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Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma

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Background: To investigate the impact of perioperative chemo(radio)therapy in advanced primary urethral carcinoma (PUC).

Patients and methods: A series of 124 patients (86 men, 38 women) were diagnosed with and underwent surgery for PUC in 10 referral centers between 1993 and 2012. Kaplan–Meier analysis with log-rank testing was used to investigate the impact of perioperative chemo(radio)therapy on overall survival (OS). The median follow-up was 21 months (mean: 32 months; interquartile range: 5–48).

Results: Neoadjuvant chemotherapy (NAC), neoadjuvant chemoradiotherapy (N-CRT) plus adjuvant chemotherapy (ACH), and ACH was delivered in 12 (31%), 6 (15%) and 21 (54%) of these patients, respectively. Receipt of NAC/N-CRT was associated with clinically node-positive disease (cN+; $P = 0.033$) and lower utilization of cystectomy at surgery ($P = 0.015$). The objective response rate to NAC and N-CRT was 25% and 33%, respectively. The 3-year OS for patients with objective response to neoadjuvant treatment (complete/partial response) was 100% and 58.3% for those with stable or progressive disease ($P = 0.30$). Of the 26 patients staged ≥cT3 and/or cN+ disease, 16 (62%) received perioperative chemo(radio)therapy and 10 upfront surgery without perioperative chemotherapy (38%). The 3-year OS for this locally advanced subset of patients (≥cT3 and/or cN+) who received NAC ($N = 5$), N-CRT ($N = 3$), surgery-only ($N = 10$) and surgery plus ACH ($N = 8$) was 100%, 100%, 50% and 20%, respectively ($P = 0.016$). Among these 26 patients, receipt of neoadjuvant treatment was significantly associated with improved 3-year relapse-free survival (RFS) ($P = 0.022$) and OS ($P = 0.022$). Proximal tumor location correlated with inferior 3-year RFS and OS ($P = 0.056/0.005$).

Conclusion: In this series, patients who received NAC/N-CRT for cT3 and/or cN+ PUC appeared to demonstrate improved survival compared with those who underwent upfront surgery with or without ACH.

Key words: primary urethral carcinoma, adjuvant, neoadjuvant, chemotherapy, chemoradiotherapy

introduction

Primary urethral carcinoma (PUC) is an uncommon but potentially lethal genitourinary malignancy that meets the definition of a 'rare cancer,' accounting for well under 1% of all malignancies. The estimated annual incidence of PUC is 650 new cases in Europe (age-standardized ratio of 1.6/million in men and 0.6/million in women), and based on an analysis of the Surveillance, Epidemiology and End Results registry, the age-standardized rate was reported to be three times higher in the United States (4.3/million in men and 1.5/million in women) [1, 2].

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Prognosis of patients with PUC mainly depends on pathologic tumor and nodal stage, with distal urethral tumors exhibiting significantly improved survival rates compared with proximal tumors [3]. While surgery-only series have reported 5-year overall survival (OS) rates in advanced PUC of only ~40% [4], recent retrospective studies have emphasized that modern platinum-based polychemotherapeutic regimens can be effective in prolonging survival even in lymph node-positive disease [5]. Yet, these reports have also supported the critical role of consolidative surgery after chemotherapy for achieving long-term survival in patients with locally advanced urethral cancer [5]. Therefore, optimizing treatment of advanced urethral cancer has recently become the focus of international health care authorities aiming at improving oncological efficacy and quality of life of patients with this disease [3].

Given the rarity of this cancer, there remain critical gaps in our understanding of the optimal management of patients with PUC. In particular, there are no reports we are aware of addressing the timing of perioperative chemotherapy in patients with clinically advanced PUC. In order to evaluate this clinical need, we have assembled a multi-institutional collaborative with the aim of determining the impact of neoadjuvant and adjuvant treatment in patients undergoing surgery for PUC.

patients and methods

patient cohort

In this Institutional-Review Board approved retrospective observational multicenter analysis, we reviewed the clinical and pathologic records of a total of 124 consecutive patients (86 men, 38 women) obtained from 10 prospectively maintained databases who underwent surgery for PUC at 10 academic centers between 1993 and 2012. Patients with evidence of distant metastatic disease on cross-sectional imaging before primary treatment were excluded from analysis.

perioperative treatment and assessment of response

In order to understand the timing of perioperative chemotherapy, this study assessed the subset of patients receiving neoadjuvant chemotherapy (NAC), neoadjuvant chemoradiotherapy (N-CRT) and adjuvant chemotherapy (ACH) around the time of surgical resection. Assessment of response to neoadjuvant treatment was based on endoscopic and cross-sectional imaging findings. The number of treatment cycles and the time interval between perioperative chemo (radio)therapy and surgery was recorded. Objective response to neoadjuvant chemo(radio)therapy was defined as partial (PR) or complete response (CR) [5]. ACH was administered to the discretion of the treating physician based on pathological risk factors in specimens. For those receiving N-CRT, a dose of 40–45 Gy was delivered to the pelvic region by external beam radiotherapy with an additional boost to the primary tumor of 20–24 Gy delivered either by intensity-modulated radiation therapy or by brachytherapy. To better understand the role of surgery in advanced stages, outcomes of patients who underwent surgery-only for ≥cT3 and/or cN+ disease ($N = 10$) were additionally evaluated.

surgery

The modality of surgical treatment included transurethral resection, partial/total urethrectomy and radical cystectomy with urethrectomy and urinary diversion. Bilateral regional lymph node dissection (LND) was carried out at the discretion of the treating surgeon based on intraoperative findings and preoperative cross-sectional imaging. The level of LND was based on the location of the primary tumor and typically included the inguinal lymph nodes, external and internal iliac, obturator and common iliac lymph nodes.

clinical and histologic assessment

The following clinical and pathologic parameters were assessed: age at surgery, gender, clinical and pathologic tumor stage, clinical and pathologic lymph node tumor involvement, underlying histology, tumor grade, tumor location (proximal versus distal), preoperative serum creatinine level, modality of surgery for primary treatment and modality of treatment of recurrence. In men, proximal tumor location was defined as tumors located in the prostatic, membranous or bulbar urethra and anteriorly when located in the penile urethra and fossa navicularis. In women, proximal tumor location was defined as tumors located in the proximal two thirds of the urethra and anteriorly when located in the distal third [6].

The histologic assessment was carried out at the center-specific pathology department and was based on the WHO grading system and tumor–node–metastasis classification as approved by the AJCC [7]. The pathologic macro- and microscopic evaluation of specimens included cross-sectioning of the entire specimen with immunohistochemical staining to identify the presence of urothelial, squamous cell and adenocarcinoma or rarer entities [8]. Lymphovascular invasion was defined as the presence of malignant cells within an endothelial cell line [9].

follow-up

Electronic hospital charts and physician records were reviewed to determine clinical outcomes. Patients generally were seen postoperatively at least every 3–4 months for the first year, semiannually for the second and third years, and annually thereafter. Follow-up examinations included cross-sectional imaging with computed tomography or magnetic resonance imaging. In addition to physical examination with laboratory testing, i.v. pyelography, cystoscopy, urine cytology, urethral washings and bone scintigraphy were carried out if indicated. Kaplan–Meier analysis with log-rank testing was used to investigate the impact of perioperative chemotherapy on relapse-free survival (RFS) and OS. Relapse was defined as either local recurrence in the surgical field, intraurethrally or in distant organs. For determining RFS, clinical outcomes were measured from the date of surgery to the date of first documented relapse or last follow-up visit when the patients had not experienced relapse. For OS, the date of death was determined by death certificates or hospital charts or the last follow-up visit when patients were still alive [10].

statistical analysis

For univariable analysis, χ^2 and Fisher's exact tests were used for nominal data and Student's t-test for scaled data. Kaplan–Meier plots were used to estimate RFS and OS using log-rank testing.

P values are two-sided and $P < 0.05$ was considered significant. Statistical analysis was carried out using JMP® 11.0. Values are given as mean ± SEM for normally distributed or as median (range) for non-normally distributed variables.

results

In the total cohort ($N = 124$), the median follow-up was 21 months [mean: 32 months; interquartile range (IQR): 5–48, total range: 3–200]. The median age at surgery was 66 years (IQR: 58–76). Of the 124 patients, stage cT3 and/or cN+ was present in 26 (21%). Of these 26 patients, 16 (62%) received perioperative chemotherapy and 10 (38%) surgery without perioperative chemotherapy. A flowchart describing the selection process of the included patients is provided in supplementary File S1, available at *Annals of Oncology* online.

Perioperative chemotherapy was administered in 39 patients (31%). Of these 39 patients, 12 (31%) received NAC, 6 (15%) N-CRT plus ACH and 21 (54%) ACH. The different chemotherapeutic regimens administered for perioperative chemotherapy are listed in Table 1. The median number (total range) of cycles of NAC, N-CRT and ACH was 3 (2–6), 3 (1–4) and 4 (2–6), respectively ($P = 0.52$). The median time interval (total range, in days) between surgery and NAC, N-CRT and ACH only was 36 (23–102), 80 (53–113) and 59 (28–600), $P = 0.48$, respectively. The objective response rate to NAC and N-CRT (defined as CR or PR) was 25% and 33%, respectively (see Table 1). The 3-year OS for patients with objective response to neoadjuvant treatment (CR, PR) was 100% and 58.3% for those with stable disease or progressive disease ($P = 0.30$).

Among patients treated with perioperative chemotherapy, receipt of neoadjuvant chemo(radio)therapy was significantly associated with clinically node-positive tumor stage (cN+; $P = 0.046$) and a lower utilization rate of radical cystectomy at surgery ($P = 0.015$). No significant associations were found between the timing of perioperative chemotherapy and age, gender, clinical and pathologic tumor stage, tumor location (proximal versus distal), underlying histology, tumor grade, preoperative serum creatinine level and modality of treatment of relapse (see Table 2).

Relapse occurred in 23 of the 39 patients (59%) with a corresponding 3-year RFS of 54%. In univariable analysis, RFS was only significantly associated with pathologically advanced tumor stage (≥pT3, $P = 0.034$). There were a total of 12 (30.8%) deaths during the study period, and OS was similarly only associated with pathologically advanced tumor stage ($P = 0.030$). No significant associations were found between RFS/OS and modality and number of chemotherapy cycles administered, age, gender, pathological nodal involvement, tumor location, tumor grade, clinical tumor and nodal stage, histological subtype and modality of treatment of relapse (see Table 3).

In the 39 patients receiving perioperative chemo(radio) therapy, the type of chemotherapy (cisplatin- versus noncisplatin-based; 57.2% versus 57.8%; $P = 0.63$) and the number of administered chemotherapeutic cycles (≥4 versus <4; 61.7% versus 48.9%, $P = 0.34$) were not associated with improved 3-year OS.

Among the 16 patients treated with perioperative chemotherapy for cT3 and/or cN+ disease, the 3-year OS was 61%, respectively. The 3-year OS for patients with ≥cT3 and/or cN+ disease who received NAC ($N = 5$), N-CRT ($N = 3$), surgery-only ($N = 10$) or surgery plus ACH ($N = 8$) was 100%, 100%, 50% and 20%, respectively ($P = 0.016$). Among these 26 patients, receipt of neoadjuvant treatment was significantly associated with improved 3-year RFS ($P = 0.022$) and OS ($P = 0.022$). Proximal tumor location correlated with inferior 3-year RFS and OS ($P = 0.056/0.005$). No significant differences were found for other parameter listed in Table 3.

Table 1. Chemotherapeutic regimens and response to neoadjuvant treatment in the 39 patients undergoing perioperative treatment of primary urethral carcinoma

	NAC	N-CRT + ACH	ACH
Number of patients (%)	12 (31)	6 (15)	21 (54)
Mitomycin C/5-FU-based			
Mitomycin C/5-FU	0	1 (SD)	0
5-FU only	0	0	1
Cisplatinum-based			
Cisplatin/gemcitabine	2 (CR, PD)	2 (CR, PR)	4
Cisplatin/gemcitabine/paclitaxel	2 (PR, SD)	1 (PD)	1
Dose-dense MVAC	1 (PR)	0	0
MVAC	1 (PD)	0	0
Cisplatin/paclitaxel/ifosfamide	1 (PD)	0	1
Cisplatin/paclitaxel/5-FU	1 (SD)	0	0
Cisplatin/paclitaxel	1 (PD)	0	5
Cisplatin only	1 (PD)	1 (PD)	1
Carboplatinum-based			
Paclitaxel/carboplatin/gemcitabine	1 (PD)	0	0
Paclitaxel/carboplatin	0	0	1
Carboplatin/gemcitabine/abraxane	1 (SD)	0	0
Carboplatin/paclitaxel/ifosfamide	0	0	2
Carboplatin/gemcitabine	0	0	1
Gemcitabine-based			
Gemcitabine/paclitaxel	0	1 (PD)	1
Taxol/gemcitabine	0	0	1
Other regimens			
Carmustin/IL-2	0	0	1
Dacarbazine	0	0	1

5-FU, 5-fluorouracil; ACH, adjuvant chemotherapy; CR, complete response; IL-2, interleukin-2; MVAC, methotrexat/cisplatin/doxorubicin/vinblastin; NAC, neoadjuvant chemotherapy; N-CRT, neoadjuvant chemoradiotherapy; PR, partial response; PD, progressive disease; SD, stable disease.

discussion

The optimal timing of perioperative chemotherapy in patients with advanced PUC is unknown. Since PUC is a rare tumor entity, we set up a collaborative database and accrued a total of 124 cases to inform the role of perioperative chemotherapy. Of these 124 patients, 39 received perioperative chemotherapy (31%).

As would be expected, delivery of NAC was associated with clinically node-positive disease. This finding suggests that the decision making for NAC in this cohort was based on evidence of nodal involvement at cross-sectional imaging. In our cohort, patients with advanced clinical stage (≥cT3 and/or cN+) were more likely to undergo perioperative chemotherapy before surgery (62% versus 38%). Interestingly, patients with clinically advanced tumor stage and/or node-positive disease exhibited improved RFS and OS when treated in the neoadjuvant setting with either NAC or N-CRT compared with patients treated only with surgery or surgery plus ACH. Among the 39 patients, RFS and OS were only associated with pathologically advanced tumor stage at surgery but not with modality and duration (cycles) of perioperative chemotherapy. These findings underline the prognostic impact of pathologic tumor extent after completion of perioperative chemotherapy. Although the objective response rate of neoadjuvant treatment was relatively low, administration of neoadjuvant treatment was associated with

Table 2. Univariable Pearson's χ^2 Fisher's exact test for clinical and pathologic parameters in the 39 patients receiving perioperative chemotherapy

	NAC	N-CRT + ACH	ACH	*P* value
Number of patients (%)	12 (31)	6 (15)	21 (54)	
Follow-up time				
Median	12	30	36	0.23
Mean	19	30	24	
IQR	3–50	3–60	4–60	
Gender				
Male	9 (75.0)	3 (50.0)	14 (66.7)	0.57
Female	3 (25.0)	3 (50.0)	7 (33.3)	
Age				
Median	61	59	66	0.95
IQR	56–74	49–66	62–71	
cT stage				
cTX	0 (0)	0 (0)	0 (0)	0.10
cTa	1 (8.3)	0 (0)	2 (9.5)	
cTis	0 (0)	0 (0)	0 (0)	
cT1	2 (16.7)	1 (16.7)	6 (28.6)	
cT2	5 (41.7)	2 (33.3)	5 (23.8)	
cT3	2 (16.7)	2 (33.3)	3 (14.3)	
cT4	2 (16.7)	1 (16.7)	5 (23.8)	
cTa-T2	8 (66.7)	3 (50.0)	13 (61.9)	
cT3-T4	4 (33.3)	3 (50.0)	8 (38.1)	
pT stage				
pT0	0 (0)	0 (0)	0 (0)	0.58
pTa	0 (0)	0 (0)	0 (0)	
pTis	1 (8.3)	0 (0)	1 (4.8)	
pT1	0 (0)	0 (0)	5 (23.8)	
pT2	5 (41.7)	2 (33.3)	6 (28.6)	
pT3	5 (41.7)	1 (16.7)	2 (9.5)	
pT4	1 (8.3)	3 (50.0)	7 (33.3)	
pTa-T2	6 (50.0)	2 (33.3)	12 (57.1)	
pT3-T4	6 (50.0)	4 (66.7)	9 (42.9)	
cN stage				
cNX	3 (25.0)	2 (33.3)	0 (0)	0.046
cN0	5 (41.7)	2 (33.3)	17 (81.0)	
cN+	4 (33.3)	2 (33.3)	4 (19.0)	
pN stage				
pNX	6 (50.0)	2 (33.3)	7 (33.3)	0.07
pN0	3 (25.0)	1 (16.7)	12 (57.1)	
pN1-2	3 (25.0)	3 (50.0)	2 (9.5)	
Tumor grade at primary diagnosis				
G1	0 (0)	1 (16.7)	0 (0)	0.18
G2	3 (25.0)	0 (0)	3 (14.3)	
G3	9 (75.0)	5 (83.3)	18 (85.7)	
Histology				
UC	4 (33.3)	1 (16.7)	12 (57.1)	0.23
SCC	5 (41.7)	3 (50.0)	3 (14.3)	
AC	2 (16.7)	2 (33.3)	2 (9.5)	
Mixed	1 (8.3)	0 (0)	2 (9.5)	
Unclassified	0 (0)	0 (0)	2 (9.5)	
Tumor location				
Proximal	7 (58.3)	3 (50.0)	14 (66.7)	0.44
Distal	5 (41.7)	3 (50.0)	7 (33.3)	
Preoperative serum creatinine level (mg/dl)				
Median	0.9	0.9	1.0	0.70
Mean	1.0	0.9	1.0	
IQR	0.8–1.2	0.7–1.1	0.7–1.2	
Surgical modality of primary treatment				
TUR only	1 (8.3)	0 (0)	5 (23.8)	0.015
Partial urethrectomy	0 (0)	1 (16.7)	0 (0)	
Urethrectomy	5 (41.7)	2 (33.3)	5 (23.8)	
Cyst(oprostat)ectomy plus urethrectomy	3 (25.0)	0 (0)	11 (52.4)	
Other	3 (25.0)	3 (50.0)	0 (0)	
Modality of treatment of local/urethral relapse				
Surgery	3 (25.0)	0 (0)	3 (14.3)	0.41
Radiotherapy	3 (25.0)	0 (0)	3 (14.3)	0.63
Chemotherapy	0 (0)	0 (0)	0 (0)	–
Receipt of palliative (systemic) chemotherapy	3 (25.0)	1 (16.7)	9 (42.9)	0.36

AC, adenocarcinoma; ACH, adjuvant chemotherapy; IQR, interquartile range; NAC, neoadjuvant chemotherapy; N-CRT, neoadjuvant chemoradiotherapy; SCC, squamous cell carcinoma; TUR, transurethral resection; UC, urothelial carcinoma.

improved 3-year RFS and OS in the subset of patients with locally advanced disease. Additionally, proximal tumor location was associated with inferior RFS and OS which is in line with prior studies [1, 2, 4]. These data suggest that patients with proximal tumor location and clinically advanced stages may benefit most from neoadjuvant treatment. Despite the fact that patients treated with neoadjuvant chemo(radio)therapy had similar rates of pathologically advanced stages and proximal tumor location at surgery compared with patients treated with adjuvant therapy, they were less likely to undergo cystectomy. Similar to bladder cancer [11], this finding hints at the possibility that neoadjuvant chemo(radio)therapy may exert a beneficial impact on the primary tumor extent and facilitate the surgical approach.

We found that OS rates in patients with clinically advanced stages (≥cT3 and/or cN+) did not differ between those treated either with NAC or with N-CRT plus ACH whereas ACH was associated with decreased OS. The underlying histology did not influence survival. These findings suggest that delivery of neoadjuvant chemo(radio)therapy is critical for survival in advanced stages. Owing to these findings and the low number of patients, we combined patients treated with NAC and N-CRT plus ACH into one group for final survival analysis.

Although the number of included cases is low and the present results have to be interpreted carefully, some meaningful conclusions can be drawn from these results. First, our findings suggest that the presence of clinically enlarged lymph nodes should alert clinicians of the possible presence of lymph node metastatic disease, especially in case of advanced clinical tumor stage and proximal tumor location, and should therefore be an

Table 3. Relapse-free and overall survival for patients treated with or without perioperative chemo(radio)therapy according to clinical and pathologic tumor characteristics

Parameters	Total cohort with perioperative chemotherapy ($N = 39$)				cT3 and/or cN+ (with or without perioperative chemotherapy) ($N = 26$)			
	RFS		OS		RFS		OS	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
NAC/N-CRT plus ACH versus ACH only	0.91 (0.42–1.90)	0.97	0.98 (0.32–2.96)	0.80	0.14 (0.01–0.78) (for NAC/N-CRT plus ACH versus ACH/surgery-only)	**0.022**	0.10 (0.01–0.71) (for NAC/N-CRT plus ACH versus ACH/surgery-only)	**0.024**
≥pT3 versus ≤pT2	**2.6 (1.1–6.8)**	**0.030**	**5.5 (1.2–35.4)**	**0.034**	1.23 (0.43–4.47)	0.70	1.02 (0.22–7.16)	0.98
≥cT3 versus ≤cT2	2.1 (0.9–5.3)	0.26	2.3 (0.5–9.7)	0.10	–	–	–	–
cN+ versus cN0	2.5 (0.8–7.2)	0.25	2.5 (0.5–11.6)	0.11	–	–	–	–
cNX versus cN0	4.1 (0.2–28.9)	0.17	7.0 (0.3–68.39)	0.28	–	–	–	–
Tumor location proximal versus distal	1.9 (0.7–5.4)	0.35	2.1 (0.5–14.3)	0.20	2.33 (0.98–5.95)	0.056	10.11 (1.82–188.90)	**0.005**
Tumor grade G1/G2 versus G3	2.3 (0.7–10.0)	0.21	3.2 (0.6–59.8)	0.17	5.97 (0.57–50.61)	0.13	4.66 (0.84–86.90)	0.08
Histology								
UC versus SCC	0.7 (0.2–2.6)	0.49	1.1 (0.1–22.0)	0.53	1.10 (0.41–3.04)	0.84	2.17 (0.41–15.95)	0.36
UC versus AC	0.3 (0.1–1.4)	0.84	0.8 (0.1–16.2)	0.13	0.66 (0.04–3.71)	0.68	0.01 (0–3.27)	0.23
Gender								
Male versus female	0.6 (0.2–1.7)	0.13	0.3 (0.1–1.4)	0.32	1.23 (0.54–2.86)	0.61	0.54 (0.11–2.05)	0.36
Age								
>65 years versus ≤65 years	1.7 (0.5–6.4)	0.59	1.6 (0.3–11.4)	0.38	1.48 (0.59–3.76)	0.39	1.23 (0.29–5.22)	0.77
Treatment of relapse								
Surgery	–	–	0.4 (0.1–1.2)	0.08	–	–	0.19 (0.01–1.17)	0.07
Radiotherapy	–	–	0.3 (0–1.5)	0.15	–	–	2.28 (0.31–11.76)	0.31
Palliative (systemic) chemotherapy	–	–	1.4 (0.6–3.4)	0.42	–	–	2.56 (0.52–10.50)	0.22

Bold values indicate statistically significant difference.

AC, adenocarcinoma; ACH, adjuvant chemotherapy; BSC, best supportive care; OS, overall survival; RFS, relapse-free survival; RR, relative risk; SCC, squamous cell carcinoma; UC, urothelial carcinoma.

impetus to deliver neoadjuvant chemo(radio)therapy. This finding is in line with studies reporting a high degree of concordance between clinical and pathological staging in PUC [3]. Another explanatory approach for the worse prognosis of patients with ACH may be that utilization of radical cystectomy with urinary diversion adversely affects performance status and postoperative renal function thereby delaying timely delivery of chemotherapy after surgery [11]. However, in our cohort, preoperative serum creatinine levels were not different between the three groups which suggests that renal function did not impact on the decision making for perioperative treatment.

Similar to our findings, a prior series reported outcomes in 44 patients treated uniformly with chemotherapy without radiotherapy for advanced primary urethral cancer with squamous cell carcinoma (SCC) and adenocarcinoma being the most prevalent histological entities. Patients were subjected to specific cisplatin-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was reported to be much higher with 72%. The median OS of the entire cohort was 32 months. Of note, patients who underwent surgery after chemotherapy had significantly improved OS compared with those who were managed with chemotherapy alone [5].

Another recent series reported that CR to concurrent chemoradiotherapy (consisting of two cycles of 5-fluorouracil/mitomycin C and 45–55 Gy over the span of 5 weeks) in T3 SCC of the urethra was observed in 79% of the patients. Consolidation surgery was, however, only initiated if patients never responded to their 'modified Nigro-protocol' or developed local recurrence. Despite the high primary response rate of ~80%, the corresponding 5-year disease-free and OS rates were moderate with 43% and 52% [12].

In our series, we found that the 3-year OS rate in patients with ≥cT3 and/or cN+ stage was relatively high at 61%. Of note, all patients treated with NAC/N-CRT were alive after 5 years. Therefore, these data suggest that consolidation surgery may be of prognostic importance at the time of completion of neoadjuvant chemo(radio)therapy which may also obviate the need for aggressive salvage surgery in case of relapse. In terms of the effects of salvage treatment on OS, we found that neither surgery nor radiotherapy exerted a beneficial impact on survival. These data highlight, once more, the importance of the decision making for primary treatment in advanced PUC. In this regard, we recently reported that clinical nodal stage is a strong predictor for oncological outcomes in primary urethral cancer [13].

Our study has several limitations inherent to the retrospective, small size, and multicenter nature of the analysis, which of course is requisite given the rarity of the disease. Possible biases include absence of regional LND in approximately half of the patients and interobserver variabilities in the clinical staging and pathological assessment of specimens. We could not adjust for patient preferences, toxicities of perioperative treatment and comorbidities which may have impacted on the clinical decision making for either NAC or ACH. In this regard, an important alternative explanation for these findings is that patients who were healthier (with better renal function) received neoadjuvant chemo(radio)therapy and less healthy patients did not, particularly in the setting of advanced disease. Yet, preoperative serum creatinine levels were not different between the three groups and all patients were fit enough to undergo either ACH after surgery or neoadjuvant treatment before surgery. In addition, all patients were treated in academic centers by multidisciplinary teams dedicated to the management of lower urinary tract cancer. Notwithstanding, owing to these limitations, the results of this multicenter pooled analysis provide new insights into the management of this rare disease and await further prospective validation.

This is, to our knowledge, the first series that demonstrates the prognostic benefit of NAC and N-CRT with ACH in a consecutive series of patients who underwent perioperative chemotherapy plus surgery for advanced PUC. Further studies should yield a better understanding of how perioperative chemotherapy exerts a positive effect on survival in order to selectively advocate its use in advanced PUC.

conclusion

In this series, patients who received NAC or chemoradiotherapy for locally advanced PUC (≥cT3 and/or cN+) appeared to demonstrate improved survival compared with those who underwent upfront surgery with or without ACH.

disclosure

The authors have declared no conflicts of interest.

references

1. Visser O, Adolfsson J, Rossi S et al. The RARECARE working group: incidence and survival of rare urogenital cancers in Europe. Eur J Cancer 2011; 48: 456–464.
2. Swartz MA, Porter M, Lin DW, Weiss NS. Incidence of primary urethral carcinoma in the United States. Urology 2006; 68: 1164–1168.
3. Gakis G, Witjes JA, Compérat E et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013; 64: 823–830.
4. Gheiler EL, Tefilli M, Tiguert R et al. Management of primary urethral cancer. Urology 1998; 52: 487–493.
5. Dayyani F, Pettaway CA, Kamat AM et al. 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: 1171–1177.
6. Carroll PR, Dixon CM. Surgical anatomy of the male and female urethra. Urol Clin North Am 1992; 19: 339–346.
7. Sobin LH, Wittekind C. TNM Classification of Malignant Tumors, 6th edition. New York: Wiley-Liss 2002.
8. Shim JW, Cho KS, Choi YD et al. Diagnostic algorithm for papillary urothelial tumors in the urinary bladder. Virchows Arch 2008; 452: 353–362.
9. Brunocilla E, Pernetti R, Martorana G. The prognostic role of lymphovascular invasion in urothelial-cell carcinoma of upper and lower urinary tract. Anticancer Res 2011; 31: 3503–3506.
10. Rink M, Fajkovic H, Cha EK et al. Death certificates are valid for the determination of cause of death in patients with upper and lower tract urothelial carcinoma. Eur Urol 2012; 61: 854–855.
11. Gakis G, Efstathiou JA, Lerner SP et al. ICUD-EAU International Consultation on Bladder Cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2013; 63: 45–57.
12. Kent M, Zinman L, Girshovich L, Sands J, Vanni A. Combined chemoradiation as primary treatment for invasive male urethral cancer. J Urol 2015; 193: 532–537.
13. Gakis G, Morgan TM, Efstathiou JA et al. Prognostic factors and outcomes in primary urethral cancer: results of the international collaboration on primary urethral carcinoma. World J Urol 2015 May 17 [epub ahead of print], doi: 10.1007/s00345-015-1583-7.