Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

The Role of Adjuvant Radiotherapy in the Treatment of Pleural Mesothelioma

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ABSTRACT

Background. Pleural mesothelioma is a rare but aggressive form of cancer. Local recurrence represents the majority of treatment failures and overall survival (OS) outcomes remain dismal. Adding locoregional treatment with radiotherapy after surgical resection has been considered but its role remains uncertain.

Objective. The purpose of this study was to evaluate the outcomes of adjuvant radiation therapy (RT) for patients with malignant pleural mesothelioma.

Methods. The National Cancer Data Base (NCDB) was queried (2004–2013) for patients with malignant mesothelioma. Patients were divided into three groups: observation, surgery alone, and surgery followed by adjuvant RT. Statistics included Fisher's exact or Chi square tests to analyze categorical proportions between groups, Kaplan–Meier analysis to evaluate OS, and Cox proportional hazards modeling to determine variables associated with OS. Propensity matching was performed to make comparisons between homogenous groups.

Results. Overall, the surgery plus radiotherapy group had a higher median survival (21.4 months) compared with surgery alone (16.59 months) [$p < 0.001$]. RT was more likely to be delivered after extrapleural pneumonectomy than with lung-sparing surgical approaches. On multivariable analysis, receipt of surgery plus radiotherapy, chemotherapy administration, and higher socioeconomic status were associated with improved OS ($p < 0.0001$). After propensity matching, receipt of surgery plus radiotherapy and chemotherapy administration were still associated with improved OS ($p < 0.05$).

Conclusions. In the treatment of malignant pleural mesothelioma, adjuvant radiotherapy after surgical intervention was associated with improved OS. This study is the largest study of adjuvant radiotherapy to date, and our findings highlight the need for additional prospective data.

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Pleural mesothelioma is a rare form of cancer, but its incidence is increasing.[1] It represents an aggressive malignancy, with a median survival of ≤ 12 months.[2] The optimal treatment for pleural mesothelioma remains controversial.[1] Different surgical techniques, systemic chemotherapy, and radiation therapy (RT) have all been used as single modality treatments with varying degrees of success. Trimodality treatment with chemotherapy, surgery, and radiotherapy is the most aggressive approach to therapy;[1] however, for all treatment strategies, local recurrence represents the majority of treatment failures and overall survival (OS) outcomes remain dismal.[3]

Because of this, adding locoregional treatment with radiotherapy after surgical resection has been considered but its role remains uncertain. Part of this uncertainty may be due to the inherent issues and toxicities associated with delivering radiotherapy after surgical intervention in

patients with already limited pulmonary function.[4,5] In addition, older radiotherapy, surgical, and chemotherapy techniques used in older radiation studies make it difficult to extrapolate findings to the present day. Finally, the rarity of cases limits the power of statistical analysis. Large, national retrospective reviews on the incorporation of radiation into the treatment paradigm (as single-agent therapy or part of multimodality therapy) have found conflicting results.[6,7] To better understand the role of radiotherapy, specifically in the adjuvant setting after surgical intervention, we utilized the large, contemporary National Cancer Data Base (NCDB) to study the effect of adjuvant radiotherapy on survival outcomes.

MATERIALS AND METHODS

This study used the NCDB, which is a hospital-based database under the administration of the American College of Surgeons and the American Cancer Society and accounts for 70% of new cancer diagnoses in the US.[8–14] The most recently released NCDB dataset corresponded to the years 2004–2013. For inclusion, patients required histological diagnostic confirmation and a recorded vital status. Patients without proper staging were removed; however, patients with metastatic disease were still included as local progression remains a leading cause of death.[3]

Patients were divided into three groups: no local therapy (hereby defined as the observation group), surgery alone, and surgery followed by adjuvant RT. The observation group was kept to serve as a helpful comparison baseline for the two local intervention groups. For patients receiving adjuvant radiotherapy, only patients receiving at least 40 Gy were included to exclude patients undergoing palliative radiotherapy. Information collected on each patient included demographic data, comorbidity information, clinicopathologic tumor parameters, and treatment characteristics. All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using JMP version 13 (SAS Institute, Inc., Cary, NC, USA). Fisher's exact or Chi square tests were used to analyze categorical proportions between groups. The Kaplan–Meier method was used for survival analysis, and comparisons between the two treatment paradigms were performed using the log-rank test for all patients. OS was defined as the interval between the date of diagnosis and the date of death or last contact. Multivariable Cox proportional hazards modeling was additionally used to identify variables associated with OS in the entire cohort. Variables included in the multivariable analysis were those found to be statistically significant on univariate analysis. Median follow-up was calculated using the reverse Kaplan–Meier method.

Propensity score matching was performed using age, sex, stage, Charlson–Deyo comorbidity score, and residential setting as the matching variables to reduce the influence of heterogeneity on survival outcomes. Multivariable Cox proportional hazards modeling was additionally used to identify variables associated with OS in the matched cohort.

RESULTS

In total, 24,914 patients met the inclusion criteria. Of these, 17,262 (69.3%) patients received no local intervention, 5918 (23.8%) patients underwent surgery alone, and 762 (3.1%) patients received surgery plus radiation. Table 1 displays the demographic and clinical characteristics of the analyzed patients. The majority of patients were male, Caucasian, had locoregional disease, and had a Charlson–Deyo comorbidity score of 0. Epithelioid histology had the highest incidence and the most common age of presentation was between 71 and 80 years.

A greater proportion of patients who received adjuvant radiotherapy had locoregional disease, private insurance, higher income, epithelioid histology, and lower Charlson–Deyo comorbidity score. Patients who received adjuvant radiotherapy were also more likely to receive chemotherapy. These factors are summarized in Table 2. In addition, in patients who had undergone surgery, radiation was more common in the group undergoing EPP rather than lung-sparing surgery such as pleurectomy and decortication.

The median follow-up was 60.9 months. In the whole cohort, the surgery plus radiotherapy group had the highest median survival (21.4 months) compared with observation (7.6 months) and surgery alone (16.59) months. The surgery plus radiation group also had the highest rates of survival at 1 and 2 years compared with the observation and surgery alone groups. These results are summarized in Table 3.

On multivariable analysis, male sex, advancing age, higher Charlson–Deyo comorbidity score, fibroid (sarcomatoid) and biphasic histologies, and lower socioeconomic status were associated with worse OS. In contrast, receipt of surgery plus radiotherapy, chemotherapy administration, and higher socioeconomic status were associated with improved OS. These results are tabulated in Table 4.

Propensity score matching was performed using age, sex, stage, Charlson–Deyo comorbidity score, and residential setting as the matching variables (electronic supplementary Table 1). After matching, there were 454 patients in the surgery alone group and 454 patients in the surgery plus radiotherapy group. On multivariable analysis of this matched cohort, receipt of surgery and chemotherapy administration were associated with improved OS. In

TABLE 1 Patient characteristics

Category	Variable	Frequency	Total (%)	p Value
Sex	Male	18,698	75.1	p < 0.0001
	Female	6216	25.0	
Race	White	22,941	93.0	p < 0.0001
	Black	1215	4.9	
	Other	509	2.1	
Hispanic origin	Hispanic	1042	4.5	
	Non-Hispanic	22,367	95.6	
Age at diagnosis, years	0–40	523	2.1	p < 0.0001
	41–50	956	3.8	
	51–60	2817	11.3	
	61–70	6297	25.3	
	71–80	8435	33.9	
	80 +	5886	23.6	
Insurance status	Uninsured	492	2.0	p < 0.0001
	Private insurance	6673	27.5	
	Medicare/Medicaid/Government	17,085	70.5	
Median income quartile, US$	< 30,000	2337	9.8	p < 0.0001
	30,000–35,999	4117	17.3	
	36,000–45,999	6861	28.8	
	46,000 +	10,502	44.1	
Residence	Metro	19,746	82.8	p < 0.0001
	Urban	3604	15.1	
	Rural	479	2.0	
Disease burden	Locoregional	9664	58.1	p < 0.0001
	Metastatic	6976	41.9	
Histology	Mesothelioma, NOS	10,989	44.1	p < 0.0001
	Fibroid	2581	10.4	
	Epithelioid	9025	36.2	
	Biphasic	1645	6.6	
	Other	674	2.7	
Charleston comorbidity score	0	17,321	69.5	p < 0.0001
	1	5499	22.1	
	2 +	2094	8.4	
Chemotherapy	Not administered	11,984	49.9	p = 0.0841
	Administered	12,009	50.1	

NOS not otherwise specified

contrast, fibroid (sarcomatoid) and biphasic histologies were associated with worse OS. These results are tabulated in Table 5.

DISCUSSION

Given the lack of clear evidence to guide adjuvant management for malignant pleural mesothelioma, the current study provides important information regarding the utility of adjuvant radiotherapy for patients in this patient population. To our knowledge, this is the largest study to date to specifically examine the use, role, and benefit of adjuvant radiotherapy after surgical intervention. Several observations can be made from our analysis. First, the majority of patients do not undergo locoregional intervention with surgery or radiation. This may be due to the poor prognosis of these patients and the high age of presentation precluding intensive locoregional treatment. This is supported by the fact that approximately 50% of this group also did not receive chemotherapy, suggesting that performance status may have prohibited aggressive treatment. Second, male sex, elevated comorbidity score, and the presence of sarcomatoid, mixed or desmoplastic histology (represented by the fibrinous and biphasic groups in

TABLE 2 Practice patterns in malignant mesothelioma

Category	Variable	Observation [n = 17,262] (%)	Surgery only [n = 5918] (%)	Surgery and radiation [n = 762] (%)	Chi square
Sex	Male	13,219 (76.6)	4156 (70.2)	557 (73.1)	p < 0.0001
	Female	4043 (23.4)	1762 (29.8)	205 (26.9)	
Race	White	15,905 (93.0)	5454 (93.1)	707 (93.8)	p < 0.0001
	Black	850 (5.0)	294 (5.0)	23 (3.1)	
	Other	346 (2.0)	110 (2.0)	24 (3.2)	
Hispanic origin	Hispanic	703 (4.4)	264 (4.7)	32 (4.4)	p = 0.5667
	Non-Hispanic	15,459 (95.6)	5366 (95.3)	693 (95.6)	
Age at diagnosis, years	0–40	172 (1.0)	313 (60.1)	21 (2.8)	p < 0.0001
	41–50	436 (2.5)	423 (43.7)	53 (7.0)	
	51–60	1574 (9.1)	938 (32.5)	199 (26.1)	
	61–70	3941 (22.8)	1175 (27.5)	309 (40.6)	
	71–80	6174 (35.8)	1769 (20.5)	162 (21.3)	
	80 +	4965 (28.8)	700 (11.6)	18 (2.4)	
Insurance status	Uninsured	359 (2.1)	107 (1.8)	10 (1.4)	p < 0.0001
	Private insurance	3825 (22.5)	2260 (39.3)	371 (51.7)	
	Medicare/Medicaid/ Government	12,800 (75.4)	3386 (58.9)	336 (46.9)	
Median income quartile, US$	< 30,000	1663 (10.1)	515 (9.1)	58 (8.0)	p < 0.0001
	30,000–35,999	2963 (17.9)	891 (15.8)	105 (14.5)	
	36,000–45,999	4908 (29.7)	1527 (27.1)	191 (26.3)	
	46,000 +	6995 (42.3)	2710 (48.0)	317 (51.2)	
Residence	Metro	13,659 (82.7)	4705 (83.1)	613 (84.0)	p = 0.8903
	Urban	2517 (15.2)	847 (15.0)	102 (14.0)	
	Rural	337 (2.0)	113 (2.0)	15 (2.1)	
Disease burden	Locoregional	6282 (53.8)	2599 (68.0)	500 (77.8)	p < 0.0001
	Metastatic	5392 (46.2)	1221 (32.0)	143 (22.3)	
Histology	Mesothelioma, NOS	8565 (49.6)	1852 (31.3)	154 (20.2)	p < 0.0001
	Fibroid	1899 (11.0)	494 (8.3)	59 (7.7)	
	Epithelioid	5522 (32.0)	2739 (46.3)	427 (56.0)	
	Biphasic	915 (5.3)	586 (9.9)	93 (12.2)	
	Other	361 (2.1)	247 (4.2)	29 (3.8)	
Charleston comorbidity score	0	11,602 (67.2)	4336 (73.3)	644 (84.5)	p < 0.0001
	1	3979 (23.1)	1251 (21.1)	101 (13.3)	
	2 +	1681 (9.7)	331 (5.6)	17 (2.2)	
Chemotherapy	Not administered	8993 (53.6)	2358 (41.3)	205 (27.3)	p < 0.0001
	Administered	7777 (46.4)	3355 (58.7)	545 (72.7)	

NOS not otherwise specified

the NCDB) were associated with worse OS. These findings are in accordance with, and give credence to, a previous European Organization for Research and Treatment of Cancer (EORTC) prognostic model for malignant pleural mesothelioma patients who observed worse survival outcomes in patients with these prognostic factors.[15,16]

In addition, our analysis found a significant OS benefit for patients receiving non-palliative doses of radiotherapy after surgical intervention. This benefit remained even after multivariable analysis and propensity score matching. This suggests that there are patients (well-selected with good performance status) who may benefit from additional locoregional therapy with adjuvant radiation. This finding

TABLE 3 Long-term survival data based on treatment alone

	Overall	Observation	Surgery alone	Surgery and radiation	p-Value
Median follow-up, months	60.91	63.44	57.72	64.43	NSS
Median survival, months (95% CI)	9.63 (9.46–9.89)	7.59 (7.39–7.75)	16.59 (15.84–17.31)	21.42 (19.71–22.51)	p < 0.001
1-year survival (%)	43.3	35.9	60.2	76.5	p < 0.001
2-year survival (%)	22.8	16.6	38.8	42.7	p < 0.001

NSS non-statistically significant, *CI* confidence interval

TABLE 4 Factors associated with overall survival on multivariable analysis

Category	Variable	Hazard ratio	p-Value
Sex	Male	1.23	p < 0.0001
	Female	Reference	
Age at diagnosis, years	0–40	Reference	p < 0.0001
	41–50	1.12	
	51–60	1.46	
	61–70	1.54	
	71–80	1.71	
	80 +	2.31	
Median income quartile, US$	< 30,000	Reference	p < 0.0001
	30,000–35,999	0.88	
	36,000–45,999	0.88	
	46,000 +	0.82	
Disease burden	Locoregional	Reference	p < 0.0001
	Metastatic	1.35	
Histology	Mesothelioma, NOS	1.18	p < 0.0001
	Fibroid	2.23	
	Epithelioid	Reference	
	Biphasic	1.56	
	Other	2.19	
Charleston comorbidity score	0	Reference	p < 0.0001
	1	1.13	
	2 +	1.28	
Chemotherapy	Not administered	Reference	p < 0.0001
	Administered	0.65	
Treatment	Observation	Reference	p < 0.0001
	Surgery only	0.70	
	Surgery and radiation	0.63	

NOS not otherwise specified

makes sense given that the majority of malignant pleural mesothelioma patients fail locally and die from local progression of disease.[3]

The delivery of adjuvant radiotherapy after surgical intervention has changed over the years. After an initial study showed that intraoperative radiotherapy was not a beneficial treatment at the time of surgery,[17] a phase II trial examining the role of three-dimensional conformal radiotherapy (3D-CRT) to the hemithorax after extrapleural pneumonectomy (EPP) was conducted and showed good locoregional control results.[18] Eventually, intensity-modulated radiotherapy (IMRT), which uses multiple beams to modulate the radiation dose to the body, became prevalent. Unfortunately, initial reports using IMRT noted high mortality rates due to fatal pneumonitis of the contralateral lung after hemithoracic IMRT status post EPP.[4,19] However, these studies extrapolated radiation dose constraints

TABLE 5 Factors associated with overall survival on multivariable analysis of the matched cohort

Category	Variable	Hazard ratio	p-Value
Histology	Mesothelioma, NOS	1.19	$p < 0.0001$
	Fibroid	2.71	
	Epithelioid	Reference	
	Biphasic	1.62	
Chemotherapy	Not administered	Reference	$p = 0.0369$
	Administered	0.84	
Treatment	Surgery only	Reference	$p = 0.0313$
	Surgery and radiation	0.88	

NOS not otherwise specified

from lung cancer[5] and newer studies using more stringent dose constraints have reported lower rates of radiation pneumonitis.[20–25]

Just as radiation planning and delivery have advanced, so have surgical techniques. EPP has been historically used, but lung-sparing approaches such as pleurectomy and decortication have been developed and are used on the majority of patients.[26] Retrospective comparisons of EPP and lung-sparing approaches have suggested that a lung-sparing approach is equivalent to improved survival outcomes with fewer complications.[26–29] However, treatment guidelines conflict on the role of lung-sparing surgery as part of a curative treatment plan due to concerns that it is less of an oncologic procedure.[30,31] This distinction on the type of surgery performed is relevant for any discussion of post-surgical radiation. Radiotherapy to the pleural cavity and not the entire hemithorax has been developed and has been shown to be both feasible and safe.[32–34] We found that patients who underwent EPP were more likely to receive adjuvant radiation, possibly due to concerns about the increased risk of ipsilateral radiation pneumonitis after pleurectomy due to the large volume of ipsilateral lung being irradiated. However, prospective studies suggest that the risk remains low if stringent constraints are used.[32–34] As further radiotherapy advances are made, including the increased utilization of proton therapy, there may be further improvement in local control rates and survival outcomes, as well as reduced toxicities.

There are several limitations with our analysis. First, the retrospective nature of this study means we must acknowledge the possibility of selection bias. Propensity score matching was performed to minimize its effects. Second, the NCDB does not keep track of several end-points such as tolerance of therapy, cancer-specific survival, and local/regional control, and does not include information on the reasoning behind treatment decisions or data on the use of targeted or salvage treatments. Finally,

although the NCDB accounts for 70% of new US cancer diagnoses, only Commission on Cancer-accredited facilities collect data for the NCDB. Overall, these limitations do not diminish the need for further study of the role of adjuvant therapy for malignant pleural mesothelioma.

CONCLUSIONS

In the treatment of malignant pleural mesothelioma, adjuvant radiotherapy after surgical intervention was associated with improved OS. A greater proportion of patients who received adjuvant radiotherapy had locoregional disease, private insurance, higher income, epithelioid histology, and lower Charlson–Deyo comorbidity score. RT was more likely to be delivered after EPP than with lung-sparing surgical approaches. Patients who received adjuvant radiotherapy were also more likely to receive chemotherapy. On multivariable analysis, male sex, advancing age, higher Charlson–Deyo comorbidity score, fibroid (sarcomatoid) and biphasic histologies, and lower socioeconomic status were associated with worse OS. In contrast, receipt of surgery plus radiotherapy, chemotherapy administration, and higher socioeconomic status were associated with improved OS. After propensity score matching between the surgery-alone group and the surgery plus radiotherapy group, the receipt of radiotherapy and chemotherapy was still associated with improved OS on multivariable analysis. This study is the largest study of adjuvant radiotherapy to date, and our findings highlight the need for additional prospective data. We eagerly await the results of the currently ongoing clinical trials on this topic.

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