RURAL, REMOTE AND REGIONAL SURGERY

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Current trends in penile cancer survivorship amongst remote patients and Aboriginal people in Western Australia

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Abstract

Background: Penile cancer is a rare urological malignancy, accounting for less than 1% of all cancers in males. Given its rarity, few studies exist reporting survival outcomes. The primary objective of this project was to review the mortality of patients diagnosed with penile cancer in Western Australia between 1992 and 2017 and to determine if Aboriginal and Torres Strait Islander people and patients in rural and remote regions experience discrepancies in survival outcomes.

Methods: All cases of penile cancer recorded within the Western Australia Cancer Registry between 1992 and 2017 were reviewed. Analysis was performed using chi-squared test of association, binomial logistic regression and survival analysis was conducted using Kaplan Meier and Cox Regression analysis.

Results: One hundred eighty-six cases of penile cancer were identified; 62 patients (33%) were from regional or remote locations and nine patients (4.8%) were Aboriginal. 13 of the regional or remote patients and 5 of the Aboriginal patients died from penile cancer. Patients who were Aboriginal (HR 6.512, CI 2.123–19.968; $P = 0.001$) or from regional or remote Western Australia (HR 2.382, CI 1.050–5.401; $P = 0.038$) were at an increased risk of penile cancer-specific mortality.

Conclusions: Aboriginal people with penile cancer and men from regional and remote Western Australia experience worse penile cancer-specific survival outcomes.

Introduction

Penile cancer is a particularly rare urological malignancy, accounting for less than 1% of all cancers in males and possessing a worldwide incidence of ~26 000 cases annually.[1] Penile cancer is particularly uncommon in developed countries, contributing to only 0.2% of all male malignancies in the USA.[1] Penile cancer is however responsible for up to 10–20% of all male cancers in particular

regions of Africa, Asia and South America.[2–4] With an age-standardized incidence of 6.15 per 100 000 man years and a crude annual incidence of **1.18** per 100 000, the state of Maranhão has the highest incidence of penile cancer in Brazil and highest recorded incidence globally.[5] In Australia, the age-standardized incidence of penile cancer is **0.8** per 100 000 man years, compared with **1.44** in the United Kingdom and **0.66** in the USA.[6]

Penile cancer is most commonly diagnosed in men aged 50 to 70 years with the most common site of occurrence being the glans penis (48%) followed by the prepuce (21%), glans and prepuce (9%), coronal sulcus (6%) and shaft (<2%).[2,7,8] Known risk factors for penile cancer include phimosis and human papillomavirus (HPV) infection.[6,9] Although the reported prevalence of HPV in penile cancer is highly variable, ~40% of penile cancers can be attributed to HPV, with genotypes 16 and 18 the most commonly detected.[10,11] Tobacco smoking, low socioeconomic status and inflammatory conditions including lichen sclerosus have also shown an association with an increased risk of developing penile cancer.[6,9,12]

Penile cancer is rare in males who underwent pre-pubertal circumcision.[12] A systematic review and meta-analysis performed in 2011 found circumcision prevented invasive penile cancer if performed prior to 18 years of age (OR = 0.33, 95% CI 0.13–0.83).[13] The protective benefits of circumcision were however lost when boys with no history of phimosis were excluded, with the benefits of circumcision likely secondary to the prevention of phimosis.[13,14]

Given its rarity, few comprehensive studies exist documenting long-term trends in penile cancer mortality, however, lymph node involvement has been shown as the most significant prognostic factor for determining overall survival.[15–18] Progression of lymph node involvement has been demonstrated to reduce 5-year cancer-specific survival (CSS) with pN0 CSS at 85–100%, pN1 at 79–89%, pN2 at 17–60% and pN3 at 0–17%.[3]

The primary objective of the following project was to review the survivorship of penile cancer patients within an Australian context. Specifically, the survival of patients diagnosed with penile cancer in Western Australia between 1992 and 2017 was explored. Secondary objectives were to specifically review the survival outcomes of penile cancer patients diagnosed from rural and remote regions and to determine whether Aboriginal people experience discrepancies in survival outcomes. Differences in survival outcomes of penile cancer patients living in rural or remote locations and Aboriginal people has not, to the authors knowledge, been published within the literature.

Ethics

Ethical approval was granted by the Western Australian Department of Health (Approval number: RGS0000000729) and the Western Australian Aboriginal Health Ethics Committee (Approval number: 941).

Methods

We performed a comprehensive, retrospective review of prospectively documented cases of penile cancer as recorded within the Western Australia Cancer Registry (WACR) between 1992 and 2017. Data from 2018 and 2019 was not available at time of request. Patient characteristics, Aboriginal status, demographic location, and recordable disease characteristics were reviewed and analysed. Statistical analysis was performed using SPSS version 26 and included chi-squared test of association, binomial logistic regression and survival analysis utilizing Cox Regression analysis and Kaplan Meier survival curves. An alpha value of 0.05 was used for all statistical tests.

Results

Patient demographics and disease characteristics

One hundred eighty-six cases of invasive penile cancer were recorded in the Western Australia Cancer Registry between 1992 and 2017. The maximum number of diagnoses in a single year was 15 in 2012. Figure 1 represents the number of diagnoses and penile cancer deaths in each individual year. Figure 2 represents the correlation between the year of diagnosis and number of cases diagnosed each year.

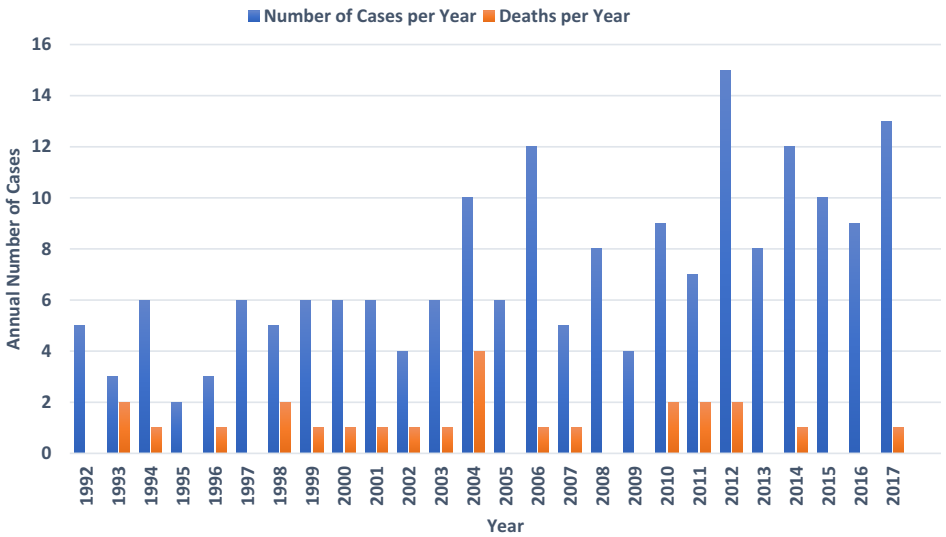

Fig. 1. Penile cancer cases and deaths per year in Western Australia (1992–2017).

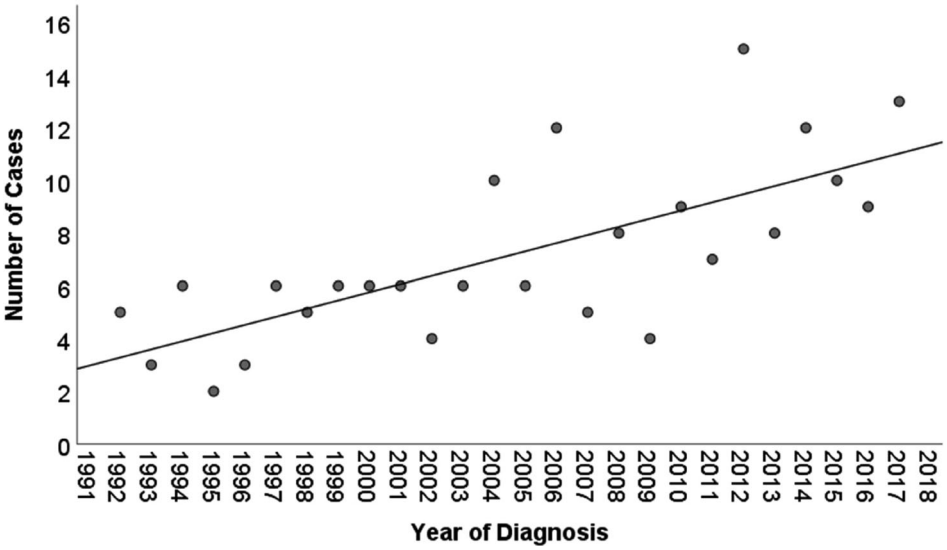

Fig. 2. Correlation between year of diagnosis and number of cases.

Results of the Pearson correlation indicate that there was a significant positive association between the year of diagnosis and number of annual diagnoses ($r = 0.719$, $P < 0.001$), with an increasing incidence of penile cancer cases being recorded in later years. No association was found between the year of diagnoses and penile cancer deaths.

Table 1 summarizes the demographic, geographical and available clinical characteristics of patients diagnosed with invasive penile cancer. The youngest patient was 27 years old and the oldest patient was 91 years old at the time of diagnosis (mean = 64 years old, median = 67 years old). One third of diagnoses were from patients residing in rural or remote Western Australia and nine patients (4.8%) were recorded as Aboriginal. The majority of Aboriginal patients (67%) were from rural or remote Western Australia.

Patient survival

The overall survival of patients over the 26-year time period was 54.8%; 25 patients (13.4%) died from penile cancer, corresponding to a penile cancer-specific survival of 86.6%. The 5-year penile cancer-specific survival was 90.9%. The average penile cancer-specific survival for the 25 patients who died from penile cancer was 25 months with a median of 11 months (range = 0 months to 164 months). The most penile cancer deaths in a single year, as represented in Figure 1, was four in 2004.

Table 2 represents univariate, chi-squared analysis of penile cancer deaths according to patient location, age, Aboriginal status and disease grade. Aboriginal patients ($P = 0.003$) and outer regional and remote patients ($P = 0.011$) were found to be associated with an increased risk of penile cancer-specific death. Aboriginal patients and outer regional and remote patients comprised only 4.8% and 33% of the total patient population respectively. However, 20% of patients who died from penile cancer were Aboriginal, 55% of all Aboriginal patients died from penile cancer and 55% of all patients who died from penile cancer were from outer regional or remote Western Australia.

Table 1 Patient characteristics

Patient characteristic	Number
Age group:	
20–39	13 (7.0%)
40–59	53 (28.5%)
60–79	85 (45.7%)
80 +	35 (18.8%)
Location of patient:	
Outer regional/remote	62 (33.3%)
Inner regional/city	124 (66.7%)
Aboriginal/Torres Strait Islander status:	
Aboriginal	9 (4.8%)
Outer regional/remote	6 (3.2%)
Inner regional/city	3 (1.6%)
Non-Aboriginal or unknown/not recorded	177 (95.2%)
Grade of lesion:	
Low grade	35 (18.8%)
Intermediate grade	63 (33.9%)
High grade	26 (14.0%)
Unknown/non-recorded	62 (33.3%)

Table 2 Patient survivorship – univariate analysis

Patient factor	Penile cancer deaths	*P*-value
Location of patient:		
City/inner regional	12 (48%)	
Outer regional/remote	13 (52%)	0.011
Aboriginal/Torres Strait Islander:		
Aboriginal	5 (20%)	0.003
Not Aboriginal/not recorded	20 (80%)	
Age of patient:		
20–39	3 (12%)	0.207
40–59	4 (16%)	0.114
60–79	11 (44%)	0.491
80 +	7 (28%)	0.181
Grade of lesion:		
Low grade	2 (8%)	0.263
Intermediate grade	8 (32%)	0.513
High grade	7 (28%)	0.110
Unknown/non-recorded	8 (32%)	0.538

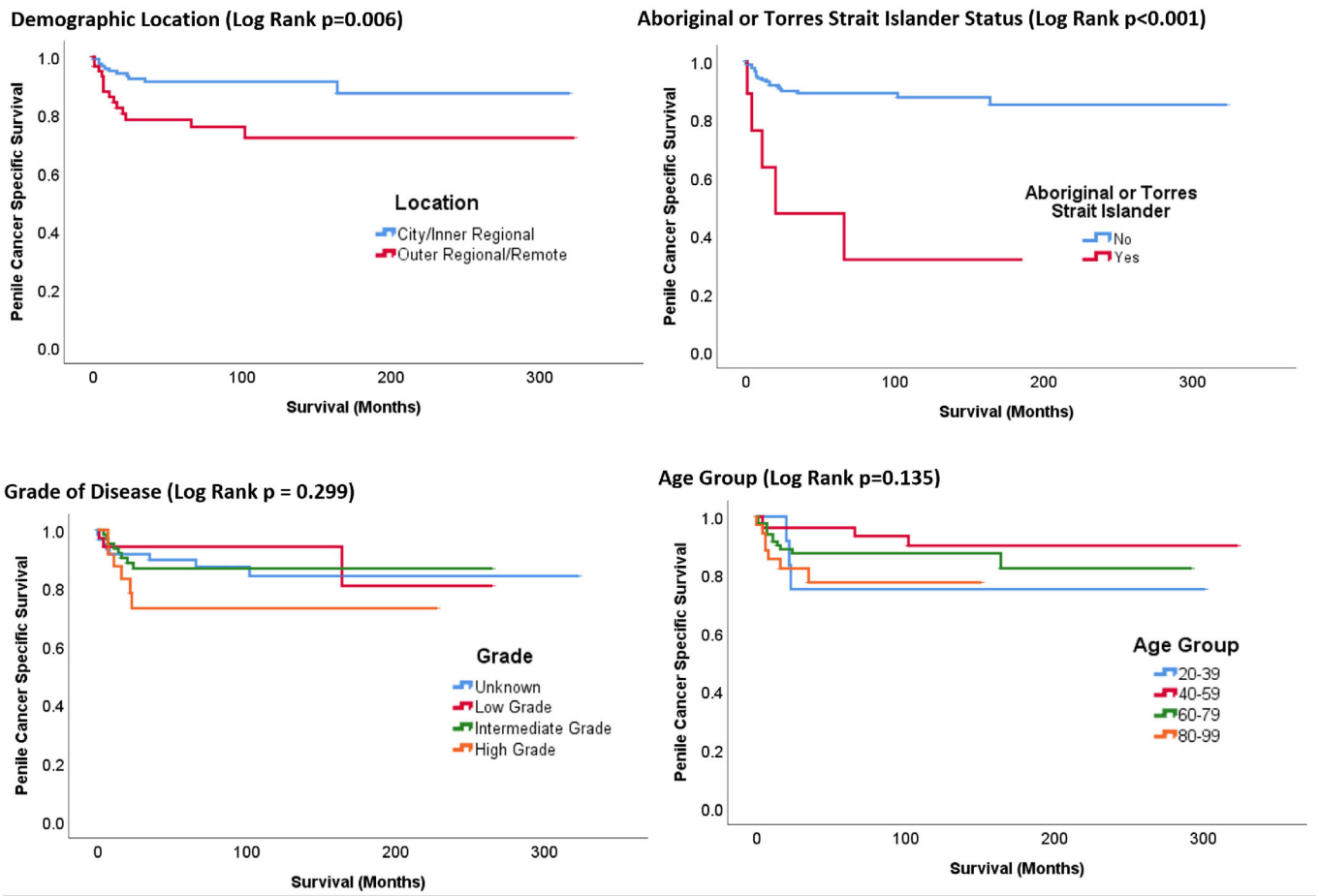

Fig. 3. Kaplan Meier survival curves for penile cancer-specific survival.

Table 3 Patient survivorship – binomial and cox regression analysis

	Binomial logistic regression			Cox regression		
Variable	Odds ratio	Confidence interval	*P*-value	Hazard ratio	Confidence interval	*P*-value
Aboriginal	7.342	1.684–32.010	0.008	6.512	2.123–19.968	0.001
Age > 50 years	0.963	0.320–2.899	0.946	1.530	0.546–4.284	0.418
High-grade disease	2.194	0.730–6.593	0.162	2.152	0.827–5.598	0.116
Outer regional or remote location	2.578	1.046–6.350	0.040	2.382	1.050–5.401	0.038

Seventy-two percent of patients who died from penile cancer were aged over 60, with the youngest patient who died from penile cancer being 28 years old. Neither age nor grade of disease were significantly associated with penile cancer death.

Binomial logistic regression, with penile cancer survival as the dichotomous, dependent variable, identified Aboriginal patients (OR 7.342, CI 1.684–32.010; $P = 0.008$) and outer regional and remote patients (OR 2.578, CI 1.046–6.350; $P = 0.040$) as being at an independent and statistically significant increased risk of dying from penile cancer. No significant difference was identified when characterizing patients according to age greater than 50 or high-grade disease.

Figure 3 represents Kaplan Meier survival curves for patient location, Aboriginal status, grade of disease and age group. Survival curves for Aboriginal status ($P < 0.001$) and location ($P = 0.006$) representing demonstrable and statistically significant differences in penile cancer-specific survival. Cox Regression survival analysis, as represented in Table 3, confirms that patients from Western Australia who were Aboriginal (HR 6.512, CI 2.123–19.968; $P = 0.001$) or from an outer regional or remote location (HR 2.382, CI 1.050–5.401; $P = 0.038$) were at an independent and significantly increased risk of penile cancer-specific mortality during the defined study period.

Discussion

This is the largest study examining penile cancer survivorship within an Australasian population, identifying 186 patients with invasive disease over 26 years. Additionally, this is the first study

within Australasia to specifically review penile cancer survivorship in Aboriginal people and comparing survivorship across different geographic locations.

One-third of patients were identified to live in outer regional or remote Western Australia and ~5% of the total patient cohort identified as Aboriginal. Aboriginal patients and patients from outer regional and remote Western Australia were identified as being at an independent and statistically significant risk of increased penile cancer-associated mortality. The marked differences in survival outcomes for Aboriginal people and patients from remote and regional locations corroborate a comprehensive breadth of literature demonstrating poorer overall survival outcomes and cancer-specific outcomes for these populations.

Aboriginal people experience a greater burden of poor health and have a shorter life expectancy than the rest of the Australian population.[19,20] Reasons for poorer health status amongst Aboriginal people is multifaceted and complex. Reasons which have been explored include systemic social, educational, economic and environmental disadvantage and often a lack of culturally appropriate and accessible health care services.[20–22]

Aboriginal people experience an increased incidence of certain cancers, a higher stage of disease and lower cancer-specific survival compared with non-Aboriginal Australians.[21] In regards to incidence, a review of four state-based cancer registries identified a higher incidence of lung and other smoking-related cancers, cervical, uterine and liver cancer as compared with non-Aboriginal Australians.[23] A national study found that for all cancers combined, survival in the first year after diagnosis for Aboriginal people was 63.8% compared with 83.4% for non-Aboriginal Australians.[22] Similarly, cause-specific survival at 1 and 5 years was 64.7% and 47.0% respectively for Aboriginal people, compared with 80.1% and 65.6% for non-Aboriginal Australians.[22]

Aboriginal people comprise around 3% of the total Australian population but a higher proportion reside in remote communities which poses an additional risk for poorer survival. Numerous studies have demonstrated poorer cancer associated mortality for rural and remote cancer patients in Australia.[24–26] Additionally, reviews of state-based cancer registry databases has suggested that due to inaccurate or incomplete records, cancer incidence rates for Aboriginal people are potentially under-estimated by 15% to 25%.[23]

The overall median age of the patient cohort was 67 which corresponds with the literature. A review of penile cancer cases in Norway from 1956 to 2015 reported a median age of diagnosis of 69 and the median age of diagnosis in New South Wales between 2001 and 2009 was 67.5.[6,27] Although no statistical significance was found in regards to patient age and penile cancer-specific survival, it is clinically relevant that 13 patients under the age of 39 were identified, the youngest being 27 years old, and three patients under the age of 39 died from penile cancer with the youngest being 28 years old.

A positive correlation was identified between the year of diagnosis and number of cases with a trend towards more cases in more recent years. Population growth is likely a confounding factor contributing to this finding and the impact of this requires further analysis. Additionally, circumcision rates in Australia have decreased from 50% in the 1970s to 13% in 2003.[28] Neonatal circumcisions is recognized as a protective mechanism against the development of penile cancer, however, given its rarity, circumcision is not generally accepted as being an appropriate prophylactic procedure.[13] It is speculative as to whether a decline in circumcision rates may have impacted the incidence of penile cancer, however, it is most probable that any potential impact would not yet be apparent at a population level.

There are a number of recognized limitations to this study. As previously described, the likely under-reporting of Aboriginal status may have affected the results. Patients who may have died from advanced or metastatic disease in particularly remote regions of the State may not have had histopathology sent or accurate cause of death recorded within state registry databases. In regards to disease characteristics, 33% of patients did not have a disease grade recorded within the WACR. Similarly, as the study involved a review of a state-based cancer registry databases as opposed to medical records, specific disease and clinically relevant characteristics including TNM stage, HPV status, previous premalignant lesions, circumcision status and treatment modalities was not specifically reviewed. Additionally, Tis and Ta disease is available on review of individual histopathology and institutional records, however only invasive disease is currently accessible within the WACR.

To accurately understand why rural and Aboriginal patients experience worse outcomes, a review of relevant barriers to care is required. For example, it is plausible that delayed presentation, limited access to primary healthcare services, delayed or limited access to subspeciality services and multidisciplinary care and potentially reduced surveillance or follow-up would have contributed to poorer health outcomes for rural and remote patients. Notably, 67% of Aboriginal patients were from rural or remote communities which is likely an important contributing determinant to poorer outcomes amongst this patient population. A review into HPV status, circumcision rates and the incidence and management of phimosis amongst rural and Aboriginal communities would also provide clinically relevant information.

Detailed exploration into nodal status and management of nodal disease is particularly important when reviewing penile cancer mortality. Due to incomplete and fragmented health records, our study was unfortunately limited by an inability to comprehensively explore clinical and pathological staging of nodal disease, utility of appropriate nodal sampling, for example, sentinel lymph node biopsy, and the use of lymph node dissection. For example, it would be particularly useful to know which patients met criteria for and subsequently underwent sentinel lymph node sampling and lymph node dissection. Appropriate surgical management of lymph nodes is essential for optimization of patient outcomes and despite its associated morbidity, lymph node dissection must not be underutilized for appropriate patients.[29] Due to limited access to tertiary and subspeciality healthcare facilities, suboptimal or delayed management of nodal disease for rural patients may have contributed to poorer survival outcomes. Similarly, reviewing management of nodal disease amongst Aboriginal patients would be particularly insightful to determine whether Aboriginal patients were presenting with more advanced disease and whether discrepancies in management of nodal disease may have influenced survival outcomes.

This study clearly demonstrates that over a 26-year time frame, penile cancer patients in Western Australia who are Aboriginal or who reside in rural or remote regions experience a significantly reduced penile cancer-specific survival. The reasons for these findings are multifactorial and require further analysis from a holistic, biopsychosocial approach. Further research is necessary to understand disease characteristics in these populations, the identification of barriers to care and quality of life implications of both the disease and treatment.[30] Public health measures and education, for example, improved evidence-based internet resources, are important to increase awareness about penile cancer amongst the general population and also clinicians.[31] Engagement with relevant key stakeholders is of paramount importance in improving data collection, addressing health discrepancies and improving outcomes.

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Conflict of interest

None declared.

Author contributions

Simeon Ngweso: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; writing – original draft; writing – review and editing. **Tatenda Nzenza:** Data curation; methodology; project administration; writing – original draft. **Kevin McMillan:** Conceptualization; methodology; project administration; supervision; writing – review and editing. **David Sofield:** Data curation; project administration; supervision; writing – review and editing. **Mikhail Lozinskiy:** Supervision; writing – review and editing. **Dickon Hayne:** Conceptualization; project administration; supervision; writing – review and editing.

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