Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies


CRD summary
The review evaluated whether adjuvant chemotherapy was able to increase the overall and disease-free survival of patients with muscle-invasive bladder carcinoma who had undergone radical cystectomy. The authors concluded that the review results favour the use of adjuvant chemotherapy but larger studies are needed. Limitations in the review process and reporting mean that the conclusions have to be regarded with caution.

Authors' objectives
To evaluate whether adjuvant chemotherapy is able to increase the disease-free survival (DFS) and overall survival (OS) of patients with muscle-invasive bladder carcinoma who have undergone radical cystectomy.

Searching
MEDLINE and the ASCO, ESMO and Federation of European Cancer Societies websites were searched up to December 2004; the search terms were reported. In addition, the references of reviews and relevant articles were screened and relevant lectures from conferences were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies of patients randomised to receive or not receive chemotherapy after radical cystectomy, and who had not been previously treated with chemotherapy, were eligible for inclusion. Any chemotherapy regimen was eligible. The patients in the included studies received three or four cycles of cisplatin or cisplatin in combination with doxorubicin (epirubicin), cyclophosphamide, methotrexate and/or vinblastine.

Participants included in the review
Studies of patients with muscle-invasive bladder carcinoma were eligible for inclusion. Where reported, the median age of the patients in the included studies ranged from 59 to 64 years and the proportion of women from 10 to 26%.

Outcomes assessed in the review
Studies reporting DFS and OS were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. However, two reviewers independently performed all calculations. The number of events (death and disease-progression) were extracted directly, or were estimated from the median survival times assuming an exponential distribution of survival. If median survival times were not reported they were estimated from Kaplan-Meier curves.
Actual or estimated DFS and OS at 3 or 5 years and median survival times were also extracted, where reported. Risk ratios were calculated using the numbers of events for each survival outcome.

**Methods of synthesis**

How were the studies combined?
The RCTs were pooled in a statistical meta-analysis using both random-effects and fixed-effect models and were reported together with the 95% confidence interval (CI).

How were differences between studies investigated?
The reviewers assessed statistical heterogeneity using a chi-squared test (p<0.10 considered statistically significant).

**Results of the review**

Five RCTs (n=350) were included.

The pooled risk ratio of 0.74 (95% CI: 0.62, 0.88, p=0.001; based on 5 studies) for OS showed a significant benefit for adjuvant chemotherapy compared with surgery alone. The pooled risk ratio for DFS was 0.65 (95% CI: 0.54, 0.78, p<0.001; based on 4 studies), again showing a significant benefit for adjuvant chemotherapy. There was no evidence of statistical heterogeneity for either outcome (p=0.75 and p=0.10, respectively).

The 5-year absolute benefit in favour of adjuvant chemotherapy was 11% for OS and 16% for DFS. The number-needed-to-treat was 9 for OS and 6 for DFS.

**Authors’ conclusions**
The results favour the use of adjuvant chemotherapy but larger studies are needed. Current ongoing trials can help to better identify patients who would benefit from chemotherapy for muscle-invasive bladder carcinoma.

**CRD commentary**
The review stated a clear question and inclusion criteria. The search to identify published and unpublished studies was adequate but it was unclear whether any language restrictions were applied. It was also unclear whether any measures were taken to reduce errors and bias in the study selection and data extraction processes, and no validity assessments were performed. The analyses were based on the number of events, which had to be estimated from other reported summary statistics in most of the studies. The results for the number of events were not reported, making it difficult to assess the reliability of any estimation. The reporting of the evidence synthesis was problematic: it was unclear which survival time was analysed and there were inconsistencies between the text, tables and figures. It is also unclear whether the pooled results are clinically meaningful given the differences in the treatment protocols. Overall, due to limitations in the review process and reporting, the conclusions have to be regarded with caution.

**Implications of the review for practice and research**

Practice: The authors stated that the review should not have any direct implication for clinical practice. They also stated that as the presence of micrometastasis is one of the major causes of death in patients with muscle-invasive bladder carcinoma, chemotherapy given in the peri-operative setting should be considered a fundamental part of the integrated treatment.

Research: The authors stated that individual patient data meta-analyses and new, larger RCTs on adjuvant chemotherapy are needed.

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