



Recurrence, Progression, and Follow-Up in Non–Muscle-Invasive Bladder Cancer

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Abstract

Non–muscle-invasive bladder cancer (NMIBC) is characterized by a high risk of recurrence after transurethral resection of an initial tumor; the 1-yr recurrence rate is 15–61%, and the 5-yr recurrence rate is 31–78%. These figures represent the heterogeneous character of NMIBC. The treatment and follow-up (FU) strategy vary depending on initial and subsequent clinical and histopathological characteristics. Clinical prognostic factors for recurrence and progression are size, multiplicity, reaction to intravesical therapy, grade, stage, and the presence of carcinoma in situ. In addition, recurrence anywhere in the bladder at first FU cystoscopy after transurethral resection is one of the most important prognostic factors for time to progression.

The major goals in treating patients with NMIBC are to prevent the high number of recurrences and to prevent muscle-invasive progression. In this review, risks of recurrence and progression are analyzed and discussed in separate sections, including clinical and pathological results, applied treatments, and diagnostics. Finally, means and recommendations for FU are discussed.

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1. Introduction

With approximately 357 000 new cases per year, tumors of the urinary tract contribute significantly to the overall human cancer burden [1]. Of all urinary tract malignancies, bladder cancer is the most common and accounts for 5% of all diagnosed cancers. In Europe, the highest incidence is reported in the western and southern parts of the continent [2]. Up to 85% of patients with bladder cancer present with disease confined to the mucosa (stage Ta and Tis) or submucosa (stage T1). These non–muscle-invasive tumors are treated totally differently from muscle-invasive tumors. In non–muscle-invasive disease, transurethral resection

(TUR) paired with adjuvant intravesical chemotherapy or immunotherapy is the treatment of choice; in muscle-invasive disease, cystectomy is the most appropriate curative option.

Non–muscle-invasive bladder cancer (NMIBC) can be divided into three groups [3]. The first group consists of a minority of patients (20–30%) who have a relatively benign type of transitional cell carcinoma (TCC) with a low recurrence rate. These low-risk tumors do not show progression. The second and largest group consists of patients who frequently develop a non–muscle-invasive recurrence but seldom experience progression. The third, small group consists of patients who have a relatively

aggressive non-muscle-invasive tumor at presentation; despite maximum treatment, up to 45% of these patients will develop muscle-invasive cancer.

The high number of recurrences is also reflected in high costs that make NMIBC one of the most expensive diseases to treat, with an estimated cost of US\$96,000 to US\$187,000 per patient from diagnosis to death in the United States [4]. From both a patient and economic point of view, therefore, it is important to reduce the number of recurrences.

Accordingly, the major goals in treating patients with NMIBC are to prevent the high number of recurrences and to prevent muscle-invasive progression. In this review, the risks of recurrence and progression are analyzed and various means of follow-up (FU) are recommended.

2. Patient characteristics

More than 30 yr ago, it had already been shown that smokers have an increased risk for bladder cancer compared to nonsmokers. Furthermore, women who smoke the same number of cigarettes compared to men have been shown to have a higher risk of developing bladder cancer [5]. Quitting smoking decreases the risk of developing bladder cancer by more than 30% after 1–4 yr and by more than 60% after 25 yr, but the risk never returns to the level enjoyed by nonsmokers [6,7]. However, an association between tobacco consumption and progression or death resulting from bladder cancer has never been found [6].

Occupational exposure is the second most important risk factor associated with bladder cancer. The two groups of chemicals known to cause bladder cancer are aromatic amines (used in the textile/dye and rubber tire industries) and polycyclic aromatic hydrocarbons (used in the aluminum, coal, and roofing industries) [7]. Some of these chemicals are no longer widely used.

Sex is not a prognostic factor in NMIBC. Age, however, has some prognostic value. Narayana et al found that increasing age was of some prognostic value in NMIBC ($p = 0.08$) [8].

3. Prognostic factors of recurrence

Although transurethral resection of bladder tumor (TURBT) is an essential diagnostic tool and an effective treatment for bladder cancer, 45% of patients will have tumor recurrence within 12 mo of TURBT alone. Tumor recurrence can be attributed to a combination of missed tumors, incomplete initial resection, reimplantation of tumor cells after resection, and *de novo* tumor occurrence in high-risk urothelium. Several factors influence the recurrence rate (eg, clinical and pathological results, applied treatments, and diagnostics).

3.1. Clinical and pathological factors

Clinical prognostic factors for tumor recurrence are multiplicity [9–12], tumor stage [11,12], tumor grade [11,13], and tumor size [10,13]. However, the strongest prognostic factor

for recurrence is the result of the first cystoscopy done 3 mo after TURBT [9].

A more individually tailored FU scheme for NMIBC patients dependent on their risk profile would help to reduce patient burden and costs. Several studies have focused on identifying and quantifying prognostic factors for risk of recurrence [13–15]; these studies ultimately led to a classic way of categorizing and dividing patients into three groups: low, intermediate, and high risk [3,10]. Nevertheless, when these risk groups are applied, no distinction is made between risk of recurrence and progression. In order to separately predict the short-term and long-term risks of both recurrence and progression, the European Organization for Research and Treatment of Cancer (EORTC) developed a scoring system and risk tables [16]; these will be discussed later.

3.2. Role of treatment

Primary complete TUR is the recommended treatment for NMIBC. A second TUR has to be performed in the case of high-grade malignancy or incomplete resection. After resection, one single instillation with a chemotherapeutic agent within 24 h decreases the recurrence rate by almost 50% [17]. In low-risk NMIBC, one immediate instillation is the treatment of choice.

Patients with an intermediate-risk tumor (40–50% of all NMIBC cases) often develop recurrence but rarely progression. In an attempt to reduce the number of recurrences, a series of intravesical instillations is given postoperatively. The recurrence rate of NMIBC after intravesical chemotherapy decreases in the short term, but in the long term, this benefit disappears; the influence on the long-term recurrence rate (>5 yr) is <10%. Furthermore, progression is not prevented by chemotherapy use.

High-risk NMIBC must be handled using the most effective treatments to prevent frequent recurrences, and bacillus Calmette-Guérin (BCG) instillations are the treatment of choice. Recently, Malmström performed a meta-analysis of nine trials (including individual data from 2820 patients) comparing long-term results of mitomycin C (MMC) and BCG treatment for NMIBC [18]. In this analysis, there was no difference in the time to first recurrence ($p = 0.09$) between BCG and MMC. However, in the case of BCG maintenance, a 32% reduction in risk of recurrence on BCG compared to MMC was found ($p < 0.0001$), while there was a 28% risk increase ($p = 0.006$) for BCG in the trials without maintenance. Earlier, Lamm et al also showed significantly improved recurrence-free survival time in high-risk NMIBC with BCG maintenance therapy, but they also found increased side-effects; 5% of patients had to stop during induction therapy and 20% of patients during maintenance therapy [19,20].

3.3. Role of urine markers

Cystoscopy is the gold standard in the treatment of NMIBC. Cytology, which has a high selectivity and low sensitivity, is also widely applied. Urine markers, which generally have a

higher sensitivity and lower specificity than cytology [21–23], could be used to replace some of the cystoscopies and cytologies. For primary diagnosis, cystoscopy is part of the work-up; therefore, a specific marker, such as cytology, may be useful. Surveillance of patients with high-risk NMIBC requires frequent cystoscopy with a specific urine marker like cytology. In contrast, for patients with low- or intermediate-risk tumors, the cystoscopy frequency may be lowered and a urine marker may be used to tailor the FU scheme [24].

Many tests have been investigated in patients. Some, such as BTA stat and NMP22, give instant results but have a lower accuracy [25,26]. Others, such as Immunocyt, FISH UroVysion, and microsatellite analysis have a higher sensitivity and specificity but require support from a specialized laboratory and validation of the test for routine use [25–27]. In conclusion, cytology is of low value in patients with low- and intermediate-risk NMIBC. Whether a urine marker will be helpful in the surveillance of these patients and whether it will tailor the FU scheme is still not clear.

3.4. Role of fluorescence cystoscopy

White-light cystoscopy (WLC) is the gold standard for visualization of suspicious lesions during TURBT. Despite complete removal of all visible tumors at WLC, resection does not seem to be radical in up to 21% of patients with a single tumor and in up to 46% of patients with multiple tumors [28]. Recent studies suggest that porphyrin-based fluorescence cystoscopy (FC) can improve the endoscopic detection of bladder tumors [29,30]. FC is performed by blue light after a 1 h intravesical instillation with hexaminolevulinic acid. This substance is converted to porphyrins that preferentially accumulate in neoplastic cells, resulting in red fluorescence when illuminated with blue light [31]. Recent studies suggest that FC may be more sensitive than WLC for detecting bladder tumors. Grossman compared WLC with FC in a large multicenter trial. In 298 patients, FC detected at least one additional Ta lesion in 29% of patients and at least one additional T1 lesion in 15% of patients [32]. The detection rate for Ta and T1 lesions was 95% and 95% for FC compared to 83% and 86% for white light, respectively ($p = 0.0001$).

This effect is even better in carcinoma in situ (CIS). Fradet studied detection of CIS and found a detection rate of 92% for FC and 68% for WLC [33]. Furthermore, an excellent indication for FC is positive urine cytology and negative WLC [34,35]. Malignancy was detected by FC in 63 of 77 patients (82%) with positive cytology as opposed to 43 of 271 patients (16%) with negative cytology. Altogether, it can be concluded that FC improves detection of NMIBC [30,32,33,36]. But does this improved detection result in actual benefit for patients?

Jocham et al studied whether FC improves the treatment of NMIBC patients [31]. In total, 146 patients were treated with WLC and FC. An independent urologist, blinded to the detection method used, recommended treatment plans based on biopsy results. Any differences in recommended

treatment plans arising from the two methods were recorded. Of all tumors, 96% were detected with FC, compared to 77% with WLC. This difference was particularly noticeable for CIS (95% vs 68%). As a result of improved detection, 17% of patients (22% if patients without tumors were excluded) received more appropriate treatment following FC ($p < 0.0001$). Denzinger et al also found that FC improves the oncological outcome significantly; recurrence-free survival rates after 2 and 8 yr were 88% and 73% for FC versus 71% and 45% for TUR with WLC ($p = 0.0003$) [37]. Thus, recurrence rates seem to decrease when using FC, and the oncological outcome improves significantly. A decrease in progression rate, however, has not yet been shown.

4. Prognostic factors for recurrence

A less frequent but more serious outcome is the 3–15% risk of tumor progression to muscle-invasive and/or metastatic bladder cancer. Furthermore, tumor progression can also include the chance of cancer-related death. Several factors influence the progression rate (eg, clinical and pathological results, applied treatments, and diagnostics).

4.1. Clinical and pathological factors

As for recurrence, clinical and pathological factors for NMIBC progression have been studied extensively over the past decades [16]. The 5-yr probabilities range from <1% to 45% depending on the risk classification. The most important variables for prediction of progression in NMIBC are the presence of CIS, a grade 3, and a stage T1 tumor [38]. Sylvester et al calculated the probability of progression using the same 2596 patients who participated in seven EORTC trials [16]. The weighted score was based on the same six variables as recurrence (see Table 1, section 5).

Fernandez-Gomez et al reported the data on prognostic factors from four Club Urológico Español de Tratamiento Oncológico (CUETO) trials, in which 1062 patients received BCG [39]. A recurrence at first cystoscopy, stage, grade, and prior tumor were the prognostic variables in this multivariate analysis for progression.

4.2. Role of treatment

High-risk NMIBC must be handled with the most effective treatments to prevent progression to muscle-invasive disease; the progression rate is as high as 45%. Progression is not prevented by intravesical chemotherapy, and the influence of BCG on progression is controversial. Sylvester et al performed a meta-analysis of 24 clinical trials with 4863 patients comparing TUR plus intravesical BCG to resection alone or resection plus a treatment other than BCG [40]. They found that adjuvant BCG is superior to TUR alone and more effective than adjuvant chemotherapeutic drugs with regard to progression-free survival; after a median FU of 2.5 yr, progression was seen in 9.8% in the BCG group versus 13.8% in the non-BCG group (odds ratio [OR] = 0.73, $p = 0.001$). This difference was even larger when only

Table 1 – Weights used to calculate recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2–7	3	3
≥8	6	3
Tumour diameter		
<3 cm	0	0
≥3cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

CIS = carcinoma in situ.

maintenance trials were used (OR 0.63, $p = 0.00004$). However, the FU was relatively short, resulting in a low absolute number of patients with progression: 6.4% in patients with papillary tumors and 13.9% in patients with CIS.

Recently, Malmström performed a meta-analysis of nine trials that included data from 2820 individual patients comparing long-term results of MMC and BCG treatment for NMIBC [18]. This meta-analysis showed no statistically significant differences regarding progression, overall survival, and cancer-specific survival between the two treatments.

The only proven method to decrease progressive disease is to do an early cystectomy [41,42]. Early cystectomy has three advantages. The first is good pathological staging with adequate lymph node status. The second is the early stage of the disease, which makes a nerve-sparing cystectomy possible. The third is a great reduction in the risk of late recurrences and mortality and thus a simplified FU. Nevertheless, long-term FU studies revealed that one-third of patients with T1G3 tumors treated with BCG never recur [43,44]. In those patients, cystectomy is overtreatment. The question remains: How does one select these patients? There are several features associated with poor prognosis: concomitant CIS [45], deep lamina propria invasion, lymphovascular invasion, prostatic involvement, large or multifocal tumors, persistent T1G3 disease on repeat TUR, and persistent T1G3 or CIS after BCG treatment [46].

Retrospective studies of patients with high-grade T1 tumors treated with initial intravesical therapy suggest that approximately 30% of patients will ultimately require cystectomy, and 30% will die of their disease with or without cystectomy. The risk of progression continues for

the life of the patient, and late progression is common. Initial clinical and pathologic factors can be reasonable indicators for early cystectomy. So, initial cystectomy can provide a very high cure rate for these patients and should be considered early in the treatment plan.

4.3. Molecular and genetic predictors

Fibroblast growth factor receptor 3 (FGFR3) gene mutation is a promising predictor for recurrence and progression. This mutation is associated with genetically stable low-grade and stage NMIBC [47,48]. The presence of an FGFR mutation is an indicator for better prognosis. The influence on recurrence rate is controversial. Previously, an FGFR mutation was assumed to increase the recurrence rate. However, recently, the results of a large trial with 772 NMIBC patients showed only a higher risk of recurrence (hazard ratio 2.12; $p = 0.004$) in FGFR-mutated TaG1 tumors and not in T1, G2, or G3 tumors [49].

The P53 tumor suppressor gene mutation is associated with a worse tumor outcome. Normally, the P53 tumor suppressor gene plays a protective role by regulating the cell cycle after DNA damage. Either the cell repairs its DNA or goes into apoptosis [50]. In the case of mutation, this protective mechanism does not work anymore. DNA damage remains unrepaired, and cells continue to divide, which leads to progressive genetic instability. P53 mutations can be detected by immunohistochemistry, but because of the highly variable immunostaining outcome, its diagnostic value is limited.

Ki-67 protein is a cellular proliferation marker present in all active cell cycle phases and thus is an excellent marker for cellular growth. It has also been shown that high Ki-67 expression correlates with high P53 nuclear accumulation in TCC [51]. However, studies on the use of Ki-67 as a marker for progression and recurrence gave contradictory results. Holmang et al found no correlation between high expression of Ki-67 and progression rate, whereas Asakura et al did find a correlation of high Ki-67 expression and both recurrence and progression rate [52,53]. Despite these contradictory results, Ki-67 can be implemented in the diagnosis of NMIBC.

CK20 expression is correlated with normal differentiation and maturation of cells. Decreased expression in umbrella cells only is correlated with mild disease, while decreased expression in the entire urothelium is associated with an increased recurrence and progression rate [54,55]. This makes CK20 protein expression useful in the diagnosis of NMIBC.

The above-mentioned molecular and genetic predictors can be used for better grading of bladder tumors. However, the independent prognostic role remains controversial.

5. EORTC risk tables

The basis for the EORTC risk tables was a combined analysis of individual patient data from 2596 NMIBC patients included in seven randomized EORTC trials [16]. Patients with CIS only were excluded from analysis. All

Table 2 – Probability of and progression according to total score

	Probability of recurrence at 1 yr		Probability of recurrence at 5 yr		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
Recurrence score					
0	15	(10–19)	31	(24–37)	Low risk
1–4	24	(21–26)	46	(42–49)	Intermediate risk
5–9	38	(35–41)	62	(58–65)	
10–17	61	(55–67)	78	(73–84)	High risk
Progression score					
0	0.2	(0–0.7)	0.8	(0–1.7)	Low risk
2–6	1	(0.4–1.6)	6	(5–8)	Intermediate risk
7–13	5	(4–7)	17	(14–20)	High risk
14–23	17	(10–24)	45	(35–55)	

patients underwent a TUR of the initial tumor. Afterward, 78% of all patients were treated with intravesical instillations, mostly chemotherapy. None of the patients were treated with BCG maintenance. The endpoints were time to first recurrence and time to muscle-invasive disease. Finally, a simple scoring system was derived based on six clinical and pathological factors (number of tumors, tumor size, prior recurrence rate, T stage, presence of concomitant CIS, and tumor grade). Table 1 shows the weights applied to the risk factors based on coefficients of these variables in the multivariate model. Total score in recurrence ranged from 0 (best prognosis) to 17 and in progression from 0 to 23. Patients were finally divided into four groups according to their score (Table 2); nevertheless, the last column defines the low-, intermediate-, and high-risk classification.

Thus, the risk of recurrence after TUR of the initial tumor was 15–61% after 1 yr and 31–78% after 5 yr. Unfortunately, after 1 yr, up to 17% of the non-muscle-invasive tumors will progress to a muscle-invasive tumor, and after 5 yr, up to 45% will. Schrier et al studied these progressive high-risk NMIBC patients, who have a worse prognosis compared to patients with primary muscle-invasive bladder cancer [56]. The 3-yr bladder cancer-specific survival was 67% in the primary group and 37% in the progressive group (log rank $p = 0.0015$).

The main limitation of the EORTC risk tables is that most patients were treated by old-fashioned intravesical chemotherapy regimens. Improvements of intravesical chemotherapy, the use of a single chemotherapeutic instillation after TUR, and the use of BCG in a maintenance scheme will alter the predicted patient outcome. Currently, the EORTC risk tables for maintenance BCG are being validated.

The search for better prognostic factors for recurrence and progression continues. Most studies focus on molecular tissue markers to predict the clinical course. Currently, molecular and genetic predictors such as FGFR3 and P53 gene mutations as well as Ki67 and CK20 protein expression are being weighed to improve risk profiling [57–59].

6. Means of follow-up

The most commonly used approach to follow patients with NMIBC after TUR (per American Urological Association guidelines) consists of urinalysis, cystoscopy, and cytology

every 3 mo for 2 yr, every 6 mo until 5 yr, and annually thereafter. The European Association of Urology (EAU) advocates a FU scheme according to the patient's degree of risk [24]. Using risk tables (Table 2), it is possible to predict the short-term and long-term risks of both recurrence and progression in individual patients, and the FU schedule can be tailored accordingly. Early detection of muscle-invasive and high-grade NMIBC recurrences is critical, since a delay in diagnosis and therapy is life threatening. Thus, these patients need intensive FU with frequent cystoscopies and cytology. Tumor recurrence in the low-risk group is nearly always low stage and low grade. These tumors do not present an immediate threat to the patient, and early detection is not essential for successful therapy [60–62]. The frequency of cystoscopy in these patients can subsequently be diminished. But most important are the results of the first cystoscopy after TUR at 3 mo. This is a very important prognostic factor for recurrence and progression [63–65].

7. Recommendations for follow-up

The intent of NMIBC management is to control recurrence and progression and to identify invasive tumors at the earliest possible stage. To do so, all patients should undergo a cystoscopy and urinary cytology 3 mo after TURBT. If the cystoscopy and urinary cytology are both negative, FU cystoscopy should be planned according to the risk of recurrence and progression.

In the past two decades, several FU policies have been published [9,12,13,66,67]. FU intervals vary from 3 to 12 mo and last from 3 yr to a lifetime. However, all policies have the 3-mo cystoscopy as a common recommendation.

The EAU guidelines also recommend a FU policy with the 3-mo FU interval. In patients at low risk for recurrence and progression, the subsequent cystoscopy is advised at 9 mo and consequently yearly for up to 5 yr. Patients with tumors at high risk of progression should undergo a restaging TUR to confirm radical treatment. If the resection is negative, patients should have a cystoscopy and urinary cytology every 3 mo for a period of 2 yr, every 4 mo in the third year, every 6 mo in the fourth and fifth year, and yearly thereafter. Patients with intermediate risk of progression should be checked with an in-between FU schedule using cystoscopy; urinary cytology is supplementary.

The FU of the upper urinary tract (computed tomography or intravenous urography) is recommended yearly in NMIBC patients at high risk for progression. Upper urinary tract screening in low- and intermediate-risk patients is not recommended [24].

Conflicts of interest

The authors have nothing to disclose.

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