Primary Squamous Cell Carcinoma of the Male Proximal Urethra: Outcomes from a Single Centre

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on behalf of the Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists

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Abstract

Background: Primary squamous cell carcinoma (SCC) of the male proximal urethra is an aggressive and rare urogenital malignancy.

Objective: To review the surgical management and outcomes for male proximal urethral SCCs within a single centre and to suggest an algorithm for the surgical management of these rare tumours.

Design, setting, and participants: This was a retrospective study of patients undergoing surgery for male proximal urethral SCC within a single tertiary academic centre managing rare genital tumours. Ten patients with a histological diagnosis of proximal urethral SCC were identified from an institutional database over a period of 10 yr with a median follow-up of 22.5 mo (standard deviation ± 25.77 mo).

Outcome measurements and statistical analysis: Pathological staging, surgical treatment, and neoadjuvant and adjuvant treatment were recorded. Complications according to the Clavien-Dindo classification and overall survival rates were recorded. Kaplan-Meier curves were used for overall survival.

Results and limitations: A total of 10 patients were identified of whom eight underwent panurethrectomy and radical prostatectomy. Radical inguinal lymphadenectomy was performed in five patients, which confirmed bilateral metastatic disease. Perioperative complications were reported in six patients (Clavien I and II). Within 6 mo of surgery, 90% of patients developed distant metastatic disease. Nine patients died of urethra cancer during the follow-up. One patient is still on follow-up. The median overall follow-up was 13.92 mo (range: 5–91 mo). At 5 yr, cancer-specific/overall survival was 10%. A limitation of this study is the retrospective design, which is unavoidable for such a rare disease.

Conclusions: Radical surgery allows local disease control, but despite neo/adjuvant treatment, proximal urethral SCC is associated with poor survival outcomes and progression to distant metastatic disease within 6 mo.

Patient summary: Proximal urethral squamous cell carcinoma is a rare cancer in men which is often detected late. Patients often present with problems such as voiding, urethral bleeding, or a palpable mass. Aggressive surgery allows local control, but despite this the overall survival is poor. Adjuvant and neoadjuvant radiochemotherapy can improve survival. Multicentric randomised trials are needed to identify the correct treatment modality.

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1. Introduction

Primary male urethral cancer (PUC) is a rare and aggressive tumour accounting for <1% of all genitourinary malignancies [1] and 0.02% of all cancers [2,3]. Risk factors include a history of urethral strictures, chronic irritation following intermittent self-catheterisation, previous urethrophy, external-beam radiation therapy (EBRT), radioactive seed implantation, and chronic urethral inflammation/urethritis following sexually transmitted diseases [4–11]. Patients can present with urinary obstruction, irritative voiding symptoms, haematuria, or a penile discharge that is often associated with a palpable lump in the penis or perineum [10,11].

PUCs present as variable histological subtypes. The most common histological subtypes reported in the Surveillance, Epidemiology, and End Results (SEER) review of 1615 patients were transitional cell carcinoma (TCC) representing 55%, squamous cell carcinoma (SCC) representing 21.5%, and adenocarcinoma accounting for 16.4% [12]. Of all the urethral tumours, anterior urethral tumours have a higher incidence than posterior urethral tumours [10,11]. SCC is the predominant subtype in the fossa navicularis and the anterior urethra. TCCs account for 80–90% of posterior urethral tumours [10–12].

Clinical management and prognosis are related to the clinical stage and location of the tumour at presentation [10–14]. Conventionally, the anterior urethra includes the penile and the bulbar urethra, and the posterior urethra includes the prostatic and the membranous urethra.

Proximal PUCs refer to tumours in the prostatic, membranous, and bulbous urethra, whereas distal tumours involve the penile urethra and fossa navicularis. Although this is a nonspecific nomenclature, it is now increasingly used within the literature [10,11].

In men, proximal PUCs are usually more aggressive than distal PUCs. Distal urethral tumours tend to be of low stage, with reported cure rates of 70–90% following local surgical excision and radiotherapy [10–14]. Most cases (66%) of proximal PUC are at an advanced stage at presentation. The optimal multidisciplinary treatment strategy for proximal urethral cancer is still unclear. Owing to the small number of patients who develop these proximal urethral SCC, standardised treatment options are lacking with cases often treated along local protocols on a case-by-case basis [10–14].

The aim of this study was to analyse the data regarding treatment responses and survival outcomes for patients with advanced proximal urethral SCC managed within a single institution.

2. Patients and methods

We retrospectively collected data of patients diagnosed with proximal urethral SCC from an institutional database. Data were recorded on a standardised pro forma and included patient age, histological subtypes, surgical management, postoperative complications, use of chemoradiotherapy, and overall survival (OS) rates. Only patients >18 yr old with SCC located in the proximal urethra were included in the study. Patients with a diagnosis of non-SCC (eg, melanoma, lymphoma of the urethra), prostatic adenocarcinoma, and primary bladder TCC with urethral involvement (at presentation or later) were excluded from the cohort. Patients with missing clinical information were also excluded. OS was calculated from the date of diagnosis to the date of death or last follow-up. Kaplan-Meier curves were used to show the OS.

All statistical tests were performed using the R Studio graphical interface v.0.98 for R software environment v.3.0.2.

3. Results

A total of 10 cases with histologically proven proximal urethral SCC were treated within a single centre. Fifteen patients were excluded from the study because they did not meet the inclusion criteria. Patient characteristics are shown in Table 1. The median follow-up was 21.8 mo (standard deviation ± 25.5 mo).

3.1. Clinical presentation

The mean age at presentation was 55 yr (range: 46–64 yr). Two patients had distant metastasis (pulmonary) at the time of diagnosis. Three patients presented with proximal urethral...
stricture disease, obstructive lower urinary tract symptoms (LUTS), and bleeding from the urethral meatus. Three patients presented to the emergency department with urethral bleeding and penile pain. A further two patients presented with either a urethral or a scrotal abscess and pain, and one patient presented with a palpable penile lump.

### 3.2. Diagnosis

Preoperative imaging using pelvic and penile magnetic resonance imaging showed the extent of the tumour and allowed surgical planning (Fig. 1A). Staging with computed tomography (CT) was performed preoperatively combined with ultrasound fine needle aspiration cytology (FNAC) of the inguinal lymph nodes. All patients underwent a cystoscopy and biopsy of the lesion for confirmation of the primary lesion. Where a cystoscopy was not possible due to the extensive nature of the tumour or fistulation through the scrotum, a urethrogram was performed to check the extent of the tumour and urethral involvement (Fig. 1B).

### 3.3. Surgery

In this cohort, nine patients underwent panurethrectomy combined with a radical prostatectomy, bladder neck closure, and urinary diversion (either suprapubic drainage or Mitrofanoff). Of this cohort, one patient underwent excision of a large perineal-scrotal mass combined with a bilateral orchidectomy and a total penectomy due to the extensive local invasion of the tumour, and the resulting perineal defect was covered using a pedicled gracilis flap (Fig. 2). One patient underwent a total urethrectomy combined with a cystoprostatectomy, and one patient underwent a urethrectomy sparing the prostatic urethra and perineal urethroscopy alone without excision of the prostatic urethra because he refused to undergo a prostatectomy.
3.4. Perioperative complication

A total of six patients developed perioperative complications following the surgery. Complications included post-operative ileus (n = 1; Clavien grade: II), wound infection (n = 1; Clavien grade: I), and sepsis (n = 2; Clavien grade: II), and perioperative transfusion was required in two patients (Clavien grade: II). Severe complications related to urinary derivations did not happen.

3.5. Histology

The histopathology is summarised in Table 1. Of the patients, 80% were affected by poorly differentiated G3 SCC and 70% by T3–4 disease (Table 2). Both perivascular and perineural invasion were positive in 60% of the patients.

3.6. Lymph node involvement

A total of five patients underwent bilateral inguinal lymphadenectomy. Of these patients, three had SCC diagnosed preoperatively following inguinal ultrasound and FNAC. The other two had clinically suspicious inguinal lymph nodes on cross-sectional imaging (Table 2).

The mean number of lymph nodes removed was 13.2 (range: 11–19). Four patients undergoing inguinal lymphadenectomy were found to harbour SCC within the lymph nodes, with the mean number of metastatic lymph nodes being 2 (range: 2–4), and three patients had extracapsular extension noted on pathological review of the lymph nodes. Only one patient had a pelvic lymph node dissection due to enlarged pelvic nodes on preoperative CT imaging. In this case, one out of 19 pelvic lymph nodes was positive for metastatic SCC.

3.7. Adjuvant, neoadjuvant, and additional therapy

Three patients were deemed suitable for neoadjuvant chemotherapy (cisplatin/5-fluorouracil [5-FU]/gemcitabine; Table 2). However, one patient discontinued before the completion of chemotherapy owing to side effects. Additional chemotherapy with cisplatin and 5-FU or gemcitabine was offered as a palliative treatment option in three patients who developed lung metastases postoperatively. Of these patients, two also underwent palliative pelvic EBRT for local disease control. One patient underwent EBRT and one cycle of paclitaxel.

3.8. Metastatic disease

Distant metastasis at the time of diagnosis was found in two patients (lung). However, distant metastases developed in 90% of patients on follow-up, with six developing lung metastasis and a further four developing pelvic recurrence (Table 1).

One patient, who underwent a urethrectomy and perineal urethrostomy alone without the excision of the prostatic urethra because he refused a prostatectomy, developed local recurrence at the site of the perineal urethrostomy.

3.9. Surveillance

The median overall follow-up was 13.92 mo (range: 5–91 mo). Nine patients died due to cancer progression (90%) and one is still under clinical follow-up. At 5 yr, cancer-specific survival/OS was 10%. In the subgroup of patients who had received platinum-based neoadjuvant or additional chemotherapy (n = 6), the median survival time from diagnosis was 28.1 mo (range: 15–91 mo); for patients who had not received chemotherapy (n = 4), the median survival was 6.3 mo (range: 5–10 mo).

3.10. Treatment algorithm

Based on our cohort, we have developed our own algorithm for the management of proximal urethral SCC for our centre (Fig. 3).

Table 2 – Adjuvant and neoadjuvant treatment according to the patient’s TNM stage.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Stage at diagnosis</th>
<th>Neoadjuvant therapy</th>
<th>Additional therapy</th>
<th>Time to last follow-up/death (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>T3N1M0</td>
<td>No</td>
<td>No</td>
<td>10 (Death)</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>T3N2M1</td>
<td>No</td>
<td>Yes/Cisplatin/gemcitabine</td>
<td>7 (Death)</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>T3NxM0</td>
<td>No</td>
<td>Yes/Cisplatin/fluorouracil</td>
<td>11 (Death)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>T2NxM0</td>
<td>Yes/Cisplatin/fluorouracil</td>
<td>Yes/RT</td>
<td>91 (Follow-up)</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>T3NxM0</td>
<td>No</td>
<td>Yes/RT</td>
<td>6 (Death)</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>T3NxM0</td>
<td>No</td>
<td>No</td>
<td>15 (Death)</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>T4NxM0</td>
<td>No</td>
<td>No</td>
<td>5 (Death)</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>T2NxM0</td>
<td>Yes/Cisplatin/fluorouracil</td>
<td>Yes/RT Paclitaxel—palliative</td>
<td>17 (Death)</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>T4N1M0</td>
<td>No</td>
<td>No/Cisplatin/fluorouracil</td>
<td>38 (Death)</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>T2NxM1</td>
<td>Yes/Cisplatin/gemcitabine</td>
<td>Yes/RT</td>
<td>15 (Death)</td>
</tr>
</tbody>
</table>

RT = radiotherapy; TNM = tumour, node, metastasis.
4. Discussion

In this series, we present a single-centre experience of managing rare proximal urethral SCC. Owing to the location and histology, proximal urethral SCC is one of the most aggressive urethral tumours [10–15]. More importantly, diagnosis of early proximal urethral cancer is difficult, and the presentation is often delayed by which time the
tumour causes bothersome LUTS. In our cohort, all the patients developed obstructive LUTS or infection due to locally advanced disease. Owing to these nonspecific symptoms, diagnosis of PUC is usually delayed, which then impacts the commencement of treatment. Presentation with urethral bleeding is a sign that often leads to investigation and diagnosis. Unfortunately, this sign often occurs at the stage of advanced disease [14–16].

Our cohort included patients with advanced disease with 80% presenting with pT3–4 G3 disease, and two patients had distant metastases at diagnosis. Our cohort reported a very high mortality rate (90%) of the patients who died within 13 mo of diagnosis. This is in line with the published literature on PUC. According to a SEER database analysis, the median 5- and 10-yr OS rates of PUC are 46% and 29%, respectively, whereas the cancer-specific survival rates are 68% and 60%, respectively [12].

Management of proximal PUC is still unclear owing to the lack of randomised controlled studies, which is often seen with rare cancers [13].

In 1994, Dinney et al [15] reported on a series of 23 men suffering from PUC. A squamous cell tumour was found in 19 patients (83%). Three patients (13%) had TCC and one patient (4%) had an endodermal sinus tumour of the penile urethra. The penile urethra was involved in 15 patients (65%) and the bulbomembranous urethra in eight patients (35%) [15]. The study proposed that posterior urethral tumours required an en bloc resection of the penis, scrotum, prostate, bladder, and inferior pubic rami. This study reported that for proximal urethral cancers, the survival rate was below 30% at 31 mo. Similar results were published from the Memorial Sloan-Kettering Hospital by Dalbagni et al [17]. In this retrospective study, 46 patients had primary carcinoma of the bulbar (n = 28) and anterior (n = 18) urethra. The median follow-up was 125 mo. The OS rate was 83% for superficial disease versus 36% for invasive tumours. The OS rate was 26% for tumours of the bulbar urethra versus 69% for tumours of the anterior urethra.

In our cohort, all the patients underwent radical surgery, and our preference was to offer a panurethrectomy with radical prostatectomy and bladder neck closure combined with urinary diversion using either a suprapubic catheter or a Mitrofanoff. Patients with a suprapubic catheter who remained disease free for 12 mo were then offered conversion to a Mitrofanoff. This offered local disease control in all the patients.

Where there was a large disease burden at presentation, neoadjuvant chemotherapy was used for several reasons: preoperative chemotherapy may downsize the tumour and therefore allow a complete resection [13], and possible complications from surgery might impair the administration of adjuvant chemotherapy. Four of our patients underwent neoadjuvant chemotherapy, with one patient discontinuing treatment due to chemotherapy-related side effects. However, the disease burden is extensive, and patient performance status and symptoms dictate the need for early surgery even if it is on a palliative basis.

The lymphatic spread of anterior urethral SCC is similar to that of conventional penile SCC as they share the same pattern of lymphatic drainage. Although prophylactic lymph node dissection was initially considered controversial for urethral cancers, it is now accepted that urethral SCC should be managed along similar guidelines to those offered for penile SCC with respect to the management of inguinal lymph nodes [13]. When there are metastatic inguinal lymph nodes, the risk of metastatic pelvic lymph nodes increases and often a pelvic lymphadenectomy is performed [10,11]. In this cohort, five patients underwent bilateral inguinal lymphadenectomy because of suspicious lymph nodes found on imaging or positive preoperative FNAC, and only one patient underwent a pelvic lymphadenectomy. The small number of patients in the cohort does not allow a comparison between patients treated with or without lymphadenectomy. However, based on our data, we can see that radical inguinal lymphadenectomy may be required more often than anticipated based on the perceived drainage of proximal lesions directly to the pelvic nodes.

Data regarding the role of adjuvant systemic chemotherapy in urethral cancer are scarce and derived from small retrospective case series. It has been suggested that adjuvant chemotherapy has a role in locally advanced disease, and this multimodality approach has been associated with promising results. Selection of chemotherapy regimens is determined by the tumour histology. SCCs have traditionally been treated with cisplatin/5-FU or mitomycin C/5-FU chemotherapy [13,18]. Within our cohort, four patients were treated with cisplatin/5-FU or cisplatin/gemcitabine chemotherapy. A comparison of the outcomes between surgery and surgery plus adjuvant therapy in this series is not possible owing to the small number of patients. However, in previous studies, local recurrence rates are high, ranging from 50% to 57% [18]. Even aggressive surgical resection with pelvic exenteration with or without pelvic lymph node dissection resulted in a 63% local recurrence rate [15,19]. Likewise, survival rates for surgical monotherapy for proximal PUC have been reported between 0% and 38% [20–22].

EBRT and brachytherapy implants, or a combination of both, has been used in the management of urethral tumours [10–14]. Historically, EBRT has been used in the adjuvant setting following surgery for male urethral cancer. In our cohort, two patients underwent pelvic EBRT after chemotherapy and two patients after surgery for pelvic recurrences.

Based on our small cohort, we have developed a new algorithm for the management of proximal urethral SCC (Fig. 3). For those without metastatic disease on presentation, FNAC of the inguinal lymph nodes is required before offering a panurethrectomy. Depending on the performance status of the patient, we would either offer a temporary suprapubic catheterisation (SPC) with a delayed Mitrofanoff or construct a Mitrofanoff at the time of surgery. For those with advanced disease or distant metastases on presentation, neoadjuvant chemotherapy should be offered before proceeding to surgical resection.

This study has some limitations, mainly a result of the fact that it is a retrospective review of a small case series. Unfortunately, the rare nature of this disease makes it very difficult to perform large, randomised prospective studies.
Our cohort is small, and it is not suitable for any statistical advance analysis.

5. Conclusions

Proximal primary urethral SCC is a rare tumour, and our cohort is one of the largest described in the literature. Our results offer a guide for discussing the management of patients presenting with SCC of the proximal urethra: we believe that a prompt diagnosis and a multidisciplinary approach including neoadjuvant chemotherapy and surgery are likely to be the best management strategy for this aggressive tumour. Further multi-institutional randomised trials are required to standardise treatment and investigate novel targeted therapies.

Author contributions: Asif Muneer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Castiglione, Muneer.

Acquisition of data: Alnajjar, Christodoulidou.

Analysis and interpretation of data: Castiglione.

Drafting of the manuscript: Castiglione, Albersen.

Critical revision of the manuscript for important intellectual content: Muneer, Freeman, Jameson, Mitra, Nigam, Malone.

Statistical analysis: Parnham, Castiglione.

Obtaining funding: Muneer.

Administrative, technical, or material support: Castiglione, Muneer.

Supervision: Muneer.

Other: None.

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References