Is There a Role for Cancer-Directed Surgery in Early-Stage Sarcomatoid or Biphasic Mesothelioma?

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Background. **Benefits of surgical resection for early-stage nonepithelioid malignant pleural mesothelioma (MPM) have not been clearly elucidated. This study investigated whether cancer-directed surgery affects overall survival compared with nonsurgical therapies for T1-T2 N0 M0 sarcomatoid or biphasic MPM patients.**

Methods. **Adult patients with clinical stage I or II MPM were identified in the National Cancer Database from 2004 to 2103. Patients who underwent cancer-directed surgery were matched by propensity score with patients who had received chemotherapy/radiotherapy or no treatments. Overall survival was compared using a Cox proportional hazard regression model.**

Results. **From National Cancer Database queries, 878 patients with clinical stage I or II MPM with sarcomatoid (n = 524) or biphasic (n = 354) histology were identified. Overall median survival was 5.5 months for patients with sarcomatoid mesothelioma. The cancer-directed surgery improved overall survival compared with no operation (median survival, 7.56 months vs 4.21 months, respectively; $p < 0.01$). In the biphasic group, median overall survival was 12.2 months. Again, the cancer-directed surgery improved survival compared with no operation (15.8 months vs 9.3 months, $p < 0.01$). For both histologies, the cancer-directed surgery improved overall survival compared with those who underwent chemotherapy or radiotherapy, or both, without resection ($p < 0.05$). Perioperative mortality was 6.0% at 30 days and 21.4% at 90 days.**

Conclusions. **The cancer-directed surgery is associated with improved survival in early-stage MPM patients with nonepithelioid histology compared with those who did not undergo resection or chose medical therapy. Given the high perioperative mortality, a careful patient selection and multidisciplinary evaluation is recommended.**

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Malignant pleural mesothelioma (MPM) is a highly aggressive tumor with poor survival. Despite improvement in surgical techniques that have significantly decreased perioperative mortality and the advent of effective adjuvant systemic therapy, the reported median survival in the literature remains dismal, ranging only 4 to 19 months [1, 2]. The optimal therapy for patients with MPM remains highly controversial, and the role of surgery is even less clear. Most controversy centers on whether surgery increases survival and whether a survival benefit is best achieved with extrapleural pneumonectomy or pleurectomy/decortication within a multimodal regimen and who should be offered surgical resection [3–5]. Still, it is generally believed that macroscopically complete surgical resection with adjuvant chemotherapy can provide a survival advantage in patients with epithelioid MPM, although there is no accepted role for resection of nonepithelioid histologies [6, 7].

Several retrospective institutional studies have demonstrated long-term survival benefits with aggressive surgical resection in patients with early epithelioid-type mesothelioma. However, patients with nonepithelioid histology have been largely excluded from such radical operations, although benefit is unclear. We used a propensity score-matched design to determine whether cancer-directed surgery affects overall survival compared with nonsurgical therapies for early stage T1-T2 N0 sarcomatoid or biphasic MPM patients.

Patients and Methods

Database and Patient Population

We identified patients with pleural-based histologically confirmed sarcomatoid or biphasic mesothelioma (International Classification of Diseases for Oncology, 3rd edition, code C38.4, morphology codes 9051 [fibrous/sarcomatoid] or 9053 [biphasic]) in the National Cancer Database (NCDB) diagnosed between 2004 and 2013. Approximately 70% of all newly diagnosed cancer cases in

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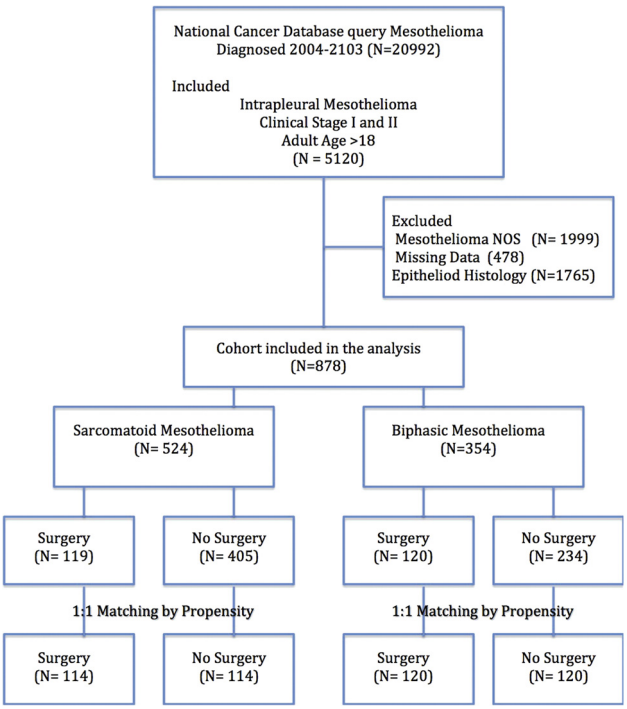

Fig 1. Flow diagram of patient selection and propensity matching. (NOS = not otherwise specified.)

the United States are reported to the NCDB [8]. Patient data on age, sex, race, comorbidities, year of diagnosis, generalized socioeconomic status and other residential information, information on the treatment facility, and tumor characteristics, and data on the type of operation and pathologic specimen factors were abstracted. Cancer-directed surgery of the primary was defined as local excision, simple/partial surgical removal of the primary, total surgical removal of the primary, debulking, or radical surgery. Those who underwent only local tumor destruction or an undefined or unknown procedure were classified as not having undergone cancer-directed surgery. Patients treated with palliative intent were also excluded.

In this analysis, we included adults with clinical or pathologic stage I or II (T1-2 N0 M0) MPM with sarcomatoid (code 9051) or biphasic morphology (code 9053). We included only individuals who did not undergo therapy with palliative intent and examined those who underwent cancer-directed surgery compared with no surgical intervention. Clinical and pathologic stages were abstracted directly from the NCDB and included separate clinical T, N, and M elements as defined by the American Joint Committee on Cancer. Excluded from the analysis were those without T stage or vital status data, patients with epithelioid histology, and mesothelioma with type not otherwise specified. The final cohort for the study is depicted in Figure 1.

Statistical Analysis

PROPENSITY SCORE MATCHING. We defined two treatment groups: those who underwent cancer-directed resection and those who did not undergo resection. The former comprised patients who underwent resection of the tumor, and the latter included patients who did not undergo cancer-directed resection and may or may not have received chemotherapy or radiotherapy, or both, as part of treatment. Chemotherapy and radiotherapy were defined as patients identified as having undergone the respective modality as part of therapy and those who did not (or if therapy was unspecified). Separately for sarcomatoid and biphasic histologies, the propensity score (the conditional probability) of undergoing resection was derived by using a multivariable logistic regression model with the baseline covariates of age, sex, race, income, year of diagnosis, population density of patients' residence, Charlson-Deyo comorbidity score, facility type, T stage, radiotherapy, and chemotherapy.

A 1-to-1 matching (without replacement) by propensity score was performed by using the nearest neighbor method with a caliper width equal to 0.1 SDs [9]. Matching was done using the psmatch2 package in Stata 14 software (StataCorp, College Station, TX). We examined balance in the categorical baseline covariates in the matched data by χ^2 test for independence. All baseline covariates were not statistically significantly different by surgical intervention except for the proportion of radiotherapy among biphasic patients. For those who underwent an operation, data on 30-day readmissions, 30-day and 90-day postoperative mortality, and vital status were used.

SURVIVAL DATA ANALYSIS. By sarcomatoid and biphasic histology, using Kaplan-Meier curves in each matched data set, overall survival from the time of diagnosis was estimated in the groups with and without cancer resection and compared using the log-rank test. Cox proportional hazards survival analysis was used to evaluate association between treatment modality and overall survival on matched pairs, stratified by histology. Scaled Schoenfeld residuals were used to evaluate the assumption for the proportional hazard.

We also compared overall survival between the resection group and a subgroup of patients who did not undergo resection but did receive chemotherapy or radiotherapy or both. An α of 0.05 was used for all hypotheses testing, and two-sided p values and 95% confidence intervals (CIs) are reported. Statistical analyses were performed in Stata 14 software. Univariable and multivariable Cox proportional hazards analyses were performed to determine demographic-, disease-, and treatment-related factors associated with survival among all (matched and unmatched) T1-T2 N0 M0 sarcomatoid and biphasic mesothelioma patients.

Results

Demographics

As shown in Figure 1, of 20,992 patients with mesothelioma queried from the NCDB, 5,120 patients who were older than 18 years with clinical stage I and II intrapleural mesothelioma were included and identified. We excluded 1,765 patients with epithelioid histology, 1,999 with

Table 1. Comparison of Demographics Between Sarcomatoid and Biphasic Mesothelioma Patients Who Underwent Resection Versus No Resection

	Sarcomatoid			Biphasic		
	Resection			Resection		
Variable	No No. (%)	Yes No. (%)	*p* Value	No No. (%)	Yes No. (%)	*p* Value
Age, years						
18–49	1 (0.9)	4 (3.5)	0.463	1 (0.8)	4 (3.3)	0.371
50–64	13 (11.4)	12 (10.5)		28 (23.3)	32 (26.7)	
65–74	37 (32.5)	42 (36.8)		47 (39.2)	49 (40.8)	
≥75	63 (55.3)	56 (49.1)		44 (36.7)	35 (29.2)	
Total	114 (100)	114 (100.0)		120 (100.0)	120 (100.0)	
Sex						
Male	104 (91.2)	104 (91.2)	1.000	96 (80.0)	95 (79.2)	0.873
Female	10 (8.8)	10 (8.8)		24 (20.0)	25 (20.8)	
Race						
White	112 (98.2)	109 (95.6)	0.503	113 (94.2)	114 (95.0)	0.903
Black	1 (0.9)	2 (1.8)		3 (2.5)	2 (1.7)	
Other	1 (0.9)	3 (2.6)		4 (3.3)	4 (3.3)	
Charlson-Deyo Score						
0	82 (71.9)	72 (63.2)	0.344	82 (68.3)	81 (67.5)	0.989
1	20 (17.5)	28 (24.6)		29 (24.2)	30 (25.0)	
≥2	12 (10.5)	14 (12.3)		9 (7.5)	9 (7.5)	
Annual median income						
<$48,000	31 (27.2)	37 (32.5)	0.385	44 (36.7)	38 (31.7)	0.414
≥$48,000	83 (72.8)	77 (67.5)		76 (63.3)	82 (68.3)	
Metropolitan area, population >1 million						
No	53 (46.5)	51 (44.7)	0.790	59 (49.2)	52 (43.3)	0.365
Yes	61 (53.5)	63 (55.3)		61 (50.8)	68 (56.7)	
Type of hospital						
Community	61 (53.5)	60 (52.6)	0.894	61 (50.8)	55 (45.8)	0.438
Academic	53 (46.5)	54 (47.4)		59 (49.2)	65 (54.2)	
Year of diagnosis						
2004–2007	43 (37.7)	41 (36.0)	0.784	37 (30.8)	34 (28.3)	0.671
2008–2013	71 (62.3)	73 (64.0)		83 (69.2)	86 (71.7)	
T stage						
T1	42 (36.8)	50 (43.9)	0.280	56 (46.7)	44 (36.7)	0.116
T2	72 (63.2)	64 (56.1)		64 (53.3)	76 (63.3)	
Radiotherapy						
No	104 (91.2)	101 (88.6)	0.509	112 (93.3)	98 (81.7)	0.006
Yes	10 (8.8)	13 (11.4)		8 (6.7)	22 (18.3)	
Chemotherapy						
No	69 (60.5)	67 (58.8)	0.787	49 (40.8)	38 (31.7)	0.140
Yes	45 (39.5)	47 (41.2)		71 (59.2)	82 (68.3)	

mesothelioma not otherwise specified, those with missing data, and patients who underwent resection for palliative intent. We identified 878 patients with clinical stage I or II intrapleural sarcomatoid (n = 524) or biphasic (n = 354) mesothelioma histology (Fig 1). In the sarcomatoid and biphasic mesothelioma groups, 114 and 120 patients who underwent cancer-directed surgery were matched 1:1 with those who had no surgical procedure, respectively. Overall in the matched data set, demographic characteristics were similar in the surgical and nonsurgical groups (Table 1). There was no difference in age, sex, preoperative comorbidities, stage, race, and household income. Among biphasic patients, however, a higher number of patients in the surgical resection group received radiation treatment than those who did not undergo resection (Table 1).

Perioperative Outcomes

Among the matched patients with sarcomatoid or biphasic mesothelioma who underwent cancer-directed

Table 2. Associations of Overall Survival With Treatment Modality Among Matched Patients, by Histology

Variable	No. (%)	6-Month Survival (%)	12-Month Survival (%)	Survival		
				Median (95% CI) Months	Hazard Ratio (95% CI)	*p* Value
Sarcomatoid patients						
All matched patients	228 (100)	48.0	24.4	5.7 (4.6–6.6)		
Surgical resection						
No	114 (50)	35.4	12.4	4.2 (3.6–5.4)	1.00	<0.001
Yes	114 (50)	60.5	36.4	7.6 (6.4–9.1)	0.51 (0.38–0.67)	
Treatment modality						
Radiotherapy or chemotherapy but no resection	50 (21.9)	48.0	14.0	5.9 (4.7–7.0)	1.00	0.015
Resection	114 (78.1)	60.5	36.4	7.6 (6.4–9.1)	0.65 (0.46–0.92)	
Biphasic patients						
All matched patients	240 (100)	75.4	50.2	12.2 (10.5–14.5)		
Surgical resection						
No	220 (50)	68.9	37.7	9.3 (7.6–10.7)	1.00	<0.001
Yes	220 (50)	81.6	61.9	15.8 (12.3–20.0)	0.57 (0.43–0.75)	
Treatment modality						
Radiotherapy or chemotherapy but no resection	74 (38.1)	81.0	41.3	9.8 (8.7–12.8)	1.00	0.002
Resection	220 (61.9)	81.6	61.9	15.8 (12.3–20.0)	0.60 (0.44–0.83)	

CI = confidence interval.

surgery, perioperative mortality was 6.0% at 30 days and 21.4% at 90 days. The perioperative mortality rates differed by histology and were 9.7% for sarcomatoid and 2.5% for biphasic at 30 days ($p = 0.021$) and were 29.8% for sarcomatoid and 13.3% for biphasic at 90 days ($p = 0.006$). Unplanned 30-day readmission was 2.6% and planned 30-day readmission was 1.71%, and this was not statistically significantly different between sarcomatoid and biphasic histologies. Median hospital length of stay was 5 days (interquartile range, 4 to 8 days).

Overall Survival

In the propensity matched cohorts (n = 228), overall median survival was 5.5 months for patients with sarcomatoid mesothelioma (Table 2). As shown in Figure 2A, the cancer-directed surgery group was associated with improved survival compared with the group with no resection (median survival, 7.56 months vs 4.21 months, respectively; $p < 0.01$). In the biphasic mesothelioma group, median overall survival was 12.2 months (Table 2). The surgery group had longer survival (15.8 months) than the no surgery group (9.3 months; $p < 0.01$, Figure 3A).

To exclude the effect of perioperative death on survival, the median survival of surgical patients who survived to 90 days was analyzed. For patients with sarcomatoid histology who underwent resection, the median survival increased from 7.56 months (95% CI, 6.37 to 9.10 months) to 12.2 months (95% CI, 8.84 to 15.08 months), and for those with biphasic histology, the median survival increased from 15.8 months (95% CI, 12.29 to 20.04 months) to 17.84 months (95% CI, 15.11 to 23.03 months).

Given that a proportion of nonsurgical patients only underwent observation, a separate analysis comparing only those who underwent therapy was performed. After excluding patients who had no therapy and comparing outcomes after different treatment modalities, in both sarcomatoid and biphasic groups, the patients who underwent surgical resection had improved survival than those who received chemotherapy or radiotherapy, or both, without surgical resection (sarcomatoid: hazard ratio, 0.65; 95% CI, 0.46 to 0.92; $p < 0.015$ [Fig 2B]; biphasic: hazard ratio, 0.6; 95% CI, 0.44 to 0.83; $p < 0.002$ [Fig 3B]).

Factors Associated With Survival on Univariate and Multivariate Analysis

To confirm our results of the matched cohort analysis, univariate and multivariate analysis was performed on the unmatched cohort. In univariate analysis, the following factors were associated with significant improvement in survival: biphasic histology, resection, chemotherapy, radiotherapy, female sex, living in a metropolitan area, and being treated at an academic center. Age older than 75 years and Charlson-Deyo Score exceeding 2 were associated with worse survival on univariate analysis (Table 3). Multivariate analyses showed T2 stage, increasing age, and a Charlson-Deyo Score exceeding 2 were negatively associated with survival, whereas biphasic histology, female sex, and chemotherapy were associated with improved survival. After adjusting for confounders, multivariate analysis showed cancer-directed surgery still had a statistically significant association with improved survival compared with

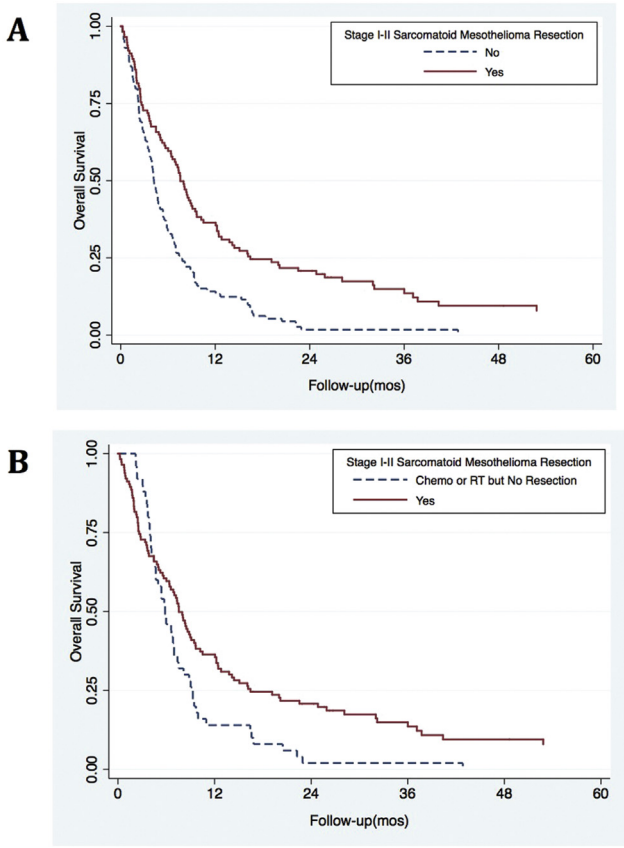

Fig 2. Overall survival of patients with sarcomatoid mesothelioma: (A) patients who did and did not undergo resection, and (B) patients who underwent resection versus those who received chemotherapy or radiotherapy (RT) or both, without resection.

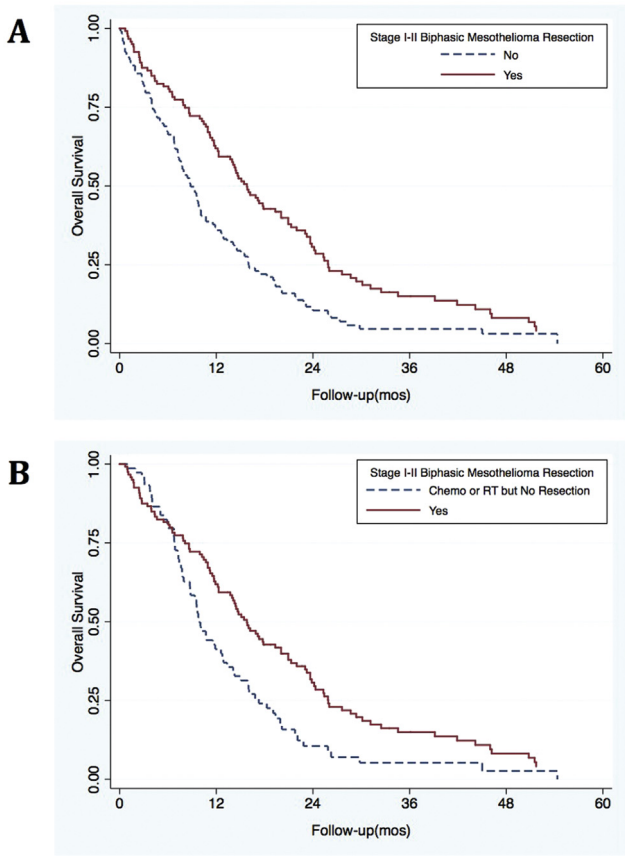

Fig 3. Overall survival of patients with biphasic mesothelioma: (A) patients who did and did not undergo resection, and (B) patients who underwent resection versus those who received chemotherapy or radiotherapy (RT) or both, without resection.

no resection (hazard ratio, 0.66; 95% CI, 0.55 to 0.78, $p < 0.001$).

Comment

The role of surgical resection for treatment of MPM remains unclear and controversial. The only randomized clinical trial performed to date, Mesothelioma and Radical Surgery (MARS I), demonstrated no improvement in survival among those who underwent extrapleural pneumonectomy compared with those who did not [10]. This trial, however, had several limitations, including flawed methodology, small sample size, and a high rate of mortality after extrapleural pneumonectomy that undermined the credibility of the findings [11]. Several institutional retrospective studies have demonstrated modest improvements in survival for selected groups of patients with MPM who underwent surgical resection [12, 13]. Uniformly, all of these studies have demonstrated improved survival for those with early-stage cancer with epithelioid histology. Utility and benefit of surgical resection for early-stage nonepithelioid MPM (sarcomatoid and biphasic) have not been clearly elucidated to date in the literature. Most current treatment paradigms do not recommend surgical therapy for nonepithelioid MPM (sarcomatoid and biphasic) due to the aggressive nature of the disease [14, 15].

Patients in our study with early-stage sarcomatoid or biphasic mesothelioma who had cancer-directed surgery survived longer than those who did not undergo resection or those who chose medical therapy (chemotherapy with or without radiotherapy) without resection. Surgical resection was one of the best independent predictors of longer survival in the multivariate analysis.

Nelson and colleagues [16] similarly analyzed the NCDB database for stage I to IV MPM patients and found that surgery-directed multimodality therapy showed improved survival. Their subgroup analysis based on histology corroborated our findings that the surgery group had statistically improved survival over the no-surgery group in patients with nonepitheliod MPM. However, the cohorts in that study included patients with stage III and IV MPM, and there was a significant amount of heterogeneity in the patient population. Moreover, whether these higher-stage patients were treated with curative intent was unclear.

The goal in our study was to minimize the heterogeneity in the data by focusing solely on stage I and II patients who most likely would have undergone resection

Table 3. Univariate and Multivariate Analysis of Demographic, Tumor, and Treatment Characteristics Associated With Risk of Death in Stage I and II Sarcomatoid or Biphasic Mesothelioma Patients

	Univariate		Multivariate	
Variable	Hazard Ratio (95% CI)	*p* Value	Hazard Ratio (95% CI)	*p* Value
Histology				
Sarcomatoid	1.00		1.00	
Biphasic	0.58 (0.51–0.68)	<0.001	0.67 (0.58–0.78)	<0.001
T stage				
T1	1.00		1.00	
T2	1.04 (0.90–1.19)	0.614	1.19 (1.02–1.38)	0.025
Resection				
No	1.00		1.00	
Yes	0.56 (0.48–0.66)	<0.001	0.66 (0.55–0.78)	<0.001
Chemotherapy				
No	1.00		1.00	
Yes	0.63 (0.54–0.72)	<0.001	0.73 (0.63–0.85)	<0.001
Radiotherapy				
No	1.00		1.00	
Yes	0.61 (0.47–0.80)	<0.001	0.85 (0.64–1.13)	0.277
Age, years				
18–49	1.00		1.00	
50–64	1.81 (0.91–3.58)	0.088	1.93	0.064
65–74	1.91 (0.98–3.72)	0.057	2.06	0.036
≥75	3.34 (1.72–6.48)	<0.001	3.05	0.001
Sex				
Male	1.00		1.00	
Female	0.67 (0.54–0.83)	<0.001	0.77 (0.61–0.97)	0.025
Race				
White	1.00		1.00	
Black	0.89 (0.58–1.38)	0.607	1.02 (0.65–1.59)	0.936
Other	0.89 (0.55–1.34)	0.494	0.95 (0.60–1.50)	0.815
Charlson-Deyo Score				
0	1.00		1.00	
1	1.03 (0.87–1.21)	0.760	1.01 (0.85–1.20)	0.910
≥2	1.56 (1.23–1.96)	<0.001	1.42 (1.12–1.81)	0.004
Type of hospital				
Community	1.00 (Ref)		1.00 (Ref)	
Academic	0.77 (0.67–0.88)	<0.001	0.94 (0.80–1.09)	0.407

CI = confidence interval; Ref = reference.

for curative intent. In our propensity score-matched analysis, cancer-directed surgery was associated with improved survival in T1-T2 N0 mesothelioma patients with biphasic or sarcomatoid histology compared with no resection, with longer median overall survival for patients with biphasic histology. There was a small subset of patients who had longer-term survival from cancer-directed surgery versus not, with point estimates of 9.5% versus 0% respective 4-year overall survival for sarcomatoid histology and 8.2% versus 3.1% respective 4-year overall survival for biphasic histology.

Our multivariate analysis showed other factors, such as age younger than 75 years, female sex, lower comorbidity scores, and receiving chemotherapy, were also independent predictors for favorable survival. Our data are consistent with findings reported in the literature. Factor such as female sex, resection at a younger age, receiving chemotherapy or radiotherapy, and having low comorbidity scores were consistently shown in the literature to be favorable prognostic factors, whereas having sarcomatoid pathology, high C-reactive protein, and low hematocrit values were associated with poor prognosis [17, 18]. The reason behind the sex difference in cancer survival has not be clearly elucidated; however, differences in tumor biology among different sex and host factors, such as circulating estrogen, have been implicated in the observed survival difference [19, 20].

Despite our results showing that surgical resection improves survival in early-stage nonepithelioid MPM, it is worth noting that median survival for sarcomatoid and biphasic MPM was only 7.6 months and 15.8 months, respectively, in these cohorts. In sarcomatoid MPM, the

cancer-directed surgery improved median survival only by 3.4 months over the nonsurgical group and by 1.7 months over the medically treated group. The biphasic MPM patients did slightly better: surgical resection improved median survival by 6.5 months over the nonsurgical group and by 6 months over the medically treated group.

Moreover, there is a significant morbidity and early mortality associated with the operation. In our analysis, among the matched patients with sarcomatoid or biphasic mesothelioma who underwent cancer-directed surgery, perioperative mortality was 6.0% at 30 days and 21.4% at 90 days. In other surgical literature, extrapleural pneumonectomy was associated with 4.5% to 10% perioperative mortality, and pleurectomy/decortication had mortality of 1.7% to 3.4%. The major morbidity rate was 18% to 24.2% for extrapleural pneumonectomy and 3.8% for pleurectomy/decortication [21, 22]. Therefore, surgeons and clinicians must be careful in selecting appropriate patients for resection, and a multidisciplinary evaluation should be made before planning for the operation. Also, an extensive discussion with the patients about the potential benefits and perceived risks must be made before undertaking the operation.

Our findings underscore the critical need for new predictive tools that can supplement or replace current methods of predicting prognosis, clinical staging, and treatment design. Efforts have been directed toward development of a predictive molecular test based on gene expression profiling that has prognostic value for identifying patients with MPM most likely to benefit from aggressive multimodality treatment [23, 24]. Bueno and colleagues [25] reported a "4-gene ratio test" that showed predictive value in analysis for their prospective clinical database for patients who underwent surgical resection for MPM. Validation of such tools with multicenter randomized studies is needed before they are incorporated into clinical staging of patients.

The NCDB, unfortunately, does not provide information on the types of operation performed. Our study purposely focused on early-stage nonepithelioid MPM to only include patients who had an operation for curative intent. There is debate among surgeons about which surgical technique is optimal [26, 27]. That question is beyond the scope of this report and can hopefully be settled in future randomized studies.

Our study has other limitations worth discussing. First, due to the nature of the NCDB data, information is lacking on how many of the patients had resection immediately and how many had it deferred. As pointed out by Vogl [28], delayed resection would give patients a prolonged survival from time of diagnosis, potentially leading to "guarantee-time bias."

Second, selection bias could have been introduced in selecting patients for different treatment modalities. We tried to address this problem by performing propensity matching analysis, but unobserved confounders not addressed in our propensity could have skewed the results.

Third, only the clinical staging information was available for the medical therapy patients, whereas the surgical therapy patients had pathologic staging information and some clinical staging information; thus, the difference in staging method could have introduced bias toward medical therapy.

Finally, the NCDB database lacks key information, such as tumor recurrence and patterns of recurrence, which can affect surgical outcome and overall survival.

Conclusion

Our results indicate that cancer-directed surgery can be a viable treatment option in early-stage mesothelioma patients with biphasic or sarcomatoid histology. However, given only a modest improvement in overall survival and high morbidity and early perioperative mortality associated with surgical intervention, a careful patient selection and multidisciplinary evaluation of the patient must be made before considering an operation. Moreover, it underscores a critical need for new predictive tools that can supplement or replace current methods of predicting prognosis, clinical staging, and treatment design.

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