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Challenging the EAU Guidelines Regarding Early Repeat Transurethral Resection

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Abstract

Background: Many authors have recently proposed early repeat transurethral resection (re-TUR) of the bladder for non-muscle-invasive bladder cancer (NMIBC). The European Association of Urology (EAU) guidelines suggest it as a mandatory procedure for patients with Ta-T1 high-grade transitional cell carcinoma (TCC) of the bladder when an incomplete TUR has been performed, in the case of multiple and large tumours, or if the pathology department reports the bladder specimen does not contain muscle tissue.

Objective: To discuss and challenge the EAU Guidelines on re-TUR by evaluating the studies available in the literature that led the NMIBC Guidelines committee to its conclusions.

Discussion: The best data reported in the literature suggesting a real benefit of re-TUR in all T1 TCC of the bladder comes from referral centres that treat patients who had their first TUR done in other institutions. An understaging rate of up 40% has been reported; however, these are not the patients we normally see in our practice. Many university hospitals reporting negative data on recurrence and progression after a second TUR had most of the first TURs performed by young residents (>70% of the cases). In addition, all the studies considered are retrospective. Recent data from experienced centres showed that the rate of understaging (pT2) after a second TUR was reduced to 0–4%. Finally, in high-risk T1 TCC, immediate radical cystectomy is indicated; therefore, these patients do not need an early re-TUR.

Conclusions: An early re-TUR in patients with NMIBC is indicated only in selected cases: when muscle tissue is not present in the specimen, when the surgeon or pathologist is not completely certain of the procedure or of the diagnosis when patients are referred by other institutions, and/or when a bladder-sparing procedure is planned.

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1. Introduction

In 2010, the European Association of Urology (EAU) guidelines committee for the treatment of non-muscle-invasive bladder cancer (NMIBC) met to update the 2008 guidelines on NMIBC. However, the paragraph regarding the indications of a second resection (repeat transurethral

resection [re-TUR]) was not changed. It reads as follows: “A repeat TUR should be considered when the initial resection has been incomplete (eg, cases where multiple and/or large tumours are present) or when the pathologist has reported that the specimen contains no muscle tissue. Repeat TUR should be performed when a high-grade Ta-T1 tumour is diagnosed or when a T1 tumour was detected at

the initial TUR" [1]. More recently, Babjuk, commenting on an article that appeared last year in *European Urology* [2], stated, "In this moment re-TUR is an unavoidable procedure for the treatment of NMIBC." The present article discusses the reasons for not following these guidelines.

2. Background

By definition the EAU guidelines are based on the results of the most important studies that have appeared in peer journals. However, no randomised trials on re-TUR were available in the literature until 2008, and the trials that were considered contain flaws and relevant discrepancies.

One example is the study from the Memorial Sloan-Kettering Cancer Centre published in 2005 [3]. In this study, Herr retrospectively evaluated the concordance of the pathologic diagnosis between an initial TUR and a second TUR in 150 patients. The results of the second resection changed the treatment in 33% of patients. He noted the inability to diagnose T1 tumours accurately without muscle tissue in the specimen. Of 23 patients with T1 lesions without muscle tissue in the primary resection, 11 (49%) were upstaged to T2 after review of the second TUR specimen. However, in this study, different urologists performed the first and second TUR, different pathologists read the first and second bladder tumour specimens, the time between initial and subsequent TUR varied, and it is not certain that a complete TUR was attempted initially. In addition, most of the patients were referred from other institutions, and the amount of muscle tissue present in the specimen that was reported by this group did not exceed 61%.

Recently Divrik et al [4] reported the results of a prospective randomised trial evaluating the impact of routine second TUR on the long-term outcome of patients with newly diagnosed T1 urothelial carcinoma. A total of 210 patients with pT1 transitional cell carcinoma (TCC) of the bladder were included: 105 patients received a second TUR 2–6 wk after the initial TUR (group 1); 105 patients had only the initial TUR (group 2). All the patients had only one mitomycin C instillation within 24 h of TUR. The mean follow-up was 66.1 mo. The results showed that in patients receiving a second TUR, residual tumour was found in 33.3% and the rate of pT2 was 7.6%. Four more patients were diagnosed with T1 plus carcinoma in situ (CIS). A major change in the treatment was adopted in 76% of the patients. The risk of CIS or pT2 was correlated with grade (2% vs 19.6%), size >3 cm (5.5% vs 14.7%), and more than one tumour (5.7% vs 17.3%).

Recurrence-free survival (RFS) was 52% in group 1 and 21% in group 2 ($p = 0.0001$). The mean RFS was 64.6 mo versus 51 mo in favour of patients receiving the second TUR. However, the number of deaths in the two groups was the same, 32% versus 36%. Only 5 of 30 patients in group 1 died of cancer compared with 11 of the 35 patients in group 2 ($p = 0.038$).

The authors concluded that a second TUR significantly decreased the recurrence and progression rate in patients with newly diagnosed T1 TCC of the bladder.

This article, commented on by Babjuk [2] and Novara and Ficarra [5], even though it was prospective and randomised, contained many flaws. Fifty percent of the patients were classified as T1G1–G2. For some pathologists T1G1 tumours are very rare or do not exist, and G2 tumours, according to the 2008 World Health Organisation classification, are defined as low grade (70%) or high grade (30%) [6].

Therefore, a clear error of pathologic classification exists, and the results obtained should be reevaluated in the light of the new classification. The authors did not mention the percentage of muscle tissue present in the specimen at the first TUR and/or the average percentage of muscle tissue in their institution. This information is one of the most important parameters of quality.

Most of the studies quoted in the article were relatively old (2001–2004). Nearly 8% of patients upstaged by the second TUR were excluded from the study after randomisation. Patients in this arm were better selected and therefore had better outcomes. Disease-specific survival of patients excluded after randomisation is a must. The trial did not fulfil the criteria of randomised studies: It was not registered. In conclusion, this study, which is the only prospective randomised one on this subject, should not be taken into consideration when defining the guidelines on NMIBC.

3. Discussion

We have defined parameters for evaluating the quality of our TURs. These are clinical parameters, such as the 3-mo recurrence and complication rate, and pathologic parameters, such as the amount of muscle tissue present in the resected specimen or associated CIS detected.

However, these parameters were not mentioned as baseline parameters in the most important articles collected for the EAU guidelines [1]. In these articles all the authors underlined the absolute need for a second TUR for reducing recurrence and understaging, but they never reported their personal data on the rate of muscle tissue present in the TUR specimen or any attempt made for improving their TURs.

We demonstrated that when dedicated teaching programmes for the treatment of NMIBC were adopted in selected centres, the 3-mo recurrence rate (3-RR) decreased from 28% to 16% and the amount of muscle tissue present in the resected specimen increased from 50% to 84%, respectively, even in not very experienced hands (ie, residents) [7].

Why should we "deliberately" re-resect a patient with NMIBC twice? If we do so, we admit we performed an incomplete, insufficient, wrong operation, an inadequate TUR. This is very clear from the data reported by the European Organisation for Research and Treatment of Cancer (EORTC) [8] where the 3-RR varied from 3.4% to 46% between different institutions and was not explained by the characteristics of the tumour but by the surgeon. However, not all the EORTC centres participating in the studies included had poor results. Some centres reported a 3-RR rate of 3.4%, 6%, and 8%. We should concentrate more

on the experienced centre with low 3-RR and try to find and discuss the reasons for their good results rather than reporting data based on old experiences.

Why is an inadequate TUR performed so frequently in Europe? The reasons are multiple and variable: too little or no time dedicated to our residents from staff members for teaching TUR. Urologists do not think enough about the real consequences of an incomplete or inadequate TUR. We are often too busy and always rushed. The most frequent reason I found is that most urologists consider TUR a small and easy operation. In fact, it is one of the first procedures that residents perform alone in the operating room. Finally, technology can also play a role. Obsolete or inappropriate technology can result in inadequate operations. The real solution to overcome the need for early re-TUR in NMIBC is to improve our initial TUR.

4. Conclusions

After a thorough evaluation of the available literature, we think that early re-TUR should be considered mandatory only in selected cases: when muscle tissue is not present in the first TUR specimen, when the surgeon is uncertain of the first TUR, when pathologists are uncertain about the correct staging/grading, in patients referred from other specialists or institutions (30% discrepancy in staging/grading), and when a bladder-sparing approach is planned. In all other cases, re-TUR is optional and depends on the accuracy of the first TUR.

Teaching programmes on TUR of NMIBC should be a specific part of urologic training for residents at the university. The EUA also should address this issue during the European School of Urology and EAU Section of Oncological Urology courses and meetings.

We must invest our effort and resources in teaching, not in redoing procedures we should do better at the beginning.

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Conflicts of interest

The author has nothing to disclose.

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