPPH, 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a.

Table 2.

Treatments delivered for each patient.

Patient #	Sex	Surgery	Photosensitizer	Neoadjuvant chemotherapy	Radiation fraction size/total dose (cCGE)	Adjuvant chemotherapy and/or immunotherapy
1	Male	ePD	HPPH	Cisplatin and alimta	235/7500	Carboplatin and Alimta
2	Male	ePD	Photofrin	Cisplatin and alimta	180/5040	Gemcitabine
3	Female	ePD	Photofrin	None	200/7000	PD1
4	Male	ePD	Photofrin	None	180/5940	Carboplatin and Alimta
5	Male	ePD	Photofrin	Carboplatin and Alimta	200/5400	Gemcitabine and Carboplatin
6	Male	ePD	Photofrin	Cisplatin and Alimta	180/5040	None
7	Male	ePD	Photofrin	Carboplatin and Alimta	180/5040	None
8	Male	ePD	HPPH	Cisplatin and Alimta	200/6000	Interferon alpha
9	Male	ePD	Photofrin	Carboplatin and Alimta	200/5000	Interferon alpha
10	Male	ePD	HPPH	None	200/7000	Cisplatin and Alimta, Interferon alpha

ePD, extended pleurectomy/decortication; HPPH, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a.

Table 3.

Failure type by patient.

Patient #	Failure (Y/N)	Type	Location
1	Y	Distant	Peritoneum
2	Y	Distant	Contralateral lung
3	Y	Distant	Peritoneum
4	Y	Local	Distant pleura
5	Y	Regional, Distant	Mediastinal nodes/bone/liver/distant nodes
6	N	None	None
7	Y	Distant	Liver
8	Y	Regional	Level 4R nodes
9	N	None	None
10	Y	Regional	Distant pleura