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ORIGINAL ARTICLE

Scrotal cancer survival is influenced by histology: a SEER study

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Abstract
Introduction Due to the scrotum's multiple layers of different tissues, scrotal cancer can present with several unique histologies. Historically, outcome arising from these different sources has been historically aggregated together. However, it remains unclear whether survival differs by histology of scrotal cancer.
Methods We queried the seventeen registries of the Surveillance, Epidemiology, and End Results database for patients diagnosed with primary scrotal cancer from 1973 to 2006. Patients were initially grouped by the following histologies: basal cell carcinoma, Extramammary Paget's Disease (EMPD), sarcoma, melanoma, squamous cell carcinoma, and adnexal skin tumors. For some analyses, the former three histologies were reclassified as Low-Risk scrotal cancer and the latter three histologies as High-Risk scrotal cancer. Kaplan–Meier survival analyses were conducted to assess the impact of histology on overall survival (OS).
Results The cohort consisted of 766 patients. Median (95% CI) OSs by histologies were basal cell carcinoma—143 (116–180), EMPD—165 (139–190), sarcoma—180 (141–219), melanoma—136 (70–203), squamous cell carcinoma—115 (97–133), and adnexal skin tumors—114 (55–174). Patients with Low-Risk scrotal cancer experienced a median (95% CI) OS of 166 (145–188) months, while patients with High-Risk scrotal cancer experienced a median (95% CI) OS of 118 (101–135) months.
Conclusions Survival of scrotal cancer depends on tumor histology. Classification of histologies into Low and High Risk can be clinically useful for counseling and clinical decisions.

Keywords Scrotal cancer · SEER program · Histology · Squamous cell carcinoma · Basal cell carcinoma · Extramammary Paget's Disease · Melanoma · Sarcoma

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Introduction

First identified by Sir Percival Pott among chimneysweeps, scrotal cancer's low incidence in the modern era can be attributed to the mitigation of causative occupational exposures [1–4]. However, these efforts have increased the difficulty in studying this virulent malignancy. Modern studies have been limited in sample size to case reports or small studies involving at most a few dozen patients [5–7]. Certain facets of scrotal cancer remain unstudied. Particularly, anatomy remains neglected in the discussion of scrotal cancer. The scrotum consists of multiple histological layers, including skin, fascia, and muscle, yielding several unique histologies: Extramammary Paget's Disease (EMPD), squamous cell carcinoma, basal cell carcinoma, and sarcoma [5, 8–10].

Wright et al. [11] used the Surveillance, Epidemiology, and End Results (SEER) database to coalesce a large cohort of 500 scrotal cancer patients diagnosed from 1973 to 2002. This study identified the histological frequency of scrotal cancer and the impact of stage on survival, but did not fully explore differences in survival by histology. Consequently,

we sought to extend this work by assessing the impact of scrotal cancer histology on survival with the advantage of additional 4 years of reporting by the SEER registry.

Methods

Patient population

We queried the SEER database's 17 registries for scrotal cancer patients meeting our inclusion criteria: (1) primary scrotal cancer (International Statistical Classifications of Diseases for Oncology, 3rd ed., scrotal site code C63.2), (2) known stage and histological type at presentation, (3) microscopically confirmed disease, and (4) diagnosis between 1973 and 2006 [12]. We excluded 36 patients with Kaposi's carcinoma, 4 with mesothelioma, and 15 with histology NOS. Cases ascertained based on death certificates or autopsies were excluded.

Variables

The following variables were extracted (Table 1): year of diagnosis, age, race, stage, and histology. Consistent with Wright et al. [11], stage was coded as localized, regional, and distant based on the SEER Historic Stage A. Patients were grouped histologically using the following ICD-03 groupings: squamous cell carcinoma (8051-8083, 8094), basal cell carcinoma (8090-8093, 8097, 8123, 8147), adnexal skin tumors (8200-8481), EMPD (8542), melanoma (8720-8772), and sarcoma (8800-8910, 9120, 9560). Based on Kaplan–Meier curves, histologies were classified into Low Risk (basal cell carcinoma, EMPD, and sarcoma) and High Risk (squamous cell carcinoma, melanoma, and adnexal skin tumors). Grade was initially collected, but was not reported due to the large amount of missing data. Follow-up was available through the end of 2006.

Statistical analysis

Frequency analysis and descriptive statistics were performed. Kaplan–Meier survival analyses assessed the impact of histology on overall survival (OS). Initial analyses assessed survival across all stages of disease. Based on clustering of survival curves, histologies were classified as Low Risk (high survival) or High Risk (low survival). Subsequent Kaplan–Meier analysis was conducted to compare survival of Low- and High-Risk groups. Additional Kaplan–Meier analyses assessed survival among patients diagnosed with one primary tumor only and survival across individual stages of disease. Mantel-Cox log-rank tests assessed statistical difference in curves. Multivariate Cox regression analyzed predictors of OS. All variables in the model were tested for proportional hazard assumptions, and all models were tested for the presence of interactions. Statistical significance in this study was set at $p < 0.05$. All analyses were performed using SPSS version 19.0.

Table 1 Patient demographics

Characteristic	Histology					
	Squamous cell carcinoma	Basal cell carcinoma	Melanoma	Sarcoma	EMPD	Adnexal skin tumor
Age (mean ± SD)	65.4 ± 14.9	70.6 ± 11.6	56.2 ± 18.3	61.0 ± 18.9	70.5 ± 9.1	67.5 ± 10.9
Race						
White	206 (76.6%)	107 (83.6%)	19 (76.0%)	136 (87.2%)	91 (54.2%)	12 (60.0%)
Black	43 (16.0%)	4 (3.1%)	0 (0%)	9 (5.8%)	0 (0%)	1 (5.0%)
Asian	12 (4.5%)	10 (7.8%)	5 (20.0%	10 (6.4%)	71 (42.3%)	6 (30.0%)
Other or unknown	8 (3.0%)	7 (5.5%)	1 (4.0%)	1 (0.6%)	6 (3.6%)	1 (5.0%)
Hispanic ethnicity						
Hispanic	18 (6.7%)	10 (7.8%)	0 (0%)	19 (12.2%)	3 (1.8%)	1 (5.0%)
Stage						
Localized	205 (76.2%)	122 (95.3%)	18 (72.0%)	122 (78.2%)	134 (79.8%)	12 (60.0%)
Regional	54 (20.1%)	6 (4.7%)	7 (28.0%)	29 (18.6%)	32 19.0%)	6 (30.0%)
Distant	10 (3.7%)	0 (0%)	0 (0%)	5 (3.2%)	2 (1.2%)	2 (10.0%)
Tumor sequence number						
One primary only	176 (65.4%)	76 (59.4%)	14 (56.0%)	106 (67.9%)	94 (56.0%)	12 (80.0%)
First of multiple tumors	41 (15.2%)	21 (16.4%)	4 (16.0%)	27 (17.3%)	32 (19.0%)	2 (10.0%)
Second of multiple tumors	39 (14.5%)	25 (19.5%)	6 (24.0%)	20 (12.8%)	36 (21.4%)	2 (10.0%)
Other	13 (4.9%)	6 (4.7%)	1 (4.0%)	3 (1.9%)	6 (3.6%)	0 (0%)

Results

Patient characteristics

The cohort consisted of 766 patients diagnosed with primary scrotal cancer from 1973 to 2006 (Table 1). Mean (SD) age was 66.4 (14.9) years. Of the cohort, 74.6% were white and 80.0% had localized disease. More than one-third of patients presented with squamous cell carcinoma (35.1%). Other patients presented with EMPD (21.9%), sarcoma (20.4%), basal cell carcinoma (16.7%), melanoma (3.3%), and adnexal skin tumors (2.6%). Finally, 482 patients developed scrotal cancer only. Scrotal cancer represented one of multiple malignancies for the remaining 284 patients.

Survival analysis by histology

Kaplan–Meier analysis assessed OS by histology (Fig. 1). Patients with basal cell carcinoma, EMPD, and sarcoma experienced higher OS, with median (95% CI) survival of 143 (116–180), 165 (139–190), and 180 (141–219) months, respectively. Patients with melanoma, squamous cell carcinoma, and adnexal skin tumors experienced the lowest OS, with median (95% CI) survivals of 136 (70–203), 115 (97–133), and 114 (55–174) months, respectively.

In additional analysis, the 482 patients who developed only scrotal cancer were isolated. Among this cohort, similar Kaplan–Meier analysis was conducted to assess the impact of histology on OS among patients diagnosed only with scrotal cancer (Fig. 2). In this smaller cohort, basal cell carcinoma, EMPD, and sarcoma tumors were again associated with higher OS.

Histology survival by disease stage

Further analyses assessed the impact of stage of disease on survival by histology. Table 2 demonstrates OS among patients with localized, regional, and distant disease while controlling for other variables. In multivariate analysis, stage predicted OS of scrotal cancer. Compared to patients with localized disease, patients with regional (HR: 1.896, 95% CI: 1.441–2.496) and distant (HR: 6.695, 95% CI: 3.958–11.326) disease experienced significantly higher overall mortality.

Kaplan–Meier analysis also was produced for patients diagnosed with localized and regional disease (data not shown). Relative survival for most histologies did not differ by disease stage. Among patients with both localized and regional disease, patients with EMPD and sarcoma experienced the highest survival, while patients with squamous cell carcinoma and melanoma experienced the lowest survival. Survival among adnexal skin tumors and basal cell carcinomas was more heterogeneous. Overall, adnexal skin tumor histology conferred relatively lower survival (Table 1). However, patients diagnosed with localized adnexal skin tumors experienced relatively high

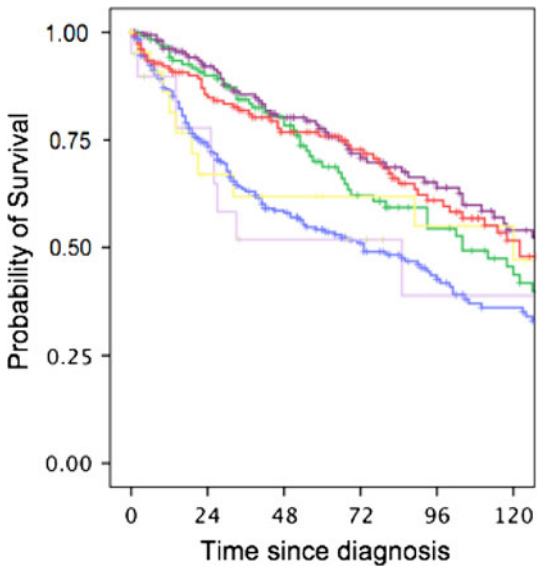

Fig. 1 Kaplan–Meier curves of overall survival for patients with scrotal cancer stratified by histology: sarcoma—*red* (156 patients), melanoma—*yellow* (25 patients), squamous cell carcinoma—*blue* (269 patients), Extramammary Paget's disease—*purple* (168 patients), adnexal skin tumors—*lavender* (20 patients), basal cell carcinoma—*green* (128 patients). This analysis included all patients, regardless of tumor sequence

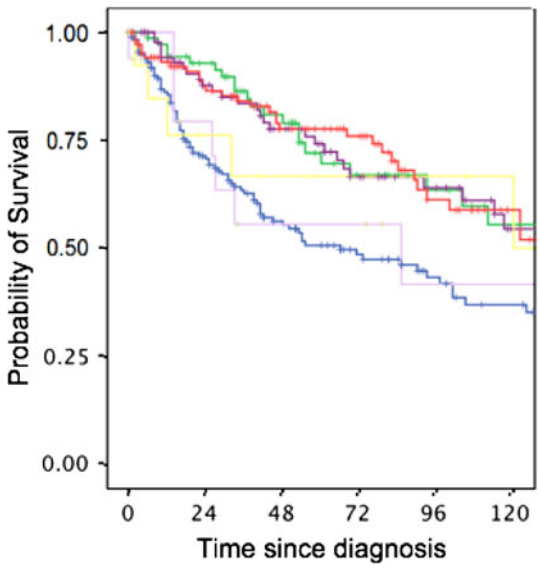

Fig. 2 Kaplan–Meier analysis of overall survival for patients diagnosed only with scrotal cancer stratified by histology. This analysis excluded patients diagnosed with a second malignancy other than scrotal cancer: sarcoma—*red* (106 patients), melanoma—*yellow* (14 patients), squamous cell carcinoma—*blue* (176 patients), Extramammary Paget's disease—*purple* (94 patients), adnexal skin tumors—*lavender* (16 patients), basal cell carcinoma—*green* (76 patients)

Table 2 Cox regression analysis of overall survival

Variable	Crude OR	95% CI	Adjusted OR*	95% CI
Age	1.064	1.054–1.075	1.069	1.058–1.080
Year of diagnosis	0.992	0.979–1.005	0.990	0.976–1.004
Race				
White	Reference		Reference	
Black	1.173	0.794–1.733	1.638	1.088–2.467
Asian	0.897	0.662–1.215	1.978	0.751–1.552
Other	0.514	0.072–3.668	0.792	0.108–5.779
Tumor sequence				
One primary only	Reference		Reference	
First of multiple tumors	0.867	0.661–1.137	0.827	0.624–1.097
Second of multiple tumors	1.551	1.188–2.025	1.097	0.827–1.456
Other	1.738	1.043–2.894	1.282	0.760–2.162
Stage				
Localized	Reference		Reference	
Regional	1.838	1.415–2.388	1.896	1.441–2.496
Distant	5.559	3.462–8.926	6.695	3.958–11.326
Histology				
Squamous cell carcinoma	Reference		Reference	
Basal cell carcinoma	0.009	0.491–0.903	0.590	0.432–0.807
Adnexal tumors	0.954	0.502–1.811	0.869	0.452–1.671
EMPD	0.513	0.379–0.693	0.409	0.289–0.578
Melanoma	0.802	0.453–1.418	1.269	0.704–2.285
Sarcoma	0.585	0.433–0.789	0.528	0.389–0.717

survival, similar to that of EMPD, sarcoma, and basal cell carcinoma. Conversely, overall basal cell carcinoma conferred relatively higher survival. However, patients diagnosed with regional basal cell carcinoma experienced relatively low survival, similar to that of squamous cell carcinoma, melanoma, and adnexal skin tumors. It should be noted that the small number of patients with distant disease precluded independent analysis of this subset of patients.

Low- and high-risk histologies

Kaplan–Meier curves of all stages of disease demonstrated clustering of OS different histologies into two broad groups (Fig. 1). These findings correlate with results of multivariate analysis (Table 2). Based on this clustering, patients were placed into two survival groups: Low Risk (sarcoma, EMPD, and basal cell carcinoma) and High Risk (melanoma, squamous cell carcinoma, and adnexal skin tumors). Kaplan–Meier analysis assessed the difference in OS by risk category (Fig. 3). Patients with Low-Risk and High-Risk scrotal cancer experienced a median (95% CI) OS of 166 (145–188) and 118 (101–135) months, respectively, a statistically significant difference (log-rank, $p < 0.001$).

Discussion

Scrotal cancer survival depends on histology

Scrotal cancer is often considered a single neoplasm; however, the scrotum consists of multiple types of tissue. Just as the breast consists of fat, muscle, blood vessels, ducts, and lobules, the scrotum consists of multiple layers, including skin, fascia, and muscle. This study demonstrates that patient survival depends on the histology of disease, derived from separate components of the scrotum. For example, a patient diagnosed with basal cell carcinoma survives 29 months longer than patients diagnosed with adnexal skin tumors (Fig. 1). This survival difference did not depend on the presence of other malignancies (Fig. 2).

Many of these histologies are associated with multiple primary malignancies. For example, basal cell carcinoma and melanoma can present as multiple primary tumors. Additionally, EMPD can serve as a harbinger for other primary malignancies, such gastrointestinal tumors. Consequently, this dramatic heterogeneity in survival based on histology reflects a shift in the conception of scrotal cancer. Scrotal cancer should be considered a composite of

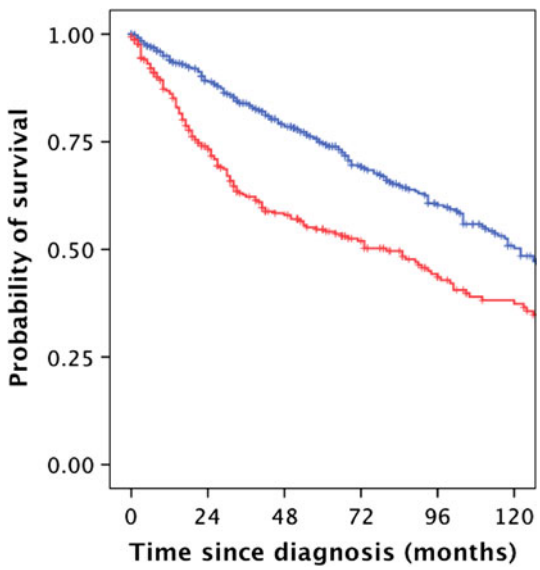

Fig. 3 Kaplan–Meier analysis of 5-year overall survival for patients with scrotal cancer stratified by histology into two prognostic tiers: Low-Risk (sarcoma, EMPD, and basal cell carcinoma) and High-Risk scrotal cancer (melanoma, squamous cell carcinoma, and adnexal skin tumors). Low-Risk scrotal cancer is presented in *blue*, and High-Risk scrotal cancer is in *red*. Log-rank $p < 0.001$

separate and unique diseases that arise from unique components of the scrotum.

Survival-based dichotomy of scrotal cancer histology

Scrotal cancer should no longer be considered a homogenous disease in terms of outcome prognostication, which is often conveyed to patients by many oncologists in our anecdotal experience. Not all histological types share the same prognosis. Many scrotal cancer histologies do share similar prognoses (Table 2). Specifically, patients diagnosed with sarcoma, EMPD, and basal cell carcinoma share similar median OS of 143–180 months, while patients diagnosed with melanoma, squamous cell carcinoma, and adnexal skin tumors share a median OS of 114–136 months (Fig. 3).

This natural dichotomization seen in Kaplan–Meier analysis (Figs. 1 2) and multivariate Cox regression analysis (Table 2) lends itself to subclassification into lower-risk and higher-risk scrotal cancer, termed here Low Risk and High Risk, respectively. When combined, patients with Low-Risk scrotal cancer experience significantly higher OS compared to High-Risk scrotal cancer (log-rank, $p < 0.001$) (Fig. 3). For the most part, this dichotomy also persisted among patients diagnosed with localized and regional disease. This classification may be helpful for clinicians when counseling patients.

Future investigations

Though each histological subtype of scrotal cancer may behave differently, sorting them by prognosis may be clinically helpful. This representation of lower-risk versus higher-risk scrotal cancer may better facilitate counseling and clinical decisions. Nonetheless, further studies are needed to better understand the unique behaviors of the histological subtypes of scrotal cancer. Specifically, do these subtypes respond to treatment modalities differently? Additionally, demographics such as race and ethnicity differ across these histologies. However, analysis of these differences extends beyond the scope of this study. Further analyses might investigate whether similar socio-demographical variables contribute to these different outcomes. As the SEER database and other databases continue to expand, larger sample sizes should help elucidate clinically meaningful classifications of scrotal cancer as a clinical trial is clearly unlikely with such a rare disease.

Study limitations

There are several limitations inherent to the type of study we have conducted. SEER captures approximately 26% of the population, but we have not studied the entire US population [12]. Additionally, as noted by Wright et al. [11], misclassification or missing data points, though rare, may bias the SEER database. Finally, the retrospective nature of this study precluded further analysis of differences in etiology or likelihood of metastasis by histology. Prospective longitudinal studies or cross-sectional histopathological analyses might better assess whether subtypes also differ with respect to other outcome measures, such as metastasis and morbidity.

Conclusions

Scrotal cancer is a heterogeneous neoplasm, with variable survival based on tumor histology. Though appearing to arise from the same anatomical site, this disease can exhibit diverse histology. Depending on the patient's histological subtype, median survival can range from 114 to 180 months. Clinically, scrotal cancers can be subclassified by histology into lower-risk or higher-risk disease. Prospective and histopathological studies are needed to further elucidate the prognostic ramifications of the histological subtypes of scrotal cancer.

Conflict of interest The authors declare that they have no conflict of interest.

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