Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma

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Published online ahead of print at www.jco.org on June 20, 2016.

Funded in part by the National Institutes of Health/National Cancer Institute Cancer Center Support Grant No. P30 CA008748 and in part by Lilly Oncology.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00715611.

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0732-183X/16/3423w-2761w/\$20.00

DOI: 10.1200/JCO.2016.67.2675

ABSTRACT

Purpose

We conducted a two-center phase II study to determine the safety of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) after chemotherapy and pleurectomy-decortication (P/D) as part of a multimodality lung-sparing treatment.

Patients and Methods

Patients received up to four cycles of pemetrexed plus platinum. If feasible, P/D was performed. Hemithoracic IMPRINT was administered to a planned dose of 50.4 Gy in 28 fractions. The primary end point was the incidence of grade 3 or greater radiation pneumonitis (RP).

Results

A total of 45 patients were enrolled; 18 were not evaluable (because of disease progression before radiation therapy [RT], $n = 9$; refusal of surgery or RT, $n = 5$; extrapleural pneumonectomy at time of surgery, $n = 2$; or chemotherapy complications, $n = 2$). A total of 26 patients received pemetrexed plus cisplatin, 18 received pemetrexed plus carboplatin, and four received a combination. Thirteen patients (28.9%) had a partial response, 15 patients (33.3%) experienced disease progression, one patient died during chemotherapy, and all others had stable disease. Eight patients underwent P/D or an extended P/D, and 13 underwent a partial P/D. A total of 27 patients started IMPRINT (median dose, 46.8 Gy; range, 28.8 to 50.4 Gy) and were evaluable for the primary end point (median follow-up, 21.6 months). Six patients experienced grade 2 RP, and two patients experienced grade 3 RP; all recovered after corticosteroid initiation. No grade 4 or 5 radiation-related toxicities were observed. The median progression-free survival and overall survival (OS) were 12.4 and 23.7 months, respectively; the 2-year OS was 59% in patients with resectable tumors and was 25% in patients with unresectable tumors.

Conclusions

Hemithoracic IMPRINT for malignant pleural mesothelioma (MPM) is safe and has an acceptable rate of RP. Its incorporation with chemotherapy and P/D forms a new lung-sparing treatment paradigm for patients with locally advanced MPM.

J Clin Oncol 34:2761-2768. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Adjuvant hemithoracic radiation therapy (RT) has been used to decrease the risk of locoregional recurrences after extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma (MPM).¹⁻⁴ However, lung-sparing pleurectomy-decortication (P/D) is increasingly a preferred surgical approach for MPM.^{5,6} Safe delivery of cytotoxic radiation to the hemithorax with two intact radiosensitive

lungs is challenging. Conventional matched photon-electron radiation techniques are insufficiently able to spare the underlying ipsilateral lung, so the techniques result in excess toxicity.⁷ We therefore developed a novel, highly conformal, hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) technique to target the entire ipsilateral pleura and maximally spare both the ipsilateral and contralateral lungs.^{8,9} In prior reports, this approach was safe, with a 20% incidence of grade 3 or greater radiation pneumonitis (RP), comparable to

the incidence in other high-risk settings. Given the importance of multimodality therapy to reduce and delay recurrence, we sought to evaluate the feasibility and safety of hemithoracic IMPRINT as part of a multimodality treatment approach in a two-center phase II study.

PATIENTS AND METHODS

A total of 45 patients were enrolled at Memorial Sloan Kettering Cancer Center (MSKCC) and MD Anderson Cancer Center (MDACC) after written informed consent on this institutional review board–approved phase II study (NCT00715611) between August 2008 and July 2014. The MDACC joined in December 2012. Inclusion criteria were as follows: pathologically confirmed MPM (any histology), no distant metastatic disease, no prior chemotherapy for MPM, no prior RT (except for localized prostate or pelvic radiation), age 18 years or older, Karnofsky performance status (KPS) of 70% or greater, postoperative predicted forced expiratory volume at 1 minute (FEV₁) of 30% or greater, diffusing capacity of the lung for carbon monoxide (DLCO) greater than 35%, and adequate hematologic, renal, and hepatic functions. Patients may have undergone prior partial P/D if residual disease remained (those patients were treated only with chemotherapy and radiation in this study). Exclusion criteria were pregnancy, resectable disease that required an EPP, active infection, concurrent active malignancy, serious unstable medical illness, uncontrollable third space fluid, and active congestive heart failure.

Treatment Plan

Chemotherapy. Patients received pemetrexed (500 mg/m²) and either cisplatin (75 mg/m²) or carboplatin (AUC, 5 mg) every 21 days for four or fewer cycles at the discretion of the treating medical oncologist. Standard supportive medications, including folic acid supplementation and vitamin B₁₂, were administered. Routine dose adjustments were used for

hematologic, renal, and neural toxicities. After two cycles, response was assessed on a repeat chest computed tomography (CT) scan. Patients without disease progression and with good chemotherapy tolerance received two more cycles before resection, if feasible. All imaging studies were reviewed by a reference radiologist according to the modified RECIST for MPM.¹⁰

Surgery. Patients deemed to have resectable tumors underwent surgery 4 to 6 weeks after chemotherapy; the goal was a macroscopic complete resection (MCR) by lung-sparing surgical techniques according to the recommendations for uniform definitions of surgical techniques for MPM of the International Association for the Study of Lung Cancer International Staging Committee.¹¹ Extended P/D is the removal of all gross tumor along with resection of the diaphragm and/or pericardium. P/D is the removal of all gross tumor with a parietal and visceral pleurectomy but without diaphragm or pericardial resection. Partial pleurectomy is the partial removal of parietal and/or visceral pleural tissue and/or resection with residual gross tumor.

Hemithoracic IMPRINT Technique

Using our previously described hemithoracic pleural intensity-modulated radiation therapy (IMRT)^{8,12} procedure and dose constraints (Appendix Table A1, online only), RT began 4 to 6 weeks after chemotherapy or 8 or fewer weeks postoperatively. Patients were reevaluated by the radiation oncologist to ensure sufficient recovery from surgery and/or chemotherapy, defined as a KPS of 70% or greater, no oxygen dependence, and no signs of disease progression. Patients were immobilized in supine position, and their arms were raised above their heads. Gross tumor volume was delineated on the basis of an ¹⁸F-fluorodeoxyglucose positron-emission tomography–CT scan at simulation. A four-dimensional CT was performed to account for respiratory motion. The clinical target volume was defined as the parietal and visceral pleura, without inclusion of the fissures, that extended from the thoracic inlet superiorly to the insertion of diaphragm at the bottom of the L2

Fig 1. Consort diagram of the phase II study. EPP, extrapleural pneumonectomy; IMRT, intensity-modulated radiation therapy.

vertebral body inferiorly, along the ribs laterally, and along the mediastinal pleura, pericardium, and hilum medially. Mediastinal lymph node stations were included only if they were involved with MPM at the time of resection. A planning target volume was generated using a 6-mm internal margin and a 10-mm outer margin and was modified to cover the entire thickness of the chest wall of the ipsilateral hemithorax. Examples of treatment plans are shown in Figs 1A and 1B. IMRT was delivered with 6 MV photons by using the sliding window technique, incident from six to nine directions around the ipsilateral lung. For left-sided MPM, the beam angles typically ranged from 350° to 180°; for right-sided MPM, they ranged from 10° to 190° to maximally spare the contralateral lung. Tissue inhomogeneity correction was used. The goal was to deliver the prescription dose (50.4 Gy in 1.8 Gy per fraction) to 95% or greater of the planning target volume while

normal tissue constraints were respected; the dose was reduced, when necessary, to respect normal tissue constraints. The total lung dose was limited to a normal tissue complication probability of 25% or less. When possible, the total mean lung dose was limited to 21 Gy or fewer; volume of the total lung receiving 20 Gy (V_{20Gy}), from less than or equal to 37% to 40%; and contralateral lung (V_{20Gy}) to 7% or less. There was no V_{5Gy} limit, and no boost dose was delivered.

Follow-Up

Patients were evaluated by CT at 1 month after RT and, subsequently, every 3 months. Pulmonary function tests (PFTs) and ventilation-perfusion scans were performed at baseline, before RT, and 4 months after RT completion.

Fig 2. Example of hemithoracic pleural intensity-modulated radiation therapy (IMRT) in a patient with (A) a resected and (B) an unresectable tumor. (A) Resected tumor image is from a 70-year-old man with left-sided pT3N0M0 epithelioid malignant pleural mesothelioma (MPM) treated with four cycles of carboplatin-pemetrexed, macroscopic gross total resection by pleurectomy-decortication and hemithoracic pleural IMRT to 50.4 Gy in 28 fractions. The red line is the planning target volume. (B) Unresectable tumor image is from a 63-year-old man with right-sided pT2N2M0 epithelioid MPM treated with four cycles of cisplatin-pemetrexed; unresectable disease noted on exploratory thoracotomy and hemithoracic pleural IMRT to 48.6 Gy in 27 fractions. The red line is the planning target volume.

Study End Points and Statistical Considerations

The primary objective was to determine the safety of chemotherapy with or without P/D followed by hemithoracic pleural IMRT on the basis of grade 3 or greater RP according to NCI Common Terminology Criteria for Toxicity and Adverse Event reporting version 4.0. Systemic corticosteroids were initiated for grade 2 or greater RP. Grade 3 RP was defined as symptomatic disease that interfered with activities of daily living and required oxygen support or hospitalization. Toxicities were considered acute if they occurred within 4 months after IMRT. Patients were evaluable for the primary end point if IMRT was initiated.

A Simon two-stage design was used, and nine patients were enrolled in the first stage. If two or fewer patients experienced grade 3 or greater RP, enrollment would be extended to 27 patients. If five or fewer patients experienced grade 3 or greater RP, the regimen would be considered feasible and safe. This design discriminated between RP rates of 30% and 10% with a 90% power and a 10% type I error. Secondary end points included overall response rate (estimated along with a 95% CI), progression-free survival (PFS), and overall survival (OS). PFS and OS were estimated with the Kaplan-Meier method, starting from date of

diagnosis. OS was also calculated from start of IMRT to compare chemotherapy responders with nonresponders. PFT and lung perfusion and ventilation changes and association with grade 2 or greater RP were assessed with the Wilcoxon signed rank and the Wilcoxon rank sum test. Statistical analysis was performed in R 3.2.2 (<https://www.r-project.org/>), and survival and Hmisc packages were used.

RESULTS

Patient Characteristics

Of the 45 patients enrolled in the study (Fig 2), 18 did not receive radiation therapy and were considered not evaluable because of disease progression (n = 9), refusal of surgery or RT (n = 5), EPP (n = 2), or chemotherapy complications (n = 2). All patients received chemotherapy (pemetrexed plus cisplatin, n = 26; pemetrexed plus carboplatin, n = 18); four patients switched from

Table 1. Patient, Disease, and Treatment Characteristics

Characteristic	Patient Population					
	All		Inevaluable		Evaluable	
	No.	%	No.	%	No.	%
Age, years						
Median (range)	69 (39-80)		69 (39-76)		68 (49-80)	
Sex						
Male	41	89	18	100	23	85
Female	4	11	0	0	4	15
Ethnicity						
White	40	89	16	89	24	89
Other	5	11	2	11	3	11
KPS at baseline, %						
70	4	9	1	6	3	11
80	15	33	8	44	7	26
90	25	56	9	50	16	59
100	1	2	0	0	1	4
Histology						
Epithelioid	35	78	13	72	22	81
Biphasic	5	11	4	22	1	4
Sarcomatoid	5	11	1	6	4	15
Laterality						
Right	17	38	6	33	11	41
Left	28	62	12	67	16	59
No. of chemotherapy cycles						
1	2	4	1	6	1	4
2	5	11	3	17	2	7
3	3	7	1	6	2	7
4	35	78	13	71	22	81
Overall response rate to chemotherapy	13	30	5	28	8	30
Surgery type						
EPP	2	4	2	11	0	0
EPD	3	7	2	11	1	4
PD	4	9	0	0	4	15
Partial PD (R2)	14	31	4	22	10	37
Not resectable/NA	22	49	10	56	12	44
Pathologic stage after chemotherapy						
2	3	7	1	6	2	7
3	12	27	5	28	7	26
4	15	33	3	17	12	44
NA	15	33	9	50	6	22
Median (range) total IMRT dose, Gy			NA		46.8 (28.8-50.4)	

Abbreviations: EPP, extrapleural pneumonectomy; EPD, extended pleurectomy-decortication (removal of all gross tumor along with resection of the diaphragm and/or pericardium); IMRT, intensity-modulated radiation therapy; KPS, Karnofsky performance status; NA, not available; partial PD (R2), partial pleurectomy (partial removal of parietal and/or visceral and/or cases with residual gross tumor); PD, pleurectomy-decortication (removal of all gross tumor with a parietal and visceral pleurectomy but without diaphragmatic or pericardial resection).

pemetrexed plus cisplatin to pemetrexed plus carboplatin because of toxicity. Patients received a total of 163 cycles (median, four cycles; range, one to four cycles); 35 patients (78%) received all four cycles. The overall response rate after four cycles was 30% (95% CI, 17% to 45%); 13 patients (30%) experienced partial responses, 16 patients (36%) experienced stable disease, and 15 patients (33%) experienced disease progression. One patient died as a result of a pulmonary embolism during chemotherapy, and response could not be assessed. Chemotherapy response did not vary significantly on the basis of stage or histologic subtype.

The characteristics of the 27 evaluable patients (defined as those who initiated RT) are listed in Table 1. The median follow-up time was 21.6 months (range, 6 to 41 months). The median age at diagnosis was 67 years (range, 38 to 79 years), and the median KPS was 90%. Twenty-one evaluable patients underwent surgical exploration (extended P/D, n = 1; P/D, n = 5; partial P/D, n = 9; unresectable, n = 6); The six patients who were unresectable did not have surgery between chemotherapy and hemithoracic pleural IMRT. Five patients underwent MCR. Hemithoracic IMRT was delivered to a median dose of 46.8 Gy (range, 28.8 to 50.4 Gy). The median V_{20Gy} and V_{5Gy} and the mean lung doses are listed in Appendix Table A2 (online only).

RP

Eight patients (30%; 95% CI, 14% to 50%) developed grade 2 or greater RP (grade 2 RP, n = 6; grade 3 RP, n = 2). All patients improved with prompt initiation of prednisone, typically 40 mg once per day for a median of 2.6 months (range, 0.5 to 6.5 months). Three patients developed disease progression during the prednisone taper and required prednisone beyond 3 months, possibly because of a combination of continued grade 2 RP and disease progression. Both patients with grade 3 RP were weaned off oxygen after they required supplemental oxygen for 2 or 7 weeks, respectively. No grade 4 or 5 RP was observed.

Hemithoracic pleural IMRT resulted in a significant decrease in the median FEV₁ (pre-RT v post-RT, 82.5 v 65; $P = .002$), forced vital capacity (pre-RT v post-RT, 84 v 65; $P < .001$) and DLCO (pre-RT v post-RT, 64 v 57; $P = .02$; Appendix Table A3, online only). DLCO was significantly affected by chemotherapy and/or P/D between the baseline assessment and the pre-RT assessment ($P = .006$). Lung perfusion and ventilation were not affected after hemithoracic pleural IMRT but changed most significantly between the baseline scan and the pre-RT scan ($P = .002$ and $.005$, respectively).

The PFTs of patients without grade 2 or greater RP did not significantly decrease from baseline to pre-RT. However, lower pre-RT DLCO values showed some association with the risk of developing grade 2 or greater RP ($P = .09$; Appendix Fig A1, online only).

Other Toxicities

The most common acute toxicity was grade 3 fatigue in five patients (Table 2). This resolved within 4 months in all but one patient. One patient developed grade 3 pericarditis that required hospitalization after eight fractions. Symptoms quickly resolved with nonsteroidal anti-inflammatory drugs and colchicine. Subsequently, this patient uneventfully completed hemithoracic

pleural IMRT to a total dose of 48.6 Gy. Other common toxicities were cough, dyspnea, esophagitis, nausea, and dermatitis (Table 2).

PFS, OS, and Patterns of Recurrence

The median PFS and OS in all evaluable patients were 12.4 months and 23.7 months, respectively (Fig 3). The 1- and 2-year OS rates for patients with resectable disease were 80% and 59%, respectively (Fig 4A). The 1- and 2-year OS rates for patients with unresectable disease were 74% and 25%, respectively (Fig 4A). The 1- and 2-year OS differed markedly on the basis of the response to chemotherapy: patients with a PR had 1- and 2-year OS rates of 100% and 53%, respectively, whereas patients without a response had 1- and 2-year OS rates of 45% and 21%, respectively (Fig 4B). The majority of patients (16 [59%] of 27 patients) experienced disease failure within the radiation field—most often in sites where disease was previously present. Local failure was the first site of failure in all but one patient. However, after MCR, local failures typically occurred in new sites of disease and in conjunction with distant progression. Six patients (22%) developed mediastinal nodal failures, and 13 (48%) of 27 patients experienced distant progression, most often in the contralateral lung (n = 5), peritoneum (n = 3), bones (n = 3), and liver (n = 3).

DISCUSSION

Hemithoracic Conventional and IMRT Outcomes After EPP

Adjuvant RT for MPM was first used in the setting of EPP. We and others have demonstrated the safety and efficacy of a trimodality regimen of induction chemotherapy, EPP, and adjuvant hemithoracic RT with a conventional photon-electron technique.

Table 2. Acute and Late IMRT Toxicity

Toxicity	Toxicity Grade					
	0	1	2	3	4	5
Acute*						
Cardiopulmonary						
Radiation pneumonitis	18	1	6	2	0	0
Cough	12	12	2	1	0	0
Dyspnea	6	9	11	1	0	0
Pericarditis	26	0	0	1	0	0
Gastrointestinal						
Esophagitis	8	11	8	0	0	0
Nausea	9	7	11	0	0	0
Vomiting	20	6	1	0	0	0
Dermatitis	4	20	4	0	0	0
Fatigue	2	14	6	5	0	0
Late†						
Cardiopulmonary						
Cough	12	10	2	0	0	0
Dyspnea	7	13	4	0	0	0
Chest wall discomfort	17	4	3	0	0	0
Fatigue	7	12	4	1	0	0

Abbreviation: IMRT, intensity-modulated radiation therapy.

*Acute toxicity occurred within 4 months after completion of IMRT.

†Late toxicity occurred more than 4 months after completion of IMRT.

Fig 3. Overall survival and progression-free survival: (A) intent-to-treat analysis and (B) analysis of evaluable patients.

In a multi-institutional study, we demonstrated a median OS of 29.1 months in patients who completed all three modalities, including adjuvant RT to a total dose of 54 Gy.¹³ However, the photon-electron technique results in unavoidable inhomogeneity and underdosing along the match lines of photon and electron fields, which may lead to potentially avoidable locoregional failures.⁴ IMRT techniques were developed and resulted in more homogeneous and predictable target coverages.

Adjuvant IMRT after EPP was at first found to be quite toxic; up to 46% RT-related deaths occurred, which were largely considered related to RT-induced RP.¹⁴ Careful dosimetric analyses identified the contralateral lung RT dose as a critical predictive factor for potentially fatal RP.¹⁵ The implementation of stricter planning guidelines has resulted in marked improvements in the incidence of severe RP.¹⁶ Recently, a Swiss randomized study tested the value of adjuvant RT using 3D-conformal radiation therapy and IMRT techniques after neoadjuvant chemotherapy and EPP in 54 patients, but the study failed to show a statistically significant difference in its primary end point of locoregional relapse-free survival.¹⁷ Twenty-five patients who received radiotherapy had a median locoregional relapse-free survival of

9.4 months compared with 7.6 months in the no-radiotherapy group. The study closed early because of poor accrual and was underpowered to meet its primary end point, so the results were inconclusive.¹⁸

Conventional and Hemithoracic Pleural IMRT Outcomes After Lung-Sparing Surgery

Because of lower toxicity and equivalent or potentially higher OS, there has been a trend in surgical techniques away from EPP toward more lung-sparing surgery or P/D.^{5,19,20} P/D is a less complete surgical resection that has a higher risk of leaving microscopic disease (R1), and this provides an even stronger rationale for delivery of adjuvant RT. However, the presence of two intact lungs that have high radiosensitivity poses a formidable challenge to the safe delivery of RT to the pleura while the lung parenchyma is simultaneously spared. Initially, conventional RT techniques were applied but have been proven neither safe nor effective. In a study that used conventional hemithoracic radiation after P/D, we observed high rates of severe RP, two treatment-related deaths, and a disappointing 1-year local control rate of 42%.⁷

Fig 4. Overall survival on the basis of (A) resection status and (B) response to chemotherapy.

Therefore, we developed a unique hemithoracic pleural IMRT technique to allow maximum sparing of the ipsilateral and contralateral lungs. Our initial experience yielded acceptable toxicity and a promising median overall survival of 26 months in patients with resectable disease.⁸ We then conducted this two-center prospective phase II study to determine whether hemithoracic pleural IMRT would be feasible and safe when embedded in a multimodality program. Eight patients (30%) developed grade 2 or 3 RP, and all occurrences of RP were reversible with prompt initiation of prednisone. Interestingly, the most common toxicity was not RP but profound fatigue that sometimes lasted for months. No grade 4 or 5 toxicities were seen. This compares favorably to toxicity rates observed with conventional hemithoracic RT.

The reasons for the favorable toxicity outcomes may be multifaceted. First, we used strict lung constraints of a normal tissue complication probability of 25% or less and guidelines for the V_{20Gy} and the mean lung dose. All patients were kept to a contralateral lung V_{20Gy} of less than 7%. Second, we monitored patients closely and had a low threshold to initiate prednisone for presumed RP. Although this may have led to toxicity overreporting, all patients with RP recovered and avoided long-term oxygen use. Thus, aggressive toxicity management, in addition to respect of dosimetric normal tissue constraints, is critical to prevent severe long-term toxicities with this treatment paradigm. Third, increasing experience with this complex radiation technique is associated with improved target delineation and fewer marginal failures, as previously shown.^{12,21} During the 10 years of the development of our IMRT technique, marginal failures from contouring errors significantly decreased in years 6 to 10 compared with years 1 to 5. Finally, although it is difficult to demonstrate statistically, management of these patients by close collaboration of the multimodality MPM team likely contributed to improved outcomes and decreased toxicity.

The PFS and OS results in the evaluable patients of our study are comparable to those reported with the previously established multimodality regimen of chemotherapy, EPP, and hemithoracic radiation, and our study noted apparently less toxicity. In various

phase II trials that used EPP, median survivals of 16 to 20 months were noted. In the largest, conducted in the United States, the median OS and PFS times in the intent-to-treat population were 16.8 and 10.1 months.¹³ For patients who completed all three modalities, the median OS time was 29.1 months. We were able to achieve these same survival outcomes without the need for EPP, which thereby potentially improved the quality of life and provided more patients with an opportunity to receive multimodality therapy.

Consistent with our prior failure pattern analysis of this IMRT technique, local failures remained the most common failure site.¹² Although an integrated boost dose or combination with other aggressive local strategies may reduce local failures, the relatively high local failure rate does not necessarily mean that adjuvant IMRT was ineffective. Evaluation of local failures from MPM is challenging and subject to imaging methodology, frequency, RT fibrosis, and variable definitions of what constitutes a failure. Our study was not powered for a PFS end point, because the primary end point was to establish the safety of this novel IMRT technique. Nevertheless, the median PFS of 12.4 months with hemithoracic pleural IMRT seems promising in this patient population with advanced, largely stage III and IV MPM. More important, the median OS was 23.7 months, and the observed survival beyond the sign of first progression was nearly 12 months. This may be related to the lower toxicity experienced by these patients from this trimodality paradigm, greater reserve for additional second-line treatments, and more effective salvage treatment approaches. Additional studies are needed to elucidate the underlying reasons for this observation.

These results justify our next multicenter trial to explore the safety and feasibility of hemithoracic pleural IMRT in an additional five centers that have multidisciplinary expertise in MPM. Because there is a significant learning curve,¹² this challenging technique must be carefully exported to other centers that have multimodality expertise in MPM. Because of the low response rate and the disease progression that occurred in a subset of patients during induction chemotherapy in this study, patients in our subsequent study will undergo surgical resection followed by adjuvant

chemotherapy and subsequent IMRT. Results of this larger multicenter trial will likely position hemithoracic pleural IMRT as a key component of lung-sparing trimodality care for MPM.

In conclusion, hemithoracic pleural IMRT as part of multimodality treatment of patients with MPM and two intact lungs is feasible and safe, and it has an acceptable rate of RP. This approach represents a new lung-sparing treatment paradigm for locally advanced MPM. Larger clinical trials are planned to establish the effectiveness of this therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Honoraria: Bristol-Myers Squibb

Consulting or Advisory Role: GE Healthcare (Inst), Varian Medical Systems

Research Funding: Varian Medical Systems (Inst), Boehringer Ingelheim (Inst)

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Consulting or Advisory Role: Astra Zeneca

Research Funding: Verastem (Inst), MedImmune (Inst), Sellas Life Sciences Group (Inst), Eli Lilly (Inst)

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No relationship to disclose

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No relationship to disclose

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Research Funding: Genelux (Inst)

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Research Funding: Lilly Oncology (Inst)

Appendix

Fig A1. Pre-radiation therapy (RT) pulmonary function tests among patients with and without grade 2 or greater radiation pneumonitis. DLCO, diffusing capacity of the lung for carbon monoxide.

Structure and Constraint	Value
Combined lung	
NTCP, %	≤ 25
V _{20Gy} , %	≤ 37-40 (guideline)
Mean dose, Gy	≤ 21 (guideline)
Contralateral lung, V _{20Gy} , %	≤ 7 (guideline)
Cord, max point dose, Gy	≤ 50
Heart, V _{30Gy} , %	< 50
Esophagus, mean dose, Gy	≤ 34
Bowel	
Max point dose, Gy	≤ 55
D05, Gy	≤ 45 (50)
Kidneys, V _{18Gy} , %	≤ 33 (50)
Liver (not PTV), mean dose, Gy	≤ 30
Stomach (not PTV), mean dose, Gy	≤ 30

Abbreviations: IMRT, intensity-modulated radiation therapy; NTCP, normal tissue complication probability; PTV, planning target volume.

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Table A2. Dosimetric Lung Parameters

Parameter	Guideline	Median (range)
NTCP, %	≤ 25	25 (5 to 30)
Combined mean lung dose, Gy	≤ 21	20.19 (16.24 to 24.20)
Contralateral lung mean dose, Gy		6.04 (3.90 to 8.09)
Combined lung V _{20Gy} , %	≤ 37-40	38.8 (21.6 to 43.3)
Contralateral lung V _{20Gy} , %	≤ 7	0.7 (0.0 to 6.0)
Combined lung V _{5Gy} , %		69.0 (43.0 to 95.2)
Contralateral lung V _{5Gy} , %		51.8 (17.2 to 94.3)

Abbreviation: NTCP, normal tissue complication probability.

Table A3. PFT and VQ Scan Results at Baseline, Pre-RT, and Post-RT in Evaluable Patients

Test	No. of Evaluable Patients	Median (range) Result	P*
FEV ₁			
Baseline	26	85.5 (55-109)	
Pre-RT	26	82.5 (51-109)	.40
Post-RT	17	65 (52-94)	.002
FVC			
Baseline	26	81.5 (46-112)	
Pre-RT	26	84 (46-108)	.75
Post-RT	17	65 (46-94)	< .001
DLCO			
Baseline	26	76.5 (46-126)	
Pre-RT	25	64 (37-110)	.006
Post-RT	15	57 (34-93)	.017
Perfusion			
Baseline	22	39.35 (20.8-70.9)	
Pre-RT	15	21.9 (10-34.9)	.002
Post-RT	15	18.9 (9.2-38.2)	.28
Ventilation			
Baseline	22	32.05 (9.8-50.2)	
Pre-RT	15	17.8 (5-37.8)	.005
Post-RT	15	17.8 (5-47.5)	.79

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test; RT, radiotherapy; VQ, ventilation-perfusion.

*Wilcoxon signed rank test.