Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials


Authors’ objectives
To quantify the effect of intravesical chemotherapy on tumour recurrence following complete transurethral resection (TURB) in patients with newly diagnosed superficial bladder cancer.

Searching
Information retrieval was performed by previously described methods (see Other Publications of Related Interest no.1). A MEDLARS search was conducted covering 1966 to 1997. Cancerlit and the CD-ROM version of Current Contents were also searched. Bibliographies of all retrieved papers were manually searched. The search was limited to English language publications and published abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a minimum follow up of one year were eligible. Trials containing both patients with primary and recurrent disease were only included if data on patients with primary tumours could be analysed separately.

Specific interventions included in the review
Complete transurethral resection (TURB) alone was compared to TURB with adjuvant intravesical chemotherapy. The most commonly used drug was adriamycin, followed by mitomycin-C, thio-tepa, and cytosine arabinoside. Other drugs included epirubicin, peplomycin, neocarzinostat, and mitoxantrone. Duration of treatment ranged from a single instillation to protocols involving repeated instillation over 2 years.

Participants included in the review
Adult patients with primary superficial transitional cell carcinoma of the bladder (tumour stages Ta, T1 with or without carcinoma in situ) were eligible.

Patients with incomplete TURB were excluded. Patients with grade 1, 2 and 3 were included and none of the included patients had carcinoma in situ.

Outcomes assessed in the review
Tumour recurrence at 1, 2 and 3 years following resection was assessed.

How were decisions on the relevance of primary studies made?
A physician investigator screened initial citations in the form of abstracts.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The following data were extracted onto a data extraction form by two physicians: author and year of publication; study sample size; types of drugs used; drug dosage; and treatment schedule; duration of treatment; tumour stage or grade; and recurrence at 1, 2 or 3 years. Differences were resolved by consensus.

Methods of synthesis
How were the studies combined?
Summary odds ratios (OR) and 95% confidence intervals (CI) were calculated using the fixed-effect model of Peto et al (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Where heterogeneity was found the following potential sources were examined: length of treatment with studies stratified into:

1. Short-term protocols with either a single instillation or a few instillations delivered within a 2-month period.
2. 1-year protocols using multiple drug instillations over 1 year.
3. 2-year protocols consisting of multiple intravesical treatments over 2 years; and drug type (mitomycin-C, adriamycin, thio-tepa).

Results of the review
Eleven RCTs were included (3703 patients).

Bladder tumour recurrence at one year (all 11 studies): the use of intravesical chemotherapy highly statistically significant reduction of the recurrence rate. OR = 0.56 (95% CI: 0.48, 0.65; P < 0.00001). Statistically significant heterogeneity was found (Q = 55.6 with 20 degrees of freedom).

Investigation of heterogeneity: a wide variety in treatment schedules was used hence various elements of treatment schedules were investigated.

1. Length of treatment. a. Short term treatment (1258 patients): OR of 1-year recurrence = 0.70 (95% CI: 0.55, 0.90; P = 0.006). No significant heterogeneity was found (Q = 10.2).
   OR of 2-year recurrence = 0.68 (95% CI: 0.54, 0.85; P = 0.0007).
   b. 1-year treatment regimes (1721 patients): OR of 1-year recurrence = 0.65 (95% CI: 0.46, 0.80; P >= 0.0001). No significant heterogeneity was found (Q = 10.53 with 7 degrees of freedom). OR of 2-year recurrence = 0.69 (95% CI: 0.57, 0.83; P < 0.0001).
   c. 2-year regimes (5 RCTs, 575 patients): OR of 2-year recurrence after completion of 2 years of treatment = 0.27 (95% CI: 0.19, 0.39; P = 0.0001). OR of 1-year recurrence after one year of treatment = 0.20 (95% CI: 0.13, 0.29).

Tumour recurrence at 3 years (5 RCTs, 1371 patients): the use of intravesical chemotherapy statistically significant reduction in the recurrence rate. OR = 0.50 (95% CI: 0.40, 0.62; P < 0.0001). A stratified analysis was not possible due to the small number of studies.

Only three studies reported 5-year survival data making analysis of this end point impossible.

2. Drug type (mitomycin-C, adriamycin, thio-tepa).

No difference in effect was seen on recurrence due to statistical heterogeneity.

Adriamycin: significant heterogeneity was found. Q = 16.3 (P = 0.02).

Thio-tepa: significant heterogeneity was found. Q = 9.9 (P = 0.03).

Mitomycin-C: OR = 0.45. Q = 7.3 with 5 degrees of freedom (P > 0.01).

Authors' conclusions
Intravesical chemotherapy appears to have a major impact on decreasing the chance of recurrence of superficial
transitional cell carcinoma of the bladder. This is in contrast to prior analyses suggesting only modest efficacy in this clinical setting.

**CRD commentary**
The aims were stated and inclusion criteria defined in terms of study design, participants, intervention and outcome. Full details of the literature search were not presented in the review, though a reference was given to other sources of details of methods. By restricting the search to articles published in the English language, other relevant studies may have been omitted and no attempts were made to locate unpublished material. Validity was not assessed though included studies were limited to RCTs. Methods used to extract data were described and some relevant details of the primary studies were presented in tabular format. Statistical heterogeneity was assessed, reported and demonstrated in a forest plot and potential sources of heterogeneity explored. It was not reported whether data were extracted on an intention-to-treat basis and no mention was made of adverse reactions.

Without full details of the literature search, it cannot be judged whether most relevant studies were included and, given the heterogeneity among studies, caution must be applied when interpreting the results.

**Implications of the review for practice and research**
Practice: The authors state that intravesical chemotherapy appears to have a major impact on decreasing the chance of recurrence of superficial transitional cell carcinoma of the bladder.

Research: The authors draw attention to the lack of studies with long-term follow-up. They also state that the effect of intravesical chemotherapy on recurrence rates in patients with recurrent tumours may differ from those treated for primary disease, owing to differences in biology, and that they are conducting an additional meta-analysis including patients with recurrent tumours.

**Bibliographic details**

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**Other publications of related interest**

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Subject indexing assigned by NLM

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.