Characteristics of Malignant Pleural Mesothelioma in Women

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Background. The incidence of malignant mesothelioma (MPM) is higher in men than in women, likely due to increased occupational asbestos exposure among men. Women also appear to experience better long-term survival. This study evaluates the role of gender in relation to established prognostic factors in MPM.

Methods. We reviewed 715 cases of MPM treated with extrapleural pneumonectomy at our institution between July 1987 and December 2008. Data for patients with epithelial and nonepithelial tumors were analyzed separately. Kaplan-Meier and Cox regression analyses were used to estimate survival for various cohorts to assess the relationship between gender and survival independent of age at surgery, stage, side, and preoperative laboratory studies.

Results. Of the 702 patients with complete data available, 114 out of 450 patients with epithelial tumors and 31 out of 252 patients with nonepithelial histology were women. Women with epithelial (and not nonepithelial) disease were found to differ significantly from men with respect to younger age, higher rate of thrombocytosis, and longer survival after surgery. The effect of gender on survival of patients with epithelial disease persisted when controlling for age, stage, thrombocytosis, leukocytosis, and anemia with a multivariable analysis. No significant differences in survival were seen among patients with nonepithelial disease with regard to gender, age, or anemia.

Conclusions. In the absence of other negative prognostic factors, women with epithelial MPM demonstrated a survival advantage. These findings support an aggressive approach to treating MPM including extrapleural pneumonectomy in individuals with favorable prognostic predictors, particularly women with epithelial histology and no other risk factors.

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Malignant pleural mesothelioma (MPM) is an aggressive disease with an established association with asbestos exposure [1]. Although surgical resection-based multimodality therapy has extended median survival in patients with early-stage disease [2], the overall median survival with palliative treatment only is 6 to 9 months [3]. The incidence of MPM is higher in men than in women, likely the result of increased occupational exposure to asbestos among men. The annual rate is 14 cases per million men and 3 cases per million women in the United States [4]. Consequently, the majority of the 3,000 patients presenting with this cancer each year are men [2, 5, 6]. Interestingly, despite comprising a smaller fraction of MPM patients, women are disproportionately represented among long-term survivors of this disease [7].

The association between female gender and favorable prognosis in MPM has been inconsistently reported, possibly because the number of female patients in some series is too small to detect a significant result [5, 7, 8]. Moreover, as a consequence of the rarity of this disease, the patient cohorts studied in most series have been heterogeneous with regard to primary site of disease (pleura versus peritoneum), histologic subtype, stage, and (or) treatment received. Therefore, our objective was to evaluate the prognostic significance of gender in MPM by selecting cohorts of patients who were relatively homogeneous with regard to these factors. All patients studied had histologically confirmed MPM and underwent extrapleural pneumonectomy-based multimodality therapy with complete macroscopic cytoreduction and comprehensive pathologic staging.

Patients and Methods

With Institutional Review Board approval, we reviewed all records in our International Mesothelioma Program Patient Data Registry, consisting of 2,107 patients with biopsy-confirmed diagnosis of MPM who were evaluated at our institution between July 1987 and January 2010. Prior studies have shown that up to 44% of patients diagnosed with epithelial tumors based on biopsy may be reclassified as biphasic (nonepithelial) histology when

the entire specimen is reviewed [9], and complete staging is only assured with extrapleural pneumonectomy (EPP). Therefore, we chose to analyze only those patients who underwent complete resection with EPP. A study endpoint date of December 31, 2008 was chosen to allow for a minimum of 12 months follow-up. The electronic medical records of these patients were reviewed in detail with confirmation of their resection-based histologic diagnosis. All relevant pathologic data fields were audited with a comprehensive consensus review and resolution of any ambiguities by pulmonary pathologists as previously reported [10]. All epithelial cases were specifically evaluated to distinguish cases of well-differentiated papillary mesothelioma, as the behavior of the latter differs markedly from that of other epithelial and nonepithelial MPM cell types. Data, including age at diagnosis and at surgery, gender, preoperative complete blood count, side of surgery, histology of tumor, and perioperative mortality (in-hospital or within 30 days) were retrieved from the registry and confirmed through reference to the patients' electronic medical records. The updated vital status for each patient was confirmed as of December 31, 2009 through records, obituaries, or the Social Security Death Index. This process resulted in a dataset of 715 patients. Of these, 10 patients (8 with epithelial and 2 with nonepithelial disease) were excluded for missing laboratory data and 3 other patients with epithelial tumors were excluded for lack of sufficient staging information. Data for major in-hospital morbidity were extracted from the records for all female patients with epithelial tumors.

All patients with epithelial disease were initially staged based on three published staging systems: 6th edition AJCC (American Joint Commission on Cancer [11])/ UICC (International Union Against Cancer [12]), Brigham [2], and our recently proposed modification of the TNM (tumor-nodes-metastasis) criteria that improves the prognostic stratification for staging of patients with epithelial MPM undergoing EPP [10]. Patients with nonepithelial disease were initially classified using the AJCC/UICC and Brigham staging systems. For the purpose of our analysis and based on the need to dichotomize stage, we selected our proposed modification of the TNM staging system to stage patients with epithelial disease. This staging system most evenly distributed these patients to early (stage I or II) or advanced (stage III or IV) subsets. Moreover, the proposed modifications to the TNM staging system produced the best stratification of patients by survival. The Brigham stage was used for patients with nonepithelial disease based on similar considerations.

Survival from the date of surgery was measured for all patients including those who died in the perioperative period. In addition to stage, other candidate prognostic factors, such as age and preoperative laboratory studies, were classified into binary categories for statistical testing. Age was dichotomized at 50 years, a cutoff that has been previously used in the literature [8]. Hemoglobin was dichotomized at 11.5 g/dL for women and 13.5 g/dL for men, platelet count at 450,000/μL, and white blood cell count at 10,000/μL, based on institutionally defined boundaries of normal range.

Data for patients with epithelial and nonepithelial tumors were analyzed separately. Distributions were plotted to examine compliance with distributional assumptions and the veracity of any outliers. Descriptive statistics, including percentages and medians with ranges, are reported. Nonparametric tests were used to compare dichotomous variables in univariate analysis. Continuous data, including age and complete blood count values, were analyzed in both continuous as well as dichotomized forms. Kaplan-Meier plots were used to illustrate the cumulative proportion surviving as a function of months since surgery. Cox proportional hazards regression was used to evaluate predictors influencing survival as measured from the time of surgery to death or censoring. Observations were censored at date of last contact or close of data collection at December 31, 2009. Hazard ratios and 95% confidence intervals are reported. To focus on gender, hazard ratios were derived from models with gender and each single putative covariate as well as the interaction. Where the interaction was significant, the stratified results were also calculated. We also determined the best multiple variable model to predict survival time among all available putative predictors. These multiple variable models were constructed using a manual backward-stepwise method, and confirmed by both forward and automated backward stepwise methods. Potential predictors included gender, advanced stage, thrombocytosis (preoperative platelet count over 450,000/μL), anemia (preoperative hemoglobin under 11.5 g/dL for females or 13.5 g/dL for males), leukocytosis (preoperative white blood cell count over 10,000/μL), younger age (less than 50 years), interval from diagnosis to surgery, side of disease, and age at surgery. Results were consistent whether variables were analyzed in original continuous format or dichotomized as indicated. The criterion for inclusion in the multivariable models was 10% alpha. The SAS version 9.1 (SAS, Inc, Cary, NC) was used for statistical analysis.

Results

Between July 1987 and December 2008, 715 patients underwent EPP for MPM at our institution. After excluding patients with missing data, the final dataset was 702. For patients with epithelial histology (n = 450), 114 (25%) were women, while for patients with nonepithelial histology (n = 252), 31 (12%) were women (Table 1). Among patients with epithelial tumors, women were significantly younger at the time of surgery and represented a larger proportion of patients under age 50 and (or) with thrombocytosis. Anemia was significantly more common in men than in women in both epithelial and nonepithelial cohorts. The remaining factors (which for epithelial tumors included side, white blood cell and platelet counts, leukocytosis and advanced stage, and for nonepithelial tumors included side, age, age under 50, white blood cell and platelet counts, leukocytosis and thrombocytosis) did not differ significantly between men and women (Table 1).

Table 1. Baseline Characteristics for the Cohorts With Comparisons by Gender

Variable	Epithelial (n = 450)			Nonepithelial (n = 252)		
	Male	Female	p	Male	Female	p
Count (%)	336 (75%)	114 (25%)		221 (88%)	31 (12%)	
Right side (%)	179 (53%)	57 (50%)	0.5453	128 (58%)	13 (42%)	0.0932
Median age at surgery (years) (range)	60 (25–79)	56 (17–73)	0.0013	61 (24–81)	59 (37–73)	0.4819
Age < 50	55 (16%)	32 (28%)	0.0063	24 (11%)	5 (16%)	0.3893
Median hemoglobin (g/dL) (range)	13.7 (8.6–17.7)	12.6 (8.4–15)	<0.0001	12.6 (7.7–17.3)	11.8 (7.9–14.6)	0.0070
Anemia	149 (44%)	35 (31%)	0.0105	146 (66%)	12 (39%)	0.0032
Median WBC (K/μL) (range)	7.89 (3.96–29.23)	7.7 (3.3–21.2)	0.0797	8.09 (4.14–29.30)	8.16 (2.54–31.48)	0.9801
Leukocytosis	61 (18%)	15 (13%)	0.2185	54 (24%)	8 (26%)	0.8681
Median platelet count (K/μL) (range)	314.5 (138–1,036)	336 (139–1,574)	0.0581	352 (123–1,075)	355 (186–776)	0.4819
Thrombocytosis (%)	69 (21%)	34 (30%)	0.0414	59 (27%)	7 (23%)	0.6255
Stage I[a]	23 (7%)	10 (9%)		15 (7%)	2 (6%)	
Stage II	132 (39%)	47 (41%)		67 (30%)	12 (39%)	
Stage III	122 (36%)	34 (30%)		138 (62%)	16 (52%)	
Stage IV	59 (18%)	23 (20%)		1 (<1%)	1 (3%)	
Stage III/IV	181 (54%)	57 (50%)	0.4745	139 (63%)	17 (55%)	0.3870

[a] The recent, proposed modification to the tumor-nodes-metastasis staging system [10] was used to stage patients with epithelial disease. The Brigham staging system [2] was used to stage patients with nonepithelial disease.

Stage III/IV = patients with tumors classified as either stage III or stage IV;   WBC = white blood cell count.

In general, EPP was well tolerated. Among patients with epithelial histology, the perioperative mortality for women was 1.8% (2 of 114), compared with 6.3% (21 of 336) for men ($p = 0.0820$). Among patients with nonepithelial histology, perioperative mortality for women was 3.2% (1 of 31), compared with 4.5% (10 of 221) for men ($p = 0.9999$). The rates of major in-hospital complications for women with epithelial tumors (Table 2) were similar to those reported for men and women in prior series [13], including our own analysis of complications in 328 consecutive EPPs [2].

Table 2. Major Postoperative Morbidities for Women With Epithelial Tumors (n = 112)[a]

Length of stay	Median 10 days; range 6–97
Major morbidity rate	34.8% (39/112)
Vocal cord paresis	11.6% (13/112)
Tracheostomy	5.4% (6/112)
Bleeding requiring reoperation	3.6% (4/112)
Empyema	5.4% (6/112)
Bronchopleural fistula	1.8% (2/112)
Pulmonary embolus	1.8% (2/112)
Restrictive pericarditis	1.8% (2/112)
Chylous effusion	1.8% (2/112)
Myocardial infarction	1.8% (2/112)
Acute respiratory distress syndrome	0.9% (1/112)
Acute renal failure requiring hemodialysis	0.9% (1/112)
Stroke	0.9% (1/112)
Cardiac arrest after discharge	0.9% (1/112)

[a] One patient from 1989 and one from 1990 did not have records available for a thorough review of morbidity.

For patients with epithelial histology, univariate analysis revealed the following predictors to be associated with shorter survival: male gender, older age, increased platelet count, decreased hemoglobin levels, increased white blood cell count, and advanced stage (Table 3). On univariate analysis of patients with nonepithelial histology, the following predictors were associated with shorter survival: older age, increased platelets, decreased hemoglobin, increased white blood cell count, and advanced stage (Table 3).

Female gender conferred improved survival on univariate analysis for patients with epithelial disease overall (Fig 1) and when patients were grouped by stage (advanced versus early) and stratified by gender (Fig 2). For patients with epithelial subtype, advanced stage was associated with a 140% increase in the risk of death for women, compared with a 70% increase for men. No such association was found among patients with nonepithelial disease (Figs 3; 4). This pattern was also observed when other prognostic factors were similarly analyzed (Table 3).

Older men with epithelial histology had significantly worse survival than their younger counterparts (Fig 5). A similar trend was observed in younger (compared with older) women with epithelial tumors; however, the number of women in our cohort was insufficient to detect a statistically significant difference. No significant age-related differences in survival were seen among patients with nonepithelial disease (Fig 6).

Multiple-variable analysis demonstrated the following variables to be independent significant predictors for poor survival in patients with epithelial histology: male gender, advanced stage, age 50 or older, thrombocytosis, anemia, and leukocytosis. The adjusted hazard ratio for female gender was 0.75 (95% confidence interval [CI]:

Table 3. Univariate Analysis for Predictors of Survival

Factor	Epithelial			Nonepithelial		
	HR	95% CI	p	HR	95% CI	p
Female	0.681	0.538–0.862	0.0014	0.886	0.584–1.343	0.5678
Right side	1.018	0.831–1.246	0.8657	0.950	0.731–1.235	0.7011
Age at surgery in years	1.022	1.011–1.032	<0.0001	1.017	1.002–1.032	0.0289
Age < 50 at surgery	0.681	0.521–0.890	0.0049	0.814	0.528–1.256	0.3531
Interval diagnosis to surgery (÷1 week)	0.992	0.984–1.000	0.0372	1.001	0.985–1.018	0.8792
Hemoglobin	0.877	0.822–0.936	<0.0001	0.837	0.768–0.912	<0.0001
Anemia	1.762	1.429–2.171	<0.0001	1.429	1.089–1.876	0.0101
Male anemia	1.570	1.240–1.989	0.0002	1.428	1.064–1.918	0.0178
Female anemia	2.092	1.310–3.341	0.0020	1.397	0.610–3.200	0.4291
WBC (K/μL)	1.123	1.081–1.166	<0.0001	1.097	1.053–1.143	<0.0001
Leukocytosis	1.881	1.434–2.467	<0.0001	1.904	1.408–2.575	<0.0001
Male leukocytosis	1.852	1.369–2.506	<0.0001	1.819	1.318–2.510	0.0003
Female leukocytosis	1.815	0.997–3.372	0.0594	2.618	1.079–6.353	0.0333
Platelet count (K/μL)	1.220	1.147–1.297	<0.0001	1.213	1.116–1.318	<0.0001
Thrombocytosis	1.885	1.486–2.391	<0.0001	1.873	1.392–2.521	<0.0001
Male thrombocytosis	1.655	1.248–2.196	0.0005	1.8333	1.340–2.508	0.0002
Female thrombocytosis	3.040	1.917–4.823	<0.0001	2.189	0.852–5.624	0.1037
Stage III/IV[a]	1.870	1.518–2.304	<0.0001	1.884	1.424–2.492	<0.0001

[a] The recent, proposed modification to the tumor-node-metastasis staging system [10] was used to stage patients with epithelial disease. The Brigham staging system [2] was used to stage patients with nonepithelial disease.

CI = confidence interval;   HR = hazard ratio;   Stage III/IV = patients with tumors classified as either stage III or stage IV;   WBC = white blood cell count.
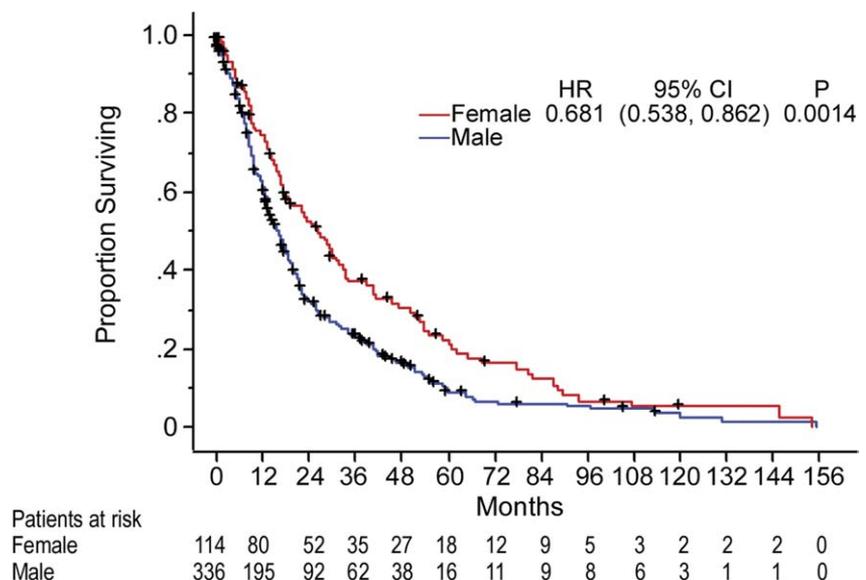
0.58 to 0.95, p = 0.017). For patients with nonepithelial disease, only stage, leukocytosis, and thrombocytosis were independent predictors of survival. Female gender was not an independent predictor of longer survival in patients with nonepithelial tumors.

Comment

Malignant pleural mesothelioma is an aggressive malignancy associated with previous asbestos exposure. As a consequence of increased occupational exposure, this cancer is much more common in men. We examined a large cohort of similarly treated patients in a retrospective analysis from a single institution to compare clinical and pathologic parameters associated with survival and to determine whether there might be a relationship with gender. As expected, patients with epithelial histology survived longer than patients with nonepithelial histology. Predictors for reduced survival duration in our cohort included advanced stage, age 50 and older, male

Fig 1. Kaplan-Meier survival curves depicting cumulative survival probability for male and female patients with epithelial malignant pleural mesothelioma. (CI = confidence interval; HR = hazard ratio.)
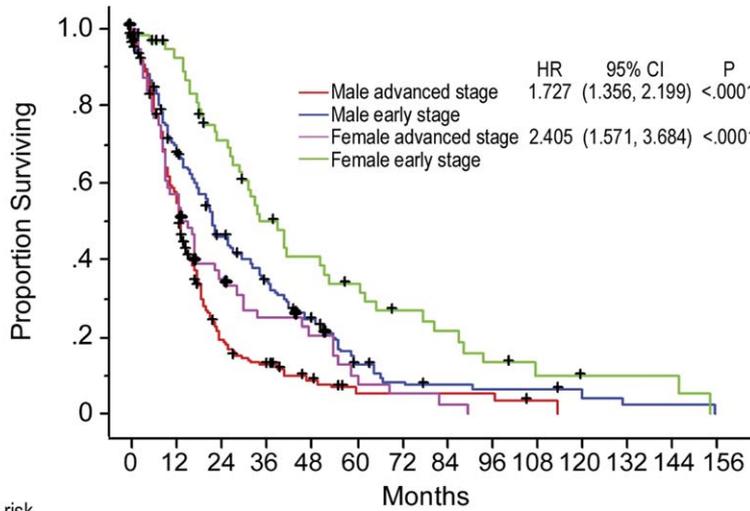
Fig 2. Kaplan-Meier survival curves depicting cumulative survival probability for patients with epithelial malignant pleural mesothelioma grouped by early versus advanced stage and stratified by gender. (CI = confidence interval; HR = hazard ratio.)

gender, anemia, thrombocytosis, and leukocytosis in patients with epithelial histology. In patients with nonepithelial histology, only advanced stage, leukocytosis, and thrombocytosis were significant predictors of shortened postoperative survival. These findings are consistent with previous reports of both single-institution and multicenter studies.

Large retrospective studies, including an analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database including 1,475 histologically confirmed cases of malignant mesothelioma between 1973 and 1984 [14], have found that female gender was associated with longer survival [6]. While these series evaluated patients who had received a vari-

ety of therapies, including chemotherapy, radiation, and (or) surgery, studies of MPM patients treated with surgery-only found a protective effect of female gender as well [15]. Moreover, analysis of five consecutive prospective phase II trials by the European Organization for Research and Treatment of Cancer drew similar conclusions for patients treated with chemotherapy [16]. In contrast, several large series have found no effect for female gender on MPM survival. These include retrospective analyses of patients treated with various therapies whose data were collected in single-center [17] and multicenter [7] registries. Similarly, evaluation of the results of seven prospective phase II trials conducted by the Cancer and Leukemia Group B found that gender
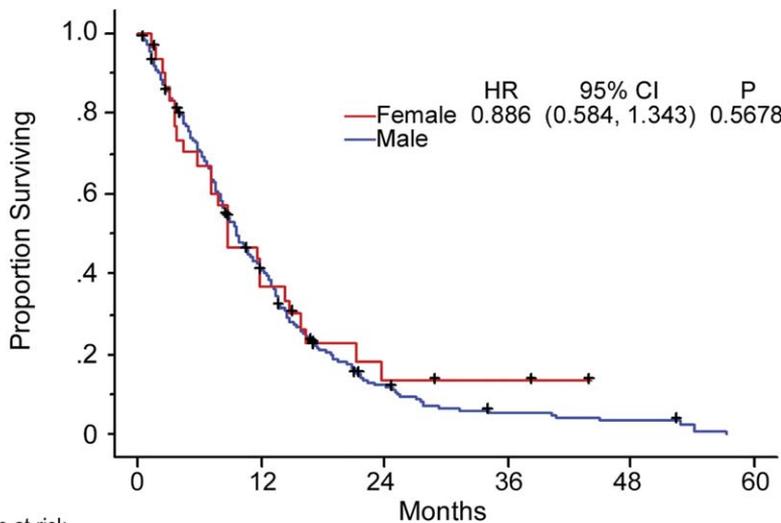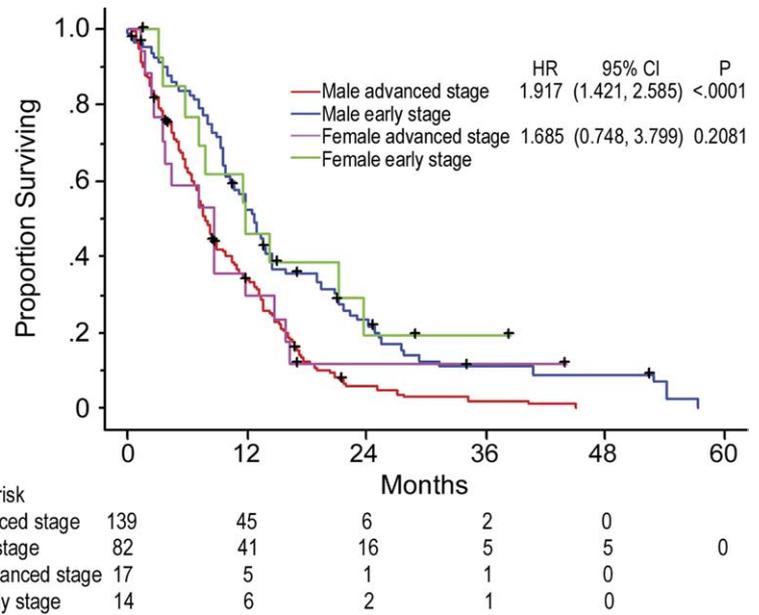

Fig 3. Kaplan-Meier survival curves depicting cumulative survival probability for male and female patients with nonepithelial malignant pleural mesothelioma. (CI = confidence interval; HR = hazard ratio.)

Fig 4. Kaplan-Meier survival curves depicting cumulative survival probability for patients with nonepithelial malignant pleural mesothelioma grouped by early versus advanced stage and stratified by gender. (CI = confidence interval; HR = hazard ratio.)
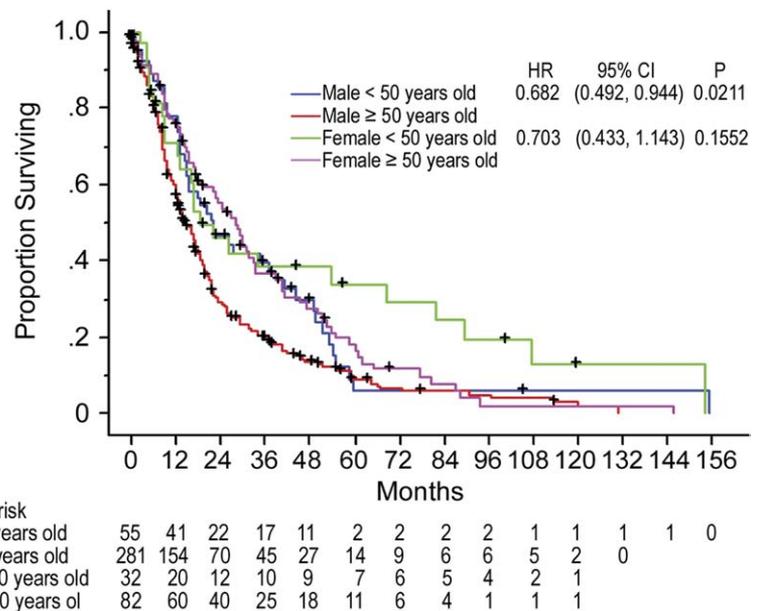

was not a significant predictor for survival in univariate or multivariable analysis [8].

It is important to note several confounding factors common to these previous studies that may have resulted in inconsistent or inaccurate conclusions. For example, several studies have included patients with peritoneal mesothelioma [5, 7, 8]. While the largest series found no significant association between site of disease and survival, this study included a disproportionate number of women (relative to men) with peritoneal mesothelioma [14]. Also, prior studies have not differentiated patients on the basis of histologic subtype, treatment strategies, or accurate pathologic staging (that is only possible with complete surgical resection). Malignant pleural mesothe-

lioma is classified into four subtypes based on histologic characteristics: epithelioid, sarcomatoid, biphasic, and desmoplastic [18]. The substantial increase in survival associated with epithelial tumors relative to the sarcomatoid, biphasic, and desmoplastic (collectively referred to as "nonepithelial") tumors is supported by numerous reports in the literature [2, 5, 6, 16]. Every prior outcome analysis in MPM, including that published regarding the two-decade experience from 1965 to 1985 at our own institution [5], has combined epithelial and nonepithelial patient cohorts, thereby confounding attempts to delineate more subtle prognostic factors for survival [10]. The current study evaluated only patients who underwent the same therapy (EPP), had complete staging, and had

Fig 5. Kaplan-Meier survival curves depicting cumulative survival probability for patients with epithelial malignant pleural mesothelioma grouped by age under 50 (versus 50 and over) and stratified by gender. (CI = confidence interval; HR = hazard ratio.)
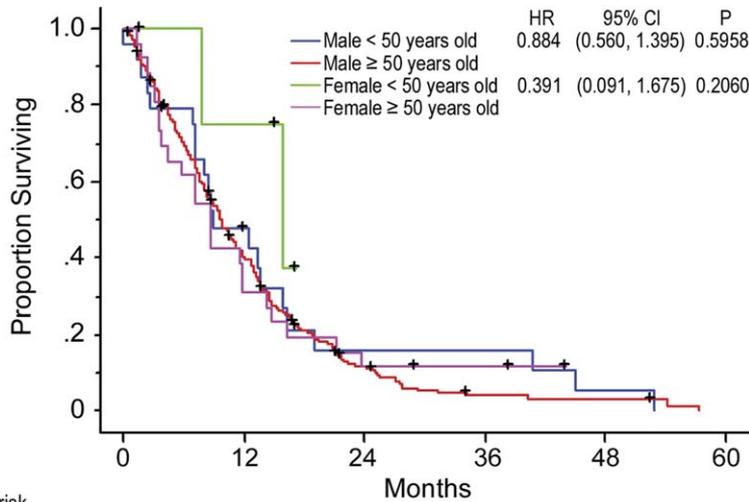
Fig 6. Kaplan-Meier survival curves depicting cumulative survival probability for patients with nonepithelial malignant pleural mesothelioma grouped by age under 50 (versus 50 and over) and stratified by gender. (CI = confidence interval; HR = hazard ratio.)

accurate determination of histologic subtype. In fact, by finding that the gender-related survival benefit is limited to patients with epithelial cell type, it is possible to conclude that the negative results from previous studies were confounded by histology.

The current study identified two potential contributors to the overall survival benefit observed for female gender in MPM. First, the proportion of women among all patients with nonepithelial disease was only half of that among all patients with epithelial disease. Previous work has demonstrated that asbestos fiber counts in lung tissue from nonepithelial EPP specimens are higher than those in epithelial specimens [19]. It is reasonable to hypothesize that the relatively smaller proportion of women among patients with nonepithelial histology observed in the current study may be a reflection of higher asbestos burden in men due to direct occupational exposure (in contrast to background or household exposure which is more common for women). Regardless, women derive a survival advantage by representing a higher proportion of patients with the more favorable epithelial cell type. Second, an inherent survival advantage was observed for women with epithelial disease that was not observed for women with nonepithelial disease. This phenomenon in women may have eluded detection because of the preponderance of men who develop this rare malignancy. Our observations were made possible by the large series of well-characterized MPM patients treated at our institution.

The chief limitation of this study is its retrospective nature, and thus covariates such as adjuvant therapy were not available for inclusion in the multivariable analysis. The study cohort represents a group of patients who underwent surgery over 20 years at a referral center for national and international patients. Surgery-based therapy was part of a variety of regimens on and off protocols, and patients were able to complete adjuvant therapy with variable consistency, frequently at outside institutions. The details of adjuvant therapy in this cohort could not be ascertained with enough accuracy to include in our analysis. Nevertheless, there is no reason to conjecture that there should be an association between gender and adjuvant therapy and thus covariates such as adjuvant therapy are unlikely to represent significant confounders in the association between gender and survival.

The survival advantage of female gender among patients with epithelial tumors implies a relation to the differential biology of the two tumor subtypes. For example, similar to other epithelial malignancies such as ovarian carcinoma, estrogen receptors may play a role in modulating tumor growth. Estrogen receptor-β is expressed by some human mesothelioma tumors and may participate in a growth suppressive function upon hormone stimulation [20]. This finding is consistent with observations in the current and prior studies [7] that younger women appear to enjoy a particularly robust survival advantage. Although data regarding menopausal status for individual patients in the current study were not available, we speculate that hormonal status may play a role in MPM survival and further work in this area may lead to new prognostic and (or) therapeutic opportunities.

We observed a survival advantage in female patients, with median survival durations for women that exceeded 30 months. This was particularly marked in women with early stage MPM, younger age, and no other risk factors. In contrast, women who had advanced disease and (or) other predictors of poor prognosis had predicted survival similar to that of their male counterparts. These findings support an aggressive treatment approach to MPM including EPP in individuals with good prognostic predictors, particularly women with epithelial histology and no other risk factors.

GENERAL THORACIC

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DISCUSSION

DR DAVID C. RICE (Houston, Texas): Very interesting study. It's a remarkable database that the Brigham group has developed.

I was curious, you showed a difference for long-term survival following cytoreductive surgery. Did you analyze or look at early survival outcomes?

And the reason I ask is when we looked at our small series of extrapleural pneumonectomies, all of our perioperative mortality occurred in men, so I was just curious if you noticed anything in your much larger series?

DR TILLEMAN: No, we didn't analyze the perioperative mortality. In general in our series, this is a low rate of 3 to 5%. The number of women in such a cohort is insufficient to detect a statistically significant difference, since there are only 20% female and they are younger.

DR RICE: Well, you had 900 cytoreductive cases.

DR TILLEMAN: Late addition: We are reporting that among patients with epithelial histology, the perioperative mortality for women undergoing EPP [extrapleural pneumonectomy] was 1.8% (2 of 114), compared to 6.3% (21 of 336) for men ($p = 0.0820$). Among patients with nonepithelial histology, perioperative mortality for women was 3.2% (1 of 31), compared to 4.5% (10 of 221) for men ($p = 1$).