ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 529.e19–529.e25

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

Prognostic performance of the 1973 and 2004 WHO grading classification in upper tract urothelial carcinoma

Bao Guan, Ph.D.*[,a,b], Shiying Tang, M.D.*[,a,b], Yonghao Zhan, Ph.D.*[,a,b], Yifan Li, Ph.D.[a,b], Dong Fang, M.D.[a,b], Ding Peng, Ph.D.[a,b], Yanqing Gong, Ph.D.[a,b], Shiming He, Ph.D.[a,b], Lei Zhang, M.D.[a,b], Kunlin Yang, M.D.[a,b], Gengyan Xiong, M.D.[a,b], Libo Liu, M.D.[a,b,c], Qun He, M.D.[a,b,c], Xuesong Li, M.D., Ph.D.[a,b,#], Liqun Zhou, M.D., Ph.D.[a,b,#]

[a] *Department of Urology, Peking University First Hospital, Xicheng, Beijing, China*
[b] *Institute of Urology, Peking University, National Urological Cancer Center, Beijing, China*
[c] *Department of Pathology, Peking University First Hospital, Xicheng, Beijing, China*

Received 11 October 2018; received in revised form 3 January 2019; accepted 13 January 2019

ABSTRACT

Background: Grading of upper tract urothelial carcinoma (UTUC) is routinely used in clinical practice; however, reports concerning prognostic performance of different grading systems are contradictory. We aim to assess the clinical reliability of the 1973 and 2004 World Health Organization (WHO) grading classification systems in UTUC.

Patients and Methods: We retrospectively evaluated 458 consecutive patients with UTUC from 2008 to 2013. The postoperative tumor grades were evaluated by a single uropathologist using the 1973 and 2004 WHO grade classification systems. The Kaplan–Meier method was used to estimate cancer-specific survival (CSS) and overall survival (OS). Univariate and multivariate analyses were used to test the association between clinical variables and the CSS and OS rates.

Results: There were 133 (29.0%) low-grade patients and 325 (71.0%) high-grade patients. The 3-year CSS rates were 87.0% and 76.0% for G2 and G3 disease and 89.0% and 80.0% for low- and high-grade disease according to the 2004 system, respectively. For all UTUC patients, there were significant differences in the CSS and OS rates between G2 and G3 cases, as well as between the low- and high-grade groups. The CSS and OS rates were significantly different between the G2 and G3 cases for the overall high-grade population (CSS: $P = 0.003$; OS: $P = 0.009$), while no significant difference emerged between low- and high-grade tumors in G2 UTUC patients (CSS: $P = 0.717$; OS: $P = 0.280$). In the subgroup of high-grade non–muscle-invasive tumors, the 1973 WHO grading system was an independent predictor of CSS ($P = 0.045$).

Conclusions: The results support the hypothesis that the 1973 WHO system is superior to the 2004 system for predicting clinical outcomes in patients with non–muscle-invasive UTUC. © 2019 Published by Elsevier Inc.

Keywords: 1973 World Health Organization; 2004 World Health Organization; Grading; Upper tract urothelial carcinoma

1. Introduction

Upper tract urothelial carcinoma (UTUC), which occurs in the pelvis and ureter, is a comparatively rare but aggressive malignant tumor that accounts for only 5% to 10% of all urothelial carcinomas, but 60% of UTUCs are invasive at diagnosis compared with 15% to 25% of bladder tumors [1]. Generally, the 1973 World Health Organization (WHO) grading classification has been identified to be an effective independent prognostic factor in patients with UTUC.

In 2004, to improve the intraobserver and interobserver variability prognostic implications of the 1973 WHO system, the WHO updated the grading classification for

#Corresponding authors. Tel.: +86-10-83572211; fax: +86-10-66552086 (Liqun Zhou) and Tel.: +86-10-83572275; fax: +86-10-66552086 (Xuesong Li).

E-mail addresses: pineneedle@sina.com (X. Li), zhoulqmail@sina.com (L. Zhou).

*These authors contributed equally to this work

https://doi.org/10.1016/j.urolonc.2019.01.013
1078-1439/

urothelial carcinoma produced by the International Society of Urological Pathology in 1998 [2]. This new grading system classified papillary urothelial neoplasm of low malignant potential and carcinoma into only 2 grades (low- and high-grade) for histological malignancy. By avoiding the influence of ambiguous intermediate grade sort (G2) of the 1973 WHO system, this new classification system was looked forward to considering the more appropriate stratification of patients into 2 subsets (low- and high-grade) with definitively well-distinguished guidelines for tumor treatment and follow-up [3]. To date, several researchers have analyzed the clinical reliability of the novel grading system. Remzi et al. [4] collected 1,363 multi-institutional UTUC patients and confirmed that high-grade was a strongly independent prognostic factor in patients treated with radical nephroureterectomy. Margulis et al. [5] established a nomogram pattern recruiting architecture, location, and tumor grade according to the 2004 WHO classification for predicting non−organ-confined UTUC.

Although the use of the 2004 grading classification system was advocated by WHO, the European Association of Urology guidelines have not reached a consensus on which grading classification system should be routinely performed in UTUC [1]. Recently, several studies have been performed to compare the prognostic role and clinical reliability of the 1973 and 2004 grading systems for patients with non−muscle-invasive tumors (NMIBC), while none of the studies compared the prognostic role of the 1973 and 2004 WHO grading systems for patients with UTUC [3,6−10].

Therefore, we aimed to compare the prognostic significance of the 1973 and 2004 WHO classifications in a consecutive series of patients with primary UTUC disease diagnosed according to the two grading systems.

2. Materials and methods

2.1. Patient selection

A total of 458 consecutive UTUC patients who underwent radical nephroureterectomy or segmental ureterectomy in Peking University First Hospital between January 2008 and December 2013 were included in this study. The pathological staging was based on the 2002 Union for International Cancer Control TNM classification system [11]. Patients were simultaneously graded as G1, G2, and G3 according to the 1973 WHO classification system and classified as having low- and high-grade tumors according to the 2004 WHO system (supplemental Figure 1). Histological features were determined by a single expert uropathologist (Q.H.). While patients with papillary urothelial neoplasm of low malignant potential were excluded from study, the 2004 WHO classification approached a 2-tier system (low- and high-grade). Furthermore, none of the patients had received neoadjuvant chemotherapy. Lymph node dissection (LND) was considered when the preoperative imaging results shown invasive UTUC or suspicious lymph node metastasis.

2.2. Follow-up

Follow-up included laboratory data, chest X-ray, urinary ultrasonography, cystoscopy, selected computed tomography, or magnetic resonance imaging every 3 months for the first 2 years, every 6 months for 5 years, and then annually. Follow-up data were obtained by reviewing the clinical and pathological databases at our institution. The coprimary endpoints of the study were all-cause and cancer-specific deaths. Overall survival (OS) and cancer-specific survival (CSS) were calculated from the date of surgery to the date of all-cause death and cancer-specific death.

2.3. Statistical analysis

The Kaplan−Meier method was used to estimate CSS and OS after surgery. Survival data from the G2 and G3 patient subgroups or low- and high-grade cases were compared by the log-rank test. Univariate and multivariate Cox proportional hazards regression models, including patient age, gender, pathological stage, lymph node status, tumor architecture, and size as predictive factors, were used to test the association between clinical variables and the CSS and OS rates. Survivors without the event of interest were censored at the date of last follow-up. All statistical analyses were performed using SPSS 20.0 (Chicago, IL, USA). Two-sided $P < 0.05$ was considered statistically significant.

3. Results

The clinicopathological characteristics of 458 patients with UTUC, including 211 (46.1%) males and 247 (53.9%) females, are summarized in Table 1. The relationship between the 1973 and 2004 WHO classification in our cohort is shown in Fig. 1. Supplemental Table 1 shows the correlation of tumor grade and the 2 grading classification systems.

3.1. Comparison of 2 grading systems in prognostic performance

The median follow-up was 45 months (range: 1−98) with a mean of 46.6 months. During the follow-up period, a total of 152 (33.2%) patients died, 124 (27.1%) patients due to UTUC. Kaplan−Meier plots of OS and CSS stratified by the 1973 and 2004 WHO grading systems are shown in supplemental Figure 2. The difference between OS and CSS was statistically significant between G2 and G3 patients as well as between low- and high-risk diseases. The 3-year CSS rates were 87.0% and 76.0% for G2 and G3 disease and 89.0% and 80.0% for low- and high-grade disease, respectively.

Because some G2 lesions were classified as low-grade or high-grade urothelial carcinomas and G3 lesions as high-grade urothelial carcinomas, survival analysis was performed in the subgroup of high-grade UTUC patients or G2

Table 1
Clinicopathological characteristics of the 458 patients in UTUC

Variable	Patients, n	Median (IQR) or %
Age, years	458	69 (61–75)
Gender		
Male	211	46.1%
Female	247	53.9%
History of smoking		
Negative	370	80.8%
Positive	88	19.2%
Tumor size, cm		3.0 (2.0–4.3)
Architecture		
Papillary	358	78.2%
Sessile	100	21.8%
Tumor multifocality		
Negative	385	84.1%
Positive	73	15.9%
Pathological T stage		
pTa		
pT1	20	
164	4.4%	
35.8%		
pT2	127	27.7%
pT3	137	29.9%
pT4	11	2.2%
N status		
N0 or Nx	424	92.6%
N1	34	7.4%
WHO 1973 grade		
G1	8	1.7%
G2	267	58.3%
G3	183	40.0%
WHO 2004 grade		
Low-grade	133	29.0%
High-grade	325	71.0%

UTUC = upper tract urothelial carcinoma; WHO = world health organization; Nx = unknown.

patients to assess the prognostic reliability of the 2 grading classification systems. The Kaplan–Meier OS and CSS plots showed the best survival in G2 high-grade cases compared with the G3 high-grade group (OS: $P = 0.009$; CSS: $P = 0.003$) (Fig. 2A and B). However, there were no significant differences between low- and high-grade patients with G2 disease (OS: $P = 0.280$; CSS: $P = 0.717$) (Fig. 2C and D). In addition, univariate analysis identified that gender, tumor size, tumor stage, location, lymph node status, and 1973 grading were associated with CSS in high-grade UTUC patients, but multivariate analysis indicated that the tumor grade according to the 1973 WHO classification was not an independent predictor of CSS in patients with high-grade lesions (supplemental Table 2).

3.2. Predictive value of the 1973 grading system in the high-grade non–muscle-invasive UTUC

In 2017, Viktor et al. [3] reviewed 20 articles that described the 1973 and 2004 WHO Grading Classification Systems and reported that the progression rates in grade 3 patients were higher than those in high-grade patients in patients with NMIBC. Therefore, we divided high-grade UTUC patients into 2 subgroups: the NMIBC and muscle-invasive tumor groups. In the subgroup of high-grade UTUC patients with NMIBC, the Kaplan–Meier CSS plot showed the best survival in G2 cases compared with the G3 group ($P = 0.033$) (Fig. 3A), but Fig. 3B shows that there was no significant difference in OS between them ($P = 0.152$). However, there were no significant differences in the subgroup of muscle-invasive tumors for CSS or OS (OS: $P = 0.181$; CSS: $P = 0.233$) (Fig. 3C and D). Univariate analysis identified that the tumor location and tumor grade according to the 1973 WHO classification were associated with CSS in high-grade patients with NMIBC. After adjusting for clinicopathological variables, the 1973 WHO classification was an independent predictor of CSS in multivariate analysis and the CSS rates for the patients with G3 tumors were 2.894 times higher than for those with G2 tumors (95%CI: 1.022–8.196) in non–muscle-invasive high-grade patients (Table 2).

4. Discussion

In 1973, the WHO reached a consensus that G1 carcinomas (well-differentiated) are defined as showing only mild degrees of cytological atypia and infrequent mitotic figures; G3 carcinomas (poorly differentiated) are defined as showing marked nuclear pleomorphism, loss of maturation from the base to the surface, and mitotic activity; and G2 carcinomas (moderately differentiated) comprise all tumors between these extremes [12]. One of the main shortcomings of the 1973 WHO grading system is the adoption of criteria that are too vague to determine the grade, resulting in most cases falling into the intermediate category (G2). Consequently, the lack of clarity between the 3 grades may adversely affect prognostic predictions due to high intra- and interobserver variability. In our series, 142 out of 267

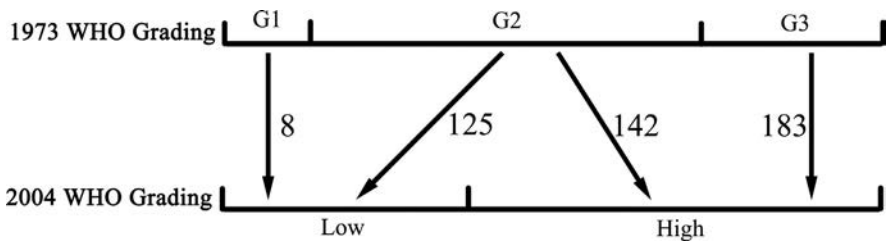

Fig. 1. The relationship between the 1973 WHO and 2004 grading classification systems.

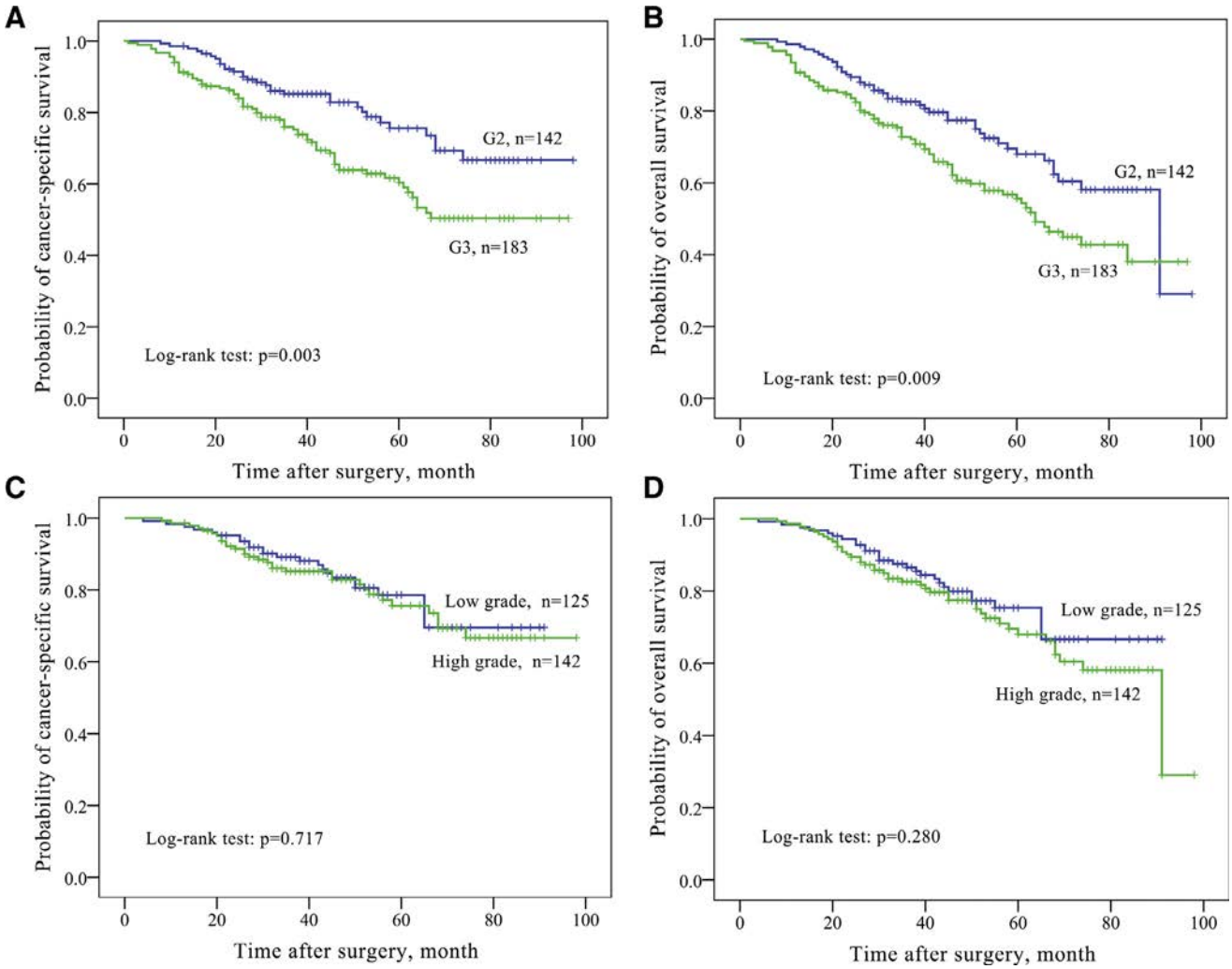

Fig. 2. Kaplan–Meier analysis demonstrated CSS and OS was associated with the 1973 grading systems in the high-grade subgroups. (A) and (B) Comparison between patients with G2 and G3 tumors in the subgroup of high-grade cases. (C) and (D) Comparison between patients with low- and high-grade tumors in G2 patients. CSS = cancer-specific survival; overall survival (OS).

(53.2%) G2 WHO 1973 UTUC cases were categorized as "high-grade" according to the International Society of Urological Pathology/WHO 2004 system. The resulting increase in "high-grade" lesions in the new grading system compared to the "grade 3" lesions of the WHO 1973 grading system led to a failure to distinguish certain patients with a relatively unfavorable prognosis, posing a clinical dilemma for the practicing urologist.

To explore the clinical reliability of the 2 grading systems, several studies have compared the 2 WHO urothelial carcinoma grading systems, while all of these studies were based on bladder cancer, especially NMIBC. Wolfgang et al. [6] enrolled 310 pT1 bladder cancer patients and found that there were no significant CSS differences between high-grade and low-grade bladder cancer according to the 2004 WHO classification, while the correlation was ascertained between the 1973 WHO grading classification and prognosis of patients. A study performed by Federico et al. [7] reported that the recurrence-free survival and progression-free survival rates significantly differed between the G2 and G3 subgroups in patients with high-grade Ta bladder cancer. Furthermore, they confirmed that only the grade assessed according to the 1973 WHO classification was significantly predictive of both recurrence-free survival and progression-free survival. Chen et al. [13] identified that the 1973 WHO Classification is more suitable for predicting tumor recurrence. Overall, these studies suggested that the 1973 WHO classification system predicted the risk of recurrence or progression in primary bladder carcinomas more accurately than the 2004 WHO system.

Though important similarities exist between UTUC and bladder cancer, such as their histological classification, there were some important differences from clinicopathological feature to prognosis [14,15]. Several studies revealed that approximately 60% of UTUC were invasive at diagnosis compared with 15% to 25% of bladder tumors and that UTUC had a relatively worse prognosis [16]. In

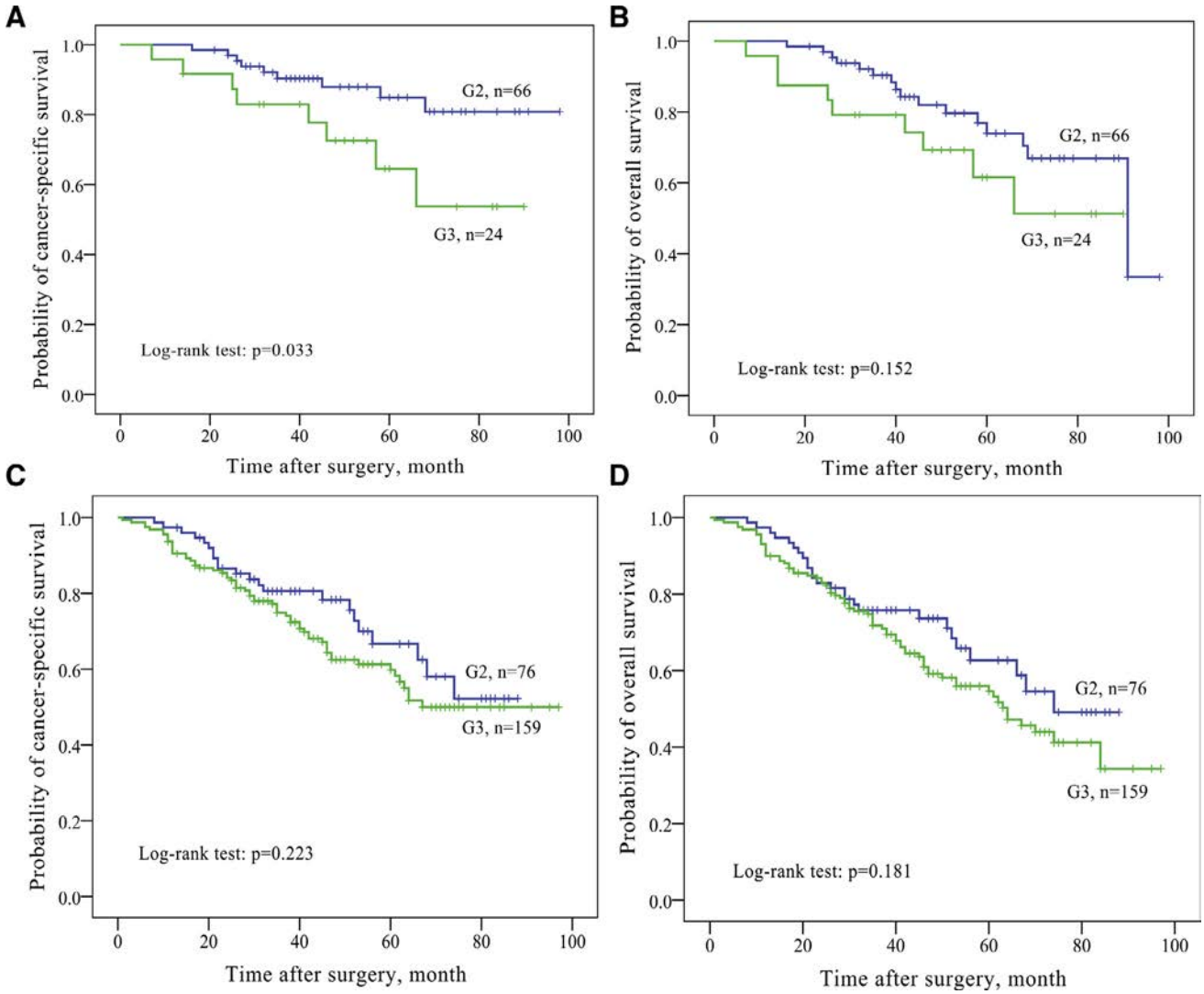

Fig. 3. Kaplan–Meier analysis of CSS and OS in high-grade patients with different tumor stages. (A) and (B) Comparison between patients with the 1973 WHO classification in the patients with high-grade and non-muscle-invasive tumors. (C) and (D) Comparison between patients with the 1973 WHO classification in the patients with high-grade and muscle-invasive tumors. CSS = cancer-specific survival; overall survival (OS).

our cohort, our study implied that although some patients were diagnosed with high-grade tumors according to the 2004 WHO classification, the prognosis of these patients with G3 lesions according to 1973 WHO classification was unfavorable. However, there was no significant difference between low- and high-grade tumors in CSS or OS according to the 2004 WHO classification in patients with G2. This result indicated that the new classification system did

Table 2
Univariate and multivariate Cox analysis predicting cancer-specific survival in high-grade non–muscle-invasive UTUC

Variables	Univariable			Multivariable		
	HR	95%CI	P	HR	95%CI	*P*
Age	0.980	0.931–1.032	0.446	0.967	0.910–1.027	0.269
Gender (female vs. male)	0.652	0.248–1.716	0.386	0.828	0.277–2.480	0.736
Tumor size (<3 vs. >3 cm)	0.989	0.376–2.600	0.981	1.058	0.343–3.262	0.921
Architecture (papilly vs. sessile)	1.992	0.757–5.240	0.163	1.918	0.653–5.630	0.236
Tumor focality (negative vs. positive)	1.402	0.454–4.332	0.557	1.170	0.345–3.961	0.801
Tumor location (renal pelvis vs. ureter)	3.510	1.143–10.772	0.028	4.002	1.216–13.169	0.023
N status (N0/Nx vs. N1)	–	–	–	–	–	–
1973 WHO grading (G2 vs. G3)	2.703	1.040–7.020	0.041	2.894	1.022–8.196	0.045

UTUC = upper tract urothelial carcinoma; Nx = unknown.

not exhibit its deserved predictive value in certain UTUC patients. Therefore, it is essential for urologists to divide tumors into G2 and G3 groups in high-grade populations.

Considering that the 1973 WHO grading classification was more accurate in predicting recurrence and progression than the 2004 grading system in NMIBC, we divided our cohorts into 2 parts: non–muscle-invasive and muscle-invasive tumors. Of all the patients with high-grade tumors, the CSS rates of G2 and G3 showed significant differences in the subgroup of NMIBC, but not in muscle-invasive ones, which indicated that the prognostic value of the 1973 WHO classification was more remarkable in non–muscle-invasive UTUC tumors compared to patients with muscle-invasive tumors. The effects of these 2 grading classifications on the prognosis of UTUC were similar to those of bladder cancer mentioned above. After adjusting for selected risk factors in a Cox multivariate model, tumor grade was an independent predictive factor of CSS in non–muscle-invasive high-grade patients, conferring a 2.894-times higher risk of cancer-specific death for G3 tumors than G2 tumors. The results supported the hypothesis that the 1973 WHO classification has greater prognostic reliability for UTUC patients than the 2004 WHO system, especially in NMIBC.

Intratumor heterogeneity which may harbor tumor evolution, disturb the pathological diagnosis just relying on results from several tumor tissue slides and hinder personalized-medicine strategies have been studied by many centers. Ali et al. [17] reported that high-grade serous ovarian cancer on 31 spatially and temporally separated tumor specimens shown divergent genomic tapestries. Marco et al. [18] performed exome sequencing on multiple spatially separated primary renal carcinomas, and found that the tumor genomics landscape depicted from single samples site presented different mutation profiles and prognosis, and foster diverse allelic-imbalance profiles. These studies revealed that the extent of intratumor heterogeneity could be greatly variable, ranging from 0 to over thousands mutations found to be heterogeneous within primary single tumor site [19,20]. Therefore, the evaluation of pathological tumor grade depending on HE staining should be updated. Recently, the biomarkers such as Bcl-2, RON, and c-met protein have been identified as a prognostic value for UTUC patients, and exploring more promising and novel molecular markers are becoming increasingly of great importance [21,22].

The limitations of the present study included the use of retrospective data from a single institution and a comparably short follow-up period. In addition, our study did not acquire information on tumor recurrence and progression, which were also important indicators in evaluating prognosis. Finally, our cohort failed to assess interobserver reproducibility and intraobserver repeatability, which are essential in clinical practice.

5. Conclusions

In this study, we compared the prognostic significance of the 1973 and 2004 WHO grading systems by evaluating a large cohort of UTUC patients. Overall, our results showed that the 1973 WHO system is superior to the 2004 system in predicting the clinical outcomes of patients with non–muscle-invasive UTUC. Besides, novel and more predictive molecular markers should be confirmed to guide clinical treatment and prognosis evaluation.

ACKNOWLEDGMENTS

This work was supported by grants from the Natural Science Foundation of Beijing (7152146), the Clinical Features Research of the Capital (no. Z151100004015173) and the Capital Health Research and Development of Special (2016-1-4077).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.01.013.

References

[1] Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on upper urinary tract urothelial carcinoma: 2017 Update. Eur Urol 2017;73:111–22.
[2] Bircan S, Candir O, Serel TA. Comparison of WHO 1973, WHO/ISUP 1998, WHO 1999 grade and combined scoring systems in evaluation of bladder carcinoma. Urol Int 2004;73:201–8.
[3] Soukup V, Capoun O, Cohen D, Hernandez V, Babjuk M, Burger M, et al. Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization grading classification systems in non-muscle-invasive bladder cancer: a European association of urology non-muscle invasive bladder cancer guidelines panel systematic review. Eur Urol 2017;72:801–13.
[4] Remzi M, Haitel A, Margulis V, Karakiewicz P, Montorsi F, Kikuchi E, et al. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. BJU Int 2009;103:307–11.
[5] Margulis V, Youssef RF, Karakiewicz PI, Lotan Y, Wood CG, Zigeuner R, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol 2010;184:453–8.
[6] Otto W, Denzinger S, Fritsche HM, Burger M, Wieland WF, Hofstadter F, et al. The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. BJU Int 2011;107:404–8.
[7] Pellucchi F, Freschi M, Moschini M, Rocchini L, Maccagnano C, Nazareno S, et al. Oncological predictive value of the 2004 World Health Organisation grading classification in primary T1 non-muscle-invasive bladder cancer. A step forward or back? BJU Int 2015;115:267–73.
[8] MacLennan GT, Kirkali Z, Cheng L. Histologic grading of noninvasive papillary urothelial neoplasms. Eur Urol 2007;51:889–97:discussion 97-8.
[9] Cao D, Vollmer RT, Luly J, Jain S, Roytman TM, Ferris CW, et al. Comparison of 2004 and 1973 World Health Organization grading

systems and their relationship to pathologic staging for predicting long-term prognosis in patients with urothelial carcinoma. Urology 2010;76:593–9.
[10] Gontero P, Gillo A, Fiorito C, Oderda M, Pacchioni D, Casetta G, et al. Prognostic factors of 'high-grade' Ta bladder cancers according to the WHO 2004 classification: are these equivalent to 'high-risk' non-muscle-invasive bladder cancer? Urol Int 2014;92:136–42.
[11] Humphrey PA. Urinary bladder pathology 2004: an update. Ann Diagn Pathol 2004;8:380–9.
[12] Sabesan S, Zalcberg J. Telehealth. N Engl J Med 2018;378:402.
[13] Chen Z, Ding W, Xu K, Tan J, Sun C, Gou Y, et al. The 1973 WHO Classification is more suitable than the 2004 WHO Classification for predicting prognosis in non-muscle-invasive bladder cancer. PloS One 2012;7:e47199.
[14] Green DA, Rink M, Xylinas E, Matin SF, Stenzl A, Roupret M, et al. Urothelial carcinoma of the bladder and the upper tract: disparate twins. J Urol 2013;189:1214–21.
[15] Sfakianos JP, Cha EK, Iyer G, Scott SN, Zabor EC, Shah RH, et al. Genomic characterization of upper tract urothelial carcinoma. Eur Urol 2015;68:970–7.
[16] Kochmanski M, Dominowski R, Maciszewski J, Arentowicz S. The influence of biometeorologic conditions on morbidity. Polski Merkuriusz Lekarski 1996;1:147–9.
[17] Bashashati A, Ha G, Tone A, Ding J, Prentice LM, Roth A, et al. Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling. J Pathol 2013;231:21–34.
[18] Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883–92.
[19] McGranahan N, Swanton C. Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. Cancer Cell 2015;27:15–26.
[20] McGranahan N, Swanton C. Heterogeneity and tumor evolution: past, present, and the future. Cell 2017;168:613–28.
[21] Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 2012;62:100–14.
[22] Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol 2018;73:111–22.