Recent advances in the management of superficial bladder tumors

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Superficial bladder tumors are by far the most common form of bladder cancer managed by practicing urologists. Indeed up to 75% of initial tumors fall in this category and because of the high recurrence rate, superficial tumors represent over 90% of tumor events being treated. New diagnostic methods have been developed to improve the sensitivity of tumor detection of both cystoscopy and urinary cytology. Risk stratification of patients based on simple clinical parameters provides new opportunities for adapting monitoring strategies as well as providing a rationale for the use of intravesical chemotherapy and immunotherapy. Finally, recent pathological substratification of stage T1 grade 3 may allow a stepwise approach to the management of this high risk tumor. Collectively, all these advances bring us a stepforward in tailoring the management of superficial bladder tumor patients by minimizing the burden of unnecessary investigations and treatments while safely identifying those patients with high risk disease that deserve more aggressive treatment.

Key Words: bladder cancer, urinary cytology, bladder tumor markers, management, ImmunoCyt

Improved diagnosis and monitoring

Cystoscopy has always been considered the gold standard method for the diagnosis of new or recurrent bladder tumors. However, until recently, limited information existed on the true sensitivity and specificity of this diagnostic tool. A French study of diagnostic tests performed in 10 different centers using bladder biopsy as the gold standard, showed cystoscopy to be at best 90% sensitive and specific. Indeed, up to 10% of lesions interpreted as bladder tumors were benign on biopsy while a similar percentage of false negative cystoscopies were positive on biopsy.[1]

Fluorescence endoscopy using 5-Aminolevulinic acid (ALA) is a developing technology designed to enhance the sensitivity of cystoscopy. The technique involves the instillation of 1.5 g of 5-ALA in 50 ml of $NaHPO_4$ intravesically 2 1/2 hours before cystoscopy performed with incoherent (non laser) blue light illumination. Zaak et al. recently reported on 1012 fluorescence cystoscopies showing detection of 34% more bladder tumors missed by standard cystoscopy.[2] Moreover, 39% of the non-visible lesions were high grade. This technique also appears to improve the

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TABLE 1. **Metaanalysis of diagnostic tests**

Tests	NB studies	Nb patients	Sensitivity	Specificity
Cytology[6,8,9,29,31-38]	14	1383	38%	93%
BTA stat[31-38]	10	1366	66%	72%
BTA trak[29,33,40,44,45]	5	566	67%	84%
NMP22 [29,30,32-34,41-44]	9	595	66%	77%
ImmunoCyt[1,6,8,9,41]	5	1493	90%	72%

quality of transurethral resection of bladder tumors as shown in two randomized studies. In the first, reported by Riedl et al, 102 patients were randomized to white light (51) versus 5-ALA fluorescence TUR (51).[3] The recurrence rate at a second look TUR performed few months after initial resection showed recurrence in 20/51 (39%) of the white light compared to 8/51 (16%) of the 5-ALA TUR (p=0.005). In another study reported by Filbeck at the AUA 2001, a similar design was used in 191 TUR patients followed for a median of 21 months.[4] Recurrence rate was 26% in 103 white light TUR patients compared to 11% in 88 5-ALA TUR (p=0.009). This technique is likely to become an important adjunct to our diagnostic armamentarium.

Urinary cytology is recommended in diagnostic guidelines mostly for its ability to detect cancers non visible at cystoscopy located either in the bladder or in the upper urinary tract and the prostate. Urinary cytology in most studies has shown a very high specificity and positive predictive value. When obvious cancer cells are identified by the pathologist, cancer will be found either immediately or on follow-up and usually will be of high grade.[5] However, urinary cytology lacks sensitivity particularly for the detection of low grade low stage tumors due to inherent limitation of morphological criteria to distinguish low grade tumor cells from normal urothelial cells. Urine tests based on detection of proteins such as BTA stat and BTA tract as well as NMP22 have shown higher sensitivity than urinary cytology in several trials (Table 1). However, the specificity of these tests is significantly lower than urinary cytology and thus cannot replace its clinical utility. On the other hand, the average sensitivity observed in numerous studies is between 65% and 70%, a level that is considered not sufficient to decrease the need of invasive cystoscopies. We developed the ImmunoCyt test as an adjunct to urinary cytology following the concept of immunopathology used to improve diagnostic accuracy in other disease states. ImmunoCyt test is based on a cocktail of fluorescent antibodies against tumor antigens particularly expressed in low grade tumors that can be applied on the same slides used for urinary cytology. In the initial studies performed in several Canadian centers but using one central laboratory, the overall sensitivity of urinary cytology combined with ImmunoCyt reached 96%.[6] Several other studies have shown overall sensitivity varying from 80% to 100% with a cumulative sensitivity of 90% in 1493 cases studied.[1,6-8] As shown in Table 2, while urinary cytology had a sensitivity of 70% on the average for the detection of 25 cumulative carcinoma in situ lesions, the addition of ImmunoCyt improved sensitivity to 100%. Similarly, the incorporation of ImmunoCyt in the urinary cytology technique improved detection of 160 grade 3 tumors from 75% to 94% suggesting that a negative combined result provide a very high negative predictive value for high grade lesions. Moreover, ImmunoCyt also improved the sensitivity of detection of low grade low stage tumors from a 50% range to 90%. Finally, Lodde et al. recently showed that the combination of ImmunoCyt and urinary cytology were very sensitive and specific for the detection of upper urinary tract tumors in a study of 37 patients.[9] Monitoring of the upper tract is of particular importance in patients with

TABLE 2. **Sensitivity of urine cytology alone or combined with ImmunoCyt according to stage and grade**

Tumors	Numbers	Urinary cytology	ImmunoCyt + urinary cytology
Ta	247	42%	87%
T1	105	68%	96%
T2+	66	77%	91%
TIS	25	70%	100%
Grade 1	111	24%	82%
Grade 2	167	55%	93%
Grade 3	160	75%	94%

TABLE 3. **Risk of recurrence and progression after initial bladder tumor**

	Quebec Study (Allard et al.[11])				
Parmar[12] criteria	**Number (%)**	**pT1G3 (%)**	**3 yr Progr. (%)**	**Recurrence (%) 1 year**	**2 years**
Low (S, C-)	184 (59)	6	1	22	39
Intermediate (M, C-, or S, C+)	99 (32)	12	6	52	63
High (M, C+)	30 (9)	17	10	73	77

S: single; M: multiple; C-: negative cystoscopy at 3 months; C+: positive cystoscopy at 3 months

high risk superficial bladder tumors who have been reported to develop urinary tract TCC in up to 29% of cases over a fifteen year follow-up.[10]

Management according to risk categories

Several studies over the last two decades have shown repeatedly that grade, stage T1 versus Ta, size larger than 3 cm, and multifocal tumors are independent predictors of high risk of recurrence.[11] However, the number of tumors is the most important prognostic factor of recurrence at 3 months and the recurrence at 3 months is also the best predictor of further recurrence. Based on these observations, a risk stratification using the two simple clinical findings of number of tumors at TUR and bladder status at first follow-up cystoscopy after 3 months was proposed by Parmar et al.[12] Applying these criteria to a population of patients with superficial papillary tumors at first diagnosis, we could identify a low risk category representing 60% of patients that have a single tumor at TUR and negative cystoscopy at 3 months (Table 3).[11] The yearly recurrence rate is approximately 20% with almost no cancer progression over a three-year follow-up. The intermediate risk category which represents an additional 30% of patients have a recurrence of 50% in the first year and an additional 10% in the second year with a progression rate of 6% over 3 years. They are those patients with either multiple tumors at TUR and negative first cystoscopy (C-) or single tumor at TUR and recurrence at 3 months (C+). Finally, high risk patients representing only 10% of the population are those with both multiple tumors and positive cystoscopy at 3 months. These patients will almost universally recur and the progression at 3 years is more than 10%. The grade 3 cancers, however, represent a high risk group which often present as carcinoma in situ or superficially invasive T1 tumors and have a higher progression rate. Thus, in our risk classification, grade 3 tumors are considered high risk irrespective of the number at TUR and the status of their follow-up cystoscopy.

Follow-up strategies

Using this stratification, the group of Marberger in Vienna investigated different follow-up strategies as illustrated in Figure 1. Low risk patients can be followed with ImmunoCyt and cytology at 3 or 6 months interval with a cystoscopy when the tests are positive or every 12 months for those with negative tests. For intermediate group patients, ImmunoCyt

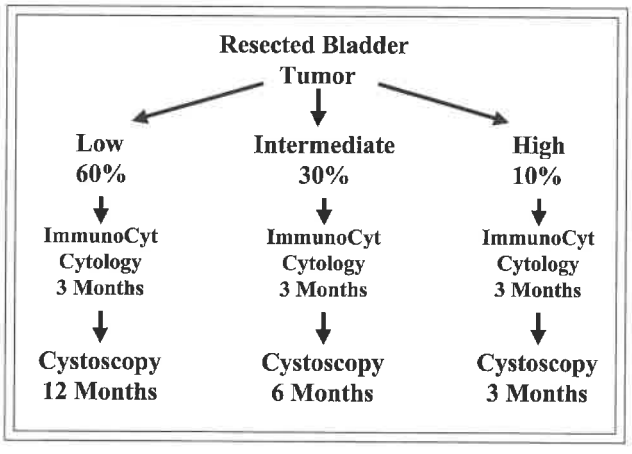

Figure 1. Proposed follow-up strategies according to risk of recurrence and progression. The percentages indicate the proportion of patients.

and cytology should be performed every 3 months with cystoscopy every 6 months if negative. Finally, for the high risk group, both ImmunoCyt and cytology, and cystoscopy are performed every 3 months to minimize the risk of missing high risk recurrences more likely to progress rapidly. Using this suggested protocol for the follow-up of 327 patients, they estimated that 886 cystoscopies could be avoided over one year. Only nine tumors, five pTa grade 1 and four pTa G2 all <1 cm, would have been detected with a delay of 6 months at most (Marberger's presentation at the EAU 2001). We have been following a similar strategy for the last 2 years which has resulted in a 40% reduction in the number of cystoscopies and a good patient compliance. Although urologists from UK and Sweden have proposed yearly cystoscopy without any safety net, it is our opinion that patient compliance is improved if non invasive testing is performed at more regular interval. Nam et al. have estimated the pharmacoeconomic of using non invasive detection tests and showed it to be cost effective.[13]

Intravesical therapies

Another significant advance of the last decade has been the identification of intravesical therapy to reduce recurrence and even treat high grade lesions. The Canadian discovery of the efficacy of the Bacillus Calmette-Guerin to treat carcinoma *in situ* by Morales et al. has been widely reproduced in several clinical trials around the world.[14] BCG therapy is the most effective method to treat high risk lesions and has been shown superior to intravesical chemotherapy with Adriamycin or Mitomycin C in several randomized trials.[15-18] However, intravesical BCG is associated with significant toxicitiy and morbidity and should in our view be reserved to the high risk patients. The use of a single intravesical instillation of chemotherapy immediately after TUR of bladder tumor has been extensively studied in Europe. Oesterlinck first reported in 1993 results of a randomized EORTC trial in 431 low risk tumors and showed a 50% reduction of recurrence with the use of Epirubicin compared to water instillation.[19] Tolley et al. reported similar findings with single instillation of Mitomycin C compared to water and also showed a lack of improvement by multiple weekly instillations compared to the single instillation immediately after TUR.[20] Bouffioux et al. also found no benefit of maintenance therapy with Adriamycin or Mitomycin C over single instillation alone.[21] The mechanism of action of this treatment may be due on one hand to the prevention of tumor implantation at the time of TUR. However, Propert et al. clearly demonstrated the efficacy of Epirubicin at eliminating 46% of 1 cm marker tumors left purposely at TUR in patients randomized to single instillation of Epirubicin or water.[22]

Based on the above findings, most European urologists will use single instillation chemotherapy in every patient after TUR. However, for cost consideration, we have adopted a treatment strategy that call upon the risk categories described above (Figure 2). In patients with a single initial tumor or recurrence more than 18 months after initial TUR, no immediate therapy is performed. Single dose Mytomicyn C or Adriamycin at the time of TUR is used for those patients with recurrence less than 18 months after TUR and/or multiple tumors. In all grade 3 superficial tumors (Ta, T1 or TIS) and in patients recurring despite single instillation, BCG intravesical therapy is our preferred treatment.

Patients with tumor recurrence after BCG intravesical therapy represent a significant challenge. Radical cystectomy is the safest approach although clearly some patients with carcinoma *in situ* refractory to BCG may experience a long evolution without progression. The use of p53 immunostaining as a prognostic marker offers in our opinion a way to sort out those patients that may benefit from further conservative treatments. Although not predictive of initial response to BCG therapy, p53 immunostaining of recurrent tumors after BCG therapy showed that positive tumors progressed rapidly and almost universally as compared to a low 15% risk of progression in patients with negative tumors.[23] New therapies such as Valrubicin[24] or the use of Interferon-

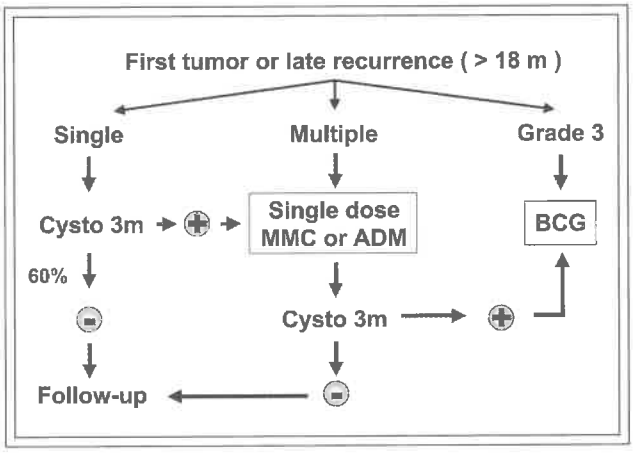

Figure 2. Algorithm for intravesical therapy after TUR of superficial bladder tumor.

alpha combined with low dose BCG[25] offer additional opportunities for the low risk patients. On the other hand, we strongly recommend radical cystectomy for those patients with p53 recurrent tumors after BCG therapy for high risk superficial disease.

Management of T1 grade 3 bladder cancer

T1 G3 bladder tumors represent less than 10% of cases seen in routine urology practice and are a very heterogenous group of tumors. Several studies have shown a tendency of over staging by primary pathologists. Indeed, an EORTC study showed that of 96 tumors classified as T1 by local pathologists, 53% were downstaged to Ta tumors by central review.[19] Similarly, a Swiss study of 235 tumors classified as T1 locally showed 34% downstaging to Ta tumors by central review.[26] Clearly, a reevaluation of pathology slides should be the first critical step in the management of T1 G3 patients.

Another important consideration is the tendency for urologists to understage T1 G3 tumors. Indeed, re-TUR of T1 G3 within 2-3 weeks will upstage 30% to 40% of tumors. The latter observation has led several urology schools to recommend radical cystectomy as the best option for T1 G3 cancers. Although immediate cystectomy may represent the best chance of cure in those patients at high risk for cancer progression, it is an over treatment for almost 70% of patients with an associated risk of morbidity and mortality. To resolve the dilemma between conservative and aggressive management of these tumors, it is important to recognize the source of cancer progression. Risk of progression from T1 G3 will come from one or more of the following: unrecognized muscle-invasive cancer, invasive recurrence from associated carcinoma *in situ*, systemic progression from existing lymph node metastases (present in approximately 5% of cases) and/or uppertract tumors that will develop in 15% of patients over long follow-up.[10]

Substratification of T1 G3 tumors offers new opportunities for a stepwise approach to the problem.[27] The depth of invasion above or below the *muscularis mucosae* has been proposed as an important risk stratification (Figure 3). In one study, no progression was found in 75 pT1 tumors with invasion above the *muscularis mucosae* and no associated carcinoma *in situ*. By contrast, 42% of the 44 pT1 tumors invading beyond *muscularis mucosae* or with associated carcinoma in situ progressed over a three-year period. The *muscularis mucosae* is however not

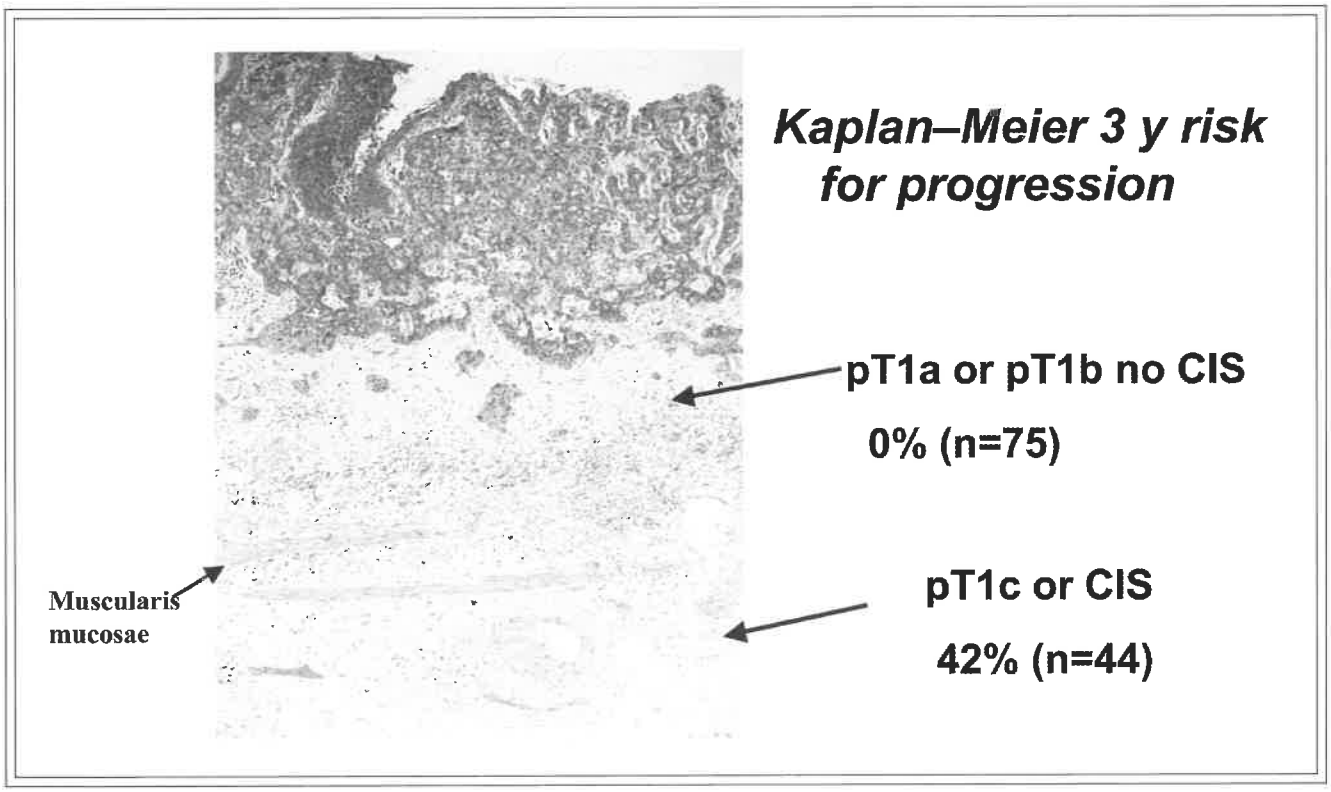

Figure 3. Microstaging pT1 and clinical outcome.

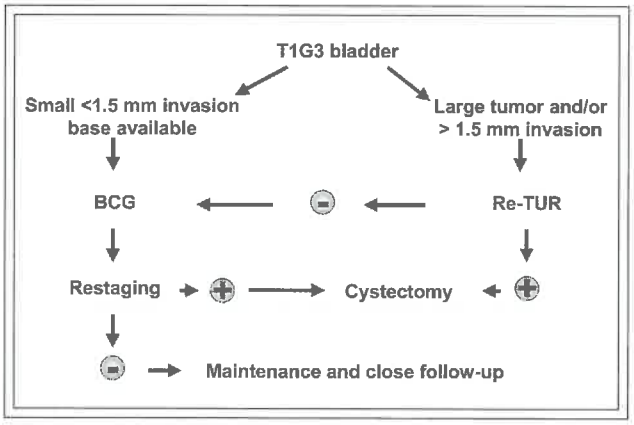

Figure 4. Aggressive conservative approach to T1G3 bladder cancer.

identifiable in over 40% of cases. To overcome this limitation, Chen et al. proposed the use of a micrometric evaluation of the depth of invasion as performed for melanoma and cervical carcinoma.[28] They found, like in other cancers, a cut-off of 1.5 mm as the level beyond which the presence of muscle invasive disease was most likely.

Based on the many considerations discussed above, we are currently using a typically Canadian aggressive conservative approach whereby in patients with small tumors with invasion limited above the *muscularis mucosae* or of less than 1.5 mm depth and with a base separately resected which is clear of tumor, we propose intravesical BCG and restaging TUR 3 months later (Figure 4). If restaging is negative, maintenance BCG therapy is proposed, while if restaging showed recurrence, cystectomy is proposed for all muscle invasive cancer but also superficial recurrences that are p53 positive. On the other hand, for a large tumor, where the probability of incomplete resection is higher and/or for tumors that invade beyond the *muscularis mucosae* or beyond 1.5 mm, re-TUR is proposed within two to three weeks. If re-TUR is negative, patients are treated with BCG therapy but if re-TUR shows persistent cancer, a cystectomy is proposed as the initial treatment.

Conclusion

The management of superficial bladder cancer is a significant challenge due to the heterogeneity of tumor behaviour and the many approaches available. This review has attempted to provide an update on the most recent advances as well as algorithms to facilitate management decisions based on simple risk categories. We believe that the new diagnostic methods provide opportunity for safer and less morbid monitoring of patients. On the other hand, more precise methods are now available to stratify and treat more effectively high risk bladder cancer patients. □

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