

# The pathology of bladder cancer: an update on selected issues

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## OBJECTIVE

To achieve a closer relationship between urologists and pathologists and to use a common language and identical objectives in the pathology of bladder cancer.

## METHODS AND RESULTS

Special emphasis was given to an analysis of the new World Health Organization (WHO)

grading system, to the interpretation of the last Tumour-Nodes-Metastasis staging rules, and to identifying new markers of prognostic significance in clinical practice. A consensus was achieved on the main points.

## CONCLUSIONS

The 2004 WHO grading system must become acceptable to clinicians, perhaps by a minimal modification of the present terminology.

Simple transurethral resection-biopsy should be expressed in terms of clinical rather than pathological staging. Although there are substantial improvements, no new markers can be recommended for routine use in histopathology at present.

## KEYWORDS

bladder cancer, staging, grading, markers

## INTRODUCTION

The Uro-pathology Working Group (European Society of Pathology) and the European Society of Uro-pathology met in Palermo, on 18 June 2005, for a workshop held during the 78th Congress of the Italian Society of Urology. In this paper we summarize the discussions and conclusions of the bladder tumour subcommittee.

In a previous meeting, this subcommittee discussed what the pathologist requires from the urologist regarding urothelial tumours [1]. During this meeting, attention was given to additional issues, e.g. the need: (a) for both disciplines to adopt the same language and to avoid misinterpretation of data, with special reference to stage and grade; (b) to use a second staging transurethral resection (TUR) in superficial high-grade tumours; (c) to obtain and examine multiple biopsies from the normal-looking mucosa ('mapping'); (d) to submit samples from the prostatic urethra if total cystectomy is envisaged; and (e) to identify prognostic biomarkers beyond staging and grading that can provide more precise data. Therefore immunohistochemical techniques, chromosome analysis, genomics, proteomics and other markers received particular attention, and were widely discussed among pathologists and urologists.

This paper summarizes the conclusions reached by the bladder tumour subcommittee.

## TUMOUR STAGING

The TNM classification of malignant tumours is now universally adopted; it is revised every 5 years, and the latest edition was published in 2002 [2]. There is controversy about the proper way to classify superficial papillary tumours removed by TUR. They are classified as Ta and T1 by some, who apply the clinical classification, whereas others apply the pathological classification (pTa and pT1) for the same TUR material. The description of the local staging for superficial papillary bladder tumours under the category pT seems to be favoured by pathologists rather than by clinicians. In any case, there is great confusion as to the proper terminology to be adopted in such cases, even among editors of medical journals.

In the panel, a few considerations were proposed. According to the original booklet of the TNM classification in 1987 (very minimal changes were introduced in the subsequent editions, including the last, published in 2002 [3]), the general rules of TNM system, applicable to all sites, are as follows: (a) All

cases should be confirmed microscopically; (b) for assessing local extension, the clinical classification (T stage) is based on evidence acquired before treatment. Such evidence arises from physical examination, imaging, endoscopy, biopsy, surgical exploration and other relevant examinations; (c) pathological classification (after surgery, histopathological classification = pT) is based on the evidence acquired before treatment, supplemented or modified by the additional evidence acquired from surgery and from pathological examination. The pathological assessment of the primary tumour entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category. The last sentence represented a substantial change in the fourth edition compared to the previous ones. In the specific section devoted to the urinary bladder, it is emphasized again that for the assessment of clinical categories, a biopsy is mandatory.

Therefore, the opinion that the pT category is to be applied whenever a histopathology report is available cannot be accepted, because a biopsy is mandatory in every case. The controversy arises about the dilemma of whether a TUR specimen can be considered merely as a biopsy or as a surgical procedure 'adequate to evaluate the highest pT category'. For small, pedunculated papillary lesion it is

likely that, in the hands of an experienced surgeon, the biopsy corresponds to a complete removal of the tumour. Only in such ideal cases does the procedure provide sufficient evidence to evaluate the highest pT category. The situation becomes more critical for tumours showing invasion of the lamina propria (T1), especially those of high grade. The likelihood of understaging such cases is very high, approaching 30–50% in some series. The need for a repeat TUR for such indications will be discussed later in this report.

Therefore, if the pathological staging is meant to assess the real local extension of the tumour, simple TUR does not appear to provide adequate material and there is a prevalent opinion among urologists that the pT category should be applied, as a rule, only to total cystectomy or other surgical specimens containing the whole thickness of the bladder wall.

In any case, the use of a uniform language appears desirable. In a recent book [4], different terminology was originally proposed in the various chapters by various authors. The same lesions were described as Ta and T1, or pT and pT1, according to personal preference. It was agreed with the editors to use a uniform language, by adopting the clinical, rather than the pathological, classification for superficial tumours throughout the text.

It is obvious that for deeply infiltrating tumours a TUR-biopsy is seldom curative and fully adequate for a proper pathological staging.

## TUMOUR GRADING

### THE RATIONALE FOR A NEW GRADING SYSTEM

The prognostic significance of grading is well known. Indeed, grading is an essential component of factors predicting the recurrence and progression of bladder tumours [5,6]. The 1973 WHO grading system has been used for several decades [7]; it includes papilloma and three grades of urothelial carcinoma, based on the worst grade present. Grade 1 (G1) was defined as well differentiated papillary urothelial carcinoma, G2 as moderately differentiated and G3 as poorly differentiated carcinoma.

The discrimination among these three grades is made by the pathologist, considering the degree of architectural and cytological abnormalities of the tumours. A detailed description of the criteria used to define differentiation and the distribution of cases among the three grades was reported in a recent review by Montironi *et al.* [8]. Although this classification was widely adopted by clinicians and pathologists, it presented a few limitations and disadvantages. The main objections were:

- The primary G1 urothelial tumours are defined as carcinomas, despite, as a rule, not behaving as malignant tumours, not metastasising, having a great capacity for recurrence but a low potential for progression and death.
- There was a tendency to classify as G1 only the very well differentiated tumours, and as G3 the very poorly differentiated ones, combining into the G2 category all the other cases (in some reported series the G2 tumours represent up to 65% of cases). Therefore, tumours with varying degrees of differentiation were classified as G2, so that a subdivision of such cases into G2A and G2B was suggested [9].
- There was some disagreement between the reports by peripheral and referee pathologists in multicentre international trials, indicating that the assignment of grade was influenced, to some degree, by subjective rather than by objective criteria.

For these reasons attempts were made to obtain greater reproducibility and accuracy for the grading of urothelial neoplasms.

### THE NEW INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY (ISUP)-WHO GRADING SYSTEM

In 1998 the ISUP introduced a new classification, which is now adopted and recognized as the 2004 WHO grading system [10]. The new classification applies to papillary noninvasive (Ta) urothelial neoplasms, and distinguishes between papilloma, inverted papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low- and high-grade papillary urothelial carcinoma (L and HGPUC). Two main issues remain controversial after the introduction of the 2004 WHO grading system: the adequacy and clinical significance of PUNLMP; and the therapeutic approach for HGPUC, a category including some previously G2 and G3

tumours. The term PUNLMP was introduced to replace G1 TCC (1973 WHO), thereby avoiding the term 'carcinoma' for these lesions.

However, there is no true correspondence among both grading categories [11]. Low-grade carcinoma corresponds to some G1 and G2 tumours, and high-grade carcinoma includes some G2 and all G3 TCC. Despite several years having elapsed since its introduction, it became clear that even in 2005, the new classification has not yet met with universal consensus and has not been widely adopted.

One of the main criticisms is of the new term PUNLMP, which is too long if used in full, too cumbersome and difficult to pronounce if the acronym is adopted and, last but not least, it represents a potential cause of anxiety for the patient. It is true that the term carcinoma is avoided, but the term malignancy is introduced, which, even if defined as of low potential, might be a cause of greater concern than the scientific term 'carcinoma'.

In terms of clinical significance, data from available clinical trials suggest a recurrence rate, stage progression and cancer death for PUNLMP of 38%, 3.3% and 1.3%, respectively. By contrast, the reported tumour recurrence, stage progression and cancer-related death rates are 50%, 10% and 4.5% for LGPUC. It seems therefore that PUNLMP has a much less aggressive behaviour than noninvasive LGPUC. Although these findings suggest some clinical value for the PUNLMP concept, it is considered at present that additional studies are needed to ascertain whether its introduction has added clinically relevant prognostic value.

HGPUC, as defined by the 2004 WHO classification, is a more heterogeneous group than the former G3 tumours, as it results from previous G2 and all G3 cases. At present there is limited information on how to treat these patients. It seems that this group of tumours is aggressive, with a level of molecular alterations similar to invasively growing tumours. Although recurrence and stage-progression rates for cohorts with HGPUC are slightly lower than the corresponding rates for TaG3 tumours (1973 WHO), this difference does not yet justify a change in the follow-up regimen for these high-risk lesions; however, clinical trials on this issue are lacking at present.

On May 11–12, 2001, an International Consultation on the diagnosis of noninvasive urothelial neoplasms was held in Ancona, Italy, under the leadership of Prof Rodolfo Montironi. A full report of this meeting was published in the bulletin of a North-Italian Uro-Oncological Working Group [12]. It was summarized in subsequent papers [13,14] that also cover the topic of pre-neoplastic lesions, which will not be discussed here. The participants in this International Consultation, which included some of the present authors, concluded that the new schemes had resulted in a marked variation in interpretation and definition, leading to confusion and frustration among pathologists and clinicians. Most participants in the Ancona meeting suggested a revision and a 'telescopic ramification' of the 1973 WHO classification, rather than its complete abandonment. A few participants, from various disciplines and different parts of the world, recommended that both classifications should be used by pathologists in their reports, with the double advantage to make clinicians accustomed to the new classification, and to allow validation of the new scheme in terms of reproducibility and prognostic value [1,14].

Despite these recommendation, such a double report is seldom used and, in the aforementioned Italian 'Suggestions for guidelines in bladder cancer' published in 2005 [4], the new classification was used only in the chapter dealing with pathology, whereas the G1–3 classification was uniformly adopted in all the other chapters dealing with diagnosis, surgery, chemotherapy and radiotherapy. This is easy to understand whenever the results of older trials were reported, but it also confirms a definite resistance from clinicians to use the new classification.

At the Palermo meeting, most panellists suggested that double reporting should be continued for at least another 2 years, whereas one of the present authors opined that the new WHO classification should be adopted with no further delay and prospectively. Obviously, the old grading system will continue to be used for the retrospective analysis of studies implemented before the new classification was introduced.

A few suggestions were made to avoid the term PUNLMP and its full wording. The same

category of tumours might be termed Ga urothelial neoplasms, thereby avoiding to mention either carcinoma or malignancy. The category Ga for grading would parallel the category Ta used for staging, indicating in both cases tumours of low malignant potential. An alternative term might be 'papillary urothelial dysplasia', as suggested by Montironi *et al.* in 1998 [15]. The new terms LGUC and HGUC can be applied also to solid, infiltrating urothelial cancer.

### OTHER ISSUES ABOUT BIOPSY

It was considered that additional resection of the bladder base after a previous TUR provides clinically useful information on tumour extension. Also, it was felt that all hyperaemic or velvety areas of urothelium are to be sampled to exclude carcinoma *in situ* (CIS). Random mucosal biopsies are commonly taken from macroscopically normal urothelium distant from the tumour site, to determine the extent of involvement. Ideally, random samples should be obtained from predetermined sites in four vesical quadrants. Some urologists also submit biopsy specimens of the urethra to assess other areas of the urothelium, particularly in patients with HGPUC or CIS.

There was agreement that multiple random biopsies (so-called 'bladder mapping') is no longer necessary in TaGa cases, especially in those with additional good prognostic factors (single, papillary, primary tumours), as shown by the European Organisation for Research and Treatment of Cancer Urological Group [16]. Mapping is still indicated in T1 LG and all HG tumours [17,18]. The value of deep biopsy of the prostatic urethra if subsequent cystectomy is contemplated is still open to debate.

A repeat biopsy for T1 LG or HG is now considered mandatory by most authorities, considering the high detection of residual tumour in the detrusor muscle after repeat TUR [19,20,21].

### THE SEARCH FOR NEW MARKERS

#### PROGNOSTIC MARKERS

The last question was about the possibility of increasing the predictive value of staging, grading and the other classical prognostic

factors [5] by adding to the routine any new histochemical or biomolecular techniques, seeking new markers of independent prognostic value on multivariate analysis.

The topic was extensively reviewed in three reports [22–24]. Two main fields are of urological importance, i.e. prognostic markers in superficial (Ta/T1) bladder tumours, and markers potentially helpful in selecting the best possible treatment for patients with invasive bladder cancer; and the clinical significance of studies using DNA array technology. It is hoped that this information can guide clinicians to predict the response to pre-surgical systemic chemotherapy, irradiation or other treatments.

For prognostic markers in stage Ta/T1 tumours, many new markers have been investigated in recent years. Although none of them can be recommended at present for routine use, these studies represent a substantial improvement in knowledge of the disease. It is considered that p53 and the tumour-proliferation index are the most promising immunohistochemical markers. However, after extensive investigation on the prognostic role of p53 during the last decade, the evidence is insufficient to conclude whether changes in p53 are valid markers of outcome in this subset of bladder tumours. For tumour proliferation, markers such as Ki-67 yield more promising results. Increasing evidence suggests that the increasing proliferation rate in bladder tumours can be used to define more objectively the pathological grade of bladder tumours. Indeed, a significant increase in proliferation rate in all categories of the 2004 WHO grading system can objectively establish the risk categories. However, the use of the Ki-67 proliferation index for the prognosis of bladder cancer awaits validation in clinically prospective studies.

Another relevant issue actively under investigation is the question of whether presently available biomarkers can guide uro-oncologists to apply pre-surgical systemic chemotherapy. On this point, a few clinical trials are ongoing with various chemotherapeutic regimens, mainly using p53, epidermal growth factor receptor, tumour proliferation rate, p16, pRb or HER2/neu. These studies are best considered as promising research investigations, but none of them can be recommended at present for routine use.

Concerning the use of DNA arrays as prognosticators in bladder cancer, it was felt that studies at present are limited, but some reports show >70% correct classification of bladder tumours for prognostic groups of patients, and therefore it should be considered as a promising research tool.

### RECENT ISSUES IN MOLECULAR PATHOGENESIS OF BLADDER CANCER

The reader is referred to the reviews cited above [22–24] for an extensive bibliography. p53, Ki-67, MIB1 labelling index, many growth factors, DNA ploidy, telomerase, and various of markers have been studied and found to be of some prognostic relevance. However, none of them can be recommended at present for routine use.

Recent advances in the understanding of the pathogenesis of bladder cancer, such as mutations of the fibroblast growth factor receptor-3 (FGFR-3) and HRAS genes, and deletions of several regions on chromosome 9 (not only in developed tumours but also in adjacent 'normal looking' urothelium) might define a low-risk pathway for bladder tumours and represent future therapeutic targets.

### INTERFERENCE WITH ADDITIONAL METABOLIC PATHWAYS

The receptor tyrosine kinase (RTK)-Ras pathway, deletion of chromosome 9, and mutation of FGFR-3 and HRAS genes are further promising avenues of research of potential prognostic value.

Superficial (stage Ta or T1) bladder tumours have at least two pathways for development and progression that might explain the differences in the invasive and metastatic potential of the disease among different cases. Activation of RTK-Ras pathway and deletion of chromosome 9 are mainly responsible for the early development of papillary Ta superficial bladder tumours, which also includes mutation of FGFR-3 in 60–70%, and of HRAS in 30–40% of cases. Partial or total deletion of chromosome 9 occurs in urothelial hyperplasia and low-grade papillary Ta tumours. Both 9q and 9p losses are involved in the development of these neoplastic lesions. Indeed, a tumour-suppressor gene might be located in the region at 9q32–33 (*DBCCR1*). It was also

suggested that another tumour suppressor-gene is located in the 9p21 region in the *INK4A/ARF* locus, because the region encodes both p16 and p14. Homozygous deletion of this region down-regulates both the retinoblastoma (RB) and p53 pathways, which arrest cell-cycle progression. Furthermore, homozygous deletion at the *INK4A/ARF* locus is associated with superficial cancer having recurrent tumours that are larger and of higher grade. Although chromosome 9 deletions were initially indicated to be early events in the development of low-grade Ta bladder tumours, they were subsequently revealed to participate in the development of high-grade cancer and, sometimes, of dysplasia and CIS.

### INACTIVATION OF p53 AND RB FUNCTIONS

Although chromosome 9 deletions might be partly involved in the development of high-grade Ta or T1 bladder cancer and CIS, the pivotal pathway is the inactivation of both p53 and RB functions. The inactivation of the p53 function is shown by mutation of *TP53* or homozygous deletion of p14. Lack of RB gene expression or hyperphosphorylated pRB protein may result in a dysfunctional RB gene. Thus, both the p53 and RB dysfunctions are simultaneously found in more than half of high-grade T1 bladder cancers. Activation of the RTK-Ras pathway and deletion of chromosome 9 might be responsible for the development of low-grade Ta disease. The deletion of 9p might be involved in the development of high-grade Ta disease. For the progression of Ta disease or CIS to T1, functional defects of the p53 and/or RB pathways might be required.

### CONCLUSIONS AND RECOMMENDATIONS

- Use clinical stage (Ta or T1) in superficial bladder tumours instead of pathological stage (pTa or pT1).
- Superficial low-grade papillary tumours and UC represent a different disease, both clinically and pathologically. Therefore the term carcinoma should be avoided for the former lesions.
- The introduction of the 2004 grading system for noninvasive (Ta) bladder tumours (papilloma, inverted papilloma, PUNLMP, low-grade or high-grade carcinoma) is encouraged. It is suggested that a new term (Ga urothelial neoplasms) might be used instead of PUNLMP and its expansion.

- The use of 2004 WHO grading in stage T1 tumours (low-grade or high-grade) is also encouraged.
- The 1973 WHO grading system should also be mentioned in the pathology report until the 2004 WHO grading system is fully validated.
- As HGPEC (2004 WHO) shows slightly lower recurrence and stage progression rates than corresponding rates for TaG3 tumours (1973 WHO), this difference does not justify a change in the follow-up regimen for these high-risk lesions.
- Despite considerable advances in the search for valid prognostic biomarkers, at the protein or genetic level in bladder cancer, none of them can be recommended at present for routine use.
- Biomarkers for the response to systemic chemotherapy in invasive bladder cancer should be a priority in bladder cancer research.

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### CONFLICT OF INTEREST

None declared.

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e-mail: michpav@tin.it
- Abbreviations:** TUR, transurethral resection; ISUP, International Society of Urological Pathology; PUNLMP, papillary urothelial neoplasm of low malignant potential; (L)HGP(UC), (low-) high-grade papillary (urothelial carcinoma); CIS, carcinoma *in situ*; FGFR-3, fibroblast growth factor receptor-3; RTK, receptor tyrosine kinase; RB, retinoblastoma.