



Challenging the EAU Guidelines on Non–Muscle-Invasive Bladder Cancer (NMIBC): Single Instillation of Chemotherapy After Transurethral Resection of NMIBC and Chemotherapy Versus Bacillus Calmette-Guérin in Treatment of Intermediate-Risk Tumours

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Abstract

Context: Although the 2008 European Association of Urology (EAU) guidelines provide an excellent evidence-based framework for the management of non-muscle-invasive bladder cancer (NMIBC), some topics have been questioned and discussed by many authors and remain controversial.

Objective: To comment on the current EAU guidelines on NMIBC by taking into account new data published in 2009 in peer-reviewed urologic journals and once again discussing relevant data that were available when the guidelines were prepared.

Evidence acquisition: Two important guidelines have been challenged: (1) the use of a single instillation of a chemotherapeutic agent after transurethral resection (TUR) in all patients with NMIBC and (2) chemotherapy versus bacillus Calmette-Guérin (BCG) in the treatment of intermediate-risk tumours. The most important recent publications (2009), including randomised studies and meta-analyses, have been considered and evaluated.

Evidence synthesis: Based on a review of the current EAU guidelines and recent literature, a single instillation of a chemotherapeutic agent after TUR should be administered only in primary, solitary, low-grade NMIBCs. The first-line treatment of intermediate-risk tumours should be the instillation of BCG once a week for 6 wk, followed by maintenance for 1–3 yr. Mitomycin C is still the first treatment of choice for intermediate-risk and low-risk NMIBC patients (single, recurrent, low-grade tumour).

Conclusions: A complete TUR of the bladder tumour plus immediate, postoperative, chemotherapeutic instillation is recommended for all patients with primary, solitary NMIBC, except in those with bladder wall perforation. For these low-risk tumours, no further therapy is required. For intermediate-risk disease, intravesical induction BCG plus maintenance should be considered the first choice, while intravesical chemotherapy should be considered for intermediate-risk and low-risk tumours (single, recurrent, low-grade NMIBC). In these patients, one immediate single instillation of chemotherapy should not be administered after TUR.

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1. Introduction

Currently, there is wide variation in the practice of non-muscle-invasive bladder cancer (NMIBC) management in the urologic community. Clinical practice guidelines provide an evidence-based framework for clinical management that can assist in decision making, help standardise best practice, and, ultimately, enhance patient outcomes. The European Association of Urology (EAU) guidelines [1] have contributed to an excellent evidence-based framework for the management of NMIBC. However, there are contentious areas and gaps in evidence-based knowledge that need to be addressed through expert discussion. Therefore, a debate challenging some recommendations included in the EAU guidelines was organised during the European Section of Oncological Urology meeting held in Vienna, Austria, in January 2010. Two main topics were addressed and discussed during the debate: the role of one immediate single instillation of a chemotherapeutic agent after transurethral resection (TUR) of NMIBC and the treatment of intermediate-risk NMIBCs with either bacillus Calmette-Guérin (BCG) or chemotherapy. Dr. Palou, as a coauthor of the EAU guidelines on NMIBC, explained and supported the decisions outlined in the guidelines [1], while Dr. Brausi discussed and criticised the final statements of the committee. A discussion of the conclusions of this well-structured and successful debate is relevant to urologists in their everyday practice in the community setting and will hopefully encourage a more uniform approach to NMIBC management.

2. Evidence acquisition

The most important recent articles published in peer-reviewed journals in 2009 and not available at the time of the drafting of the 2008 EAU guidelines were evaluated and discussed. Large, randomised, prospective, multicentre studies and new meta-analyses on the two topics under discussion were produced and reported. The results of older but still relevant studies on the use of one immediate single instillation after TUR of NMIBC were also reevaluated.

A Medline search was conducted to identify published literature in the English language related to the treatment of NMIBC. Keywords included *non-muscle-invasive bladder cancer*, *bacillus Calmette-Guérin*, *intravesical chemotherapy*, and *transurethral resection of the bladder tumour*. The lists of review and original papers generated by the search were reviewed to identify additional applicable literature. The articles with the highest level of evidence were identified and were critically reviewed. Modifications of the EAU guidelines were recommended, as appropriate.

3. Evidence synthesis

3.1. Transurethral resection of the bladder tumour and an immediate single postoperative instillation of chemotherapy

3.1.1. EAU guidelines and supporting evidence

The EAU guidelines recommend transurethral resection of the bladder tumour (TURBT) as the gold standard for the

initial diagnosis and treatment of NMIBC [1–6]. After TURBT, the 10-yr disease-specific survival is 85% for Ta tumours and 70% for T1 tumours [7]. The EAU guidelines [1] also advocate an immediate single instillation of chemotherapy following TURBT for the treatment of all NMIBC, regardless of level of risk. A European Organisation for the Research and Treatment of Cancer (EORTC) meta-analysis showed that a single, immediate instillation of intravesical chemotherapy following TURBT results in a 12% absolute reduction in tumour recurrence (decrease of 39% in odds of recurrence). No significant differences in efficacy were noted among the chemotherapeutic agents studied [8], indicating that the choice of chemotherapeutic drug is optional. In an American Urological Association meta-analysis, TURBT and single-dose mitomycin C (MMC) resulted in a 17% absolute reduction in recurrences compared to TURBT alone when all patient risk groups were considered [5].

3.1.2. Additional evidence

According to Sylvester et al [4], the number of patients needed to treat is 8.5, which means that at least 8–9 patients should be treated with one instillation of epirubicin or MMC after TUR to prevent one recurrence. The final conclusion is that after TUR, a relevant number of patients with NMIBC will receive an instillation of chemotherapy that will not be effective. We also have to ask what the risk of progression would be if these patients were left untreated. The risk of progression of untreated patients has been reported to be about 2% [9]. In addition, side-effects of chemotherapy instillations should be considered and evaluated. In a recent meta-analysis, about 22% of patients at low or intermediate risk complained of side-effects [10]. Finally, costs should be discussed. A relevant reduction in costs will be obtained if a single instillation of chemotherapy is administered only in single, primary, low-grade tumours. Timing of the instillation is important: Risk of recurrence has been found to double if the instillation is not given within 24 h of TURBT [11]. In fact, the best results have been noted when the chemotherapeutic instillation is given within a few hours of TURBT. However, an immediate, single instillation of chemotherapy should be avoided in cases of overt or suspected intra- or extraperitoneal perforation, as complications have been noted in these patients [12].

Despite level 1 evidence supporting its use, perioperative chemotherapy is not widely used. In the United States, only 4% of eligible patients received a single instillation of a chemotherapeutic agent after TUR [10].

Other important questions remain about the usefulness of a single instillation after TUR.

3.1.2.1. Is a single instillation of chemotherapy after transurethral resection useful in multiple tumours? A recent meta-analysis [10] of eight randomised trials ($n = 1776$) including only patients with low- and intermediate-risk NMIBC found that the recurrence rate (RR) in patients who underwent TURBT plus an immediate chemotherapeutic instillation in all studies was significantly lower (24–62%) than in patients

who underwent TURBT alone (48–77%). However, this was evident only in primary single tumours; in patients with multiple tumours, there were no significant differences in RRs between the two groups. The conclusion: A single instillation of a chemotherapeutic agent after TUR is not useful for multiple tumours.

3.1.2.2. Is a single instillation of a chemotherapeutic agent after transurethral resection useful in high-grade patients? Dobruch and Herr [10] found that the impact of a single immediate postoperative chemotherapeutic instillation in high-grade tumours could not be assessed due to the small number of patients with these tumours (ie, >70% of patients presented with single, primary, low-grade tumours). However, a prospective randomised study by Zincke et al [13] found no significant benefit of a single immediate chemotherapeutic instillation following TURBT versus TURBT alone in patients with carcinoma in situ (CIS). In addition, results from a small randomised study by Cai et al also found no significant benefit of an early postoperative chemotherapeutic instillation in high-risk patients receiving BCG therapy. In this study, a single instillation of chemotherapy followed by BCG at the standard schedule was compared to BCG alone at the standard schedule [14]. The conclusion: A single instillation of chemotherapy is not useful in high-grade tumours.

3.1.2.3. Is a single instillation of chemotherapy useful in all tumours regardless of diameter? Recently, Berrum-Svennung et al showed that only small recurrences (ie, tumours <5 mm) are prevented by a single immediate chemotherapeutic instillation [15]. These tumours could easily be fulgurated using local anaesthesia at follow-up cystoscopy. The conclusion: A single instillation of chemotherapy is not useful in tumours >5 mm.

3.1.2.4. Does a single instillation last over time? Solsona et al found that a single instillation of MMC was able to decrease the rate of early recurrences (≤ 2 yr after TURBT) but not late recurrences (> 2 yr after TURBT) [16]. The conclusion: A single instillation of chemotherapy after TUR does not last > 2 yr).

3.1.2.5. Is a single instillation of chemotherapy useful in recurrent tumours? Gudjónsson et al found that treatment with a single, early instillation of epirubicin after TURBT reduces the likelihood of tumour recurrences in patients with primary, solitary NMIBC but provides no clear advantage in patients with recurrent or multiple tumours [17]. These findings suggest that the benefit of a single early chemotherapeutic instillation may be minimal in patients at intermediate or high risk of recurrence. The conclusion: A single instillation of chemotherapy after TUR is not useful in recurrent tumours.

Given these findings, further studies examining the value of a single immediate postoperative instillation of chemotherapy in patients with intermediate- and high-risk NMIBC are warranted. In the meantime, new recommendations

should be suggested to the urologic community. These recommendations are listed in the conclusions of this article.

3.2. Management of intermediate-risk disease

3.2.1. EAU guidelines and supporting evidence

The EAU guidelines recommend one immediate single instillation of chemotherapy after TUR, followed by either adjuvant BCG with maintenance (≥ 1 yr) or further instillations of chemotherapy (6–12 mo) for intermediate-risk NMIBC [1]. An EORTC meta-analysis of 24 trials ($n = 4863$) showed that BCG maintenance therapy was associated with a 37% reduction in the risk of tumour progression compared to the control groups (TURBT alone, TURBT plus intravesical chemotherapy, TURBT plus another immunotherapy) [18]. Another meta-analysis of nine trials comparing BCG to MMC found that BCG maintenance was significantly superior to MMC for the prevention of tumour progression [19].

3.2.2. Additional evidence

There are three important recent publications on intermediate-risk tumours that should be taken into account when considering the EAU guidelines.

The first study is an individual patient meta-analysis of the long-term outcome of nine randomised studies with 2820 patients comparing MMC to BCG for NMIBC [20]. Seventy-four percent of patients included were at intermediate risk. The mean follow-up was 4.4 yr. The conclusions were that BCG with maintenance was more effective than MMC in preventing recurrence, and there was no difference in progression, overall survival (OS), and disease-specific survival (DSS) between the two arms. However, a trend in favour of BCG in reducing progression was observed.

The second study looked at the long-term efficacy of maintenance BCG versus maintenance MMC instillation therapy in frequently recurrent TaT1 tumours without CIS and was a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-yr follow-up. The results showed an RR of 59% versus 80% in favour of BCG ($p = 0.005$). Fewer progressions ($p = 0.1$) and cancer-specific deaths ($p = 0.2$) were observed in patients treated with BCG. The conclusions were that maintenance BCG resulted in a significant long-term reduction in RR in intermediate-risk NMIBC compared to MMC. There was a weak trend for fewer progressions and cancer-specific deaths in patients who received BCG [21].

The third study is a phase 3 prospective randomised trial (30911) from the EORTC Genito-Urinary Group. This trial compared the long-term efficacy of six weekly intravesical instillations of epirubicin, BCG, and BCG plus isoniazid, followed by three weekly maintenance instillations at months 3, 6, 12, 18, 24, 30, and 36 after TUR in patients with intermediate- and high-risk NMIBC ($n = 837$). Median follow-up was 9.2 yr. Time to first recurrence ($p < 0.0001$), time to distant metastases ($p = 0.03$), and OS ($p = 0.02$) and DSS ($p = 0.03$) were all significantly prolonged in the two BCG arms compared to the epirubicin arm. The investigators concluded that both intermediate- and high-risk patients benefit from BCG therapy [22].

4. Conclusions

4.1. One immediate single instillation of chemotherapy after transurethral resection

There are no randomised studies comparing a single instillation after TUR followed by a cycle of six instillations of chemotherapy or BCG in intermediate- or high-risk NMIBC that show a benefit in favour of the single-instillation group. However, there are randomised studies (although they have some flaws) and other consistent data showing that one immediate single instillation of chemotherapy after TUR is not useful in intermediate- or high-risk tumours.

A complete TURBT is recommended for all patients with NMIBC; appropriate accepted TURBT techniques should be utilised, and a bladder diagram is advisable. An immediate, single, postoperative instillation of chemotherapy is recommended for all primary, solitary, low-grade NMIBCs, except in those with obvious or suspected bladder wall perforation. For these patients, no further therapy is necessary. The choice of chemotherapeutic agent is optional.

The EAU guidelines on one immediate single instillation should be rephrased as follows: “A single instillation of a chemotherapeutic agent after TUR should be administered only in primary, solitary, low-grade NMIBC. For these tumours, no further therapy is necessary.”

4.2. Treatment of intermediate-risk tumours

The available data in the literature do not allow us to declare chemotherapy better than BCG. Chemotherapy does not affect progression [23]. However, several studies and meta-analyses have reported that maintenance BCG reduces progression in intermediate-risk tumours and in high-risk tumours. A minimal reduction of 4% in progression rate has consistently been reported [9]. We can conclude that maintenance BCG in intermediate-risk NMIBC has considerable potential to reduce progression and cancer-specific mortality. Therefore, is it justified to treat a patient at this risk level (10% probability of progression) with instillation therapy other than the one that is believed to reduce the risk of progression?

The intermediate-risk tumour group is a heterogeneous group of tumours. We include in the same group a single, recurrent, low-grade NMIBC and five or more recurrent, low-grade tumours (two or three recurrences per year). We should categorise and select patients at intermediate risk into the following risk groups: (1) low- or intermediate-risk NMIBC (single, recurrent, low grade) and (2) intermediate- or high-risk NMIBC (multiple, recurrent, low-grade). Therapy should be tailored according to these risk groups: MMC for the low- or intermediate-risk group and BCG for the intermediate- or high-risk group.

Based on the review of the most recent data and evidence, we should recommend the following treatment for intermediate-risk disease: BCG induction plus maintenance following a complete TURBT should be the first

option, with chemotherapy induction plus 6–12 mo maintenance for patients who do not tolerate BCG.

Further studies on intermediate-risk patients are needed to better identify the risk level of each patient and therefore the most appropriate therapy.

Conflicts of interest

The author has nothing to disclose.

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