Malignant Pleural Mesothelioma
A Population-Based Study of Survival

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Introduction: This study characterizes the overall survival (OS) and variables affecting OS in patients with malignant pleural mesothelioma.
Methods: A total of 9701 patients with malignant pleural mesothelioma, diagnosed from 1973 to 2006, were retrospectively analyzed using the population-based surveillance, epidemiology, and end results database.
Results: The 6-month, 1-year, and 5-year OS were 55, 33, and 5%, respectively. Significantly adverse prognostic factors from univariate analyses included older age, male gender, higher tumor grade, nonepithelioid histology, higher stage, no cancer-directed surgery, and no radiotherapy. Race was not significant. Patients undergoing cancer-directed surgery and radiotherapy, when grouped by stage, histology, or grade, had the best median survival (versus radiotherapy or surgery alone or no surgery/radiotherapy). From Cox proportional hazards analyses, grade (range, 1–4) was associated with a hazard ratio (HR) of >1.5 ($p < 0.0001$), and not undergoing cancer-directed surgery was associated with a HR of >1.4 ($p < 0.0001$). Male gender and older age were also significantly adverse factors. Tumor histology (HR = 1.5) and nonlocalized stage (HR = 1.3) were significant in a Cox model omitting tumor grade. With grade and histology included in the Cox model, the HRs of histology and stage were of smaller magnitude and not significant.
Conclusions: From a population-based registry analysis of patients with malignant pleural mesothelioma, tumor grade and cancer-directed surgery seem to have the greatest impact on OS. Although being amenable to surgery likely reflects more indolent disease and/or better performance status and cardiopulmonary function, the significantly favorable impact of surgery, accounting for tumor grade, histology, and stage, may reflect a therapeutic benefit.

Key Words: Mesothelioma, Pleural, Population-based, Grade, Histology.

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Malignant mesothelioma is a relatively rare cancer arising from the mesothelial lining of pleura as well as the peritoneal cavities, tunica vaginalis, and pericardium. Most (~80%) cases arise from the pleural mesothelium, and of these, most (~60–70%) are associated with asbestos exposure.[1] Several studies have reported on the epidemiology of mesothelioma from patients registered in the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database.[1–5] There are presently ~2500 to 3000 malignant mesothelioma cases per year, mostly among older, white males; the United States incidence seems to have peaked in the years 2000–2005. The recent decline in incidence is attributable to declining asbestos exposure, and this trend is expected to continue.[1]

Pleural mesothelioma is an often debilitating malignancy with a very poor prognosis, in part because malignant mesothelioma is often diagnosed when patients become symptomatic with advanced-stage disease. For untreated disease, the median survival (MS) is generally less than a year. Treatment options generally include palliative surgical resection, radiation therapy, chemotherapy, and/or pleurodesis, which can palliate symptoms of pain and respiratory decline, delay symptomatic progression, and/or prolong survival. Radical, curative-intent multimodality therapy, with extrapleural pneumonectomy, adjuvant hemithoracic radiation therapy, and adjuvant chemotherapy (referred to as trimodality therapy), can be offered to select few patients with localized disease and adequate pulmonary and cardiac function.[6,7] In these patients, epithelioid histology (versus sarcomatoid or mixed histologies), no regional lymph node involvement, and negative surgical margins are favorable predictors of survival outcome.[8,9] Among patients with favorable prognostic factors, the MS can be on the order of 4 to 5 years.[8,10]

This study offers a descriptive, retrospective analysis of patients with malignant pleural mesothelioma registered in the population-based SEER database. This study was undertaken with the goal of better characterizing the overall survival (OS) of malignant pleural mesothelioma and the risk factors affecting OS. Recently, there have been several Italian population-based studies of survival among patients with malignant pleural mesothelioma.[11–13] To our knowledge, this is the first article in over 20 years[14] to analyze the OS of patients registered in the SEER database with a diagnosis of malignant pleural mesothelioma, and it currently represents

the largest survival analysis of patients with malignant pleural mesothelioma.

METHODS

Patient Database

The SEER Program collects information from population-based cancer registries throughout the United States. Serial registry data are deidentified and submitted to the National Cancer Institute on a biannual basis. The SEER 17 registries include patients registered from 1973 to 2006. Nine of the 17 registries date back to 1973–1975, 4 registries date back to 1992, and 4 registries date back to 2000.

Patients were selected with the SEER Stat case listing session using the following criteria: SEER database field "Site rec with Kaposi and mesothelioma" = "mesothelioma" and SEER database field "Site recode" = "pleura" (n = 9392) or "lung and bronchus" (n = 309). Only patients actively followed were included (i.e., autopsy and death certificate only cases were excluded). Only cases of malignant mesothelioma were included (i.e., cases registered as benign were excluded). Patients with pleural mesothelioma were grouped with patients with lung or bronchus mesothelioma and are referred to as pleural mesothelioma in the remaining text.

For patients diagnosed from 1973 to 2003, the "SEER historic Stage A" variable of localized, regional (direct extension and/or nodal involvement), and distant (distant nodal sites and/or distant metastases) was used to stage patients. For patients diagnosed from 2004 to 2006, the "summary stage 2000" variable (also grouped into localized, regional, or distant subgroups) was used. Histology was classified as epithelioid, fibrous (including spindled, sarcomatoid, and desmoplastic mesothelioma and fibrous mesothelioma, not otherwise specified), biphasic (i.e., mixed histology), or mesothelioma, not otherwise specified. The SEER database also records whether or not a patient has undergone cancer-directed surgery, which the SEER program considers as any curative or palliative surgery that removes cancer, excluding biopsies that remove only a fragment or portion of tumor.

Statistical Analysis

Stata version 9.2 (StataCorp, College Station, TX) was used for data analysis. Actuarial OS was calculated using the Kaplan-Meier method. For univariate analyses comparing OS between subgroups, the log-rank test was used. For multivariate analyses (MVA) assessing the significance and hazard ratios (HRs) of prognostic variables, Cox proportional hazards models were used.

RESULTS

Patient and Tumor Characteristics

Table 1 summarizes the patient and tumor characteristics of the study patients. The median age at the time of diagnosis was 72 years. Seventy-four percent are white males. Most (57%) patients had distant disease.

Mesothelioma tumor grade was not available in 90% of patients. In the 1970s to 1980s, 5% of patients' tumors were

TABLE 1. Patient and Tumor Characteristics

N	9701
Age, median (range)	72 (17–103)
≤39	111 (1%)
40–49	384 (4%)
50–59	1191 (12%)
60–69	2377 (25%)
70–79	3495 (36%)
≥80	2143 (22%)
Race	
White	8894 (92%)
Black	469 (5%)
Other	324 (3%)
Unknown	14 (<1%)
Gender	
Male	7820 (81%)
Female	1881 (19%)
Year diagnosed	
1970s	577 (6%)
1980s	1589 (16%)
1990s	2862 (30%)
2000s	4673 (48%)
Grade	
Well differentiated (grade I)	157 (2%)
Moderately differentiated (grade II)	106 (1%)
Poorly differentiated (grade III)	581 (6%)
Undifferentiated; anaplastic (grade IV)	162 (2%)
Unknown	8695 (90%)
Histology	
Epithelioid	2079 (21%)
Fibrous subtypes[a]	776 (8%)
Biphasic (mixed)	424 (4%)
Mesothelioma, NOS	6422 (66%)
SEER stage	
Localized	1141 (12%)
Regional	1730 (18%)
Distant	5556 (57%)
Unknown/unstaged	1274 (13%)
Surgery	
Performed	2139 (22%)
Radical extent[b]	480
Less than radical extent[b]	1183
Not otherwise specified	476
Not performed	7317 (75%)
Unknown	245 (3%)
Radiation	
Performed	1459 (15%)
Not performed	8079 (83%)
Unknown	163 (2%)
Radiation and surgery performed[c]	522 (5%)
Surgery performed; no radiation[c]	1561 (16%)
Radiation performed; no surgery[c]	883 (9%)
No surgery or radiation[c]	6346 (65%)

[a] Includes spindled, sarcomatoid, and desmoplastic mesothelioma and fibrous mesothelioma, NOS (not otherwise specified).

[b] For primary pleural malignancies, the extent of surgery is characterized by a general coding scheme. Radical resection in the table refers to SEER codes specifying "total removal" or "radical" resection. For primary lung malignancies, radical resection is considered any surgical code describing pneumonectomy.

[c] Excludes patients with unknown variable(s), and thus totals of those undergoing surgery versus not undergoing surgery do not equal the total from the rows above and totals of those undergoing radiation versus not undergoing radiation do not equal the total from the rows above.

SEER, Surveillance, Epidemiology, and End Results.

TABLE 2. Grade versus Histology

	Well Differentiated (Grade 1)	Moderately Differentiated (Grade 2)	Poorly Differentiated (Grade 3)	Undifferentiated; Anaplastic (Grade 4)	Unknown
Epithelioid	75 (26%)	39 (13%)	148 (51%)	31 (11%)	1786
Fibrous subtypes[a]	4 (6%)	9 (14%)	32 (51%)	18 (29%)	713
Biphasic	2 (6%)	3 (8%)	24 (67%)	7 (19%)	388
Unknown (NOS)	76	55	377	106	5808

Percentages reflect percentage of patients with a given histology who have a given grade (excluding patients with unknown variables).
[a] Includes spindled, sarcomatoid, and desmoplastic mesothelioma and fibrous mesothelioma, NOS (not otherwise specified).

assigned a grade in the SEER database, whereas in the 1990s to 2000s, 12% of patients were assigned a grade. Histology was not explicitly registered in 66% of patients. In the SEER database, 18% of patients from the 1970s, 29% from the 1980s to 1990s, and 41% from the 2000s were registered with a specific mesothelioma histology.

Among patients with known tumor grade, there was no significant difference in the distribution of tumor grade between white versus nonwhite patients ($p = 0.20$ with χ^2 test), male versus female patients ($p = 0.46$), or different decades ($p = 0.87$). Among patients with known tumor histology, there was no significant difference in the distribution of tumor histology between white versus nonwhite patients ($p = 0.93$ with χ^2 test) or male versus female patients ($p = 0.22$). Despite significant differences in the histology distribution between decades (data not shown), no appreciable trends could be ascertained.

Table 2 shows the tumor grade grouped by histology. For each histology group, most patients (>50%) were classified as having poorly differentiated, grade 3 disease. For epithelioid, fibrous subtypes and biphasic mesothelioma histology, 39, 20, and 14%, respectively, were classified as having well to moderately differentiated, grade 1 to 2 disease ($p < 0.0001$).

Patient Treatments

Cancer-directed surgery was performed in 22% of patients, radiation was performed in 15%, and radiation and surgery were performed in 5%. Most patients underwent a less than radical-extent surgery (see Table 1 footnote). Thirty-six percent of patients with well to moderately differentiated grade mesothelioma versus 25% with poorly differentiated or undifferentiated/anaplastic grade mesothelioma underwent cancer-directed surgery ($p = 0.0008$). The percentage of patients undergoing radiation did not significantly differ between grade groups. Neither the percentage of patients undergoing cancer-directed surgery nor the percentage of patients undergoing radiation differed significantly between histology groups.

Patient Survival

The 6-month, 1-year, and 5-year OS of patients with malignant pleural mesothelioma were 55, 33, and 5%, respectively. Table 3 outlines the univariate analyses of variables potentially impacting OS. Adverse prognostic factors included older age, male gender, higher grade disease, nonepithelioid histology, higher stage disease, no cancer-directed surgery, and no radiation therapy.

Table 3 also shows the univariate analyses grouped by stage. Older age was an adverse risk factor for all stages. Race was not significant for any stage group. A more recent calendar year of diagnosis was a favorable risk factor among patients with distant disease (HR = 0.994 per year) and an unfavorable risk factor among those with localized disease (HR = 1.015 per year). For all stages, the variables of grade (lower grade was favorable), histology (epithelioid was favorable), and surgery (undergoing cancer-directed surgery was favorable) were significant. Although undergoing radiation was favorable (significant for regional and distant disease), the magnitude of benefit in MS was small (<2–3 months). Undergoing a more radical resection resulted in a greater MS among patients with distant disease; a nonsignificant benefit of a more radical resection was also observed among patients with regional disease. Among patients undergoing radical resection and radiation, the MS was 17.0 months for localized disease ($n = 14$), 18.4 months for regional disease ($n = 68$), and 17.2 months for distant disease ($n = 121$).

Table 4 shows the MS grouped by treatment (surgery and radiation) and tumor grade. Cancer-directed surgery resulted in an improved OS for all grade groups; these differences were significant for all but the highest grade. Radiation resulted an improved OS for all grade groups, although only significant for poorly differentiated, grade 3 disease. Patients receiving radiation for low-grade disease had a superior MS versus those not treated with radiation (difference of >10 months), although this was not significant. With increasing grade, the MS after surgery plus radiation was 58.0, 13.0, 11.5, and 6.3 months, whereas the MS of patients receiving no radiation or surgery was 16.8, 10.8, 3.3, and 2.8 months.

Table 5 shows the MS grouped by treatment (surgery and radiation) and tumor histology. Cancer-directed surgery resulted in a significantly ($p < 0.0001$) improved OS for all histology groups. Radiation resulted in a significantly improved OS for the epithelioid and mixed/biphasic histologies, albeit with a small incremental benefit in MS (<3–4 months).

All variables potentially impacting OS were analyzed using multivariate Cox proportional hazards analyses, as shown in Table 6. The variables of surgery plus radiation, no radiation or surgery, and extent of surgery were omitted because of covariance with the variable of surgery. Stage was

TABLE 3. Univariate Analyses of Variables Potentially Affecting Survival: Median Survival (M)

	All Patients	Localized	Regional	Distant
Age				
≤49	11.6	25.9	12.9	8.6
50–59	11.6	13.4	12.5	10.9
60–69	8.9	11.8	8.2	8.3
70–79	6.5	7.6	6.1	6.5
≥80	3.7	3.6	3.3	3.7
p	<0.0001	<0.0001	<0.0001	<0.0001
Race				
White	7.2	9.1	7.5	6.8
Black	5.7	5.0	7.2	5.0
Other	5.9	5.8	6.7	5.2
p (white vs. nonwhite)	0.25	0.058	0.64	0.35
p (white vs. black)	0.27	0.32	0.89	0.31
Gender				
Male	6.9	8.6	7.2	6.5
Female	7.7	12.3	8.6	7.0
p	<0.0001	<0.0001	<0.0001	<0.0001
Calendar year of diagnosis				
1970s	7.2	12.8	7.8	5.5
1980s	7.5	10.9	7.6	6.5
1990s	6.8	8.7	7.7	6.5
2000s	7.1	7.7	7.1	7.0
p	0.51	0.0009	0.59	0.001
Grade				
Well differentiated (grade I)	19.3	22.7	19.0	19.3
Moderately differentiated (grade II)	11.6	9.0	10.7	12.7
Poorly differentiated (grade III)	4.7	7.0	7.0	3.9
Undifferentiated; anaplastic (grade IV)	2.7	4.0	4.3	3.2
Unknown	7.2	8.9	7.5	6.8
p (excluding unknown grade)	<0.0001	0.0002	<0.0001	<0.0001
Histology				
Epithelioid	11.1	11.4	11.6	11.0
Fibrous subtypes[a]	4.5	9.9	4.8	3.6
Biphasic	7.2	7.0	9.2	6.3
Unknown (NOS)	7.2	9.0	7.0	6.7
p (epithelioid vs. known others)	<0.0001	0.017	<0.0001	<0.0001
SEER stage				
Localized	8.9	8.9	NA	NA
Regional	7.4	NA	7.4	NA
Distant	6.7	NA	NA	6.7
p (localized vs. regional or distant)	<0.0001	NA	NA	NA
p (distant vs. regional or localized)	<0.0001	NA	NA	NA
Surgery				
Cancer-directed surgery	11.4	15.8	11.3	10.7
No cancer-directed surgery	6.0	7.4	5.1	5.2
p	<0.0001	<0.0001	<0.0001	<0.0001
Radiation				
Yes	8.6	10.1	9.5	7.7
No	6.7	8.8	6.7	6.4
p	0.0008	0.64	0.002	0.033
Extent of surgery				
Radical resection[b]	15.3	14.9	14.6	15.6
Less than radical resection[b]	9.6	15.0	10.3	8.7
Not otherwise specified	12.1	16.6	9.6	11.1
p (omitting NOS)	<0.0001	0.60	0.16	<0.0001
Radiation and surgery performed	13.0	14.7	15.1	12.2
Surgery performed; no radiation	11.0	13.0	9.9	10.0
Radiation performed; no surgery	6.6	8.4	7.1	5.5
No surgery or radiation	5.9	7.0	5.6	5.9

All *p* values are calculated from log-rank tests. For the continuous variables of age and year of diagnosis, the log-rank test compared groups as stratified. For age and year of diagnosis, a univariate Cox regression analysis was also performed; the calculated *p* values from the Cox regression analyses (data not shown) were similar to those shown for the log-rank test.

[a] Includes spindled, sarcomatoid, and desmoplastic mesothelioma and fibrous mesothelioma, NOS (not otherwise specified).

[b] See footnotes of Table 1 for description of extent of surgery.

SEER, Surveillance, Epidemiology, and End Results.

TABLE 4. Median Survival After Surgery and/or Radiation, Grouped by Tumor Grade

	Well Differentiated (Grade 1)	Moderately Differentiated (Grade 2)	Poorly Differentiated (Grade 3)	Undifferentiated; Anaplastic (Grade 4)
Median survivals				
Surgery				
Cancer-directed surgery	21.6	12.5	7.3	5.1
No cancer-directed surgery	17.0	11.4	3.8	3.2
p	0.012	0.034	<0.0001	0.67
Radiation				
Yes	30.4	12.0	8.3	4.9
No	19.1	11.5	3.8	2.9
p	0.11	0.70	<0.0001	0.12
Radiation and surgery performed	58.0	13.0	11.5	6.3
Surgery performed; no radiation	19.7	12.0	6.1	3.0
Radiation performed; no surgery	19.0	11.5	7.7	4.3
No surgery or radiation	16.8	10.8	3.3	2.8

TABLE 5. Median Survival After Surgery and/or Radiation, Grouped by Tumor Histology

	Epithelioid	Fibrous Subtypes[a]	Mixed/ Biphasic
Median survivals			
Surgery			
Cancer-directed surgery	14.9	9.8	9.9
No cancer-directed surgery	8.9	3.2	5.5
p	<0.0001	<0.0001	<0.0001
Radiation			
Yes	14.2	5.0	8.9
No	10.2	3.9	6.2
p	<0.0001	0.91	0.018
Radiation and surgery performed	18.5	11.0	13.8
Surgery performed; no radiation	13.5	9.6	8.8
Radiation performed; no surgery	8.2	4.3	5.8
No surgery or radiation	9.0	2.3	5.4

[a] Includes spindled, sarcomatoid, and desmoplastic mesothelioma and fibrous mesothelioma, NOS (not otherwise specified).

analyzed in the Cox models using localized disease (compared with regional or distant disease) and distant disease (compared with localized or regional disease) as separate variables.

Because relatively few patients had tumor grade and/or histology registered in the SEER database, separate Cox models were run excluding grade and histology (8128 patients were evaluated), excluding grade (2907 patients were evaluated), excluding histology (903 patients were evaluated), and including grade and histology (361 patients were evaluated). In all Cox models, older age was a significantly adverse prognostic factor (with a HR of 1.02 per year). Male gender was a significantly adverse risk factor (HR = 1.23–1.33) in all Cox models except the one in which histology was omitted. Grade was significant ($p < 0.0001$), with a HR >1.5 in both models in which grade was included. Histology was significant ($p < 0.0001$), with a HR >1.5 in the model in which grade was excluded. However, when grade was included in the Cox model, histology (with a HR of 1.15) was not significant. In the Cox model in which grade and histology were included, SEER stage was not a significant factor. In all Cox models, undergoing surgical resection (HR ~0.6–0.7) was a significantly ($p < 0.0001$) favorable factor.

DISCUSSION

This study and others[11–19] have shown that malignant pleural mesothelioma is characterized by a poor OS. From this analysis, several variables significantly affect OS, although mesothelioma grade and cancer-directed surgery seem to affect OS to the greatest extent. From Cox analyses, a higher grade (in increments from 1 to 4) was associated with a significant ($p < 0.0001$) HR of >1.5, and not undergoing surgery was associated with a significant ($p < 0.0001$) HR of 1.4 to 1.7 (inverse of 0.59–0.72; Table 6). A younger age at diagnosis was also significantly favorable ($p < 0.0001$), consistent with other population-based studies.[12,13] Although localized mesothelioma stage likely portends a more favorable prognosis, and distant mesothelioma stage a less favorable prognosis, in the Cox models, these variables were relatively less significant (or not significant) and were associated with HRs of smaller magnitude, compared with tumor grade.

Interestingly, the MS of localized mesothelioma (and therefore the discrepancy between localized, regional, and distant stage) seems to have diminished with more recent decade (Table 3). Reasons for this are difficult to ascertain and likely attributable to multiple factors that a retrospective study cannot address. This finding is perhaps counterintuitive, as it might be expected that improved thoracic imaging developed in recent decades would result in more accurate mesothelioma staging and therefore improved survival of patients with localized disease. However, an alternative consequence of improved imaging technology is that it may allow for the detection of more biologically aggressive disease at an earlier stage, which could account for the worse survival with a more recent diagnosis of localized mesothelioma. Another explanation is that the misdiagnosis of benign

TABLE 6. Cox Proportional Hazards Analyses of Variables Potentially Affecting Overall Survival

Cox Model	Omit Grade and Histology	Omit Grade	Omit Histology	All Variables
Patients analyzed	8128	2907	903	361
Age: older age (per year)				
HR (confidence interval)	1.021 (1.019–1.023)	1.020 (1.016–1.024)	1.019 (1.012–1.026)	1.023 (1.011–1.035)
p	<0.0001	<0.0001	<0.0001	<0.0001
Race: white (vs. all others)				
HR (confidence interval)	0.913 (0.841–0.992)	1.058 (0.910–1.231)	0.954 (0.753–1.209)	1.517 (0.954–2.412)
p	0.031	0.46	0.70	0.078
Gender: male				
HR (confidence interval)	1.232 (1.161–1.307)	1.329 (1.199–1.473)	1.100 (0.933–1.298)	1.319 (1.008–1.724)
p	<0.0001	<0.0001	0.26	0.043
Year diagnosed (per year)				
HR (confidence interval)	0.992 (0.989–0.995)	1.002 (0.996–1.008)	0.994 (0.983–1.005)	0.999 (0.978–1.022)
p	<0.0001	0.46	0.30	0.97
Grade: higher grade				
HR (confidence interval)	Not analyzed	Not analyzed	1.585 (1.465–1.715)	1.548 (1.364–1.756)
p			<0.0001	<0.0001
Histology: nonepithelioid				
HR (confidence interval)	Not analyzed	1.511 (1.388–1.645)	Not analyzed	1.148 (0.861–1.532)
p		<0.0001		0.35
SEER stage (localized vs. distant/regional)				
HR (confidence interval)	0.805 (0.752–0.862)	0.764 (0.668–0.873)	0.983 (0.761–1.270)	0.844 (0.554–1.286)
p	<0.0001	<0.0001	0.90	0.43
SEER stage (distant vs. localized/regional)				
HR (confidence interval)	0.978 (0.922–1.037)	1.059 (0.960–1.169)	1.196 (1.003–1.425)	1.118 (0.836–1.496)
p	0.47	0.26	0.046	0.46
Surgery				
HR (confidence interval)	0.664 (0.627–0.704)	0.586 (0.535–0.642)	0.718 (0.610–0.846)	0.615 (0.476–0.794)
p	<0.0001	<0.0001	<0.0001	<0.0001
Radiation				
HR (confidence interval)	1.045 (0.980–1.115)	1.049 (0.940–1.171)	0.772 (0.645–0.923)	0.936 (0.694–1.261)
p	0.18	0.39	0.005	0.67

HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

conditions as malignant mesothelioma (discussed below) is more likely to have occurred in earlier decades.

Tumor histology (HR = 1.5) was significant in the Cox model omitting grade, although its HR was reduced (1.15) and not significant after incorporating grade into the Cox model (albeit with far few patients evaluable). From many studies, histology is a highly significant prognostic factor for mesothelioma,[9,11–13,15–22] and perhaps the discrepancy of data from this study versus other studies reflects, in part, the covariance of histology and grade and/or other confounding biologic variables. Epithelioid tumors were significantly ($p < 0.0001$) more likely to be lower grade (Table 2). A study from Memorial Sloan Kettering demonstrated that mesothelioma histology (HR = 1.7, $p < 0.001$) is associated with a greater and more significant HR than cancer stage (HR = 1.2, $p = 0.1$).[18] In a multi-institutional study of patients undergoing resection for mesothelioma, stage and histology had similar HRs (1.3–1.4).[22]

It must be acknowledged that there are complexities and uncertainties in the pathologic diagnosis of mesothelioma, which therefore limits the interpretation of retrospective analyses such as this study. A Swedish study demonstrated that mesothelioma is more likely to be classified as biphasic subtype if a larger biopsy sample is obtained; the authors suggest that low-grade disease should reflect relatively indolent variants of epithelial mesothelioma and higher grade disease more aggressive epithelioid, sarcomatoid, or biphasic types.[23] In this study, the increase in the recording of grade and histology in more recent decades may be partially attributable to the more recent use of immunohistochemistry for differentiating mesothelioma from other malignancies and benign conditions and for characterizing mesothelioma subtypes.[24,25]

Several studies have shown that male gender is an adverse prognostic factor for OS.[13,16–18] In this study, male gender was associated with a significantly ($p < 0.0001$) worse OS on univariate analyses for each stage group, albeit with a MS decrement (versus females) of <4 months, <6 weeks, and <2 weeks for localized, regional, and distant stage, respectively (Table 3), and an adverse HR of 1.1–1.3 with Cox analyses (although not significant in Cox model omitting histology). Although white race was significantly

favorable with univariate analyses, its affect on OS varied between the different Cox models and was a nonsignificantly adverse prognostic factor (HR = 1.5, $p = 0.078$) in the Cox model including grade and histology. Among patients with known grade and/or histology, there were not significant differences in the distribution of grade or histology among patients of different race to account for the discrepancy of HRs between the different Cox models. Perhaps, among those patients for whom tumor grade and/or histology was not available (most of the patients in this study), the distribution of adverse pathologic features was skewed toward nonwhite patients. Calendar year of diagnosis was not significant in Cox models incorporating tumor grade and/or histology, consistent with other population-based studies showing that the calendar year or era of diagnosis is not significant.[11–13]

The benefit of surgical resection on OS has been demonstrated by us and others,[18] although other studies suggest a benefit only in local recurrence, but not OS, after surgery.[9,26,27] The observed OS benefit of cancer-directed surgery for pleural mesothelioma likely reflects a combination of selection of patients who can tolerate surgery, more indolent disease being amenable to surgical resection, and a therapeutic benefit from surgery. The Cox analyses that incorporate tumor grade, histology, and stage account for the extent and aggressiveness of the tumor (albeit with a spectrum of disease extent included within each stage group), and thus these analyses do suggest a possible therapeutic benefit of surgery. Other factors used to select patients for surgery, such as performance status, pulmonary function, cardiac function, and comorbid conditions, were not accounted for in our analyses and also likely contribute to the survival benefit of surgery. A recent SEER analysis of patients with abdominal mesothelioma has also shown an OS benefit after surgery.[28]

Interestingly, the benefit of radical versus less than radical resection was significant only for patients with distant disease (Table 3). Presumably, the benefit seen with distant disease reflects patient selection and/or more accurate staging after resection, although conceivably select patients with metastatic disease may benefit from aggressive debulking. Another explanation is that some patients may have been inaccurately staged as having had distant disease based on criteria for lung cancer (i.e., positive pleural cytology). Because of the retrospective nature of this study, it is not appropriately designed to address how extent of resection impacts outcome.

Univariate analyses in this study suggest that undergoing radiation seems to offer a significant OS benefit for regional and distant disease (Table 2), poorly differentiated mesothelioma (Table 4), and epithelioid or mixed/biphasic histologies (Table 5). In the Cox analyses, undergoing radiation was only significant in the Cox model that included grade but omitted histology (HR of 1.3 for not undergoing radiation). The best MS was observed among the patients undergoing cancer-directed surgery and radiation (Tables 3–5), particularly patients undergoing radical resection and radiation. Although several studies suggest that adjuvant radiation after pleurectomy[29] or extrapleural pneumonectomy[10,22,30,31] may favorably impact OS, other studies have not demonstrated adjuvant radiation to afford an OS benefit,[21,32,33] albeit not with as large of a cohort of patients as in this study nor with a direct comparison of treatment groups. At least two population-based studies from Italy have demonstrated no significant benefit of any treatment (surgery and/or radiation) for mesothelioma.[11,13]

Weaknesses of this study include the retrospective nature of the study and the inability to account for other relevant variables, such as performance status,[15–17,19] weight loss,[17,19,20] hematological abnormalities,[16,17,19,20] lactate dehydrogenase levels,[19] presenting symptoms,[15,17–19] or exposure to tobacco and/or asbestos.[18,20] Other weaknesses of this study include the lack of reported grade and histology in most patients, despite >95% having pathologic diagnosis (data not shown), and lack of specific information on disease extent. The tumor pathology cannot be systematically reviewed, using modern immunohistochemistry techniques, to verify and specify the pathologic diagnosis. Whether patients were treated with curative-intent versus palliative-intent therapy cannot be determined. Presumably, most of the patients received palliative-intent therapy; only 5% of all patients and 4% of patients with localized disease (data not shown) underwent radiation and surgery. Also, one cannot determine who received chemotherapy or what chemotherapy agents were delivered nor can one determine the radiation dose or radiation fields. Some patients may have received radiation to the drain sites only.[34,35] Another weakness of this study is that mesothelioma is a rare malignancy for which patients are often referred to specialized centers, many of which do not register cases with the SEER program. Thus, this analysis may not accurately reflect the outcomes of patients referred to these specialized centers.

The strengths of the study include the large number of patients analyzed from an unbiased population-based registry. Because of the large numbers of patients, variables such as race, pathologic histology and grade, gender, age, undergoing radiation, and undergoing surgical resection could be analyzed.

CONCLUSIONS

From a hypothesis generating, retrospective, population-based registry analysis of malignant pleural mesothelioma patients, tumor grade, histology, and cancer-directed surgery seem to have the greatest impact on OS. When incorporating grade in a Cox proportional hazards model, histology is no longer significant, suggesting that grade may be more prognostic. Although being amenable to surgery likely reflects more indolent disease and/or better performance status and cardiopulmonary function, the significantly favorable impact of surgery, when accounting for tumor grade, histology, and stage, may reflect a therapeutic benefit. Future prospective trials, stratified by patient and tumor-related factors, could perhaps better define the optimal treatment. Although accruing patients with rare diseases, such as mesothelioma, into prospective trials is often challenging, efforts are being made to enroll patients into studies striving to better understand the role of trimodality therapy.[6]

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