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ORIGINAL ARTICLE

Prognostic value of PD-L1 combined positive score in patients with upper tract urothelial carcinoma

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Abstract

Purpose Upper tract urothelial carcinoma (UTUC) is relatively rare in Western countries. The impact of programmed death-ligand 1 (PD-L1) expression on UTUC remains unclear because previous studies have focused on bladder UC. We investigated the association of PD-L1 expression with clinicopathological features and prognosis in patients with UTUC.

Methods We retrospectively reviewed the patients with UTUC that we treated at our institute from 2013 to 2018. In total, 105 patients with UTUC undergoing radical nephroureterectomy were analyzed to evaluate the PD-L1 expression on representative whole-tissue sections using the Combined Positive Score (CPS; Dako 22C3 pharmDx assay). A PD-L1 CPS ≥ 10 was considered positive.

Results Among the 105 UTUC cases, 17.1% exhibited positive PD-L1 expression. A CPS ≥ 10 was significantly associated with higher tumor stage (≥ T2, $p = 0.034$) and lymph node invasion at diagnosis ($p = 0.021$). A multivariable analysis indicated that a CPS ≥ 10 was an independent prognostic predictor of shorter cancer-specific survival (hazard ratio [HR] = 4.59, 95% confidence interval [CI] = 1.66 − 12.7, $p = 0.003$) and overall survival (HR = 2.51, 95% CI = 1.19 − 5.27, $p = 0.015$).

Conclusions A PD-L1 CPS ≥ 10 in UTUC was associated with adverse pathological features and independently predicted worse cancer-specific and overall survival.

Keywords Combined positive score · Immune checkpoint inhibitor · Programmed death-ligand 1 · Survival · Upper tract urothelial carcinoma

Introduction

Upper tract (renal pelvis and ureter) urothelial carcinoma (UTUC) is uncommon in Western countries and constitutes 5% to10% of all UCs [1]. However, the incidence of UTUC is relatively high in Taiwan, and several studies have

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reported that some risk factors such as ingestion of aristolochic acid-containing Chinese herbs or arsenic-contaminated artesian-well water may be responsible for the high incidence [2, 3]. Kang et al. [4] reported that the recurrence rates after primary UTUC in the bladder and contralateral upper tract were 31.2% and 5.8%, respectively.

Programmed death-ligand 1 (PD-L1), a cell surface glycoprotein, serves as a negative checkpoint in immunity and interacts with its receptor, programmed death-1 (PD-1), to protect normal cells from excessive immune responses and tissue damage [5]. PD-L1 has been reported in UCs and its expression in tumor cells is associated with advanced tumor stage and poor prognosis [6, 7].

The impact of PD-L1 expression on UTUC remains unclear because previous studies have mainly concentrated on bladder UC. Two meta-analysis studies have demonstrated that PD-L1 positivity in UC was correlated with more advanced tumor stage and poorer outcomes, especially in bladder UC [8, 9]. However, some differences have been observed in etiology, gene expression and response to chemotherapy between UTUC and bladder UC [10]. No evidence has indicated that these findings in bladder UC can be applied to UTUC. In the present study, we investigated the association of PD-L1 expression with the clinicopathological features and clinical prognosis of patients with UTUC to further understand the significance of PD-L1 in the era of immunotherapy.

Patients and methods

Study population

From 2013 to 2018, 640 patients were diagnosed with UTUC at our institute. To minimize the specimen heterogeneity, only patients undergoing radical nephroureterectomy (RNU) were retrospectively reviewed. Exclusion criteria included patients with neoadjuvant systemic treatment or distant metastasis at the time of diagnosis, muscle-invasive bladder UC before or after RNU, or lack of PD-L1 staining. Finally, a total of 105 patients met the criteria and were included in this study. The specimens were retrieved from the surgical pathology database of Kaohsiung Chang Gung Memorial Hospital (KCGMH). Lymph node staging was determined by radiologists based on imaging or by the treating physicians who decided the final lymph node status. The pathologic tumor stage was determined according to the 2017 American Joint Committee on Cancer TNM staging for renal pelvis and ureter cancer. Locoregional recurrence was defined by recurrent lesion at previous operation site or retroperitoneal lymph node enlargement observed on computed tomography scans during the follow-up period. Distant metastasis was defined as any suspicious lesion evidenced by radiological images and clinical symptoms based on chart review. Additionally, recurrent bladder cancer was determined according to postoperative cystoscopic follow-up and pathological confirmation. Furthermore, previous bladder cancer history and the cause of death during the follow-up period were determined by the treating physicians, chart review, or death certificates. This study was approved by the institutional review board of KCGMH (No. 2002050051).

Immunochemistry

The surgical tissue samples were fixed in formalin. Serial slides, with a thickness of 4 μm, were sectioned from the blocks of tumor specimens for immunohistochemical analysis. Dako mouse monoclonal anti – PD-L1 antibody (clone: 22C3), purchased from Agilent Technologies Inc. (Santa Clara, CA, USA), was used for the immunohistochemical analysis with EnVision FLEX Visualization System for Dako Autostainer Link 48 according to the manufacturer's instructions.

Immunohistochemical analysis

The results of the immunohistochemical analysis were interpreted by a genitourinary pathologist (MTS) based on the manufacturer's algorithm. Any convincing partial or complete linear membrane staining of viable tumor cells and any convincing membrane and/or cytoplasmic staining of lymphocytes and macrophages within tumor nests and/or immediately adjacent supporting stroma were considered PD-L1 staining and were included in scoring. PD-L1 protein expression in UC was determined using the Combined Positive Score (CPS), which corresponds to the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. To assess the best discriminative cutoff value of PD-L1 CPS for UTUC cancer-specific and overall survival, an SAS macro (%FINDCUT) was used to dichotomize patients [11]. Our data revealed that the PD-L1 CPS cutoff of 10 was the best discriminator for UTUC cancer-specific and overall survival (data not shown). Therefore, PD-L1 was considered to have no expression when the specimen had a CPS of less than 10. Specimens with a CPS equal to or over 10 were regarded as containing PD-L1 expression [12]. Figure 1 illustrates the negative expression and positive expression of PD-L1 as evidenced through immunohistochemical staining.

Statistical analysis

The relationships between PD-L1 expression, clinical characteristics and pathological features were examined with Fisher's exact test. The Kaplan – Meier method was applied

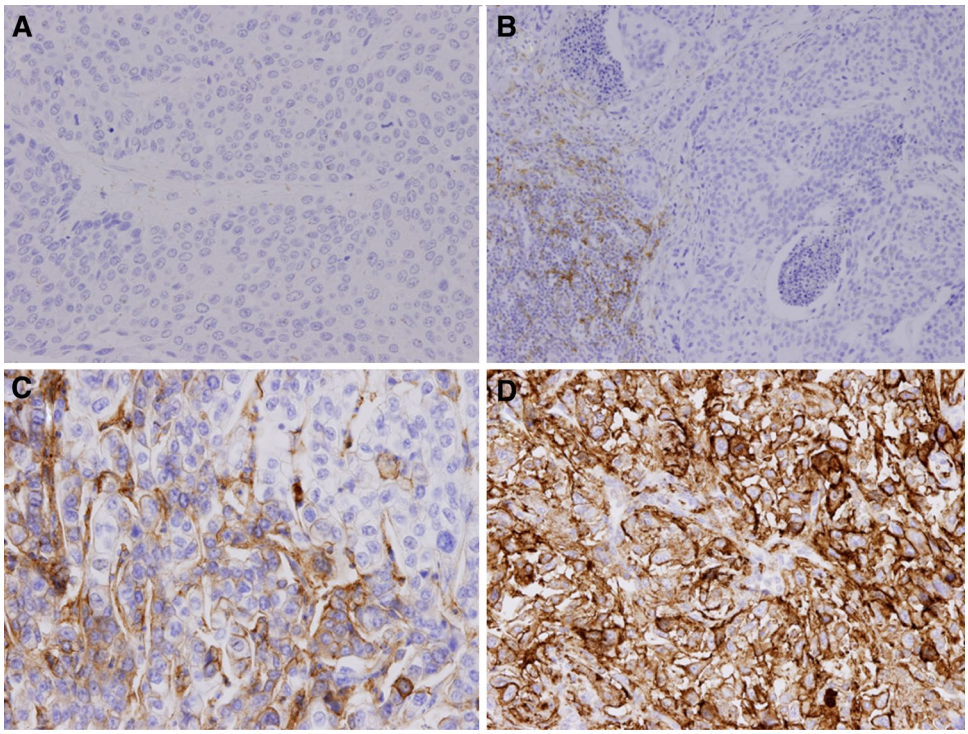

Fig. 1 Immunohistochemical stain for PD-L1 expression in UTUC samples by clone 22C3. The CPS was used to evaluate PD-L1 expression. **a** and **b** represent PD-L1 negative expression, whereas **c** and **d** represent PD-L1 positive expression. **a** CPS = 0; **b** CPS < 10; **c** CPS = 60; **d** CPS = 100

to evaluate the survival, and differences were tested using the log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to assess prognostic indicators, including age, PD-L1 expression, TNM classification, and other clinicopathological characteristics. Variables significant on univariable analysis were included to perform multivariable analysis by forward stepwise selection. The level of significance was set at $p < 0.05$. All statistical computations were performed using SPSS version 20.

Results

Patient characteristics

Patient demographic characteristics are listed in Table 1. This study included 105 patients with a consistent distribution of gender. Among the 105 patients, 63 (60%) were older than 65 years, and the median age was 68 years. Fifteen (14.3%) patients had enlarged retroperitoneal lymph node before RNU and none of them received neoadjuvant chemotherapy or immunotherapy.

Association of PD-L1 expression with clinicopathological characteristics

Among the 105 patients, 18 (17.1%) had a PD-L1 CPS ≥ 10 (Table 1). The follow-up duration was significantly shorter in patients with a PD-L1 CPS ≥ 10 (14.1 ± 12.3 months vs. 27.3 ± 16.5 months, $p = 0.002$, Table 1). Patients with PD-L1 CPS ≥ 10 were significantly associated with higher T stage (≥ T2, $p = 0.034$), lymph node invasion at diagnosis ($p = 0.021$), and less bladder recurrence ($p = 0.006$) (Table 1).

Association of PD-L1 expression with cancer-specific survival and overall survival

Among the 105 patients, the median follow-up time after initial treatment was 23.5 months (range, 1 – 67.6 months). During this period, 55 patients died, and 26 patients died of UTUC-related causes. A Kaplan–Meier analysis revealed that a PD-L1 CPS ≥ 10 was significantly associated with shorter cancer-specific survival (CSS) ($p < 0.001$) and overall survival (OS) ($p = 0.036$) (Fig. 2). Due to the few events, the number of variables that could be included on multivariable analysis was limited to established predictors of oncologic outcomes (such as T and N stages) to find the predictors and improve the statistical accuracy. On the multivariable analysis by forward stepwise selection for OS, PD-L1 CPS ≥ 10 was an independent predictor of shorter OS (hazard ratio [HR] = 2.51, 95% confidence interval [CI] = 1.19 – 5.27, $p = 0.015$) in addition to age > 65 years and higher T stage (Table 2). To evaluate the factors predicting CSS, the multivariable analysis also indicated that PD-L1 CPS ≥ 10 (HR = 4.59, 95% CI = 1.66 – 12.7, $p = 0.003$), higher T stage, and lymph node invasion at diagnosis were independent predictors of shorter CSS (Table 2).

Table 1 Association of PD-L1 expression with clinicopathological characteristics in 105 patients with UTUC

	PD-L1 CPS ≥ 10 N (%)	PD-L1 CPS < 10 N (%)	p value
Patient number	18 (17.1)	87 (82.9)	
Follow duration	14.1 ± 12.3 (mo)	27.3 ± 16.5 (mo)	0.002*
Age			
> 65 yr	9 (50)	54 (62.1)	0.43
≤ 65 yr	9 (50)	33 (37.9)	
Gender			
Male	11 (61.1)	41 (47.1)	0.311
Female	7 (38.9)	46 (52.9)	
Pathologic stage			
pTa/is	0 (0)	26 (29.9)	0.02*
pT1	3 (16.7)	13 (14.9)	
pT2	5 (27.8)	16 (18.4)	
pT3	8 (44.4)	26 (29.9)	
pT4	2 (11.1)	6 (6.9)	
Muscle-invasive tumor			
< T2	3 (16.7)	39 (44.8)	0.034*
≥ T2	15 (83.3)	48 (55.2)	
Lymph node status			
N0/Nx	12 (66.7)	78 (89.7)	0.021*
N1/N2	6 (33.3)	9 (10.3)	
Papillary feature			
Absent	8 (44.4)	23 (26.4)	0.158
Present	10 (55.6)	64 (73.6)	
Tumor grade			
Low	0 (0)	11 (12.6)	0.205
High	18 (100)	76 (87.4)	
Lymphovascular invasion			
Absent	10 (55.6)	61 (70.1)	0.272
Present	8 (44.4)	26 (29.9)	
Concomitant CIS			
Absent	7 (38.9)	35 (40.2)	1.000
Present	11 (61.1)	52 (59.8)	
Squamous differentiation			
Absent	11 (61.1)	67 (77)	0.234
Present	7 (38.9)	20 (23)	
Margin positive			
Negative	16 (88.9)	77 (88.5)	1.000
Positive	2 (11.1)	10 (11.5)	
Tumor necrosis			
Absent	7 (38.9)	54 (62.1)	0.114
Present	11 (61.1)	33 (37.9)	
Multifocal tumor			
Solitary	13 (72.2)	60 (69)	1.000
Multifocal	5 (27.8)	27 (31)	
Bladder recurrence			
Yes	0 (0)	25 (28.7)	0.006*
No	18 (100)	62 (71.3)	
Locoregional recurrence			
Yes	7 (38.9)	18 (20.7)	0.128
No	11 (61.1)	69 (79.3)	

Table 1 (continued)

	PD-L1 CPS ≥ 10 N (%)	PD-L1 CPS < 10 N (%)	p value
Distant metastasis			
Yes	5 (27.8)	17 (19.5)	0.525
No	13 (72.2)	70 (80.5)	
Adjuvant chemotherapy			
Yes	1 (5.6)	7 (8)	1.000
No	17 (94.4)	80 (92)	
Palliative chemotherapy			
Yes	2 (11.1)	7 (8)	0.65
No	16 (88.9)	80 (92)	
Palliative immunotherapy			
Yes	5 (27.8)	3 (3.4)	0.004*
No	13 (72.2)	84 (96.6)	
Overall death	10 (55.6)	45 (51.7)	
Death due to UTUC	8 (44.4)	18 (20.7)	

CIS carcinoma in situ

*indicates $p < 0.05$

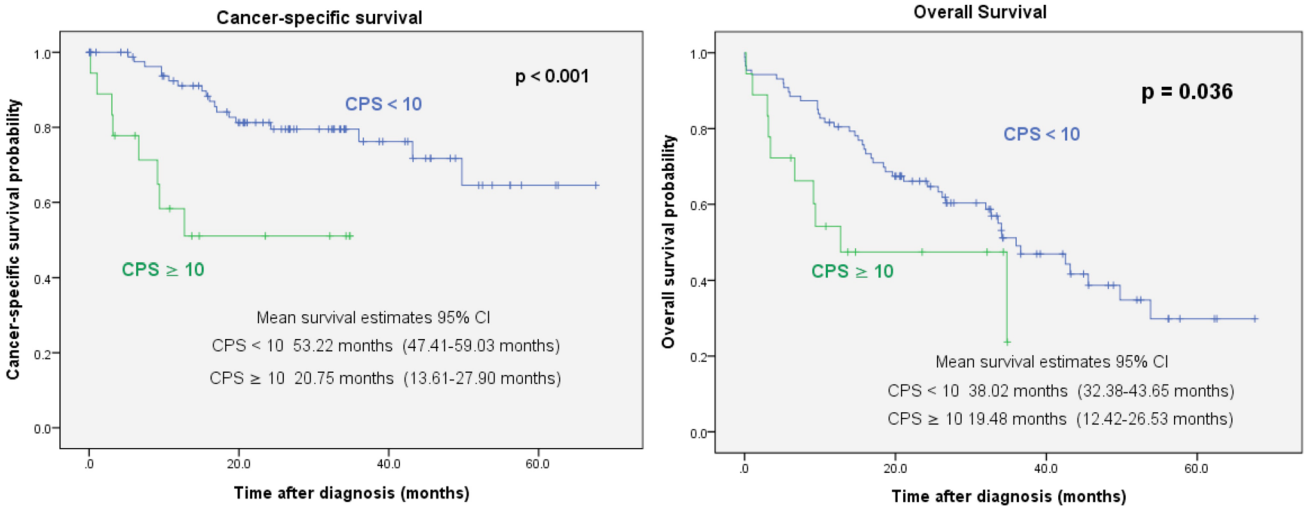

Fig. 2 Association of PD-L1 expression with cancer-specific survival and overall survival in 105 patients with UTUC

Subset analysis with groups of similar follow-up time

Further subset analysis was done in a subgroup of 74 patients (70.5% of the total cohort, 16 patients in PD-L1 CPS ≥ 10 group and 58 patients in PD-L1 CPS < 10 group) with similar follow-up time. Using NCSS 10 Statistical Software (LLC, Kaysville, Utah, USA), the greedy method was used for matching unequal size in the two groups. The results of subset analysis are shown in supplementary Tables 1 and 2. In subset analysis, patients with PD-L1 CPS ≥ 10 have higher percentages of higher T stage and lymph node invasion at diagnosis (but there was no statistically significant difference, supplementary Table 1). PD-L1 CPS ≥ 10 was not an independent predictor of shorter CSS and OS (supplementary Table 2).

Discussion

Immune checkpoint inhibitors, particularly against the PD-L1/PD-1 pathway, have demonstrated promising anti-tumor ability and improved outcomes in UC [13–16]. These results highlight the association between PD-L1 expression and clinicopathological characteristics as well as oncological outcomes. To date, most published studies have focused on bladder UC [7, 17–21], whereas only few studies addressing UTUC have been published [22–26], as summarized in Table 3. To our knowledge, this is the first

Table 2 Univariable and multivariable analyses by forward stepwise selection of clinicopathological features for the prediction of CSS and OS in patients with UTUC

	Cancer-specific survival				Overall survival			
	Univariable		Multivariable*		Univariable		Multivariable*	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (year)								
> 65 vs. ≤ 65	2.45 (1.02 – 5.87)	0.044			3.97 (2.04 – 7.73)	< 0.001	4.10 (2.06 – 8.17)	< 0.001
PD-L1 expression								
CPS ≥ 10 vs. < 10	4.33 (1.82 – 10.33)	0.001	4.59 (1.66 – 12.7)	0.003	2.09 (1.04 – 4.23)	0.04	2.51 (1.19 – 5.27)	0.015
T stage		< 0.001		0.001		0.001		0.004
Ta/is	Referent		Referent		Referent		Referent	
T1	1.87 (0.26 – 13.39)	0.531	1.08 (0.15 – 7.98)	0.943	2.02 (0.73 – 5.60)	0.175	1.55 (0.56 – 4.33)	0.399
T2	3.52 (0.64 – 19.49)	0.15	2.45 (0.42 – 14.3)	0.318	2.95 (1.15 – 7.53)	0.024	2.37 (0.92 – 6.10)	0.073
T3	7.29 (1.58 – 33.71)	0.011	4.30 (0.85 – 21.7)	0.077	4.03 (1.69 – 9.64)	0.002	2.40 (0.97 – 5.93)	0.058
T4	30.42 (5.91 – 156.5)	< 0.001	20.6 (3.49 – 121.4)	0.001	8.64 (2.93 – 25.5)	< 0.001	7.98 (2.66 – 23.9)	< 0.001
Lymph node status								
N1/N2 vs. N0/Nx	6.43 (2.87 – 14.4)	< 0.001	3.00 (1.18 – 7.67)	0.022	2.62 (1.34 – 5.14)	0.005		
Adjuvant chemotherapy								
Yes vs. No	3.22 (1.19 – 8.70)	0.021			1.97 (0.83 – 4.67)	0.126		
Palliative chemotherapy								
Yes vs. No	3.10 (1.24 – 7.72)	0.015			1.29 (0.55 – 3.02)	0.553		
Palliative immunotherapy								
Yes vs. No	2.27 (0.67 – 7.67)	0.186			1.05 (0.33 – 3.39)	0.935		

*Variables significant on univariable analysis were included to perform multivariable analysis by forward stepwise selection

Table 3 Review of the current literature on PD-L1 expression and associated outcomes in patients with UTUC

First author and year	Patient number	Clone	Cutoff for PD-L1 (+)	Tissue analysis	Impact on pathological feature	Impact on prognosis
Skala, 2017 [23]	149	5H1	≥ 5% of TCs	Whole-tissue sections	Higher grade, T stage and LVI	Worse CSS at TPS ≥ 50%
Krabbe, 2017 [22]	423	E1L3N	≥ 1% of TCs	TMA	Lower T stage	Better RFS and OS in OCD
Zhang, 2017 [24]	162	E1L3N	≥ 5% of TCs	Whole-tissue sections	N.S	PD-L1 (+) on tumor cells = > shorter CSS
Miyama, 2018 [25]	271	SP263	≥ 5% of TCs	TMA	Higher T stage and LVI	Shorter MFS and OS at high platelet count
Arriola, 2019 [26]	72	E1J2J	≥ 1% of TCs	Whole-tissue sections	Higher T stage, squamous differentiation	N.S
Present study	105	22C3	CPS ≥ 10	Whole-tissue sections	Higher T stage, LN invasion at diagnosis	Shorter CSS and OS

TCs tumor cells; *CPS* combined positive score; *TMA* tissue microarray; *LVI* lymphovascular invasion; *N.S* not significant; *CSS* cancer-specific survival; *RFS* recurrence-free survival; *OS* overall survival; *MFS* metastasis-free survival; *OCD* organ confined disease; *LN* lymph node

study to evaluate the association of PD-L1 expression with clinicopathological features and prognosis using a PD-L1 CPS of 10 or more as a biomarker in patients with UTUC. Our study indicated that a PD-L1 CPS ≥ 10 was associated with higher tumor stage (≥ T2), lymph node invasion and less bladder recurrence (0 vs. 28.7%). The latter case was likely due to greater hazard risk of CSS and OS in patients with PD-L1 CPS ≥ 10. This study demonstrated the impact of PD-L1 expression on adverse pathological features and poor prognosis.

Conflicting evidence exists regarding the role of PD-L1 expression in the pathological features and prognosis of UTUC. Skala et al. [23] examined the whole-tumor sections of 149 patients with UTUC by defining PD-L1 positivity (clone 5H1) with a cutoff value of 5%. In their study, 23.5% of primary UTUC cases tested positive for PD-L1. PD-L1

expression was correlated with higher tumor grade, T stage, and lymphovascular invasion. CSS was significantly associated only with PD-L1 expression based on a cutoff value of 50%. Zhang et al. [24] used different PD-L1 clones with the same positivity cutoff value of 5% to examine the whole-tissue sections of 162 UTUC cases. They discovered no significant association between PD-L1 expression and tumor stage or adverse pathological features. However, PD-L1 positivity in tumor cells was an independent predictor of shorter CSS, and PD-L1 positivity in tumor-infiltrating mononuclear cells was associated with longer CSS. Taken together, the results from these studies indicate that PD-L1 expression has the potential to predict adverse clinicopathological features and poor prognosis, which is in accordance with our findings.

However, Krabbe et al. [22] reported an opposite result for PD-L1 expression using tissue microarrays (TMAs) in 423 UTUC cases. In their cohort, 26.2% of patients exhibited PD-L1 positivity in tumor cells based on a cutoff value of 1%, and PD-L1 positivity predicted favorable prognosis among patients with organ-confined tumor. Various elements can explain these contradictory results, such as differences in the ethnicity of the study cohort, PD-L1 antibody clones used, cutoff value selected to indicate positivity, or staining protocols adopted. In addition, the tumor tissues were analyzed using TMAs in their study, which might have resulted in underestimated heterogeneity and limited accuracy of PD-L1 positivity in tissues [27]. By contrast, in the present study, we used whole-tissue sections to minimize the heterogeneity.

The definition of PD-L1 positivity in the present study is determined using the CPS (in tumor cells and immune cells). However, in aforementioned studies [22–26], they defined PD-L1 positivity as expression in tumor cells only (Table 3). Heterogeneity varies among several PD-L1 staining methods because testing for PD-L1 has not been standardized yet. Over the past years, increasing attention has been paid on the significance of PD-L1 expression in tumor-infiltrating immune cells. Bellmunt et al. [19] reported that PD-L1 positivity in tumor-infiltrating immune cells was associated with longer OS in patients with metastatic bladder UC. By comparing four PD-L1 immunohistochemistry assays (22C3, 28–8, SP142, and SP263), Hirsch et al. [28] discovered that a higher variability of results in tumor-infiltrating immune cell staining than in tumor cell staining because of the lack of training in immune cell scoring. Based on a clinical trial [16], incorporating tumor-associated inflammatory cells into the PD-L1 positivity was more helpful when selecting responders than using tumor cells alone. This finding was also observed in a meta-analysis study [9], which indicated that PD-L1 expression obtained using the CPS offered a clearer dichotomy between responders and non-responders receiving immune checkpoint inhibitors. In addition, the CPS can be determined easily without the need to calculate tumor and immune cells separately. Therefore, the CPS scoring system could be a good way to predict tumor prognosis and identify which patients will benefit the most from PD-1/PD-L1 – targeted therapies.

In our study, PD-L1 CPS positivity was associated with higher tumor stage and worse prognosis. Binding of PD-L1 to PD-1 may deliver an inhibitory signal to suppress the activation of cytotoxic T cells, which helps tumor cells evade the host immune attack [29]. In addition to PD-1, PD-L1 also interacts with B7.1 to block its ability to activate T cells. The PD-L1 expression in tumors has been linked to tumor progression and unfavorable prognosis [29]. This may explain why PD-L1 expression (CPS ≥ 10) was absent in lower T stage (pTa/is) in our study. In bladder UC, previous studies have demonstrated that patients with higher primary T stage had higher percentages of PD-L1 expression [7, 17]. With respect to UTUC, higher percentages of PD-L1 expression were also observed in patients with higher T stage [23, 25]. Therefore, there seems to be an association between higher tumor stage and higher PD-L1 expression in UC. This finding raised the question of whether neoadjuvant or adjuvant systemic therapy can achieve pathologic downstaging or survival benefit in patients with UTUC and a CPS ≥ 10. The impact of neoadjuvant chemotherapy on high-risk or locally advanced UTUC remains controversial. Two meta-analysis studies [30, 31] suggested that neoadjuvant chemotherapy group had higher downstaging rate, better overall survival, recurrence-free survival and cancer-specific survival when compared to controls. Recently, a multi-institutional retrospective study [32] showed the complete response rate of 10.1% and pathologic downstaging rate of 44.9% in 267 UTUC patients receiving neoadjuvant chemotherapy. In addition, pathologic downstaging is a strong predictor of survival outcomes [32]. However, these studies were all retrospective, and there was a possibility of patient selection bias. Further prospective randomized studies are needed to provide better evidence. Interestingly, the PURE-01 study [33] reported a promising complete response rate of 54.3% in cases with muscle-invasive bladder UC and a CPS ≥ 10, receiving neoadjuvant pembrolizumab treatment. Whether the results observed from bladder UC could be applicable to UTUC remains unclear. Further prospective and randomized trials are warranted to investigate the efficacy of neoadjuvant PD-1/PD-L1 inhibitors or chemotherapy in patients with UTUC and a CPS ≥ 10.

In our study, the regimens for adjuvant and first-line palliative chemotherapy were gemcitabine and cisplatin in most patients. For patients with impaired renal function, dose-reduction or split-dose administration of cisplatin was used. One patient received gemcitabine alone for adjuvant chemotherapy due to old age and comorbidities. One patient received gemcitabine alone for first-line palliative chemotherapy due to chronic kidney disease stage 5. For

palliative immunotherapy, pembrolizumab was used in most patients; other regimens were nivolumab and atezolizumab. Based on 2020 National Comprehensive Cancer Network (NCCN) guidelines, adjuvant chemotherapy is considered for patients with UTUC ≥ pT2 and/or pN + . In this retrospective study, however, adjuvant chemotherapy is not routinely given for patients with UTUC ≥ pT2 and/or pN + due to impaired renal function or other comorbidities. Higher percentage of patients receiving adjuvant chemotherapy in the PD-L1 CPS < 10 group may have potential impact on survival data. Therefore, we incorporated adjuvant chemotherapy into univariable and multivariable analyses, and the result still indicated that PD-L1 CPS ≥ 10 is a statistically significant predictor of worse survival. Further prospective and large series of study will be needed to draw the solid conclusion.

In our study, the difference in follow-up duration of the two groups is partly due to the nature of retrospective study and partly due to higher percentage of cancer death in patients with CPS ≥ 10. In subset analysis, the results are different from those in total cohort. After subset selection with similar follow-up time, the further smaller sample size naturally limits the power of analysis and might have other selection bias, resulting in the missing significance of predicting CSS and OS.

The strengths of this study include the comprehensive evaluation of PD-L1 expression using whole-tissue sections and a validated anti − PD-L1 antibody in both tumor and immune cells. Whole-tissue sections minimize the heterogeneity further than TMAs do. Our study has some limitations. First, this was a retrospective study with a short median follow-up duration of 23.5 months. Not all specimens were included during the study period. Second, lymph node dissection (LND) is not routinely performed during RNU because the survival benefit related to the procedure remains unclear. In our institute, LND is only performed in patients with suspicion of nodal invasion evident in imaging. Most patients' unknown nodal status was determined on the basis of imaging, which might have resulted in some nodal metastasis being occulted. Third, this study lacks a central pathological review. However, immunohistochemistry interpretation was performed by an experienced genitourinary pathologist blinded to clinical outcomes. Moreover, additional studies are necessary to evaluate whether PD-L1 positivity can be used in conjunction with mutational load, gene expression subtypes, or other biomarkers as effective predictors or prognosticators in the era of personalized medicine [13, 33]. In addition, due to our sample size and few events, we could not perform analysis incorporating all known independent predictors of survival to see how PD-L1 CPS ≥ 10 would improve prognostic ability. We limited the number of variables incorporated into univariable and multivariable analyses due to the limited number of events. However, we used the prognostic variables with the most impact (such as T and N stages).

Conclusions

Our data indicate that PD-L1 CPS positivity with a cutoff value of 10 occurred in 17.1% of UTUC cases. A PD-L1 CPS ≥ 10 was significantly associated with adverse pathological features, including higher tumor stage and lymph node invasion at diagnosis. More importantly, a PD-L1 CPS ≥ 10 was an independent prognosticator of shorter CSS and OS in patients with UTUC.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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