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Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database

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Abstract

Background—This study was conducted to determine how malignant pleural mesothelioma (MPM) histology was associated with the use of surgery and survival.

Methods—Overall survival of patients with stage I–III epithelioid, sarcomatoid, and biphasic MPM in the Surveillance, Epidemiology, and End Results database from 2004–2010 was evaluated using multivariate Cox proportional hazards models.

Results—Of 1183 patients who met inclusion criteria, histologic subtype was epithelioid in 811 patients (69%), biphasic in 148 patients (12%), and sarcomatoid in 224 patients (19%). Median survival was 14 mo in the epithelioid group, 10 mo in the biphasic group, and 4 mo in the sarcomatoid group ($P < 0.01$). Cancer-directed surgery was used more often in patients with epithelioid (37%, 299/811) and biphasic (44%, 65/148) histologies as compared with patients with sarcomatoid histology (26%, 58/224; $P < 0.01$). Among patients who underwent surgery, median survival was 19 mo in the epithelioid group, 12 mo in the biphasic group, and 4 mo in the sarcomatoid group ($P < 0.01$). In multivariate analysis, surgery was associated with improved survival in the epithelioid group (hazard ratio [HR] 0.72; $P < 0.01$) but not in biphasic (HR 0.73; $P = 0.19$) or sarcomatoid (HR 0.79; $P = 0.18$) groups.

Conclusions—Cancer-directed surgery is associated with significantly improved survival for MPM patients with epithelioid histology, but patients with sarcomatoid and biphasic histologies have poor prognoses that may not be favored by operative treatment. The specific histology should

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Uncited Tables: Tables 2 and 4.

be identified before treatment, so that surgery can be offered to patients with epithelioid histology, as these patients are most likely to benefit.

Keywords

Mesothelioma; SEER; Epithelioid; Sarcomatoid; Biphasic; Fibrous; Surgery

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare but aggressive and often fatal malignancy [1]. Most patients present with advanced disease, and the median overall survival is approximately 1 y [1]. The recommended treatment for mesothelioma is dependent on both stage and histology. Previous studies have found epithelioid MPM to portend a better prognosis than sarcomatoid or biphasic histologic subtypes [2–12]. Therefore, it is recommended that patients with medically operable clinical stage I–III epithelioid or mixed histology disease undergo multimodality therapy including surgery [1]. Current National Comprehensive Cancer Network (NCCN) guidelines [13] recommend chemotherapy alone for all patients who have sarcomatoid histology, as well as for medically inoperable or clinical stage IV patients.

Despite these guidelines, the relative benefit of surgery for mesothelioma compared with nonsurgical therapy has not been well quantified, and different opinions exist with regards to benefit of surgery when applied alone or in conjunction with chemotherapy [14–17]. Furthermore, there is a lack of data to establish the relative efficacy of extrapleural pneumonectomy (EPP) compared with pleurectomy and decortication (P/D), leading to further controversy [15,18–22]. A randomized feasibility study did not find that EPP improved outcomes compared with chemotherapy alone for patients with mesothelioma [23–25]. In addition, several studies have shown that a small but significant number of patients with nonepithelioid MPM undergo surgery as the initial cancer-directed therapy [2,8,10,11,14]. This study was undertaken to improve the level of evidence available to clinicians who are considering offering surgery to patients with mesothelioma using a population-based database to better quantify the survival benefits of surgery. Specifically, the purpose of this study was to assess outcomes of patients who did or did not receive cancer-directed surgery for epithelioid, sarcomatoid, and biphasic subtypes of MPM stratified by stage using population-based data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program database that has captured a geographically diverse cohort of patients diagnosed with MPM.

2. Methods

We reviewed the SEER database from 2004–2010 for patients with stage I–III MPM by ICD-O-3 morphology codes 9050–9053 and 9055. Cases before 2004 were not included for analysis because specific American Joint Committee on Cancer's TNM staging (sixth edition) [26] information was not recorded in the SEER database until 2004. Only patients whose histologic subtype was known were included in the study. For this study, we used the more commonly used term “sarcomatoid” when describing the mesotheliomas recorded as “fibrous” in SEER because fibrous mesothelioma in SEER refers to sarcomatoid

mesothelioma as well as the different subtypes of sarcomatoid mesothelioma (including spindled, sarcomatoid and desmoplastic mesothelioma, and fibrous mesothelioma not otherwise specified) [8,27]. The SEER database records whether cancer-directed surgery was performed, where cancer-directed surgery includes both curative and palliative surgery [8,28]. Frequency of EPP and P/D is not recorded. Patients were further excluded if laterality (right or left) was unknown or if race was unknown. Patients with stage IV disease were excluded, as surgery is usually not indicated as a treatment option for this group regardless of histology. In addition, one patient identified as having T stage = 0 was also excluded from analysis because of concerns over discordancy in staging. Extracted variables include age, sex, race, marital status, laterality, histology, surgery, stage, reasons for not performing surgery, year of diagnosis, vital status, and time to last available reported survival time point.

Patients were stratified into subgroups based on histology and SEER-recorded overall stage. Our primary analysis was to examine the effects of cancer-directed surgery according to histologic MPM subtype and stage on overall survival. We assessed for predictors of receiving cancer-directed surgery using univariate and multivariate logistic regression analysis including age at diagnosis, sex, race, histology, marital status, stage, radiation use, and laterality in the model. Kaplan–Meier analysis was performed to determine the association of histologic subtype and tumor stage on survival. Surgery as a predictor of survival was assessed using multivariate Cox proportional hazards model for each histologic subtype. The following covariates were used: age at diagnosis, sex, known race, known histology, marital status (known married or unmarried), radiation use, laterality (known right or left-sided primary disease), and disease stage (I–III) according to the American Joint Committee on Cancer's TNM staging (sixth edition) [26].

Cancer-directed surgery in the SEER database does not include details regarding the specific type of surgery. To assess the potential impact of including palliative procedures in the surgical group, a sensitivity analysis was performed where only patients who received likely curative-intent surgery (SEER codes of “total surgical removal of primary site” and “radical surgery”) were considered to have undergone surgical resection. To assess the potential selection bias of surgery being more likely used in patients with less extensive local disease or smaller tumor burdens, we also performed a sensitivity analysis where we included T and N statuses into our Cox proportional hazard models.

All statistical analyses were performed using Stata Statistical Software: Release 12.0, StataCorp LP, College Station, TX. A *P* value of 0.05 was used to define statistical significance. Exemption from institutional review board approval was obtained before data analysis.

3. Results

Of 4935 patients with MPM identified in the SEER database between 2004 and 2010, 1183 patients met study criteria (Fig. 1). The majority of patients were white, male, and aged ≥70 y, with a right-sided disease (Table 1). A total of 69% of patients had epithelioid histology

(*n* = 811), whereas 19% had sarcomatoid histology (*n* = 244) and 12% had biphasic histology (*n* = 148).

A total of 422 patients received cancer-directed surgery (36%). Percentage of patients receiving surgery during the study period ranged from 32%–42% for epithelioid, 18%–34% for sarcomatoid, and 37%–50% for biphasic subtypes. From years 2004–2010, we observed a decreasing trend of patients receiving cancer-directed surgery for epithelioid subtype (*P* = 0.08) but not for sarcomatoid (*P* = 0.73) or biphasic subtypes (*P* = 0.80). Only a small number of patients (13%, *n* = 159) received radiation therapy. When stratified by histologic subtype, cancer-directed surgery was used more often in patients with epithelioid (37%, *n* = 299) and biphasic MPM (44%, *n* = 65) than sarcomatoid MPM (26%, *n* = 58; *P* < 0.01).

Median survival in the entire cohort was 14 mo in the epithelioid group, 10 mo in the biphasic group, and 4 mo in the sarcomatoid group (*P* < 0.01) Kaplan–Meier curves demonstrate that patients with epithelioid subtype had improved survival compared with sarcomatoid or biphasic subtype (Fig. 2) and that survival did not differ by stage for epithelioid (*P* = 0.15), sarcomatoid (*P* = 0.18), or biphasic subtype (*P* = 0.53; Fig. 3A–C).

Among patients who underwent surgery, median survival was 19 mo in the epithelioid group, 4 mo in the sarcomatoid group, and 12 mo in the biphasic group (*P* < 0.01). For patients who did not undergo surgery, median survival was 10 mo in the epithelioid group, 3 mo in the sarcomatoid group, and 8 mo in the biphasic group (*P* < 0.01). Kaplan–Meier survival curves for each histologic subtype stratified by surgery or no surgery are shown in Figure 4A–C. By univariate analysis, surgery was associated with increased survival for epithelioid (*P* < 0.01), sarcomatoid (*P* = 0.03), and biphasic MPM (*P* = 0.03). However, when we limited the univariate analysis to only patients who had undergone “curative-intent surgery” (SEER codes “total removal of surgery site” and “radical surgery”), surgery was not associated with increased survival for sar-comatoid and biphasic subtypes (*P* = 0.40 and 0.26), respectively, whereas surgery remained associated with increased survival for epithelioid MPM (*P* = 0.02). In a Cox proportional hazards model for each histologic subtype, surgery was associated with improved survival in only the epithelioid group (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.60–0.87; *P* < 0.01) but not in sarcomatoid (HR 0.79; 95% CI 0.56–1.12; *P* = 0.18) or biphasic (HR 0.73; 95% CI 0.45–1.17; *P* = 0.19) groups. These findings did not change significantly when we limited the analysis to patients who underwent “curative-intent surgery” or when we added T and N status as covariates in our Cox proportional hazards models.

Table 3 shows median survival grouped by treatment (surgery or no surgery) for each histologic subtype and broken down by stage. We found that the increasing stage was not associated with worse survival within the histologic subtype (Table 3). Furthermore, patients with stage III epithelioid subtype have improved survival compared with stage I sarcomatoid MPM. We next examined the effect of surgery on 1, 3, and 5-y survival for each histologic subtype and found survival to be greatest in the first year; however, survival quickly drops by year 3, regardless of surgical intervention. Collectively, these data show patients with epithelioid subtype MPM have greater median survival as compared with sarcomatoid and biphasic MPM. Furthermore, cancer-directed surgery was associated with improved survival

for patients with epithelioid subtype MPM only. Increasing stage was not associated with worse survival.

Table 5 shows the results of multivariate survival analysis limited to patients who underwent cancer-directed surgery. Factors that were associated with worse survival included increasing age per year increase (HR 1.03 per year; 95% CI 1.02–1.04; $P < 0.01$), sarcomatoid histology (HR 2.68; 95% CI 1.90–3.78; $P < 0.01$), and biphasic histology (HR 1.62; 95% CI 1.16–2.25; $P < 0.01$). These results did not change significantly when we limited the analysis to only patients who underwent likely curative-intent surgery.

4. Discussion

MPM is an aggressive tumor associated with poor outcomes, yet the best treatment options remain controversial, in particular with regards to the role of surgery in treatment of this disease. In this population-based study, surgery was associated with improved survival in the epithelioid group but not in biphasic or sarcomatoid groups. Specifically, median survival for patients with epithelioid subtype MPM was 19 mo with surgery and 14 mo for patients who did not undergo surgery ($P < 0.01$). For the biphasic subtype, median survival was 12 mo for the surgery group and 10 mo for the nonsurgical (68%) group ($P = 0.03$). Of note, for the sarcomatoid subtype, median survival was 4 mo for the surgery group and 3 mo for the nonsurgical group ($P = 0.03$). Although cancer-directed surgery was used more often in epithelioid and biphasic patients compared with sarcomatoid patients, there was still a significant percentage (26%) that underwent surgery in the sarcomatoid group, and the percentage of patients with sarcomatoid subtype MPM receiving surgery did not significantly differ from years 2004–2010. The results of this study quantify the impact of histology and stage on survival after cancer-directed surgery for stage I–III MPM.

This is the first population-based study that evaluates the effect of cancer-directed surgery on survival according to specific American Joint Committee on Cancer stage within each histologic subtype. Previous population-based analyses, with the exception of one study of the International Association for the Study of Lung Cancer (IASLC) international MPM database performed by Rusch *et al.* [10], were limited by a lack of specific stage information [6–8,13,28–32]. Although Rusch *et al.* did report survival stratified by stage, they did not evaluate the survival of each histologic subtype stratified by stage. Because we had specific stage and histologic information, we were able to demonstrate that histology was a more important prognostic factor than stage. Of note, we demonstrated that for patients with early stage (stage I or stage II) sarcomatoid disease who underwent surgery, their survival was an abysmal 4 mo, which was the same as early stage sarcomatoid patients who did not undergo surgery, and far worse than the survival for patients with epithelioid or biphasic disease.

In this analysis, we did not observe statistically significant differences in overall survival between stages for any histologic subtype. This was similar to results reported by the Rusch *et al.* [10] in the IASLC-IMIG study, which did not find differences in median survival between stages for patients who underwent any type of cancer-directed surgery. Rusch et al. did observe differences in survival when the analysis was limited to patients who underwent curative-intent cancer-directed surgery–median survival was 30, 22, 16, and 12 for stage I,

II, III, and IV MPM. In our SEER study, we were unable to distinguish between patients undergoing curative-intent or palliative surgery.

We may have been unable to detect differences in survival by stage for each histologic subtype, as clinical and pathologic staging is not distinguished clearly in the SEER database. The SEER database uses “best available” staging, where tumor stage recorded in SEER is based on pathologic information when surgery was the initial cancer-directed therapy and clinical information if patients had neoadjuvant therapy before surgery or surgery was not performed [33]. Currently, the NCCN recommends patients with clinical stage I–III mesothelioma to either undergo induction therapy or surgery as the initial cancer-directed therapy [34]. Therefore, SEER stage information could be composed of a fairly equal distribution of clinical and pathologic staging. This would affect our ability to distinguish differences in survival between stage groups or detect associations within stage groups.

Even if staging was clearly identified as pathologic or clinical staging, difficulties in determining MPM stage exist. One study that evaluated the association between clinical and pathologic staging in a cohort of 164 patients that underwent radical resection for MPM found that clinical staging underestimated the disease extent in 46.3% of the patients for T stage and 31.1% for N stage, subsequently understaging the IMIG stage in 44.5% of the patients [35]. Cases were also overstaged 10% of the time. The IASLC study similarly found discrepancies between clinical and pathologic staging. Upstaging occurred in approximately 80% of the patients with cTNM stage I, 70% with stage II, and 22.8% with stage III tumors [10]. Although we observed benefit in survival for the epithelioid subtype, we may have been underpowered to detect a benefit of surgery for nonepithelioid subtypes. In addition, misdiagnosis of mesothelioma has been known to occur, which could also confound our results [28,36,37].

Additionally, we did not find N status to be associated with worse survival in patients receiving surgery for MPM. Several studies that have investigated the impact of nodal metastatic disease on survival have found N status to correlate with worse long-term survival [38–41]. A study by Bolukbas *et al.* [42], however, did not find lymph node metastasis to impact survival in patients with IMIG stage III MPM after lung-sparing pleurectomy. It is possible that we did not observe nodal status to be associated with worse survival due to limitations of SEER staging, as discussed previously.

The major strength of this study is in providing survival information by histology and stage on a contemporary cohort of patients with MPM, so that confounding variables could be controlled for. This is the largest population-based study of American patients, to date. A previous SEER-based population analysis of patients with MPM was limited by a lack of stratification by stage for each histologic subtype, as histologic data were not available before 2004 [13,28].

4.1. Limitations

Limitations of this study are similar to previous SEER studies on mesothelioma and the retrospective nature of this study [8]. Using the SEER database, we were unable to study factors used to select patients for surgery that could contribute to the survival benefit of

surgery, such as performance status, cardiopulmonary function, other comorbid conditions, severity of presenting symptoms, and exposure to tobacco and/or asbestos. Furthermore, we were unable to systematically review and verify tumor pathology using immunohistochemistry techniques or study the effects of stage and histologic subtype based on tumor grade.

The SEER database also does not have chemotherapy information. Thus, we do not know whether patients who did not undergo surgery or radiation received chemotherapy or only supportive care. In addition, we do not know whether patients who undergo surgery receive adjuvant chemotherapy. In the IASLC MPM study, median survival was 19,13, and 8 mo for patients who underwent surgery for epithelioid, biphasic, and sarcomatoid disease, respectively–these numbers are higher than those reported in our study. We speculate that this discrepancy could be from differences in multimodality adjuvant therapy given–in the IASCLC, of patients who underwent curative-intent surgery, 1162 (68%) underwent adjuvant radiation, chemotherapy, or both whereas presumably, there were fewer patients in the SEER database who underwent multimodality therapy.

Based on data available in the SEER database, it was not possible to specifically analyze the effects of palliative-intent versus curative-intent therapy as detailed cancer-directed surgery information is not recorded in the SEER database. Thus, our results may have included patients who received palliative-intent surgery, making it difficult to evaluate the true impact of surgery on survival, and may underestimate the benefits of curative-intent surgery. To better evaluate the true impact of curative-intent surgery, a sensitivity analysis was performed analyzing only patients who received surgery coded as “total surgical removal of primary site” and “radical surgery” in the SEER database. The results from this analysis were consistent with the results from our primary analysis when we included patients receiving any type of cancer-directed surgery.

It was not possible to evaluate the utility for type of surgery received (EPP *versus* P/D); however, there is a lack of convincing evidence regarding the superiority for one procedure over the other. To date, the superiority of EPP over P/D has not been established, as data from randomized controlled trials are not available [15,19–22]. A retrospective analysis of 663 patients reported enhanced survival after P/D compared with EPP; however, this finding may have been confounded by selection bias [18,22]. Furthermore, a randomized feasibility study did not find that EPP improved outcomes compared with chemotherapy alone in patients with MPM [23–25].

Finally, as noted previously, clinical and pathologic staging is not distinguished clearly in the SEER database. Stage migration could have occurred in a group of patients who did not undergo induction chemotherapy and were initially clinically staged I, II, or III, who then underwent surgery and were upstaged to pathologic stage IV disease. These patients would have been excluded from the analyses, which would bias our results in favor of the cancer-directed surgery group. However, one must also consider the possibility that patients clinically staged I–III who received induction chemotherapy but were then upstaged to stage IV disease after surgery would have also been included in the analysis–this could bias our results in favor of patients who did not receive cancer-directed surgery.

5. Conclusions

In summary, cancer-directed surgery is associated with improved survival for MPM patients with epithelioid histology. Although operative treatment is recommended for patients with biphasic histology per NCCN guidelines [1], surgery was not associated with improved survival in this cohort of patients. As expected, outcomes of patients with sarcomatoid histology were not improved by operative treatment. Although guidelines do not recommend surgery for sarcomatoid patients, over 25% of patients with this histology had cancer-directed surgery in this SEER cohort. These findings demonstrate that the specific histology of patients with MPM should be identified before treatment whenever possible, so that patients with nonepithelioid histologies and particularly sarcomatoid MPM are not exposed to the risks of surgery, as these patients are less likely to benefit. In addition, this article provides further rationale to consider epithelioid and non-epithelioid MPM histology separately in any prospective or retrospective study of MPM patients.

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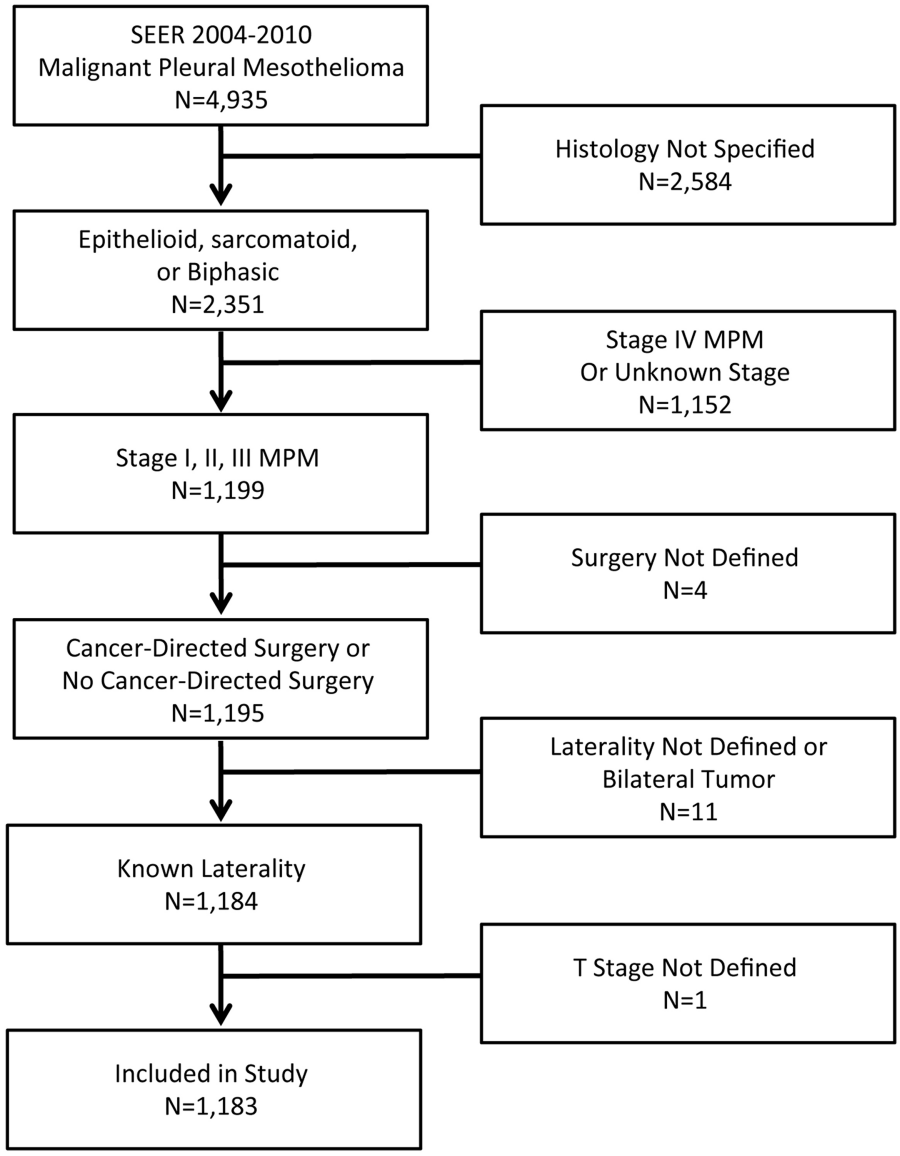

Fig. 1. Sample inclusion and exclusion selection criteria

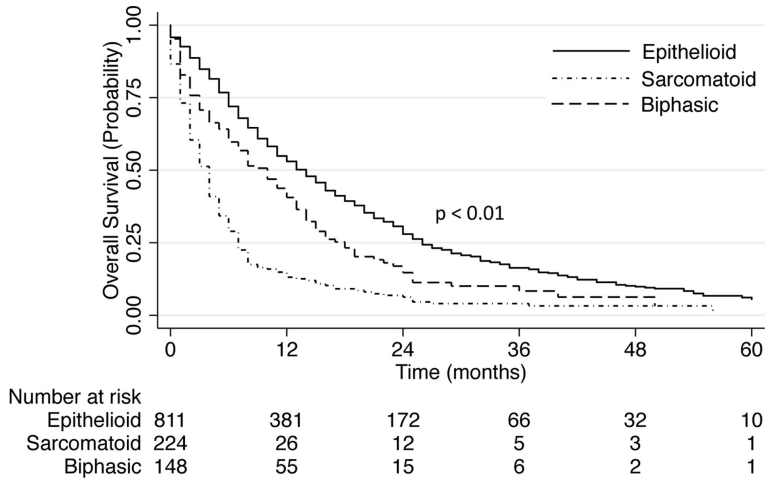

Fig. 2. Unadjusted Kaplan–Meier survival for patients with MPM, stratified by histologic subtype

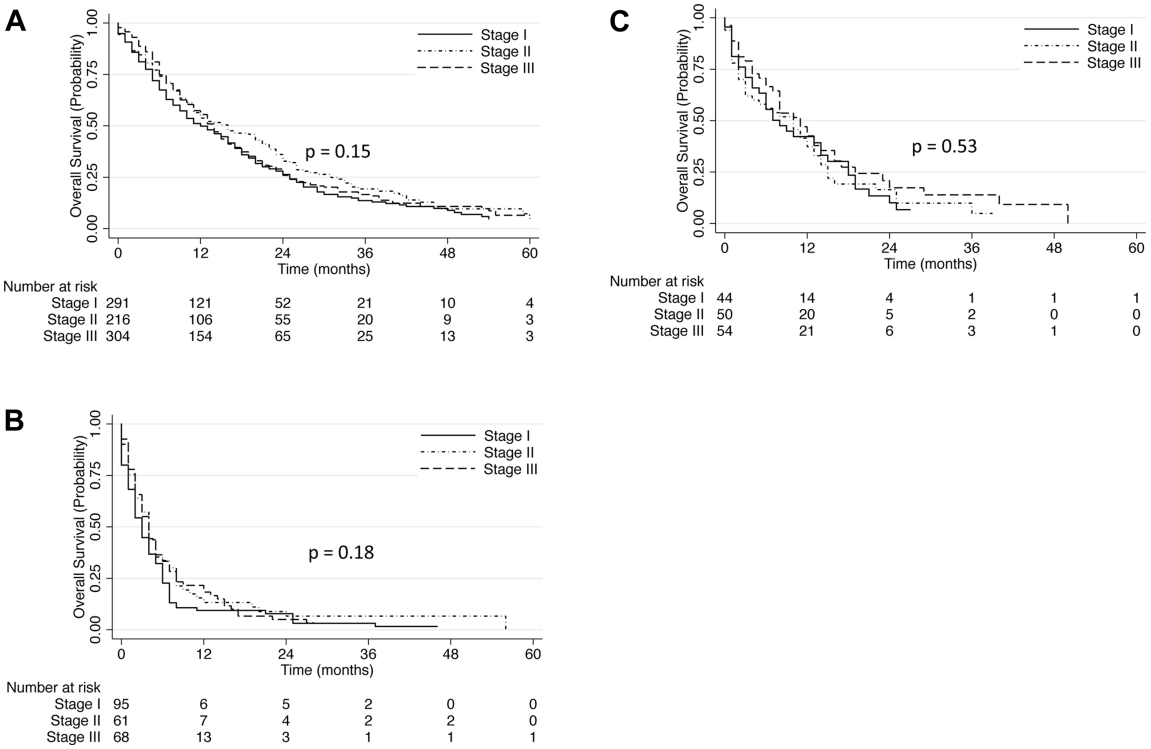

Fig. 3. Unadjusted Kaplan–Meier overall survival by best staging for patients with epithelioid (A), sarcomatoid (B), and biphasic (C) subtype MPM

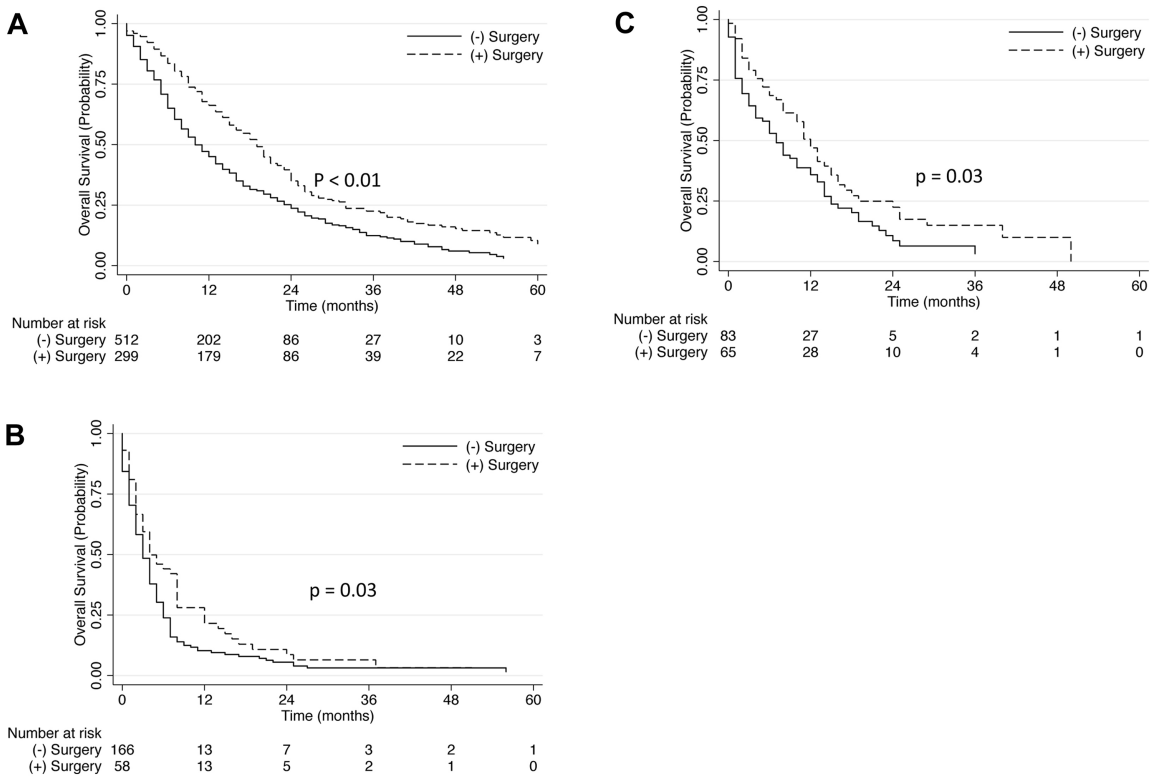

Fig. 4. Unadjusted Kaplan–Meier overall survival for patients receiving cancer-directed surgery versus no surgery for epithelioid (A), sarcomatoid (B), and biphasic (C) subtype MPM

Table 1
Patient, disease, and treatment characteristics (*N* = 1183)

Characteristics	Number of patients	All patients, %
Sex		
Male	948	80
Female	235	20
Age (y)		
29–49	34	3
50–59	126	11
60–69	328	28
70–79	405	34
80+	290	25
Race		
White	1102	93
Black	46	4
Other	31	2.62
Unknown	4	0.34
Laterality		
Right	697	59
Left	486	41
Disease stage		
I	430	36
II	327	28
III	426	36
T stage		
T1	504	43
T2	423	36
T3	256	22
N Stage		
N0	914	77
N1	73	6
N2	196	17
M stage		
M0	1183	100
M1	0	0
Histology		
Epithelioid	811	69
Sarcomatoid	224	19
Biphasic	148	12
Radiation therapy	159	13
Cancer-directed surgery	422	36

Table 2

Variables associated with receiving cancer-directed surgery (*n* = 422)

Variable	*n*	Frequency receiving cancer-directed surgery (%)	Adjusted odds ratio	Multivariate *P* value	Adjusted 95% CI	
					Lower	Upper
Female sex	91	22	0.96	0.82	0.68	1.36
Age			0.96	<0.01	0.95	0.97
Race						
White	397	94	Reference	Reference	Reference	Reference
Black	13	3	0.79	0.51	0.38	1.62
Other	11	3	0.84	0.69	0.35	1.99
Marital status						
Single	113	27	Reference	Reference	Reference	Reference
Married	303	72	1.00	1.00	0.74	1.35
Laterality						
Right	243	58	Reference	Reference	Reference	Reference
Left	179	42	1.10	0.47	0.84	1.45
Disease stage						
I	87	20	Reference	Reference	Reference	Reference
II	117	28	2.00	<0.01	1.41	2.84
III	218	52	2.86	<0.01	2.06	3.98
Histology						
Epithelioid	299	71	Reference	Reference	Reference	Reference
Sarcomatoid	58	14	0.77	0.16	0.53	1.11
Biphasic	65	15	1.30	0.20	0.87	1.95
Radiation therapy	119	28	4.97	<0.01	3.30	7.48

Table 3
Median survival based on stage and histologic subtype (*N* = 1183)

Median survival estimates with or without cancer-directed surgery	Disease stage*		
	I, (95% CI)	II, (95% CI)	III, (95% CI)
Epithelioid			
(−) Surgery	8 (6–11)	11 (7–19)	10 (7–13)
(+) Surgery	18 (15–25)	21 (13–24)	18 (15–20)
Sarcomatoid			
(−) Surgery	3 (2–4)	4 (1–5)	3 (2–5)
(+) Surgery	4 (0.001–25)	4 (2–8)	5 (2–8)
Biphasic			
(−) Surgery	15 (1–21)	6 (1–14)	6 (1–not reached)
(+) Surgery	6 (2–18)	11 (3–15)	13 (8–17)

*Per the American Joint Committee on Cancer's *Cancer Staging Manual Sixth Edition* [26].

Table 4

Effect of cancer-directed surgery on 1,3, and 5-y survival by histology (*N* = 1183)

Histologic subtype		Disease stage*	1 y, %	3 y, %	5 y, %
Epithelioid	I	(−) Surgery	36	5	1
		(+) Surgery	59	15	3
	II	(−) Surgery	44	6	1
		(+) Surgery	59	15	3
	III	(−) Surgery	40	5	0
		(+) Surgery	61	11	2
Sarcomatoid	I	(−) Surgery	5	1	0
		(+) Surgery	17	8	0
	II	(−) Surgery	5	2	0
		(+) Surgery	22	4	0
	III	(−) Surgery	16	2	1
		(+) Surgery	26	0	0
Biphasic	Stage I	(−) Surgery	34	3	3
		(+) Surgery	22	0	0
	Stage II	(−) Surgery	34	3	0
		(+) Surgery	50	6	0
	Stage III	(−) Surgery	25	0	0
		(+) Surgery	45	8	0

*Per the American Joint Committee on Cancer's *Cancer Staging Manual Sixth Edition* [26].

Table 5

Risk of death for patients with mesothelioma undergoing cancer-directed surgery from 2004–2010 (*n* = 416)

Predictor	Adjusted HR	Adjusted 95% CI		Multivariate P value
		Lower	Upper	
Female sex				
Age	1.03	1.02	1.04	<0.01
Race				
White	Reference	Reference	Reference	Reference
Black	1.27	0.66	2.44	0.47
Other	0.90	0.41	1.98	0.80
Marital status				
Single	Reference	Reference	Reference	Reference
Married	1.03	0.78	1.35	0.85
Laterality				
Right	Reference	Reference	Reference	Reference
Left	0.95	0.75	1.21	0.69
Disease stage				
I	Reference	Reference	Reference	Reference
II	0.78	0.32	1.88	0.58
III	0.78	0.34	1.80	0.57
T stage				
T1	Reference	Reference	Reference	Reference
T2	1.22	0.54	2.77	0.63
T3	1.35	0.63	2.90	0.44
N Stage				
N0	Reference	Reference	Reference	Reference
N1	1.24	0.72	2.11	0.44
N2	1.24	0.84	1.83	0.29
Histology				
Epithelioid	Reference	Reference	Reference	Reference
Sarcomatoid	2.68	1.90	3.78	<0.01
Biphasic	1.62	1.16	2.25	<0.01
Radiation therapy	0.80	0.61	1.96	0.12