Return to intended oncologic treatment after surgery for malignant pleural mesothelioma

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ABSTRACT

Objective: Trimodality therapy may prolong survival for patients with resectable malignant pleural mesothelioma. However, many patients are unable to complete therapy. We sought to identify risk factors for failing to complete adjuvant intensity-modulated radiation therapy after cytoreduction for malignant pleural mesothelioma.

Methods: We performed a single-institution review of those who received an extrapleural pneumonectomy or pleurectomy/decortication for malignant pleural mesothelioma from 2004 to 2017. Multivariable logistic regression was used to assess preoperative or intraoperative risk factors associated with failing to complete adjuvant intensity-modulated radiation therapy.

Results: A total of 160 patients were identified, among whom 94 (59%) received an extrapleural pneumonectomy and 66 (41%) received a pleurectomy/decortication. Adjuvant intensity-modulated radiation therapy was completed among 105 patients (66%). Reasons for failing to complete adjuvant intensity-modulated radiation therapy included mortality (19), dose constraints (21), postoperative morbidity or delayed recovery (11), and refused or unknown status (4). On multivariable analysis, American Society of Anesthesiologists 3+ classification ($P = .002$) and smoking history ($P = .022$) were associated with failure to complete adjuvant intensity-modulated radiation therapy, whereas forced expiratory volume in 1 second 70% or less of predicted and pStage 4 (T4) were significant on univariable analysis only. Other factors, including extrapleural pneumonectomy or pleurectomy/decortication, margin status, age, and histology, were not associated with receiving adjuvant intensity-modulated radiation therapy.

Conclusions: Many patients are unable to complete adjuvant intensity-modulated radiation therapy after cytoreduction. Failure to complete adjuvant intensity-modulated radiation therapy was associated with worse preoperative comorbidity, but not the type of surgery or margin status. (J Thorac Cardiovasc Surg 2019;158:924-9)

Rate of completing adjuvant IMRT.

Central Message

After cytoreductive surgery for MPM, only 66% of patients were able to complete adjuvant IMRT as intended.

Perspective

We identified that worse baseline comorbidity status, as manifested by American Society of Anesthesiologists classification and smoking history, was associated with decreased odds of completing adjuvant IMRT. However, other factors, including receiving an EPP or margin status, were not associated with decreased use of adjuvant IMRT.

See Commentaries on pages 930 and 932.

Malignant pleural mesothelioma (MPM) is an aggressive and rapidly fatal malignancy. Median survival after diagnosis remains 10 months, despite therapeutic advancements.¹ Several phase II observational studies have shown prolonged survival with trimodality therapy, which consists of neoadjuvant chemotherapy, cytoreductive surgery, and

adjuvant radiation.²⁻⁶ Excellent rates of local control can be achieved with extrapleural pneumonectomy (EPP) and adjuvant intensity-modulated radiation therapy (IMRT) with minimal toxicity to the remaining lung,⁷⁻¹² and adjuvant IMRT can also be delivered with the lung in situ.¹³⁻¹⁶

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Abbreviations and Acronyms

EPP = extrapleural pneumonectomy
MPM = malignant pleural mesothelioma
P/D = pleurectomy/decortication

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However, many patients are unable to complete intended therapy. Risks of postoperative morbidity or mortality after cytoreductive surgery remain high and present as a major burden. In a large nationwide study among 3058 surgical patients, 90-day mortality after cytoreductive surgery for MPM was found to be 15.5%.¹⁷ Results from a phase II trial showed that of 77 patients given induction chemotherapy, only 40 (52%) were able to complete cytoreductive surgery and adjuvant radiotherapy.²

At our institution, our standard treatment practice is to administer adjuvant IMRT after cytoreduction (Figure 1). The objective of this study was to determine factors that were associated with failing to complete adjuvant IMRT. We hypothesized that failing to complete adjuvant IMRT could be predicted using preoperative or intraoperative information. Our purpose with this retrospective review was to identify patients who would be unable to complete adjuvant IMRT as intended, and therefore be unable to achieve optimal locoregional control.

MATERIAL AND METHODS

Patient Selection

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center, which waived the requirement for informed consent. A prospectively maintained departmental database was queried to identify patients who underwent a pleurectomy/decortication (P/D) or EPP for MPM from January 1, 2004, to September 31, 2017. Patients who received an extended P/D were included as a P/D for the purposes of this analysis. Patients who received

an exploratory thoracotomy with a partial P/D without an attempt at maximal cytoreduction were excluded from analysis. We also excluded patients for whom there was no intent to provide adjuvant IMRT, which occurred most often after pleurectomy/decortication earlier in the study period (n = 5).

Preoperative Evaluation and Surgical Details

All patients were staged with a positron emission tomography/computed tomography, bronchoscopy, laparoscopy, and mediastinoscopy. Patients with N2 disease or those with evidence of metastases are excluded from consideration for cytoreductive surgery. Pulmonary function was evaluated with spirometry and quantitative ventilation/perfusion scanning. Patients who received a P/D were required to be physiologically capable of also receiving EPP. The operative choice of performing an EPP or P/D was according to the discretion of the operating surgeon. Carefully selected patients with biphasic histology were considered for cytoreduction. Neoadjuvant chemotherapy regimen consisted of a platinum-based chemotherapy doublet with pemetrexed.

Radiation Therapy

The IMRT protocol was delivered as previously described.⁷ The dose prescribed to the planned target volume was 45 to 50 Gy in 25 daily fractions, with a boost to 55 to 60 Gy provided for positive margins or areas at high risk for residual tumor.

Variable Definitions

All covariates were collected and maintained in a prospectively maintained departmental database with additional chart review performed. The American Joint Committee on Cancer Seventh Edition was used to define pathologic stage. Epithelioid, biphasic, or sarcomatoid histologic subtype reflected findings among the final pathologic specimen after resection. Weight loss and smoking history were abstracted from preoperative history and physical intake forms. Weight loss represented any self-reported weight loss by the patient. Postoperative complications were defined according to previously published criteria.¹⁸ The reason for not receiving adjuvant IMRT was determined by the treating radiation oncologist and abstracted from statements within clinic progress notes. Reasons included delayed recovery or morbidity, patient refusal or undocumented reason, and dose constraints. Large areas of remaining or recurrent bulky tumor observed on imaging were often unable to be treated to limit toxicity to nearby organs. In the case of patient death before the outpatient radiation oncology follow-up, the patient was deemed to have not completed adjuvant IMRT because of mortality. Patients who started adjuvant IMRT and failed to complete the treatment were considered to have not received adjuvant IMRT for the purposes of this study.

* No evidence of N2, N3, or T4 disease

FIGURE 1. Treatment strategy framework at MD Anderson Cancer Center (2018). Patients typically receive staging with mediastinoscopy, diagnostic laparoscopy, and positron emission tomography followed by induction chemotherapy. *Diag. Lap.*, Diagnostic laparoscopy; *IMRT*, intensity-modulated radiation therapy; *PET*, positron emission tomography.

FIGURE 2. Rate of completing adjuvant IMRT according to type of surgery. *IMRT*, Intensity-modulated radiation therapy.

Statistical Methods

Chi-square or Fisher exact test was used to compare frequency of categorical variables. Student *t* test or Mann–Whitney test was used to evaluate for differences in continuous variables, where appropriate. Cochran–Armitage test was used to evaluate for trends in adjuvant IMRT use during the study duration. A univariable logistic regression model was used to evaluate for factors associated with completion of adjuvant IMRT. Covariates with *P* less than .25 or those of clinical interest were evaluated for multivariable analysis. Robust standard errors were used for regression analysis. The final model was selected using backward selection criteria. All tests were 2 sided. All statistics were performed using STATA version 14.2 (StataCorp LP, College Station, Tex).

RESULTS

Patient Characteristics

A total of 160 patients were identified, among whom 94 (59%) received an EPP and 66 (41%) received a P/D. After resection, only 15 patients (9%) had grossly positive margins. Most patients had pathologically stage III or IV stage, despite being aggressively staged with mediastinoscopy. The 30-day mortality was higher after EPP (6%, 6/94) versus P/D (0%, 0/66) (*P* = .038). However, the 90-day mortality was not higher after EPP (13%, 12/94) versus P/D (4/66, 6%) (*P* = .130).

Adjuvant IMRT was completed among 105 patients (66%) (Figure 2). Characteristics of those able to complete adjuvant IMRT are shown in Table 1. The median number of days to complete all intended adjuvant IMRT was 102 days postoperatively (interquartile range, 90–116 days). Reasons for not being able to complete adjuvant IMRT were as follows: 19 (12%) mortality, 21 (13%) dose constraints, 11 (7%) postoperative morbidity or delayed recovery, and 4 (3%) refused or unknown status (Table 2). There were no trends identified in the rate of receiving adjuvant IMRT over the study duration period (*P* = .927). The rate of receiving adjuvant IMRT among those who experienced cardiovascular or pulmonary complications was approximately half of those who did not (*P* < .01 for all, Table 1).

Prognostic Factors Toward Completing Adjuvant Intensity-Modulated Radiation Therapy

A prognostic model to identify preoperative or intraoperative factors that were associated with failure to receive adjuvant IMRT is shown in Table 3. Although suffering from complications was strongly associated with failing to receive adjuvant IMRT, we restricted this analysis to information that would be available preoperatively or intraoperatively. Pathologic stage and histologic subtype were included because of inaccuracy with clinical staging of mesothelioma.^{19–21}

Preoperative American Society of Anesthesiologists 3+ classification was strongly associated with failure to receive adjuvant IMRT (hazard ratio, 0.27; 95% confidence interval, 0.12–0.63; *P* = .002), as was smoking history (hazard ratio, 0.42; 95% confidence interval, 0.20–0.88; *P* = .022). Patients with forced expiratory volume in 1 second 70% or less than predicted and pathologic stage IV (T4) showed a decreased likelihood of completing adjuvant IMRT on univariable analysis; however, these differences disappeared after multivariable adjustment. Nonepithelioid subtype, older age, and preoperative weight loss were not associated with failure to complete adjuvant IMRT. In addition, the rate of completing adjuvant radiation was not different among those who received EPP or P/D, nor was it different among patients who received an R0/R1 resection versus those who received an R2 resection.

DISCUSSION

Many patients are unable to complete adjuvant IMRT after cytoreductive surgery for MPM, with one-third of patients discontinuing treatment. Our results parallel those of several phase II trials for trimodality therapy. We identified that worse preoperative comorbidity status, as identified by American Society of Anesthesiologists status and smoking history, was associated with decreased likelihood of receiving adjuvant IMRT. The importance of perioperative complications toward receiving adjuvant treatment is underscored by the observation that the rate

TABLE 1. Characteristics of patients able to complete adjuvant intensity-modulated radiation therapy

	Adjuvant IMRT (n = 105)*	No adjuvant IMRT (n = 55)*	P value
Age, mean (SD), y	61.5 ± 8.25	63.0 ± 7.80	.255
Male sex	80 (76%)	43 (78%)	.777
Weight loss	22 (21%)	8 (15%)	.324
Smoking history	52 (50%)	39 (71%)	.013
ASA classification			.001
1	8 (8%)	0	
2	36 (34%)	8 (15%)	
3	60 (57%)	44 (80%)	
4	1 (1.0%)	3 (5%)	
% predicted FEV1, mean (SD)	78.1 ± 16.8	73.3 ± 14.6	.075
Neoadjuvant chemotherapy	72 (69%)	36 (65%)	.689
Resection type			.364
P/D	46 (44%)	20 (36%)	
EPP	59 (56%)	35 (63%)	
Histologic subtype			.277
Epithelioid	83 (79%)	39 (71%)	
Biphasic	18 (17%)	15 (27%)	
Sarcomatoid	4 (4%)	1 (2%)	
Margin status			.292
R0/R1	97 (92%)	48 (87%)	
R2	8 (8%)	7 (13%)	
Pathologic stage			.145
Stage I	6 (6%)	2 (4%)	
Stage II	16 (15%)	4 (7%)	
Stage III	56 (53%)	26 (47%)	
Stage IV	27 (26%)	23 (42%)	
Length of stay, median (IQR)	8 (6-11)	10 (7-21)	.001
Pulmonary complications	39 (37%)	34 (62%)	.003
Cardiovascular complications	38 (36%)	34 (62%)	.002
Readmission to ICU postoperatively	5 (5%)	8 (15%)	.063

IMRT, Intensity-modulated radiation therapy; SD, standard deviation; ASA, American Society of Anesthesiologists; FEV1, forced expiratory volume in 1 second; P/D, pleurectomy/decortication; EPP, extrapleural pneumonectomy; IQR, interquartile range; ICU, intensive care unit. *Indicates N (%) unless otherwise stated.

of completing adjuvant IMRT was approximately half among those who experienced cardiovascular or pulmonary complications. However, in our population, we did not observe that receiving an EPP or P/D influenced the rate of receiving adjuvant IMRT. In addition, the extent of resection, whether an R0/R1 or R2, was also not associated with the likelihood of receiving adjuvant IMRT.

Median survival has been shown to be significantly higher among those who are able to complete trimodality therapy. In a prospective phase II trial, 16.8-month median survival was observed among the entire intent-to-treat study

TABLE 2. Reasons for failing to complete adjuvant intensity-modulated radiation therapy

	EPP (N = 94)	P/D (N = 66)	P value
Mortality	15 (16%)	4 (6%)	.277
Dose constraints	10 (11%)	11 (17%)	
Postoperative morbidity or delayed recovery	7 (7%)	4 (6%)	
Refused or unknown status	3 (3%)	1 (2%)	

EPP, Extrapleural pneumonectomy; P/D, pleurectomy/decortication.

cohort that received induction chemotherapy, and was extended to 29.1 months among those who were able to complete EPP and adjuvant radiation per protocol.² It is unclear whether survivorship bias, which results from the “survivors” and those with more favorable disease biology preferentially finishing therapy, explains these results. In addition to concerns regarding survivorship bias, the patients who are unable to complete trimodality therapy represent those who had an adverse event that was significant enough to result in discontinued treatment. Determining the rate of returning to intended oncologic treatment and factors that may predict completing intended oncologic treatment may lead to important advancements in patient selection for cytoreductive surgery.

Study Limitations

Limitations of this study include the risk of residual confounding in this retrospective study. There may also be important unmeasured confounding relationships that were not accounted for. In addition, our outcomes represent those of an experienced and high-volume academic center and may not be generalizable to other institutions. Patients who receive cytoreductive surgery at our institution represent carefully selected surgical candidates. Last, although this study represents a relatively large series for mesothelioma, the power of this study is an additional limitation. Although there were no statistically significant differences between EPP or P/D in the reason for failing to complete adjuvant IMRT, this may represent a type II error.

CONCLUSIONS

Because of the high rate of failing to complete subsequent adjuvant therapy after cytoreduction for MPM, our findings support highly selective patient selection. Patients with higher baseline comorbidity should not be considered for cytoreduction. We were unable to show that the margin status and receiving an EPP or P/D had any relationship with receiving adjuvant IMRT.

TABLE 3. Univariable and multivariable preoperative or intraoperative factors associated with completing adjuvant intensity-modulated radiation therapy

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per y)	0.98 (0.94-1.02)	.262		
Sex, female	1.12 (0.51-2.45)	.777		
Weight loss	1.56 (0.64-3.78)	.328		
Smoking history	0.40 (0.20-0.81)	.011	0.42 (0.20-0.88)	.022
ASA classification				
1-2 (reference)	-		-	
3+	0.24 (0.10-0.55)	.001	0.27 (0.12-0.63)	.002
FEV1				
>70% (reference)	-		-	
≤70%	0.50 (0.26-0.98)	.043	0.55 (0.27-1.12)	.103
Histologic subtype				
Epithelioid (reference)	-		-	
Nonepithelioid	0.65 (0.31-1.37)	.254		
Induction chemotherapy	1.15 (0.58-2.31)	.690		
Resection type				
P/D (reference)	-		-	
EPP	0.73 (0.37-1.44)	.366		
Margin status				
R0-R1 (reference)	-		-	
R2	0.57 (0.19-1.66)	.299		
Pathologic stage				
Stage I-II (reference)	-		-	
Stage III	0.59 (0.21-1.63)	.306	0.79 (0.25-2.52)	.697
Stage IV (T4)	0.32 (0.11-0.93)	.036	0.43 (0.13-1.42)	.165

Postoperative complications, ICU readmission, and prolonged length of stay were statistically significant on univariable analysis but were not included because of not being known to the treating provider preoperatively or intraoperatively. OR, Odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; FEV1, forced expiratory volume in 1 second; P/D, pleurectomy/decortication; EPP, extrapleural pneumonectomy.

Webcast

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Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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