



Editorial

An Immediate Instillation after Transurethral Resection of Bladder Tumor in Non–Muscle-Invasive Bladder Cancer: Has the Evidence Changed?

Richard J. Sylvester^{a,*}, Willem Oosterlinck^b

^a EORTC Headquarters, Brussels, Belgium

^b Department of Urology, Ghent University Hospital, Ghent, Belgium

In the last year, three papers [1–3] have been published suggesting that an immediate instillation after transurethral resection of bladder tumor (TURBT) should be abandoned in multiple or high-grade non–muscle-invasive bladder tumors and that it is clinically meaningless in low-risk tumors. Are their arguments correct?

The European Association of Urology (EAU) guidelines on non–muscle-invasive urothelial carcinoma of the bladder (and, to a lesser extent, the American Urological Association guidelines) recommend that an immediate instillation of chemotherapy be given after TURBT in all patients with non–muscle-invasive bladder cancer [4,5]. The one exception is in patients with an extended TURBT, for whom there is a risk of bladder perforation and extravasation of the drug.

The basis for these recommendations is a meta-analysis published in 2004 (1476 patients) that showed a reduction of 39% in the odds of recurrence in patients who received one immediate instillation as the sole treatment after TURBT [6]. There was a clear effect in patients with a single tumor (odds ratio [OR]: 0.61, $p = 0.0005$; 849 patients from four studies) and a strong suggestion of an effect in patients with multiple tumors (OR: 0.44, $p = 0.06$; 111 patients from two studies). It was emphasized that an immediate instillation was, by itself, insufficient treatment in patients with multiple tumors who are at high risk of recurrence.

Studies that have been published after the meta-analysis [6] have not contradicted the conclusions of the meta-analysis or the EAU guidelines. Berrum-Svennung et al confirmed the results of the meta-analysis and found that a single instillation of epirubicin as the only treatment after TURBT significantly delayed the time to first recurrence during the 2-yr study period ($p = 0.02$) [1]. Gudjonsson et al

also found that a single instillation of epirubicin after TURBT significantly delayed the time to first recurrence during a follow-up period extending up to 6 yr when no further treatment was given prior to recurrence ($p = 0.016$) [2].

Cai et al studied the effect of an immediate instillation in 161 high-risk patients scheduled to receive 3 yr of treatment with bacillus Calmette-Guérin (BCG) [3]. It is only in this study that no statistically significant difference between the two treatment groups was detected for time to first recurrence ($p = 0.095$). This study, however, was largely underpowered to detect realistic differences in treatment efficacy, so the results of this trial are inconclusive despite showing a trend favoring an immediate instillation. At a median follow-up of 15 mo, 50.6% were recurrence free in the control group versus 57.5% in the group that received an immediate instillation [7].

Despite the support of these findings, these same authors have questioned the benefit of an immediate instillation:

- An immediate instillation prevents only small tumor recurrences, and half of them can be easily fulgurated in the office under local anesthesia [1].
- An immediate instillation is not cost effective, as >8.5 patients should be treated to spare one TURBT [1].
- An immediate instillation is not useful in higher risk patients [1–3].

In patients with good-quality TURBT and a strict follow-up schedule, most recurrences should be small. A reduction in the overall recurrence rate, even in the rate of small recurrences, may, as advocated in the EAU guidelines,

* Corresponding author. EORTC Headquarters, 83 avenue E Mounier, Bte 11, 1200 Brussels, Belgium. Tel. +322 774 1613; Fax: +322 772 3545. E-mail address: richard.sylvester@eortc.be (R.J. Sylvester).

permit a less aggressive follow-up schedule in low-risk tumors and spare patients the psychological stress associated with a recurrence [8]. Although hospitalization and anesthesia are spared, cystoscopy with fulguration remains an aggressive procedure and TURBT was still necessary in half of the patients who recurred.

With regard to cost effectiveness, one cannot deny that many patients may receive the instillation without medical benefit. Cost benefit depends on many factors that are not medical alone and especially depends on the health care system in a given country. No proper cost comparisons have been made to date.

With regard to the usefulness of immediate instillation in higher risk patients, Berrum-Svennung et al did not specifically look at this issue in their study [1]. Gudjonsson et al [2] found that an immediate instillation prevented recurrence in the low-risk patients (approximately 50% of the patients), that is, in primary patients, in patients with single tumors, and in patients with a modified European Organization for Research and Treatment of Cancer (EORTC) risk score <3. They claimed, however, that there was little or no benefit in patients who were at intermediate or high risk of recurrence, that is, in recurrent patients, in patients with multiple tumors, and in patients with a modified EORTC risk score of ≥ 3 .

It should be remembered that an immediate instillation works through the destruction of circulating tumor cells that could implant at the site of the resection and through the chemoresection of residual disease after TURBT. The effect of an immediate instillation occurs early on, mainly during the first 1 or 2 yr, with a possible dilution of the treatment effect with longer follow-up [9]. In this new study by Gudjonsson et al [2], which is underpowered to make reliable subgroup analyses, the follow-up extended out to 6 yr, potentially diluting the size of any treatment effect occurring within the first 2 yr of follow-up. In 117 patients with multiple tumors, there was some separation in the time to recurrence curves, starting at 6 mo in favor of the immediate instillation group, that disappeared at 2 yr. At 1 yr in patients with multiple tumors, approximately 35% were recurrence free after an immediate instillation as compared with 20% after TURBT alone. These results are consistent with those of the meta-analysis [6], in which for patients with multiple tumors, 35% remained recurrence free after an immediate instillation as compared with 18.5% after TURBT alone. As in the meta-analysis, in which the suggestion of a benefit in patients with multiple tumors was based on concordant results in two studies, the number of patients with intermediate- to high-risk tumors in this new study [2] is also too small to draw definitive conclusions in this subgroup.

Where does all this leave us? The three new trials mentioned above do not allow us to draw any definitive conclusions beyond those given in the meta-analysis. They should not be used as a justification not to give an immediate instillation in certain subgroups of patients, such as in those patients who are at intermediate or high risk of recurrence. The real issue in intermediate- and high-risk patients is not whether an immediate instillation

provides any benefit as compared with TURBT alone but rather the role of an immediate instillation in patients who will receive additional intravesical instillations of chemotherapy or BCG.

Unfortunately, this issue cannot currently be addressed with hard data. No conclusions can be drawn from the Cai et al study with BCG due to the flaws mentioned above [3,7]. The value of an immediate instillation in patients receiving additional chemotherapy was assessed in a recent systematic review of the role of intravesical chemotherapy. Based on very limited data from five studies in mixed patient populations, the results suggest that an immediate instillation may still be necessary if further chemotherapy is given during only 6 mo; however, the instillation might not be necessary if chemotherapy is given during 12 mo. An immediate instillation might not be less effective than a delayed course of multiple instillations in low- to intermediate-risk patients [10]. Obviously, there are economic, convenience, and quality-of-life reasons to limit the number of instillations to as few as possible.

The only way to be able definitively to determine the value of an immediate instillation in intermediate- and high-risk patients is to carry out well-conducted randomized phase 3 trials according to today's standards. This includes assessment in patients undergoing fluorescent cystoscopy/TURBT and in patients undergoing a second TURBT. While these procedures may result in less residual disease, the risk of implantation is still present. Additionally, further health economic assessments are required to get a proper overview of this topic.

Current subgroup analyses clearly are exploratory and have their dangers and limitations. Until there is sufficient evidence to the contrary, we believe that an immediate instillation after TURBT should still be recommended in all patients with non-muscle-invasive bladder cancer.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] Berrum-Svennung I, Gransfors T, Jahnsen S, Boman H, Holmang S. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. *J Urol* 2008;179:101–6.
- [2] Gudjonsson S, Adell L, Merdasa F, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomised multicentre study. *Eur Urol* 2009;55:773–80.
- [3] Cai T, Nesi G, Tinacci G, et al. Can early single dose instillation of epirubicin improve bacillus Calmette-Guérin efficacy in patients with nonmuscle invasive high risk bladder cancer? Results from a prospective, randomized, double-blind controlled study. *J Urol* 2008;180:110–5.
- [4] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2008;54:303–14.
- [5] Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol* 2007;178:2314–30.

- [6] Sylvester RJ, Oosterlinck W, van der Meijden APM. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol* 2004;171:2186–90.
- [7] Sylvester RJ, Oosterlinck W, O'Donnell M. Letter to the editor. Re: Cai T, Nesi G, Tinacci G et al. Can early single dose instillation of epirubicin improve bacillus Calmette-Guérin efficacy in patients with nonmuscle invasive high risk bladder cancer? Results from a prospective, randomized, double-blind controlled study. *J Urol* 2009;181:410.
- [8] Oosterlinck W, Sylvester R, editors. Letter to the editor. Re: Berrum-Svennung I, Gransfors T, Jahnsen S, Boman H and Holmang S. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. *J Urol* 2008;180:2255–6.
- [9] Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow up. *J Urol* 1999;161:1120–3.
- [10] Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. *Eur Urol* 2008;53:709–19.