Diagnostic and Prognostic Factors in Non-Muscle-Invasive Bladder Cancer and Their Influence on Treatment and Outcomes

Willem Oosterlinck a,*, Fred Witjes b, Richard Sylvester c

a Department of Urology, Ghent University Hospital, Belgium
b Radboud University, Nijmegen Medical Centre, Department of Urology (659), Nijmegen, The Netherlands
c European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium

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Abstract

Objectives: This paper explores the diagnostic and staging procedures available for bladder cancer, the prognostic factors for recurrence and progression of non-muscle-invasive tumours, and the indications for intravesical therapy and cystectomy in patients with non-muscle-invasive, recurrent disease.

Methods: The authors reviewed the literature on diagnosis of bladder cancer, prognostic factors for recurrence and progression of non-muscle-invasive disease, and the indications for intravesical therapy and cystectomy.

Results: The presence of malignant cells at urinary cytology suggests a high-grade tumour in the urinary tract, but negative urinary cytology does not exclude a low-grade cancer. Transurethral resection of the bladder (TURB) is undertaken in non-muscle-invasive bladder tumours to aid diagnosis and to remove visible lesions and is more effective when guided by blue-light fluorescence than by white light. Repeated TURB may be required because of the risk of residual tumour after initial TURB. A tool from the European Organisation for Research and Treatment of Cancer (EORTC) can be used to assess an individual patient's risk of bladder cancer recurrence and progression. Further treatment options are intravesical chemotherapy, intravesical bacille Calmette-Guérin (BCG) immunotherapy, and cystectomy. Immediate cystectomy is advocated by many specialists for patients with non-muscle-invasive tumour who are at high risk of progression or who do not respond to BCG therapy.

Conclusions: Urinary cytology and TURB (preferably under the guidance of fluorescence cystoscopy if carcinoma in situ is suspected) are the mainstays of bladder cancer diagnosis and staging. The likelihood of recurrence or progression can be assessed using a tool developed by the EORTC that is based on common prognostic factors. Patients with disease progression can be offered cystectomy.

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1. Introduction
An initial diagnosis of bladder cancer is typically made during investigations prompted by gross haematuria. Sometimes bladder exploration is undertaken because of symptoms of irritation, which may be provoked by carcinoma in situ (CIS), or because the patient has recurrent urinary tract infection. Bladder cancer may also be diagnosed via ultrasound detection of intraluminal filling defects. Approximately 75–85% of patients with bladder cancer present with tumours confined to the mucosa (Ta or Tis) or the submucosa (T1). This paper explores the diagnostic and staging procedures available for bladder cancer, the prognostic factors for recurrence and progression of non-muscle-invasive tumours, and the indications for intravesical therapy and cystectomy in patients with non-muscle-invasive, recurrent disease.

2. Diagnostic and staging procedures

2.1. Urinary cytology
Urinary cytology is an important tool in the diagnostic work-up of bladder cancer. The finding of malignant cells in voided urine or a bladder washing specimen is an indication that there may be a high-grade tumour somewhere in the urinary tract— anywhere from the calyx to the proximal urethra. In addition, negative urinary cytology does not exclude the presence of a low-grade cancer.

Cytological interpretation is investigator-dependent [1] and can be hampered by low cellular yield, urinary tract infection, stones, or intravesical instillations. Nevertheless, in experienced hands, the specificity of urinary cytology exceeds 90% [2].

CIS, which can occur on its own or with Ta or T1 tumours, may present as velvety, reddish areas that are difficult to distinguish from inflammation; in some cases, the lesions are not visible at all. Therefore, if the urinary cytology is positive, biopsies from normal-looking mucosa (ie, random biopsies) or from selected areas of the mucosa are recommended for the detection of CIS. The likelihood of detecting CIS in low-risk tumours is extremely small, and the choice of adjuvant intravesical therapy should not be affected by the results of random biopsy [3]. As such, mucosal biopsies are not recommended if urinary cytology is negative.

There have been reports of the involvement of the prostatic urethral ducts in male patients with Ta or T1 bladder tumours [4,5]. Although the exact likelihood of this involvement is not known, it seems to be associated with bladder tumours located in the trigone or the bladder neck, the presence of bladder CIS, or multiple bladder tumours [4,5]. Biopsies of the prostatic urethra are recommended if these tumour criteria are fulfilled and if cytology is positive or abnormalities are visible in the prostatic urethra.

2.2. Initial transurethral resection
The goals of an initial transurethral resection of the bladder (TURB) in non-muscle-invasive bladder tumours are to make a correct diagnosis and to remove all visible lesions. The variability in the 3-mo recurrence rate of bladder cancer and the high incidence of tumour detection at repeated TURB suggest that the initial resection is often incomplete [6]. Indeed, the completeness of TURB is probably an important prognostic factor.

2.3. Fluorescence cystoscopy
Standard TURB is guided by white light, whereas fluorescence cystoscopy (also known as photodynamic diagnosis) uses blue light after intravesical instillation of a photosensitiser, usually 5-aminolevulinic acid or hexylaminolevulinate (Hexvix). It has been confirmed that fluorescence-guided biopsies and resections are more sensitive than conventional procedures in the detection of malignant tumours, particularly CIS [7–9]. Fluorescence-guided TURB also improves recurrence-free survival, as demonstrated by small, randomised clinical trials [10–12], but its definitive impact on improvement of outcomes, including progression rates, remains unproven.

2.4. Second resection
There is a significant risk of residual tumour after the initial TURB of Ta or T1 tumours [6,13–16]; persistent disease has been observed in 33–53% of patients after the resection of T1 tumours, and a second TURB can increase recurrence-free and progression-free survival [17–19].

The tumour may be understaged at the initial resection; 10% of high-grade tumours that have been designated Ta or T1 at first TURB are likely to have been understaged and will actually be muscle-invasive. Correct staging is important because the treatment requirements of a Ta or T1 high-grade tumour and a T2 tumour are completely different.
3. Factors predicting recurrence and progression after TURB

The classic way to categorise patients with Ta or T1 tumours is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it has been proposed that patients can be divided into low-risk, intermediate-risk, and high-risk groups [20]. Categorisation of this type, however, does not usually differentiate between the risk of recurrence and the risk of progression. Although prognostic factors may indicate a high risk for recurrence, the risk of progression may still be low, whereas other tumours may have a high risk of both recurrence and progression.

The European Organisation for Research and Treatment of Cancer (EORTC) has developed a scoring system and risk tables for bladder cancer [21] based on the organisation’s database of 2596 patients diagnosed with Ta or T1 tumours in seven EORTC trials. Of these patients, 78% received intravesical treatment, mostly chemotherapy, but did not undergo a repeated TURB or receive maintenance bacillus Calmette-Guérin (BCG) treatment. The scoring system (Table 1) takes into account the six most significant clinical and pathological factors: number of tumours, tumour size, prior recurrence rate, T category, presence of concomitant CIS, and tumour grade. Table 2 shows how the score is used to determine a patient’s risk of disease recurrence and progression.

4. Intravesical chemotherapy according to risk group

Although a TURB can eradicate a Ta or T1 bladder cancer completely, tumours recur in a high proportion of cases and progress to muscle-invasive bladder cancer in a limited number. Adjuvant therapy should, therefore, be considered for all patients.

4.1. Single, immediate, postoperative intravesical instillation of chemotherapy

In a meta-analysis of seven randomised trials involving a total of 1476 patients followed up for a median of 3.4 yr, one immediate instillation of chemotherapy after TURB decreased the proportion of recurrence by 12% (from 48.4% with no

| Table 1 – Weighting used to calculate recurrence and progression scores |
|-----------------------------|---------------|---------------|
| Factor                      | Recurrence    | Progression   |
| Number of tumours           | 0             | 0             |
| Single                      | 3             | 3             |
| 2–7                         | 6             | 3             |
| ≥8                          | 3             | 3             |
| Tumour diameter             | 0             | 0             |
| <3 cm                       | 3             | 3             |
| ≥3 cm                       | 3             | 3             |
| Prior recurrence rate       | 0             | 0             |
| Primary tumour              | 2             | 2             |
| ≤1 recurrence/year          | 4             | 2             |
| >1 recurrence/year          | 4             | 2             |
| Category                    | 0             | 0             |
| Ta                          | 1             | 4             |
| T1                          | 1             | 6             |
| CIS                         | 0             | 0             |
| No                          | 0             | 0             |
| Yes                         | 1             | 6             |
| Grade                       | 0             | 0             |
| G1                          | 0             | 0             |
| G2                          | 1             | 0             |
| G3                          | 2             | 5             |
| Total score                 | 0–17          | 0–23          |

| Table 2 – Probability of recurrence and progression according to total score |
|-----------------------------|---------------|---------------|
| Recurrence score            | Probability of recurrence at 1 yr (95% CI) | Probability of recurrence at 5 yr (95% CI) | Recurrence risk group |
| 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%)  | High risk               |
| 10–17                       | 61% (55–67%)  | 78% (73–84%)  | High risk               |

| Progression score           | Probability of progression at 1 yr (95% CI) | Probability of progression at 5 yr (95% CI) | Progression risk group |
| 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%)  | High risk               |

CI = confidence interval.
chemotherapy to 36.7% after a single instillation) and reduced the odds of recurrence by 39% [22]. The 12% reduction means that 8.5 patients need to be treated to prevent one recurrence. The benefit was confirmed in patients with either single or multiple tumours. No differences in efficacy were reported between different drug regimens [22].

The effect of the single postoperative infusion of chemotherapy can be explained either by the destruction of circulating tumour cells immediately after TURB or as an ablative effect (chemoresection) of residual tumour cells.

The timing of the chemotherapy instillation is crucial. In the studies included in the meta-analysis, the instillation was administered within 24 h of TURB [22]. In another study, a 2-fold increase in the risk of recurrence was reported among patients who received a delayed instillation versus same-day instillation [23]. Severe complications can be associated with extravasation of the drug [24], so immediate instillation should be avoided in cases of overt or suspected intraperitoneal or extraperitoneal perforation, which are most likely to appear during extensive TURB procedures. Also, clear instructions should be given to the nursing staff for controlling the free flow of the bladder catheter at the end of the instillation.

4.2. Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on the patient’s prognosis. A single, immediate instillation may be considered as the standard treatment for patients who have a low risk of tumour recurrence [22]; there is no need for further treatment unless there is a recurrence. For other patients, however, a single chemotherapy instillation is an incomplete treatment because there remains a considerable likelihood of recurrence and/or progression.

The effect of the immediate instillation of chemotherapy occurs during the first and second years [25,26]. Thereafter, the choice between further chemotherapy or immunotherapy depends largely on the risk that needs to be reduced (ie, recurrence or progression).

Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression [27,28]. A combined analysis of EORTC and Medical Research Council (MRC) data comparing intravesical chemotherapy with TURB alone has shown that chemotherapy prevents recurrence but not progression [29]. The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence has been confirmed by two other meta-analyses of studies of primary [30] and recurrent [31] tumours.

There is still controversy over the optimal duration and frequency of intravesical chemotherapy instillations. The findings of a systematic review of randomised clinical trials suggest that these parameters remain undefined because of conflicting data [32]. One randomised trial has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduces the recurrence rate of bladder cancer [33]. Researchers undertaking another randomised trial report that the treatment concentration is more important than the duration [34]. In view of these data, which need confirmation, it seems advisable to ask the patient not to consume any liquids on the morning before instillation and to dissolve the drug in a buffered solution at optimal pH.

Mitomicin C at a dose of 40 mg and epirubicin at a dose of 50 mg have been used most widely, generally dissolved in 50 ml of buffered solution. Evidence is lacking, however, on the optimal concentration of the regimen as well as on frequency of the instillations. Differences among different drugs have not been identified but have not been studied extensively by any means.

5. Intravesical BCG immunotherapy

The largest analysis of multivariate, prognostic factors [35] in patients treated with BCG identified similar prognostic factors for recurrence and progression to those seen with chemotherapy. Contrary to most previous studies, however, female gender and CIS were also important for recurrence, whereas CIS was not retained as an important prognostic factor in a multivariate model for progression. Also contrary to previous studies, age was identified as a predictor for worse response to BCG.

Four meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy in preventing recurrence of Ta or T1 tumours [36–39]. Two further meta-analyses have demonstrated the superiority of BCG over TURB alone or TURB plus chemotherapy in the prevention of tumour progression [27,40]. One of these meta-analyses [27], carried out by the EORTC, assessed data from 4863 patients enrolled in 24 randomised trials. A total of 3967 (81.6%) patients had only papillary tumours, and 896 (18.4%) had primary or concomitant CIS. Based on a median follow-up of 2.5 yr (maximum 15 yr), progression was seen in 260 of 2658 patients (9.8%) receiving BCG, compared to 304
of 2205 (13.8%) in the control groups (TURB alone, TURB plus intravesical chemotherapy, or TURB plus another immunotherapy). This result shows a reduction of 27% in the odds of progression with BCG treatment ($p = 0.001$) compared to the other strategies. The size of the reduction is similar in patients with Ta or T1 papillary tumours and those with CIS. Two meta-analyses [40,41], however, have suggested that inclusion of patients who had been previously treated with intravesical chemotherapy created a possible bias in favour of BCG.

For optimal efficacy, BCG must be given in a maintenance schedule [27,28,39]. In a meta-analysis of 20 trials in which some form of BCG maintenance was given, the odds of progression were reduced by 37% ($p = 0.00004$) [27]. In other meta-analyses, at least 1 yr of maintenance BCG was required to show the superiority of BCG over mitomycin C in preventing recurrence or progression [28,39]. Many different maintenance schedules have been used, ranging from a total of 10 instillations given over 18 wk to 30 instillations given over 3 yr [42]. The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown.

To reduce toxicity, one-third-dose and one-quarter-dose instillations of BCG have been proposed. Comparing one-third-dose to full-dose BCG in 500 patients, the Spanish Oncology Group (CUETO) noted no overall difference in efficacy [43,44], though there was a suggestion that a full dose of BCG may be more effective in multifocal disease. Fewer patients reported toxicity with the reduced dose. Furthermore, though the incidence of severe systemic toxicity was similar in the standard-dose and reduced-dose arms at around 5 yr [43], it was significantly lower in the reduced dose arm at extended follow-up [44]. The same research group also conducted a prospective randomised trial that showed that a further reduction to a one-sixth dose reduced efficacy for preventing recurrences without any further reduction in toxicity [45].

Serious side effects of BCG are encountered by less than 5% of patients and can be effectively treated in almost all cases [46]. Major complications can appear after systemic absorption of the drug, so BCG should not be administered during the first 2 wk after TURB or after traumatic catheterisation.

5.1. Indications for BCG

Although BCG is a very effective treatment for bladder cancer, there is a consensus view that it should not be given to all patients with non-muscle-invasive disease because of the risk of toxicity. Ultimately, the choice of treatment depends on the patient’s risk of recurrence and progression.

BCG does not alter the natural disease course in tumours at low risk of recurrence and progression, and it may be considered to be overtreatment. BCG (including a maintenance schedule) is indicated for patients with tumours at high risk of progression and who have not undergone cystectomy. BCG (for at least 1 yr) can be offered to patients at intermediate risk if they tolerate chemotherapy badly or if their disease continues to recur despite repeated chemotherapy instillations.

Patients with non-muscle-invasive recurrences after intravesical chemotherapy can benefit from BCG instillations [40]. Similarly, selected patients who develop non-muscle-invasive recurrences after BCG may respond to intravesical chemotherapy or device-assisted chemotherapy instillations; however, experience is limited and such strategies are considered experimental. Because of the high risk of muscle-invasive tumour, an immediate cystectomy is strongly advocated after BCG failure [47,48].

5.2. Failure of BCG treatment

Treatment with BCG is considered to have been ineffective in the following situations: (1) whenever muscle-invasive tumour is detected during follow-up; (2) if high-grade, non-muscle-invasive tumour is present at both 3 and 6 mo post BCG [49] (when tumour is present at 3 mo, an additional BCG course leads to complete response in more than 50% of patients with either papillary tumours or CIS [47]); or (3) when there is any deterioration of the disease, such as increased number of recurrences, higher T level or grade, or appearance of CIS despite an initial response to BCG.

6. Cystectomy for non-muscle-invasive bladder cancer

Many specialists consider immediate cystectomy to be a reasonable proposition for patients with non-muscle-invasive tumour who are at high risk of progression. According to the EORTC risk tables, these are patients with multiple recurrent, high-grade tumours; high-grade T1 tumours; or high-grade tumours with concomitant CIS.

Cystectomy is also advocated in patients with non-muscle-invasive bladder cancer who do not respond to BCG therapy, as explained above. Delaying cystectomy in patients with non-muscle-invasive tumours that are at high risk of progression may lead to decreased disease-specific survival [50].
7. Conclusions

Urinary cytology and TURB are key diagnostic and staging procedures in bladder cancer, and the latter is more sensitive when guided by fluorescence cystoscopy than by conventional white-light cystoscopy. Fluorescence-guided TURB also improves rates of recurrence-free survival compared to the conventional procedure, but its impact on outcomes, including progression rates, remains unproven.

There is a significant risk of residual tumour after initial TURB of Ta or T1 bladder tumours; a second TURB can increase recurrence-free and progression-free survival and enable restaging where required. Risk factors for recurrence and progression form the basis of a scoring system for individual patients, as devised by the EORTC.

Adjuvant therapy should be considered for all patients. A single postoperative intravesical instillation of chemotherapy, delivered immediately after TURB, reduces the risk of recurrence by 12% (versus no early instillation) in patients with either single or multiple tumours. Immediate instillation should be avoided in cases of overt or suspected intraperitoneal or extraperitoneal perforation. The need for further adjuvant intravesical therapy depends on the clinical prognostic factors of the tumours.

Post-TURB instillation of BCG is superior to TURB alone or TURB plus chemotherapy in preventing recurrence and progression of high-grade Ta or T1 tumours and is ideally given in a maintenance schedule of at least 1 yr. Because of toxicity, the use of BCG should be outweighed in patients at high risk for recurrence but at low risk for progression. The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown. To avoid toxicity, BCG should not be administered during the first 2 wk after TURB or after traumatic catheterisation. Studies of reduced-dose BCG instillations suggest that a one-third dose is as effective as full-dose BCG, although the full dose may be more effective in multifocal disease. Efficacy is reduced when the dose is reduced to one-sixth.

Patients with non-muscle-invasive recurrences after intravesical chemotherapy may benefit from BCG instillations (and vice versa). Both strategies are considered experimental, and an immediate cystectomy is strongly advocated after BCG failure. Many specialists advocate immediate cystectomy for patients with non-muscle-invasive tumour who are at high risk of progression.

Conflicts of interest

Willem Oosterlinck and Fred Witjes have received honoraria from GE Healthcare for presenting at meetings. Professor Oosterlinck has also received honoraria from Organon for presenting.

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