



COVID-19 pandemic impact on uro-oncological disease outcomes at an Italian tertiary referral center

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Abstract

Purpose To assess differences in referral and pathologic outcomes for uro-oncology cases prior to and during the COVID pandemic, comparing clinical and pathological data of cancer surgeries performed at an academic referral center between 2019 and 2020.

Methods We collected data of 880 prostate biopsies, 393 robot-assisted radical prostatectomies (RARP) for prostate cancer (PCa), 767 trans-urethral resections of bladder tumor (TURB) and 134 radical cystectomies (RC) for bladder cancer (BCa), 29 radical nephro-ureterectomies (RNU) for upper tract urothelial carcinoma, 130 partial nephrectomies (PN) and 12 radical nephrectomies (RN) for renal cancer, and 41 orchifuniclectomies for testicular cancer. Data of patients treated in 2019 (before COVID-19 pandemic) were compared to patients treated in 2020 (during pandemic).

Results No significant decline in uro-oncological surgical activity was seen between 2019 and 2020. No significant increase in time between diagnosis and surgery was observed for all considered cancers. No differences in terms of main pathologic features were observed in patients undergoing RARP, TURB, RNU, RN/PN, or orchifuniclectomy. A higher proportion of ISUP grade 3 and 4 PCa were diagnosed in 2020 at biopsy ($p = 0.001$), but this did not translate into worse pathological grade/stage at RARP. In 2020, more advanced disease features were seen after RC, including lymph node involvement ($p = 0.01$) and non-organ confined disease ($p = 0.02$).

Conclusion Neither decline in uro-oncologic activity nor delay between diagnosis and treatment was observed at our institution during the first year of COVID-19 pandemic. No significant worsening of cancer disease features was found in 2020 except for muscle-invasive BCa.

Keywords Uro-oncology · Covid-19 · Upstaging · Cancer · Pathological outcomes · Delay

Introduction

The rapid spread of coronavirus disease 2019 (COVID-19) throughout the world has had dramatic effects on healthcare systems. The hospitals have become quickly overwhelmed and a reallocation of medical resources has been made necessary to face the crisis [1]. As a consequence, the level of activity of medical disciplines not primarily involved in the management of COVID-19 patients has reduced and

all “non-urgent” procedures have been postponed. Uro-oncological consultations and surgeries have also reported a dramatic reduction, raising concerns about the risks of adverse oncologic outcomes related to delayed diagnosis and/or treatment [2, 3]. Several recommendations have been recently published to guide the management of urological conditions during these troubled times [4–6]. In the meantime, evidence has accumulated supporting the idea that most uro-oncologic elective surgeries can be safely postponed when the availability of health care resources is limited [7]. However, concerns remained on the possibility that COVID-19 pandemic-related constraints on healthcare access might translate into more advanced disease features [6]. Given the prolongation of the current crisis, the centralization of uro-oncological surgeries in “COVID-19-free”

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tertiary urological centers could be a smart alternative to guarantee a timely, high-quality, and effective treatment of genitourinary cancer patients [3, 8].

Aim of this study was to evaluate if COVID-19 pandemic has actually led to more advanced disease features in urological cancers, including prostate cancer (PCa), bladder cancer (BCa), upper tract urothelial carcinoma (UTUC), renal cancer, and testicular cancer at an academic referral center.

Patients and methods

Institutional review board approval was obtained before the initiation of the study. Patients treated for suspected or confirmed urologic cancer between January 2019 and December 2020 at a single academic referral center (Division of Urology, Department of Surgical Sciences, University of Torino) were included. In detail, we collected baseline data and tumor-related features of patients who underwent prostate biopsy and/or robot-assisted radical prostatectomy (RARP) for PCa, trans-urethral resection of bladder tumor (TURB) and/or radical cystectomy (RC) for BCa, radical nephroureterectomy (RNU) for high-risk UTUC, partial nephrectomy (PN) or radical nephrectomy (RN) for renal cancer, and orchifuniclectomy for testicular cancer. Moreover, the time between the occurrence of symptoms/diagnosis and surgery was evaluated. Only patients with complete data regarding the variables of interest were retained for the analysis.

Statistical analysis

The primary endpoint of the study was to assess differences in referral and pathologic outcomes for uro-oncology cases prior to and during the COVID pandemic. We hypothesized that COVID-19 pandemic might have led to a shift towards higher pathological tumor stage/grade, possibly due to a delay in diagnosis and/or surgical schedule. To test our hypothesis, data of patients treated in 2019 (before COVID-19 pandemic) were compared to those of patients treated in 2020 (during COVID-19 pandemic). A comparative analysis by trimester was performed for all evaluated procedures except for RC, since all patients receiving RC underwent surgery ≤ 30 days from the time of surgical indication.

Categorical variables were reported as absolute numbers and proportions while continuous variables as medians with interquartile ranges (IQR) or means with standard deviation (SD) when appropriate. Chi-square and Mann–Whitney *U*-tests were performed for categorical and continuous variables to compare the populations, respectively. Statistical analyses were performed using STATA 13 (Stata Corp., College Station, TX, USA). All tests were two-sided and $p < 0.05$ was considered as statistically significant.

Results

Prostate cancer

Overall, 880 patients received prostate biopsy for suspicion of PCa. Among these, 414 (47%) underwent biopsy in 2019 and 466 (53%) in 2020, respectively (Suppl. Table 1). A higher number of patients received pre-biopsy magnetic resonance imaging (MRI) (84% vs 75%, $p = 0.002$) and subsequent fusion biopsy (73% vs 64%, $p = 0.003$) in 2020 compared to 2019. Notably, a higher proportion of ISUP grade 3 and 4 and a lower proportion of ISUP grade 2 was observed in 2020 compared to 2019 ($p = 0.001$).

After confirmation of PCa, RP was performed in 207 (54%) and 186 (47%) patients in 2019 and 2020, respectively (Table 1, Fig. 1A). In 2020, a higher proportion of robotic-assisted (97% vs 90%, $p = 0.008$) and nerve-sparing procedures (71% vs 62%, $p = 0.04$) was observed. With regard to pathological findings, a lower rate of seminal vesicle invasion (8% vs 15%, $p = 0.02$) and positive surgical margins (8% vs 20%, $p < 0.001$) was reported in 2020 as compared to 2019. However, no difference in terms of tumor stage, ISUP grade, and lymph node involvement was found.

When focusing on the time between PCa diagnosis and definitive surgery, no difference was reported between 2019 (median of 102 days) and 2020 (median of 105 days) (Fig. 1B). Eleven patients were postponed due to COVID-19 positivity ascertained during preoperative work-up. After diagnosis of low-risk PCa, 27 patients were addressed to active surveillance in 2019 and 18 in 2020.

Bladder cancer

Overall, 767 patients underwent TURB for suspected BCa. Among these, 407 (53%) and 360 (47%) were treated in 2019 and 2020, respectively (Fig. 1C). Baseline patients' and tumor's characteristics are depicted in Table 2. No difference in tumor stage/grade between patients treated in 2019 and 2020 was reported. Similarly, the time between the occurrence of symptoms and TURB did not significantly differ over the study period (Fig. 1D).

RC was performed in 58 (43%) and 76 (57%) patients in 2019 and 2020, respectively (Fig. 1G). Notably, a shift towards a higher rate of lymph node involvement (16% in 2019 vs 36% in 2020, $p = 0.01$) and non-organ confined disease (55% vs 74%, $p = 0.025$) at surgery was observed during the study period (Table 3). The time between the indication for surgical treatment (after TURB or at the completion of neoadjuvant chemotherapy) and RC did not differ between groups and remained within 30 days in all cases.

Table 1 Descriptive characteristics for the cohort of 393 patients treated with radical prostatectomy between January 2019 and December 2020

| Variables | Year of radical prostatectomy | | <i>p</i> value |
|------------------------------------------------------|-------------------------------|-------------|----------------|
| | 2019 | 2020 | |
| Number of patients, <i>n</i> (%) | 207(53) | 186(47) | |
| Age, median, years (IQR) | 68(62–72) | 69(62–72) | 0.2 |
| PSA, mean (SD) | 10.2(12.7) | 10.0(14.4) | 0.9 |
| MRI execution, <i>n</i> (%) | 191(92) | 169(92) | 0.5 |
| Clinical tumor stage (with MRI or DRE), <i>n</i> (%) | | | |
| cT1 | 18(9) | 13(7) | 0.8 |
| cT2 | 137(66) | 125(67) | |
| cT3a | 26(13) | 27(15) | |
| cT3b | 6(3) | 3(2) | |
| cT4 | 0(0) | 1(1) | |
| Robotic approach, <i>n</i> (%) | 187(90) | 180(97) | 0.008 |
| Nerve-sparing surgery, <i>n</i> (%) | 129(62) | 130(71) | 0.04 |
| ISUP grade at RP, <i>n</i> (%) | | | |
| 1 | 1(0) | 1(0) | 0.1 |
| 2 | 94(46) | 72(39) | |
| 3 | 72(35) | 81(44) | |
| 4 | 15(7) | 20(11) | |
| 5 | 24(12) | 12(6) | |
| Pathological tumor stage, <i>n</i> (%) | | | |
| pT2a | 20(10) | 14(7) | 0.2 |
| pT2b | 9(4) | 14(7) | |
| pT2c | 83(40) | 87(47) | |
| pT3a | 63(30) | 56(30) | |
| pT3b | 31(15) | 15(8) | |
| pT4 | 1(1) | 0(0) | |
| Extracapsular extension, <i>n</i> (%) | 93(45) | 71(39) | 0.1 |
| Seminal vesicle invasion, <i>n</i> (%) | 31(15) | 15(8) | 0.02 |
| Nodal tumor stage, <i>n</i> (%) | | | |
| N0 | 106(51) | 110(59) | 0.3 |
| N+ | 24(12) | 17(9) | |
| NX | 77(37) | 59(32) | |
| Positive surgical margins, <i>n</i> (%) | 42(20) | 15(8) | <0.001 |
| Time from diagnosis to treatment, days, median (IQR) | 102(79–139) | 105(72–141) | 0.9 |

Upper tract urothelial carcinoma

Overall, 29 patients underwent RNU for UTUC. Of these, 16 (55%) and 13 (45%) were treated in 2019 and 2020, respectively (Suppl. Table 2). No difference in terms of pre-operative nor postoperative characteristics was found when comparing patients treated before and during COVID-19 pandemic. No difference was reported with regard to the

time between the indication for surgery (either at diagnosis or after diagnostic ureteroscopy) and RNU (Fig. 1H).

Renal cancer

Overall, 142 patients were treated with either PN (92%) or RN (8%). Of these, 69 (49%) and 73 (51%) were treated in 2019 and 2020, respectively. No increase in the rate of RNs was seen in 2020. No differences in terms of pathological features or time between diagnosis and surgery were reported (Suppl. Table 3 and Fig. 1E, F).

Testicular cancer

Overall, 41 patients underwent orchifuniculectomy for testicular cancer. Of these, 24 (58%) and 17 (42%) were treated in 2019 and 2020, respectively. No differences in terms of pathological features were reported. Median time between diagnosis and surgery always remained below 2 weeks (Suppl. Table 4).

Discussion

With the prolongation of COVID-19 crisis, recommendations have been published to guide the urologists in the management of urological conditions, identifying four levels of priority. Depending on the resources and capacity, surgical treatment was recommended only for high-priority and emergency cases during COVID-19 pandemic, while intermediate-priority cases were considered only outside the COVID-19 surge [4]. Surgery was reported to be harmful in asymptomatic patients who subsequently tested COVID-19 positive [9], while older patients with comorbidity and cancer were found to be at higher risk of COVID-19 infection, severe manifestation of the disease, and fatal outcome [10].

As for elective uro-oncologic procedures, most of them were found to be safely postponed, or even changed to another treatment modality, given a limited availability of healthcare resources [7]. The main concern in delaying uro-oncological surgeries resides in the risk of cancer progression, and a potentially significant backlog of patients in need of cancer care, given the high incidence of these neoplasms [6]. As shown in a previous study conducted by our group, the cumulative delay in consultations and surgeries could have a ripple effect on future patients, further exacerbating potential adverse outcomes [3]. The risk of cancer progression obviously varies according to the type and grade of cancer, as highlighted by a recent collaborative review by Wallis et al. [1]. According to their results, treatment of most patients with intermediate- and high-risk PCa can be deferred 3–6 months without significant change in outcomes [11], while active surveillance should be the

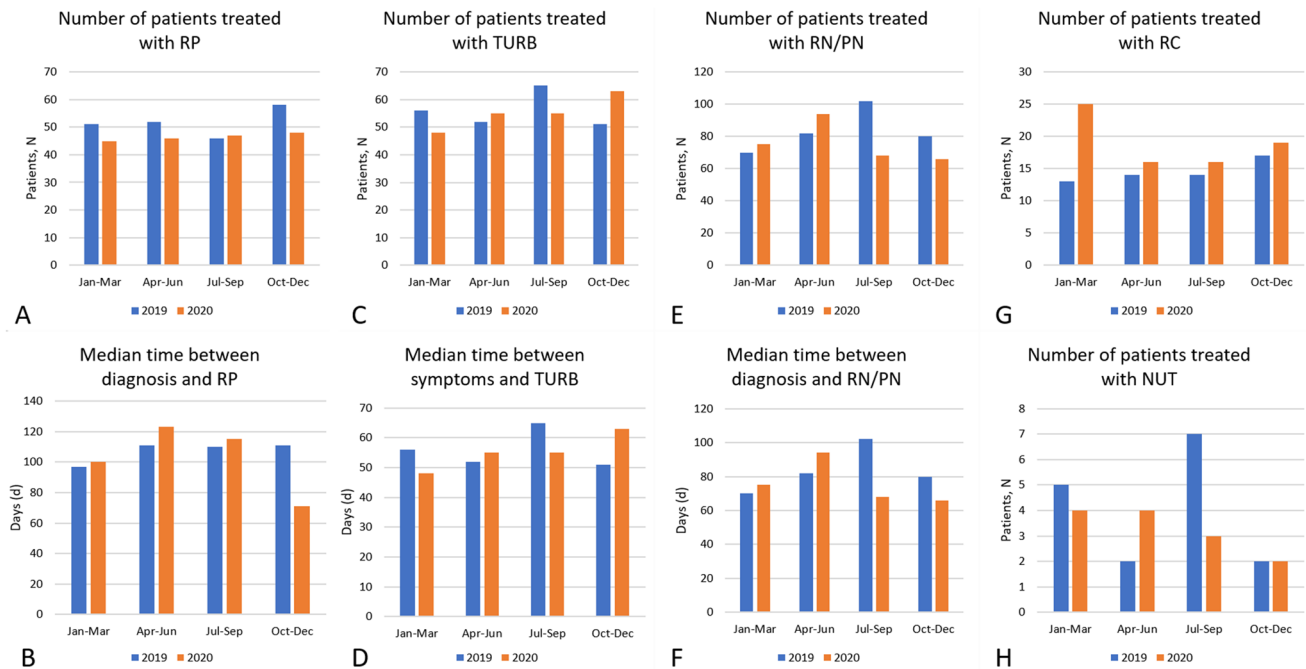


Fig. 1 Number of patients treated with RP (A), TURB (C), RN/PN (E), RC (G), NUT (H) for oncologic reasons. Median time between diagnosis and RP (B), between symptoms and TURB (D), between diagnosis and RN/PN (F). Analyses per trimester. RP radical pros-

tatectomy, TURB trans-urethral resection of bladder, RN radical nephrectomy, PN partial nephrectomy, RC radical cystectomy, NUT radical nephroureterectomy

preferred modality for low-risk PCa; the value of neoadjuvant androgen deprivation therapy is questionable and is not recommended. Patients with low-grade non-muscle-invasive BCa are unlikely to suffer from a 3–6 months delay, even if a re-evaluation is advised in case of new symptoms; on the contrary, risk of progression is seen for muscle-invasive BCa with RC delays beyond 12 weeks from diagnosis or completion of neoadjuvant chemotherapy. For patients with high-grade UTUC, delays of 12 weeks in RNU do not seem to be associated with adverse survival outcomes. As for renal tumors, surgery may be safely deferred for T1/T2 renal masses, while locally advanced tumors should be treated expeditiously [1]. Surgical delay should be avoided when testicular cancer is suspected, also considering that orchifuniculectomy is typically performed in day-hospital and give a minimal burden on healthcare system [1].

During the COVID-19 pandemic, our regional health system was reorganized to create “COVID-19 hospitals” for the acute management of COVID-19 patients, while relieving this burden (or at least a part of it) for regional cancer referral centers like ours. It is our belief that the centralization of the uro-oncological activity in referral centers is essential to guarantee safe and high-quality treatments, and even more in time of crisis such as the COVID-19 pandemic.

Despite our efforts in maintaining our uro-oncological activity during COVID-19 pandemic, we would have expected a marked decrease in the number of our procedures

performed in 2020, as compared to 2019. On the contrary, no substantial decline was observed in our activity, likely as a consequence of our role as referral center, where urgent and oncologic procedures were allowed even during the pandemic. More importantly, no delay between diagnosis/indication and surgery was found, as compared to the procedures of 2019. We were surprised by the low rate of patients whose surgeries were postponed due to COVID-19 positivity at preoperative workup. Unfortunately, we were not able to retrieve the data about a potential COVID-19 infection before preoperative workup, which might have caused a delay in the treatment. Following the recommendations of the European Association of Urology (EAU) [4, 5], priority was given to RC, which were all performed within 30 days from the indication or the completion of neoadjuvant chemotherapy (that was administered when indicated, notwithstanding the COVID-19). Locally advanced renal tumors, high-risk PCa, and high-grade UTUC were also expeditiously treated. A mild decline in the number of TURBs was observed, probably because of the deferral of in-office surveillance cystoscopies of patients with known low-grade BCa. While respecting the priority for the treatment of high-risk cancers, however, we continued to treat all urological neoplasms, as a tertiary referral center.

The most interesting results of the present study reside in the pathologic data resulting from our procedures: we had hypothesized a shift towards more advanced disease

Table 2 Descriptive characteristics for the cohort of 767 patients who underwent trans-urethral resection of the bladder between Jan 2019 and Dec 2020

| Variables | Year of TURB | | | <i>p</i> value |
|-----------------------------------------------------|--------------|-----------|-----------|----------------|
| | Total | 2019 | 2020 | |
| Number of patients | 767 | 407(53) | 360(47) | |
| Median age (IQR), years | 73(66–80) | 73(67–80) | 73(66–80) | 0.8 |
| Gender, <i>n</i> (%) | | | | |
| Female | 154(20) | 86(21) | 68(19) | 0.4 |
| Male | 613(80) | 321(79) | 292(81) | |
| Primary vs recurrent tumor, <i>n</i> (%) | | | | |
| Primary | 393(51) | 209(51) | 184(51) | 0.9 |
| Recurrent | 374(49) | 198(49) | 176(49) | |
| Pathological tumor stage, <i>n</i> (%) | | | | |
| pT0 | 84(11) | 46(11) | 38(11) | 0.4 |
| pTa | 291(38) | 148(37) | 143(40) | |
| pTis | 8(1) | 2(0.5) | 6(2) | |
| pT1 | 298(39) | 165(41) | 133(37) | |
| pT2 | 86(11) | 46(11) | 40(11) | |
| Pathological tumor grade, <i>n</i> (%) | | | | |
| Low grade | 195(28) | 95(26) | 100(31) | 0.2 |
| High grade | 492(72) | 269(74) | 223(69) | |
| Concomitant CIS, <i>n</i> (%) | 40(5) | 20(5) | 20(6) | 0.7 |
| Lymphovascular invasion, <i>n</i> (%) | 40(6) | 18(5) | 22(7) | 0.09 |
| Histological variants, <i>n</i> (%) | 72(9) | 29(7) | 43(12) | 0.02 |
| Reason for performing TURB, <i>n</i> (%) | | | | |
| Hematuria | 273(36) | 145(36) | 128(36) | 0.9 |
| Incidental diagnosis | 125(16) | 64(16) | 61(17) | |
| Other symptoms | 60(8) | 32(8) | 28(8) | |
| Recurrence at follow-up | 309(40) | 166(41) | 143(40) | |
| Median time from diagnosis to treatment, days (IQR) | 56(34–82) | 55(35–82) | 56(34–83) | 0.8 |

features, especially during the last months of 2020, as a consequence of late diagnoses. Nevertheless, no significant differences in terms of main pathologic features were observed in patients who underwent RARP, TURB, RNU and radical/partial nephrectomy, probably because of the lack of surgical delay. A shift towards more aggressive disease was seen for prostate biopsy, where a higher proportion of ISUP grade 3 and 4 was diagnosed in 2020. This is hardly due to a deferral in urological consultations or PSA dosage, considering the long natural history of PCa; more likely, it can be associated to the increase in fusion biopsies, which increase the diagnostic accuracy especially for cancers at high cellularity [12, 13]. The only cancer where more advanced disease features were seen at surgery, such as lymph node involvement and non-organ confined disease, was BCa with indication for RC. This might reflect the aggressiveness of high-risk and muscle-invasive urothelial cancer, supporting once more the need for a urgent treatment in all circumstances. The management of testicular cancer deserves a separate chapter, as it must be promptly treated at all times, and minimally impacts on the healthcare system as orchifunicectomy is a

quick procedure that requires a 1-day hospitalization. In line with these considerations, in our center, we did not observe any differences in terms of pathological features or surgical delay between 2019 and 2020.

This study is not devoid of limitations, mainly due to its monocentric design that might limit the generalizability of pathologic and referral trends. Furthermore, the short time span of study might hamper the evaluation of the effects of delayed screening due to COVID-19.

Conclusion

The volume of our uro-oncologic activity remained substantially stable between 2019 and 2020. Noteworthy is the absence of substantial delay in the treatment of uro-oncological diseases at our institution during the first year of COVID-19 pandemic. Importantly, no significant worsening of cancer disease features was found in 2020 except for muscle-invasive BCa, which requires a prompt treatment. However, the risk of submerged disease and late diagnoses

Table 3 Descriptive characteristics for the cohort of 134 patients who underwent radical cystectomy between January 2019 and December 2020

| Variables | year of radical cystectomy | | | <i>p</i> value |
|------------------------------------------------|----------------------------|-----------|-----------|----------------|
| | Total | 2019 | 2020 | |
| Number of patients | 134 | 58(43) | 76(57) | |
| Median age (IQR), years | 73(65–78) | 73(64–77) | 73(66–79) | 0.6 |
| Gender, <i>n</i> (%) | | | | |
| Female | 33(25) | 17(30) | 16(21) | 0.3 |
| Male | 101(75) | 41(70) | 60(79) | |
| BMI, median (IQR) | 26(23–28) | 25(23–27) | 26(23–28) | 0.7 |
| Primary vs recurrent tumor at RC, <i>n</i> (%) | | | | |
| Primary | 71(53) | 30(52) | 41(54) | 0.8 |
| Recurrent | 63(47) | 28(48) | 35(46) | |
| Reason for performing RC, <i>n</i> (%) | | | | |
| Very high-risk NMIBC/BCG unresponsive NMIBC | 43(32) | 19(33) | 24(32) | 0.9 |
| Muscle-invasive bladder cancer | 91(68) | 39(67) | 52(68) | |
| Neoadjuvant chemotherapy, <i>n</i> (%) | 29(22) | 14(24) | 15(20) | 0.5 |
| Preoperative hydronephrosis, <i>n</i> (%) | 41(31) | 16(28) | 25(33) | 0.5 |
| Pathological tumor stage, <i>n</i> (%) | | | | |
| pT0 | 14(10) | 6(10) | 8(11) | 0.2 |
| pTa | 5(4) | 1(2) | 4(5) | |
| pTis | 6(4) | 3(5) | 3(4) | |
| pT1 | 15(11) | 11(19) | 4(5) | |
| pT2 | 15(11) | 7(12) | 8(11) | |
| pT3 | 39(29) | 17(29) | 22(29) | |
| pT4 | 40(30) | 13(22) | 27(38) | |
| Non-organ confined disease, <i>n</i> (%) | 88(66) | 32(55) | 56(74) | 0.025 |
| Pathological tumor grade, <i>n</i> (%) | | | | |
| Low grade | 4(3) | 1(2) | 3(4) | 0.5 |
| High grade | 116(94) | 51(98) | 65(96) | |
| Concomitant CIS, <i>n</i> (%) | 58(43) | 20(34) | 38(50) | 0.07 |
| Lymphovascular invasion, <i>n</i> (%) | 72(54) | 26(45) | 46(61) | 0.07 |
| Histological variants, <i>n</i> (%) | 45(34) | 20(34) | 25(33) | 0.8 |
| Nodal tumor stage, <i>n</i> (%) | | | | |
| N0 | 98(73) | 49(84) | 49(64) | 0.01 |
| N+ | 36(27) | 9(16) | 27(36) | |
| Urinary diversion, <i>n</i> (%) | | | | |
| Ureterocutaneostomy | 9(7) | 4(7) | 5(7) | 0.6 |
| Ileum conduit | 82(63) | 39(67) | 43(59) | |
| Orthotopic neobladder/ileal pouch | 40(31) | 15(26) | 25(34) | |

cannot be ruled out, and might become apparent in a longer time span.

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Data availability Original data can be requested directly to the corresponding author.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval The procedures performed in this work were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The need of Institutional Ethics Committee approval was waived due to retrospective nature of the study, using only aggregate data.

Consent to participate All patients signed an informed consent for retrospective use of anonymized data for research purposes.

Consent for publications All patients signed an informed consent for retrospective use of anonymized data for research purposes.

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