Cross-sectional Study

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Urothelial cancer: state of art in Ukraine and improvement pathways

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Aim: This study aims to assess the effectiveness of urothelial cancer treatment in Ukraine, utilizing population-based data from the National Cancer Registry. The primary goal is to evaluate trends and approaches to therapy, with a focus on overall survival rates in patients with urothelial tumors.

Materials and methods: A retrospective cross-sectional analysis was conducted based on the National Cancer Registry, involving 12 698 patients (2008–2020) with urothelial tumors of the upper urinary tract (UTUC) and bladder cancer (BC) who underwent surgical treatment. Demographic indicators, surgical interventions, complications, and survival rates were analyzed.

Results: The average age for all patients was 70 years. The number of patients undergoing radical treatment was 1820 (15%) among BC and 573 (59%) among UTUC. The 30-day readmission rate was low for both, with a slightly higher preference for UTUC (2.3 vs. 4.6%). Whereas grade III or higher CI-Dindo complications were seen in only 0.2% of cases. Notable findings include low frequency of neoadjuvant (7%) and adjuvant chemotherapy (28%) among patients with invasive urothelial carcinomas. Median eGFR for invasive UTUC before and after surgery was 63.2 and 51.4 ml/min, respectively ($P = 0.00054$). The directly opposite trend was seen in BC—61.2 and 68.7 ml/min, respectively ($P = 0.0026$). For BC, the overall survival rates by stages were: I—73%, II—49%, III—18%, and IV—11% ($\chi^2 = 1807.207$; $P = 0.000001$). As for UTUC, the 5-year overall survival rates corresponded to the literature data, but there was a pronounced negative trend towards a decrease in this indicator after a 10-year period for all stages ($\chi^2 = 146.298$; $P = 0.000003$).

Conclusion: The study emphasizes the importance of effective systemic treatments, adherence to treatment guidelines, and the need for multidisciplinary consultations among Ukrainian patients with urothelial cancer.

Keywords: bladder cancer, organ-sparing surgery, radical cystectomy, radical nephroureterectomy, upper tract urothelial cancer, urothelial cancer

Introduction

The source of development for urothelial carcinoma is the lining urothelium of the urinary tract. In terms of frequency, this type of cancer ranks fourth among oncological diseases in men and seventh in women[1,2]. The disease is quite aggressive, and the primary treatment methods include radical nephroureterectomy (RNU) for upper urinary tract carcinomas (UTUC) and radical cystectomy (RC) for bladder cancer (BC). Both locations have a high potential for progression, and ~50% of patients in the overall population require systemic therapy. Currently, there is only one effective chemotherapy regimen based on platinum-consisting drugs, but its use is often limited by a decline in kidney function, occurring in ~25–80% of cases[3–6]. Checkpoint inhibitors, which can be quite effectively used, do not impact kidney function; however, the sensitivity to this treatment modality is limited to 18–42% of patients[7]. General improvement in immune agents and combination therapy looks quite promising

HIGHLIGHTS

- Systemic treatment needs: There is a critical need for effective systemic treatments and adherence to established treatment guidelines for urothelial cancer in Ukraine.
- Surgical quality and renal function: Improvements in surgical intervention quality are necessary, especially considering the significant impact on renal function in UTUC patients post-surgery.
- Survival rates and treatment approaches: Survival rates for bladder cancer patients are lower compared to global data, and a kidney-sparing approach for invasive UTUC shows comparable survival outcomes to radical nephroureterectomy.
- Multidisciplinary collaboration: Enhanced multidisciplinary consultations are essential to address chronic kidney disease, optimize adjuvant treatments, and improve follow-up care for urothelial cancer patients in Ukraine.

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in terms of increasing cancer-specific survival[8,9]. Although even in developed countries, this financial burden is challenging for society to manage and often overwhelming for most individuals[10].

Despite the common origin of UTUC and BC, they differ clinically and thus require different treatment approaches. Current information on the genetic profile of UTUC suggests not only tumor heterogeneity within one localization but also genetic differences from bladder cancer. Identifying agents for prognosis and selecting appropriate systemic treatment for patients require validation in multicenter clinical trials. Given the clinical diversity and complexity of the selected patient group, the necessity of effective methods to optimize therapy through genetic analysis is focused on the adequate selection and individualization of therapeutic approaches[11–13].

The objective of this study was to conduct a nationwide analysis based on the National Cancer Registry with the primary goal of determining the effectiveness of urothelial cancer treatment in Ukraine and the secondary goal of identifying key trends and approaches to therapy with an assessment of their impact on overall survival rates.

Materials and methods

Study design

The study design had a population-based retrospective cross-sectional character. The analysis was based on data from the National Cancer Registry from 2008 to 2020. In total, the medical documentation of 12 698 patients with UTUC and BC who underwent surgical treatment was analyzed. Histological variants, including squamous cell carcinoma, adenocarcinoma, cribriform carcinoma, urothelial carcinoma with squamous metaplasia, and mixed variants, were excluded from the analysis. Patients receiving only palliative care/systemic treatment due to primary metastatic disease were not included in the database.

For further analysis, cases were split into BC and UTUC cohorts. Subgroup analysis was performed in accordance with the T-stage and surgical approach (organ-sparing vs. radical intervention).

Treatment modalities

The surgical intervention should have included total tumor removal. For superficial tumors in BC, endoscopic treatment—transurethral resection of the bladder—was considered a standard of care. For UTUC, considering the lack of sufficient material and technical support in Ukraine, cases of organ-sparing treatment for superficial (T1) tumors via endoscopic, laparoscopic, or open methods were included in the analysis. In cases of invasive or locally advanced tumors, only those with radical or partial cystectomy (where total bladder removal was contraindicated due to comorbidities) for BC and radical nephroureterectomy or resection of the upper urinary tract segment for UTUC were included in the final patient base. Cases involving trimodal therapy were excluded from the study due to frequent protocol violations associated with this treatment modality, making their inclusion in the final analysis problematic.

The number of patients with invasive disease who received neoadjuvant or adjuvant platinum-based chemotherapy for both tumor locations was estimated. The use of single-dose intravesical instillation following endoscopic management for non-invasive tumors was assessed. Deviations from the recommended follow-up strategies for all T-stages were documented.

Quality assessment

The quality indicator for transurethral bladder resection (TUR) was the presence of the detrusor muscle in the specimen. The quality of laparoscopic/open surgical procedures was determined by evaluating the pathological resection margins and rates of R-positive status. The absence of margin status was considered indicative of potential incomplete tumor removal or inadequate pathological assessment of the specimen, which could negatively impact survival.

Changes in estimated glomerular filtration rates (eGFR) were analyzed before surgery and three months post-surgery for both invasive BC and UTUC patients. This parameter assessed the ability to receive standard platinum-based chemotherapy regimens either before or after surgery. Additionally, we have compared the survival of patients who underwent RNUE and further treatment in high-volume center (National Cancer Institute of Ukraine) to the rest of the country's data.

Statistical analysis

Statistical analysis was performed by creating maximally homogeneous patient groups with BC and UTUC, having the necessary notified parameters for further analysis. The primary analysis goals included determining the average age at diagnosis, detection rates based on gender, frequency of diagnosis verification before surgery, the volume of surgical intervention, and the frequency of postoperative complications based on data on 30-day readmission. Complications were assessed using Clavien–Dindo scoring. eGFR was calculated for invasive urothelial carcinomas using the Cockcroft-Gault formula.

In statistical analysis, the frequency of primary goal parameters was analyzed based on the standardized incidence ratio (SIR) and 95% CI by adding covariates of age, gender, and disease stage. Statistical associations were considered only when a confidence interval was present at levels of 0.05 and 0.01. Group comparisons were conducted before survival curve construction using the *t*-Student criterion for parametric data and Pearson's χ^2 test for non-parametric data. The Fisher's z-test was used for group comparison under normal distribution conditions (within < -1.96 to > 1.96). A P value greater than 0.05 was considered acceptable for group comparisons.

Cumulative survival curves were constructed using the Kaplan–Meier analysis. The model was chosen due to a high likelihood of patient dropout from observation (log-rank test), providing a statistical characterization in selecting this type of analysis. Data processing was performed using Statistica v.13.0, and the database is available for viewing in Microsoft Excel MS Office 2017. Please add a statement in your methods section to say that the work has been reported in line with the STROCSS criteria[14].

Results

The demographic indicators of patients corresponding to the primary goals are presented in Table 1. The average age at diagnosis for both pathologies was close to 70 years, with patients being slightly older in cases of UTUC. In both groups, the

Table 1

Demographic and treatment quality indicators for Bladder Cancer (BC) and Upper Tract Urothelial Carcinoma (UTUC).

Indicator/disease	BC ($n = 11\,733$)	UTUC (968)
Age, years	69.0 ± 8.8	72.0 ± 7.7
Sex, m/w, *n* (%)	10 169 (86.7) / 1564 (13.3)	847 (87.5) / 121 (12.5)
Organ-sparing / radical surgical treatment, *n* (%)	9913 (84.5) / 1820 (15.5)	395 (40.8) / 573 (59.2)
30-day postoperative complication rate, %	2.3	4.6
Non-standard postoperative management, %	39	58

m, man; w, woman.

number of male outnumbered female patients. For BC, endoscopic treatment was more typical, while radical cystectomy was conducted only in 15.5% of cases. This is explained by the prevalence of non-muscle-invasive bladder tumors at primary diagnosis. On the other hand, organ-sparing treatment was more typical for invasive UTUC (40,8%), where it was used as a treatment option for both muscle-invasive and non-invasive lesions.

The 30-day hospitalization rate was low for both pathologies regardless of the stage, with a slightly higher preference for UTUC. The complication rate higher than III degree according to the Clavien–Dindo averaged 0.2% for all patients. Rates of violation of the recommended postoperative management (untimely introduction or violation of approved schemes for preventive local or systemic chemotherapy, irregular conduction of follow-up cystoscopies or computed tomography) was high in both cohorts (see Table 1).

A notable finding is the frequency of neoadjuvant (7%) and adjuvant chemotherapy (28%) among patients with invasive and locally advanced urothelial carcinomas without regional lymph node involvement. Whereas median eGFR for invasive UTUC before and after surgery was 63.2 and 51.4 ml/min, respectively ($P = 0.00054$). The directly opposite trend was seen in BC—61.2 and 68.7 ml/min, respectively ($P = 0.0026$).

Subsequent analysis included the construction of survival curves by stages for both pathologies, as shown in Figure 1. For BC, the overall survival rates by stages were: I—73%, II—49%, III—18%, and IV—11% ($\chi^2 = 1807.207$; $P = 0.000001$). These findings directly correlate with the parameters of effective monitoring and the frequency of systemic chemotherapy usage. More detailed analysis revealed the absence of the detrusor muscle in TUR specimens in 4376 (44.1%) cases. Margin status in muscle-invasive disease was negative in 931 (51.2%) patients, positive in 287 (15.7%) and not applicable in 602 (33.1%). Additionally, the treatment results for T-stages III and IV were unsatisfactory, indicating a potentially low percentage of effective systemic treatment.

As for UTUC, the 5-year overall survival rates corresponded to the literature data, but there was a pronounced negative trend towards a decrease in this indicator after a 10-year period for all stages (Fig. 2; $\chi^2 = 146.298$; $P = 0.000003$). This may be associated with the prevalence of radical interventions and the subsequent development of renal failure, leading to ineffective systemic therapy and progression of cancer or concomitant pathology with associated mortality. Overall, organ-sparing treatment for invasive UTUC did not significantly differ from radical nephroureterectomy (RNU) in terms of 5-year survival across Ukraine (51.3 vs. 51%; log-rank test, $P = 0.63$), as seen in Figure 3. However, it is worth noting that the average age of patients in the organ-sparing treatment group was higher than that in the radical nephroureterectomy (RNU) group (72.0 ± 5.4 vs. 66.0 ± 7.8 years, $P = 0.0034$), which undoubtedly influenced the final statistical indicators. Margin status in muscle-invasive disease was negative in 413 (42,7%) patients, positive in 128 (13.2%) and not applicable in 427 (44.1%). The most statistically comparable groups in terms of demographic indicators were the RNU groups conducted at the National Cancer Institute and other medical institutions in Ukraine (Fig. 4; log-rank test, $P < 0{,}001$). The obtained data indicate a 15% advantage in the overall survival of patients who underwent RNU at a referent oncological center (high-volume center) compared to other medical institutions in Ukraine.

Another analyzed aspect was the comparison of survival rates between patients with invasive stages of BC and renal UTUC who underwent primary radical treatment. We obtained comparable 5- and 10-year survival rates for these groups of patients, with a statistically insignificant 7% advantage for BC over UTUC (Fig. 5; log-rank test, $P = 0.072$). Therefore, despite genetic and clinical differences in treatment, these pathologies in the population seem to have quite similar prognoses under the condition of invasion into the muscular layer.

Discussion

The incidence of bladder cancer increases with age, with about 9 out of 10 patients being over 55 years old, and an average of 73. The risk of developing bladder cancer is ~1 in 27 for men and 1 in 89 for women. Among localized forms, about 75% of carcinomas are non-invasive and can be effectively removed endoscopically, while the remaining 25% require radical cystectomy as the initial treatment step. The overall 5-year survival rate for invasive forms with radical treatment is 70%, but for locally advanced and metastatic stages, this rate significantly drops to 36% and 5%, respectively[15]

Upper urinary tract carcinomas are relatively rare, constituting only 5% of all urothelial tumors. Early detection of these formations is challenging, given the clinical complexity and the paucity of symptoms, resulting in delayed diagnosis and potentially ineffective treatment. Approximately 60% of UTUCs are invasive at the time of the initial tomography[15]. These tumors often affect the bladder concomitantly (8–13%) or secondarily after surgical treatment (30–51%). To stratify patients and determine the prognosis for UTUC, they are categorized into high and low-risk groups. According to the European Association of Urologists guidelines, endoscopic organ-sparing treatment is possible for the low-risk group, but it is associated with relatively high recurrence rates[16,17]. In contrast, for high-risk tumors, resection of the affected segment of the upper urinary tract is not commonly used by many surgeons due to technical complexity despite satisfactory oncological outcomes[8]. The key problem of UTUC is the frequency of renal insufficiency, significantly limiting the use of combined treatment[4–6]. In this context, the use of organ-sparing treatment appears to be a promising method to improve the final treatment outcomes[18,19].

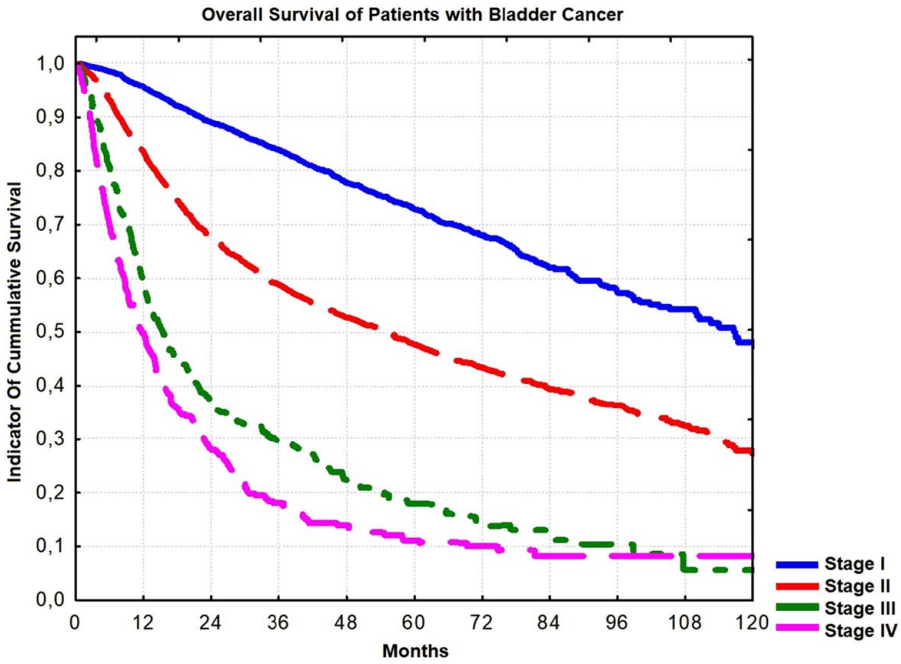

Figure 1. Overall survival of patients with bladder cancer by stages.

In the present study, we identified that the analyzed population exhibited an aggressive disease course of urothelial cancer. Cancer-specific survival rates for localized BC and UTUC are lower compared to the rates reported in the literature[20,21]. With the presence of an invasive growth, less than half of the patients have survived a 5-year period from the start of treatment. This situation may be influenced by several factors:

(1) Limited choice of systemic agents.
(2) Differences in the surgical level in different centers.
(3) Frequent development of renal insufficiency during treatment, significantly limiting effective chemotherapy.
(4) Untimely or incorrect administration of adjuvant treatment.
(5) Age category of patients undergoing treatment.

As of today, there is one effective line of systemic chemotherapy in reserve for the treatment of urothelial cancer, which is cisplatin-based (Gem-Cis or MVAC schemes). All other schemes based on

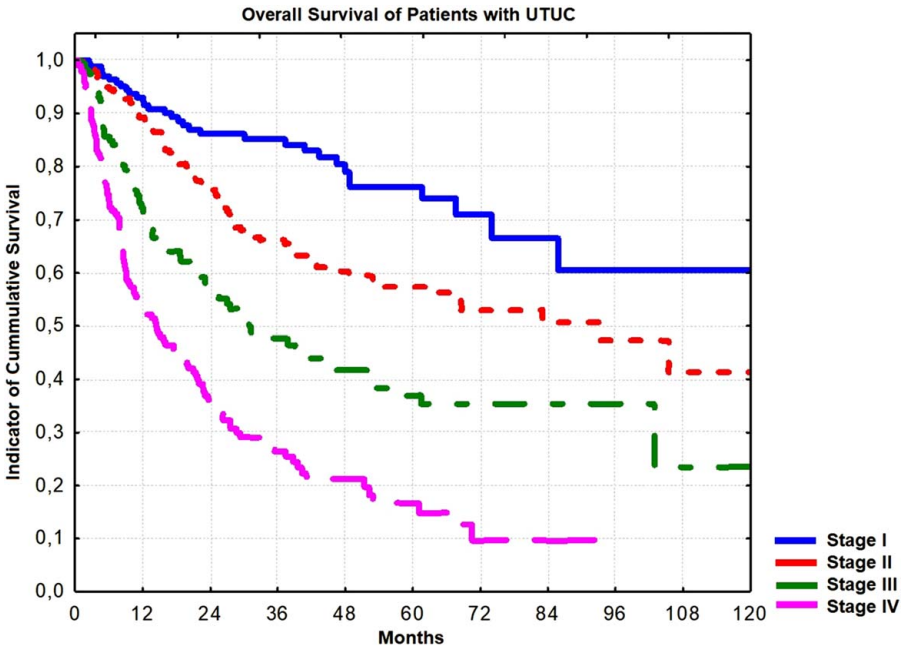

Figure 2. Overall survival of patients with UTUC by stages. UTUC, upper tract urothelial cancer.

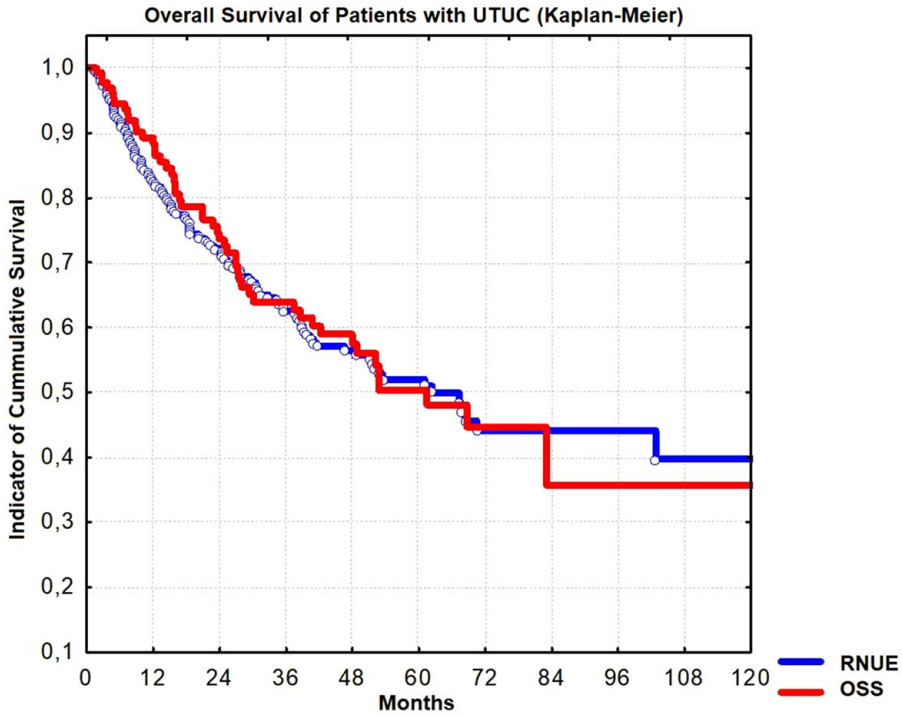

Figure 3. Overall survival of patients with UTUC undergoing RNUE and OSS. OSS, organ-sparing surgery; RNUE, radical nephroureterectomy; UTUC, upper tract urothelial cancer.

carboplatin, taxanes, etoposide, methotrexate, and other chemotherapeutic variations are unfortunately highly ineffective (with a 5–29% likelihood of response)[22,23]. Immune checkpoint inhibitors available today have not shown the expected results, with an objective response rate of 30% for non-metastatic lesions[24]. Although combination therapy has shown promising results, its use is currently limited to metastatic disease[8,9]. Therefore, urologists face a challenging choice in selecting the right treatment strategy for urothelial cancer, which typically involves a combination of surgical and systemic treatment.

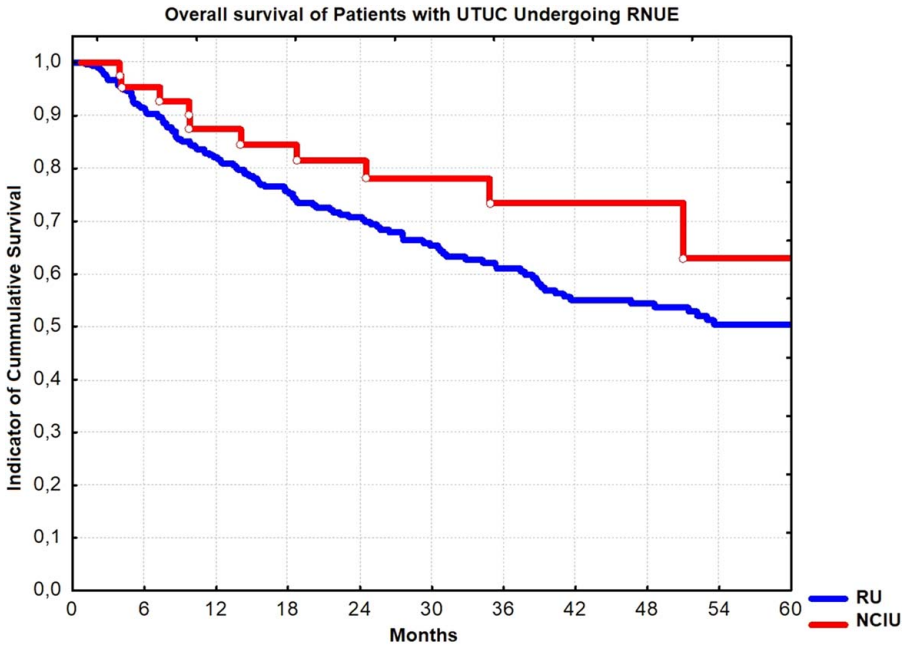

Figure 4. Difference in patients survival between patients undergoing RNUE in Oncological Referent Center and Rest of Ukraine. NCIU, oncological referent center; RNUE, radical nephroureterectomy; RU, rest Ukraine; UTUC, upper tract urothelial cancer.

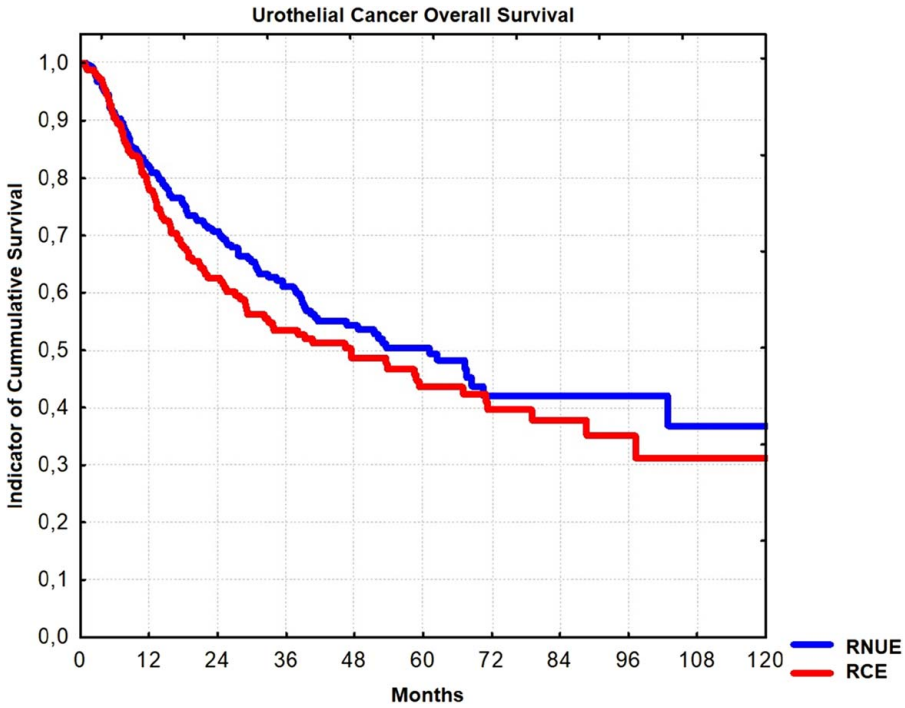

Figure 5. Comparison of survival between patients undergoing RCE and RNUE. RCE, radical cystectomy; RNUE, radical nephroureterectomy.

The technical skills of the surgeon performing tumor removal play a crucial role in the final outcome of treatment[25,26]. After accounting for major risk factors, high-volume centers were linked to better outcomes, including lower inpatient mortality, shorter hospital stays, and reduced costs, compared to low-volume centers[25]. The execution of the surgical intervention should be based on oncological principles, ensuring safety for the patient and accompanied by the necessary administration of topical agents in accordance with existing treatment guidelines[27]. Failure to adhere to widely accepted rules leads to a high recurrence rate in the urinary tract, consequently resulting in the progression of the disease and the patient's death. Adequate and effective use of both local chemotherapy (mitomycin C, Bacillus Calmette-Guérin) and systemic therapy (regimens: gemcitabine–cisplatin, carboplatin–gemcitabine, pembrolizumab, atezolizumab, and others), and if necessary, their combinations, are essential for improving treatment outcomes[27]. Current research has identified that 39% and 58% of cases with BC and UTUC, respectively, received postoperative management that did not adhere to established clinical guidelines.

It is important to note that 33% of patients with invasive BC and 44% of patients with UTUC lacked margin status information in their final pathology reports. Margin status is crucial for determining the need for adjuvant treatment and assessing patient prognosis. Additionally, 13% of BC cases and 16% of UTUC cases had positive surgical margins, which is linked to poorer outcomes. Positive margins significantly affect prognosis and can lead to lower survival rates in these patients[28].

It is well-established that perioperative chemotherapy (neoadjuvant/adjuvant) increases median survival. Long-term results show a 16% reduction in the risk of death, with the hazard ratio indicating improved 10-year survival rates, which increase from 30 to 36% with the use of neoadjuvant chemotherapy[29]. Additionally, preoperative systemic treatment can reduce the complexity of the primary tumor, facilitating a more successful surgical intervention[30]. Adjuvant chemotherapy was also shown to improve recurrence-free survival, locoregional recurrence-free survival and metastasis-free survival with absolute benefits of 11%, 11%, and 8%, respectively[31].

One of the crucial factors influencing the course of the disease and the overall survival of patients is the development of chronic kidney insufficiency[24,32]. For BC, bilateral involvement and progression of irreversible parenchymal dystrophy in both kidneys is more typical. However, surgical intervention usually removes obstruction, resulting in improved kidney function in some patients. In the present study we report an overall improvement of eGFR from 61.2 to 68.7 ml/min ($P = 0.0026$) before and after surgery. This indicates that obstruction relief after surgery due to invasive BC may lead to a general improvement in kidney function making systemic therapy more feasible.

On the other hand, for UTUC a unilateral terminal involvement is more frequently met, essentially leading to an elderly patient with a single functioning kidney. The frequency of kidney insufficiency in UTUC reaches 70% of the total number of patients after surgery[24]. This was also noticed in our study, which showed a remarkable decrease of eGFR from 63.2 to 51.4 ml/min after surgery ($P = 0.00054$).

Changes in glomerular filtration affect the survival of patients in two ways:

(1) Restricting the use of systemic therapy.
(2) Triggering endogenous mechanisms of progression of concomitant pathology.

For BC and UTUC, the approaches to overcome the risks of reduced glomerular filtration are different. In the case of bladder cancer, it is clinically significant to promptly remove the obstruction (nephrostomy or radical cystectomy) and conduct

maximally effective chemotherapy. In cases of UTUC, the issue of chronic kidney insufficiency is more important, and the reduction of its stage is possible through organ-preserving treatment[33]. Unfortunately we were not able to analyze organ-sparing approaches in bladder cancer due to inconsistent data and many standard procedures violations in the database; however, we were successful in comparing these approaches in UTUC. Our results showed equal 5-year overall survival (51.3 vs. 51%) for radical nephroureterectomy and partial ureterectomy. This highlights the possibility of performing organ-sparing surgery for UTUC with equivalent oncological outcomes in cases where the affected kidney function is preserved[33].

This study has several limitations that should be considered when interpreting the results. First, the retrospective design inherently carries risks of bias and limits the ability to establish causality. Second, the study relied on registry data, which may lack detailed clinical information. Third, the generalizability of the findings may be limited to the Ukrainian population, given differences in healthcare systems, treatment protocols, and patient demographics in other countries. Comparisons with international data should be made cautiously, considering these contextual differences. Fourth, the analysis of renal function changes (eGFR) before and after surgery did not control for other factors that might influence kidney function, such as pre-existing chronic kidney disease, hypertension, or diabetes, which could confound the results. Despite these limitations, the study provides valuable insights into the treatment and outcomes of urothelial cancer in Ukraine and underscores the need for continuous improvement and adherence to evidence-based practices in oncology care.

Conclusion

The results of the nationwide analysis showed that the most critical categories of patients, differing in survival rates from global data. The main strategies to improve survival rates include:

(1) The use of recommended intravesical chemotherapy regimens for bladder cancer is essential for preventing recurrence and, consequently, further disease progression
(2) Improvement of surgical skills in medical centers treating patients with bladder cancer or upper tract urothelial carcinoma is crucial. Alternatively, concentrating patients in highly specialized centers with a higher frequency of such clinical cases can enhance outcomes. Ensuring R0 resection adequacy through mandatory biopsy of resection margins is essential, including clearly defining the transition boundaries from organ-preserving treatment to organ-invasive treatment.
(3) Systematization of approaches to the systemic treatment of urothelial cancer is necessary. This includes involving a clinical oncologist and a radiation oncologist in multidisciplinary consultations to determine the timing and extent of combined treatment before initiating any therapy.
(4) Increasing the frequency of organ-preserving surgeries for upper tract urothelial carcinoma is essential. Utilizing segmental resection of the upper urinary tract in patients with preserved kidney function aims to improve survival outcomes and quality of life while reducing the risk of chronic kidney disease. Preserving the kidney in this context is a safe surgical intervention that does not compromise oncological treatment outcomes.

Ethical approval

The study was approved by the Institutional Review Boards and the local ethics committees (local ethics committee agreement № 134, Kyiv, 26.03.2019;) and was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines. The databases used in the study are the intellectual property of the National Cancer Institute of Ukraine.

Consent

Informed consent for data archiving and sharing were signed by all the participants. All patients' data were anonymised. A copy of the written consents is available for review by the Editor-in-Chief of this journal on reasonable request

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Author contribution

Conceptualization: M.P., P.G., E.S. Data curation: M.P. Formal analysis: M.P. Supervision: P.G., E.S. Writing—original draft preparation: M.P. Writing—review and editing: P.G., E.S.

Conflicts of interest disclosure

The authors declare no conflicts of interest and no financial interest in preparing this article.

Research registration unique identifying number (UIN)

Information about patients was received from the National Cancer Registry of Ukraine, therefore no recruitment process was performed. Data were anonymised prior to analysis. A standard of care treatment was used for all the patients. Therefore no new intervention comparison was done. Current study does not require registration according to the Helsinki Declaration in the clinical trial regisrty.

Guarantor

Maksym Pikul.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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