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ORIGINAL ARTICLE

Real-world outcomes of adjuvant immunotherapy candidates with upper tract urothelial carcinoma: results of a multicenter cohort study

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Abstract

Background Recent clinical trials have reported improved disease-free survival rates of patients with stage pT3–4/ypT2–4 or pN + upper tract urothelial carcinoma (UTUC) on adjuvant nivolumab therapy. However, the appropriateness of the patient selection criteria used in clinical practice remains uncertain.

Methods We retrospectively analyzed 895 patients who underwent nephroureterectomy to treat UTUC. The patients were divided into two groups: grade pT3–4 and/or pN + without neoadjuvant chemotherapy (NAC) or grade ypT2–4 and/or ypN + on NAC (adjuvant immunotherapy candidates) and others (not candidates for adjuvant immunotherapy). Kaplan–Meier curves were drawn to assess the oncological outcomes, including recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). Cox proportional hazards models were used to identify significant prognostic factors for oncological outcomes.

Results The Kaplan–Meier curves revealed notably inferior RFS, CSS, and OS of patients who were candidates for adjuvant immunotherapy. Multivariate analysis revealed that pathological T and N grade and lymphovascular invasion (LVI) status were independent risk factors for poor RFS, CSS, and OS.

Conclusion In total, 44.8% of patients were candidates for adjuvant immunotherapy. In addition to pathological T and N status, LVI was a significant predictor of survival, and may thus play a pivotal role in the selection of patients eligible for adjuvant immunotherapy.

Keywords Upper tract urothelial carcinoma · Neoadjuvant chemotherapy · Adjuvant candidate

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare condition responsible for 10% of all renal tumors and 5% of all urothelial tumors, but its incidence has increased in recent decades [1, 2]. At diagnosis, tumors are twice as likely to occur in the renal pelvis than the ureter [3]. Radical nephroureterectomy with bladder cuff excision is the recommended standard treatment for long-term disease control. However, high-risk cases characterized by high tumor grade or invasiveness are significantly more likely to experience recurrence and progression [4].

Recent clinical trials have explored various perioperative treatment strategies [5, 6]. The POUT trial showed

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that UTUC patients of grade ≥ pT2 and/or pN + benefited from adjuvant chemotherapy [5]. However, prescription of cytotoxic chemotherapy for all patients with UTUC of grade ≥ pT2 is impractical because advanced age and renal impairment may be contraindications. The CheckMate 274 trial showed that adjuvant nivolumab therapy improved the disease-free survival (DFS) of patients with grade pT3–4/ypT2–4 or pN + urothelial carcinoma [6]. However, the appropriateness of such selection criteria in real-world clinical practice remains uncertain. In the CheckMate 274 trial, a sub-analysis revealed no difference in the UTUC DFS between patients who did and did not receive adjuvant nivolumab [6]. Thus, more precise criteria for selecting UTUC patients who may be candidates for adjuvant immunotherapy are required.

Here, we retrospectively examined the oncological outcomes of UTUC patients eligible for adjuvant immunotherapy using the CheckMate 274 criteria. We also developed a novel risk model facilitating prediction of the clinical trajectory by both patients and physicians.

Patients and methods

Patients

We enrolled patients who underwent radical nephroureterectomy between January 2012 and December 2021 at TheJikei University Hospital and 16 affiliated facilities (The JIKEI-YAYOI Collaborative Group). The exclusion criteria were a lack of clinical detail (n = 35), pathological T0 stage (n = 2), indeterminate pathological findings (n = 2), and non-urothelial carcinoma (n = 39). A total of 895 patients were finally included, of whom 71 received neoadjuvant chemotherapy (NAC) and 824 did not.

Neoadjuvant and adjuvant chemotherapy

The decision to start NAC was usually based on clinical T3–4 and N + status, but was ultimately dependent on a discussion between each patient and the treating physicians. Adjuvant chemotherapy was considered if the pathological grade was pT4 or N + . The NAC/adjuvant chemotherapy regimen was either gemcitabine/cisplatin or gemcitabine/carboplatin. The regimen was selected by certificated urologists or medical oncologists who considered patient age, performance status, and kidney and cardiovascular function. No patients received adjuvant immunotherapy after nephroureterectomy.

Surgical procedure

All surgical procedures were performed by certified urologists; an open or laparoscopic approach was chosen based on the preferences of the patients and urologists. All surgeries were standard radical nephroureterectomies with excision of the bladder cuff. The extent of lymph node dissection (if any) was at the discretion of the urologists. This study was approved by The Jikei University Institutional Review Board [approval no. 33-260(10,878)].

Clinicopathological data

We retrieved baseline demographic and clinicopathological data, operative and management data, and follow-up and oncological outcome data. The patients were divided into groups with and without NAC prior to radical nephroureterectomy. Tumor staging followed the recommendations of the American Joint Committee on Cancer (8th ed., 2017). Lymphovascular invasion (LVI) was defined as tumor cells within the endothelial linings of vascular or lymphatic channels. Tumor grading and variant classification followed the guidelines of the 2016 World Health Organization [7]. We divided the patients into two groups: pT3–4 and/or pN + status not receiving NAC or ypT2–4 and/or ypN + status on NAC (adjuvant immunotherapy candidates), and others (not candidates for adjuvant immunotherapy).

Study outcomes

Recurrence was defined as late disease outside the urinary tract and bladder. Routine monitoring included complete blood counts, liver and kidney function tests, chest X-rays, urine cytology, cystoscopy, and abdominal computed tomography conducted at 3–6-month intervals over the first postoperative 2 years and every 2 years thereafter. The primary outcome was the effect of trial eligibility for adjuvant immunotherapy on oncological outcomes. Secondary outcomes included the additional effect of LVI status to the clinical trial criteria on prognosis and risk model development.

Statistical analysis

The significance of associations between histological variants and clinicopathological variables was evaluated using

Table 1 Patients' characteristics

Variable	Without NAC		With NAC		p value (with NAC vs without NAC)	p value (candidate vs non-candidate)
	Adjuvant therapy candidate	Adjuvant therapy non-candidate	Adjuvant therapy candidate	Adjuvant therapy non-candidate		
Number of patients	356	468	45	26		
Age, year (range)	74 (44–91)	74 (32–94)	70 (53–84)	69 (51–83)	< 0.001	0.2
Follow-up, month (range)	22 (1–112)	34 (1–135)	5 (2–97)	29 (2–100)	0.65	< 0.001
Sex, *n* (%)						
Male	253 (71.1)	335 (71.6)	31 (68.9)	15 (57.7)	0.24	0.99
Female	103 (28.9)	133 (28.4)	14 (31.1)	11 (42.3)		
Charlson comorbidity index, *n* (%)						
0	258 (72.5)	380 (81.2)	32 (71.1)	16 (61.6)	< 0.01	< 0.01
1	76 (21.3)	74 (15.8)	7 (15.6)	1 (3.8)		
≥ 2	22 (6.2)	14 (3.0)	6 (13.3)	9 (34.6)		
Laterality, *n* (%)						
Right	161 (45.2)	234 (50.0)	26 (57.8)	15 (57.8)	0.11	0.26
Left	195 (54.8)	234 (50.0)	19 (42.2)	11 (46.2)		
Hydronephrosis, *n* (%)						
Absent	159 (44.7)	238 (50.9)	20 (44.4)	14 (53.8)	0.96	0.06
Present	197 (55.3)	230 (49.1)	25 (55.6)	12 (46.2)		
Neoadjuvant Chemotherapy, *n* (%)						
Cisplatin-based regimens	0 (0.0)	0 (0.0)	40 (88.9)	23 (88.5)	< 0.001	0.91
Operative method, *n* (%)						
Open	118 (33.1)	118 (25.2)	7 (15.6)	3 (11.5)	0.008	0.026
Laparoscopic	238 (66.9)	350 (74.8)	38 (84.4)	23 (88.5)		
Tumor location, *n* (%)						
Renal pelvis	182 (51.2)	217 (46.4)	20 (44.4)	16 (61.5)	0.78	0.098
Ureter	147 (41.3)	227 (48.5)	22 (48.9)	10 (38.5)		
Both	27 (7.6)	24 (5.1)	3 (6.7)	0 (0.0)		
Tumor Grade, *n* (%)						
Low grade	11 (3.1)	146 (31.2)	2 (4.4)	5 (19.2)	0.007	< 0.001
High grade	311 (87.4)	284 (60.9)	43 (95.6)	21 (80.8)		
NR	34 (9.6)	38 (8.1)	0 (0.0)	0 (0.0)		
Histology, *n* (%)						
Pure UC	330 (92.7)	462 (98.7)	45 (100)	25 (96.2)	0.29	< 0.001
UC with variant histology	26 (7.3)	6 (1.3)	0 (0.0)	1 (3.8)		
Pathological T stage						
(y)pTis/a/1	5 (1.4)	367 (78.4)	0 (0.0)	26 (100)	0.094	< 0.001
(y)pT2	3 (0.84)	101 (21.6)	8 (17.8)	0 (0.0)		
(y)pT3	308 (86.5)	0 (0.0)	29 (64.4)	0 (0.0)		
(y)pT4	40 (7.3)	0 (0.0)	8 (17.8)	0 (0.0)		
Lymph node status, *n* (%)						
pN0	101 (28.4)	131 (28.0)	17 (37.8)	12 (46.2)	0.003	< 0.001
pN1-2	62 (17.4)	0 (0.0)	11 (24.4)	0 (0.0)		
pNx	193 (54.2)	337 (72.0)	17 (37.8)	14 (53.8)		
Concomitant CIS, *n* (%)						
Absent	302 (84.8)	394 (84.2)	37 (82.2)	21 (80.8)	0.54	0.83
Present	54 (15.2)	74 (15.8)	8 (17.8)	5 (19.2)		
LVI, *n* (%)						
Absent	143 (40.2)	416 (88.9)	24 (53.3)	25 (96.2)	0.84	< 0.001
Present	213 (59.8)	52 (11.1)	21 (46.7)	1 (3.8)		

Table 1 (continued)

Variable	Without NAC		With NAC		p value (with NAC vs without NAC)	p value (candidate vs non-candidate)
	Adjuvant therapy candidate	Adjuvant therapy non-candidate	Adjuvant therapy candidate	Adjuvant therapy non-candidate		
Adjuvant chemotherapy, *n* (%)						
Absent	252 (70.8)	457 (97.6)	38 (84.4)	26 (100)	0.33	< 0.001
Present	104 (29.2)	11 (2.4)	7 (15.6)	0 (0.0)		

CIS carcinoma in situ, *LVI* lymphovascular invasion, *NAC* neoadjuvant chemotherapy, *UC* urothelial carcinoma

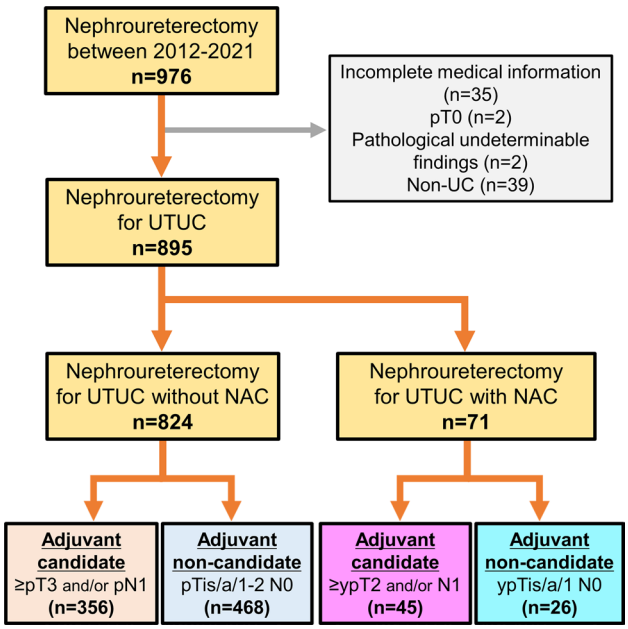

Fig. 1 Flow diagram of patient inclusion

the chi-squared test or Fisher's exact test. The durations of recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) from the day of nephroureterectomy were computed using the Kaplan–Meier method; log-rank comparisons were employed when necessary. Variables that affected the RFS, CSS, and OS were identified using Cox proportional hazards regression models. We evaluated the effect of addition of LVI status to the CheckMate 274 criteria of the risk model, followed by a comparison of the Harrell concordance index (c-index) [8] values of the basic model, which considers pT3–4/ypT2–4 and/or pN + status, and the LVI model, which considers pT3–4/ypT2–4 and/or pN + or LVI + status, in UTUC patients. A p-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Stata software (version 13.1; Stata Corp., TX, USA).

Results

Patient demographics

Patient characteristics are summarized in Table 1. Of the 895 included patients, 71 (7.9%) received NAC and 824 (92.0%) did not. The median age was 74 years (range: 32–94 years). The median follow-up duration was 28 months (range: 1–135 months). Lymph node dissection was performed in 334 patients (37.3%); 73 (8.2%) had lymph node involvement. Adjuvant chemotherapy was prescribed for 122 patients (13.6%) after radical nephroureterectomy. The clinicopathological characteristics of UTUC patients receiving NAC and not are shown in Table 1. Of all patients, 44.8% were candidates for adjuvant immunotherapy. Of these 401 patients, 45 (11.2%) received NAC (Fig. 1). Table 1 compares the clinicopathological characteristics of patients who were and were not candidates for adjuvant immunotherapy. The median number of cycles administered in the NAC group was 3 (range: 1–5). The chemotherapy regimens used in this group included gemcitabine plus cisplatin (88.7%, n = 63), gemcitabine plus carboplatin (9.9%, n = 7), and dose-dense methotrexate-vinblastine-adriamycin-cisplatin (n = 1). Similarly, the median number of cycles administered in the AC group was 3 (range: 1–5). The chemotherapy regimens used in this group included gemcitabine plus cisplatin (48.4%, n = 59), gemcitabine plus carboplatin (45.9%, n = 56), and dose-dense methotrexate-vinblastine-adriamycin-cisplatin (n = 1). In total, six patients received other regimens, including gemcitabine + nedaplatin (n = 3) and gemcitabine alone (n = 3). (Supplementary Table 1).

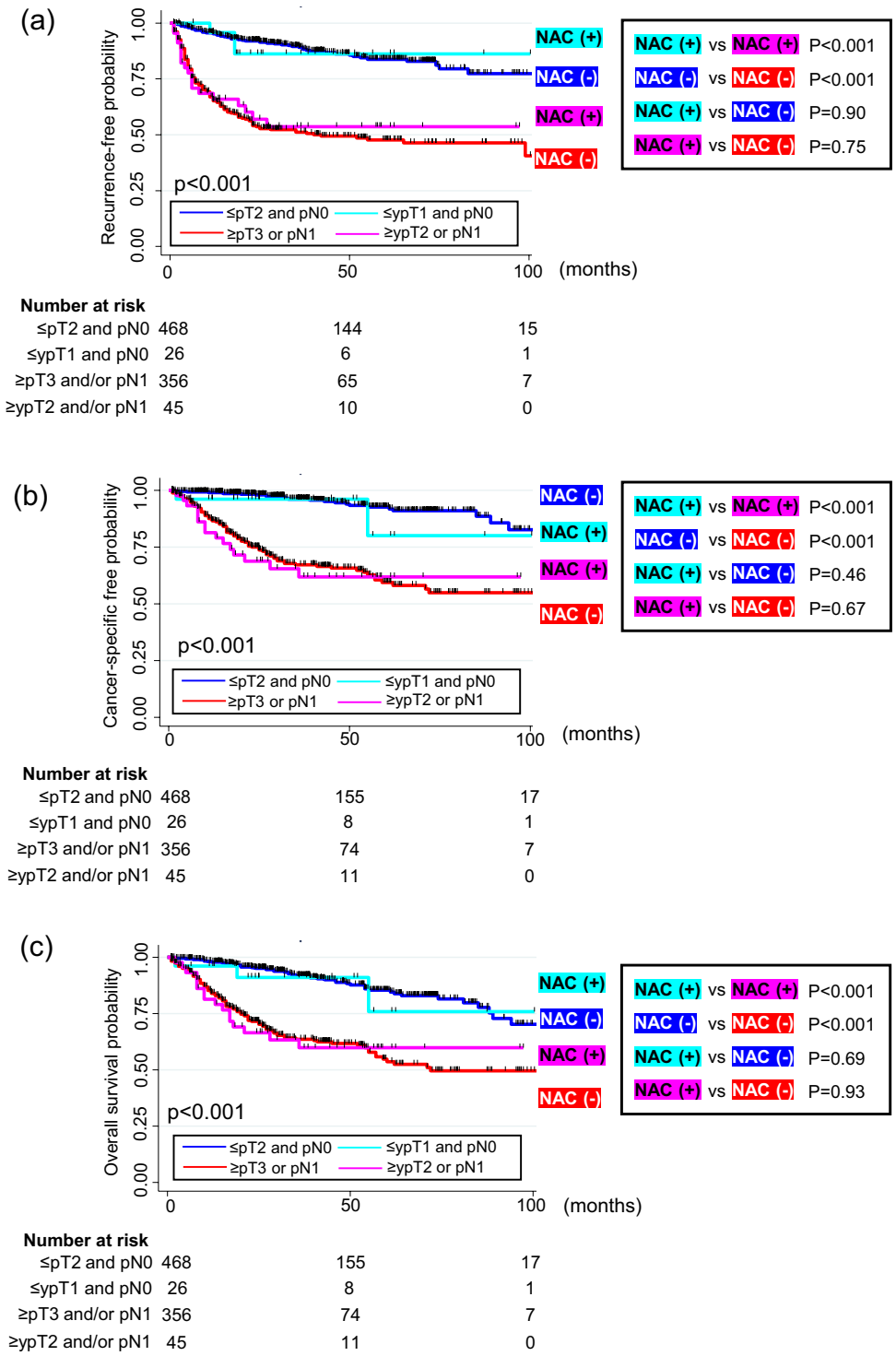

Fig. 2 Recurrence-free (**a**), cancer-specific (**b**), and overall survival (**c**) rates of upper tract urothelial carcinoma candidates for adjuvant immune therapy and those receiving neoadjuvant chemotherapy (NAC)

Oncological outcomes

During follow-up, 232 (25.9%) patients developed metastases; there were 145 (16.2%) cases of cancer-specific mortality and 189 (21.1%) patients died of any cause. The 3-year RFS, CSS, and OS rates were 72.2%, 83.1%, and 79.0%, respectively. The Kaplan–Meier curves revealed

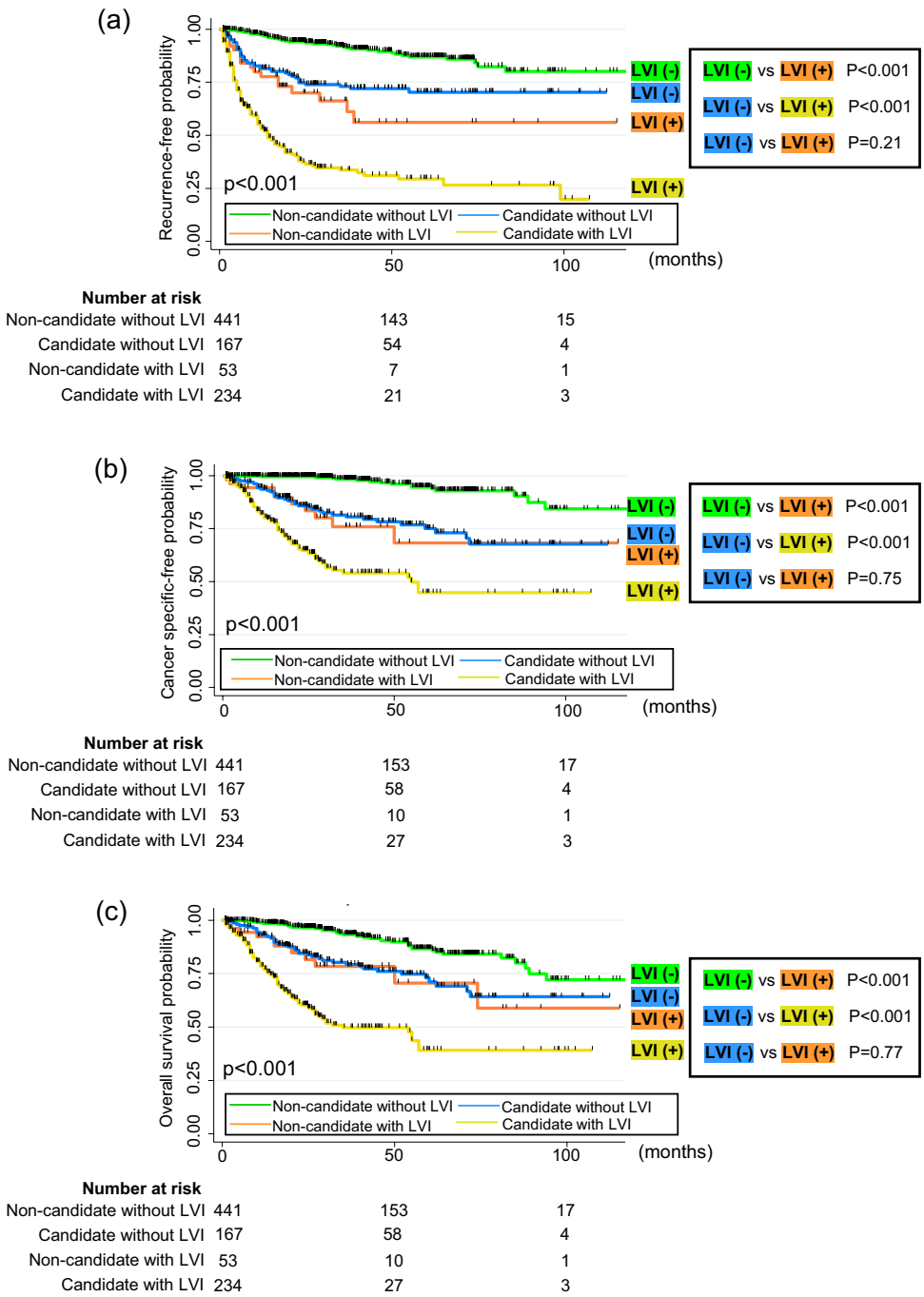

Fig. 3 Recurrence-free (**a**), cancer-specific (**b**), and overall survival (**c**) rates of upper tract urothelial carcinoma candidates for adjuvant immune therapy and those of lymphovascular invasion (LVI) status

significantly inferior RFS, CSS, and OS among candidates for adjuvant immunotherapy ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively) (Supplementary Fig. 1a–c). In contrast, the RFS, CSS, and OS did not differ significantly between candidates for adjuvant immunotherapy on NAC and not on NAC ($p = 0.75$, $p = 0.67$, and $p = 0.93$, respectively) (Fig. 2a–c). Similar trends were observed in those who were not candidates for adjuvant immunotherapy ($p = 0.90$, $p = 0.46$, and $p = 0.69$, respectively) (Fig. 2a–c). The 3-year RFS, CSS, and OS, stratified by the criteria used

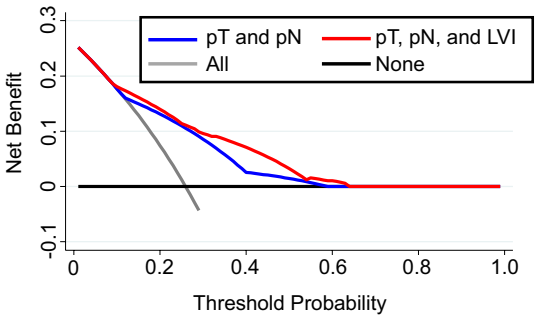

Fig. 4 Recurrence predictions based on decision curve analyses. Basic model: pT3–4 and pN + (ypT2–4 and pN +) status. New model: basic model with the addition of LVI status

to select candidates for adjuvant immunotherapy and NAC induction, are summarized in Supplementary Table 2.

Establishment of a novel risk model

Multivariate Cox's regression analysis revealed that pathological T and N stages and LVI status independently affected RFS (hazard ratio [HR] = 2.68, p < 0.001; HR = 1.88, p = 0.001; HR = 3.28, p < 0.001, respectively), CSS (HR = 4.46, p < 0.001; HR = 1.72, p = 0.017; HR = 2.67, p < 0.001, respectively), and OS (HR = 2.65, p < 0.001; HR = 1.75, p = 0.009; HR = 2.35, p < 0.001, respectively). We next stratified patients by pathological T and N stage and LVI status. We found significant differences in RFS, CSS, and OS between patients with and without LVI among those who were candidates for adjuvant immunotherapy (p < 0.001, p < 0.001, and p < 0.001, respectively) (Fig. 3a–c) and those who were not (p < 0.001, p < 0.001, and p < 0.001, respectively) (Fig. 3a–c). Notably, we detected no significant difference in RFS, CSS, or OS between candidates for adjuvant immunotherapy without LVI and non-candidates for adjuvant immunotherapy with LVI (p = 0.21, p = 0.75, and

Table 2 Multivariate analysis for survival

Covariant	Recurrence free survival			Cancer-specific survival			Overall survival		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age, (continuous)	0.99	0.98–1.02	0.93	1.01	0.99–1.03	0.55	1.02	1.00–1.04	0.039
Sex									
Female	1.07	0.81–1.42	0.62	0.81	0.55–1.18	0.27	0.65	0.46–0.91	0.013
Charlson comorbidity index									
≥2	1.4	0.84–2.36	0.2	0.73	0.32–1.66	0.45	0.85	0.43–1.67	0.63
Tumor location									
Ureter	1.23	0.90–1.69	0.19	1.37	0.90–2.07	0.14	1.48	0.98–12.12	0.068
Both	1.1	0.64–1.89	0.74	0.57	0.24–1.38	0.22	0.87	0.42–1.80	0.71
Hydronephrosis									
Present	1.08	0.80–1.46	0.62	1.4	0.93–2.12	0.11	1.15	0.81–1.63	0.44
Pathological T stage									
≥pT3 or ypT2	2.68	1.89–3.81	< 0.001	4.46	2.71–7.35	< 0.001	2.65	1.80–3.89	< 0.001
Lymph node status									
pN1	1.88	1.31–2.71	0.001	1.72	1.10–2.70	0.017	1.75	1.15–2.68	0.009
Histology									
UC with variant histology	1.38	0.78–2.47	0.27	1.14	0.72–1.79	0.58	1.74	0.95–3.20	0.072
Concomitant CIS									
Present	0.92	0.64–1.33	0.67	1.14	0.72–1.79	0.58	1.03	0.69–1.53	0.89
LVI									
Present	3.28	2.43–4.43	< 0.001	2.67	1.81–3.94	< 0.001	2.35	1.69–3.28	< 0.001
Adjuvant chemotherapy									
Present	0.99	0.71–1.38	0.96	1.17	0.78–1.75	0.46	1.03	0.71–1.51	0.86

CIS carcinoma in situ, *IVR* intravesical recurrence, *LVI* lymphovascular invasion, *UC* urothelial carcinoma

p = 0.77, respectively) (Fig. 3b, c). We subjected the pathological T and N stage and LVI status data to decision curve analysis. Incorporating LVI status improved the prediction of recurrence relative to the basic model incorporating the pathological T and N stages only; the c-indices were 0.79 and 0.73, respectively (Fig. 4).

Discussion

We explored the oncological outcomes of patients eligible for adjuvant immunotherapy after nephroureterectomy to treat UTUC. In total, 44.8% of the patients were candidates. The Kaplan–Meier curves revealed significantly inferior RFS, CSS, and OS for candidate patients compared to the others. Notably, there was no significant difference in RFS, CSS, or OS between candidates for adjuvant immunotherapy who did and did not receive NAC. Similar trends were observed in those who were not candidates for adjuvant immunotherapy, suggesting that the adjuvant immunotherapy candidate criteria can be used to stratify UTUC patients post-nephroureterectomy. Multivariate analyses showed that pathological T stage (pT3–4 or ypT2–4), pathological N stage, and LVI were independent predictors of oncological outcomes. To the best of our knowledge, this study enrolled the largest number of candidates for adjuvant immunotherapy following nephroureterectomy to date among studies evaluating oncological outcomes. This retrospective study collected big data from multiple centers; bias associated with clinician subjectivity and between-facility variations in patient evaluation/treatment were thus minimized Table 2.

Two clinical trials have assessed the efficacy of adjuvant immunotherapy in patients with bladder urothelial carcinoma and UTUC [6, 9]. The CheckMate 274 trial used nivolumab (anti-PD-1) as adjuvant therapy; the IMvigor 010 trial employed atezolizumab (anti-PD-L1). In both studies, the NAC selection criteria included M0 status and either grade ypT2–4 and/or ypN + in patients who received NAC or grade pT3–4 and/or pN + patients who did not receive NAC because the focus was on patients at high risk of recurrence. The results of the two clinical trials are contradictory. The patient characteristics and study designs differed, but an explanation of the difference remains elusive. Both trials performed subgroup analyses of patients with various clinicopathological factors when investigating the efficacy of adjuvant immunotherapy. In both studies, pT3–4 status tended to be associated with favorable outcomes in patients on adjuvant immunotherapy. Here, we show that, in addition to pathological T and N status, LVI status significantly predicted oncological outcomes. A recent meta-analysis found that LVI status was associated with increased recurrence and mortality in UTUC patients [10]. LVI status was not investigated in the two cited clinical trials [6, 9]. In the present study, LVI status enhanced the predictive power for oncological outcomes compared to that of the conventional model employing only pathological T and N status. In our cohort, 58.4% of patients who were candidates for adjuvant immunotherapy exhibited LVI. Thus, in the cohorts of the CheckMate 274 and IMvigor 010 trials, the proportions of patients with LVI may have been relatively high, and LVI status may thus explain the conflicting results of the two trials. Notably, Miura et al. investigated the oncological outcomes of urothelial carcinoma patients eligible for adjuvant immunotherapy based on the clinical impact of LVI status [11]; this approach was validated in the present study. In the CheckMate 274 trial, sub-analysis revealed no difference in the DFS rates of UTUC patients who received and did not receive adjuvant nivolumab [6]; this result merits further consideration. The present work suggests that the clinical impact of LVI is poorly understood. Several phase 3 trials on perioperative immunotherapy are underway (NCT04209114, NCT03924856, NCT04700124, and NCT03924895). We expect that the effects of LVI status will be explored in subgroup or post-hoc analyses; the results may lead to changes in the criteria used for selecting UTUC patients who may benefit from adjuvant therapy.

Our study had some limitations. First, although this was a multicenter study, it was retrospective and had a relatively short follow-up. Second, follow-up was not completely standardized; the nature and frequency of the examinations varied. Third, the pathological data were from individual facilities; there was no centralized pathology review. Fourth, the NAC regimens were not completely standardized, potentially influencing the oncological outcomes of UTUC patients who received NAC prior to nephroureterectomy. Finally, no patient received adjuvant nivolumab after nephroureterectomy, in contrast to the contemporary clinical trend.

Conclusion

In total, 44.8% of the patients in this study were candidates for adjuvant immunotherapy. The adjuvant immunotherapy candidate criteria defined by CheckMate 274 trial can be used to stratify UTUC patients post-nephroureterectomy. Additionally, pathological T and N status and LVI status were predictive of success, thus the LVI status may also be considered when selecting suitable candidates for adjuvant immunotherapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-023-02424-9.

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Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

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

References

1. Redrow GP, Matin SF (2016) Upper tract urothelial carcinoma: epidemiology, high risk populations and detection. Minerva Urol Nefrol 68(4):350–358
2. Munoz JJ, Ellison LM (2000) Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol 164(5):1523–1525
3. Favaretto RL, Shariat SF, Chade DC et al (2010) The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 58(4):574–580
4. Lughezzani G, Burger M, Margulis V et al (2012) Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 62(1):100–114
5. Birtle A, Johnson M, Chester J et al (2020) Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet 395(10232):1268–1277
6. Bajorin DF, Witjes JA, Gschwend JE et al (2021) Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 384(22):2102–2114
7. Humphrey PA, Moch H, Cubilla AL et al (2016) The 2016 WHO classification of tumours of the urinary system and male genital organs-part b: prostate and bladder tumours. Eur Urol 70(1):106–119
8. Harrell FE Jr, Califf RM, Pryor DB et al (1982) Evaluating the yield of medical tests. JAMA 247(18):2543–2546
9. Bellmunt J, Hussain M, Gschwend JE et al (2021) Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 22(4):525–537
10. Stangl-Kremser J, Muto G, Grosso AA et al (2022) The impact of lymphovascular invasion in patients treated with radical nephroureterectomy for upper tract urothelial carcinoma: An extensive updated systematic review and meta-analysis. Urol Oncol 40(6):243–261
11. Miura Y, Hatakeyama S, Tanaka T et al (2022) Prognostic impact of eligibility for adjuvant immunotherapy in locally advanced urothelial cancer. BJUI Compass 3(2):146–153