SCIENTIFIC ARTICLE

Meta-analysis of global variations in grade of pT1 urothelial bladder cancer and supplementary evaluation of a Sri Lankan cohort

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Urothelial bladder cancer; pT1; tumour grade; reproducibility of results; pathology

Abstract

Introduction

Bladder cancer grading is fraught with ambiguity. We aimed to conduct a meta-analysis of grading of pT1 urothelial cancers and assess histopathology and outcomes in a Sri Lankan pT1 bladder cancer cohort.

Patients and Method

A meta-analysis of grading of pT1 urothelial cancers was conducted as per PRISMA guidelines. A second meta-analysis of the proportion of pTa/NMIBC at disease presentation was conducted to assess impact of delayed presentation on grading. Analysis was supplemented with data from a cohort of Sri Lankan patients.

Results

In the meta-analysis, the overall pooled pT1 HG prevalence was 75.3%[95% CI:68.3%-81.7%]. The pT1 HG prevalence was significantly higher (p=4.916878e-11) among the European, Japanese and Taiwanese studies at 90.1% [95% CI: 85.3%-94.0%] compared to the rest of the countries at 56.1% [95% CI:46.5%-65.4%]. The overall pooled pTa/NMIBC prevalence was 44.2% [95% CI:36.4%-52.1%]. The pTa/NMIBC percentage among Europe, China and Taiwan was 66.9%[95% CI:62.4%-71.2%] and it was 37.6% [95% CI:29.0%-46.6%] in Turkey and other Asian countries indicating a significant difference(P=1.08e-08). In the Sri Lankan cohort of 66 enrolled patients, 31(47%) had pT1, of which 61% were low-grade (LG). The 5-year progression-free survival (PFS) of pT1 was 60.9%. In LG it was 85.7% and 22.2% in high-grade (HG) (P = 0.0006).

Conclusion

There is a global variation of percentages of pT1 LG versus HG disease in bladder cancer specimens at presentation which could be attributed to delay in treatment with stage migration, ethnic variations in tumour biology, and interobserver variability in assigning a grade of tumour, and needs further study.

Introduction

Histopathology is crucial in guiding bladder cancer management. However, grading systems are ambiguous with significant prognostic and management implications.

In 1973 a WHO team of pathologists proposed a three-tier system for urothelial cancers with grading being assigned from the least to the most severe degree as G1/G2/G3[1], based on the severity of anaplasia. With incorporation of the 1997 international society of urological pathology (ISUP) classification in the 2004 WHO publication, pT1 tumours (tumours invading lamina propria) were suggested to be graded as per a two-tier low-grade (LG) and high-grade (HG) system[2]. One of the main intentions of the 2004 classification was to reduce the inter-observer variability and to improve prognostication[3]. The 2016 classification also continued the two-tier LG/HG grading[4]. Despite the European association of urology (EAU) guidelines adopting the 2004/2016 systems, the use of both 1973 and 2004/2016 systems are recommended for non-muscle invasive bladder cancer (NMIBC) in their 2021 updates[5,6].

Both the 1973 and 2004 systems have their weaknesses. The 1973 3-tier system "encourages" more NMIBC patients to be assigned to the middle category (G2)[3]. In the 2004 system, a large number of G2 and all G3 patients are assigned to HG category, which may lead to the overtreatment of many patients.[3]

Many authors from North America and Europe suggest that most pT1 tumours *should* be categorized as HG.[7,8] An analysis of two large national databases from USA

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(N=92,827) of mostly transurethral resection of bladder tumours (TURBT), showed pT1 LG categorization fell with time and was less likely at an academic institution.[8] The percentage of pT1 LG/pT1 total in the two studies was 15.6% and 18.5% in 2014. In two Sri Lankan studies from 2016 and 2020, the percentage of pT1 LG/pT1 total was 70% [9] and 44% [10], being much higher than in the literature from Europe and North America.

The objectives of our study were to assess the global variation in grading of pT1 urothelial cancers, and the proportion of non-invasive papillary carcinoma in non-muscle invasive bladder cancer (pTa/NMIBC) at disease presentation in order to evaluate the possible impact of delays in presentation on the tumor grade. Further we compared the global variation with local data to assess whether similar findings can be seen in Sri Lanka as well.

Patients and Methods

A review was conducted of articles on PUBMED over the last 10 years 2011-2021 by searching on keywords ('bladder cancer' or 'bladder tumor' or 'urothelial cancer' or 'urothelial carcinoma') AND ('T1'), with population-based or institution-based study recruitment, where tumor samples were obtained at TURBT. Specific searches of papers on PUBMED were also done for individual countries (India, Pakistan, Bangladesh, Nepal, Malaysia, South Korea, Egypt, Turkey, China, Iran) on NMIBC instead of pT1. We also analyzed the papers identified in the previous search for the proportion of pTa/NMIBC at presentation. This was to assess the possible impact of treatment delays on grading of pT1 disease. We excluded studies in languages other than English, case reports, letters and grading using the WHO 1973 classification (Figure 1).

The overall prevalence (pooled estimate) of pTa and pT1 HG among the studies was determined by performing a random-effects meta-analysis of proportions using the Der Simoniane Laird model. The number of pTa and pT1 HG patients amongst the total sample in each study was considered for the analysis and inverse variance weighting was used to pool the studies. Cochran Q test and I^2 were used to assess the heterogeneity between the studies. A separate stratified analysis was done after categorising countries based on their geographical distribution and the observed percentages of the LG/HG and pTa/NMIBC ratios. Forest plots were developed to summarize the results of the meta-analysis.

A urothelial bladder cancer cohort who underwent TURBT, were prospectively enrolled, by convenient sampling, from June 2013 to January 2017, from two teaching hospital urology departments of Sri Lanka. All patients provided written informed consent. The histopathology of the TURBT specimens, classified as per the WHO 2004 grading system, and the outcome details were reviewed retrospectively.

Kaplan–Meier survival analysis was used to analyze the cancer-specific survival (CSS) and overall survival (OS). OS was defined as the time from the first TURBT to death from any cause. CSS was defined as the time from the first TURBT to death from causes related to bladder cancer. Disease-free survival was defined as time to tumor progression i.e. clinical, radiological or histopathological evidence of recurrence with stage T2 or more, or metastasis. Survival rates were compared using Kaplan–Meier estimate curves with the log-rank test.

For all statistical tests a significance level of 5% was considered. Analysis was done using R software version 3.6.3.

Ethical approval was obtained from the ethical review committee of the Faculty of Medicine, University of Colombo (EC-12-088 / 19th October, 2012) and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Results

Meta-analysis of pT1 HG and pTa tumours

The PUBMED and GOOGLE scholar review (Figure 1) identified 23 relevant articles which showed pT1 HG percentage (c.f LG) ranging from 80-100% in reports from Europe, Canada, Japan and Taiwan [5, 11-17]. The pT1 HG percentages obtained from China, Egypt, Turkey and Sri Lanka range from 27-82% [Egypt 55-82%[18,19]; China 60-77%[20-22]; Turkey 27-66% [23-26]; Sri Lanka 30-56% [9,10]] (further details in online supplementary information 1). Overall pooled prevalence of pT1 HG among all the studies was 75.3% [95% confidence interval (CI): 68.3% - 81.7%] where the studies showed substantial heterogeneity (I2 = 97.4% [95% CI: 96.8%-97.9%]. A pooled prevalence of pT1 HG among the European, Japanese and Taiwanese studies was 90.1% [95% CI: 85.3% - 94.0%] and the rest of the countries (China, Egypt, Turkey and Sri Lanka) showed a prevalence of 56.1% [95% CI: 46.5% - 65.4%], illustrating a significant difference in the prevalence of pT1 HG between the groups ($P < 0.0001$) (Figure 2). The above categorization of countries into two groups was made arbitrarily by the authors following observation of the disparities in pT1 HG percentages.

In the evaluation of proportion of pTa/NMIBC, European reports showed a range of 50-75%[5,27-29]. Chinese studies also showed a similar percentage of 55-75% [30-32] while reports from Turkey and other Asian countries showed lower percentages of pTa/NMIBC at presentation ranging from 4-

65% (Turkey 30-65%[33-41]; Iran 58%[42]; Malaysia 54%[43]; Nepal 43% [44]; India 47-55%[45-47]; Egypt 3-33%[18,19,45-47]; Pakistan 4%[51]; Sri Lanka 17-47%[9,10,52-54]) (online supplementary information 2 and Figure 3).

Overall pooled prevalence of pTa among all the studies was 44.2% [95% CI: 36.4% - 52.1%] where the studies showed substantial heterogeneity (I2 = 98.9% [95% CI: 98.7% - 99.0%]. A pooled prevalence of pTa among Europe, China and Taiwan was 66.9% [95% CI: 62.4% - 71.2%] and the rest of the countries (Turkey and other Asian countries) showed a prevalence of 37.6% [95% CI: 29.0% - 46.6%], illustrating a significant difference in the prevalence of pTa between the groups (P < 0.0001). The above categorization of countries into two groups was also made arbitrarily by the authors following observation of the disparities in pTa/NMIBC percentages.

Sri Lankan data

Pathological assessment of TURBT specimens of the sixty-six patients enrolled showed 71% (47/66) to be NMIBC. Of this 66% (31/47) were pT1 patients, with low grade seen in 61%(n=19) and high grade in 39% (n=12). The grading was assigned as per the WHO 2004 grading system and the standard criteria used can be seen in selected micrographs from our patients (Figure 4 and 5). The pT1 LG showed better OS and CSS over HG (*P*=0.003 and *P*=0.01 respectively) (Figure 6 and 7). The pT1 tumours showed a 5-year progression-free survival (PFS) of 60.9% (43.9% - 84.5%) where progression was considered as advance in stage to MIBC, diagnosis of metastasis, or death caused by urothelial cancer. The PFS in pT1 LG was higher than pT1 HG (P < 0.0001) where the 5-year PFS for pT1 LG was 85.7% (69.2% - 100.0%) and for pT1 HG 22.2% (6.5% - 75.4%) (Figure 8).

Discussion

The meta-analysis and our study findings show marked regional differences across the globe of LG and HG in pT1 disease in TURBT specimens. Predominant HG allocation of most pT1 disease is seen in studies from Europe, Canada, Japan and Taiwan, and comparatively larger proportions are assigned to LG disease in Asian studies (apart from Japan and Taiwan). Regional differences in the epidemiological pattern of grades of NMIBC have been seen in other studies as well using the 1973, G1-G3 grading system. Wang et al in their EORTC risk table study on a Chinese population identified a low percentage of G1 tumours - 18.6% in the study group; 20.0% in the validation group; 22.9% in the external validation group.[55] This phenomenon was similar in Japanese reports with G1 being 13-24% [56-58] and in Korean patients 22%.[59] This is in contrast to large population studies from Europe where the G1 percentage is higher, 33% [5] and 43%.[60] The above studies support regional and ethnic differences in proportions of lower (G1/LG) and higher (G3/HG) grade tumours at TURBT. Ethnic differences in tumor biology are therefore a possible explanation for the findings of our study and other studies showing regional differences in grading.

In a systematic review of grading classification systems of NMIBC patients undergoing transurethral resection of bladder tumor (TURBT), the EAU Guidelines Panel found the inter-observer reproducibility for the WHO 1973 system as 'poor', with kappa values of 0.003–0.365 and that for the WHO 2004/2016 system as 'poor to fair' (kappa values 0.17–0.516).[3] A single-institution study from the UK on TURBT or biopsy specimens showed that reproducibility of grading utilizing the 2004 system was 'good' (Kappa = 0.69) and for the 1973 system to be 'fair' (Kappa = 0.25).[61] Tosoni et al found that in a single-institution series of TURBT specimens, there was a discrepancy in the grading of 38% of patients evaluated by two uropathologists.[62] In a single-institution USA study of TURBT specimens, reassessment of histopathology by dedicated uropathologists showed a change in the original diagnosis in 27% including a change in grade in 5%; this implied a potential change in treatment in 15% of patients.[63] The evidence from the above studies could imply an interobserver variation to account for the regional differences in grades of the pT1 patients in our meta-analysis.

The grade of the tumor is an important factor in identifying those NMIBC at risk of progression. The EAU guidelines panel systematic review identified progression rates in NMIBC of 3% versus 9% versus 28% in G1 vs G2 vs G3 patients, and 2% versus 4% versus 19% in PUNLMP vs LG vs HG, respectively.[3] Chen et al found 5-year progression-free survival rates in a cohort from China in NMIBC of PUNLMP vs LG vs HG at 100%, 90.9% and 54.8%, respectively.[64] While the above 2 studies as well as other reports found the 1973 system better at predicting progression in NMIBC, both systems have been validated as being a useful prognostic indicator of progression.[3,5,64]

Similarly, our study also shows a statistically significant difference in the 5-year overall, cancer-specific and progression-free survival for the pT1 LG versus HG using the 2004 system, despite the marked differences in the ratio of LG versus HG tumours in comparison to studies from countries in the west. This points towards an actual regional difference in grading rather than a grading difference merely due to inter-observer variability.

Many reports have suggested the superior ability of the WHO 1973 system to predict progression compared to the WHO

2004/2016 system.[3,5,64] In the 2004/2016 classification, essentially 80% or more of pT1 tumours in Europe and North America are classified as HG, making it a single-tier system, thereby reducing the prognostic ability of the WHO 2004/2016 system in pT1 disease within those countries. Cao et al imply that grading is of *relative* importance when classifying pT1 tumours [65]. However treating all HG patients who have similar risk factors, the same as G3 patients, may lead to overtreatment [3]. The larger proportions of LG patients within the pT1 subgroup in China, Egypt, Turkey and Sri Lanka as found in the literature and in our study, may suggest that the 2004/2016 system possibly better prognosticates pT1 patients in these countries compared to western populations.

Stage migration of pTa LG tumours to pT1 due to delays in presentation or diagnosis can also be postulated to account for these findings. Stage migration is possible due to variable delays in treatment in different countries. It is possible that stage migration of the tumours from pTa (majority LG) to pT1 accounts for observed global grade differences in pT1 disease in TURBT. The European and Chinese studies show a higher proportion of pTa/NMIBC in comparison to Turkey, Egypt and other Asian countries e.g. Iran, Malaysia, India, Pakistan, and Sri Lanka. However, in Chinese studies which have a similar proportion of pTa/NMIBC to European studies, the pT1 LG patent number is very much higher than in Europe. So this factor alone may not explain the higher percentage of pT1 LG tumours in China and other Asian regions.

The risk stratification of the EAU guidelines for the management of NMIBC, updated in 2021, is based on the EORTC risk tables [6]. The current guideline has a 4-tiered risk allotment for NMIBC patients, with a new very high-risk group identified. It includes patients based on tumor staging, grading, presence of carcinoma in situ (CIS), and risk[6]. Either the WHO 1973 or the 2004/2016 grading system can be used to stratify the patients, however, the panel recommends the WHO 1973 system if available, due to better prognostic value.[6] The ISUP expert opinion paper based on literature review strongly suggests dividing the T1 HG group into intermediate and high-grade groups based on the WHO 1973 system.[66] These guidelines and recommendations will however depend on the reliability of the assigned grading of the tumor. The regional variations in the grading of pT1 patients may lead to patients being assigned to different risk groups dependent on a contentious grade allocation.

Limitations of our study include small patient numbers in our cohort. However, a similar pattern of tumour grades was demonstrated in previous studies from Sri Lanka and is also seen in many regional Asian studies. In the pooled analysis of the meta-analysis, categorization of data from countries was done arbitrarily following observation of the individual national data. This was with the intention of initial identification of the issues with grading. While our study identifies the issues in tumor grading and postulates possible explanations for the findings, definitive answers for the observations need to be sought by prospective studies with the participation of uropathologists from varying countries to overcome the possible issues due to interobserver variability.

Conclusion

There is gross variation in the percentages of pT1 LG versus HG disease in transurethral resection specimens in different countries from various regions across the globe. European, Canadian, Japanese and Taiwanese studies show a much higher percentage of pT1 HG disease when compared with other Asian studies. While ethnic variations in tumor biology could account for these differences, other factors such as interobserver variability in assigning grade of tumor and delay in treatment with stage migration could also contribute, and need further study

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