

Testicular Mesothelioma: An Analysis of Epidemiology, Patient Outcomes, and Prognostic Factors



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OBJECTIVES	To characterize demographic features, clinical characteristics, and oncologic outcomes of mesothelioma of the testis.
METHODS	A population based search was performed using the National Cancer Institute's SEER 18 database. Patients diagnosed with malignant mesothelioma of the male genital organs from 1973 to 2015 were identified. Data on patient age, race, tumor laterality, histologic subtype, tumor extent, tumor size, tumor grade, treatment, cause of death, and survival months was collected. Primary outcomes were overall survival (OS) and disease-specific survival (DSS).
RESULTS	A total of 113 patients with testicular mesothelioma were identified. The 5-year OS and DSS for all patients was 49% and 58%, and the 10-year OS and DSS was 33% and 45%, respectively. Biphasic mesotheliomas were associated with worse OS compared to general mesotheliomas and epithelioid subtypes ($P = .043$ and $P = .039$, respectively). Median survival time was not reached in patients with T1 disease while OS was 1.7 years and DSS was 1.8 years for patients with T4 disease ($OS P = .002$, $DSS P < .001$). Tumors greater than or equal to 4 cm were associated with worse OS and DSS ($OS P = .025$, $DSS P = .047$).
CONCLUSION	This rare malignancy has significant mortality, with poor survival associated with biphasic subtypes, higher disease stage, and a critical tumor size cutoff of 4 cm. UROLOGY 126: 140–144, 2019. © 2019 Elsevier Inc.

Malignant mesotheliomas are uncommon tumors that may involve the pleura, pericardium, peritoneum, and tunica vaginalis testis.^{1,2} Mesothelioma of the testis is extremely rare, comprising less than 5% of all mesotheliomas.^{1,3,4} The first case of testicular mesothelioma was described in 1957 by Barbera and Rubino, and since then, fewer than 250 cases had been reported as of 2016.^{5,6} Standard incidence rates for extrapleural mesothelioma are 2.1 cases per million and are 0.2 cases per million for paratesticular mesothelioma specifically.⁶

Mesotheliomas arise from the serosal membranes of coelomic cavities and include the tunica vaginalis, which originates as an outpouching from the abdominal peritoneum.⁴ The etiology of malignant genital mesothelioma remains unknown, but it has been suggested that local trauma, inflammation, and asbestos exposure may play

a role.^{1,4,7-11} Even so, some cases may present without any identifiable risk factors.¹⁰

Despite occurring most commonly in patients between the sixth and eighth decade of life, 10% of cases occur in patients under 25 years of age.^{1,2,4,8} Most testicular mesotheliomas present with nonspecific symptoms including scrotal enlargement, with a hydrocele present in over half of patients, or painless scrotal mass, seen in about one-third of patients.^{1-3,7,10,12}

One of the major problems with paratesticular mesotheliomas is the difficulty associated with diagnosing these tumors preoperatively, resulting in the majority of cases being diagnosed intraoperatively or postoperatively.⁴ These tumors are aggressive and are often associated with a poor prognosis with high rates of distant metastases and death.¹³ Current treatments include complete surgical excision which may be achieved via radical orchiectomy, radiotherapy, and chemotherapy.^{3,7,14} If signs of metastasis are present in inguinal lymph nodes, inguinal lymph node dissection is recommended.¹⁰ However, despite aggressive surgical procedures or systemic adjuvant therapies, prognosis remains relatively poor.¹⁵

Small case reports and series from single institutions and literature reviews on testicular mesothelioma have been published, but because of the rarity of this malignancy, reports have been limited in number of

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patients.^{1,3,7-10,13,16,17} We use the SEER database to evaluate demographic and clinical features and oncologic outcomes for patients with mesothelioma of the testis diagnosed from 1973 through 2015.

MATERIALS AND METHODS

A population-based search for patients diagnosed with malignant mesothelioma of the male genital organs was performed using the National Cancer Institute's SEER 18 database [www.seer.cancer.gov]. No Internal Review Board approval was required for this publicly available database that provides information with no personal identifiers.

Patients diagnosed with malignant mesothelioma of the male genital organs from 1973 to 2015, the widest date ranges available in the latest version of the software, were reviewed. Site specific codes were used to identify all primary tumors that originated in the male genital organs (International Classification of Disease for Oncology, third edition site codes C60.0-C63.9). Preliminary analysis showed that a substantial proportion of malignancies were coded to regions other than the testis, including the penis, spermatic cord, and other specified and unspecified regions of the male genital organs. Because the tunica vaginalis testis is the most common male genital organ containing mesothelial tissue, and based on a prior SEER study including communication with a SEER registry quality control specialist who confirmed miscoding may have occurred for location, we treated all mesotheliomas of the male genital tract as originating in the testis and refer to them as such throughout the remainder of this paper.² Histologic codes were used to identify all malignant mesotheliomas (International Classification of Disease for Oncology, third edition histology codes 9050-9055), which included the following histologic subtypes: "mesothelioma," "fibrous mesothelioma," "epithelial mesothelioma," and "biphasic mesothelioma."

The following primary data were extracted for analysis: patient age, race, histologic subtype, laterality of the tumor, tumor extent, tumor size, tumor grade, treatment with surgery and/or radiation therapy, cause of death, and survival months. Data on laterality and the use of radiation therapy was only available for cases until 2011. Tumor grade was reclassified as either low-grade for well or moderately-differentiated histology, or high-grade for poorly differentiated or undifferentiated histology. Tumor staging was manually reclassified using extent of disease and clinical stage to conform with the established American Joint Committee on Cancer seventh edition TNM classification for testicular cancer (American Cancer Society, [www.cancer.org]), not including serum levels of tumor markers.

Primary outcome was defined as time in months from diagnosis to death from any cause for overall survival (OS), and time from diagnosis to death-specific to the cancer-related diagnosis for disease-specific survival (DSS). Descriptive epidemiological and survival statistics were calculated for all variables. OS and DSS curves were calculated using the Kaplan-Meier method and differences were tested using the log-rank test. Covariates were assessed with univariate analysis. Statistical significance was set at the $P < .05$ threshold. Statistical analyses were performed using SPSS 21 software (IBM Corp., Armonk, NY).

RESULTS

The search identified 113 patients with malignant mesothelioma of the testis from 1973 to 2015. Demographic results including

Table 1. Demographic and clinicopathologic features (n = 113)

Age	Years
Mean	61.5 ± 18.3
Median	64
Min	11
Max	94
Characteristic	Percentage (n)
Race	
White	86.7% (98)
Black	8.8% (10)
Other	3.5% (4)
Unknown	0.9% (1)
Tumor grade	
Low-grade	15.9% (18)
High-grade	7.1% (8)
Unknown	77.0% (87)
Laterality	
Left	15.9% (18)
Right	25.7% (29)
Unknown	58.4% (66)
Histologic subtype	
General mesothelioma	71.7% (81)
Fibrous type	1.8% (2)
Epithelioid type	21.2% (24)
Biphasic type	5.3% (6)
T stage	
T1	25.7% (29)
T2	26.5% (30)
T3	11.5% (13)
T4	19.5% (22)
Unknown	16.8% (19)
Nodal disease	
No nodal involvement	62.8% (71)
Nodal involvement	9.7% (11)
Unknown	27.4% (31)
Metastatic disease	
No metastatic disease	64.6% (73)
Metastatic disease	6.2% (7)
Unknown	29.2% (33)
Surgical resection	
Yes	98.2% (111)
No	1.8% (2)
Radiation therapy performed	
Yes	5.3% (6)
No	71.7% (81)
Unknown	23.0% (26)
Size (cm)	
Mean	3.3 ± 2.8
Median	2.5

breakdown by race, tumor laterality, histologic subtype, tumor grade, tumor stage, and treatments are reported in Table 1. On histologic subtype analysis, after removing general mesotheliomas to only assess specific histologic subtypes, epithelioid comprised 75% of cases, biphasic 18.8% of cases, and fibrous 6.2% of cases.

Overall, 56 patients (49.5%) within this cohort survived. The 5 and 10-year OS and DSS for all patients with malignant mesothelioma was 49% and 58%, and 33% and 45%, respectively (Fig. 1, Supplementary Table 1). On univariate analysis, greater age was associated with worse survival (OS $P < .001$, DSS $P = .003$, Table 2). Ethnicity, and when reported tumor laterality, was not significantly associated with survival outcomes.

When reported, high tumor grade was associated with worse survival prognosis compared to low tumor grade, with median OS

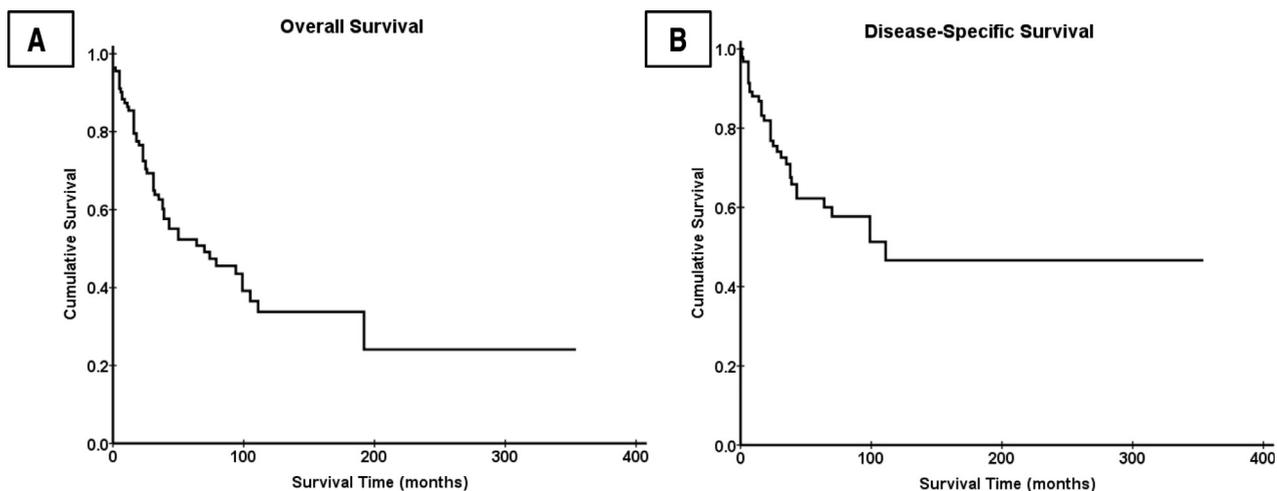


Figure 1. Survival analysis of patients with testicular mesothelioma. Kaplan-Meier analysis of (A) overall survival and (B) disease-specific survival are shown for all patients.

of 2.7 years and DSS of 5.7 years, respectively (OS $P = .012$, DSS $P = .007$) (Supplementary Fig. 1A, B, Table 2). Neither median OS nor DSS were reached in patients with low-grade tumors.

Extent of disease on presentation was significantly associated with survival, as higher tumor stage was associated with worse survival and significantly poorer OS and DSS (Supplementary Fig. 2, Table 2). Median survival time was not reached in patients with T1 disease, while for patients with T4 disease OS was 1.7 years and DSS was 1.8 years (OS $P = .002$, DSS $P < .001$). Poorer DSS was also significantly associated with nodal involvement and metastatic disease ($P = .008$ and $P = .031$, respectively, Supplementary Fig. 3, Table 2). The association between OS and nodal involvement or metastatic disease was not significant. Increasing tumor size was associated with worse survival (OS $P = .005$, DSS $P = .001$). When stratified by size

cutoffs, tumors greater than or equal to 4 cm were associated with worse OS and DSS (OS $P = .025$, DSS $P = .047$, Fig. 2, Table 2).

Among the various histologic subtypes, biphasic mesotheliomas had a particularly dismal prognosis compared with the rest of the cohort (OS 1.5 years, DSS 1.5 years), and was associated with significantly worse outcomes compared to general mesotheliomas (OS $P = .043$, DSS $P = .020$) and epithelioid subtypes (OS $P = .039$, DSS $P = .122$, Supplementary Fig. 1C, D, Table 2). When used, beam radiation therapy was not associated with improved survival outcomes (OS $P = .979$, DSS $P = .872$, Table 2).

DISCUSSION

Mesothelioma of the testis is a very rare malignancy, with the potential for local invasion and metastatic disease. The current literature on this topic is extremely limited and comprised of single case reports, small case series, and literature reviews. To our knowledge, there have been no large-scale studies assessing prognostic indicators and oncologic outcomes associated with this disease. Better understanding of the natural history and stage distribution of mesothelioma of the testis is important because it establishes benchmarks and allows providers to better counsel patients. Additionally, future studies and clinical trials may need this information to aid in study design, allowing more focused attention on patient outcomes. Our study is the first to analyze population-level data on demographics, clinicopathologic features, treatments, and oncologic outcomes of this rare malignancy, with a focus on the identification of prognostic factors for overall and DSS.

We found that a majority of patients present with T1 and T2 disease, and approximately 20% present with T3 or higher disease. Demographic findings in this study were consistent with previous studies.^{1,2,10,13,17} Of tumors where specific histologic subtype was reported, epithelioid type was most common. This breakdown by histologic subtype was in line with a review of the literature, where epithelial type was most common (60.8%-75%), followed by biphasic (25%-37.3%), and fibrous (1.9%) subtypes.¹⁵

Table 2. Univariate analysis of variables using Kaplan-Meier method (n = 113)

Characteristic	OS (Log-Rank P)	DSS (Log-Rank P)
Age at diagnosis	<.001	.003
Race (White vs non-White)	.142	.315
Tumor grade	.012	.007
Laterality	.183	.181
Subtypes		
General vs fibrous	.460	.866
General vs epithelioid	.866	.690
General vs biphasic	.043	.020
Fibrous vs epithelioid	.508	.758
Fibrous vs biphasic	.212	.266
Epithelioid vs biphasic	.039	.122
Radiation therapy performed	.979	.872
T stage (ordinal)	.002	<.001
Nodal involvement	.143	.008
Metastatic disease	.156	.031
Size (continuous)	.005	.001
Size		
≥ 2 cm	.319	.251
≥ 3 cm	.442	.587
≥ 4 cm	.025	.047
≥ 5 cm	.056	.133

The bolded P values are those that were statistically significant, using the threshold $P < .05$.

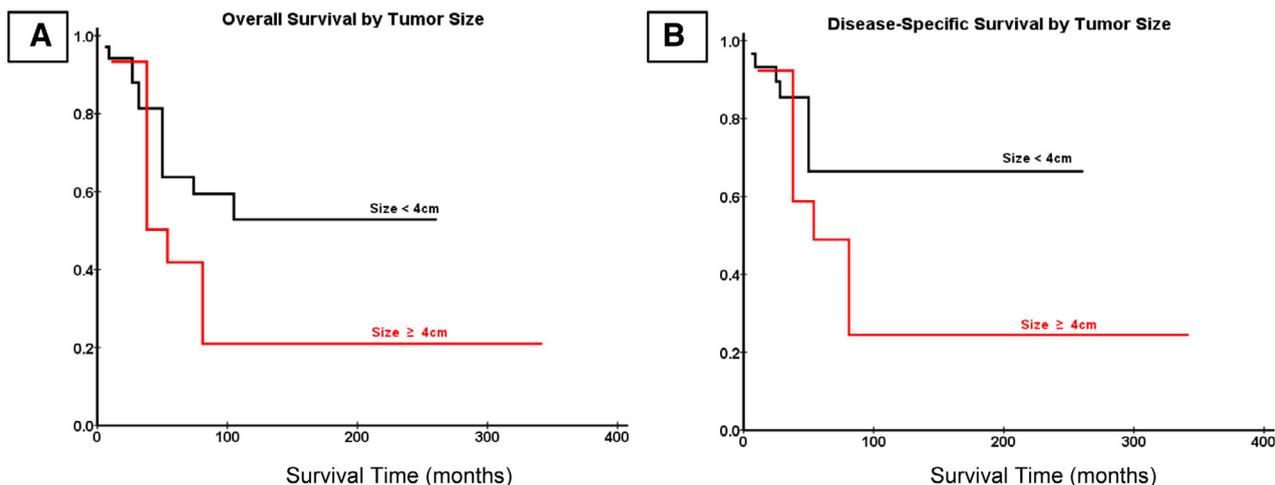


Figure 2. Kaplan Meier (A) overall and (B) disease-specific survival estimates of testicular mesothelioma based on critical tumor cutoff size of 4 cm. (Color version available online.)

In a case series of 15 patients, epithelioid type comprised 53% of cases, biphasic comprised 27% of cases, and 20% of cases were not specified.¹⁷ While small variations in the exact proportions of these histologies exist, our results are congruent with the current pattern in literature, where epithelioid has been established as having the highest prevalence.

One case series reported on the incidence of nodal involvement and metastatic disease, and found a higher incidence of node positive disease (33% compared to our 9.7%), but almost identical rates of metastatic disease (7% compared to our 6.2%).¹⁷ The incongruity in nodal involvement may be attributable to differences patient population. The case series was from patients at a tertiary care center where there may be more advanced disease, whereas the public database used in this study collects information from any participating facility across the nation. Our results should be more indicative of the real-world incidence of nodal and metastatic disease due to the population-based nature of the database. While our results did show lower rates of nodal involvement and metastatic disease than previously reported, the frequency is not insignificant and necessitates appropriate attention during the diagnostic process.

In the limited literature reporting on oncologic outcomes, these tumors are recognized as being particularly aggressive with dismal survival outcomes. A prior literature review reported a median survival of 23 months while another study reported a 53% 2-year survival, slightly lower than the 62% 2-year survival we identified.^{4,10} Our analysis revealed superior survival outcomes, which may be attributable to the larger sample size of our study, including patients cared for at both community-based and tertiary care settings.

Among tumor histologies, we determined that biphasic subtypes were significantly associated with poorer OS and DSS. The only other survival analysis of histologic subtype reported improved survival associated with

epithelioid subtypes and did not comment on biphasic subtypes.¹⁷ In concordance with the findings of our study and the case series, nonepithelioid subtypes are associated with worse prognosis among malignant pleural mesotheliomas and malignant parietal mesotheliomas.^{18,19} Our study found that high tumor stage was associated with worse OS and DSS, while the presence of nodal involvement and metastatic disease were associated with worse DSS. In congruence with the literature, a review of 73 cases of testicular mesothelioma identified metastatic disease to be significantly correlated with shorter survival times.⁴

The pattern of tumor size is one of the most relevant findings of our study. When treated as a continuous variable, unsurprisingly, larger tumor size was also associated with poorer OS and DSS. Notably, when stratified by size, tumors that were 4 cm or greater were significantly associated with worse OS and DSS. With this finding, we are the first to identify a critical size cutoff after which tumor size is associated with significantly worse oncologic outcomes.

In terms of treatment, almost all patients (98.2%) underwent surgical resection of the tumor, and only 5.3% were known to have received radiation therapy. While there was a trend of improved OS and DSS in patients who did not receive radiation, it is not possible to determine whether adjuvant therapy has an impact on outcomes given the small cohort. These findings are congruent with treatment of pleural mesothelioma, as there is no evidence of prolonged survival with radiation and its use is largely limited to palliation of symptoms.²⁰

There are several limitations to acknowledge in this study, including an inherent risk of bias with a retrospective observational study. Additionally, data on tumor grade was very limited and the use of chemotherapy and asbestos exposure history is not available in this database. Finally, due to the extreme rarity of this tumor and subsequent small sample size, we were not able to perform a

multivariable analysis. Nevertheless, this study is the first to analyze malignant mesothelioma of the testis on a population level, and to identify tumor characteristics significantly associated with poor survival outcomes. Given the paucity of data on this tumor, the information presented here on tumor characteristics and oncologic outcomes adds to the current literature in a meaningful way.

CONCLUSION

Testicular mesothelioma is an extremely rare malignancy with significant mortality. Increased age at diagnosis, biphasic histology, high tumor grade and stage, nodal involvement, and metastatic disease were all associated with poor survival. A critical cutoff for tumor size was identified, where tumors 4 cm or greater were associated with worse overall and DSS. Further study on this rare malignancy is warranted.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.01.009>.

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