A population-based analysis of the epidemiology of penile cancer in Newfoundland and Labrador

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ABSTRACT

Introduction: Penile cancers are a rare subset of carcinomas accounting for <1% of all diagnosed malignancies. There have been recent reports of increasing incidence globally; however, there is limited Canadian literature pertaining to these neoplasms. The province of Newfoundland and Labrador (NL) represents an important entity to study, possessing the highest national incidence of cancer, along with a plethora of relevant risk factors for penile cancer.

Methods: A retrospective chart analysis of all patients with a diagnosis of penile cancer in NL between the years of 2006 and 2018 was conducted. The main outcomes included overall incidence, proportion with metastatic disease, tumor demographics, and overall survival (OS). Incidence among the male population was calculated using Statistics Canada annual reports.

Results: An identified 81 cases satisfied the inclusion criteria, with a median age at diagnosis of 65 (interquartile range 20) years. Crude incidence of penile cancer ranged from 1.20 to 4.27/100 000 males in 2007 and 2010, respectively, while the average age-standardized incidence was 2.34/100 000 males across the study timeframe. Metastatic disease was noted in 17 (21.0%)

KEY MESSAGES

- Penile cancer is a rare, yet aggressive malignancy often associated with significant patient morbidity and mortality.
- Rates of penile malignancy are higher in the Canadian province of NL compared to previously reported Western jurisdictions.
- High incidences of penile cancer observed in NL are likely the multifactorial result of chronic inflammation, high rates of modifiable risk factors, and diagnostic delays.
- There are requirements for improved monitoring and reporting of penile cancer and relevant risk factors in NL.

patients, with a five-year OS of 74% for all penile malignancies, decreasing to 66% in those with invasive squamous cell carcinoma.
Conclusions: The incidence of penile cancer in our population was higher than reported Western jurisdictions and showed frequent rates of metastatic spread. These observations are likely multifactorial, resultant of chronic inflammation paired with high rates of modifiable risk factors and diagnostic delays. An evident need for greater examination and improved reporting of these malignancies in the province was identified.

INTRODUCTION

Penile cancer is a devastating malignancy associated with detrimental impacts on patient quality of life (QoL) and a poor prognosis in the absence of early intervention.[1,2] These rare malignancies have traditionally accounted for fewer than 1% of all cancer diagnoses, however, mixed reporting regarding current trends suggests an increasing incidence globally.[3–5] Contemporary global age-standardized incidence rates (ASIR) are reported at 0.8/100,000, however, these have been shown to vary relative to geographical location with highest rates typically observed in less developed nations and infrequent reports in the Western world.[2,6,7] There has been limited research conducted on these malignancies in Canada, however, Lagace et al. (2020) reported the incidence of invasive penile squamous cell carcinoma (SCC) at 0.61/100,000 males with a significant increase in crude incidence rate between 1992 and 2010.[8] Interestingly, the Atlantic Canadian provinces demonstrated ASIR significantly higher than the national average, indicating a greater occurrence of invasive SCC of the penis in these regions.[8] Similarly, Janes et al. (2023) reported an increased incidence of penile cancer in Newfoundland and Labrador (NL) during the COVID19 pandemic, however, these findings were speculated as a secondary result of delayed diagnosis resultant from pandemic-induced shifts in healthcare delivery.[9]

Despite improvements, several gaps in our understanding of these rare malignancies remain, as there is still a lack of extant literature surrounding penile cancer, especially in Canada.[3,10] One such area that may benefit from further examination of these malignancies is the province of NL. There is a paucity of existing literature surrounding penile cancer in NL and a plethora of prevalent risk factors among this population, paired with some literature evidencing an increasing incidence among industrialized nations.[7] Further, the province has the highest national incidence of cancer along with the lowest rates of circumcision, and empiric observations of high rates of penile malignancy.[11–14] These considerations, compounded by the status of the province as a microcosm for rare malignancies, indicating the possibility for a founder effect, warrants greater examination of penile cancer in NL.[11]

The purpose of the present study was to assess the epidemiology and outcomes of penile cancer diagnoses in NL. We hypothesized that the province would have a higher overall

incidence of penile cancer diagnoses relative to other reported jurisdictions in the Western world. Additionally, we suspected that incidence of these malignancies has increased in the province over the study timeframe.

METHODS

This study was approved by the provincial health research ethics board at Memorial University (St. Johns, Newfoundland and Labrador, Canada). This population-based study was conducted with all patients with a valid Medical Care Plan (MCP) number from January 1, 2006, to December 31, 2017. Significant variation in the provincial population of NL was observed during the study period with the male population ranging from 250,402 – 262,513 in 2007 and 2016, respectively.

Data extraction/sources

All provincial diagnoses of malignancy are recorded in the Newfoundland and Labrador Cancer Care Registry (NLCCR) as mandated by the Newfoundland and Labrador Personal Health Information Act. This study conducted a population-based retrospective chart analysis of patients in this database with a first diagnosis of penile cancer diagnosis in NL between the years of 2006 and 2018. Cases were identified using International Classification of Diseases for Oncology, 3rd revision (ICD-O3) code C60 and sub-codes defining malignant neoplasms of the penis. All diagnoses of penile cancer identified were included in the data analysis. Tumour behaviour in the NLCCR was classified as either invasive or in-situ disease. While SCC is typically classified as invasive compared with in-situ disease, for the purposes of this study we have made the distinction between invasive SCC and all penile malignancies.

Patients identified in the NLCCR were cross-referenced with the provincial medical database to provide further variables including patient demographics, tumour characteristics, prevalent risk factors, management, and outcomes. Assessed risk factors included neonatal circumcision status, obesity and body mass index (BMI), tobacco usage, Human Immunodeficiency Virus (HIV) and Human Papilloma Virus (HPV) status along with localized anatomical factors where available. These variables were dichotomised as present or absent for each patient. Obesity was defined as any BMI ≥ 30, while smoking status was recorded in a trichotomous fashion as never, former, or current smokers.

Statistical analysis

All statistical analyses were conducted using SPSS version 27.0 (IBM Corporation, Armonk, NY). Demographic characteristics of the study cohort were presented as percentages and absolute counts for categorial variables, while means and standard deviations were used to report continuous variables. Crude and age-standardized incidence rates (ASIR) were calculated using Statistics Canada population estimates with the respective male population for each examined year as the denominator and reported as incidence per 100,000 person-years. Kaplan-Meir curves

depicting overall survival of the cohort were generated for all cases of penile malignancy and for identified cases of SCC, exclusively.

RESULTS

Incidence

A total of 82 cases of penile cancer were identified in the NLCCR between 2006 and 2018 with one exclusion for recurrent disease, therefore, 81 patients were included in the final incidence analysis. Annual incidence varied drastically across the study timeframe, ranging from 1.20/100,000 reported in 2007 to 4.27/100,000 reported in 2010. Average crude incidence of penile malignancy as well as penile invasive SCC were reported at 2.62/100,000 (95% CI 2.05 – 3.19) and 1.81/100,000 (95 % CI 1.34 – 2.28) across the study period, respectively. Average ASIR was 2.34/100,000 000 (95% CI 1.83–2.84) for all penile malignancies and 1.60/100,000 (95% CI 1.18–2.10) when examining SCC exclusively. Full breakdown for of crude and ASIR by total cases and SCC only is displayed in Figure 1.

Patient demographics

The median age of males diagnosed with penile cancer was 65 (IQR=20) years of age. Previous malignancy was noted in 13 (16%) members of the cohort. HPV associated disease was reported for only 9 (11.1%) patients, however, this variable was inconsistently documented. There were no observed reports of HIV positive status amongst our sample. Patient demographic and risk factor profiles were available and assessed for 65 (80%) cases, for which a full breakdown is detailed in Table 1.

Malignancy characteristics

The most common presentations of the primary tumour were carcinoma in-situ (Tis) and T1 lesions, each reported in 23 (28.4%) cases, while early-stage disease (0 – II) was identified in 59 (72.8%) patients. Stage was not reported or not applicable for 6 (7.4%) patients. Similarly, grade was absent from 35 (43.2%) reports with the most common presentation amongst reported cases being G2 disease seen in 22 (27.2%) patients. Lmyphovascular invasion and perineural invasion were each identified in 5 (6.2%) independent cases, respectively, while a further 3 (3.7%) patients with both. There were 17 (21.0%) patients with documented disease spread at diagnosis. There were no documented reports of progression from non-invasive to invasive disease. Further classification of disease characteristics is summarized in Table 2.

Disease management & outcomes

Surgical resection was the most common treatment for penile cancer with 56 (69.1%) patients receiving operative intervention. Individual radio- and chemotherapy were utilized in 4 and 1 case, respectively, while concurrent dual-modality treatment regimens were employed in 5 (6.2%) patients. A full overview of employed treatment modalities for all cases of penile cancer and exclusively for cases of invasive SCC can be found in Table 3.

There were 33 (40.7%) individuals deceased within the study period, 13 (39.4%) of whom succumbed to their malignancy. When exclusively examining patients with invasive SCC there were 25 (44.6%) mortalities in the study timeframe, with 13 (52.0%) deaths attributable to penile malignancy. There were 5 (6.2%) patients for whom definitive cause of death could not be elicited. The 5-year OS amongst the entire cohort was 74% whereas 5-year OS for SCC was 66%. Kaplan-Meir survival curves depicting overall survival are displayed in Figure 2.

DISCUSSION

The present study sought to assess the epidemiology of penile cancer in NL with our results demonstrating an absence of incidence trends, however, consistently documented an elevated incidence compared with reported global ASIR. In the most recent and comprehensive reviews on the epidemiology of penile cancer to date, the worldwide ASIR was reported at approximately 0.8/100,000.[6,7] American data assessed using the Survival, Epidemiology and End Results (SEER) program has demonstrated similar or lesser values for the occurrence of penile cancer with suggestions of multifactorial increases in incidence over time.[15,16] Canadian Cancer Statistics data from 2018 indicated an overall incidence rate of approximately 1.05/100,000 when calculated from the Statistics Canada male population at this time.[13] These reports are consistent with current epidemiological interpretations of lower incidence amongst developed nations.[2,6,7]

Despite limited undertaken research in Canada, a small subset of studies has examined penile cancer in variable national settings. Lagace et al. (2020) reported national ASIR of penile SCC between 1992 and 2010 at 0.68/100,000 males and noted four provinces, including NL, to have significantly higher rates than the rest of the country.[8] The results of the present study provide further support for the findings of these authors given the consistently elevated incidence of penile cancer above previously reported averages during the study timeframe. Two additional Canadian studies conducted by Mahmud et al. (2017) and Beech et al. (2015) documented incidence rates lower than 1/100,000 at their institutions between 2000 – 2010 and 2005 – 2015, respectively.[10,17] An important difference between our study and that of the previous authors was the inclusion of SCC in-situ along with other malignant penile afflictions. In allowing comparability, we dichotomised the presented data into categories representing all cases of penile malignancy and as those exclusively SCC. As such, our findings of an elevated incidence rate are further justified with an average ASIR of 1.60/100,000 for penile SCC across the study timeframe. Our results provide further support for the incidental discovery by Janes et al. (2023) which suggested an elevated incidence of penile cancer in NL during the COVID19 pandemic.[9] However, contrary to previous speculations, our findings suggest increased incidence was not exclusive to pandemic-induced delays and provide evidence of ongoing high rates of penile malignancy in NL.

Evidently, the occurrence of penile cancer in NL is greater than that reported in previously published North American literature, the reasons for which are likely multifactorial owing to possible genetic interaction in the presence of chronic localized inflammation paired with high rates of modifiable risk factors. The presence of the foreskin in men remains one of the

most important considerations for contraction of HPV infection among sexually active males.[18] Extant literature has suggested some evidence of a protective effect of neonatal circumcision with reduction in rates of HPV and, by extension, penile malignancy.[18,19] While there was a near absence of neonatal circumcision amongst our cohort, this undertaking remains a controversial topic with current Canadian guidelines as poor penile hygiene, and associated subsequent chronic inflammation, are more significant considerations in risk for development.[20–22]Despite the inability to completely represent risk factor profile due to lack of consistent reporting, a large percentage of our study population still presented with various localized and systemic risk factors for penile cancer.

Plausibly, the numerous documented etiologic factors from a localized anatomical level including phimosis, chronic inflammation, poor hygiene, balanitis xerotica obliterans (BXO) and penile trauma likely had a significant impact on the development of penile malignancies.[23–28] Phimosis and BXO were present in 32.3% and 37.1% of accessible patient cases, respectively**,** and were likely to be underreported amongst our cohort as they are not documented in the same manner as systemic-level conditions at our institution. In addition to localized concerns, smoking and obesity status, amongst other modifiable risk factors, have also been implicated in the development of penile cancer and are more frequently reported.[21,29] Our study demonstrated a history of smoking in 50% of individuals for whom reports were available while 40% were classified as obese. Evidently, despite inadequate access to reported data in our province a plethora of prevalent risk factors were still identified amongst a large proportion of our study population. Such findings provide explanations which may have contributed to a greater predisposition to penile cancer and subsequent impacts to quality of life (QoL) and overall survival (OS).

Canadian data has indicated a median cancer specific survival (CSS) of 60% for individuals afflicted with penile cancer at 8.5 years.[10] Median CSS for our population could not be defined, however, our results indicated an OS of 74% at 5 years which decreased to 66% in those with invasive penile SCC. The OS for individuals diagnosed with penile cancer is often multifactorial, with numerous studies indicating an average 5-year OS from 60 – 65%.[30–32] Findings of the present study indicated OS in our population equivalent to or better than that reported by previous authors. These results directly contrast the findings of Janes et al. (2023) who found 40% mortality over a 28-month period throughout the COVID-19 pandemic in which significant diagnostic delays were documented. Our observed high survival rate is likely a result of the early-stage presentation (Tis – T2) documented in approximately 73% of patients diagnosed with penile cancer during the study timeframe. Such findings further support the necessity for early-stage diagnosis and timely intervention in preventing detrimental outcomes for this patient population.

The undertaking of this population-based study further revealed an inability to collect complete risk and survival data for several patients diagnosed with penile cancer, a finding that has been mirrored in various previous publications in this area.[10,17,33] While these findings do not

impact conclusion surrounding incidence, they impair the ability to draw definitive conclusions regarding CSS and disease development. Future research should focus on eliciting a full risk factor profile for the examined population while also attempting to examine additional potential factors that may have contributed to the observed high rates of penile cancer in NL. Given the elevated diagnoses amongst this population it would be appropriate to develop a database designed to track and monitor these neoplasms as understanding and management of these rare malignancies in the western world continues to evolve.

Limitations

Several limitations that must be considered when interpreting the results of the present analysis. The major identified limitation exists in the lack of consistency in reporting of penile cancer over time, as such we were unable to retrieve complete information on several variables, including grading and staging, for these malignancies. The lack of documentation pertaining to pertinent risk factors amongst our cohort poses a further limitation to the ability to quantify relevant risk for developing penile cancer in our population. Despite these considerations, we are confident our results reflect an elevated incidence of penile cancer relative to extant literature that prompts the need for greater investigation of these malignancies in our province. A further important consideration exists in the unique population profile that has typically been present in NL, which may limit the applicability of our results to other populations. Such drawbacks are inherent to any retrospective, population-based study, however, we believe that the long duration of follow up paired with a global trend in increasing incidence of these tumours justifies the generalization of our findings and provides a comprehensive epidemiologic picture of penile cancer.

CONCLUSIONS

The present study demonstrated higher rates of penile cancer in NL than previously reported in other western jurisdictions. These observations are likely multifactorial, resultant from chronic inflammation paired with high rates of modifiable risk factors and potential genetic interplay. There is an evident need for greater examination and discussion of these malignancies in the province aimed at educating males around this often-lethal malignancy.

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FIGURES AND TABLES

Figure 1. Crude and age-standardized incidence of penile cancer cases in NL from 2006–2018 per 100000. (A) All reported penile malignancy (n=81); and (B) cases of invasive SCC only (n=56).

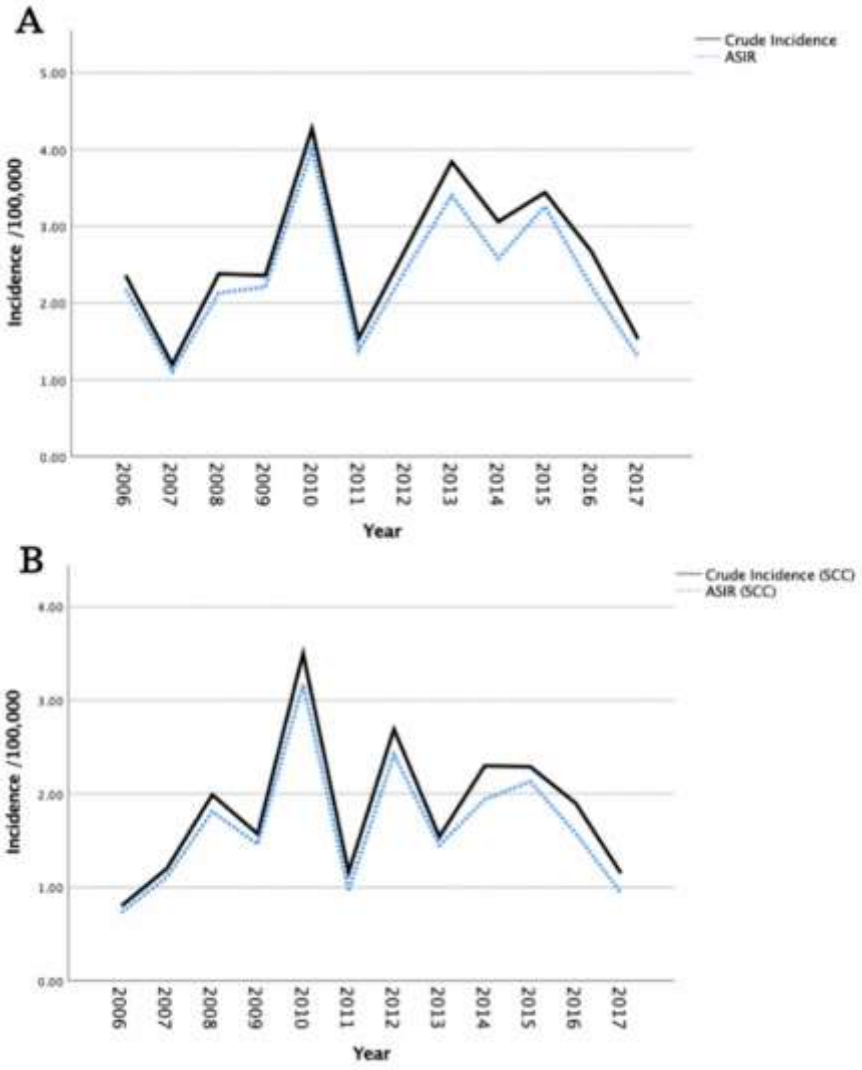

Figure 2. Kaplan-Meir survival curve depicting time to death in males diagnosed with penile cancer between January 1, 2006, and December 31, 2017. (A) All reported penile malignancy (n=81); and (B) cases of invasive SCC only (n=56).

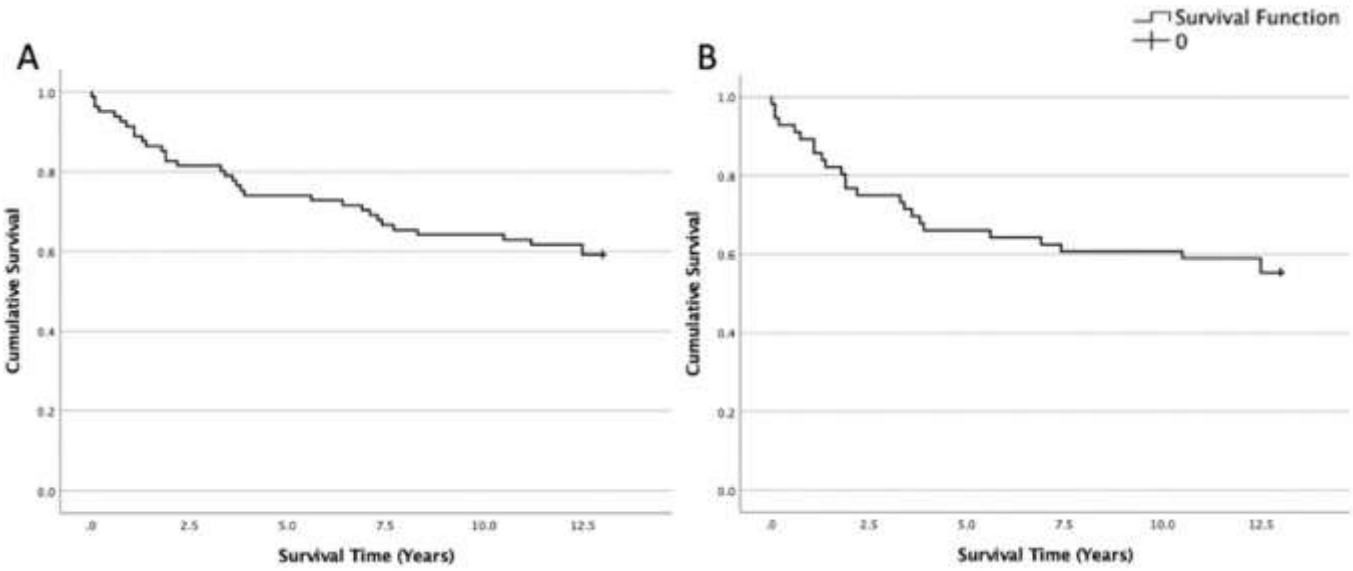

Table 1. Patient demographics for males diagnosed with penile cancer in NL from 2006–2018		
Patient Demographics & Risk Profile	**Mean (±SD)**	**n (%) (n=81)**
Age (n=81)	62.93 (±13.92)	
BMI (n=50)	30.65 (±9.53)	
Obesity		
Yes		26 (32.1%)
No		27 (33.3%)
Unknown		28 (34.6%)
Smoking status		
Never		29 (35.8%)
Former		16 (19.6%)
Current		17 (21.0%)
Unknown		19 (23.5%)
BXO		
Yes		23 (28.4%)
No		34 (42.0%)
Unknown		24 (29.6%)

Phimosis		
Yes		20 (24.7%)
No		38 (46.9%)
Unknown		23 (28.4%)
HPV status		
Positive		9 (11.1%)
Negative		56 (69.1%)
Unknown		16 (19.8%)
HIV status		
Positive		0 (0.0%)
Negative		65 (80.2%)
Unknown		16 (19.8%)
Neonatal sircumcision		
Uncircumcised		55 (68.0%)
Circumcised		5 (6.0%)
Unknown		21 (26.0%)

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Table 2. Characteristics of malignancy for males diagnosed with penile cancer in NL from 2006–2018

Malignancy characteristics	**All cases (n=81)**	**Invasive SCC (n=56)**
Initial anatomic site, n (%)		
Foreskin	16 (19.8%)	6 (10.7%)
Glans	32 (39.5%)	22 (39.3%)
Overlapping/multiple	16 (19.8%)	15 (26.8%)
Penile shaft	5 (6.2%)	4 (7.1%)
NOS	12 (14.8%)	9 (16.1%)
Nodal involvement, n (%)		
Ipsilateral inguinal	10 (12.4%)	10 (17.9%)
Bilateral inguinal	5 (6.2%)	5 (8.9%)
Pelvic	4 (4.9%)	4 (7.1%)
Unknown	16 (19.6%)	12 (21.4%)
Distant metastases, n (%)		
M0	63 (77.9%)	43 (76.8%)
M1	2 (2.5%)	2 (3.6%)
MX	16 (19.6%)	12 (21.4%)
Stage, n (%)		

0	23 (28.4%)	0 (0.0%)
I	23 (28.4%)	21 (37.5%)
II	13 (16.0%	13 (23.2%)
III	6 (7.4%)	6 (10.7%)
IV	10 (12.3%)	10 (17.9%)
Not applicable	1 (1.2%)	0 (0.0%)
Unknown	5 (6.2%)	5 (8.9%)
Grade, n (%)		
G1	20 (24.7%)	20 (35.1%
G2	22 (27.2%)	21 (36.8%)
G3	4 (4.9%)	4 (7.0%)
Unknown/not applicable	35 (43.2%)	12 (21.1%)
Histology, n (%)		
Squamous cell carcinoma (SCC)	56 (69.1%)	56 (100.0%)
SCC in-situ	23 (28.4%)	
Other	2 (2.5%)	
Malignant melanoma	1 (1.2%)	
Kaposi's sarcoma of the penis	1 (1.2%)	

NOS: not otherwise specified.

Table 3. Treatment modalities employed in the management of individuals diagnosed with penile cancer in NL from 2006–2018

Treatment modality	**All cases (n=81)**	**Invasive SCC (n=56)**
None, n (%)	4 (4.9%)	3 (5.3%)
Topical immunotherapy, n (%)	11 (13.5%)	4 (7.1%)
Surgery, n (%)	56 (69.1%)	41 (73.2%)
Circumcision	13 (16.0%)	4 (7.1%)
Partial penectomy	31 (38.2%)	27 (48.2%)
Total penectomy	7 (8.6%)	7 (8.6%)
Local excision	4 (4.9%)	2 (3.6%)
Other	1 (1.2%)	1 (1.8%)
Chemotherapy, n (%)	6 (10.3%)	6 (10.7%)
Radiotherapy, n (%)	9 (11.1%)	8 (14.3%)
Documentation unavailable, n (%)	17 (20.1%)	12 (21.4%)

Note: Patients were not classified exclusively into one category and may have had multiple employed treatment modalities.