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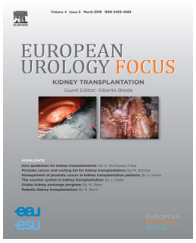

Review – Urothelial Cancer

# Current Disease Management of Primary Urethral Carcinoma

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## Abstract

*Context:* Primary urethral cancer (PUC) is a rare cancer entity. Owing to the low incidence of this malignancy, the main body of literature consists mainly of case reports, making evidence-based management recommendations difficult.
*Objective:* To review reported disease management strategies of PUC and their impact on oncological outcomes.
*Evidence acquisition:* A systematic research was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement using Medline, Scopus, and Web of Science, to find studies of the past 10 yr including ≥20 patients, and investigating treatment strategies and their impact on outcomes of the three most frequent histologies: urothelial carcinoma, adenocarcinoma, and squamous cell carcinoma.
*Evidence synthesis:* In localized PUC, penis-sparing surgery can be performed in males, while in females, complete urethrectomy with surrounding tissue is advised to minimize recurrence due to positive margins. Radiotherapy (RT) has worse survival and recurrence rates, as well as more adverse effects, than surgery, limiting its use in genital-preserving therapy. Locally advanced PUC should be treated with multimodal therapy, as monotherapies result in inferior recurrence and survival rates. Extent of surgery is still undecided, favoring radical cyst (oprostat)ectomy with total urethrectomy (RCU). Lymph node involvement is a predictor of survival, highlighting the role of lymph node dissection for disease control and staging. RT can improve survival in combination with surgery and/or chemotherapy (CHT). Neoadjuvant platinum-based CHT can improve overall and recurrence-free survival. At recurrence, salvage therapy with surgery and/or CHT can improve survival. Superficial urothelial carcinoma of the prostatic urethra can be treated with transurethral resection. Stromal invasion often features concomitant bladder cancer with a poor prognosis and requires RCU with or without systemic preoperative CHT.
*Conclusions:* PUC is a rare malignancy with an often poor natural course, requiring a stage- and gender-specific risk-based treatment strategy. The role of systematic perioperative CHT and the extent of surgery are becoming more important.
*Patient summary:* In this review, we looked at the treatment options for primary urethral cancer. We found that while an organ-confined disease can be managed with local resection, growth beyond the organ border makes a combination of different treatment modalities, such as surgery and systematic chemotherapy, necessary to improve outcomes.


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## 1. Introduction

Primary urethral cancer (PUC) is a rare malignancy that makes up <1% of all malignancies worldwide. It occurs almost three times as often in males than in females, and its incidence rises in the elderly (ie, >75 yr old) [1–4].

Suggested etiologies for PUC are chronic irritations of the urethra due to catheterization, chronic inflammation secondary to infection, radiation, urethral diverticula, and strictures [5–7]. An association between squamous cell carcinoma (SCC) and genital lichen sclerosus is also reported as a potential risk factor [8].

PUC has several histological subtypes arising from different cell types with potentially different biological and clinical behavior, requiring varied therapeutic approaches. The predominant histological type is urothelial carcinoma (UC) and is present in 54–65% of cases, followed by SCC (16–22%) and adenocarcinoma (AC; 10–16%). Other, rarer histological types include melanoma or sarcoma. Subtypes are not evenly distributed between genders, and their different origins can be explained by different urethral anatomies between the two sexes [1,3]. The differences have led to recent proposals for a new histological classification of PUC [9]. There is no doubt today that the diagnosis, therapy, and follow-up will depend on the histological classification and anatomic specifications of each tumor in the future. Until then, we try to develop individualized, risk-based, gender-specific strategies based on the existing evidence.

Most publications on PUC were based on small patient cohorts or case reports only. This results in limited knowledge on the optimal management of PUC compared with other malignancies. However, in recent years, larger, population-based and multicentric studies were published, providing new insights into this rare malignancy with a variable natural history. We aim to give an overview of the current literature in context with the established knowledge on PUC to help guide modern, optimized diagnosis and clinical management.

## 2. Evidence acquisition

To find all English studies of the past 10 yr investigating the therapeutic management of PUC, a systematic research was conducted in December 2018 in several online databases (PubMed, Cochrane, Scopus, and Web of Science) with the following search terms: ((((therapy) OR management) AND "last 10 years"[PDat])) AND (((urethral carcinoma) OR urethral cancer) AND "last 10 years"[PDat]). We included all original studies with a minimum of 20 patients. The minimum number of patients was chosen to assess statistically valuable data without omitting potential information on this disease. Studies had to focus on SCC, transitional cell carcinoma, or AC as a primary histology to provide a review of the most common patient groups of this rare malignancy. Interventions necessary for inclusion consisted of surgery, radiotherapy, and/or chemotherapy (CHT). An additional, similar systematic search was performed to find all original articles reporting on the diagnosis and treatment of UC of the prostatic urethra with the following search terms: (((outcome) AND ((urothelial carcinoma) OR transitional carcinoma)) AND prostatic urethra) AND "last 10 years"[PDat]). Reported overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), and/or recurrence-free survival (RFS) were the obligatory primary endpoints for inclusion. Studies investigating the same cohort were included, as long as new evidence on outcome was provided. The Newcastle-Ottawa Score was used to assess risk of bias across the studies [10]. Studies with a score of ≥6 were considered to be of "high quality".

## 3. Evidence synthesis

A total of 12 studies with 7853 patients were included according to the statement of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocols (Fig. 1, and Tables 1 and 2) [11–20]. Two large multicentric studies reported on the same cohort [14,15]. Three other studies were of single-center nature [13,16,21]. The rest of the studies investigated cohorts of the Surveillance, Epidemiology, and End Results (SEER) database or of the National Cancer Database (NCDB). A proposal of clinical disease management in consolidation of our findings and the guidelines of the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) is presented in Fig. 2 [22,23].

### 3.1. *Diagnostic evaluation and staging*

Clinicopathological staging and grading for PUC adheres to the classification given by the Union for International Cancer Control in 2017 and the World Health Organization in 2016 (Table 3) [24,25]. Approximately 50% of patients have locally advanced disease when they become symptomatic [26], presenting with macrohematuria, urethral bleeding, an extraurethral mass, and subvesical obstruction. Urine cytology has limited sensitivity of 50–80%, depending on the underlying histology [27]. Transurethral resection (TUR) or a cold biopsy is necessary for a histological confirmation [28]. In addition, cystoscopy of the bladder should be performed to detect concomitant bladder tumor, as urethral cancer could also be originating from the bladder through micrometastasis [29]. Indeed, approximately 2–5% of patients with superficial and 40–60% with muscle-invasive bladder cancer develop urethral cancer later on [29]. In contrast, Gakis et al [30] reported one case (0.9%) of secondary bladder cancer 41 mo after initial therapy for PUC.

Enlarged regional lymph nodes (LNs) are likely to represent metastatic disease (84%), making assessment of disease extent with pelvic magnetic resonance imaging for local staging obligatory [13,31,32]. Additionally, LN biopsy is proposed by the NCCN as well. Further, patients with invasive disease should receive computer tomography of the abdomen and thorax, or chest x-ray to detect distant metastasis [22].

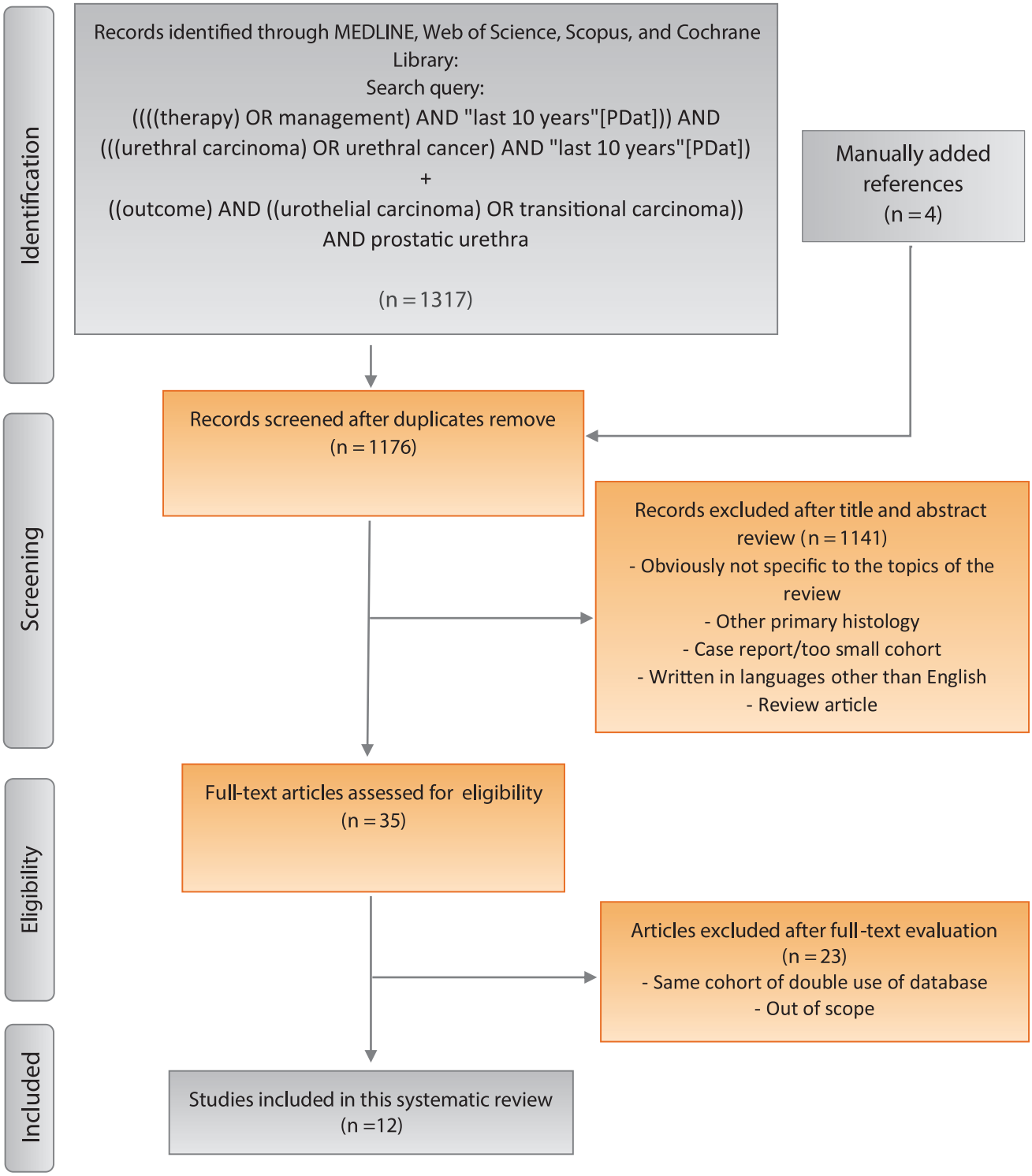


**Fig. 1 – Flow chart for article selection process to analyze the current disease management of primary urethral cancer according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.**

### 3.2. *Treatment of localized PUC*

#### 3.2.1. *Surgical approach in men and women*

While in the past, partial penectomy was the predominant option for treatment of PUC in men, today, current guidelines agree that surgical preservation of the penis can be achieved while maintaining good local cancer control [22,23,33]. This strategy has, indeed, become the preferred option. A distal location of the primary tumor has been shown to result in better survival [14,15,17]. Of note, the NCCN always recommends urethrectomy in men with or without cystoprostatectomy if the tumor is located in the

**Table 1 – Baseline characteristics, treatment, and outcomes of included studies investigating primary urethral cancer.**

| Author and year | *N* | Study design | Histology, *n* (%) | Stage, *n* (%) | Treatment | Survival rate (%) | Median survival time (mo) | Important findings | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Cahn et al (2017) [11] | 1749 | PUC pts. with locally advanced PUC (NCDB database) 2004–2013 | SCC: 513 (29.3)<br>UC:848 (48.5)<br>AC: 388 (22.2) | NR | -Local excision or CHT or RT<br>-RCU ± RT<br>-MMT: RCU + CHT ± RT | NR | OS for monotherapy: 30.1<br>OS for RCU ± RT: 42.6<br>OS for MMT: 33.4 | -No difference in outcome in OS depending on type of monotherapy<br>-In MMT patients only, OS improved in patients with UC histology (HR 0.61; 95% CI = 0.45–0.83; $p = 0.0016$) | 8 |
| Champ et al (2012) [12] | 359 | Female pts. with urethral or paraurethral cancer (SEER database) 1983–2008 | SCC: 92 (25.6)<br>UC: 85 (23.7)<br>AC: 133 (37.0)<br>Other: 49 (13.7) | T1–2: 177 (49.3)<br>T3–4: 179 (49.9)<br>Tx: 3 (0.8)<br>N0: 214 (66.9)<br>M0: 159 (100) | -Surgery (ablation, resection, none)<br>-RT (neoadjuvant, adjuvant, combined) | 5-yr OS: 43%<br>10-yr OS: 32%<br>5-yr CSS: 53%<br>10-yr CSS: 46% | NR | -Surgery only was associated with longer CSS (HR 0.60; 95% CI = 0.39–0.93)<br>-(Additional) RT and extent of surgery had no effect on CSS | 5 |
| Dayyani et al (2013) [13] | 44 | PUC pts. treated with CHT and/or surgery 2005–2009[a] | SCC: 17(39)<br>UC: 8 (19)<br>AC: 13 (30)<br>Other: 6 (13) | T1–2: 1 (2)<br>T3–4: 43 (98)<br>N0: 18 (41)<br>M0: 57 (84) | -Surgery + CHT (urethrectomy, RCU, LND, APE, penectomy, prostatectomy, other)<br>-CHT (CGI, Gem FLP, ITP, MVAC, other)<br>-CHT + surgery<br>-Other | 3-yr-RFS in platinum-based CHT: 50% | OS: 31.7<br>OS in platinum-based CHT + RCU: 25.6 | -OS of CHT patients improved by surgery (HR 0.4; 95% CI = 0.18–0.87; $p = 0.02$) | 6 |
| Gakis et al (2015) [14] | 124 | Nonmetastatic PUC pts. 1993–2012[b] | Only reported for subgroup with perioperative CHT ($n = 39$):<br>SCC: 11 (28.2)<br>UC: 17 (43.6)<br>AC: 6 (15.4)<br>Mixed: 3 (7.7)<br>Other: 2 (5.1) | ≤cT2N0: 98 (79.0)<br>≥cT3 and/or cN+: 26 (21.0) | -Surgery only<br>-Neoadjuvant CHT<br>-Neoadjuvant RCT + adjuvant CHT<br>-Adjuvant CHT<br>CHT regime:<br>-Mitomycin ± 5-FU<br>-Cisplatinum-based<br>-Gemcitabine based<br>-Other | 3-yr OS in CHT: 61%<br>3-yr OS in ≥ cT3 and/or cN+:<br>CHT + RCU: 100%<br>RCT: 100%<br>CHT + RCU: 20%<br>Surgery only: 50%<br>For patients with objective response to CHT + RCU:<br>3-yr OS in stable disease: 100%<br>3-yr OS in progressive disease: 58.3% | NR | -Improved 3-yr RFS (RR: 0.14; $p = 0.022$) and OS (RR: 0.10; $p = 0.024$) with neoadjuvant therapy in locally advanced patients | 8 |
| Gakis et al (2018) [15] | 139 | Nonmetastatic PUC pts. (prospective database) 1993–2012[b] | SCC: 55 (39.6)<br>UC: 71 (51.0)<br>AC: 10 (7.2)<br>Other: 3 (2.2) | ≤pT2: 84 (60.4)<br>≥pT3: 38 (27.4)<br>pTx: 17(12.2)<br>pN0: 48 (34.5) | Surgery (endoscopic, RCU and/or [partial] urethrectomy, prostatectomy) ± LND<br>RCT (40–45 Gy to pelvis + 20–24 Gy to primary tumor)± CHT<br>CHT (neoadjuvant, adjuvant, both) | 3-yr OS:<br>-No recurrence: 86.5%<br>-Solitary or concomitant recurrence: 74.5%<br>-Extraurethral recurrence: 48.2%<br>3-yr OS in patients with ST:<br>-RCT: 84.9%<br>-Surgery: 71.6%<br>-None: 38.0% | NR | -OS for patients with ST (surgery or RCT), comparable with patients with no recurrence ($p = 0.65$)<br>-In univariable analysis, OS improved for patients with ST (surgery or RCT) vs without surgery/RCT ST (overall $p < 0.045$); no difference in OS in surgery ST vs RCT ST | 8 |

**Table 1 (*Continued*)**

| Author and year | *N* | Study design | Histology, *n* (%) | Stage, *n* (%) | Treatment | Survival rate (%) | Median survival time (mo) | Important findings | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Peyton et al (2018) [16] | 39 | Female PUC pts. 2003–2017[a] | SCC: 5 (13)<br>UC: 11 (28)<br>AC: 22 (56)<br>Other: 1 (3) | Tis: 2 (5)<br>T1–2: 13 (33)<br>T3–4: 24 (62)<br>N0/Nx: 27 (69)<br>M0/Mx: 36 (92) | -Surgery (local excision, RCU) ± adjuvant CHT/RT/RCT<br>-Neoadjuvant RCT + RCU<br>-CHT<br>-RCT<br>Therapy regimes:<br>-Neoadjuvant: Cis ± etoposide + RT; Gem/Cis + RT; paclitaxel + RT; 5-FU/mitomycin + RT<br>-Adjuvant: RT; Gem/Cis; Carbo ± Taxol ± RT; Cis ± 5-FU + RT; 5-FU/oxaliplatin; pembrolizumab; RCU urethrectomy | NR | Nonmetastatic pts.:<br>OS in ≤ T1: 99<br>OS in ≥ T2:<br>-Overall: 36<br>-UC: 18<br>-SCC: 7<br>-AC: 48<br>-MMT: 36<br>-Non-MMT: 16<br>RFS in ≤ T1: Not reached<br>RFS in ≥ T2:<br>-Overall: 46<br>-MMT 58 mo<br>-Non-MMT: 16 mo | -No difference in OS and RFS with the use of MMT compared with monotherapy<br>Patients with recurrence or progression:<br>-No difference in OS with ST<br>-No difference in OS and RFS in patients with MMT compared with non-MMT | 6 |
| Rabbani (2011) [17] | 2065 | Male PUC pts. (SEER database) 1973–2006 | SCC: 245 (11.9)<br>UC: 1603 (77.6)<br>AC: 103 (5.0)<br>Other: 114 (5.5) | Ta/cis: 871 (42.2)<br>T1–2: 806 (39.0)<br>T3–4: 184 (8.9)<br>Tx: 204 (9.9)<br>N0: 1480 (71.7)<br>M0/Mx: 1966 (95.2) | -Surgery (none/biopsy, ablation, simple excision, radical resection, not otherwise specified, and unknown)<br>-RT (none, external beam radiation alone, brachytherapy, combination of external beam and brachytherapy, not otherwise specified, and unknown) | 5-yr OS: 46.2<br>10-yr OS: 29.3 | NR | Multivariable analysis:<br>-OS and CSS improved with RCU compared with no intervention/biopsy (HR 1.56; $p < 0.001$/HR 1.66; $p = 0.002$)<br>-CSS improved with surgery alone compared with RT alone or no treatment ($p = 0.001$/$p < 0.001$)<br>-CSS improved with surgery + RT compared with no surgery and no RT ($p = 0.017$) | 7 |
| Son et al (2018) [18] | 2614 | Nonmetastatic PUC pts. with surgery and/or RT (NCDB) 2004–2013 | SCC: 622 (24)<br>UC: 1509 (58)<br>AC: 306 (12)<br>Other: 177 (7) | T0–1: 724 (28)<br>T2: 515 (19)<br>T3–4: 570 (21.8)<br>Tx: 805 (31)<br>N0: 1635 (62) | -Surgery (local or radical)<br>-RT ± external beam radiotherapy (median ≥60 Gy to pelvis) ± CHT<br>-Surgery + RT (median ≥30.6 Gy)<br>-No local therapy | 3-yr OS:<br>-All pts. 54%<br>-SCC: 41%<br>-UC: 33%<br>-AC: 42%<br>-No local treatment: 37%<br>-Surgery: 58%<br>-RT ± CHT: 44%<br>-Surgery + RT: 57%<br>3-yr OS in T1–2 N0:<br>Surgery: 28%<br>Surgery + RT: 60%<br>RT: 42%<br>3-yr OS in T3–4 and/or N+:<br>No local therapy: 28%<br>RT: 44%<br>Surgery + RT: 52% | | -OS in all treatment types was associated with CHT and RCT (overall $p < 0.05$)<br>-Absence of local therapy was an independent factor for worse OS (no HR reported)<br>-Postoperative RT was an independent factor for improved OS in general (HR 0.77) and locally advanced patients (HR 0.58), but stratified to histology only in UC (HR 0.45) and AC (see below) (all $p \leq 0.01$)<br>-In early stage, there was no difference in OS according to treatment<br>-In AC patients, OS was better with RT or surgery + RT compared with surgery alone (HR 0.20 and 0.27), but OS was worse with chemotherapy (HR 3.43; all $p \leq 0.01$) | 8 |

**Table 1 (*Continued*)**

| Author and year | *N* | Study design | Histology, *n* (%) | Stage, *n* (%) | Treatment | Survival rate (%) | Median survival time (mo) | Important findings | NOS |
|---|---|---|---|---|---|---|---|---|---|
| Wei et al (2017) [19] | 453 | PUC pts. (SEER database) 2004–2013 | SCC: 165 (36.4)<br>UC: 202 (44.6)<br>AC: 86 (19) | T0–1: 134 (29.6)<br>T2: 115 (25.6)<br>T3–4/x: 203 (44.8)<br>N0: 313 (69.1)<br>M0: 377 (83.2) | -Surgery<br>-RT<br>-Surgery + RT | 5-yr CSS in men/women: 52.52/44.89<br>5-yr OS in men/women: 38.52/35.88 | CSS men/women: 63/52<br>OS men/women: 32/39 | -Significantly better OS for women 8 when surgery is performed (HR 0.56; $p = 0.03$) | |

AC = adenocarcinoma; Carbo = carboplatin; CGI = cisplatin, gemcitabine, and ifosfamide; CHT = chemotherapy; CI = confidence interval; Cis = cisplatin; CSS = cancer-specific survival; 5-FU = 5-fluorouracil; Gem = gemcitabine; Gem-FLP = gemcitabine, 5-fluorouracil, leucovorin, and cisplatin; HR = hazard ratio; ITP = ifosfamide, paclitaxel, and cisplatin; LND = lymph node dissection; MMT = multimodal therapy (consisting of a combination of surgery, chemotherapy, and radiotherapy); MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; NCDB = National Cancer Database; NOS = Newcastle-Ottawa Score; NR = not reported; OS = overall survival; pts. = patients; PUC = primary urethral cancer; RCT = radiochemotherapy; RCU = radical cyst(oprostat)ectomy with total urethrectomy; RFS = recurrence-free survival; RR = risk ratio; RT = radiotherapy; SCC = squamous cell carcinoma; SEER = Surveillance, Epidemiology and End Results; Taxol = paclitaxel; UC = urothelial carcinoma.

[a] Single-institutional study.

[b] Multi-institutional study of 10 clinical centers; a prospective databank was used for retrospective assessment.

bulbous urethra [23]. While several retrospective series have reported no recurrence after local excision in males, positive margins have been found to increase the risk of recurrence. Therefore, as recommended by the EAU guidelines, complete circumferential excision, especially of the proximal margin, should be performed in combination with a perineal urethrostomy [22,34].

In contrast, in women, current guidelines recommend removal of the complete urethra with a wide margin of periurethral tissue and the bulbocavernous muscle up to the bladder neck and pelvic bone [22,23,35], since a simultaneous proximal and distal tumor location results in shorter PFS [36,37]. In these cases, a suprapubic urostomy or pouch is necessary for urinary diversion. While partial urethrectomy or TUR in women can be performed, recurrence rates were up to 60% and survival decreased significantly [38]. In case of female PUC in urethral diverticula, diverticulectomy has been proposed in a recent review [39]. However, the low number of assessed patients was suboptimal for reporting relevant outcomes; 50% of patients with T2 stage ($n = 3$) were disease free after a mean follow-up of 66 mo. Importance of thorough surgical excision of the primary lesion is the key to local disease control. Thus, partial urethrectomy should be considered only if complete tumor resection can be guaranteed, as PFS and OS are the most important endpoints in this disease with limited salvage therapeutic options in case of failure. Interestingly, in contrast to EAU guidelines, the NCCN does not recommend bladder-sparing surgery in women at all [23].

#### 3.2.2. *Radiotherapy in female patients*

Local radiotherapy (RT) with a median of 50–65 Gy through external beam therapy or brachytherapy can provide an alternative to surgery in women [37]. While treatment is possible and 5-yr survival is up to 41%, almost half of the patients suffer from treatment-related adverse effects such as stenosis, fistulas, hemorrhage of the bladder, and/or necrosis [37]. Furthermore, worse outcome at extension of the tumor over the whole urethra has to be taken into consideration [37]. A recent single-center study by Derksen et al [21] demonstrated better survival in surgically treated patients than in RT-treated patients, although no statistical analysis was given. A population-based NCDB study by Son et al [18] revealed no benefits in OS for patients treated with surgery combined with RT for stage T1-T2, limiting recommendation for a combined therapeutic approach. The NCCN recommends chemoradiotherapy in T2 patients as an alternative to surgery; however, currently available data are sparse and mostly restricted to case reports [23].

### 3.3. *Treatment of locally advanced PUC*

According to NCCN guidelines, primary treatment of patients with unsuspicious LNs consists of chemoradiation (CRT) and possibly surgery, neoadjuvant CHT with consolidative surgery, or RT monotherapy. At clinically positive LN metastasis, consolidative surgery is considered optional in combination with CHT and/or RT [23].

**Table 2 – Baseline characteristics, treatment, and outcomes of included studies investigating urothelial cancer of the prostatic urethra.**

| Author and year | *N* | Study design | Stage, *n* (%) | Treatment | Survival rate (%) | Median survival time (mo) | Important findings | NOS |
|---|---|---|---|---|---|---|---|---|
| Gofrit et al (2009) [58] | 20 | Pts. without stromal invasion, tumor extension of bladder cancer, or previous MIBC 1988–2005 | NR | 6/12 wk BCG therapy + TURP | Only prostatic:<br>5-yr RFS: 90%<br>Prostatic urethra and bladder:<br>5-yr RFS: 30% | NR | Higher complete response rates compared with pooled data of studies with BCG therapy only (95.3% vs 66%; $p < 0.001$) when analyzing prostatic invasion only; no difference when comparing pts. with tumor in bladder and prostatic urethra | 6 |
| Ichihara et al (2014) [59] | 46 | Pts. treated with RC 1990–2016 | Stage of bladder cancer:<br>≤T1: 11 (24)<br>T2: 7 (15)<br>T3: 6 (13)<br>T4: 22 (48) | RC ± chemotherapy (MVAC) | Contiguous pattern[a]:<br>5-yr OS: 34.4%<br>Noncontiguous:<br>5-yr OS: 50.9% | NR | Stromal invasion (HR 6.82; $p = 0.04$) and lymph node metastasis (HR 6.97; $p = 0.03$) associated with worse OS in MVAC | 7 |
| Knoedler et al (2014) [60] | 201 | Pts. treated with RC 1980–2006 | Stage of urothelial cancer of prostatic urethra:<br>Tis: 93 (46)<br>T2: 43 (21)<br>T4a: 66 (32)<br>Stage of bladder cancer:<br>≤T1: 82 (40)<br>T2: 40 (20)<br>T3: 16 (8)<br>Associated CIS: 33 (16) | RC ± chemotherapy | 5-yr local RFS:<br>-Tis: 55%<br>-T2: 71%<br>-T4a: 67%<br>5-yr CSS total:<br>-Tis: 73%<br>-T2: 57%<br>-T4a: 21%<br>5-yr CSS prostatic only:<br>-Tis: 83%<br>-T2: 73%<br>5-yr CSS + conc. bladder cancer only:<br>-Tis: 58%<br>-T2: 17%<br>5-yr OS:<br>-Tis: 54%<br>-T2: 51%<br>-T4a: 15% | NR | In multivariable analysis, higher prostatic tumor stage (HR 2.17; $p = 0.009$), lymph node invasion (HR 2.06; $p = 0.003$), and concurrent bladder cancer (HR 4.50; $p < 0.001$) associated with worse CSS | 7 |

BCG = bacillus Calmètte-Guerin; CIS = carcinoma in situ; HR = hazard ratio; MIBC = muscle-invasive bladder cancer; MVAC methotrexate, vinblastine, doxorubicin, and cisplatin; NR = not reported; NOS = Newcastle-Ottawa Score; OS = Overall Survival; pts. = patients; RC = radical cystoprostatectomy; RFS = recurrence-free survival; TURP = transurethral resection of the prostate.

[a] Contiguous pattern was defined as T4 stadium and represented direct invasion of bladder cancer into the prostate.

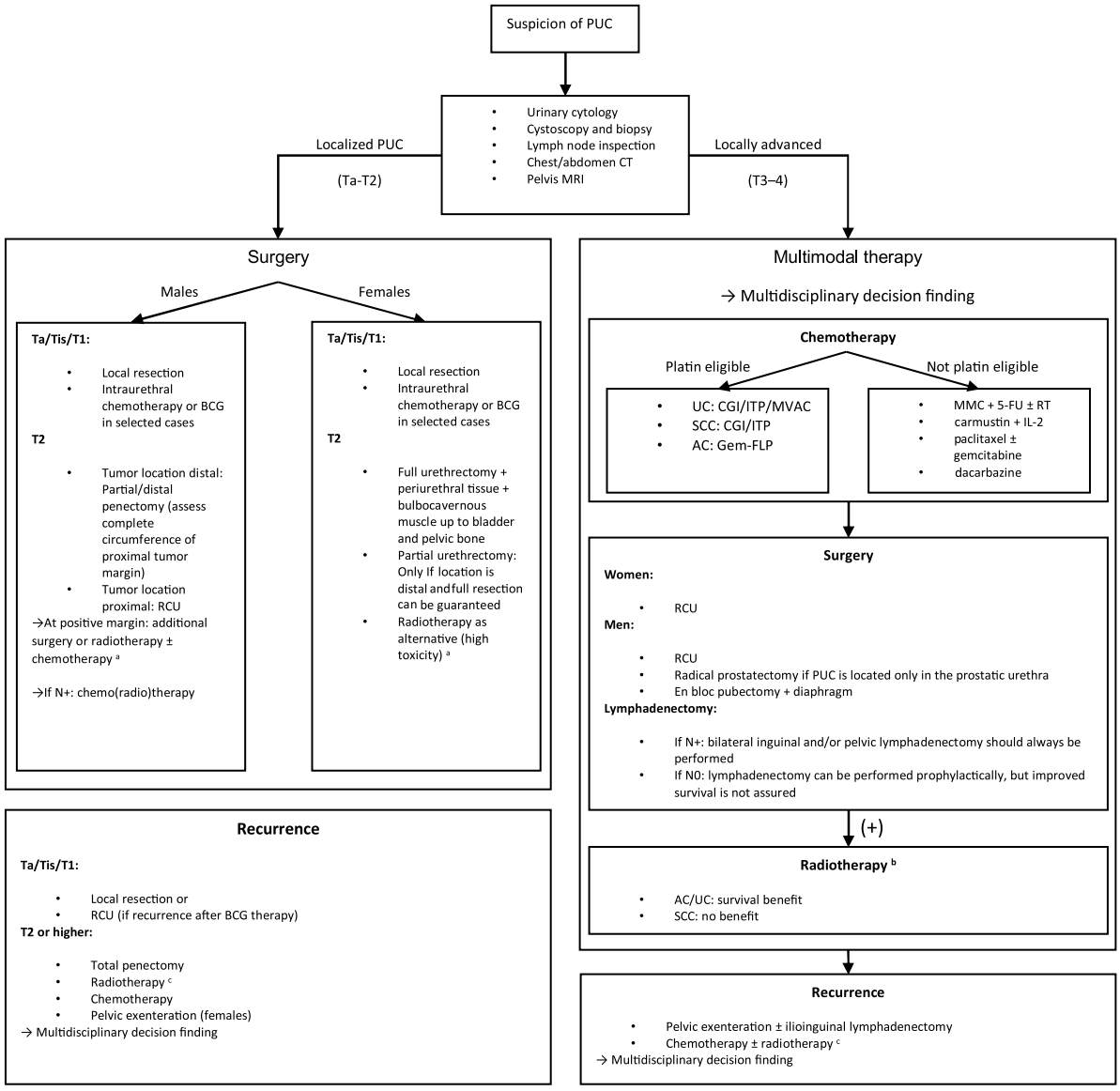


**Fig. 2 – Suggested disease management of primary urethral carcinoma.**
**AC = adenocarcinoma; BCG = bacillus-Calmètte-Guerin therapy; CGI = cisplatin, gemcitabine, and ifosfamide; CT = computer tomography; 5-FU = 5-fluorouracil; Gem-FLP = gemcitabine, 5-fluorouracil, leucovorin, and cisplatin; IL-2 = interleukin-2; ITP = ifosfamide, paclitaxel, and cisplatin; MMC = mitomycin; MRI = magnetic resonance imaging; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; N0 = no lymph node metastasis; N+ = lymph node metastasis; PUC = primary urethral carcinoma; RCU = radical cyst(oprostat)ectomy with total urethrectomy; RT = radiotherapy; SCC = squamous cell carcinoma; UC = urothelial carcinoma.**
**[a]cT2cN0 should receive 66–70 Gy external beam radiation therapy (EBRT) to the tumor with possible prophylactic treatment of regional lymph nodes. N + should receive 45–50 Gy EBRT to the tumor (boost to 66–70 Gy if possible) and regional lymph nodes according to location (boost to 54–66 Gy if possible). Concurrent chemotherapy according to bladder cancer regimens should be considered. In females, EBRT with 50–55 Gy to the tumor (with a boost of 10–15 Gy if possible) and the lymph nodes has been proposed.**
**[b]45–50.4 Gy EBRT to resection bed, and inguinal and pelvic lymph nodes. Boost resection margins and extranodal extensions to 54–60 Gy and areas of gross residual disease to 66–70 Gy EBRT. Concurrent chemotherapy according to bladder cancer regimens should be considered.**
**[c]66–74 Gy EBRT to gross disease in suspected areas of recurrence (up to 74 Gy for larger tumors and non-UC) and, if possible, 45–50.4 Gy to regional lymph nodes.**

While the EAU guidelines strongly recommend interdisciplinary disease management, suggestions for curative CRT for SCC and platinum-based neoadjuvant CHT for other histological subtypes are weak [22].

### 3.3.1. *Surgery for the primary tumor*

Advanced PUC requires a radical surgical approach, often consisting of radical cyst(oprostat)ectomy with total urethrectomy (RCU) or a (partial) penectomy. Other surgical procedures such as anterior pelvic exenteration in women have also been reported [13]. Historical cohorts report long-term OS rates of 11–42% in women and 0–38% in men with advanced PUC [40]. In several smaller studies, males who underwent pelvic exenteration combined with en bloc pubectomy including the genitourethral diaphragm (possibly with lymphadenectomy and RT) had fewer recurrences

**Table 3 – TNM classification and 2016 WHO grading for primary urethral carcinoma.**

| T—primary tumor | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Urethra (male and female) | |
| Ta | Noninvasive papillary, polypoid, or verrucous carcinoma |
| Tis | Carcinoma in situ |
| T1 | Tumor invades subepithelial connective tissue |
| T2 | Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle |
| T3 | Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension) |
| T4 | Tumor invades other adjacent organs (invasion of the bladder) |
| Urothelial (transitional cell) carcinoma of the prostate | |
| Tis pu | Carcinoma in situ, involvement of prostatic urethra |
| Tis pd | Carcinoma in situ, involvement of prostatic ducts |
| T1 | Tumor invades subepithelial connective tissue (for tumors involving prostatic urethra only) |
| T2 | Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle |
| T3 | Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension) |
| T4 | Tumor invades other adjacent organs (invasion of the bladder or rectum) |
| N—regional lymph nodes | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single lymph node |
| N2 | Metastasis in multiple lymph nodes |
| M—distant metastasis | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Grading of urothelial urethral carcinoma | |
| PUNLMP | Papillary urothelial neoplasm of low malignant potential |
| Low grade | Well differentiated |
| High grade | Poorly differentiated |
| Grading of nonurothelial urethral carcinoma | |
| Gx | Tumor grade not assessable |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |

TNM = tumor-node-metastasis; WHO = World Health Organization.

(24%) than patients without en bloc resection in proximal PUC (63%) [41,42]. However, with no unified study design preventing selection bias, the results have to be interpreted with care. Indeed, a retrospective cohort study by Dalbagni et al [43] reported RFS of 51% after 5 yr for patients treated with surgery only, with only 56% being metastasis free. Only a few cases of advanced PUC have been managed with penile/urethral preservation [35,41]. Nevertheless, since the quality of life is generally gravely decreased after radical surgical approaches, future research should aim at identifying a personalized multimodal approach to advanced PUC to improve oncological results as well as preserving genital and urethral integrity.

#### 3.3.2. *Lymphadenectomy*

Similar to UC of the other locations, pathological LN metastasis is an independent prognostic factor for worse OS in PUC patients even with no metastasis at diagnosis ($p < 0.001$) [31,44]. Patients with pathological LN metastasis have been reported to have significantly lower RFS rates and shorter CSS after 5 yr (overall $p = 0.01$) [38]. The differential lymph drainage of anterior PUC into inguinal LN and of tumors located in the posterior urethra to the pelvic LNs has to be taken into consideration for clinical decision making [45]. At RCU, a lymphadenectomy template similar to bladder cancer can be performed, including all pelvic LNs [46]. However, due to the drainage of PUC in distal location into the inguinal LNs, a combined inguinal and pelvic lymphadenectomy is advised, especially in PUC that reaches beyond the bulbous into the pendulous urethra. If the PUC is located solely in the distal pendulous urethra, sole resection of the superficial and deep inguinal LNs can be considered. Owing to the difficulty in assessing LN status clinically by current imaging tools, prophylactic treatment has been suggested [35]. However, due to the scarcity of data, no definite statement can be made regarding the therapeutic value of an adequate lymphadenectomy template in patients with PUC.

#### 3.3.3. *Multimodal treatment*

While still underused today, multimodal therapy (MMT), consisting of a combination of surgery, CHT, and/or RT, is probably necessary for most patients with advanced PUC. Peyton et al [16] could not prove significant improvement in

OS or RFS for patients treated with MMT compared with those treated with monotherapy (ie, median OS of 36 vs 16 mo and median RFS of 58 vs 16 mo), likely due to its small cohort size.

Several smaller studies have reported promising OS of up to 83% after 1 yr of CRT [41]. However, high heterogeneity in treatment regimens and study populations limits interpretation of the results. For example, Thyavihally et al [47] showed median 5-yr OS and 5-yr RFS of only 49% and 23%, respectively. If systemic CHT is provided before surgery, response to this treatment is essential for sustained OS [48]. In the follow-up of combined RT and concurrent CHT with 5-fluorouracil and mitomycin, all nonresponders died during the follow-up, even those who underwent salvage surgery. Of 15 patients with an objective response, four out of five patients who suffered disease recurrence were alive 5 yr after salvage surgery [48]. These findings suggest a beneficial effect of MMT on oncological outcomes. Furthermore, concurrent RT and CHT may help in genital preservation strategies similarly to bladder cancer [41,49]. However, outcomes for patients with advanced PUC are still relatively poor despite MMT. Well-designed prospective studies are needed to assess the optimal treatment strategy, and benefits and shortcomings of different modalities. Until then, our strategy has been to offer MMT, consisting of surgery and neoadjuvant CHT, as building blocks that can be enhanced in select cases with adjuvant RT, to all patients with advanced PUC, with the hope of resulting in durable local and distant disease control.

#### 3.3.4. *Influence of RT on survival outcomes*

A positive effect of the combination of surgery and RT compared with monotherapy has been reported previously [41]. While surgery alone was associated with better CSS than RT alone in the SEER studies of Rabbani [17] ($p = 0.018$) and Champ et al [12] ($p = 0.001$), Wei et al [19] found surgery to be an independent factor for better OS and CSS in women treated with RT ($p = 0.003$). Furthermore, Son et al [18] reported that in the NCDB cohort, the absence of local therapy (surgery and/or RT) was an independent factor for worse OS (no $p$ value reported). In addition, the combination of surgery and adjuvant RT resulted in the best OS probabilities ($p < 0.01$). Interestingly, the use of both RT alone (hazard ratio [HR] 0.20; 95% confidence interval [CI], 0.07–0.60) and in combination with surgery (HR 0.27; 95% CI, 0.10–0.75) were associated with better OS in patients with AC histology, while CHT alone was associated with worse OS (HR 3.43; 95% CI, 1.40–8.39; $p < 0.01$). In UC patients, adjuvant RT improved OS as well (HR 0.45; 95% CI, 0.26–0.77; $p < 0.01$), while there was no difference of OS in patients with SCC who received adjuvant RT. From the investigated studies, it seems that RT monotherapy is inferior to a combined approach with surgery. Indeed, past studies reported 5-yr OS of only 0–25% in males and up to 50% in females treated with RT monotherapy [40]. Moreover, 2-yr recurrence rates of 95% have been reported under RT monotherapy, with a limited local control of under 50% at 5 yr [42]. Gakis et al [15] observed a more frequent use of palliative CHT in patients with initial RT, possibly indicating a higher risk of metastasis. These findings suggest that a combination with other treatment modalities is preferable to improve OS in patients, especially in patients with AC and UC histologies.

#### 3.3.5. *Influence of systemic CHT on survival outcomes*

CHT regimens for PUC depend on the underlying histology. While a platinum-based therapy is preferable for UC and SCC, chemotherapeutic strategies for AC differ based on the origin of cancer [50]. Therefore, a correct therapy schema is difficult to assess for PUC, especially because of a possible overlap in histological features [9]. Platinum-based therapy is the most common CHT already proposed in an early, larger cohort study by Dinney et al [42], where prolonged survival for metastatic patients with CHT was reported. Similar to bladder cancer [51], perioperative CHT seems to improve oncological survival. Reported alternatives for patients who are unable to receive a platinum-based CHT are rare and consist of mitomycin/5-fluorouracil with or without RT, paclitaxel with or without gemcitabine, carmustin/interleukin-2, or dacarbazine [14,16]. Mitomycin and 5-fluorouracil in combination with concurrent RT showed promising results, with more than half of the patients being disease free after 5 yr [48].

Median OS of patients treated with platinum-based CHT in the single-center study of Dayyani et al [13] was 25.6 mo, which is shorter than the rate reported for the complete cohort (31.7 mo). However, the median OS of alive patients at the median follow-up was 42.0 mo with a 3-yr survival rate of 50%, supporting the beneficial impact of platinum-based CHT [13]. Potential CHT regimes included cisplatin, gemcitabine, and ifosfamide (CGI); ifosfamide, paclitaxel, and cisplatin (ITP); or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) for UC patients; CGI or ITP for SCC patients; and gemcitabine, 5-fluorouracil, leucovorin, and cisplatin for AC patients. Resection of the primary tumor together with perioperative CHT resulted in longer OS than CHT alone ($p = 0.02$) [13].

Finally, in a large study based on a multi-institutional cohort, Gakis et al [14] have shown that 3-yr OS and PFS were significantly improved by neoadjuvant CHT with or without adjuvant therapy, compared with adjuvant therapy, only in patients with advanced disease($p = 0.022$ and $p = 0.024$, respectively). Although this implies superiority of neoadjuvant treatment to adjuvant treatment, evidence is vague at best.

### 3.4. *Therapy for recurrent PUC*

Local or distant recurrence after initial therapy occurs in up to 71% of patients after 5 yr, with median 5-yr RFS of 24–63% [38,41]. Of note, recurrence occurs more often in proximal than in distal location (50–57% vs 8–33%) [42,52]. While prevention of recurrence and progression is essential for improving OS, investigation of salvage therapy after recurrence is sparse. The EAU guidelines suggest RT or surgery, while the NCCN considers systemic (mono)therapy as well [22,23]. Peyton et al [16] reported no difference in OS between patients presenting with metastasis and those

who experienced disease recurrence treated with a salvage therapy ($p = 0.56$).

In the largest study to date, Gakis et al [15] stratified outcomes according to therapy for disease recurrence. Clinical LN metastasis and distal tumor location were independent prognostic factors for recurrence. Only extraurethral recurrence significantly affected 3-yr OS compared with no recurrence (48.5% vs 86.5%, $p = 0.002$), while a solitary or concomitant recurrence did not (74.5%). In contrast to these results, Peyton et al [16] reported that salvage surgery or CRT improved 3-yr OS ($p < 0.001$ and $p = 0.045$, respectively) to almost match that of patients without recurrence ($p = 0.065$). Interestingly, no difference in survival was observed between different salvage therapies. However, reasons for this can be attributed to the limited information given by the NCDB and a focus on female nonmetastatic patients. This strongly suggests superiority of salvage therapy, albeit no specific recommendations can yet be given regarding the best therapeutic modality.

### 3.5. *Treatment of UC of the prostate*

UC in the prostatic urethra is a rare disease and often features concomitant bladder cancer (Table 2). Many patients already have stromal invasion at the point of diagnosis, which in turn affects OS, making careful assessment even more important [53,54]. Historically, prognosis for these patients was poor, with only a few 2-yr survivors being present [53]. Owing to this, efforts have been made to optimize therapy. A combined approach of TUR and bacillus Calmètte-Guerin (BCG) therapy in patients with noninvasive disease can suffice to assure satisfactory outcomes with complete response rates of up to 75% and 5-yr RFS rates of 90% [55–57]. This is also recommended by the current guidelines and is in line with the findings of Gofrit et al [58], who reported a better response rate of patients treated with TUR of the bladder B and BCG compared with BCG therapy only [22 23]. A thorough follow-up with cystoscopy and urine cytology is important to identify recurrences early, which are often best treated with radical RCU with or without perioperative CHT [55–57].

Prostatic involvement of PUC is invasive in 7.6–16.6% of cases and is associated with 12–48% non–muscle-invasive concomitant bladder cancer. Both these factors were found to be associated with worse outcomes [56,59,60]. If involvement of prostatic ducts and acini is present, UC in the prostatic urethra is often located at 5 or 7 o'clock superficially, but deeper invasion cannot be ruled out and a radical RCU is advised [61,62]. Since LN invasion often occurs above the iliac bifurcation and possibly affects OS, platinum-based neoadjuvant CHT as well as neoadjuvant RT has been proposed in the past. This combination has resulted in improved OS, while recommendations on adjuvant therapy cannot be made yet [56].

An extended pelvic lymphadenectomy is strongly recommended in patients with nodal invasion, those with disease recurrence, or those who did not respond to BCG therapy [22,56]. However, most current studies include patients with concomitant bladder cancer, making a proper assessment of the biological and clinical impact of UC of the prostatic urethra on survival difficult.

## 4. Conclusions

PUC is a rare malignancy with weak evidence mostly from studies with few patients. Location, sex, and nodal involvement affect therapy and prognosis, and have to be taken into consideration to achieve the best disease management. Localized, low-grade disease can be treated with penile-sparing surgery in males, while female patients require urethrectomy with extensive margins. Positive margins result in significantly worse survival and should be avoided at all costs. RT should be offered only to female patients in whom surgery is refused or impossible.

In locally advanced PUC, surgery usually consists of (partial) penectomy or RCU. Anterior pelvic exenteration can be improved by en bloc resection. LN metastasis is associated with worse survival and lymphadenectomy should be considered prophylactically in advanced PUC patients, as it informs about tumor stage and has, potentially, a therapeutic benefit.

Advanced disease should be treated with MMT to increase OS and RFS. In some cases, CRT can even result in genital preservation. While RT improves outcome especially in patients with AC and UC histology, a multimodal approach is beneficial. Platinum-based CHT can improve OS and PFS, and should be used in a neoadjuvant setting followed by surgery.

Research on recurrence is still sparse. However, salvage therapy is likely to improve oncological outcomes, warranting a multidisciplinary approach to therapy based on evidence.

UC of the prostatic urethra is rare and often occurs with concomitant bladder cancer. If noninvasive, a TUR and consecutive BCG therapy can be attempted with curative intent. Carcinomas with stromal invasion and BCG-unresponsive patients with recurrence require a radical surgical approach with RCU and lymphadenectomy. Neoadjuvant RT or platinum-based CHT should be considered in all patients with advanced disease.

PUC is still largely under-researched, rendering an adequate recommendation for therapy difficult. Future research should focus on multi-institutional studies to increase population sizes, and improve our knowledge and understanding of this malignancy.

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## References

[1] Visser O, Adolfsson J, Rossi S, et al. Incidence and survival of rare urogenital cancers in Europe. Eur J Cancer 2012;48:456–64.
[2] Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer 2011;47:2493–511.
[3] Swartz MA, Porter MP, Lin DW, Weiss NS. Incidence of primary urethral carcinoma in the United States. Urology 2006;68:1164–8.
[4] Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. Urol Oncol 2009;27:653–67.
[5] Van de Voorde W, Meertens B, Baert L, Lauweryns J. Urethral squamous cell carcinoma associated with urethral stricture and urethroplasty. Eur J Surg Oncol 1994;20:478–83.
[6] Thomas AA, Rackley RR, Lee U, Goldman HB, Vasavada SP, Hansel DE. Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations. J Urol 2008;180:2463–7.
[7] Cupp MR, Malek RS, Goellner JR, Espy MJ, Smith TF. Detection of human papillomavirus DNA in primary squamous cell carcinoma of the male urethra. Urology 1996;48:551–5.
[8] Guo H, Peng X, Jin C, Wang L, Chen F, Sa Y. Lichen sclerosus accompanied by urethral squamous cell carcinoma: a retrospective study from a urethral referral center. Am J Mens Health 2018;12:1692–9.
[9] Zhang M, Adeniran AJ, Vikram R, et al. Carcinoma of the urethra. Hum Pathol 2018;72:35–44.
[10] Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Web site http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf Ottawa Hospital Research Institute; 2000
[11] Cahn DB, Handorf E, Ristau BT, et al. Contemporary practice patterns and survival outcomes for locally advanced urethral malignancies: a National Cancer Database analysis. Urol Oncol 2017;35(670):e15–21.
[12] Champ CE, Hegarty SE, Shen X, et al. Prognostic factors and outcomes after definitive treatment of female urethral cancer: a population-based analysis. Urology 2012;80:374–81.
[13] Dayyani F, Pettaway CA, Kamat AM, Munsell MF, Sircar K, Pagliaro LC. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol 2013;31:1171–7.
[14] Gakis G, Morgan TM, Daneshmand S, et al. Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma. Ann Oncol 2015;26:1754–9.
[15] Gakis G, Schubert T, Morgan TM, et al. The prognostic effect of salvage surgery and radiotherapy in patients with recurrent primary urethral carcinoma. Urol Oncol 2018;36(10), e7–4.
[16] Peyton CC, Azizi M, Chipollini J, et al. Survival outcomes associated with female primary urethral carcinoma: review of a single institutional experience. Clin Genitourin Cancer 2018;16, e1003–13.
[17] Rabbani F. Prognostic factors in male urethral cancer. Cancer 2011;117:2426–34.
[18] Son CH, Liauw SL, Hasan Y, Solanki AA. Optimizing the role of surgery and radiation therapy in urethral cancer based on histology and disease extent. Int J Radiat Oncol Biol Phys 2018;102:304–13.
[19] Wei Y, Wu YP, Xu N, et al. Sex-related differences in clinicopathological features and survival of patients with primary urethral carcinoma: a population-based study. OncoTargets Ther 2017;10:3381–9.
[20] Moher D, Shamseer L, Clarke M, et al. Preferred Reporting Items for Systematic Review and Meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[21] Derksen JW, Visser O, de la Riviere GB, Meuleman EJ, Heldeweg EA, Lagerveld BW. Primary urethral carcinoma in females: an epidemiologic study on demographical factors, histological types, tumour stage and survival. World J Urol 2013;31:147–53.
[22] Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013;64:823–30.
[23] Spiess PE, Agarwal N, Bangs R, et al. Bladder cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:1240–67.
[24] Comperat E, Varinot J. Immunochemical and molecular assessment of urothelial neoplasms and aspects of the 2016 World Health Organization classification. Histopathology 2016;69:717–26.
[25] Brierley DJ, Gospodarowicz K, Wittekind C, editors. TNM classification of malignant tumours. ed. 8. UICC International Union Against Cancer. Wiley/Blackwell; 2017. p. 208.
[26] Gheiler EL, Tefilli MV, Tiguert R, de Oliveira JG, Pontes JE, Wood Jr DP. Management of primary urethral cancer. Urology 1998;52:487–93.
[27] Touijer AK, Dalbagni G. Role of voided urine cytology in diagnosing primary urethral carcinoma. Urology 2004;63:33–5.
[28] Donat SM, Wei DC, McGuire MS, Herr HW. The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. J Urol 2001;165:1580–4.
[29] Kakizoe T, Tobisu K. Transitional cell carcinoma of the urethra in men and women associated with bladder cancer. Jpn J Clin Oncol 1998;28:357–9.
[30] Gakis G, Efstathiou JA, Daneshmand S, et al. Oncological outcomes of patients with concomitant bladder and urethral carcinoma. Urol Int 2016;97:134–41.
[31] Gakis G, Morgan TM, Efstathiou JA, et al. Prognostic factors and outcomes in primary urethral cancer: results from the international collaboration on primary urethral carcinoma. World J Urol 2016;34:97–103.
[32] Itani M, Kielar A, Menias CO, et al. MRI of female urethra and periurethral pathologies. Int Urogynecol J 2016;27:195–204.
[33] Smith Y, Hadway P, Ahmed S, Perry MJ, Corbishley CM, Watkin NA. Penile-preserving surgery for male distal urethral carcinoma. BJU Int 2007;100:82–7.
[34] Torbrand C, Hakansson U, Ehrnstrom R, Liedberg F. Diagnosing distal urethral carcinomas in men might be only the tip of the iceberg. Clin Genitourin Cancer 2017;15:e1131–1135.
[35] Karnes RJ, Breau RH, Lightner DJ. Surgery for urethral cancer. Urol Clin North Am 2010;37:445–57.
[36] Kang M, Jeong CW, Kwak C, Kim HH, Ku JH. Survival outcomes and predictive factors for female urethral cancer: Long-term experience with Korean patients. J Korean Med Sci 2015;30:1143–9.
[37] Garden AS, Zagars GK, Delclos L. Primary carcinoma of the female urethra. Results of radiation therapy. Cancer 1993;71:3102–8.
[38] Dimarco DS, Dimarco CS, Zincke H, et al. Surgical treatment for local control of female urethral carcinoma. Urol Oncol 2004;22:404–9.
[39] Ahmed K, Dasgupta R, Vats A, et al. Urethral diverticular carcinoma: an overview of current trends in diagnosis and management. Int Urol Nephrol 2010;42:331–41.

[40] Zinman LN, Vanni AJ. Management of proximal primary urethral cancer: should multidisciplinary therapy be the gold standard? Urol Clin North Am 2016;43:505–13.
[41] Dayyani F, Hoffman K, Eifel P, et al. Management of advanced primary urethral carcinomas. BJU Int 2014;114:25–31.
[42] Dinney CPN, Johnson DE, Swanson DA, Babaian RJ, Von Eschenbach AC. Therapy and prognosis for male anterior urethral carcinoma: an update. Urology 1994;43:506–14.
[43] Dalbagni G, Zhang Z-F, Lacombe L, Herr HW. Male urethral carcinoma: analysis of treatment outcome. Urology 1999;53:1126–32.
[44] Lughezzani G, Jeldres C, Isbarn H, et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 2010;75:118–24.
[45] Ray B, Canto AR, Whitmore WF. Experience with primary carcinoma of the male urethra. J Urol 1977;117:591–4.
[46] Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447–61.
[47] Thyavihally YB, Tongaonkar HB, Srivastava SK, Mahantshetty U, Kumar P, Raibhattanavar SG. Clinical outcome of 36 male patients with primary urethral carcinoma: a single center experience. Int J Urol 2006;13:716–20.
[48] Cohen MS, Triaca V, Billmeyer B, et al. Coordinated chemoradiation therapy with genital preservation for the treatment of primary invasive carcinoma of the male urethra. J Urol 2008;179:536–41.
[49] Ploussard G, Daneshmand S, Efstathiou JA, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. Eur Urol 2014;66:120–37.
[50] DeConti RC. Chemotherapy of squamous cell carcinoma of the skin. Semin Oncol 2012;39:145–9.
[51] Zargar H, Espiritu PN, Fairey AS, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol 2015;67:241–9.
[52] Dalbagni G, Zhang ZF, Lacombe L, Herr HW. Female urethral carcinoma: an analysis of treatment outcome and a plea for a standardized management strategy. Br J Urol 1998;82:835–41.
[53] Matzkin H, Soloway MS, Hardeman S. Transitional cell carcinoma of the prostate. J Urol 1991;146:1207–12.
[54] Njinou Ngninkeu B, Lorge F, Moulin P, Jamart J, Van Cangh PJ. Transitional cell carcinoma involving the prostate: a clinico-pathological retrospective study of 76 cases. J Urol 2003; 169:149–52.
[55] Palou Redorta J, Schatteman P, Huguet Perez J, et al. Intravesical instillations with bacillus Calmette-Guerin for the treatment of carcinoma in situ involving prostatic ducts. Eur Urol 2006;49: 834–838, discussion 838.
[56] Palou J, Baniel J, Klotz L, et al. Urothelial carcinoma of the prostate. Urology 2007;69(1 Suppl):50–61.
[57] Schellhammer PF, Ladaga LE, Moriarty RP. Intravesical bacillus Calmette-Guerin for treatment of superficial transitional cell carcinoma of the prostatic urethra in association with carcinoma of the bladder. J Urol 1995;153:53–6.
[58] Gofrit ON, Pode D, Pizov G, Zorn KC, Katz R, Shapiro A. Prostatic urothelial carcinoma: is transurethral prostatectomy necessary before bacillus Calmette-Guerin immunotherapy? BJU Int 2009;103:905–8.
[59] Ichihara K, Masumori N, Kitamura H, Hasegawa T, Tsukamoto T. Clinical outcomes of urothelial carcinoma of the prostate detected in radical cystectomy specimens. Int J Clin Oncol 2014;19:152–6.
[60] Knoedler JJ, Boorjian SA, Tollefson MK, et al. Urothelial carcinoma involving the prostate: the association of revised tumour stage and coexistent bladder cancer with survival after radical cystectomy. BJU Int 2014;114:832–6.
[61] Sakamoto N, Tsuneyoshi M, Naito S, Kumazawa J. An adequate sampling of the prostate to identify prostatic involvement by urothelial carcinoma in bladder cancer patients. J Urol 1993;149:318–21.
[62] Solsona E, Iborra I, Ricos JV, Monros JL, Casanova JL, Almenar S. The prostate involvement as prognostic factor in patients with superficial bladder tumors. J Urol 1995;154:1710–3.