# *Primary malignancies of the epididymis: clinical characteristics and prognostic factors*

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***Introduction:*** *We sought to describe clinical characteristics and identify prognostic factors among patients with primary malignancies of the epididymis (PMEs).*

***Materials and methods:*** *The Surveillance, Epidemiology, and End Results (SEER) database (1975-2015) was queried to identify patients with PME. Descriptive statistics and multivariable Cox proportional hazards models were used.*

***Results:*** *Eighty-nine patients with PME were identified. Median age was 57 years (5-85), and median overall survival (OS) was 16.8 years. The most commonly represented histologies were rhabdomyosarcoma (19.1%), B-cell lymphoma (16.9%), leiomyosarcoma (16.9%), and liposarcoma (12.4%). In multivariable analysis, tumor size ≥ 4 cm was associated with worse OS (HR = 4.46, p = 0.01) compared to tumors < 4 cm. Patients with nonsarcomatoid histology had OS similar to patients with sarcomatoid histology (HR = 0.95, p = 0.92). Disease with regional invasion (HR = 5.19, p = 0.007) and distant metastasis (HR = 29.80, p = 0.0002) had worse OS compared to localized disease. Receipt of radiotherapy was associated with enhanced OS (HR = 0.10, p = 0.006), whereas receipt of chemotherapy was not associated with OS.*

***Conclusions:*** *We describe the largest cohort of PMEs to date. Larger lesions and tumor stage were independently associated with poor overall survival, while receipt of radiotherapy was associated with enhanced overall survival.*

**Key Words:** epididymal, paratesticular, malignancy, spermatic, neoplasia

## Introduction

Prior to transport through the vas deferens, spermatozoa produced in the seminiferous tubules of the testis are stored in the epididymis. This structure overlies the testis and promotes spermatozoa maturation and acquisition of motility prior to ejaculation.[1] Despite their related physiologic function, the incidence of primary malignancy between the testes and epididymis varies considerably. While testicular cancer is the most common solid tumor in young adult males and accounts for 1% of all male cancers, primary epididymal tumors are exceedingly rare, accounting for only 0.03% of all male cancers.[2-4] Given its low incidence, previous studies are limited to case reports and case series.[5] The paucity of data available prevents adequate analysis of risk factors, prognosis, and treatment and management of this disease.

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Clinical management of primary malignancies of the epididymis (PMEs) is presently based on treatment of testicular and other para-testicular cancers. The current therapeutic approach requires transinguinal exploration with radical orchiectomy if intraoperative frozen section indicates malignancy. However, the clinical benefit of other surgical considerations including retroperitoneal lymphadenectomy, chemotherapy, and radiotherapy remain controversial.[6-8] Neither the American Urological Association (AUA) nor the European Association of Urology (EAU) have published clinical practice guidelines for primary epididymal cancer treatment, highlighting the need for high-quality data to guide clinical practice.

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute to analyze patients diagnosed with PMEs between 1973 and 2015. This dataset is the largest population-based, prospectively collected, cancer registry in the United States with a high level of case ascertainment and completeness of reporting.[9] We aim to identify demographic and oncologic characteristics, treatment outcomes, and risk factors associated with all-cause and cancer-specific mortality among patients with primary epididymal cancer.

## Materials and methods

### *Data source*

The National Cancer Institute's SEER program covers data from 18 population-based registries and represents approximately 28% of the population.[10] The SEER*Stat software (Version 8.3.6) case listing session was used to identify patients from the SEER 18 (November 2018 submission) database. This study was deemed exempt by our local institutional review board.

### *Cohort selection and variables*

Our primary cohort consisted of patients diagnosed between 1975 and 2015 with primary malignancies of the epididymis based on the International Classification of Disease for Oncology Version 3 (ICD-O-3) coding system: site code C63.0 (epididymis).

Covariates included in the analysis were age at diagnosis, race, relationship status, median family income, year of diagnosis, tumor histology, tumor size, tumor laterality, tumor stage, tumor grade, presence/absence of lymph node invasion, surgery, receipt of chemotherapy (yes/no), and receipt of radiotherapy (yes/no). Chemotherapy and radiotherapy variables are based on the receipt of chemotherapy or radiotherapy in a patient's first-course treatment.

### *Statistical analysis*

Patient and disease characteristics were analyzed using descriptive statistics, including proportions, median, and mean ± standard deviations. Categorical variables were analyzed by the $\chi 2$ test or Fisher's exact test as appropriate. Normally distributed continuous variables were analyzed by Student's t-test, while skewed continuous variables were analyzed by the Wilcoxon rank-sum test. The Cox proportional hazards model was used to identify factors associated with overall survival, while the Fine and Gray subdistribution hazards model for competing risks was used to identify factors associated with disease-specific survival.[12] In the latter analysis, non-cancer-related death was the competing event. For both models, univariate analyses were conducted, and covariates with $p < 0.20$ were included in the multivariable analysis.

All data were analyzed using R v3.5.3 (R Foundation for Statistical Computing), and extension packages including "survival" and "survminer" were used. The significance level for all statistical tests was set at 0.05, and all tests were two-sided.

## Results

Eighty-nine patients with PMEs were included in this study. Patient demographics, disease characteristics, and oncologic treatment history are summarized in Table 1. Patient age at diagnosis ± standard deviation was 50.55 ± 21.48 years. Most patients were white (86.5%), married (67.4%), and diagnosed after 2000 (60.7%). The distribution of median family income brackets was relatively equal: > $80,000 (32.6%), $65,000-$80,000 (32.6%), and < $65,000 (34.8%). Most tumors (n = 52, 58.4%) were sarcomas. The most commonly represented histologies were rhabdomyosarcoma (19.1%), B-cell lymphoma (16.9%), leiomyosarcoma (16.9%), and liposarcoma (12.4%). A complete description of the tumor histology for each patient is given in Table 2. Though the size of many tumors was unknown (43.8%), among tumors with known size, most were < 4 cm (29.2%). Additionally, most tumors were left-sided (57.3%), localized to the paratesticular region (50.6%), and without lymph node invasion (93.3%). Surgically, most patients received partial resection (57.3%). Finally, 15.7% of patients of patients received radiotherapy, while 38.2% of patients received chemotherapy.

Median overall survival was 16.8 years. Factors associated with overall survival are detailed in Table 3. In univariate analysis, age, relationship status, and tumor histology were significantly associated with

TABLE 1. **Overall cohort**

| **Characteristic** | | **n (%)** |
|---|---|---|
| Total | | 89 (100.0) |
| Age at diagnosis (mean (SD)) | | 50.55 (21.48) |
| Age at diagnosis (median (range)) | | 57 (5-85) |
| Age at diagnosis | < 45 | 32 (36.0) |
| | 45-65 | 29 (32.6) |
| | 66+ | 28 (31.5) |
| Race | White | 77 (86.5) |
| | Black | 6 (6.7) |
| | Other | 6 (6.7) |
| Relationship status | Married | 60 (67.4) |
| | Single | 23 (25.8) |
| | Other | 6 (6.7) |
| Median family income | > $80,000 | 29 (32.6) |
| | $65,000-$80,000 | 29 (32.6) |
| | < $65,000 | 31 (34.8) |
| Year of diagnosis | Pre-2000 | 35 (39.3) |
| | 2000 and onward | 54 (60.7) |
| Tumor histology | Rhabdomyosarcoma | 17 (19.1) |
| | B-cell lymphoma | 15 (16.9) |
| | Leiomyosarcoma | 15 (16.9) |
| | Liposarcoma | 11 (12.4) |
| | Other | 31 (34.8) |
| Tumor size | < 4 cm | 26 (29.2) |
| | ≥ 4 cm | 24 (27.0) |
| | Unknown | 39 (43.8) |
| Laterality | Left | 51 (57.3) |
| | Right | 38 (42.7) |
| Tumor stage | Localized | 45 (50.6) |
| | Regional invasion | 12 (13.5) |
| | Distant metastasis | 9 (10.1) |
| | Unknown | 23 (25.8) |
| Grade | Well differentiated; Grade I | 11 (12.4) |
| | Moderately differentiated; Grade II | 13 (14.6) |
| | Poorly differentiated; Grade III | 9 (10.1) |
| | Undifferentiated; anaplastic; Grade IV | 5 (5.6) |
| | Unknown | 51 (57.3) |
| Lymph node invasion | Node negative | 83 (93.3) |
| | Node positive | 6 (6.7) |
| Surgery | Partial surgery | 51 (57.3) |
| | Radical surgery | 17 (19.1) |
| | Surgery, NOS | 7 (7.9) |
| | Excisional biopsy | 13 (14.6) |
| | Unknown | 1 (1.1) |
| Received radiotherapy (yes) | | 14 (15.7) |
| Received chemotherapy (yes) | | 34 (38.2) |

TABLE 2. **Individual tumor histologies**

| Primary tumor histology | Count |
|---|---|
| Rhabdomyosarcoma, NOS | 3 |
| Mixed type rhabdomyosarcoma | 2 |
| Embryonal rhabdomyosarcoma | 9 |
| Spindle cell rhabdomyosarcoma | 1 |
| Alveolar rhabdomyosarcoma | 2 |
| Non-small cell carcinoma | 1 |
| Adenocarcinoma, NOS | 2 |
| Carcinoid tumor, NOS | 2 |
| Cystadenocarcinoma, NOS | 1 |
| Papillary serous cystadenocarcinoma | 1 |
| Sex cord-gonadal stromal tumor | 1 |
| Spindle cell sarcoma | 2 |
| Fibrosarcoma, NOS | 1 |
| Malignant fibrous histiocytoma | 3 |
| Liposarcoma, NOS | 2 |
| Liposarcoma, well differentiated | 7 |
| Mixed liposarcoma | 1 |
| Dedifferentiated liposarcoma | 1 |
| Leiomyosarcoma, NOS | 15 |
| Clear cell sarcoma, NOS | 1 |
| Mesothelioma, NOS | 4 |
| Epithelioid mesothelioma | 1 |
| Seminoma | 2 |
| Yolk sac tumor | 1 |
| Teratocarcinoma | 1 |
| Kaposi sarcoma | 1 |
| Malignant lymphoma, small B lymphocytic, NOS | 1 |
| Diffuse large B-cell lymphoma (DLBCL) | 11 |
| Follicular lymphoma, grade 1 | 1 |
| Follicular lymphoma, grade 2 | 1 |
| Marginal zone lymphoma of mucosa-associated lymphoid tissue | 1 |
| Chronic lymphocytic leukemia/ small lymphocytic lymphoma | 1 |
| Myeloid sarcoma | 1 |
| Papillary adenocarcinoma, NOS | 1 |
| Clear cell adenocarcinoma, NOS | 1 |
| Neoplasm, NOS | 2 |
| **Total** | **89** |

overall survival. In multivariable analysis, patients who were between 45 and 65 years old (HR = 14.10, 95% CI 3.12-63.69, p = 0.0005) and those who were over 65 (HR = 30.37, 95% CI 5.74-160.77, p < 0.0001) had worse overall survival compared to patients who were < 45 years old. Compared to married patients, unmarried patients had worse overall survival (HR = 4.42, 95% CI 1.37-14.33, p = 0.01). Tumor size of ≥ 4 cm was associated with worse overall survival (HR = 4.46, 95% CI 1.37-14.5, p = 0.013), compared to tumor size < 4 cm. Patients with regional invasion (HR = 5.19, 95% CI 1.57-17.17, p = 0.007) and distant metastasis (HR = 29.80, 95% CI 4.87-182.45, p = 0.0002) had worse overall survival compared to patients with disease localized to the paratesticular region. Finally, receipt of radiotherapy was associated with enhanced overall survival (HR = 0.10, 95% CI 0.02-0.52, p = 0.006).

Factors associated with cancer-specific mortality, identified via competing-risk subdistribution hazard analysis, are detailed in Table 4. Univariate analysis revealed age between 45 and 65 to be associated with cancer-specific mortality (HR = 4.84, 95% CI 1.05-22.31, p = 0.043), though the magnitude of this association was reduced upon multivariate analysis (HR = 4.16, 95% CI 0.84-20.65, p = 0.081). There was a trend for tumor size ≥ 4cm in univariate analysis (HR = 6.07, 95% CI 0.7-50.8, p = 0.096), though this was lost upon multivariate adjustment. No other covariates were associated with cancer-specific mortality.

## Discussion

Primary tumors of the epididymis are rare paratesticular malignancies, and the current literature is limited to isolated case reports and small, single-institution series. Therefore, there are currently no widely accepted or standardized treatment protocols, and the clinicopathological features, prognostic factors, and outcomes of this entity remain unknown. The present study is the first to describe population-level data on demographics, clinical characteristics, and oncologic outcomes, and to identify prognostic factors associated with overall and disease-specific survival among patients with these rare malignancies.

We found that the majority of PMEs were histologically sarcomas, and the most commonly represented subtypes were all soft tissue sarcomas: rhabdomyosarcoma (19.1%), leiomyosarcoma (16.9%), and liposarcoma (12.4%). This distribution is consistent with what has been previously reported.[2,14-16] Additionally, our finding of 4 PMEs that were histologically germ cell tumors (2 seminoma, 1 yolk sac tumor, and 1 teratocarcinoma) tumors is, while

TABLE 3. **Factors associated with all-cause mortality: univariable and multivariable Cox proportional hazards analysis**

| Characteristic | | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | **HR (95% CI)** | **p value** | **HR (95% CI)** | **p value** |
| Age at diagnosis | < 45 | Ref | | Ref | |
| | 45-65 | 6.86 (1.93-24.35) | 0.003 | 14.10 (3.12-63.69) | 0.0005 |
| | 66+ | 7.96 (2.33-27.21) | 0.001 | 30.37 (5.74-160.77) | < 0.0001 |
| Race | White | Ref | | | |
| | Nonwhite | 0.54 (0.13-2.27) | 0.400 | | |
| Relationship status | Married | Ref | | Ref | |
| | Unmarried | 0.38 (0.16-0.87) | 0.023 | 4.42 (1.37-14.33) | 0.013 |
| Median family income | > $80,000 | Ref | | | |
| | $65,000-$80,000 | 1.32 (0.55-3.16) | 0.528 | | |
| | < $65,000 | 1.53 (0.64-3.67) | 0.340 | | |
| Year of diagnosis | Pre-2000 | Ref | | | |
| | 2000 and onward | 0.61 (0.28-1.35) | 0.224 | | |
| Tumor histology | Sarcomatoid | Ref | | Ref | |
| | Nonsarcomatoid | 3.09 (1.51-6.33) | 0.002 | 0.95 (0.35-2.57) | 0.92 |
| Tumor size | < 4 cm | Ref | | Ref | |
| | ≥ 4 cm | 2.12 (0.77-5.85) | 0.146 | 4.46 (1.37-14.5) | 0.013 |
| Laterality | Left | Ref | | | |
| | Right | 1.16 (0.57-2.37) | 0.676 | | |
| Tumor stage | Localized | Ref | | Ref | |
| | Regional invasion | 1.87 (0.71-4.92) | 0.206 | 5.19 (1.57-17.17) | 0.007 |
| | Distant metastasis | 2.17 (0.7-6.67) | 0.178 | 29.80 (4.87-182.45) | 0.0002 |
| Grade | Well differentiated; Grade I | Ref | | | |
| | Moderately differentiated; Grade II | 2.9 (0.54-15.52) | 0.214 | | |
| | Poorly differentiated; Grade III | 2.25 (0.41-12.33) | 0.349 | | |
| | Undifferentiated; anaplastic; Grade IV | 1.73 (0.15-19.73) | 0.657 | | |
| Lymph node invasion | Node negative | Ref | | | |
| | Node positive | 0.44 (0.06-3.24) | 0.421 | | |
| Surgery | Partial surgery | Ref | | | |
| | Radical surgery | 1.28 (0.5-3.26) | 0.605 | | |
| | Surgery, NOS | 1.06 (0.35-3.23) | 0.917 | | |
| | Excisional biopsy | 0.85 (0.29-2.51) | 0.766 | | |
| Received radiotherapy | No | Ref | | Ref | |
| | Yes | 0.29 (0.07-1.21) | 0.089 | 0.10 (0.02-0.52) | 0.006 |
| Received chemotherapy | No | Ref | | Ref | |
| | Yes | 0.59 (0.27-1.28) | 0.182 | 0.49 (0.17-1.45) | 0.20 |

variables with $p < 0.20$ in univariate analysis were included in the multivariable model

TABLE 4. **Factors associated with cancer-specific morality: univariable and multivariable competing risks subdistribution hazards model**

| Characteristic | | Univariable | | Multivariable | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p value | HR (95% CI) | p value |
| Age at diagnosis | < 45 | Ref | | Ref | |
| | 45-65 | 4.84 (1.05-22.31) | 0.043 | 4.16 (0.84-20.65) | 0.081 |
| | 66+ | 0.53 (0.05-5.94) | 0.600 | 0.55 (0.04-8.19) | 0.67 |
| Race | White | Ref | | | |
| | Nonwhite | 0.8 (0.11-5.94) | 0.830 | | |
| Relationship status | Married | Ref | | | |
| | Unmarried | 0.59 (0.16-2.2) | 0.430 | | |
| Median family income | > $80,000 | Ref | | | |
| | $65,000-$80,000 | 2.18 (0.54-8.8) | 0.270 | | |
| | < $65,000 | 0.67 (0.11-3.9) | 0.650 | | |
| Year of diagnosis | Pre-2000 | Ref | | | |
| | 2000 and onward | 0.57 (0.18-1.85) | 0.350 | | |
| Tumor histology | Sarcomatoid | Ref | | | |
| | Nonsarcomatoid | 2.03 (0.63-6.49) | 0.23 | | |
| Tumor size | < 4 cm | Ref | | Ref | |
| | ≥ 4 cm | 6.07 (0.73-50.8) | 0.096 | 3.73 (0.33-42.52) | 0.29 |
| Laterality | Left | Ref | | | |
| | Right | 1.82 (0.57-5.89) | 0.310 | | |
| Tumor stage | Localized | Ref | | Ref | |
| | Regional invasion | 3.1 (0.72-13.36) | 0.130 | 2.19 (0.35-13.76) | 0.4 |
| | Distant metastasis | 1.45 (0.17-12.68) | 0.740 | 1.2 (0.16-9.12) | 0.86 |
| Lymph node invasion | Node negative | Ref | | | |
| | Node positive | 1.67 (0.23-11.9) | 0.610 | | |
| Surgery | Partial surgery | Ref | | | |
| | Radical surgery | 2.11 (0.52-8.61) | 0.300 | | |
| | Surgery, NOS | 2.46 (0.5-12.21) | 0.270 | | |
| | Excisional biopsy | 0.76 (0.09-6.34) | 0.800 | | |
| Received radiotherapy | No | Ref | | | |
| | Yes | 0.54 (0.07-4.43) | 0.570 | | |
| Received chemotherapy | No | Ref | | | |
| | Yes | 0.62 (0.16-2.37) | 0.480 | | |

variables with $p < 0.20$ in univariate analysis were included in the multivariable model

surprising, consistent with prior reports of primary epididymal germ cell tumors, which are thought to arise from embryonic migration of testicular tissue into the epididymis.[17,18] In univariate analysis, we found that nonsarcomatoid histology was associated with increased risk of all-cause mortality, though this association was lost upon multivariate adjustment. Given the paucity of other studies examining prognostic factors in PMEs, it is difficult to identify specific mechanisms that may underlie this observation. However, population-based studies have identified that 40% to 50% of patients with soft tissue sarcomas initially present with metastatic or locally advanced disease, a rate that is much higher than patients with carcinoma.[19,20] Similarly, there is evidence that patients with soft tissue sarcomas present with tumors that are approximately five-fold larger in size than the average carcinoma.[21] These epidemiologic

findings among patients with soft tissue sarcomas are consistent with our multivariable hazards regression analysis for overall survival. Indeed, after adjusting for stage at presentation and tumor size, we found that the univariate association with histology vanished, while patients with regional/distant disease and tumors at least 4 cm in size were found to have increased risk of all-cause mortality.

In a competing risk-adjusted multivariable analysis for factors associated with cancer-specific mortality, the only association found was a trend toward increased risk among patients between 45 and 65 years of age, with no increased risk among patients age 66 and over. Interestingly, similar results were found in a SEER study of patients with primary spermatic cord tumors – another rare, paratesticular tumor.[22] Here, Rodriguez et al report average 5-year disease-specific survival of 78% among patients between 40 and 59 years of age, while patients between 60 and 79 years of age achieved a superior 5-year disease-specific survival rate of 82%.[22] It is not clear why this younger, middle-aged group of patients may experience slightly increased cancer-specific mortality; however, older patients are more likely to die of other, non-cancer causes, potentially driving a slightly higher disease-specific survival rate. Though our analysis was adjusted for the competing risk of non-cancer-related death, this phenomenon may drive the trend toward increased risk of cancer-specific mortality among patients aged between 45 and 65 years.

The treatment of PMEs is based upon the treatment of other paratesticular lesions, and primarily involves surgical resection. Studies have found simple excision is inadequate, leading to residual microscopic disease in roughly one third of patients.[23,24] It is relatively well-established that optimal resection involves radical inguinal orchiectomy with high ligation of the spermatic cord.[25] However, the role of adjuvant therapy, including retroperitoneal lymph node dissection (RPLND), radiotherapy, and chemotherapy, remains poorly understood. In the present study, we found that radiotherapy conferred a significantly reduced risk of all-cause mortality in multivariate analysis. These results are consistent with outcomes reported in small, single-institution case series of adjuvant radiotherapy among patients with paratesticular sarcoma.[23,27,28] Catton et al reported 100% local disease control among six patients treated with adjuvant groin radiation, and Ballo et al similarly reported no disease recurrence in three patients treated with adjuvant radiotherapy.[23,27] These prior reports are limited by their cohort size. To this end, our study is an important first contribution of population-level data suggesting the efficacy of radiotherapy among patients with PMEs and paratesticular tumors.

This study should be considered in the context of its limitations. First, an inherent limitation in the study of PMEs is the rarity of the disease. We used a national cancer registry to amass the largest cohort of patients with PMEs thus far. Despite this, our cohort only contained 89 patients and our statistical analyses are accordingly limited in power. Second, a study using SEER data is subject to limitations that are common to all studies of large datasets. These include missing data and lack of granularity for certain variables. In particular, the radiotherapy variable fails to convey the specific administered dose/regimen. Finally, SEER data only captures first-line treatment and demographic information. In particular, though most PME patients were coded as having undergone partial surgery, it is possible these patients ultimately received radical surgery as part of their extended therapy. In a similar vein, it is possible that certain demographic covariates (e.g. relationship status) may change over the course of a patient's disease, representing a shift that SEER would not ascertain.

## Conclusion

In conclusion, we used a national database to describe the largest cohort of patients with primary malignancies of the epididymis thus far. We detailed patient demography, clinical characteristics, and disease outcomes, and identified prognostic factors associated with all-cause mortality and cancer-specific mortality. Future studies examining larger, potentially multinational cohorts of patients with PMEs and other paratesticular malignancies are warranted to inform evidence-based management of this patient population. □

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