Perioperative Intravesical Chemotherapy in Non–Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis

Michael R. Abern, MD; Richmond A. Owusu, BS; Mark R. Anderson, MD; Edward N. Rampersaud, MD; and Brant A. Inman, MD, MS, FRCSC

Abstract
The role for a single dose of intravesical chemotherapy (IVC) after transurethral resection (TUR) remains unclear in patients with non–muscle-invasive bladder cancer (NMIBC). Several recent randomized clinical trials (RCTs) have evaluated its effect on recurrence, prompting this systematic review of RCTs comparing a single immediate postoperative dose of IVC versus placebo within 24 hours of TUR of NMIBC, and this meta-analysis using a random-effects model to predict the pooled relative risk (RR) of tumor recurrence. Subanalyses pooled studies by drug type and a meta-regression was performed to determine the effect of underlying patient risk factors on the efficacy of a single dose of IVC. A total of 3103 patients were randomized in the 18 RCTs that met inclusion criteria. The recurrence rate in patients receiving perioperative IVC and TUR was 37% versus 50% in the TUR-alone group. The pooled RR of recurrence for IVC and TUR was 0.67 (95% CI, 0.56–0.79), corresponding to a 13% absolute reduction and a number needed to treat of 7.2 patients to avoid 1 recurrence. The proportions of patients with tumor risk factors (T1, high-grade, multifocal, or recurrent) were not associated with IVC efficacy. A single dose of IVC administered within 24 hours of TUR of NMIBC was found to result in a reduction in tumor recurrence (RR, 0.67; 95% CI, 0.56–0.79). Patients with higher-risk tumor features seem to benefit at a similar rate.

Currently, 2.4% of all people born in the United States will develop bladder cancer during their lifetime. In 2012, the estimated incidence of bladder cancer was 73,510, with a 3:1 male-to-female ratio, and accounted for 14,880 deaths. At initial presentation, 75% to 85% are non–muscle-invasive bladder cancers (NMIBCs), which include stages Ta, T1, and Tis. Several studies have shown a benefit of immediate intravesical chemotherapy (IVC) after transurethral resection (TUR) in reducing tumor recurrence. In 2004, Sylvester et al performed a meta-analysis of 7 randomized clinical trials (RCTs) comparing cancer recurrence rates in patients undergoing TUR alone against a combination of TUR and a single immediate postoperative dose of IVC. The study found that over a median follow-up of 3.4 years, 37% of patients in the combined group had experienced a recurrence compared with 48% in the TUR-alone group (odds ratio, 0.61; 95% CI, 0.49–0.75).

Since the Sylvester meta-analysis, several additional RCTs have been performed, some with new chemotherapeutic agents, showing conflicting results regarding the effect of single-dose IVC on NMIBC recurrence. As a result, existing clinical guidelines provide differing recommendations to practitioners. For example, the American Urologic Association does not recommend the routine use of a single dose of IVC immediately after TUR for patients without a diagnosis of bladder cancer because of diagnostic uncertainty and increased cost. Rather it is listed as optional for men with small-volume, low-grade Ta bladder cancer. The European Association of Urology, however, does recommend that a single dose of immediate postoperative IVC be administered after TUR of a bladder lesion, with additional therapy decisions based on EORTC risk category. Finally, NCCN recommends a single dose of IVC within 24 hours of a “nonextensive” TUR of a bladder tumor during which the bladder was not perforated.

In light of new RCTs and conflicting clinical guidelines, the authors sought to reassess the effect of im-
mediate postoperative IVC through performing an updated systematic literature review and meta-analysis. The primary goal is to determine the effect of a single dose of IVC after TUR on NMIBC recurrence rates. In addition, the authors seek to analyze whether this effect varies by drug or by baseline patient risk factors.

Methods

Literature Search Strategy
The authors searched the Cochrane Controlled Trials Register (CENTRAL), ClinicalTrials.gov, PubMed, and Embase electronic databases for studies published in all available years and in any language. Search concepts were defined for the intervention, disease state, and study type and were combined. The exploded MeSH search terms used to identify articles were “controlled clinical trial,” “intravesical administration,” and “urinary bladder neoplasms.” In addition, reference lists of included studies were screened for missed studies.

Selection Criteria
The study included RCTs that compared TUR alone with the combination of TUR and a single dose of IVC (TUR+IVC) administered within 24 hours of surgery for the treatment of bladder cancer. Figure 1 depicts the search results and manuscript screening process, including reasons for trial exclusion. No manuscript was excluded based on method of analysis, definition of success, language of publication, or perceived quality. Criteria required that at least 75% of study patients not be previously reported.

Outcome and Underlying Risk Assessment
The primary outcome was bladder cancer recurrence. Time to recurrence and landmark analyses were not performed because of variability in trial design and reporting, making these analyses impracticable. Additionally, wherever possible, the authors abstracted clinical factors known to affect the underlying bladder cancer recurrence risk, including tumor size, multifocality, grade, stage, number of prior tumor occurrences, and the presence of carcinoma in situ (CIS).

Statistical Methods
Individual study effect sizes were expressed as relative risks (RR) with their 95% confidence intervals (95% CI) and examined with forest plots. Individual studies were pooled into a summary RR using an inverse variance weighted random-effects model with a restricted maximum likelihood estimator of residual heterogeneity ($\tau^2$). Between-study heterogeneity was measured using $\tau^2$ and the Higgins-Thompson $I^2$ statistic, and homogeneity was tested with Cochran’s Q test. To examine for potential temporal trends in study outcomes, a cumulative pooling was performed, indexed on the year of study publication. Publication bias was investigated using cumulative pooling (this time with study variance as the indexing variable), funnel plots (using both the Duval-Tweedie trim and fill method and Egger’s test for asymmetry), normal quantile (QQ) plots, and Galbraith radial plots. The sensitivity of this
analysis to influential individual studies was evaluated using a leave-one-out (aka jackknife) approach and by verifying studentized residuals, Cook’s distance, and DFFITS. Finally, to examine the effect of underlying risk on effect size, mixed-effects meta-regression models were created using study-level patient risk variables of multifocality, grade, stage, and number of prior recurrences as effect moderators. These models were summarized using bubble plots, with the bubble area inversely proportional to individual study variance. All statistical analyses were performed using R 2.14.2 with packages metafor, Hmisc, and car installed.

### Results

A total of 18 RCTs published between 1976 and 2011 met the selection criteria and were included in the analysis (Table 1). These studies used 7 drugs and a variety of doses and dwell times. Because 10 of the studies excluded patients with CIS, and only 2 explicitly reported the number of patients with CIS, this factor could not be used as a predictor of recurrence. Only 11 studies reported all of the 4 examined predictors of tumor recurrence, with only 6 reporting tumor sizes. Although 13 studies reported some data on toxicity, only 8 of these reported toxicity in the control group, making comparisons difficult.

#### Tumor Recurrence

Overall, 3103 patients were randomized in the 18 analyzed trials, of which 43% experienced recurrence (1346/3103). In the TUR-alone group, 50% (769/1527) of patients experienced recurrence compared with 37% (577/1576) in the TUR+IVC group. This corresponds to a 13% absolute reduction in recurrence and a number needed to treat of 7.2 patients to avoid 1 recurrence. Although 17 trials favored TUR+IVC, only 11 reached statistical significance. Using a random-effects model, the pooled RR of recurrence was 0.67 (95% CI, 0.56–0.79), in favor of TUR+IVC (Figure 2). Cumulative meta-analysis showed that the TUR+IVC treatment effect has been stable over time and not subject to temporal changes (Figure 3).

#### Study Drug, Dose, and Dwell Time

When trial outcomes were analyzed by drug, gemcitabine and interferon \( \alpha \)-2b did not show a benefit on recurrence, whereas the other 5 drugs did (Figure 4). Because epirubicin and mitomycin were administered to most of the patients in the trials, a separate random-effects model was performed on this subset. The RR for recurrence was 0.71 (95% CI, 0.64–0.78), which was similar to that of the overall analysis. The dwell time of the drugs ranged from 25 to 120 minutes, with 60 minutes being the most commonly reported duration of therapy. Drug doses and concentrations varied for thiotepa, epirubicin,
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Journal</th>
<th>Country</th>
<th>Drug</th>
<th>Dose</th>
<th>n</th>
<th>Multifocal</th>
<th>Low-Grade</th>
<th>pT1</th>
<th>CIS</th>
<th>Primary</th>
<th>Recurring</th>
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<td>Ali-El-Dein et al</td>
<td>1997</td>
<td>Br J Urol</td>
<td>Egypt</td>
<td>Epirubicin</td>
<td>50 mg/50 mL</td>
<td>55</td>
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<td>Urol J</td>
<td>Iran</td>
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<td>52%</td>
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<td>5% (8)</td>
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<td>UK</td>
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<td>42% (8)</td>
<td>0</td>
<td>20%</td>
<td>0</td>
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<td>Epirubicin</td>
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<td>20% (16)</td>
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<td>Egypt</td>
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<td>Actas Urol Exp</td>
<td>Spain</td>
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<td>Japan</td>
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<td>38% (78)</td>
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<td>1999</td>
<td>J Urol</td>
<td>Finland</td>
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<td>Multiple</td>
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<td>40 mg/40 mL</td>
<td>152</td>
<td>21% (32)</td>
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<td>0</td>
<td>100% (152)</td>
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<td>1983</td>
<td>J Urol</td>
<td>US</td>
<td>Multiple</td>
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<td>61</td>
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<td>5% (3)</td>
<td>34%</td>
<td>20%</td>
<td>12%</td>
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Abbreviations: CIS, carcinoma in situ; MRC, Medical Research Council Working Party on Urological Cancer. Subgroup on Superficial Bladder Cancer; UK, United Kingdom; US, United States.
and mitomycin. A statistically significant benefit in recurrence was seen for all except the lowest studied dose of thiotepa (30 mg/50 mL), although no clear dose–response relationships were seen for the other drugs.

**Underlying Patient Risk**

The 18 studies enrolled variable proportions of patients with high-risk (for recurrence) tumor characteristics. Most of the studies did not report the necessary data to calculate the EORTC risk classification system now widely used to stratify patients into low-, intermediate-, or high-risk of recurrence or progression. However, the authors were able to analyze the relationship between the proportion of patients with T1, multifocal, recurrent, and high-grade tumors and the RR for a single dose of perioperative IVC (Figure 5). None of these underlying risk factors significantly reduced between-study heterogeneity, suggesting that underlying risk could not be adequately accounted for in this analysis. Additionally, this analysis suggests that patients with tumors that are high-grade, T1, or multifocal or that are recurrent should not necessarily be excluded from receiving IVC in addition to TUR.

**Heterogeneity, Influence, and Publication Bias**

The overall I² measure of between-study inconsistency was 75%. To assess whether any individual study was particularly responsible for between-study heterogeneity in this pooling, the authors conducted a thorough study of influence. The leave-one-out analysis suggested that the De Nunzio et al study was an outlier, because the I² decreased to 75% from 61% when it was removed. When each of the other individual 17 studies was removed, the I² ranged from 71% to 77%, essentially unchanged from the overall pooled value of 75%, suggesting that none of the other studies was overly influential. Examination of plots of Cook’s distance, studentized residuals, and DFFITS also suggested that study pooling was sensitive to the De Nunzio study. The pooled RR for IVC increased from 0.67 (95% CI, 0.56–0.79) when all studies were included, to 0.72 (95% CI, 0.62–0.82) when the De Nunzio study was removed.

To examine the possibility of publication bias, the authors visually evaluated several plots, including the standard funnel plot, the Galbraith radial plot, the normal QQ plot, and the Duval-Tweedie trim-fill funnel plot. The plots suggested the existence of publication bias and this was confirmed with Egger’s test, which suggested that small trials in the analysis disproportionally contribute to the protective effect of IVC (z = –4.78; P <.001).

**Discussion**

A single dose of perioperative IVC after TUR was shown to reduce recurrence of NMIBC in a prior meta-analysis; however, recent RCTs have failed to...
show a significant benefit. Despite this, this updated meta-analysis redemonstrates a reduction of recurrence risk when IVC is given immediately after TUR. The authors also noted that significant clinical heterogeneity exists in the underlying studies, including variation in the type of drug used, the dose and dwell time, and, most importantly, differences in the tumor characteristics of the patients enrolled (ie, underlying risk). The authors therefore attempted to determine whether any particular drug was more effective and whether any particular group of patients did not benefit from treatment.

With regard to drug, gemcitabine and interferon had less efficacy with regard to the recurrence rate of NMIBC, although the pooled sample sizes for these drugs were modest. Contrarily, the pooled results for epirubicin, thiotepa, and mitomycin C suggested a significant reduction in recurrence rate. The dose for mitomycin (30–40 mg in a variety of concentrations) and epirubicin (50–80 mg in 100 mL) had little effect on the RR for recurrence. However, thiotepa administered as a 90-mg dose resulted in a significant reduction in recurrence, whereas the benefit was not demonstrated in the study that used one-third of that dose. The other 4 drugs represented in this analysis were only studied in 1 trial, making a dose–response analysis infeasible.

Although not statistically significant, studies with a higher proportion of patients with low-grade or unifocal tumors had better reduction in risk of recurrence with IVC, whereas a relationship between the proportion of patients with pT1 or recurrent tumors was less evident. However, these analyses should be considered exploratory and interpreted with caution, because they are at risk of ecologic bias/fallacy. One way to determine which patients benefit most from this intervention, and to determine the cost-efficacy.

Conclusions
A single dose of IVC administered within 24 hours of TUR of an NMIBC results in a reduction in tumor recurrence (RR, 0.67; 95% CI, 0.57–0.79). This benefit is present for mitomycin C, thiotepa, epirubicin, pirarubicin, and doxorubicin, but not for gemcitabine or interferon α. When analyzed at the study level, individual tumor risk factors, such as recurrent, multifocal, high grade, and T1 stage, did not appear to alter the efficacy of a single dose of IVC. Consistent reporting of tumor size and toxicities is needed to better understand which patients benefit most from this intervention, and to determine the cost-efficacy.

References
3. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer.
Perioperative Intravesical Chemotherapy in Bladder Cancer

Figure 5  Bubble plots displaying relative risk of tumor recurrence against baseline tumor risk factors. Solid line represents inverse variance-weighted meta-regression trend line. (A) Proportion of patients with pT1 tumors. (B) Proportion of patients with multifocal tumors. (C) Proportion of patients with recurrent tumors. (D) Proportion of patients with high-grade tumors.


