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ORIGINAL ARTICLE

The clinicopathological characteristics and prognostic value of squamous differentiation in patients with bladder urothelial carcinoma: a meta-analysis

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Abstract

Purpose Urothelial carcinoma with squamous differentiation (UCSD) is the most common histologic variant in bladder cancer (BCa). Previously, some studies have linked the presence of UCSD with the risk of worse survival outcomes in BCa patients. However, such association is still controversial. In this study, we performed a meta-analysis to clarify the clinicopathological characteristics and to further investigate the prognostic value of UCSD in BCa.

Methods A systematic literature search was performed in electronic databases including PubMed, Embase, Chinese National Knowledge Infrastructure and Wanfang Data until October 2018. Subgroup analyses were performed according to different treatments and study outcomes.

Results Total of 13,284 patients were enrolled in 19 studies which were included in this meta-analysis. The percentage of female patients with UCSD was significantly higher than those with pure urothelial carcinoma. UCSD was correlated with tumor stage T3/T4, tumor grade 3, positive surgical margin, and lymph node involvement. Moreover, the recurrence rate was higher in patients with UCSD after surgery. UCSD was associated with poorer disease-free survival (DFS). No significant difference of cancer-specific survival (CSS) or overall survival (OS) was found on multivariable analysis between the two groups.

Conclusions Our study demonstrated that UCSD in BCa was associated not only with unfavorable clinicopathological features, but also with high risk of recurrence and poorer prognosis for DFS. However, UCSD is not independently significant for CSS and OS. Well-designed randomized study with larger sample size is warranted to verify the findings and to further explore the role of UCSD in BCa.

Keywords Squamous differentiation · Bladder urothelial carcinoma · Prognosis · Meta-analysis

Introduction

Bladder cancer (BCa) is the second common cancer in urinary and male genital system and the 10th most common cancer in the world [1]. It is estimated that, in 2018, BCa accounts for 81,190 new cases and 17,240 cancer-related deaths in the United States (US) [2]. Furthermore, BCa is more common in men than in women. Especially in men older than 80 years, BCa is the fourth leading cause of cancer-associated mortality in the US [2]. The stage and grade of tumor have largely accepted for directing therapy and predicting outcome of BCa [3, 4]. In addition, histological type is another important factor should be considered to relate the prognosis of BCa [5].

More than 90% of BCa are classified as urothelial carcinoma, which include pure urothelial carcinoma of bladder

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(PUCB) and urothelial carcinoma with divergent differentiation or histologic variants. Urothelial carcinoma with divergent differentiation is defined by tumors arising within the urothelial tract, in which some percentage of ''usual type'' urothelial carcinoma is present along with other morphologies [6]. The incidence of histologic variants in studies ranges from 10.4 to 33% [6–13]. Previous studies have reported that urothelial carcinoma with histologic variants was associated with advanced tumor stage, extravesical disease, lymph node invasion, and positive soft tissue surgical margin [8, 11, 14, 15]. The presence of histologic variants was also associated with worse cancer-specific survival (CSS) or overall survival (OS) [9, 15, 16]. However, other studies showed that variant histology did not significantly influence the outcomes of BCa compared to PUCB [8, 10–12, 14]. These conflicting results might be explained by different types of histologic variants.

Urothelial carcinoma with squamous differentiation (UCSD) is the most common histologic variant and defined by the presence of intercellular bridges and/or keratinization [6, 17]. Previous studies showed that urothelial carcinoma with other variants except squamous differentiation (SD) was associated with increased disease recurrence and cancer-specific mortality (CSM) compared to PUCB [8, 13, 15] and patients with non-SD variants had shorter OS and poorer CSS compared to those with SD [18]. When the role of SD in BCa was examined, inconsistent results were obtained with some studies demonstrated that patients with UCSD had a significantly higher risk for poorer survival outcome [19–21], while other reports found no differences in survival outcomes [8, 22–24]. At present, the prognostic and clinical value of SD in BCa have not been fully determined.

In this meta-analysis, we aimed to clarify the clinical characteristics of patients with UCSD and to assess whether the presence of SD in patients with UCSD indicates a worse prognosis when compared to those with PUCB.

Methods

This meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [25]. Protocol of this study was registered in PROSPERO under number CRD42018116633.

Search strategy

A systematic literature search was performed in electronic databases including PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang Data until October 2018. The following terms were used for the literature search: "bladder cancer" OR "bladder tumor" OR "bladder carcinoma" OR "urothelial carcinoma" OR "transitional cell carcinoma" AND "squamous differentiation".

Inclusion and exclusion criteria

Studies included in this meta-analysis met the following criteria: (1) all the patients were diagnosed as urothelial bladder cancer that was pathologically confirmed; (2) studies investigated the clinicopathological features in patients with UCSD compared to PUCB; (3) treatment outcomes were reported in studies, such as rate of recurrence, disease-free survival (DFS), CSS, OS. The exclusion criteria were as follows: (1) case reports, non-published materials, editorials, reviews and animal experiments; (2) patients with upper tract urothelial carcinoma or other cancers; (3) studies investigated BCa with other histologic variants or pure squamous carcinoma. In addition, the most recent report or study with larger population and more complete information was used in this analysis when the same population was published in multiple studies.

Data extraction and study quality assessment

The following data were extracted from eligible studies: first author, year of publication, study country, recruitment period, patient age, gender ratio, pathological tumor stage, pathological tumor grade, treatment strategy, positive surgical margin rate, lymph node involvement rate, lymphovascular invasion (LVI) rate, follow-up time, and related survival outcomes.

For the assessment of study quality, all the included studies were evaluated by the Newcastle–Ottawa Scale (NOS) [26], which includes 8 items for the patients selection, comparability of cohorts and assessment of outcome. The literature search, data extraction and study quality assessment were conducted by two reviewers independently (XL and TD).

Study outcomes and statistics analysis

The primary outcomes in this meta-analysis were recurrence and CSS. The secondary outcomes were DFS and OS. For recurrence, we performed subgroup analysis according to different treatments.

Dichotomous variables were calculated using summarized odds ratios (ORs) with 95% confidence intervals (CIs). Mantel–Haenszel estimates were performed to compare the percentage of female, tumor stage T3/T4, tumor grade 3, carcinoma in situ (CIS), tumor multiplicity, rate of positive surgical margin, positive lymph node and LVI. Available multivariable adjusted hazard ratios (HRs) of UCSD prognostic survival were pooled in eligible studies. The heterogeneity among studies was analyzed by using chi-square

test based Q- and I^2-statistic [27]. The fixed-effect model was used when heterogeneity was not significant with a P value > 0.10; otherwise, the random-effect was applied. All results in this meta-analysis were considered as significant with a two-sided P value < 0.05. The publication bias among included studies was assessed through the inverted funnel plot visual inspection and Egger's test [28]. All the analyses were performed by RevMan (version 5.3; Cochrane Collaboration, Oxford, UK) and STATA (version 13.0; StataCorp, College Station, Texas, USA) software.

Results

Characteristics and quality assessments of eligible studies

After the initial search of the databases, 947 studies were identified following the search strategy. Excluding the duplicate reports, reviews, letters, case reports, irrelevant studies and other articles, a total of 19 studies [8, 11, 15, 20–24, 29–39] were included in this analysis (Fig. 1). The basic characteristics of all eligible studies are presented in Table 1. 13,284 patients were enrolled in these studies which were published from 2007 to 2018. All the included studies were retrospective cohort study. Most studies focused on the BCa in tumor stage T1–T4, 3 studies focused on the BCa in tumor stage T1. The main treatment approaches for patients in these studies included transurethral resection of bladder tumor (TURBT) in 3 studies and radical cystectomy (RC) in 16 studies. For the prognostic outcomes, recurrence was reported in 6 studies, DFS, CCS and OS were reported in 3, 4 and 5 studies, respectively. The results of quality assessment of included studies are presented in Supplementary Table 1. One study was in intermediate quality with six stars, the other studies were in relatively high quality with seven or more stars according to NOS assessment.

Clinicopathological characteristics

Results of meta-analysis of clinicopathological characteristics are presented in Table 2. Our results indicated that the percentage of female patients who had UCSD was significantly higher than those with PUCB (random-effect model, OR 1.70, 95% CI 1.36–2.13, $P = 0.0004$, Supplementary Fig. 1). High grade tumors and pathological stage T3/T4 tumors were more common in UCSD (random-effect model, OR 1.92, 95% CI 1.28–2.86, $P = 0.001$; random-effect model, OR 2.57, 95% CI 2.07–3.19, $P < 0.0001$; Supplementary Fig. 2 and Supplementary Fig. 3). Positive surgical margin rate and lymph node involvement rate was higher in UCSD group (random-effect model, OR 1.65, 95% CI

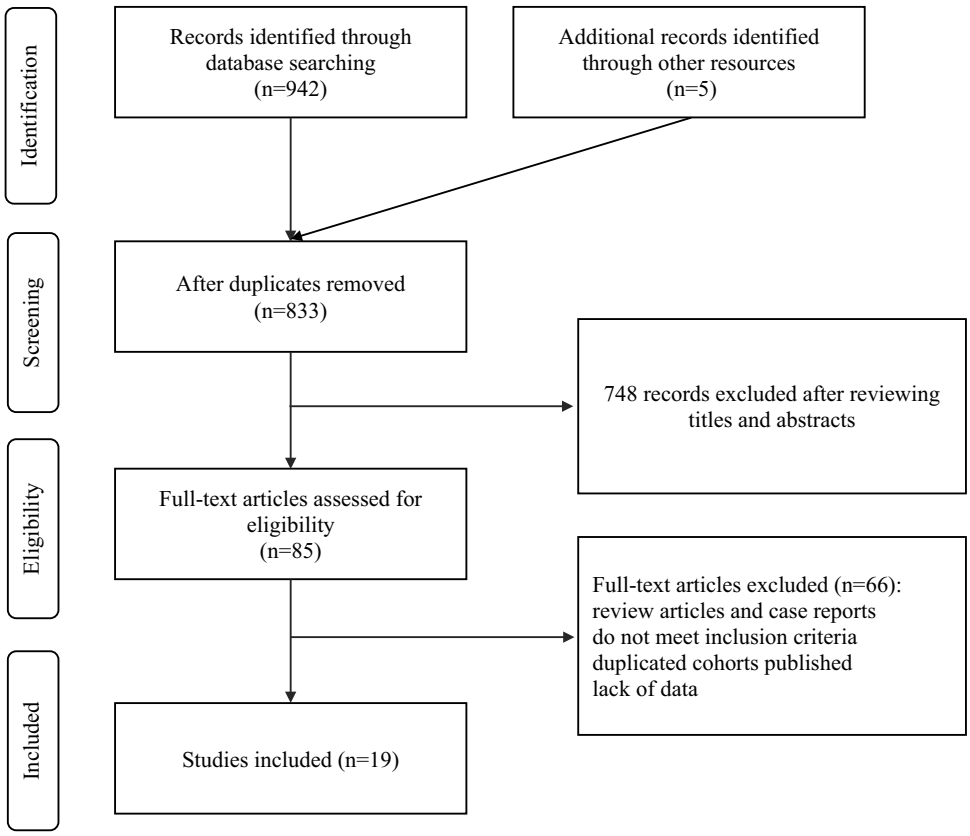

Fig. 1 Procedure of literature search and selection of included studies

Table 1 Characteristics of the included studies

Author	Year	Country	Recruitment period	No. of patients		Study design	Main treatment
				PUCB (%)	UCSD (%)		
Minato et al. [36]	2018	Japan	2003–2017	81 (80%)	20 (20%)	Retrospective	RC
Sefik et al. [39]	2018	Turkey	2006–2016	123 (88%)	17 (12%)	Retrospective	RC
Liu et al. [29]	2017	USA	2002–2014	197 (81%)	47 (19%)	Retrospective	RC
Minato et al. [20]	2017	Japan	2003–2015	29 (76%)	9 (24%)	Retrospective	RC
Li et al. [21]	2017	China	2004–2015	1449 (86%)	227 (14%)	Retrospective	TURBT or RC
Moschini et al. [11]	2017	Italy	1990–2013	729 (87%)	109 (13%)	Retrospective	RC
Mansour et al. [37]	2017	Egypt	2004–2014	937 (81%)	223 (19%)	Retrospective	RC
Gofrit et al. [30]	2016	Canada	1995–2013	140 (92%)	13 (8%)	Retrospective	TURBT or RC
Yang et al. [22]	2015	USA	2003–2013	617 (84%)	118 (16%)	Retrospective	RC
Izard et al. [31]	2015	Canada	1994–2008	2884 (90%)	325 (10%)	Retrospective	RC
Monn et al. [24]	2015	USA	2008–2013	462 (87%)	68 (13%)	Retrospective	RC
Soave et al. [15]	2015	Germany	1996–2011	389 (86%)	61 (14%)	Retrospective	RC
Bai et al. [34]	2015	China	2010–2015	208 (NA)	208 (NA)	Retrospective	TURBT or RC
Cao et al. [35]	2015	China	2005–2014	44 (69%)	20 (31%)	Retrospective	RC
Mitra et al. [23]	2014	USA	1976–2008	1244 (90%)	141 (10%)	Retrospective	RC
Gluck et al. [32]	2014	Romania	1990–2013	258 (83%)	52 (17%)	Retrospective	RC
Xylinas et al. [8]	2013	USA	2000–2008	1495 (87%)	227 (13%)	Retrospective	RC
Simone et al. [38]	2012	Italy	1999–2009	NA*	NA*	Retrospective	RC
Antunes et al. [33]	2007	Brazil	1993–2005	88 (78%)	25 (22%)	Retrospective	RC

PUCB pure urothelial carcinoma of bladder, *UCSD* urothelial carcinoma with squamous differentiation, *RC* radical cystectomy, *TURBT* transurethral resection of bladder tumor, *DFS* disease-free survival, *CSS* cancer-specific survival, *OS* overall survival, *NA* not available

*The number of patients from each group was unavailable in this study which was from a meeting record

Table 2 Results of meta-analysis of clinicopathological characteristics in patients with UCSD vs. PUCB

Clinicopathological characteristics	Number of studies	Heterogeneity		Effect model	OR	95% CI	*P* value
		I^2 (%)	*P* value				
Percentage of female patients	16	63%	0.0004	Random	1.70	1.36–2.13	**< 0.0001**
Percentage of high-grade tumors	7	62%	0.02	Random	1.92	1.28–2.86	**0.001**
Percentage of pathological stage T3/T4 tumors	13	59%	0.003	Random	2.57	2.07–3.19	**< 0.0001**
Positive surgical margin rate	6	60%	0.03	Random	1.65	1.10–2.46	**0.01**
Lymph node involvement rate	13	42%	0.05	Random	1.29	1.07–1.56	**0.009**
Percentage of CIS	9	59%	0.01	Random	0.71	0.51–0.99	**0.04**
LVI rate	6	91%	< 0.0001	Random	1.52	0.84–2.72	0.16
Percentage of tumor multiplicity	3	63%	0.07	Random	1.03	0.66–1.60	0.89
Number of patients who received NAC	4	15%	0.32	Fixed	0.77	0.48–1.25	0.29
Number of patients who received AC	5	84%	< 0.0001	Random	1.10	0.55–2.20	0.78

UCSD urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder, *OR* odds ratio, *CI* confidence interval, *NAC* neoadjuvant chemotherapy, *AC* adjuvant chemotherapy, *CIS* carcinoma in situ

1.10–2.46, $P = 0.01$; random-effect model, OR 1.29, 95% CI 1.07–1.56, $P = 0.009$; Supplementary Fig. 4 and Supplementary Fig. 5). The percentage of CIS was higher in PUCB (random-effect model, OR 0.71, 95% CI 0.51–0.99, $P = 0.04$, Supplementary Fig. 6). However, the percentage of LVI and tumor multiplicity showed no significant difference between the two groups (random-effect model, OR 1.52, 95% CI 0.84–2.72, $P = 0.16$; random-effect model, OR 1.03, 95% CI 0.66–1.60, $P = 0.89$; Supplementary Fig. 7 and Supplementary Fig. 8). There were no differences in the number of patients who received neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC) (fixed-effect model,

OR 0.77, 95% CI 0.48–1.25, $P=0.29$; random-effect model, OR 1.10, 95% CI 0.55–2.20, $P=0.78$; Supplementary Fig. 9 and Supplementary Fig. 10).

Recurrence

Disease recurrence was reported in six studies. To explore the recurrence rate after TURBT or RC, subgroup analysis was performed according to different treatments (two studies in TURBT group and four studies in RC group). The result of subgroup analysis showed the recurrence rate was significantly higher in patients who had UCSD than patients with PUCB in either the patients who underwent TURBT (fixed-effect model, OR 1.37, 95% CI 1.08–1.75, $P=0.01$; Fig. 2) or RC (random-effect model, OR 1.73, 95% CI 1.02–2.92, $P=0.04$; Fig. 3).

Prognosis

Disease-free survival

Multivariable adjusted HR of UCSD in predicting DFS of patients with BCa after RC was available in three included studies. The result showed that UCSD was associated with significantly poorer DFS (fixed-effect model, HR 1.42, 95% CI 1.08–1.86, $P=0.01$; Fig. 4)

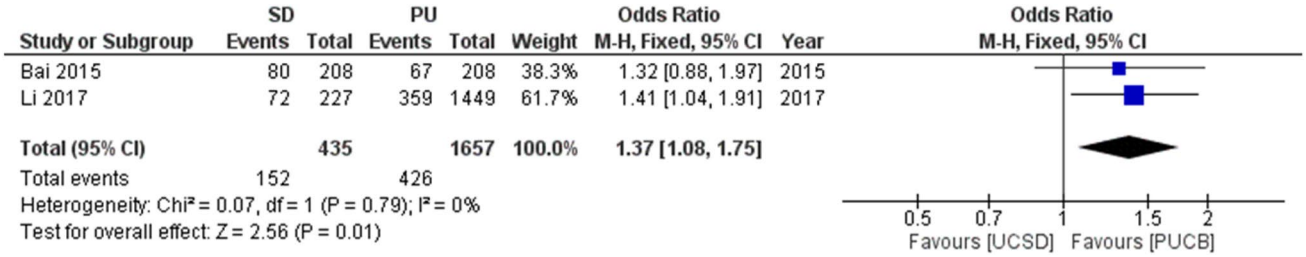

Fig. 2 Forest plots of the recurrence rate of patients who underwent TURBT in patients with UCSD vs. PUCB. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

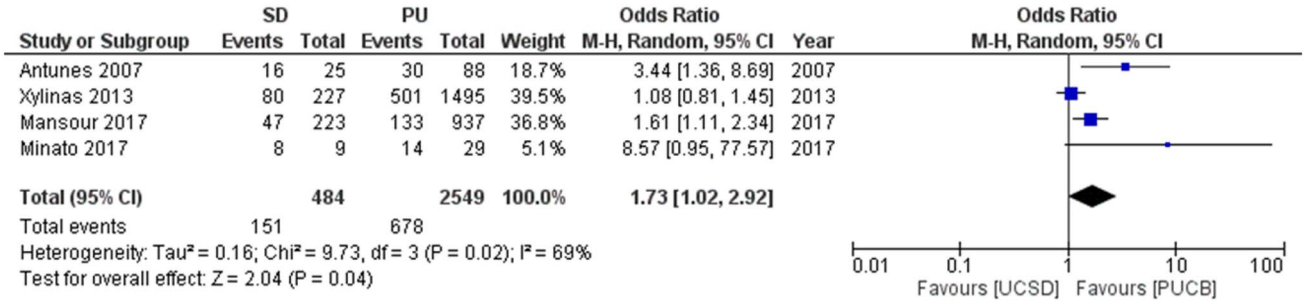

Fig. 3 Forest plots of the recurrence rate of patients who underwent RC in patients with UCSD vs. PUCB. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

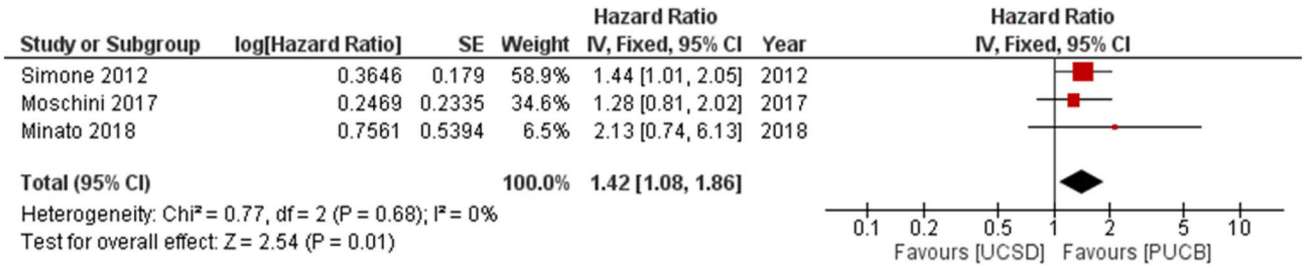

Fig. 4 Forest plots of disease-free survival in patients with UCSD vs. PUCB from multivariable analysis. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

Cancer-specific survival

There were three studies that performed univariable analyses and multivariable analyses for CSS of patients with BCa after RC, respectively. The results revealed that patients who had UCSD had worse CSS on univariable analysis (random-effect model, HR 1.65, 95% CI 1.01–2.70, $P=0.04$; Fig. 5). However, UCSD was not associated with CSS on multivariable analysis (random-effect model, HR 1.70, 95% CI 0.98–2.95, $P=0.06$; Fig. 6).

Overall survival

Multivariable analysis for OS of patients with BCa after RC was available in five studies. The result demonstrated no significant difference of OS was observed between patients with UCSD and those with PUCB (random-effect model, HR 1.12, 95% CI 0.84–1.5, $P=0.45$; Fig. 7).

Publication bias

No publication bias was detected in survival outcome comparisons through inverted funnel plot or Egger's test.

Discussion

As the second common cancer in urinary and male genital system, the BCa survival rate has not changed significantly for the last 30 years [40]. BCa showed high recurrence rate

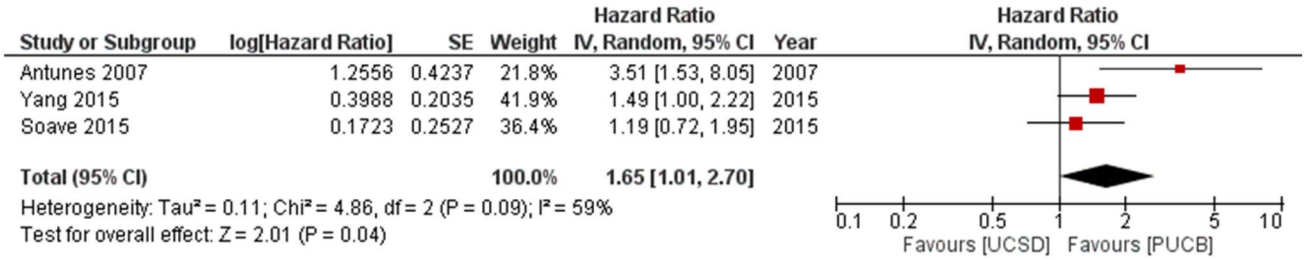

Fig. 5 Forest plots of cancer-specific survival of patients who underwent RC in patients with UCSD vs. PUCB from univariable analysis. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

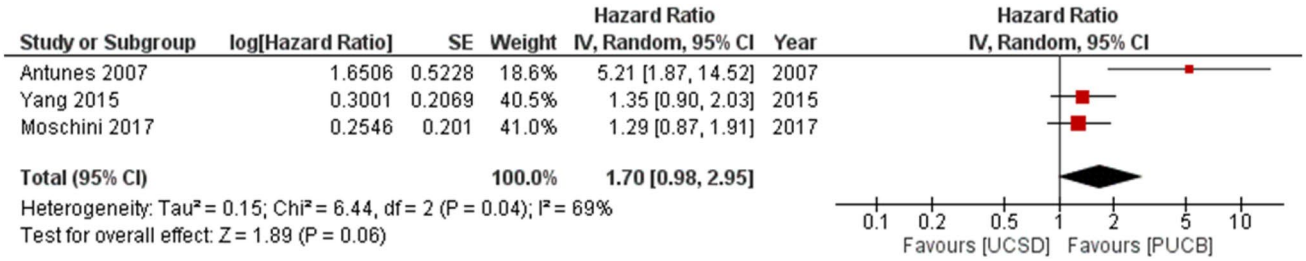

Fig. 6 Forest plots of cancer-specific survival of patients who underwent RC in patients with UCSD vs. PUCB from multivariable analysis. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

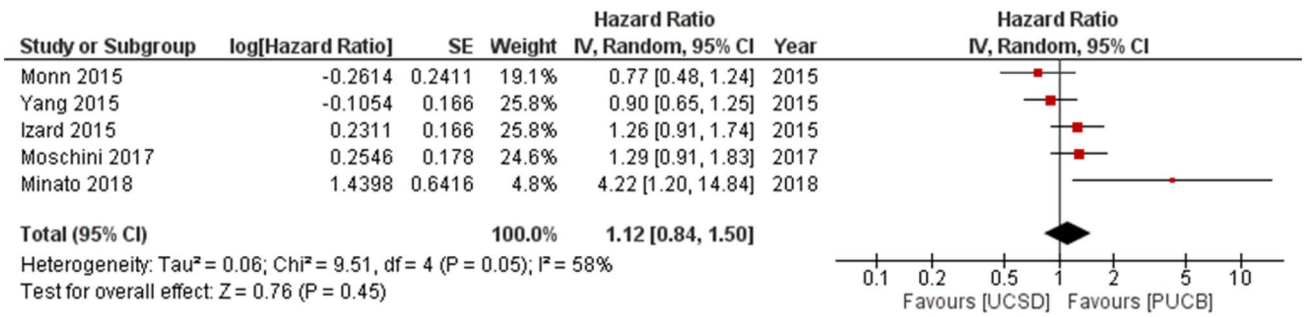

Fig. 7 Forest plots of overall survival in patients with UCSD vs. PUCB from multivariable analysis. *UCSD* urothelial carcinoma with squamous differentiation, *PUCB* pure urothelial carcinoma of bladder

for tumor stage T1 and poor survival for tumor stage T3/4 [40–42]. The prognostic factors for patients with BCa were investigated in many studies including patients' age, gender, prior recurrence rate, number of tumors, tumor size, tumor stage and grade, and the presence of concomitant CIS [43, 44]. However, the impact of histological variants should not be ignored. To the best of our knowledge, this is the first meta-analysis to investigate the clinicopathological characteristics and prognosis of different outcomes in patients with UCSD. We found that the percentage of female patients who had UCSD was significantly higher than those with PUCB. UCSD was associated with high tumor grade, pathological tumor stage T3/T4, positive surgical margin and lymph node involvement. The percentage of CIS was more common in PUCB. For the survival outcomes, we revealed that patients who had UCSD had a higher recurrence rate and worse DFS prognosis than patients with PUCB after RC, but no significant difference of CSS and OS was found between these two groups on multivariable analyses.

Although the incidence of BCa is higher in men than in women, female patients with BCa are more likely diagnosed with advanced stage tumors and have higher bladder CSM rate [45, 46]. For pathological tumor stage T3–T4 urothelial cancer of bladder, Liberman et al. [47] reported that female gender was independently associated with higher CSM. From the analysis of patients with pT4 BCa who underwent RC, Tilki et al. [48] reported that female gender was independently associated with significantly higher risk of disease recurrence and CSM, and May et al. [49] found that 5-year CSS in female patients was significantly lower than that in male patients. Interestingly the percentage of female patients and pathological tumor stage T3/T4 in our analysis was higher in patients with UCSD than those with PUCB, which could partly explain the difference in BCa recurrence rate and CSS between patients with UCSD and PUCB. We also found the percentage of high tumor grade, positive surgical margin rate and lymph node involvement rate were higher in patients with UCSD, which could contribute to the worse survival compared to patients with PUCB. These findings indicated that the adequate resection range and lymphadenectomy may both be helpful to improve the survival outcomes for patients with UCSD. Furthermore, we found that the percentage of CIS was lower in patients with UCSD than PUCB. Mazzucchelli et al. [50] found that the presence of CIS was associated with a 60% reduction of the risk of death for patients with BCa treated with RC. Moschini et al. [51] reported that the presence of CIS was associated to an increased risk of urothelial recurrence and worse CSM in pT0–pT2 patients. Yafi et al. [52] reported that the presence of concomitant CIS on cystectomy specimens did not independently affect outcomes of patients treated with RC with pelvic lymph node dissection. The results indicated that concomitant CIS maybe a predictive factor for a favorable outcome, but the impact of CIS in UCSD is still unclear.

Recently, a meta-analysis [53] specifically assessed the clinical implications of histological variants in urothelial carcinoma of the bladder. They performed a subgroup analysis according to the histological variants type and found that the pooled HR was 0.97 (95% CI 0.83, 1.11, $P=0.701$) for UCSD without any statistical significance. But they did not analyze different endpoints (CSS and OS) separately and put the data of HR from univariable and multivariable analyses together. We conducted a subgroup analysis and found that UCSD was associated with CSS on univariable analysis but was not an independent prognostic factor for CSS and OS on multivariable analysis. Several previous studies also reported that the presence of SD was associated with survival outcomes on univariable analyses [21, 33, 54–57], but not on multivariable analyses [8, 22, 24, 31, 56, 57]. These results indicated that the poor survival outcomes in patients with UCSD were associated with the unfavorable clinicopathological characteristics of tumor, such as high percentage of pT3/T4 and high tumor grade. Another potential reason for different results obtained from previous studies could be due to the different extent of SD in different patients. Liu et al. [29] found that the lymph node-positive rate was significantly higher in urothelial carcinoma with extensive SD when compared with that seen in PUCB, but not in urothelial carcinoma with focal SD. Mitra et al. [23] assessed the outcome predictors in patients with UCSD and found that wide spread presence of SD elements was associated with poor OS on univariable analysis but not on multivariable analysis. Currently, the clinical effect of different extent of SD is still unknown [17]; further study is required to make it clear.

Honma et al. [58] performed a retrospective study included 145 patients with muscle-invasive BCa treated with RC and revealed that a concomitant squamous cell carcinoma component in the specimen was the only independent predictor of local recurrence after surgery. In our meta-analysis, the recurrence rate was significantly higher in UCSD than PUCB regardless of patients who underwent TURBT or RC. Furthermore, we detected that UCSD was not associated with CSS for patients who underwent RC only. For patients who underwent TURBT, Li et al. [21] found that patients treated with re-TURBT had shorter median CSS than those who underwent RC in patients with UCSD. These results suggested that patients with UCSD treated with RC may have better outcome than patients treated with TURBT, especially for recurrence after TURBT. Our results suggest close follow-up will be necessary for patients with UCSD to detect the recurrence early, therefore, to improve CSS.

Regarding NAC or AC treatment, there were five studies that included patients who received NAC or AC in this meta-analysis, but the effect of chemotherapy for patients with UCSD is undetermined. To assess the impact of NAC

and AC in patients with variant histology at RC, two studies from Vetterlein et al. [59] and Berg et al. [60] showed that there was no significant OS benefit from NAC for patients with histological variants except neuroendocrine tumors, and no survival benefit of AC for patients with concomitant variant histology or pure variant histology. Minato et al. [20] reported 9 patients with UCSD treated with NAC followed by RC. None of the patients with UCSD achieved pathologic complete response and only one patient had pathologic downstaging. Mitra et al. [23] also found that NAC and AC administration were not significantly associated with recurrence-free survival or OS. However, Buisan et al. [61] revealed that treatment with NAC was a significant prognostic factor in multivariate analysis for PFS and CSS in patients with squamous-cell-feature muscle-invasive bladder, and found that patients with low neutrophil-to-lymphocyte ratio treated with NAC had significantly better outcomes. Thus, the patients with UCSD may benefit from multimodality therapy combined with surgery; however, further research will be required to determine the group of patients who will have better response to chemotherapy.

Several limitations should be acknowledged in this study. Firstly, there is no standard of the percentage of SD for diagnosis of variant histology, the extent of SD between different studies may be inconsistent, and the samples from TURBT may be not enough to accurately evaluate the presence of SD [62]. The different criteria for diagnosing SD may contribute to potential bias. Secondly, some studies with a small population of patients were included in our analysis, and the population from different countries. The data were not enough to perform the subgroup analysis according to race. Thirdly, the presence of heterogeneity between the enrolled studies still existed in many data analyses, which could influence the results. Furthermore, the publications which were not written in English or Chinese, or whose complete data or full text were not available were not included; this may introduce a potential enrollment bias. Finally, subgroup analyses on different gender, tumor stage or grade were not performed due to the lack of sufficient data available.

Conclusion

Our study demonstrated that the presence of SD in bladder urothelial carcinoma was associated with poor clinicopathological features, high risk of recurrence and worse clinical outcome for disease-free survival. SD should be considered as a marker for prognosis and treatment for patients with BCa. In the future, a well-designed randomized study is warranted to verify our findings and to further explore the role of SD in urinary bladder cancer.

Author contributions XL: project development, data collection, data analysis, manuscript writing, TD: data collection, data analysis, SW: data analysis, manuscript editing, SXL: data analysis, manuscript editing, DW: project development, manuscript editing, CW: project development, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent or ethics committee approval is not required for this study,because it performed a meta-analysis on previously published data.

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