Evolution Of Classification Of Bladder (Urothelial) Cancer

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Abstracts: The classification of bladder tumors has undergone a change over the years but still has not achieved success in predicting the behavior. The correct cellular classification of a tumor helps initiate appropriate treatment. Recently functional, genomic and proteomic data have been of help in aiding prognosis and modifying the treatment in many cancers. However, this data is not routinely integrated into the classification, and treatment protocols in bladder carcinoma hinge on grade and depth of invasion. An in depth understanding of the implication of grade, stage, molecular features on survival is necessary to understand the behavior of the tumor. The classification of Urothelial cancer has undergone a lot of change in terminology over the past century but we have still not identified markers (both morphologic and molecular) for preventing recurrences. It is believed that the treatment protocols should be based on a combination of these and we still have to conduct large-scale follow-up studies to identify these parameters. We present here the changes in bladder cancer classifications over the past century and the implications thereof in this review. [Agrawal U NJIRM 2015; 6(6):89-94]

Key Words: Urothelial cancer, classification.

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Introduction: Urothelial (Transitional cell) cancer of Urinary Bladder encompasses the spectrum of non-muscle-invasive (NMIUC), muscle-invasive (MIUC), and metastatic disease with an age-adjusted incidence rate of 21.1 per 100,000 population per year[1]. The extent of disease determines clinical behavior, treatment, and prognosis. The high-grade non-invasive cancers may progress to muscle-invasive tumors or have recurrences in about 30% cases[1]. The standard of care is different in various stages. Classification systems of tumors give an idea of the aggressiveness and prognosis in the patients and are thus useful indicators for clinical management of the patient. As far back as 1921, Broders' classified epitheliomas of the genito-urinary regions including cervix, labia, vagina, urethra, penis, bladder, pelvis of the kidney and ovary as Grades1-4[2]. In his classification he based the grades on the proportion of differentiated epithelium (3/4ths differentiated and 1/4th undifferentiated in Grade 1 to fully undifferentiated in Grade 4). As this classification was universal for all epithelium, be it squamous, columnar or transitional and all organs with epithelial tumors it was not taking into account the depth of invasion of the tumor or the pattern of growth. However, Broder reported that the increasing size of the tumor and grade was found to be associated with poor survival. The microscopic appearance i.e., the grade, does not always conform to the clinical behavior. Hence, a composite reporting including pattern of growth, depth of invasion and morphologic appearance were proposed by pathologists with some advocating the incorporation of clinical staging. Subsequent classifications specifically for Urothelial cancer included the pattern of growth, depth of invasion and grade of tumor. Almost all classifications to date include papillary, solid/infiltrating and mixed patterns of growth and almost invariably the solid/infiltrating pattern of growth was reported to have a worse prognosis[1].

Material and Methods: Extensive literature search was done using various internet search engines to identify review manuscripts as well as guidelines provided by WHO (World Health Organisation), UICC (Union for International Cancer Control) and ISUP (International Society of Urologic Pathologists) on urothelial carcinoma classifications from the earliest classification of Broders' who described epithelial malignancies as epitheliomas. The literature was thoroughly examined to understand the presentation, diagnostic features, tumor stage, management, and outcome of various stages and grades of urothelial carcinoma. The review does not include the various comparative studies for interobserver and intraobserver concordance for the 1972 and 2004 classifications though the conclusions of various observers has been summed up.

Urothelial cancer classifications

The earliest recorded classification of Urinary bladder tumors, proposed by Ash in 1940 classified the most benign appearing papillary tumor as carcinoma because of their great tendency to recur locally[3]. Dukes and Masina classified these tumors into low, average and high grades in 1949[4] and took account of pathological staging which included the depth of tumor invasion into the lamina propria and muscularis

propria. Based on the experience of the Institute of Urology of the University of London the subsequent modification puts more emphasis on clinical staging as pathological "staging" was not of use when only biopsy material was available[5]. In this modified classification system tumors were classified into benign papilloma, well-differentiated TCC with papillary or with solid pattern and anaplastic carcinoma which resembles TCC but with obvious cell aberration and numerous and abnormal mitoses. Wallace (1956) proposed staging into mucosal (T1), muscular (T2), perivesical (T3) and pelvi-fixation (T4)[6]. Subsequently Pugh classified the tumors into 2 grades[7]. The report of these tumors was accompanied by a note on detection of invasion or extension into lymphatics and venules as this was associated with poor prognosis[8]. The clinical staging was incorporated into the report at this time and emphasis was put on clinical assessment of the case. At this point of time multiple classifications were in use and a comparison is presented in Tables 1 & 2. The chief problem appeared to be whether to report depth of invasion in greater detail.

Consensus classifications

UICC (Union for International Cancer Control) led by Mostofi (1960)[12] for the first time attempted to formulate a classification acceptable to an international group. It was adopted by the American Tumor Registry Board and classifies the better differentiated papillary tumors as papillomas. The classification included 3 grades of Transitional cell carcinoma. In 1965 Bergkvist graded papillomas as Transitional cell tumors Grade 0 and Urothelial tumors as Transitional cell carcinoma Grade I-IV[13]. The WHO/UICC (1973) integrated classification disregarded the difference of papillomas and carcinomas and 3 grades (I-III) were proposed[11]. However, not all papillary non-invasive tumors are 'carcinomas' and it triggered the proposal for the 1998 WHO classification. The 1973 classification was also under attack for poorly defined grading criteria resulting in intra and inter-observer variation and it was felt that there was a need for better identification of patients with risk of progression[15].

The International Society of Urologic Pathologists (ISUP) developed the 2004 WHO/ISUP classification[14] which is presently in use and classified non-muscle invasive tumors into Papillary Urothelial Neoplasia of Low Malignant Potential (PUNLMP), Low Grade Papillary Urothelial Carcinoma (LGPUC) and High Grade Papillary Urothelial Carcinoma (HGPUC). Invasive neoplasms were subclassified as Lamina propria invasion and Muscularis propria invasion and graded as low or high grade. Detailed criteria of various preneoplastic conditions and grades in WHO 2004 classification led to more reproducibility. The other advantage of this classification was that the terminology used was consistent with that used in urine cytology and hence facilitated cyto-histologic correlation.

However, reporting of PUNLMP saw both intra and interobserver variability and reproducibility of this grading system was improved by exclusion of PUNLMP. As clinical management of PUNLMP and LGPUC was similar, a 2-grade system was suggested to be more viable by the International Consultation on Urological Diseases (***ICUD***)[16]. The contribution of the 2004 WHO classification was that it created a category of papillary neoplasms associated with negligible risk of progression i.e., PUNLMP, where the patient avoids the label of cancer and its associated psychosocial complications. It also identified a defined category of High grade papillary carcinoma patients who benefit from intravesical therapy (ICUD 2011)[17]. The present classification also recommends grading of tumors with histological heterogeneity into the higher grade. However, those cases in which moderate atypia and increased thickness of cell layer is seen do not appear to fit into either low or high grade. Such cases need clear guidance in quantitative criteria as the absence of clear cut-offs for each grade increase the interobserver variation. An attempt to devise an algorithm has been made by Shim et al and involves scoring of the papillary neoplasms for number of mitoses, cellular thickness and atypia along with MIB1 (proliferation marker) and p53 (tumour protein) indices[18]. However, this is a study limited to a few cases and has to be applied to a larger cohort and checked for agreement. So a revised 2004 with outcome studies is needed to properly classify the non-invasive lesions.

Role of Immunohistochemistry in classification

The role of immunohistochemistry, which is the best known diagnostic adjunct, in Urothelial tumor staging and grading has been considered and molecular studies with whole genome gene expression and subsequent immunohistochemistry for 20 genes have proved helpful in categorizing Urothelial neoplasms into 4 distinct groups[19] : a) Urobasal (Uro) A positive for cytokeratin 5, P-Cadherin, EGFR (epidermal growth

factor receptor confined to basal cells and cell cycle activity (CCNB1) confined to tumor-stroma interface; b) Squamous cell carcinoma like (SCCL) which expresses CK5, CK14, P-cadherin, EGFR and cell-cycle genes throughout the tumor parenchyma; c) Genomically Unstable (GU) type which expressed high ErbB2 and E-cadherin but not CK5, P-cadherin and EGFR; d)Urobasal (Uro) B type which shared features of both Uro A and SCCL like tumors. The three subtypes Urobasal, SCCL and GU showed important prognostic differences.

In addition, molecular classification of non-muscle invasive bladder carcinoma by methylation of tumor suppressor genes identified 3 subgroups of pTa Low-Grade, pT1 Low-Grade, and pT1 High-Grade and TSG methylation also predicted recurrence in non-muscle invasive subgroups[20]. Moreover, molecular classification of bladder carcinoma by workers of MD Anderson suggested that it was similar to breast carcinoma[21]. McConkey and colleagues identified 3 subtypes similar to breast cancer molecular subtypes a) basal subtype of invasive bladder cancer which is aggressive but is vulnerable to chemotherapy; b) a p53-like luminal subtype that's highly resistant to chemotherapy and c) high-grade luminal bladder cancer (similar to luminal B breast cancers) which may be vulnerable to targeted therapies used in those subtypes of breast cancer, including estrogen receptor blockers. It is presumed that pre-treatment analysis may guide the chemotherapy decision.

Immunoscoring for CD markers to identify the type of T-cells present has been recommended for most tumors especially colorectal carcinoma[22]. Infiltration of CD68(+)tumour associated macrophages (TAMs) was found associated with an increased risk of recurrence and poor response to BCG immunotherapy[23]. As a subgroup of Non-muscle invasive Urothelial cancer patients benefit from immunotherapy it may be of value in identifying patients who will respond to immunotherapy. Urothelial cancers evoke different degrees of cellular immunologic response including tumour infiltrating lymphocytes (TILs) and tumour associated macrophages (TAMs). Immunoscoring with CD68 (macrophage marker) and CD8 (T-cell marker) showed that high CD68 to CD8 ratio was associated with poor prognosis[24]. However, best practice recommendations by ISUP (2014) do not find a role for IHC in the distinction of dysplasia versus carcinoma in situ and in the grading of papillary urothelial carcinoma. IHC may have a limited but distinct role in staging of bladder cancer where invasion into muscularis propria is in doubt broad-spectrum cytokeratins (to identify early or obscured invasion) and desmin (distinction of muscle from desmoplasia and to highlight muscle contours for subclassification) may be helpful. However, no prognostic or predictive markers were identified[25].

Classification based management

Due to the heterogeneous outcomes of non-muscle invasive tumors it is difficult to predict the response to therapy. While recurrence is common, progression is rare. The mucosa-confined tumors (pTa) are high grade in 3-18% cases[17] and this determines progression rather than the stage. Hence the WHO 2004 classification which considers both grade and stage for reporting bladder tumors is more informative. Treatment of non-muscle invasive carcinomas (pTa, pT1) is Trans-urethral resection of bladder tumor (TURBT) followed by adjuvant intravesical chemo/immunotherapy and even preemptive cystectomy. Small tumors, <1cm in size, are removed *en bloc* with inclusion of a small part of the muscle wall though experts feel that a previously pTaG1 tumor does not necessitate deep resection. Larger tumors are removed piecemeal along with deep resection including the detrusor muscle and peripheral margins of the tumor. Random biopsies of cystoscopically normal mucosa are taken from the trigone, the bladder dome, the right, left, anterior and posterior bladder walls, and the prostate in men to rule out Carcinoma-in situ (CIS).

As the likelihood of finding CIS in low risk cases such low grade papillary tumors and negative cytology is rare, the random biopsies are not necessary. A second TUR is performed in TaT1 tumors when resection is incomplete i.e., if multifocal or if detrusor muscle is not present in the biopsy or if high grade is reported by the pathologist. The standard of care in high-risk patients with high grade, CIS or positive urine cytology is cystectomy and increases the 5-year survival in these patients. The standard of care for muscle-invasive Urothelial carcinomas (pT2-T4) is radical surgery including bilateral pelvic lymph node dissection and cystoprostatectomy with or without a urethrectomy in male and anterior exenteration including bladder in female[26].

As management of non-muscle invasive cases with CIS and pT1HG (high grade) includes radical surgery to improve overall survival it is necessary to categorize the tumors not just by the depth of invasion and morphologic grade but by biologic behavior.

Table 1: Comparison of depth of invasion in various Urothelial cancer pathological stage classifications

Stage	Wallace[6]	Jewett & Strong[9]	Marshall[10]	WHO/UICC[11]
pTa	Mucosal (T1)		Ca in situ	In situ (PIS)
pT1		Submucosal invasion	Lamina propria invasion	Invasion of stromal cores (P1a)
				Invasion of lamina propria (P1b)
pT2	Muscular(T2)	Invasion into detrusor muscle	Muscle superficial 1/2	Superficial bladder muscle invasion (P2)
			Muscle deep 1/2	Deep bladder muscle invasion (P3)
pT3	Perivesical (T3)	Invasion through detrusor	Perivesical	
pT4	Pelvi-fixation (T4)			Infiltration of adjacent organs (P4)

Table 2: Comparison of morphologic classifications of Urothelial (Transitional Cell) carcinoma over the past decade

Grade	Broder[2]	Ash[3]	Dukes and Masina[4]	Marshall[10]	Mostofi[12]	Bergkvist[13]	WHO/ UICC[11]	WHO/ISU[14]
Grade 1	Grade 1	Transitional cell carcinoma grade 1	Benign papilloma	Papilloma	Papilloma	Transitional cell tumor grade 0	Grade I	PUNLMP
						Transitional cell carcinoma grade 1		
Grade 2	Grade 2	Transitional cell carcinoma grade II	Differentiated carcinoma	Low grade carcinoma	Transitional cell carcinoma grade 1	Transitional cell carcinoma grade II	Grade II	Low Grade Urothelial carcinoma
Grade 3	Grade 3	Transitional cell carcinoma grade III	Anaplastic carcinoma	High Grade carcinoma	Transitional cell carcinoma grade II	Transitional cell carcinoma grade III	Grade III	High Grade Urothelial carcinoma
Grade 4	Grade 4	Transitional cell carcinoma grade IV			Transitional cell carcinoma grade III	Transitional cell carcinoma grade IV		

Conclusion: At present the classification of patients into 2 grades (low and high) and 2 stages (muscle invasive and non-invasive) appears to be guiding treatment. The role of cell cycle and proliferation markers has been already highlighted by molecular studies and they have been found to have a role in prognosis as well as modulation of chemotherapy and also in identifying patients likely to be responsive to

chemotherapy. Considering the importance of intravesical immunotherapy (with BCG) in preventing recurrences in Non-muscle invasive tumors, long-term outcome studies of the role of immunoscoring in predicting response to immunotherapy may be beneficial. This will help to identify markers whose incorporation into the well-established morphologic classifications can help in better clinical management of Urothelial cancer patients.

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