資料18

INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2021) 28, 814–819

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Original Article: Clinical Investigation

Discrepancy between clinical and pathological T stages in upper urinary tract urothelial carcinoma: Analysis of the Hospital-Based Cancer Registry data in Japan

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Abbreviations & Acronyms
CCCH = core cancer care hospital
CT = computed tomography
CTU = computed tomography urography
DCCH = designated cancer care hospital
EAU = European Association of Urology
HBCR = Hospital-Based Cancer Registry
MRI = magnetic resonance imaging
NOC = non-organ-confined
OC = organ-confined
TNM = tumor–node–metastasis
TUR = transurethral resection
UC = urothelial carcinoma
UCB = urothelial carcinoma of the bladder
UCP = urothelial carcinoma of the renal pelvis
UCU = urothelial carcinoma of the ureter
UICC = Union for International Cancer Control
UTUC = urothelial carcinoma of the upper urinary tract

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Received 3 October 2020; accepted 4 April 2021.
Online publication 19 May 2021

Objective: To examine the discrepancy between clinical and pathological T stages in patients with urothelial carcinoma of the upper urinary tract treated with radical surgery, and to compare them with the corresponding discrepancy in urothelial carcinoma of the bladder.

Methods: We used the Hospital-Based Cancer Registry data in Japan to extract urothelial carcinoma of the bladder cases (n = 3747) and urothelial carcinoma of the upper urinary tract cases (n = 6831), including urothelial carcinoma of the renal pelvis (n = 3295) and urothelial carcinoma of the ureter (n = 3536) with cT1-4N0M0 diagnosed in 2012–2015, histologically confirmed, and treated with radical surgery without chemotherapy or radiotherapy. We compared the T-stage discrepancy among different tumor locations.

Results: The proportions of overall T-stage discrepancy in the urothelial carcinoma of the renal pelvis (40.8%) and urothelial carcinoma of the ureter (42.9%) groups tended to be higher compared with that in the urothelial carcinoma of the bladder (38.8%) group. The upstaging rate from clinical non-muscle-invasive cancer (≤cT1) to pathological muscle-invasive cancer (≥pT2) was significantly higher in the urothelial carcinoma of the renal pelvis and urothelial carcinoma of the ureter groups compared with the urothelial carcinoma of the bladder group (P = 0.002, P < 0.0001, respectively). Upstaging from clinical organ-confined disease (≤cT2) to pathological non-organ-confined disease (≥pT3) was significantly more frequent in the urothelial carcinoma of the renal pelvis (27.8%, P < 0.0001) and urothelial carcinoma of the ureter (22.3%, P < 0.0001) groups compared with the urothelial carcinoma of the bladder (17.8%) group.

Conclusion: Discrepancy in T staging is significantly higher in patients with urothelial carcinoma of the upper urinary tract compared with those with urothelial carcinoma of the bladder, especially in those with organ-confined disease. As T-stage discrepancy might lead to missed opportunities to carry out perioperative treatment, more accurate diagnostic techniques are required to identify the appropriate urothelial carcinoma candidates for preoperative treatment.

Key words: bladder, Hospital-Based Cancer Registry, stage discrepancy, upper urinary tract, urothelial carcinoma.

Introduction

The accurate clinical staging of patients with UCB or the UTUC is essential for planning the appropriate treatment strategy. The clinical T staging for UCB patients is based on imaging findings obtained by CT and MRI, and a pathological examination of the TUR specimen. There are several reports of the rate of discrepancies between the clinical stage and pathological stages of UCB patients, ranging from 47.8% to 68.3%.[1–3]

High-evidence-level recommendations regarding the diagnosis of UTUC patients are lacking, because UTUC is rare, accounting for just 5–10% of all UC patients.[4,5] In several entities' guidelines about diagnosing UTUC, CTU is the most commonly available imaging modality, but it is difficult to identify the precise clinical T stage before radical surgery with the currently

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available imaging modalities.[4] Although this limitation results in missed opportunities to carry out lymph node dissection and perioperative chemotherapy, there are few reports of the actual frequency of discrepancies between the clinical and pathological T staging of UTUC patients in daily practice.

To determine the discrepancy rate between the clinical and pathological T stages of UTUC patients compared with UCB patients, we used the HBCR data from Japan's nationwide DCCHs and other CCCHs to retrospectively analyze the cases of the patients whose clinical T1-4N0M0 cancer was diagnosed during the 4-year period of 2012–2015, histologically confirmed and treated with radical surgery. To our knowledge, this is the first large-scale study to investigate the T-staging discrepancy for UTUC patients.

Methods

Data sources

The HBCR data including patients' characteristics, stage information and first-course treatments were submitted to the Center for Cancer Control and Information Services at Japan's National Cancer Center.[6] We used the HBCR data from the DCCHs and other CCCHs to identify all of the UCB and UTUC patients diagnosed in 2012–2015. The information of patients who are newly diagnosed with cancer is routinely collected by these hospitals. Well-trained cancer registrars at each hospital register the details of diagnosed cancer cases based on standardized criteria.

In the HBCR data, the first course of treatment is defined as a treatment that is selected to improve the cancer prognosis at an initial diagnosis. As treatment modalities, surgery includes open or laparoscopic surgery. In UCB patients, open or laparoscopic surgery generally included a radical or partial cystectomy. In UTUC patients, open or laparoscopic surgery generally included a radical nephroureterectomy.

Identification of the UCB and UTUC patients

We identified eligible patients from the HBCR data by using the following inclusion criteria: patients who (i) were newly diagnosed with a malignant tumor of the bladder (C67), renal pelvis (C65) or ureter (C66) in 2012–2015; (ii) received the first course of treatment at a DCCH or other CCCH; (iii) had undergone open or laparoscopic surgery; (iv) had UC with International Classification of Disease for Oncology 3rd edition (ICD-O-3) histology code 8120; and (v) were diagnosed with clinical Ta-T4N0M0. The exclusion criteria were patients: (i) with a urachal tumor of the bladder (C67.7); (ii) for which information of the pathological T stage was not available; or (iii) with chemotherapy or radiotherapy. The first exclusion group included patients in which it was difficult to correctly evaluate the pathological diagnosis, because the patients received some treatments before radical surgery. We thus excluded 49 patients from the present analyses.

The staging information was based on the 7th UICC TNM classification. In the UCB patients, when the clinical T stage diagnosed by the clinician was different from the pathological T stage determined by TUR, the higher T stage was used for the final clinical T-stage diagnosis.

Analysis of T-stage discrepancies stratified by the interval between diagnosis and treatment

From the eligible UCB and UTUC patients, we extracted the patients for which the dates of diagnosis and admission for treatment were available. We used the date of admission for treatment as an alternative date for treatment, as the HBCR data did not include the dates of treatment. The cases were divided into a short-interval group and a long-interval group using the cut-off of the median number of days between diagnosis and treatment. We then compared the proportions of up-, same- and downstaging between the two groups in UCB and UTUC patients, respectively.

Statistical analysis

We compared variables between groups using Fisher's exact probability test for categorical variables. All statistical comparisons were two-sided, and $P < 0.05$ was considered significant. JMP version 13.0 (SAS Institute, Cary, NC, USA) was used.

Ethical considerations

The study protocol and data processing were approved by the Tsukuba University Hospital Ethical Board (approval no. H29-267). In rare-disease research, there are some diseases for which the number of cases is <10, and the patients' privacy in such a situation should be considered before a study's publication, as the publication of data could lead to the identification of individual patients. We have therefore reported the numbers of cases <10 in the Tables as [1–3], [4–6] and [7–9] in accord with Japan's Ministry of Health, Labor and Welfare recommendations. As the present study was a retrospective analysis, the requirement for the accordance of studies involving human participants with institutional ethical standards and the Helsinki Declaration or comparable ethical standards was not applicable.

Results

We identified a total of 3747 cases of UCB with cTa-4N0M0 that were histologically confirmed and treated with radical surgery, but without radiotherapy and chemotherapy, from 556 hospitals (369 DCCHs and 187 CCCHs; Fig. 1). The UTUC group was from 620 hospitals (396 DCCHs and 224 CCCHs), and was comprised of 3295 (48.2%) patients with UCP and 3536 (51.8%) patients with UCU (Fig. 2). Table 1 summarizes the characteristics of all patients.

In the UCU group, the proportion of female patients (33.9%) was significantly higher than that in the UCB (22.3%) and UCP (28.9%) groups (both $P < 0.0001$). The patients' median ages were: UCB, 73 years (range 16–99 years); UCP, 75 years (range 28–99 years); and UCU, 75 years (range 39–98 years). The proportions of patients with ≤cT1 disease were significantly greater in the UCP (46.6%) and UCU (52.8%) groups versus the UCB (40.8%) group (both $P < 0.0001$).

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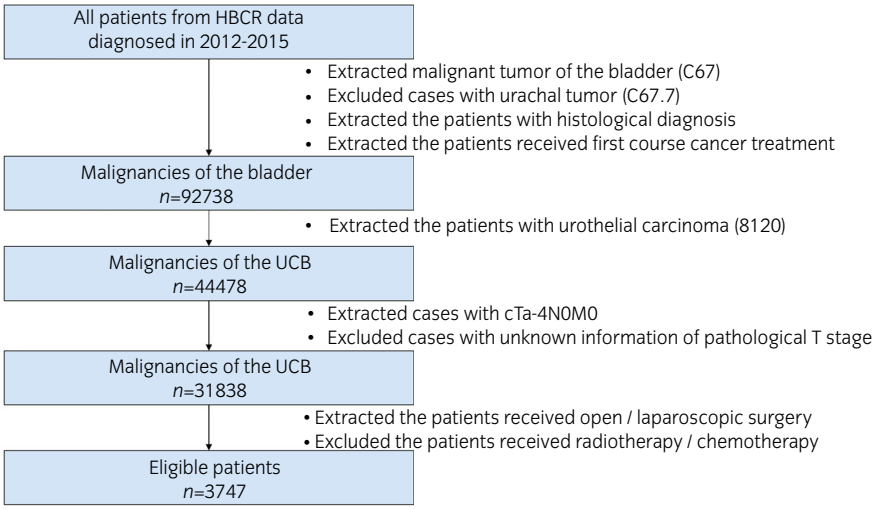

Fig. 1 Patient eligibility for the UCB group.

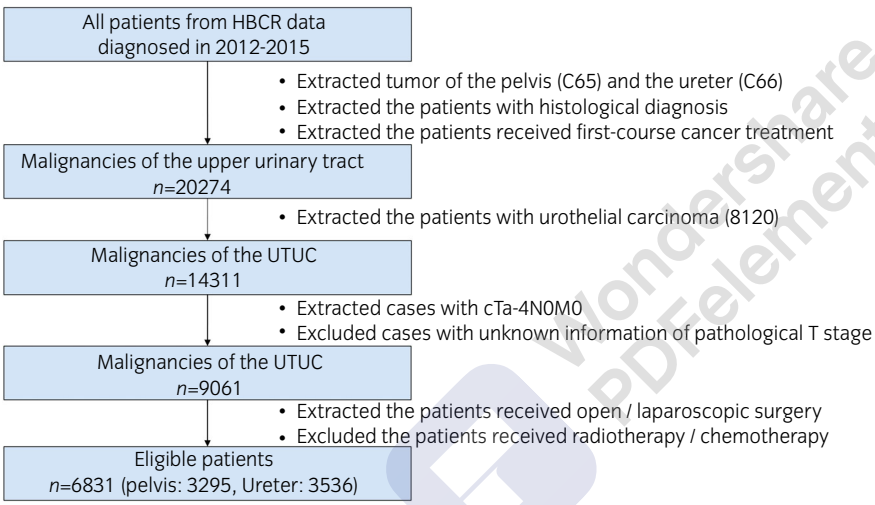

Fig. 2 Patient eligibility for the UTUC group.

Table 1 Patient characteristics

Characteristic	Bladder *n* = 3747	Pelvis *n* = 3295	Ureter *n* = 3536
Sex, *n* (%)			
Male	2912 (77.7)	2342 (71.1)	2337 (66.1)
Female	835 (22.3)	953 (28.9)	1199 (33.9)
Median age, years (range)	73 (16–99)	75 (28–99)	75 (39–98)
Clinical stage, *n* (%)			
cTa/is	396 (10.6)	334 (10.1)	545 (15.4)
cT1	1132 (30.2)	1203 (36.5)	1323 (37.4)
cT2	1411 (37.7)	799 (24.2)	1110 (31.4)
cT3	667 (17.8)	912 (27.7)	531 (15.0)
cT4	141 (3.8)	47 (1.4)	27 (0.8)
Pathological stage, *n* (%)			
pTa/is	303 (8.1)	298 (9.0)	499 (14.1)
pT1	1100 (29.4)	1033 (31.4)	968 (27.4)
pT2	1260 (33.6)	473 (14.4)	935 (26.4)
pT3	858 (22.9)	1375 (41.7)	1105 (31.3)
pT4	226 (6.0)	116 (3.5)	29 (0.8)

The proportion of patients with ≥cT3 disease was significantly higher in the UCP (29.1%) group compared with the UCB (21.6%) and UCU (15.8%) groups (both $P < 0.0001$). In contrast, the proportions of ≤pT1 disease in the UCB, UCP and UCU groups were 37.5%, 40.4% and 41.5%, respectively. In the UCP group, the proportion of ≥pT3 disease (45.2%) was significantly higher than that in the UCB (28.9%) and UCU (32.1%) groups (both $P < 0.0001$).

Figure 3 shows the proportion of overall discrepancy between the clinical T stage and the pathological T stage among the tumor locations. The discrepancy rate tended to be higher in the UTUC group: the rates in the UCB, UCP and UCU groups were 38.8%, 40.8% and 42.9%, respectively. The rates of upstaging in the UCP (29.0%) and UCU (31.5%) groups were significantly higher than that in the UCB (25.4%) group ($P = 0.002$, $P < 0.0001$, respectively).

Table 2 lists the stage discrepancies of the UCB, UCP and UCU groups within clinical strata (full data available in Tables S1–S3). The accuracy rate of UCB patients with ≤cT1 disease was significantly higher than that of the patients with

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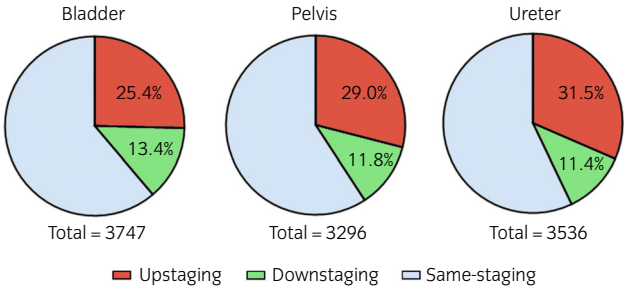

Fig. 3 The proportion of T-stage discrepancies for the overall clinical stages in the patients with UCB, UCP and UCU.

≥cT2 disease (66.1% *vs* 57.8%, $P < 0.0001$). In the UCP group, cT2 disease had the lowest accuracy rate (33.3%) among all stages; cT3 and cT4 diseases had much higher rates (80.2% and 80.9%, respectively). In the UCU group, the stage with the lowest accuracy rate was cT4 (40.7%) followed by cT2 (48.5%) and cT1 (51.5%). The stage with the highest rate was cT3 (83.1%).

To investigate the effect of the staging discrepancy from diagnosis to the start of treatment, we analyzed the proportions of T-stage discrepancy stratified by the number of days between the date of diagnosis and the date of admission for treatment; 3578 of the 3747 UCB patients and 6614 of the 6831 UTUC patients were analyzed. The median days between diagnosis and treatment in the UCB and UTUC patients were 30 days (range 0–426) and 31 days (range 0–425), respectively. The proportion of upstaging for UTUC patients of the long-interval group was significantly higher than that of the short-interval group ($P < 0.0001$; Table S4). There were no differences in the proportion of downstaging for UTUC patients between the short-interval and long-interval groups ($P = 0.97$). In contrast, the proportion of downstaging for UCB patients in the long-interval group was slightly higher than that in the short-interval group ($P = 0.045$).

The proportions of upstaging from clinical non-muscle-invasive cancer (≤cT1) to pathological muscle-invasive cancer (≥pT2) for the UCB, UCP and UCU groups were 25.6%, 30.7% and 34.2%, respectively (Fig. 4a). The upstaging rate was significantly higher in the UCP and UCU groups versus the UCB group ($P = 0.002$, $P < 0.0001$, respectively). Upstaging to pathological NOC disease (≥pT3) was observed

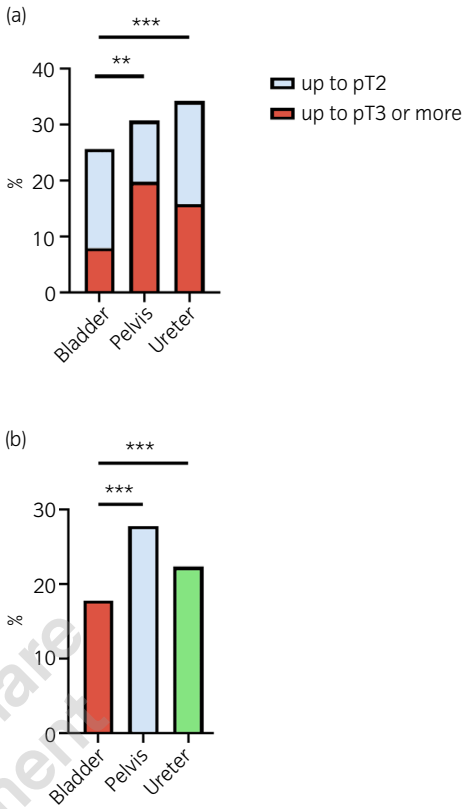

Fig. 4 The proportions of (a) upstaging from clinical non-muscle-invasive cancer (≤cT1) to pathological muscle-invasive cancer (≥pT2), and of (b) upstaging from clinical OC disease (≤cT2) to pathological NOC disease (≥pT3). $^{**}P < 0.01$, $^{***}P < 0.001$ versus the UCB group.

more frequently in UCP (19.8%) and UCU patients (15.7%) compared with UCB patients (7.9%). The proportion of downstaging from ≥cT2 to ≤pT1 was similar among the tumor locations; the proportions in the UCB, UCP and UCU groups were 12.0%, 15.1% and 14.3%, respectively.

The proportion of upstaging from clinical OC disease (≤cT2) to pathological NOC disease for the UCB, UCP and UCU groups was 17.8%, 27.8% and 22.3%, respectively (Fig. 4b). The upstaging rate was significantly higher in the UCP and UCU groups versus the UCB group (both $P < 0.0001$). The proportion of downstaging from clinical NOC disease to pathological OC disease of the UCB (30.6%)

Table 2 Stage discrepancies within clinical strata in the UCB, UCP and UCU patients

	Bladder			Pelvis			Ureter		
Clinical stage	Downstaging	Same-staging	Upstaging	Downstaging	Same-staging	Upstaging	Downstaging	Same-staging	Upstaging
Stage discrepancy within clinical strata, *n* (%)									
cTa/Tis	0 (0)	255 (64.4)	141 (35.6)	0 (0)	194 (58.1)	140 (41.9)	0 (0)	348 (63.9)	197 (36.1)
cT1	27 (2.4)	755 (66.7)	350 (30.9)	73 (6.1)	722 (60.0)	408 (33.9)	103 (7.8)	681 (51.5)	539 (40.7)
cT2	200 (14.2)	808 (57.3)	403 (28.6)	188 (23.5)	266 (33.3)	345 (43.2)	202 (18.2)	538 (48.5)	370 (33.3)
cT3	207 (31.0)	403 (60.4)	57 (8.5)	118 (12.9)	731 (80.2)	63 (6.9)	82	441	7–9†
cT4	69 (48.9)	72 (51.1)	0 (0)	7–9†	38	0	16 (59.3)	11 (40.7)	0 (0)

†The numbers of cases <10 have been reported as follows: [1–3], [4–6] and [7–9], and providing the proportion of those cases was avoided in accord with the recommendations of Japan's Ministry of Health, Labor and Welfare.

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group was significantly higher than those of the UCP (12.3%) and UCU (15.6%) groups (both $P < 0.0001$).

Discussion

The results of the present retrospective analyses of large-scale HBCR data including 10 578 patients with UC of the bladder and upper urinary tract show that the proportion of discrepancies between the clinical T stage and pathological T stage in the UTUC group tended to be higher than that in the UCB group. This difference in the discrepancy rate might be based on differences in the modalities used for the clinical T staging. Regarding the patients with ≤cT1-stage disease, the rate of accurate identification of this stage in the UCB group (66.1%) was higher versus those in the UCP (59.6%) and UCU groups (55.1%), as a TUR was usually carried out for UCB patients to accurately identify the pathological T stage before radical surgery. In contrast, regarding ≥cT2 disease, there was no significant difference in the accuracy rate in the UCB group (57.8%) versus those of the UCP (58.9%) and UCU (59.4%) groups. The reason for the similar accuracy rates is the lack of a diagnostic modality that can correctly predict the pathological T stage.

The discrepancy rate between clinical and pathological stages in bladder cancer has been described; the overall discrepancy rate in our present study (38.8%) tends to be lower than those of the earlier investigations at 47.8–68.3%.[1–3] Gray *et al*. reported 47.8% and 48.1% discrepancy rates for ≥cT2 disease and ≤cT1 disease, respectively,[3] and notably, their discrepancy rate for ≤cT1 was higher than the present study's value (48.1% *vs* 33.9%). After an initial TUR, a repeat TUR is strongly recommended due to the high prevalence of the residual tumors and upstaging to muscle-invasive disease.[7] During our study period (2012–2015), the Japanese Urological Association guidelines recommended a repeat TUR,[8] but other studies were carried out before 2009, when a repeat TUR was not frequently practiced. The present study period might thus be one of the reasons for the difference in the discrepancy of ≤cT1 patients.

However, the present analyses showed relatively high discrepancy rates of cT2 and cT3 disease in UCB patients (42.7% and 39.6%, respectively; Table 2), as was observed in previous studies. Several guidelines showed that imaging modalities cannot accurately diagnose microscopic invasion into peritumoral fat, as increased CT or MRI values also occur with inflammatory changes.[9,10] We thus speculate that the high discrepancy rate of ≥cT2 disease in UCB patients reflects the inaccuracy of diagnostic imaging.

In UTUC, it has been considered difficult to detect the accurate clinical T stage before radical surgery with the currently available imaging modalities.[4] However, several reports showed that the accuracy rate for T staging exceeded 85% between OC and NOC disease when standard criteria, such as an increased CT value of peritumoral fat for NOC disease, was used.[11,12] The present analyses obtained a similar finding; that is, that there was high agreement between the clinical and pathological T stages in cT3 disease; the accuracy rates in our UCP and UCU patients were 80.2% and 83.1%, respectively (Table 2).

In contrast, no effective T-staging criteria for the differentiation of OC disease in UTUC patients have been reported. The current EAU guidelines note that it is difficult to distinguish ≤pT2 disease by the available preoperative imaging modalities.[5,13,14] The present findings showed that upstaging to ≥pT2 from ≤cT1 occurred frequently; the proportion of upstaging in the UCP and UCU patients was 30.7% and 34.2%, respectively (Fig. 4a). Like the EAU guidelines, the present findings also showed the difficulty of making an accurate preoperative diagnosis in UTUC patients with ≤cT2 disease in a large-scale cohort. However, the EAU guidelines suggested kidney-sparing surgery as an alternative treatment option for limited low-risk UTUC patients; that is, those with no invasive aspect on CTU (≤cT1 disease), unifocal disease, tumor size <2 cm, low-grade cytology and low-grade ureteroscopy biopsy.[5] Clinicians should pay attention to the high proportion of upstaging from ≤cT1 to ≥pT2 when considering kidney-sparing surgery as a primary treatment option.

Regarding the effects of the staging discrepancy from diagnosis to the start of treatment, the proportion of upstaging in our UTUC patients was significantly higher in the long-interval group versus the short-interval group (Table S4). Waldert *et al*. reported that a longer interval between diagnosis and radical nephroureterectomy for UTUC patients was associated with features of aggressive UTUC, such as more advanced tumor stage and higher tumor grade.[15] The present findings also show that a delay in the interval from diagnosis to treatment in UTUC patients might affect tumor progression during the period until surgery. In terms of the slightly higher proportion of downstaging in the long-interval UCB patients, it is possible that those patients underwent radical surgery after undergoing a repeat TUR. However, the definitive reason has been unclear as a result of a lack of detailed information on the treatment history before radical surgery in the HBCR data.

The accuracy rate of UCP (80.9%) and UCU (83.1%) patients with cT3 disease was high (Table 2). As the 5-year cancer-specific survival rate for advanced UTUC patients is poor (<50% for pT2–3 patients, <10% for pT4 patients), neoadjuvant or adjuvant chemotherapy is considered for patients with NOC disease.[5,16–19] Neoadjuvant chemotherapy is beneficial to patients receiving cisplatin-based chemotherapy, as it avoids loss of renal function after a nephroureterectomy. However, patients with over-diagnoses (i.e. patients whose cases were downstaged based on pathology) might be given unnecessary chemotherapy. In the present cohort, as the UTUC patients with ≥cT3 disease had a highly accurate staging rate, they might have benefited from neoadjuvant chemotherapy.

In contrast, the proportions of upstaging from ≤cT2 to ≥pT3 for the UCP and UCU patients were high (27.8% and 22.3%, respectively; Fig. 4b). To correctly identify eligible patients for preoperative chemotherapy, effective tools for predicting NOC disease are required. Multiparametric MRI has been reported to be a useful modality to distinguish between OC and NOC disease in UCP patients,[20] and several reports indicated that a preoperative multivariable model improved the accuracy of identifying OC disease in UTUC patients.[21–23] These studies are expected to improve not only

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the accuracy of clinical staging, but also the oncological outcomes of UTUC patients with NOC disease.

The present study had several limitations due to the availability of retrospective data in the HBCR. There was no detailed information about the modalities, including CTU, MRI and ureteroscopy, that were generally used to determine the clinical T stages. The present analysis was limited to patients with cTa-4N0M0 urothelial carcinoma who underwent radical surgery without radiotherapy and chemotherapy. Although downstaging might occur in UCB patients with ≤cT1 disease by a repeat TUR or BCG therapy before radical cystectomy, there was no detailed information about prior treatments before cystectomy. Regarding an analysis of T-stage discrepancies stratified by the number of days between diagnosis and treatment dates, there might be some differences between the date of admission and the date of treatment. Our analyses included only data from the DCCHs and other CCCHs, which play a central role in cancer care in their regional communities. Despite these limitations, this was an investigation of a large cohort, designed to elucidate the discrepancies between the clinical stages and pathological stages of UC patients.

In conclusion, our analyses of large-scale HBCR data showed that the T-stage discrepancy among UTUC patients was observed more frequently in those with OC disease versus those with NOC disease. As T-stage discrepancies lead to missed opportunities to carry out perioperative treatments, more-accurate diagnostic techniques are required for the identification of the appropriate UTUC candidates for preoperative treatment.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. The correlation between clinical stage and pathological stage in the UCB patients.

Table S2. The correlation between clinical stage and pathological stage in the UCP patients.

Table S3. The correlation between clinical stage and pathological stage in the UCU patients.

Table S4. The T-stage discrepancy rate stratified by the number of days between the diagnosis and treatment dates.

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