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Gender differences in outcomes of patients with mesothelioma

Naomi Alpert, MS[1], **Maaike van Gerwen, MD, PhD**[1,2], **Raja Flores, MD**[3], **Emanuela Taioli, MD, PhD**[1,3,4,*]

[1]Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2]Department of Otolaryngology-Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3]Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[4]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Background—Mesothelioma is a rare and deadly form of cancer, linked to asbestos exposure. Although the United Kingdom (UK) has banned asbestos, the incidence rate remains high. Previous research has indicated that females have better survival than males, but this has never been examined in the UK.

Methods—Pleural mesothelioma cases from 2005-2014 were extracted from the UK Lung Cancer Dataset. Multivariable logistic regression was used to assess the clinical and demographic factors associated with gender. A multivariable Cox-proportional hazards model and propensity matching methods were used to assess gender differences in overall survival, while accounting for potential confounders.

Results—There were 8,479 (87.8%) males and 1,765 (17.2%) females included in the analysis. Females were significantly younger, with more epithelial histology than males. Females had significantly better overall survival (HR_{adj}: 0.85, 95% CI: 0.81-0.90). Results remained similar when stratifying by age and performance status, and when limiting to patients with epithelial histology.

Conclusions—The study increases knowledge about gender differences in mesothelioma survival and is the first to directly examine this in the UK. It further disentangles effects of age, histology and health status. Increased estrogen may improve survival, and could provide a potential target for future therapies.

Keywords

Oncological outcomes; large database analysis; Lung Cancer Dataset

[*]**Corresponding Author:** Emanuela Taioli, MD, PhD, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1133, New York, NY 10029, USA, Emanuela.Taioli@mountsinai.org, Tel: 212-659-9590.

Introduction

Malignant mesothelioma is a rare and deadly form of cancer, arising from the mesothelial cells in the pleural, peritoneal, and pericardial cavities.[1] The association between asbestos exposure and mesothelioma is well documented.[2–5] However, due to the long latency period of mesothelioma[6] we are just beginning to see moderate decreases in rates after asbestos bans and reductions in use that occurred in many countries in the 1970s-1990s.[7] Although the United Kingdom (UK) banned the use of chrysotile asbestos in 1999,[7] the incidence of mesothelioma remains one of the highest in the world (World Standardized Incidence Rate: 2.9 per 100,000 for males, 0.6 per 100,000 for females).[8] This may be due to persistent heavy asbestos exposure from common occupations, including shipbuilding, railway engineering, asbestos product manufacturing, and construction.[9, 10]

There are three histological subtypes of mesothelioma; epithelial, biphasic, and sarcomatoid, [1] and although survival for mesothelioma varies by subtype, it has remained generally poor, with median survival ranging from 8-18 months, despite the introduction of modern therapies.[1] Prior research studies using the Surveillance, Epidemiology, and End Results (SEER) data, and the National Cancer Database (NCDB) in the United States (US) have indicated significantly improved survival for female patients.[11, 12] Similar results have been found in registry-based analyses from Australia,[13] Germany,[14] and France[15] well as in single-center studies.[16–19] While some studies have suggested improved survival is due to more favorable tumor and demographic characteristics,[20–22] it may also be associated with the protective benefits of circulating estrogen and estrogen receptors in the tumor.[19, 23, 24] Due to the aggressiveness of mesothelioma, it is crucial to identify factors associated with improved prognosis, as this may provide insight into more efficacious, personalized treatments and therapies.

Given the rarity of mesothelioma, especially among females, population based registries provide a unique opportunity to examine prognostic factors, especially in countries with high incidence rates. Although similar studies have been conducted in other countries, there is currently no study directly comparing survival between females and males in the UK. The goal of this study was to use data from the UK's National Lung Cancer Audit (NLCA) to determine whether survival patterns for malignant pleural mesothelioma (MPM) by gender are consistent with what has been seen in other countries, despite differences in occupational asbestos exposure and timelines in reducing asbestos production and consumption.[7]

Materials and Methods

Data Source and Study Population

The NLCA was established in 2004 to assess potential inequalities within the United Kingdom (UK)'s National Health Service (NHS), and to address the finding that outcomes for patients with lung cancer in the UK were worse than in other countries.[25] The NLCA is commissioned by the Healthcare Quality Improvement Partnership, and administered by the Royal College of Physicians, with data submitted for approximately 100% of all incident cases from the 157 trusts within the NHS. The data set of Lung Cancer Data (LUCADA) includes information on mesothelioma cases, with data available from 2005-2014, at the

time of the data request.[25, 26] Variables available in LUCADA include patient demographics and clinical factors, tumor characteristics, treatment (including palliative care), months of follow up, and vital status. This project involves data derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). Access to the data was facilitated by the PHE Office for Data Release. All patients with mesothelioma morphology (9050/3, 9051/3, 9052/3, 9053/3), and a primary ICD-10 diagnosis code of C34, C34.x, C38.4, C45, or C45.0 in England, from 2005-2014 were included (n=10,357). As a quality control, those with an unknown diagnosis date were excluded (n_{exc}=113), for a final sample of 10,244 patients. Data received by the investigators was anonymous, and therefore the study was deemed non-human subjects research by the Icahn School of Medicine at Mount Sinai Institutional Review Board and was not subject to the General Data Protection Regulation (GDPR).

Variables

The primary outcome of interest was overall survival. LUCADA shared the number of months of follow up, and each patient's vital status at that time. The primary predictor of interest was patient gender. Other covariates of interest included age at diagnosis, histology, site, Eastern Cooperative Oncology Group (ECOG) performance status, and receipt of treatment (surgery, chemotherapy, radiotherapy) or palliative care. Although UK guidelines state that mesothelioma surgeries are palliative in intent, they are coded separately from non-interventional palliative care. Those with ICD-10 codes indicating lung or pleura as the site of the cancer (C34, C34.x, C38.4, C45.0) were coded as definitive pleural cases, while those with and ICD-10 code of C45 were considered to be missing definitive site. However, as pleural is the most common type of mesothelioma, and LUCADA is focused on lung cancer, we suspect non-pleural mesotheliomas are rare in the dataset. Other studies have also assumed that patients in this dataset with an ICD-10 code of C45 are cases of pleural mesothelioma.[27]

Statistical Analysis

Males and females were compared on demographic, clinical, and tumor characteristics using χ^2-tests. Multivariable logistic regression was run to assess the independent associations of these variables with gender, using Odds Ratios (OR) and 95% Confidence Intervals (CI). Survival was compared using Kaplan-Meier curves with the log-rank test. Univariate and multivariable Cox proportional hazards models were used to assess the association between gender and survival, while accounting for potential confounders. As ECOG status was missing for 19% of the sample, a "missing" category was created so as not to exclude these patients from multivariable analyses. Multivariable models were also adjusted for year of diagnosis to account for any changes over time. A sensitivity analysis was conducted, stratified by definitive pleural site.

Survival was also assessed using a 1:1 optimal propensity score match[28] (maximum difference=0.000001), matching on all covariates. The quality of the match was assessed using the standardized difference between groups for each covariate. Covariates with a standardized difference of <10% were considered to be well balanced. This analysis was

also run among those with epithelial status, and stratified by age at diagnosis (<65, ≥65 years) and ECOG status (0/1, 2/3).

Results

There were 10,244 patients in the sample; 8,479 (82.8%) male and 1,765 (17.2%) female. Females were significantly younger (22.1% <65 years, vs. 19.7%, p=0.0250), and significantly more likely to have epithelial histology (35.7% vs. 30.9%, p<0.0001) and worse ECOG status (10% with score 3, vs. 7.9%, p=0.0099). They were also significantly less likely to receive chemotherapy (29.1% vs. 31.4%, p=0.0495). There was no significant difference in definitive pleural site, or receipt of surgery, radiotherapy, or palliative care. (Table 1).

After adjustment, females resulted still significantly younger, with significantly more epithelial and less sarcomatoid histology than males. There was no statistically significant difference in definitive pleural site, ECOG status, and receipt of surgery, chemotherapy, radiotherapy, or palliative care (Table 2)

Median (IQR) follow up time of the sample was 9.3 (3.4-17.3) months. Overall survival was significantly better for females, compared to males (p<0.0001). At 2 years, the survival (95% CI) was 21.7% (19.7-23.7%) and 16.3% (15.5-17.1%) for females and males, respectively; at 5 years it was 5.7% (4.2-7.1%) and 3.7% (3.2%-4.2%). Survival remained significantly better for females after adjusting for all covariates (HR_{adj}:0.85, 95% CI: 0.81-0.90). Other factors significantly associated with improved survival were younger age at diagnosis, epithelial histology, definitive pleural site, lower ECOG scores, and receipt of surgery, chemotherapy, or radiotherapy. Those who received palliative care had significantly worse survival (Table 3). A sensitivity analyses stratified by definitive pleural site revealed similar and consistent results ($HR[\text{definitive pleural}]_{adj}$:0.86, 95% CI: 0.80-0.92; $HR[\text{undefined}]_{adj}$:0.85, 95% CI: 0.78-0.92).

The propensity matched cohort contained 3,110 patients, and was well balanced between males and females on all variables (|standardized difference| <0.1) (See Table, Supplemental Digital Content 1). Survival was significantly better for females than males at 2 years (22.2%, vs. 16.9%, p=0.0025) and 5 years (5.1% vs. 3.7%, p=0.0015) (HR: 0.89, 95% CI: 0.82-0.96) (Figure 1a). After stratification by age at diagnosis there were 672 patients in the propensity matched group <65 years old at diagnosis, and 2,444 in the propensity matched group ≥65 years old at diagnosis. Survival was significantly better for females, compared to males in both analyses (HR: 0.77, 95% CI: 0.65-0.90; HR: 0.90, 95% CI: 0.82-0.97, respectively) (Figure 1b–c)

There were 1,094 patients in the propensity matched cohort with epithelial histology. Females had significantly better survival (HR: 0.79, 95% CI: 0.69-0.90) (See Figure, Supplemental Digital Content 2a, which shows survival in the propensity matched cohort with epithelial histology). Results remained similar after stratification for age (HR: 0.67, 95% CI:0.51-0.88, HR: 0.87, 95% CI: 0.75-0.99, for <65 years and ≥65 years, respectively (Figure, Supplemental Digital Content 2b, which compares survival in the epithelial cohort

<65 years (n=278) and 2c, which compares survival in the epithelial cohort ≥65 years (n=912)).

After stratification by ECOG status, there were 1,714 patients in the propensity matched cohort with ECOG score of 0 or 1, and 750 in the cohort with ECOG score of 2 or 3. Survival was significantly better for females (HR: 0.81 0.73-0.90) for those with ECOG 0 or 1 (Figure, Supplemental Digital Content 3a, which compares survival for those with ECOG 0/1). For those with ECOG 2 or 3, survival was not significantly different by gender, but trended towards better survival for females (HR: 0.89, 95% CI: 0.77-1.03) (Figure, Supplemental Digital Content 3b, which compares survival for those with ECOG 2/3).

Discussion

This study included more than 10,000 mesothelioma patients; over 1,700 of them female, from the NLCA LUCADA dataset. This dataset presents a unique research opportunity, given the enduring high incidence of mesothelioma in the UK.[8] This analysis is the first to examine gender disparities in survival for MPM in this population.

Consistent with prior research from multiple different data sources[11–15] in other countries, this analysis shows significantly better survival among female patients with MPM. This difference persisted across age, health status, and tumor characteristics. Although this study and others have found that females tend to be younger and are more likely to have epithelial histology,[11, 12, 14, 29] the results of this analysis suggest that better survival among females is not entirely due to more favorable age and tumor characteristics. Although other studies have found females to have better health status and fewer comorbidities[12, 15] than males, this was not the case in the UK data set. Improved survival is unlikely to be due to treatment disparities. In fact, despite the survival benefit of chemotherapy, radiotherapy, and surgery, we found no significant difference in receipt of treatments, with females actually trending towards being treated less frequently than males.

Studies have hypothesized that more favorable histology may play a role in improved survival for females.[21] However, many population-based datasets, including this one, do not have detailed histologic subtype for a large portion of patients with mesothelioma,[11, 12, 21] making it difficult to disentangle its effect on survival. Although females were significantly more likely to have epithelial histology, we were able to remove this potential confounding effect by comparing survival within histological subtype. When limiting to those with epithelial histology, the gender difference in survival appeared to be larger than in the overall cohort, indicating that females in this UK dataset do particularly well, comparatively.

When the analysis was stratified by age, females had significantly better survival in all age groups, however, the difference was more prominent in the younger age group, both in the overall cohort, and among those with epithelial histology. When the analysis was stratified by ECOG status, females had significantly better survival when with ECOG status 0/1; this was not so among those with ECOG status 2/3. The independent prognostic value of both younger age and better ECOG status may indicate that age not only acts as a proxy for better health status, but that age itself is an important factor in the survival benefit for females. This

finding is consistent with research that has suggested circulating estrogen, which decreases as females age, and increased expression of estrogen receptor beta (ERβ) may play a role in improved survival of MPM.[23, 24, 30, 31] Studies have shown that increased expression of ERβ is an independent prognostic factor for survival,[23] possibly due to its tumor suppressor properties.[24] In addition to its role in improving survival, ERβ may also serve as a target for future treatment as it might indicate better response to therapies, including chemotherapy.[30, 31] It has been suggested that activation of expression of ERβ may have the potential to reverse biphasic histologies[32] and confer a more epithelioid phenotype.[24]

Results of this study should be interpreted within the context of the limitations of the LUCADA dataset. One major drawback is that this dataset has poor recording of stage.[27] Less than 30% of patients had this information, thus we were unable to include this variable in the statistical models. Approximately 40% of the cohort had ICD-10 diagnostic codes that did not specify whether the site of the cancer was pleural. However, we believe that mainly pleural cases were included given the nature of this dataset. Furthermore, it is reasonable to assume that non-pleural cases are rare, as others have also done.[27] Additionally, this is unlikely to have biased our results, as the distribution of these cases was very similar between males and females and a stratified sensitivity analysis showed almost identical results regardless of definitive site. Those without definitive site were more likely to be diagnosed in earlier years, where coding practices may have been less consistent. As is common in other mesothelioma registries,[11–13, 33] many patients did not have detailed information on histological subtype. However, our sample was large enough that we were able to make a robust comparison within the epithelial subgroup. Of particular importance is also the fact that this dataset does not have detailed occupational history available. Men are much more likely to have had direct occupational exposure,[2, 34] compared to domestic or environmental exposure, and this likely plays a role in disease presentation and fatality.[2] Although this information does exist in some national registries,[35] widespread inclusion of occupational exposure will be an extremely important factor in development and expansion of future mesothelioma registries.

This study increases the knowledge of prognostic factors of survival in MPM patients and is the first to directly examine gender in the UK. Given the high rates of mesothelioma in the UK, the NLCA LUCADA dataset is a rich resource for epidemiological examinations, allowing for a larger sample size, particularly of females, than can be recruited for single center studies. Compared to US studies, which often use either the NCDB (hospital based inclusion) or SEER (population based inclusion for specific geographic areas), the LUCADA records data from all 157 trusts in the NHS, providing a comparatively more complete view of this population of mesothelioma patients. We were able to look at results independent of age, histology, and performance status to isolate the survival effects of gender in this population. Future research to examine the mechanisms of these effects and the potential application to therapies is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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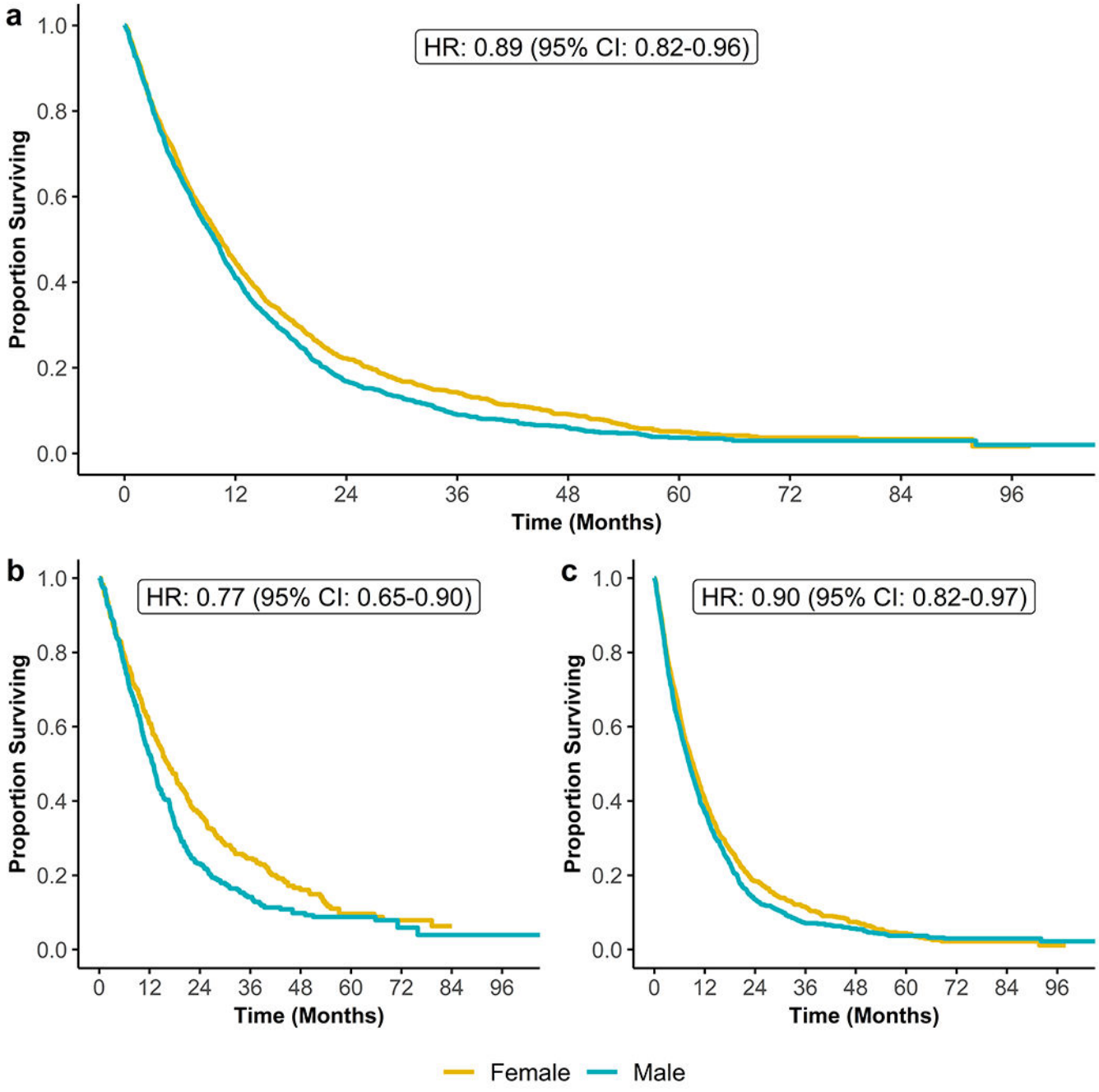

Figure 1-

Overall survival in mesothelioma patients, by gender in (a) the propensity matched cohort (n=3,110); (b) propensity matched cohort <65 years old (n=672); (c) propensity matched cohort ≥65 years (n=2,444)

Table 1-

Demographic and clinical characteristics of the sample, by gender

Variable	Males (n=8479) n(%)	Females (n=1765) n(%)	*p-value*^
Age at diagnosis (years)			0.0250
≤64	1673 (19.7)	390 (22.1)	
65-69	1587 (18.7)	306 (17.3)	
70-74	1724 (20.3)	333 (18.9)	
75-79	1726 (20.4)	334 (18.9)	
≥80	1769 (20.9)	402 (22.8)	
Histology			<.0001
Epithelial	2616 (30.9)	630 (35.7)	
Biphasic	352 (4.2)	74 (4.2)	
Sarcomatoid	542 (6.4)	79 (4.5)	
Mesothelioma, NOS	4969 (58.6)	982 (55.6)	
Site			0.3445
Definitive Pleural	4898 (57.8)	998 (56.5)	
Undefined	3581 (42.2)	767 (43.5)	
*ECOG Performance Status**			0.0099
0	1655 (19.5)	341 (19.3)	
1	3192 (37.6)	600 (34.0)	
2	1276 (15.0)	276 (15.6)	
3	668 (7.9)	176 (10.0)	
4	121 (1.4)	24 (1.4)	
Missing	1567 (18.5)	348 (19.7)	
Surgery			0.1339
No	6057 (71.4)	1292 (73.2)	
Yes	2422 (28.6)	473 (26.8)	
Chemotherapy			0.0495
No	5813 (68.6)	1252 (70.9)	
Yes	2666 (31.4)	513 (29.1)	
Radiotherapy			0.1007
No	5920 (69.8)	1267 (71.8)	
Yes	2559 (30.2)	498 (28.2)	
Palliative Care			0.1786
No	6572 (77.5)	1342 (76.0)	
Yes	1907 (22.5)	423 (24.0)	

^based on non-missing values

[*] 0-Able to carry out all normal activity without restriction; 1-restricted in physically strenuous activity, but able to walk and do light work; 2-Able to walk and capable of all self care, but unable to carry out any work. Up and about more than 50% of waking hours; 3-Capable of only limited self care, confined to bed or chair more than 50% of waking hours; 4-Completely disabled, cannot carry on any self care. Totally confined to bed or chair.

Table 2-

Factors associated with gender among mesothelioma patients

Variable	Females vs. Males
	OR_{adj}^ (95% CI)
Age at diagnosis (years)	
≤64	1.0 (ref)
65-69	0.84 (0.71-0.99)
70-74	0.82 (0.70-0.97)
75-79	0.81 (0.69-0.96)
≥80	0.91 (0.77-1.08)
Histology	
Epithelial	1.0 (ref)
Biphasic	0.90 (0.69-1.17)
Sarcomatoid	0.59 (0.45-0.75)
Mesothelioma, NOS	0.80 (0.71-0.89)
Site	
Undefined vs. Definitive Pleural	1.04 (0.93-1.15)
ECOG Performance Status *	
0	1.0 (ref)
1	0.93 (0.80-1.07)
2	1.05 (0.88-1.26)
3	1.25 (1.01-1.55)
4	0.91 (0.57-1.44)
Missing	1.05 (0.89-1.25)
Surgery	
Yes vs. No	0.9 (0.80-1.01)
Chemotherapy	
Yes vs. No	0.91 (0.80-1.03)
Radiotherapy	
Yes vs. No	0.94 (0.83-1.05)
Palliative Care	
Yes vs. No	1.03 (0.91-1.17)

^Adjusted for all variables listed and year of diagnosis

*0-Able to carry out all normal activity without restriction; 1-restricted in physically strenuous activity, but able to walk and do light work; 2-Able to walk and capable of all self care, but unable to carry out any work. Up and about more than 50% of waking hours; 3-Capable of only limited self care, confined to bed or chair more than 50% of waking hours; 4-Completely disabled, cannot carry on any self care. Totally confined to bed or chair.

Table 3-

Factors associated with mortality, mesothelioma patients

Variable	HR_{adj} ^ (95% CI)
Gender	
Female vs. Male	0.85 (0.81-0.90)
Age at diagnosis (years)	
≤64	1.0 (ref)
65-69	1.08 (1.01-1.15)
70-74	1.13 (1.06-1.20)
75-79	1.22 (1.15-1.31)
≥80	1.32 (1.23-1.41)
Histology	
Epithelial	1.0 (ref)
Biphasic	1.66 (1.49-1.85)
Sarcomatoid	2.56 (2.34-2.80)
Mesothelioma, NOS	1.21 (1.15-1.26)
Site	
Undefined vs. Definitive Pleural	1.04 (1.00-1.09)
ECOG Performance Status *	
0	1.0 (ref)
1	1.21 (1.14-1.29)
2	1.60 (1.48-1.72)
3	2.59 (2.37-2.83)
4	5.33 (4.47-6.34)
Missing	1.30 (1.22-1.39)
Surgery	
Yes vs. No	0.80 (0.76-0.84)
Chemotherapy	
Yes vs. No	0.74 (0.70-0.78)
Radiotherapy	
Yes vs. No	0.86 (0.82-0.90)
Palliative Care	
Yes vs. No	1.41 (1.34-1.49)

^ Adjusted for all variables listed and year of diagnosis

* 0-Able to carry out all normal activity without restriction; 1-restricted in physically strenuous activity, but able to walk and do light work; 2-Able to walk and capable of all self care, but unable to carry out any work. Up and about more than 50% of waking hours; 3-Capable of only limited self

care, confined to bed or chair more than 50% of waking hours; 4-Completely disabled, cannot carry on any self care. Totally confined to bed or chair.