Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder

Members of the Genitourinary Cancer Disease Site Group

The Practice Guideline was reviewed in May 2011 and put in the Education and Information section by the Genitourinary Cancer Disease Site Group (DSG) on October 24, 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol). This resulting Evidence-based Series (EBS) consists of the following 3 sections and is available on the CCO web site (http://www.cancercare.on.ca):

1. Summary
2. Full report
3. Guideline Review Summary

Release Date: November 5, 2012

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A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder

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Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder

E. Winquist, T. Waldron, R. Segal, J. Chin, H. Lukka, and the Members of the Genitourinary Cancer Disease Site Group

The 2005 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

Report Date: February 9, 2005

This practice guideline report replaces an earlier version of the report completed in 2001.

SUMMARY

Guideline Question

Should neoadjuvant chemotherapy be offered to patients with stage II or III bladder cancer before definitive local therapy with surgery and/or radical radiotherapy, with the intent of improving survival?

Target Population

These recommendations apply to adult patients newly diagnosed with stage II or stage III transitional cell carcinoma of the bladder.

Recommendations

- Neoadjuvant cisplatin-based combination chemotherapy is recommended prior to radical cystectomy, radical radiation therapy (with or without concurrent chemotherapy), or preoperative radiotherapy and cystectomy for the purpose of improving overall survival and disease-free survival.
- The current state of the evidence does not permit a recommendation for an optimal cisplatin-based combination chemotherapy regimen. However, the largest neoadjuvant trials have used standard methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) or cisplatin-methotrexate-vinblastine (CMV) for three cycles, and it is the opinion of the Genitourinary

Cancer Disease Site Group that these regimens are reasonable treatment options. Less toxic regimens such as gemcitabine-cisplatin and dose-intense MVAC plus granulocyte-colony stimulating factor have not been evaluated in randomized trials in this setting.

- Neoadjuvant single-agent cisplatin chemotherapy is not recommended.

Qualifying Statements

- MVAC and CMV chemotherapy are associated with high rates of some adverse effects. These effects should be discussed with patients, and treatment should be managed by physicians experienced in administering chemotherapy to those patients.
- These recommendations do not apply to patients with only superficial transitional cell carcinoma of the bladder, locally advanced bladder cancer that is surgically unresectable, or metastatic or bladder cancer of non-transitional histology.
- This guideline does not address the topics of concurrent chemotherapy given with radiotherapy or adjuvant chemotherapy. Adjuvant chemotherapy is addressed in a separate guideline developed by the Genitourinary Cancer Disease Site Group (see Related Guidelines).

Key Evidence

- Sixteen randomized controlled trials involving 3306 patients were identified that compared neoadjuvant chemotherapy before local therapy with local therapy alone in patients with transitional cell carcinoma of the bladder. All these trials evaluated cisplatin-based chemotherapy; three evaluated single-agent chemotherapy (n=376) and 13 evaluated combination therapy (n=2930). Patient accruals among these trials ranged from 28 to 976. Five trials of combination therapy were available in abstract form only (n=598). Five meta-analyses of the neoadjuvant chemotherapy trials were identified; the most recent of these include one based on individual patient data and another based on published data.
- In the meta-analysis based on individual patient data (n=2492 from nine trials) (1), the pooled hazard ratio for all trials (single-agent and combination) favoured neoadjuvant chemotherapy but was statistically non-significant (hazard ratio, 0.91; 95% confidence interval, 0.83 to 1.01; p=0.084). The results from a subgroup analysis showed that neoadjuvant combination chemotherapy (n=2116, from six trials) significantly improved overall survival compared with local therapy alone (pooled hazard ratio, 0.87; 95% confidence interval, 0.78 to 0.97; p=0.016) and was associated with a 13% reduction in the risk of death and a 5% absolute benefit at five years (overall survival increased from 45% to 50%). This treatment effect was observed irrespective of the type of local treatment and did not vary between subgroups of patients. Although cisplatin-based combination chemotherapy was beneficial, there was no evidence to support the use of single-agent cisplatin (pooled hazard ratio, 1.15; 95% confidence interval, 0.90 to 1.47; p=0.26). Disease-free survival, locoregional disease-free survival, and metastasis-free survival were also improved with combination chemotherapy in this meta-analysis.
- In the meta-analysis based on published data (n=2915 from 12 trials) (2), the pooled hazard ratio for all trials (single-agent and combination) was statistically significant (hazard ratio, 0.88; 95% confidence interval, 0.81 to 0.97; p=0.008) and represents a 12% reduction in the risk of death with chemotherapy compared with local therapy alone. In the subgroup analyses performed by type of chemotherapy, combination chemotherapy (n=2538 from eight trials) was associated with a statistically significant 14% reduction in the risk of death compared with local therapy alone (pooled hazard ratio=0.86; 95% confidence interval, 0.78 to 0.94; p=0.002), or an absolute survival benefit of 7% (overall survival increased from 50% to 57%). Single-agent cisplatin (n=377 from three trials) was not associated with a survival advantage (pooled hazard ratio, 1.11; 95% confidence interval, 0.86 to 1.43; p=0.41).
• The toxicities of cisplatin-based combination chemotherapy include nausea and vomiting, neutropenic sepsis in at least 10% of patients, and death in at least 1% of patients.

Future Research
• Patients who are candidates for neoadjuvant chemotherapy should be encouraged to participate in randomized controlled trials.

Related Guidelines

References
PREAMBLE: About our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

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I. QUESTION
Should neoadjuvant chemotherapy be offered to patients with stage II or III bladder cancer (1) before definitive local therapy with surgery and/or radical radiotherapy, with the intent of improving survival?

II. CHOICE OF TOPIC AND RATIONALE
Despite definitive local therapy with cystectomy and/or radical radiotherapy, approximately half of patients with muscle-invasive transitional cell carcinoma of the bladder (TCC) will ultimately die of their cancer, usually due to metastatic disease (2). Failure to cure is most often due to the presence of occult metastatic disease in sites beyond the margins of local therapy, indicating that radical local therapy alone is inadequate for the majority of patients with locally advanced TCC. Consequently, improvements in both local control and the survival of patients will require some form of effective systemic treatment.

Transitional cell carcinoma has been shown to be a chemosensitive malignancy; in phase II trials, at least a dozen different cytotoxic agents have demonstrated an effect in patients with advanced or metastatic disease (3). In the 1990s, randomized controlled trials (RCTs) studying metastatic TCC focused on determining the efficacy of chemotherapy regimens combining methotrexate, vinblastine, and cisplatin (CMV) or those agents plus doxorubicin (MVAC) (4-6). Improvements in overall response rate, progression-free survival, and overall survival favouring MVAC and CMV over conventional therapy were seen but at the expense of an increased frequency of toxic deaths and more severe myelosuppression, mucositis, and nausea and vomiting. Randomized trials in metastatic TCC reported this decade have focused on improving the effectiveness of MVAC by comparing it with combinations of gemcitabine-
cisplatin, high-dose-intensity MVAC plus granulocyte-colony stimulating factor (G-CSF), and cisplatin plus 5-fluorouracil (5-FU) and α-interferon (7-9). Although similar objective response and survival rates were observed, the former two regimens were associated with less toxicity than MVAC, and gemcitabine-cisplatin in particular is now currently in common use for the treatment of metastatic TCC.

The effectiveness of combination chemotherapy in metastatic TCC generated an interest in using it adjunctively in locally advanced TCC in an effort to improve local and systemic control, and RCTs were initiated nearly 20 years ago. The use and optimal timing of adjunctive chemotherapy remains controversial, and recent narrative reviews emphasize the limitations of the currently available clinical trial data (10,11). Chemotherapy has been given prior to (neoadjuvant) or following (adjuvant) definitive local therapy for bladder cancer, or concomitantly with radiotherapy. The theoretical advantages of neoadjuvant chemotherapy include the immediate treatment of micrometastatic disease, the ability to assess tumour response in vivo, a more effective delivery of chemotherapy before surgical disturbance and compromised patient performance status, and the theoretical possibility of bladder preservation in certain patients as a result of tumour downstaging (12). The main disadvantages to pre-emptive treatment are the time delay to definitive local therapy and the possibility of exposing some patients to unnecessary cytotoxic therapy based on inaccurate clinical staging of the disease. The potential advantages of neoadjuvant chemotherapy have made it the most frequently studied approach to adjunctive systemic treatment for locally advanced TCC. As such, the Genitourinary Cancer Disease Site Group (GU DSG) decided to systematically review the evidence on neoadjuvant chemotherapy in TCC to derive appropriate recommendations for treatment.

III. METHODS
Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (13). Evidence was selected and reviewed by two members of the PGI’s GU DSG and methodologists. Members of the GU DSG disclosed potential conflict-of-interest information. No conflicts were declared.

The practice guideline report is a convenient and up-to-date source of the best available evidence on neoadjuvant chemotherapy for TCC developed through systematic reviews and evidence synthesis. The body of evidence in this report is primarily comprised of mature RCT data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all practice guideline reports through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

A practice guideline report on the use of neoadjuvant chemotherapy in TCC was originally completed in 2001. With the publication of additional RCTs and meta-analytic reports, the GU DSG has revised and updated the 2001 report, replacing it with this document.
Literature Search Strategy

MEDLINE (January 1987 through March 2004, week 2), CANCERLIT (January 1987 through October 2002), and EMBASE (1980 through 2004, week 12) databases were searched for relevant papers. MEDLINE and CANCERLIT were searched using the following medical subject headings: “bladder neoplasms”, “carcinoma, transitional cell”, “chemotherapy, adjuvant”, and “neoadjuvant therapy”; EMBASE was searched using the following Excerpta Medica tree terms: “bladder tumor”, “bladder cancer”, “transitional cell carcinoma”, “drug therapy”, “chemotherapy”, “antineoplastic agents”, and “adjuvant therapy”. In each database, those subject headings were combined with disease and treatment-specific text words: “bladder neoplasm”, “bladder cancer”, “bladder carcinoma”, “carcinoma of the bladder”, “transitional cell carcinoma”, “neoadjuvant chemotherapy”, “neoadjuvant”, and “preoperative”. Those terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials.

In addition, the Cochrane Library databases (2003, Issue 4) and the conference proceedings of the American Society of Clinical Oncology (ASCO) (1990 through 2003) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Eligibility Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. They were fully published reports or abstracts of RCTs or meta-analyses that:
   a. compared neoadjuvant chemotherapy and definitive local therapy (cystectomy and/or radical radiotherapy with or without concurrent chemotherapy) with local therapy alone in patients with stage II or stage III TCC of the bladder.
   b. reported comparisons of overall survival and/or progression-free survival.
2. They were systematic reviews or evidence-based practice guidelines that addressed the guideline question.

Synthesizing the Evidence

Background

In the original guideline report completed in 2001, the GU DSG narratively summarized the results of 14 RCTs of neoadjuvant chemotherapy and one meta-analysis performed by the Advanced Bladder Cancer Overview Collaboration (ABCOC) (14) that pooled survival data from four of the 14 trials. The GU DSG did not perform their own meta-analysis of the trial data at that time because the majority of trials did not provide sufficient data to perform meta-analysis (seven of the 14 trials were either available only in abstract form or unpublished). The ABCOC meta-analysis has been updated twice (15,16), since the completion of the original guideline, to incorporate new trial data. The results of four more trials have been published (17-19) since the last ABCOC update in 2001. With the full publication of those four additional trials, the GU DSG decided to conduct their own meta-analysis. The GU DSG was aware that a large individual patient data (IPD) meta-analysis of the neoadjuvant chemotherapy trials was in progress by the Medical Research Council (MRC). However, they decided to proceed with a pooled analysis of the published data because IPD reports can sometimes take years to complete. Results from the MRC IPD meta-analysis were published in mid-2003 (20). The GU DSG meta-analysis was
also completed around that time and was published in early 2004 (21). The GU DSG meta-
analyses have been updated since that publication to include updated data from two of the trials
(18,19). The results of all five meta-analyses (ABCOC, MRC, and GU DSG) are summarized in
this practice guideline report.

Genitourinary Cancer Disease Site Group Meta-analysis Methods

The GU DSG considered overall survival and disease progression as the primary and
secondary endpoints for meta-analysis, respectively. The GU DSG planned to pool published
data on those endpoints for all trials and for particular subgroups of trials specified a priori.
Subgroup analyses were performed by type of chemotherapy: trials were categorized as either
evaluating single-agent or combination chemotherapy. Exploratory analyses by type of local
therapy (cystectomy versus other local therapies) and type of combination chemotherapy
(regimens including anthracyclines versus those not) were also performed.

The hazard ratio (HR) is the most appropriate statistic for pooling time-to-event
outcomes because it incorporates data from the entire survival curve and allows for censoring
(22). When the HR and its associated variance were available, those statistics were extracted
directly from the most recently reported trial results. Otherwise, the HR was estimated indirectly
from other summary statistics (e.g., 95% confidence intervals [CI] or p values) or from data
extracted from published Kaplan-Meier curves, using the methods of Parmar et al (22). If data
were not provided from which HRs could be derived, the trial was not included in the meta-
analysis. Chi-square tests were used to test for statistical heterogeneity among trials and to
assess the consistency of treatment effect across different subgroups of trials (23). Use of a
fixed-effect model was planned unless trial heterogeneity was apparent. The log-rank of
observed minus expected number of deaths and the variance of each trial were combined
across all trials to estimate an overall pooled HR. The pooled HR represents the overall risk of
death associated with neoadjuvant chemotherapy plus local therapy compared with local
therapy alone. HRs of 1.0 indicate no difference between treatment and control groups, HRs of
less than 1.0 favour neoadjuvant chemotherapy, and HRs greater than 1.0 favour local therapy
alone. Trial results were pooled using Review Manager 4.2.3 (Metaview © Update Software),
which is available through the Cochrane Collaboration.

IV. RESULTS

Literature Search Results

Twenty-two reports identified by the literature search represented 16 appropriate RCTs
of neoadjuvant chemotherapy for locally advanced TCC. The 16 RCTs are listed by comparison
in Table 1; three RCTs evaluated single-agent chemotherapy and 13 evaluated combination
chemotherapy as neoadjuvant treatment. The literature search also identified five systematic
reviews (14-16,20,24), four of which contained meta-analyses (14-16,20). A combined analysis
of two trials (Nordic Trials I and II) was also identified (25), but was omitted from this review
because both trials were included in recent meta-analyses. Notable trials excluded from this
review include those that evaluated adjuvant chemotherapy (26-31) or chemotherapy
concomitant with radiotherapy (32,33) and those that compared different neoadjuvant regimens
(34), or approaches combining neoadjuvant and adjuvant chemotherapy (35-38). Eleven of the
16 trials were published as full reports in journals (17-19,39-44), and five were published or
presented as abstracts (45-49).
Table 1. Trials included in this practice guideline report.

<table>
<thead>
<tr>
<th>No. of trials</th>
<th>No. of reports</th>
<th>Trial</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Trials comparing neoadjuvant single-agent cisplatin chemotherapy + local therapy vs. local therapy alone</td>
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<tr>
<td>3</td>
<td>4</td>
<td>CUETO, Spain</td>
<td>Martinez-Piñeiro, 1990 (50)</td>
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<tr>
<td></td>
<td></td>
<td>WMURG, UK</td>
<td>Wallace, 1991 (40)</td>
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<tr>
<td></td>
<td></td>
<td>ABCSG, Australia</td>
<td>Wallace, 1991 (40)</td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>Nordic I</td>
<td>Rintala, 1993 (52)</td>
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<tr>
<td></td>
<td></td>
<td>SWOG 8710 / Intergroup 0800</td>
<td>Grossman, 2003 (18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GISTV, Italy</td>
<td>Italian Bladder Cancer Study Group, 1996 (42)</td>
</tr>
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<td></td>
<td></td>
<td>International Collaboration of Trialists</td>
<td>International Collaboration of Trialists, 1999 (43) Hall, 2002 (53)</td>
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<td></td>
<td></td>
<td>DAVECA, 89-01</td>
<td>Sengolov, 2002 (17)</td>
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<tr>
<td></td>
<td></td>
<td>DAVECA, 89-02</td>
<td>Sengolov, 2002 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GUONE, Italy</td>
<td>Bassi, 1998 (54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTOG 89-03</td>
<td>Shipley, 1998 (44)</td>
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<tr>
<td></td>
<td></td>
<td>Font, Spain</td>
<td>Font, 1994 (46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nordic II</td>
<td>Sherif, 2002 (19)</td>
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<tr>
<td></td>
<td></td>
<td>Marcuello, Spain</td>
<td>Marcuello, 1996 (47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannobio, Italy</td>
<td>Cannobio, 1985 (48) Cannobio, 1994 (57)</td>
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<tr>
<td></td>
<td></td>
<td>Abol-Enein, Egypt</td>
<td>Abol-Enein, 1997 (49)</td>
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</table>

Abbreviations: ABCSG – Australian Bladder Cancer Study Group; CUETO – Clu-b Urológico Español de Tratamiento Oncológico; DAVECA – Danish Vesical Cancer Group; GISTV – Gruppo Italiano per lo Studio dei Tumori della Viscia/Italian Bladder Cancer Study Group; GUONE – Gruppo Uro-Oncologico del Nord Est/North Eastern Uro-Oncological Group; No – number; RTOG – Radiation Therapy Oncology Group; SWOG – Southwest Oncology Group; WMURG – West Midlands Urological Research Group.

Randomized Controlled Trials

A description of the 16 trials of neoadjuvant chemotherapy is provided in Table 2.

Trial Characteristics

Data on trial characteristics including methods of randomization and allocation concealment, whether analyses included all randomized patients, patient population, types of local therapy, and chemotherapy regimens (including drugs, doses, schedules, and the number of planned cycles) were extracted from each trial report. Only six trial reports (17-19,40,43) described the method of patient randomization; stratified randomization was employed in all six of those reports. The method of allocation concealment was reported in eight trial reports (17-19,39,40,43); central randomization procedures were used in each. Ten trials presented baseline demographic and clinical characteristics for treatment and control arms (17-19,39-41,43,44), and six of those reports (17,18,43,44) indicated that a balance in the distribution of important baseline characteristics was achieved between trial arms. Statistical analyses were based on all eligible randomized patients in only five trials (18,19,40,43).
The number of eligible randomized patients included in the 16 trials ranged from 28 to 976. The majority of patients were male (range, 79% to 88%; 11 trials), were staged with at least cT3 tumours (range, 68% to 100%; 10 trials), and had a World Health Organization (WHO) performance status of 0 (range, 0 to 2; seven trials; 99% of patients). The mean or median age range of patients was 61 to 66 years (11 trials). Ten trials used cystectomy alone (17-19,39,42,45-49) and three used radiotherapy alone (17,40) as the definitive local therapy. The remaining three trials used or allowed either cystectomy, radiotherapy, or both (41,43,44). All 16 trials used platinum-based neoadjuvant chemotherapy. Three trials assessed single-agent cisplatin (39,40), while the remainder evaluated combination chemotherapy. Five trials evaluated two-drug combinations of cisplatin with either doxorubicin, methotrexate (CM), or 5-FU (17,19,41,48), five trials evaluated cisplatin (MCV or CMV) or carboplatin (CaMV) with methotrexate and vinblastine (43,44,46,49,55), and three trials evaluated these drugs plus either doxorubicin (MVAC) or epirubicin (MVEC) (18,42,45). The number of planned chemotherapy cycles ranged from two to four. All planned cycles of single-agent cisplatin (39,40) were delivered in 75%, 88%, and 93.5% of patients, respectively. All planned cycles of CM (17), CMV (43), MVAC (18,45), and MCV (44) chemotherapy were delivered in 74% to 82%, 80%, 82% to 87%, and 84% of patients, respectively.

Table 2: Randomized trials of neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: descriptions.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Accrual Period</th>
<th>Disease Stage</th>
<th>No. Randomized (excluded)</th>
<th>Local Therapy</th>
<th>Drugs and Doses (mg/m²)</th>
<th>No. Planned Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent chemotherapy</strong></td>
<td></td>
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</tr>
<tr>
<td>CUTECA, Spain (39,50)</td>
<td>1984-1989</td>
<td>T2-T4a (Nx-2, M0)</td>
<td>122 (1)</td>
<td>cyst</td>
<td>C-100</td>
<td>3</td>
</tr>
<tr>
<td>WMURG, UK (40,51)</td>
<td>1984-1988</td>
<td>T2-T4 (Nx, M0)</td>
<td>159 (9)</td>
<td>RT 65 Gy</td>
<td>C-100</td>
<td>3</td>
</tr>
<tr>
<td>ABCSG, Australia (40)</td>
<td>1985-1988</td>
<td>T2-T4 (Nx, M0)</td>
<td>96 (9)</td>
<td>RT 55-65 Gy</td>
<td>C-100</td>
<td>2</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nordic I</td>
<td>1985-1989</td>
<td>T1G3-T4a (Nx, M0)</td>
<td>325 (14)</td>
<td>RT 20 Gy then cyst</td>
<td>CA, C-70 A-30</td>
<td>2</td>
</tr>
<tr>
<td>SWOG 8710 / Intergroup 0080 (18)</td>
<td>1987-1998</td>
<td>T2-T4a (N0, M0)</td>
<td>317 (10)</td>
<td>cyst</td>
<td>MVAC M-30-d1,15,22 V-3-d2,15,22 A-30-d2 C-70-d2</td>
<td>3</td>
</tr>
<tr>
<td>GISTV, Italy (42)</td>
<td>1989-1992</td>
<td>T2-T4 (N0, M0)</td>
<td>171 (18)</td>
<td>cyst</td>
<td>MVEC M-30-d1,15,22 V-3-d2,15,22 E-40-d2 C-70-d2</td>
<td>3</td>
</tr>
<tr>
<td>International Collaboration of Trialists (43,53)</td>
<td>1989-1995</td>
<td>T2G3-T4a (N0-x, M0)</td>
<td>976 (0)</td>
<td>cyst, RT, or RT then cyst</td>
<td>CMV C-100-d2 M-30-d1,8 V-4-d1,8</td>
<td>3</td>
</tr>
<tr>
<td>DAVECA 89-01, Denmark (17)</td>
<td>1989-1993</td>
<td>T2-T4b (Nx-3, M0)</td>
<td>33†</td>
<td>cyst</td>
<td>CM C-100 M-250</td>
<td>3</td>
</tr>
<tr>
<td>DAVECA 89-02, Denmark (17)</td>
<td>1989-1993</td>
<td>T2-T4b (Nx-3, M0)</td>
<td>120†</td>
<td>RT 60 Gy</td>
<td>CM As above</td>
<td>3</td>
</tr>
<tr>
<td>Trial</td>
<td>Accrual Period</td>
<td>Disease Stage</td>
<td>No. Randomized (excluded)</td>
<td>Local Therapy</td>
<td>Drugs and Doses (mg/m²)</td>
<td>No. Planned Cycles</td>
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<tr>
<td>GUONE, Italy (45,54)</td>
<td>1989-1995</td>
<td>CT2-CT4</td>
<td>206 (NR)</td>
<td>cyst</td>
<td>MVAC</td>
<td>4</td>
</tr>
<tr>
<td>RTOG 89-03(44)</td>
<td>1990-1993</td>
<td>T2-T4a (Nx, M0)</td>
<td>126 (3)†</td>
<td>RT 64.8 Gy + C, cyst if not CR after 39.6 Gy</td>
<td>MOV M-30-d1,15,22 C-70-d2 V-3-d2,15,22</td>
<td>2</td>
</tr>
<tr>
<td>Font, Spain (46)</td>
<td>1990-1994</td>
<td>T2-T3 (N0, M0)</td>
<td>28 (NR)</td>
<td>cyst</td>
<td>CMV</td>
<td>3</td>
</tr>
<tr>
<td>Nordic II (19)</td>
<td>1991-1997</td>
<td>T2-T4a (Nx, M0)</td>
<td>317 (8)</td>
<td>cyst</td>
<td>CM</td>
<td>3</td>
</tr>
<tr>
<td>Marcuello, Spain (47,55,56)</td>
<td>NR</td>
<td>T3b-T4a (N0, M0)</td>
<td>NR (66)</td>
<td>cyst</td>
<td>CaMV</td>
<td>3</td>
</tr>
<tr>
<td>Cannobio, Italy (48,57)</td>
<td>NR</td>
<td>T2-T4 (N0, M0)</td>
<td>104 (0)</td>
<td>cyst</td>
<td>CaMV Ca-350-d2 M-30-d1,d8 V-4-d1,d8</td>
<td>2</td>
</tr>
<tr>
<td>Abol-Enein, Egypt (49)</td>
<td>NR</td>
<td>T2 (Nx, M0)</td>
<td>196 (2)</td>
<td>cyst</td>
<td>CaMV</td>
<td>2</td>
</tr>
</tbody>
</table>

*This trial did not meet its accrual target and closed †this trial did not meet its accrual target and closed; the number of patients randomized and excluded from each trial arm was not clearly specified in the trial report; ‡this trial closed early due to high rates of neutropenia and sepsis.

Abbreviations: A – doxorubicin; ABCSG – Australian Bladder Cancer Study Group; C – cisplatin; Ca – carboplatin; CR – complete response; CUETO – Club Urológico Español de Tratamiento Oncológico; cyst – cystectomy; d – day of cycle; DAVECA – Danish Vesical Cancer Group; E – epirubicin; F – 5-fluorouracil; GISTV – Gruppo Italiano per lo Studio dei Tumori della Viscica/Italian Bladder Cancer Study Group; GUONE – Gruppo Uro-Oncologico del Nord Est/North Eastern Uro-Oncological Group; M – methotrexate; No. – number; NR – not reported; RT – radiotherapy; RTOG – Radiation Therapy Oncology Group; SWOG – Southwest Oncology Group; V – vinblastine; WMURG – West Midlands Urological Research Group.

**Trial Outcomes**

Results from the 16 trials of neoadjuvant chemotherapy for the outcomes of overall survival and disease progression are summarized in Table 3. Trial data on chemotherapy toxicity are summarized in Table 4.

**Overall survival**

Fifteen of the 16 trials provided data on overall survival, of which only two reported statistically significant differences in overall survival favouring neoadjuvant chemotherapy (41,43), and one showed a trend toward a survival improvement with chemotherapy that was of borderline statistical significance (18). All three of these trials evaluated combination chemotherapy regimens.

In 1999, the International Collaboration of Trialists reported results from the largest trial of neoadjuvant chemotherapy for TCC conducted to date (n=976) (43). The initial trial findings showed a possible survival benefit with CMV neoadjuvant chemotherapy; chemotherapy prior to local therapy reduced the risk of death by 15% compared with local therapy alone after four years (HR, 0.85; 95% CI, 0.71 to 1.02; p=0.075). In 2002, the long-term results of the trial were presented at the annual meeting of ASCO (53). Extended follow-up data were available for all 976 randomized patients after a median follow-up of 7.4 years. The updated results showed the same magnitude of risk reduction for death with chemotherapy but with greater statistical
significance (HR, 0.85; 95% CI, 0.72 to 1.00; p=0.048). Survival estimates for the treatment and control arms were 50% versus 44% at five years and 43% versus 37% at seven years, respectively, indicating an absolute survival improvement with chemotherapy in the range of 6%.

The two other trials to report survival improvements with combination chemotherapy were Nordic Cystectomy Trial I and Southwest Oncology Group (SWOG) Trial 8710/Intergroup 0800; those trials evaluated cisplatin-doxorubicin and MVAC chemotherapy, respectively. In the Nordic Cystectomy I trial (n=311) (41), patients were followed for a minimum of five years, at which point survival estimates for the treatment and control arms were 58% and 51% (p=0.10). A subgroup analysis by the stage of disease showed a statistically significant effect of chemotherapy in the 137 patients with stages T3-T4a disease (five-year survival, 52% versus 37% for chemotherapy and control, p=0.03). After an adjustment for tumour stage, the relative risk (RR) for death in patients receiving chemotherapy versus local therapy alone was statistically significant (RR, 0.69; 95% CI, 0.49 to 0.98; no p-value reported). In the SWOG/Intergroup trial (n=307) (18), patients treated with MVAC had a median survival of 77 months compared with 46 months for control patients after approximately 8.5 years of follow-up. Five-year survival was 57% with chemotherapy and 43% without chemotherapy (p=0.06). An analysis of survival data from the entire follow-up period detected a 25% reduction in the risk of death with MVAC prior to cystectomy compared with cystectomy alone that was on the border of statistical significance (HR, 0.75; 95% CI, 0.57 to 1.00; no p-value reported).

Disease progression

Eight of the 16 trials reported on disease progression-related outcomes: one trial of single-agent cisplatin (39) and seven trials studying combination chemotherapy (17,42,43,46,48,49). All eight trials reported improved progression-free survival with neoadjuvant chemotherapy; however, this improvement was proven statistically in only three trials (39,43,49). In the largest trial (n=976) (43), The International Collaboration of Trialists reported improved disease-free survival (HR=0.82; 95% CI, 0.70-0.97; p=0.019) and metastasis-free survival (HR=0.79; 95% CI, 0.66-0.93; p=0.007) with neoadjuvant CMV chemotherapy compared with local therapy alone. The results for locoregional recurrence-free survival showed a trend toward improvement with chemotherapy (HR=0.87; 95% CI, 0.73-1.02; p=0.087) that was not statistically significant. No statistically significant difference in locoregional control was detected.

Toxicity

Ten trials provided information on the toxic effects associated with neoadjuvant chemotherapy, but significant detail was provided in only a few of those (Table 4). No toxic deaths were reported with single-agent cisplatin. Two trials of combination chemotherapy (n=705) reported a total of eight toxic deaths due to chemotherapy (1.1%) (43,44). One trial studying a combination of MCV was closed early due to unexpectedly high rates of severe neutropenia with fatal sepsis in three patients (44). The International Collaboration of Trialists (43) reported that there was no evidence that neoadjuvant CMV chemotherapy increased the rates of postoperative wound infection or morbidity during or following radiotherapy (43). MVAC chemotherapy produced WHO grade 3 and 4 hematological toxicity in 48% of patients, nausea or vomiting in 9% of patients, and cardiac toxicity in 3% of patients in one trial (45). The toxicity associated with neoadjuvant MVAC was also reported in the SWOG 8710/Intergroup 0080 trial (18). In that trial, no toxic deaths were reported but neutropenic fever was observed in one patient (4%) (58), and the frequency of post-cystectomy complications was similar in both arms.
Table 3: Randomized trials of neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: trial outcomes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Follow-up</th>
<th>Overall survival:</th>
<th>Disease progression:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control vs. Neoadjuvant</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUETO, Spain (39)</td>
<td>78.2</td>
<td>6.5-yr: 37.3 vs. 35.5% p=0.95</td>
<td>0.97 (0.54 to 1.77)*</td>
</tr>
<tr>
<td>WMURG, UK (40,51)</td>
<td>16</td>
<td>3-yr: 40 vs. 39%, p=0.81 (95% CI, 0.69 to 1.61)</td>
<td>1.11 (0.67 to 1.81)*</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>Median: 24 mos† 5-yr: 30%†, p=0.77</td>
<td>NR</td>
</tr>
<tr>
<td>ABCSG, Australia (40)</td>
<td>16</td>
<td>3-yr: 41 vs. 38%, p=0.41 (95% CI, 0.72 to 2.21)</td>
<td>1.33 (0.68 to 2.62)*</td>
</tr>
<tr>
<td>Combination chemotherapy trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic I (41)</td>
<td>min=60</td>
<td>5-yr: 51 vs. 58%, p=0.1 (95% CI, 0.49 to 0.98)‡, p=NR</td>
<td>NR</td>
</tr>
<tr>
<td>SWOG 8710/Intergroup 0800 (18)</td>
<td>104.4</td>
<td>Median: 46 vs. 77 mos 5-yr: 43 vs. 57%, p=0.06</td>
<td>0.75 (0.57 to 1.00)</td>
</tr>
<tr>
<td>GISTV, Italy (42)</td>
<td>37</td>
<td>Median: 49.4 mos vs. not reached, p=NS</td>
<td>NR</td>
</tr>
<tr>
<td>International Collaboration of Trialists (43,53)</td>
<td>48</td>
<td>Median: 37.5 vs. 44 mos 3-yr: 50 vs. 55.5%</td>
<td>0.85 (0.71 to 1.02) p=0.075§</td>
</tr>
<tr>
<td>DAVECA 89-01, Denmark (17)</td>
<td>91.8</td>
<td>Median: 45.8 vs. 82.5 mos 5-yr: 46 vs. 64%, p=0.76</td>
<td>NR</td>
</tr>
<tr>
<td>DAVECA 89-02, Denmark (17)</td>
<td>77</td>
<td>Median: 16.3 vs. 19.2 mos 5-yr: 24 vs. 19%, p=0.98</td>
<td>NR</td>
</tr>
<tr>
<td>GUONE, Italy (45)</td>
<td>NR</td>
<td>3-yr: 68 vs. 62% 5-yr: 54 vs. 55%, p=NS</td>
<td>NR</td>
</tr>
<tr>
<td>Trial</td>
<td>Median Follow-up</td>
<td>Overall survival:</td>
<td>Disease progression:</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control vs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoadjuvant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 89-03</td>
<td>60</td>
<td>5-yr: 49 vs. 48%, p=NS</td>
<td>NR</td>
</tr>
<tr>
<td>(44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Font, Spain (46)</td>
<td>NR</td>
<td>4-yr: 48 vs. 69%, p=NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nordic II (19)</td>
<td>63.6</td>
<td>5-yr: 46 vs. 53%, p=0.24</td>
<td>0.80 (0.6 to 1.1)</td>
</tr>
<tr>
<td>Marcuello, Spain (55)</td>
<td>min=24</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cannobio, Italy (48)</td>
<td>36</td>
<td>6-yr: 28.5 vs. 40%, p=0.2</td>
<td>NR</td>
</tr>
<tr>
<td>Abol-Enein, Egypt (49)</td>
<td>32.2</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Hazard ratios were obtained from individual patient data (14); †overall survival reported for both control and neoadjuvant chemotherapy groups combined; ‡relative risk of death for patients who received chemotherapy compared with control group, after statistical adjustment for tumour stage; §the long-term results of this trial were presented at the 2002 annual meeting of ASCO; R. Hall presented an updated p-value for the hazard ratio for overall survival (p=0.048) (53).

Abbreviations: ABCSG – Australian Bladder Cancer Study Group; CI – confidence interval; CUETO – Club Urológico Español de Tratamiento Oncológico; DAVECA – Danish Vesical Cancer Group; DFS – disease-free survival; GISTV – Gruppo Italiano per lo Studio dei Tumori della Viscia/Italian Bladder Cancer Study Group; GUONE – Gruppo Uro-Oncologico del Nord Est/North Eastern Uro-Oncological Group; HR – hazard ratio; min – minimum; mos – months; NR – not reported; NS – non-significant; OR – odds ratio; PFS – progression-free survival; RR – relative risk; RTOG – Radiation Therapy Oncology Group; SWOG – Southwest Oncology Group; TTP – time-to-progression; vs. – versus; WMURG – West Midlands Urological Research Group; yr – year.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Neoadjuvant Chemotherapy Regimen</th>
<th>Reported Toxicities</th>
<th>No. of Deaths due to Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUETO, Spain (39)</td>
<td>C</td>
<td>Grade 3/4 hematological -hemoglobin: 0% of cycles -white blood count: 0% of cycles -granulocytes: 0% of cycles -platelets: 0% of cycles Grade 3/4 gastrointestinal -nausea and vomiting: 15% of cycles</td>
<td>NR</td>
</tr>
<tr>
<td>WMURG, UK (40)</td>
<td>C</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ABCSG, Australia (40)</td>
<td>C</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic I (52)</td>
<td>CA</td>
<td>Impaired renal function: 8/151 (5%)</td>
<td>NR</td>
</tr>
<tr>
<td>SWOG 8710 / Intergroup 0080 (18)</td>
<td>MVAC</td>
<td>Grade 3/4 hematological -granulocytopenia: 85/150 pts (57%) -thrombocytopenia: 7/150 pts (5%) -anemia: 10/150 pts (7%) Grade 3/4 gastrointestinal -nausea/vomiting: 9/150 pts (6%) -stomatitis: 15/150 pts (10%) -diarrhea/constipation: 6/150 pts (4%) Grade 3/4 other -renal: 1/150 pts (&lt;1%) -neuropathy: 3/150 pts (2%) -fatigue/lethargy/malaise: 5/150 pts (3%)</td>
<td>0</td>
</tr>
<tr>
<td>GISTV, Italy (42)</td>
<td>MVEC</td>
<td>Hematological: 35% of cycles Gastrointestinal: 4% of cycles Mucositis: 4% of cycles Renal: 2% of cycles</td>
<td>NR</td>
</tr>
<tr>
<td>International Collaboration of Trialists (43)</td>
<td>CM</td>
<td>Grade 3/4 hematological -leucopenia: 16% of pts -thrombocytopenia: 7% of pts -febrile neutropenia: 10% of pts Grade 3/4 renal toxic effects: 0% of pts Impaired renal function (causing dose decrease/delay in treatment): 28% of pts</td>
<td>5/491 (1%)</td>
</tr>
<tr>
<td>DAVECA 89-01, Denmark (17)</td>
<td>CM</td>
<td>Grade 4 leucopenia: 0% of pts Grade 3/4 vomiting: <em>majority of pts</em> Cardiopulmonary events: 0% of pts</td>
<td>NR</td>
</tr>
<tr>
<td>DAVECA 89-02, Denmark (17)</td>
<td>CM</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GUONE, Italy (45)</td>
<td>MVAC</td>
<td>Grade 3/4 hematological: 48% of pts Grade 3/4 nausea/vomiting: 9% of pts Grade 3/4 cardiac: 3% of pts</td>
<td>NR</td>
</tr>
<tr>
<td>Trial</td>
<td>Neoadjuvant Chemotherapy Regimen</td>
<td>Reported Toxicities</td>
<td>No. of Deaths due to Chemotherapy</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
</tbody>
</table>
| RTOG 89-03 (44)                   | MCV                              | Grade 3 or greater toxicity during MCV treatment:  
- leucopenia: 21% of pts  
- thrombocytopenia: 5% of pts  
- febrile neutropenia: 23% of pts  
- infection: 8% of pts  
- nausea/vomiting: 23% of pts  
Late morbidity:*  
- hematological: 13% of pts  
- renal: 8% of pts  
- neurological: 2% of pts  
- cardiac: 0% of pts  
- bladder: 13% of pts  
- intestinal: 8% of pts | 3/61 (5%) |
| Font, Spain (46)                  | CMV                              | Febrile neutropenia: 2/28 pts (7%)                                                                                                                                                                                  | NR                               |
| Nordic II (19)                    | CM                               | NR                                                                                                                                                                                                                  | 0                                |
| Marcuello, Spain (55)            | CaMV                             | NR                                                                                                                                                                                                                  | NR                               |
| Cannobio, Italy (48)             | CF/RT                            | Grade 1/2 leucopenia: 32% of pts  
Grade 2/3 nausea/vomiting: 29% of pts  
Grade 2 diarrhea: 7% of pts  
Cystitis and proctitis: 10% of pts | NR                               |
| Abol-Enein, Egypt (49)           | CaMV                             | NR                                                                                                                                                                                                                  | NR                               |

*Toxicities occurring more than 60 days after treatment.

Abbreviations: A – doxorubicin; ABCSG – Australian Bladder Cancer Study Group; C – cisplatin; Ca – carboplatin; CUETO – Club Urológico Español de Tratamiento Oncológico; DAVEGA – Danish Vesical Cancer Group; E – epirubicin; F – 5-fluorouracil; GISTV – Gruppo Italiano per lo Studio dei Tumori della Viscica/IItalian Bladder Cancer Study Group; GUONE – Gruppo Uro-Oncologico del Nord Est/Northeastern Uro-Oncological Group; M – methotrexate; No. – number; NR – not reported; pts – patients; RT – radiotherapy; RTOG – Radiation Therapy Oncology Group; SWOG – Southwest Oncology Group; V – vinblastine; WMURG – West Midlands Urological Research Group.
Meta-analyses

Early meta-analyses (1995-2001)

In 1995, the ABCOC published the first meta-analysis of neoadjuvant chemotherapy trials (14). That meta-analysis combined IPD from the three trials of single-agent cisplatin (39,40) and one trial of concurrent cisplatin not included in this review (33), with published data from one trial of combination chemotherapy (Nordic Cystectomy Trial I) (52). IPD on mortality were available for 479 patients and were combined with published data on 311 patients. The ABCOC reported an overall pooled HR of 0.91 (95% CI, 0.75 to 1.10; p=0.33) among the five trials, which favoured neoadjuvant chemotherapy but was statistically non-significant. A subgroup analysis of IPD from the three trials of single-agent cisplatin (39,40) was also statistically non-significant but favoured local therapy alone (HR, 1.11; 95% CI, 0.86 to 1.43; no p-value reported). The ABCOC concluded that the results from their pooled analyses were inconclusive because the confidence limits of all their pooled estimates crossed unity.

Since its publication in 1995, the ABCOC meta-analysis has been updated twice to include additional published data. In 1999, Parmar and Burdett (15) updated the meta-analysis to include one additional trial of combination chemotherapy (International Collaboration of Trialists)² (43) and updated trial results of the combination chemotherapy trial included in the original meta-analysis (Nordic Cystectomy Trial I) (41). That updated report included a total of five trials: the three trials of single-agent cisplatin (IPD) (39,40) and the two trials of combination chemotherapy (published data) (41,43). The authors reported a pooled HR of 0.95 (95% CI, 0.82 to 1.10) for all trials combined and an HR of 0.87 (95% CI, 0.73 to 1.04) for the subgroup of the two trials of combination chemotherapy. Those pooled estimates suggested reductions in the risk of death with neoadjuvant chemotherapy in the range of 5% to 13%; however, the results did not reach conventional statistical significance. In 2001, Stenberg and Parmar published the second update (16), which incorporated two more trials of combination chemotherapy (GUONE and SWOG 8710/Intergroup 0800³ trials) (54,58). That update brought the total number of included trials to seven (18,39,41,43,54) and detected an overall pooled HR of 0.90 (95% CI, 0.81 to 1.00), again indicating a statistically non-significant trend favouring chemotherapy. In that update, however, the subgroup analysis of data from the four trials studying combination chemotherapy (41,43,58) showed a pooled HR of 0.86 (95% CI, 0.77 to 0.97), indicating a statistically significant mortality reduction with chemotherapy.

Advanced bladder cancer meta-analysis collaboration individual patient data meta-analysis (2003)

Because previous meta-analytic reports were limited by the inclusion of only a subset of all known randomized trials, the MRC in collaboration with the ABCOC initiated a new systematic review and meta-analysis of IPD (20). The new IPD meta-analysis was conducted prospectively, with the objectives, inclusion criteria, and the methods for data extraction and analysis all specified in advance of performing the review and meta-analysis. Both published and unpublished trials were sought for inclusion. An extensive search for trials identified 14 RCTs as eligible for inclusion. Three of those trials were subsequently deemed ineligible due to the use of confounding interventions (36), chemoradiotherapy as a local treatment (44), and neoadjuvant versus adjuvant chemotherapy in the trial arms (38). In addition, one eligible trial was omitted from the review because IPD were not provided by the trial investigators (18). This left 10 trials containing 2688 patients (17,19,39,40,42,43,45,49), 88% of the total number in the 14 trials originally eligible for inclusion.

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² At the time that updated meta-analysis was published, results from the International Collaboration of Trialists trial were only available in abstract form. The abstract reported preliminary trial results; the HR for mortality was 0.95 (95% CI, 0.77 to 1.17; p=0.63) (53).

³ At the time that updated meta-analysis was published, results from the SWOG 8710/Intergroup trial were only available in abstract and poster presentation form. Preliminary trial results were presented at the 2001 annual meeting of ASCO; the HR for mortality was 0.78 (95% CI, 0.58 to 1.04) (58).
The primary endpoint for pooling was overall mortality (Table 5). Subgroup analyses by type of chemotherapy (i.e., single-agent versus combination) and type of local therapy (cystectomy alone, radiotherapy alone, or combined radiotherapy and cystectomy) were pre-planned to test for differences in treatment effect. Overall mortality data were available and amenable for pooling from nine trials (2492 patients). An overall pooled HR of 0.91 (95% CI, 0.83 to 1.01) was reported among the nine trials, translating into a 9% reduction in the risk of death and an absolute improvement in survival of 3% (48% versus 45%) with neoadjuvant chemotherapy at five years that was statistically non-significant (p=0.084). In the subgroup analyses by type of chemotherapy, the pooled HR for the three trials of single-agent cisplatin favoured local therapy alone but was non-significant (HR, 1.15; 95% CI, 0.90 to 1.47; p=0.26). Conversely, the pooled HR for trials of combination chemotherapy showed a statistically significant 13% reduction in the risk of death compared with local therapy alone (HR 0.87; 95% CI, 0.78 to 0.97; p=0.016); that magnitude of risk reduction was equivalent to an absolute survival improvement of 5% (50% versus 45%) at five years. Published data from the SWOG 8710/Intergroup 0800 trial (58), the trial for which IPD data were not provided, were included in the analysis of combination chemotherapy trials as a supplementary analysis to determine the influence of that data on the pooled results. The inclusion of that trial had little impact on the overall combined survival findings but actually increased the statistical significance of the effect (95% CI, 0.77 to 0.95; p=0.004). The subgroup analysis by type of local therapy showed no difference in the effect of chemotherapy by type of local treatment.

Secondary endpoints for pooling included disease-free survival, locoregional disease-free survival, and metastasis-free survival. Data for pooling those endpoints were available from nine trials for disease-free survival (2529 patients) and seven trials for both locoregional disease-free survival and metastasis-free survival (2180 patients). The pooled results for those three endpoints were similar to overall survival and are presented in Table 5.

Table 5: Pooled results from the Advanced Bladder Cancer Meta-analysis Collaboration individual patient data meta-analysis (2003).

<table>
<thead>
<tr>
<th>Endpoint (no. of trials/no. of patients)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Absolute Benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent cisplatin chemotherapy (3/376)</td>
<td>1.15 (0.90 to 1.47)</td>
<td>0.26</td>
<td>-5% (-14% to 4%)</td>
</tr>
<tr>
<td>Cisplatin-based combination chemotherapy (6/2116)</td>
<td>0.87 (0.78 to 0.97)</td>
<td>0.016</td>
<td>5% (1% to 9%)</td>
</tr>
<tr>
<td>All trials (9/2492)</td>
<td>0.91 (0.83 to 1.01)</td>
<td>0.084</td>
<td>3% (0% to 7%)</td>
</tr>
<tr>
<td>Disease-free survival†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent cisplatin chemotherapy (2/217)</td>
<td>1.14 (0.83 to 1.55)</td>
<td>0.42</td>
<td>-5% (-16% to 7%)</td>
</tr>
<tr>
<td>Cisplatin-based combination chemotherapy (7/2312)</td>
<td>0.81 (0.74 to 0.90)</td>
<td>0.0001</td>
<td>7% (4% to 11%)</td>
</tr>
<tr>
<td>All trials (9/2529)</td>
<td>0.84 (0.76 to 0.93)</td>
<td>0.001</td>
<td>3% (3% to 10%)</td>
</tr>
<tr>
<td>Locoregional disease-free survival‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent cisplatin chemotherapy (2/217)</td>
<td>1.12 (0.82 to 1.52)</td>
<td>0.49</td>
<td>-4% (-15% to 7%)</td>
</tr>
<tr>
<td>Cisplatin-based combination chemotherapy (5/1963)</td>
<td>0.87 (0.77 to 0.97)</td>
<td>0.012</td>
<td>5% (1% to 9%)</td>
</tr>
<tr>
<td>All trials (7/2180)</td>
<td>0.89 (0.80 to 0.99)</td>
<td>0.032</td>
<td>4% (0% to 8%)</td>
</tr>
<tr>
<td>Metastasis-free survival§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent cisplatin chemotherapy (2/217)</td>
<td>1.21 (0.88 to 1.67)</td>
<td>0.25</td>
<td>-7% (-18% to 5%)</td>
</tr>
<tr>
<td>Cisplatin-based combination chemotherapy (5/1963)</td>
<td>0.82 (0.73 to 0.92)</td>
<td>0.001</td>
<td>7% (3% to 11%)</td>
</tr>
<tr>
<td>All trials (7/2180)</td>
<td>0.86 (0.77 to 0.95)</td>
<td>0.004</td>
<td>5% (2% to 9%)</td>
</tr>
</tbody>
</table>

*Overall survival was defined as the time from randomization until death; †disease-free survival was defined as the time from randomization until first recurrence or progression (after randomization) or death, whichever happened first; ‡locoregional disease-free survival was defined as the time from randomization to first local recurrence or progression (after randomization) or death; §metastasis-free survival was defined as the time from randomization to first metastases (after randomization) or death.

Abbreviations: CI – confidence interval; no.—number.
Overall mortality

Fifteen of the 16 RCTs identified by the literature search published data on overall mortality (Table 3). One of the 15 reports did not report overall mortality by trial arm (55), leaving 3047 patients from 14 trials who could potentially be included in a meta-analysis. The data available to generate HRs further restricted the analyses to 2915 patients (96%) from 12 trials (17-19,39,40,42-45). The HR and variance for each trial were estimated using direct methods for seven trials and indirect methods for five trials.

The GU DSG detected an overall pooled HR of 0.88 (95% CI, 0.81 to 0.97) across the 12 trials of neoadjuvant chemotherapy that was statistically significant (p=0.008) and that represented a 12% reduction in the risk of death, or an absolute improvement in overall survival of 6% (95% CI, 1.5 to 9.5%), from 50% to 56% (Figure 1). The pooled HR of 1.11 (95% CI, 0.86 to 1.43) across the three single-agent chemotherapy trials was not statistically significant (p=0.41), but this subgroup analysis only includes 377 patients. The pooled HR of 0.86 (95% CI, 0.78 to 0.94) across the eight combination chemotherapy trials was also statistically significant (p=0.002) and represents a 14% reduction in the risk of death, or an absolute improvement in overall survival of 7% (95% CI, 3 to 11%), from 50% to 57%. Statistical heterogeneity was not detected in any of the analyses, so the reported HRs are based on a fixed-effect model.

In exploratory analyses, there was no evidence of an association between improved survival and the type of local therapy (cystectomy versus other local therapies) or anthracycline-containing combination chemotherapy (versus those not) (data not shown). However, those analyses included data from six trials (1130 patients) and four trials (976 patients), respectively, and therefore should be considered underpowered for the detection of small differences.

Disease progression

Eight of the 16 trials reported data on a disease progression endpoint: one trial of single-agent cisplatin (39) and seven trials studying combination chemotherapy (1729 patients) (17,42,43,46,48,49) (Table 3). Data available to generate an HR restricted the analyses to three trials (39,42,43) and a maximum of 1202 patients (70%). The three trials all reported on disease-free survival; however, the definition of that outcome was different in two trials (42) and not defined in the third trial (39). Due to the heterogeneity in defining this outcome, the GU DSG did not perform statistical pooling of disease-free survival data.

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4 For the three trials of single-agent cisplatin and the GUONE trial, the data included in the meta-analysis were not extracted from the original trial publications. For the three trials of single-agent cisplatin, the HRs and variances reported in the ABCOC meta-analysis were used (14). For the GUONE trial, the HR and variance reported in the meta-analysis by Sternberg and Parmar were used (16).
Figure 1. Meta-analysis of overall mortality results from trials comparing neoadjuvant chemotherapy prior to local therapy versus local therapy alone.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Hazard Ratio 95% CI</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Single-agent cisplatin chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG</td>
<td>1.33 [0.80, 2.23]</td>
<td></td>
</tr>
<tr>
<td>CUCTO</td>
<td>0.97 [0.62, 1.53]</td>
<td></td>
</tr>
<tr>
<td>VAMURG</td>
<td>1.11 [0.76, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.11 [0.86, 1.43]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 0.82, df = 2 (P = 0.66)
Test for overall effect: Z = 0.83 (P = 0.41)

| 02 Cisplatin-based combination chemotherapy | | |
| DAVECA 88-01 | 1.90 [0.24, 15.15] | |
| DAVECA 88-02 | 0.84 [0.56, 1.25] | |
| GISTV | 0.70 [0.44, 1.12] | |
| OUONE | 1.01 [0.92, 1.18] | |
| Int Collab Trialists | 0.85 [0.72, 1.00] | |
| Intergroup/SWOG | 0.75 [0.57, 1.00] | |
| Nordic I | 0.84 [0.61, 1.13] | |
| Nordic II | 0.80 [0.60, 1.09] | |
| RTOG 89-03 | 0.66 [0.52, 1.09] | |
| Subtotal (95% CI) | 0.86 [0.78, 0.94] | |

Test for heterogeneity: Chi² = 4.62, df = 8 (P = 0.80)
Test for overall effect: Z = 3.17 (P = 0.002)

Total (95% CI) | 0.88 [0.81, 0.97] |

Test for heterogeneity: Chi² = 9.02, df = 11 (P = 0.62)
Test for overall effect: Z = 2.67 (P = 0.008)

V. INTERPRETATION AND CONSENSUS

In the original guideline report on neoadjuvant chemotherapy for TCC (2001), the GU DSG did not recommend the use of neoadjuvant chemotherapy, either single-agent or combination, before definitive local therapy for patients with stage II or III bladder cancer. This recommendation was based on evidence from 14 randomized trials (three trials of single-agent cisplatin and 11 trials of cisplatin-based combination chemotherapy) and one IPD meta-analysis (three trials of single-agent cisplatin). At the time the recommendation was made, only four of the 11 combination chemotherapy trials were published in full, and seven were in abstract form, providing only preliminary trial data. Since the original guideline’s completion, considerably more data on combination chemotherapy has become available, including the full publication of two new meta-analyses. The new evidence prompted the GU DSG to update and revise the original guideline report.

Two recent meta-analyses of randomized trials that have analyzed IPD (nine RCTs, 2492 patients) (20) and published data (12 RCTs, 2915 patients) have both shown improved overall survival with neoadjuvant chemotherapy given prior to local therapy when compared with local therapy alone. The survival benefit is most convincing for combination cisplatin-based chemotherapy, with relative reductions in the risk for mortality that range between 13% and 14%
(HR=0.87 [IPD]; HR=0.86 [published data]) and absolute survival benefits that range from 5% to 7%. Disease-free survival is also improved with chemotherapy (HR=0.81 [IPD]; absolute benefit of 7%). The survival benefits observed appear to be due to improved locoregional and metastasis-free survival. Conversely, the evidence for a benefit with neoadjuvant single-agent cisplatin chemotherapy is very limited; however, HR estimates suggest a possible worse survival outcome with this approach compared with local therapy alone. Therefore, single-agent cisplatin should not be offered to patients with TCC of the bladder.

In December 2003, the GU DSG reviewed the new evidence and developed a set of draft recommendations. The GU DSG members reached consensus that there is now sufficient evidence to recommend cisplatin-based combination chemotherapy prior to local therapy in patients with stages II or III bladder cancer. A variety of cisplatin-based chemotherapy regimens have been evaluated in randomized trials, but the majority of patients have been treated with either combination CMV or MVAC for three cycles. Those regimens should be considered standards for neoadjuvant treatment until further data on other less toxic chemotherapy regimens (i.e., gemcitabine-cisplatin or dose-intense MVAC with G-CSF) in this setting are available. CMV and MVAC are associated with significant rates of nausea and vomiting, stomatitis, renal dysfunction, myelosuppression, and neutropenia in particular. In the two largest trials, the toxic death rates with CMV and MVAC were 1% and 0%, respectively (18,43). Therefore, neoadjuvant cisplatin-based combination chemotherapy should be administered by a physician experienced in administering chemotherapy in those patients.

The GU DSG also discussed the timing of chemotherapy, namely whether physicians should administer chemotherapy neoadjuvantly versus adjuvantly. Presently, in terms of overall survival, the evidence is strongest for neoadjuvant chemotherapy. However, many oncologists prefer the adjuvant approach due to the inaccuracy of clinical staging of bladder cancer. Therefore, adjuvant chemotherapy following cystectomy is also a reasonable treatment option in these patients. Adjuvant chemotherapy is the subject of a separate guideline developed by the GU DSG (59). Patients should be presented with these treatment options, and an informed decision about the use of neoadjuvant chemotherapy should be made based on realistic expectations, individual preferences, and the perceived risks. As the absolute benefits of neoadjuvant chemotherapy are modest, patients should also be encouraged to participate in clinical trials whenever these are available.

VI. ONGOING TRIALS
The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The GU DSG did not locate any ongoing trials evaluating the use of neoadjuvant chemotherapy in patients with stage II or III bladder cancer.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT
Draft Recommendations
Based on the evidence reviewed, the GU DSG drafted the following recommendations:

**Target Population**
These recommendations apply to adult patients newly diagnosed with stage II or stage III transitional cell carcinoma of the bladder.

**Draft Recommendations**
- Neoadjuvant cisplatin-based combination chemotherapy is recommended prior to radical cystectomy, radical radiation therapy (with or without concurrent chemotherapy), or

preoperative radiotherapy and cystectomy for the purpose of improving overall survival and disease-free survival.

- The current state of the evidence does not permit a recommendation for an optimal cisplatin-based combination chemotherapy regimen. However, the largest neoadjuvant trials have used standard MVAC or CMV for three cycles, and it is the opinion of the GU DSG that these regimens are reasonable treatment options. Less toxic regimens such as gemcitabine-cisplatin and dose-intense MVAC plus G-CSF have not been evaluated in randomized trials in this setting.

- Neoadjuvant single-agent cisplatin chemotherapy is not recommended.

Qualifying Statements

- MVAC and CMV chemotherapy are associated with high rates of some adverse effects. These effects should be discussed with patients, and treatment should be managed by physicians experienced in administering chemotherapy to these patients.

- These recommendations do not apply to patients with only superficial transitional cell carcinoma of the bladder, locally advanced bladder cancer that is surgically unresectable, or metastatic or bladder cancer of non-transitional histology.

- This guideline does not address the topics of concurrent chemotherapy given with radiotherapy or adjuvant chemotherapy. These topics are addressed in separate guidelines being developed by Cancer Care Ontario’s Practice Guidelines Initiative GU DSG.

Future Research

- Patients who are candidates for neoadjuvant chemotherapy should be encouraged to participate in randomized controlled trials.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 90 practitioners in Ontario (12 medical oncologists, 18 radiation oncologists, and 60 urologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on July 14, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The GU DSG reviewed the results of the survey.

Results

Forty-three responses were received out of the 90 surveys sent (47.8% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 29 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 6.
Table 6. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strongly agree or</td>
</tr>
<tr>
<td></td>
<td>Neither agree nor</td>
</tr>
<tr>
<td></td>
<td>Strongly disagree or</td>
</tr>
<tr>
<td></td>
<td>agree</td>
</tr>
<tr>
<td>The rationale for developing a clinical practice guideline, as</td>
<td>28 (96.6)</td>
</tr>
<tr>
<td>stated in the “Choice of Topic” section of the report, is clear.</td>
<td></td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>27 (93.1)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>The results of the trials described in the report are</td>
<td>22 (81.5)</td>
</tr>
<tr>
<td>interpreted according to my understanding of the data.</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>20 (70.0)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would</td>
<td>Very likely or</td>
</tr>
<tr>
<td>you be to make use of it in your own practice?</td>
<td>likely</td>
</tr>
<tr>
<td></td>
<td>18 (62.1)</td>
</tr>
</tbody>
</table>

Summary of Written Comments

Ten respondents (35.7%) provided written comments. The main points contained in the written comments were:

1. There was disagreement with the inclusion of trials with any local therapy (i.e., radiotherapy + cystectomy). One practitioner thought it “unwise, premature, and potentially dangerous” to recommend the use of neoadjuvant chemotherapy prior to radiotherapy, citing there is a paucity of clinical trials addressing this issue and there exists a potential to do real harm to patients (e.g., increased toxicity, radioresistance, reduced local control, inability to tolerate radiotherapy or deliver concurrent chemotherapy). The potential survival advantage of this approach even prior to surgery is modest at best and needs to be assessed with regard to toxicity (fatal toxicity rate >1%). The important question is the value of adjuvant chemotherapy in selected patients.

2. Two other practitioners were also concerned with the high toxicity associated with neoadjuvant chemotherapy. One practitioner commented that the chemotherapy regimens recommended in this report are no longer used in his/her centre for reasons of patient safety. Both practitioners thought the marginal survival benefit observed with this approach did not outweigh the additional toxicity.

3. Four practitioners stated that implementing the guideline recommendations will be difficult due to limited resources, resulting in treatment delays. Another practitioner thought that the recommendations would standardize and improve treatment of this cancer by centralizing treatment at cancer centres.

4. One practitioner noted that it will be difficult to get medical oncologists to consider neoadjuvant MVAC because of the wide use of gemcitabine-cisplatin (a less toxic regimen) in metastatic disease.

5. One practitioner suggested using the TNM staging system to describe the target patient population.
**Modifications/Actions**

1. Regarding concerns about the use neoadjuvant chemotherapy prior to radiotherapy – although an increased toxic death rate was observed in one trial (44), this is likely attributable to the unique schedule of drugs used in that trial. In the largest neoadjuvant trial (43), approximately 42% of patients received definitive treatment with radical radiotherapy and no discernable differences in efficacy or toxicity were reported in relation to the type of local therapy used.

2. Regarding concerns about the toxicity associated with neoadjuvant chemotherapy – it appears that patients receiving MVAC and CMV chemotherapy in the neoadjuvant setting have lower rates of severe toxicity including toxic death (0% and 1%, respectively, in the two largest trials). Use of chemotherapy neoadjuvantly may be more effective in bladder cancer, as often patients decline or are considered unsuitable for treatment with adjuvant chemotherapy. Although less toxic chemotherapy regimens are in use in the metastatic setting, those have not yet been tested in adjuvant or neoadjuvant RCTs so they cannot be considered as equivalent in the neoadjuvant and adjuvant settings.

3. In response to comments about the impact on resources and changes in practice patterns – the GU DSG agreed that new and more effective therapies for cancer often have such impacts and require such adjustments.

4. Regarding the use of gemcitabine-based chemotherapy in the neoadjuvant setting – extrapolating the evidence beyond the metastatic setting may not be justified based on the lower toxicity rates of other regimens reported in neoadjuvant RCTs.

5. The TNM classification system is used to describe the target patient population (Stage II and III).

**Practice Guideline Coordinating Committee Approval Process**

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Thirteen of 14 members of the PGCC returned ballots. Eleven PGCC members approved the practice guideline report as written, and two members approved the guideline and provided suggestions for consideration by the GU DSG. One member suggested the GU DSG consider how the recommendations will be implemented into practice and resource implications since practitioner feedback indicated the wide use of gemcitabine-cisplatin. The other member suggested editorial changes be made to the Key Evidence section of the Summary of the practice guideline report.

**Modifications/Actions**

The GU DSG considered the comments concerning implementation and resource implications of the recommendations but decided these issues are beyond the scope of an evidence-based practice guideline. The suggested editorial changes were made to the Summary of the practice guideline report.

**VIII. PRACTICE GUIDELINE**

The GU DSG reviewed all the feedback obtained from the external review process. After careful consideration, the GU DSG decided not to modify the draft recommendations in response to practitioner feedback. The practice guideline has been approved by the GU DSG and by the PGCC.
Target Population

These recommendations apply to adult patients newly diagnosed with stage II or stage III transitional cell carcinoma of the bladder.

Recommendations

- Neoadjuvant cisplatin-based combination chemotherapy is recommended prior to radical cystectomy, radical radiation therapy (with or without concurrent chemotherapy), or preoperative radiotherapy and cystectomy for the purpose of improving overall survival and disease-free survival.
- The current state of the evidence does not permit a recommendation for an optimal cisplatin-based combination chemotherapy regimen. However, the largest neoadjuvant trials have used standard methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) or cisplatin-methotrexate-vinblastine (CMV) for three cycles, and it is the opinion of the Genitourinary Cancer Disease Site Group that these regimens are reasonable treatment options. Less toxic regimens such as gemcitabine-cisplatin and dose-intense MVAC plus granulocyte-colony stimulating factor have not been evaluated in randomized trials in this setting.
- Neoadjuvant single-agent cisplatin chemotherapy is not recommended.

Qualifying Statements

- MVAC and CMV chemotherapy are associated with high rates of some adverse effects. These effects should be discussed with patients, and treatment should be managed by physicians experienced in administering chemotherapy to these patients.
- These recommendations do not apply to patients with only superficial transitional cell carcinoma of the bladder, locally advanced bladder cancer that is surgically unresectable, or metastatic or bladder cancer of non-transitional histology.
- This guideline does not address the topics of concurrent chemotherapy given with radiotherapy or adjuvant chemotherapy. These topics are addressed in separate guidelines being developed by Cancer Care Ontario's Practice Guidelines Initiative Genitourinary Cancer Disease Site Group.

IX. JOURNAL REFERENCE


X. CONFLICT OF INTEREST

Four of the five guideline authors disclosed they had no actual or potential conflicts related to this practice guideline report.

XI. ACKNOWLEDGEMENTS

The GU DSG would like to thank Drs. Eric Winquist, Roanne Segal, Joseph Chin, and Himu Lukka and Ms. Tricia Waldron for taking the lead in drafting and revising this practice guideline report.

For a complete list of the Genitourinary Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO web site at: http://www.cancercare.on.ca/.

REFERENCES


Evidence-based Series 3-2-2 ARCHIVED 2012

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder

Guideline Review Summary

Review Date: October 24, 2012

The 2005 guideline recommendations are ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

OVERVIEW
Evidence-based Series History
The original version of this guidance document was released by the Program in Evidence-based Care, Cancer Care Ontario, in 2001, and a second version was released in May 2005. In September 2011, the PEBC guideline update strategy was applied. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (SH) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be archived. PEBC and the Genitourinary Cancer DSG archived the recommendations found in the Practice Guideline Summary.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Question Considered
Should neoadjuvant chemotherapy be offered to patients with stage II or III bladder cancer before definitive local therapy with surgery and/or radical radiotherapy, with the intent of improving survival?

Literature Search and New Evidence
The new search (March 2004 to Sept 2011) yielded three relevant new publications from two guidelines and one RCT. A brief result of the RCT is shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations
With 68% approval from the Genitourinary Cancer DSG and in accordance with the PEBC Document Assessment and Review Protocol, PEBC decided to archive the 2005 recommendations on Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the
Bladder. Therefore this guideline will no longer be updated by PEBC. The DSG will decide if and when a new document that will cover both adjuvant and neoadjuvant chemotherapy will be produced.

Document Assessment and Review Tool

| Number and title of document under review | 3-2-2 Use of Neoadjuvant Chemotherapy in Transitional Cell Carcinoma of the Bladder |
| Date of current version                  | 5 May 2005 |
| Clinical reviewer                        | Dr. Christina Canil |
| Research coordinator                     | Chika Agbassi |
| Date DART initiated                      | 13 May 2011 |
| Date and final results / outcomes        | 24 October 2012 [ARCHIVED] |

Instructions. Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document as is? Answer Yes or No, and explain if necessary:
   - **1. Yes**
     - If No, then the document should be ARCHIVED with no further action; go to 11. If Yes, then go to 2.

2. Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:
   - **2. No, greater than 5 years have elapsed**
     - If Yes, the document can be ENDORSED with no further action; go to 11. If No, go to 3.

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:
   - **3. No**
     - If Yes, the document should be taken off the website as soon as possible. A WARNING should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.

4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:
   - **4. YES**
     - there is a designated research co-ordinator at the PEBC to carry out the literature search
     - If No, a DEFERRAL should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.

5a. Guideline Research Questions. Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The DART process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this DART form and answer NO).

**Original Question(s):**

- Should neoadjuvant chemotherapy be offered to patients with stage II or III bladder cancer before definitive local therapy with surgery and/or radical radiotherapy, with the intent of improving survival?
**Target Population:**

These recommendations apply to adult patients newly diagnosed with stage II or stage III transitional cell carcinoma of the bladder.

**5b. Inclusion and Exclusion criteria.** List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

**Inclusion criteria:**

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

3. They were fully published reports or abstracts of RCTs or meta-analyses that:
   a. compared neoadjuvant chemotherapy and definitive local therapy (cystectomy and/or radical radiotherapy with or without concurrent chemotherapy) with local therapy alone in patients with stage II or stage III TCC of the bladder.
   b. reported comparisons of overall survival and/or progression-free survival.
4. They were systematic reviews or evidence-based practice guidelines that addressed the guideline question.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below. [This section to be completed by Research Co-ordinator]

No changes to the inclusion and exclusion criteria

**Search Period:**

- March 2004 to Sept 2011 (Medline week 3 + Embase week 38)
- 2002 to 2011 (ASCO Annual Meeting)
- 2011 (AUA Annual Meeting)

**Brief Summary/Discussion of New Evidence:**

Of 85 total hits from Medline + Embase and 13 total hits from ASCO + AUA conference abstract searches, three references were found representing two guidelines and one RCT (already included in the existing guideline).

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three 21W cycles of CMV Cisplatin 70mg/m²(d1) + methotrexate 30mg/m²(d8,15) + Vinblastine 3mg/m²(d2,15,22) vs No Therapy</td>
<td>Phase III, BA06 30894 Med f/u = 8 yrs Stage T2 grade 3, T3 ,T4a and NO/X, M0 (n=976)</td>
<td>OS, MFS, LDFS, DFS, LCPS, OS,</td>
<td>CMV was significantly better than no therapy in: OS with an HR of 0.84 (95% CI: 0.72-0.99) p=0.037. DFS with an HR of 0.82 (95% CI: 0.70-0.95) p=0.008. MFS with an HR of 0.77 (95% CI: 0.66-0.90) p=0.001</td>
<td>ICT 2011</td>
<td></td>
</tr>
</tbody>
</table>

DFS= disease free survival; ICT= International Collaboration of Trialists; MFS= metastatic free survival; n= number recruited; OS= overall survival;

**New References Identified (alphabetic order):**


Literature Search Strategy:
Medline
1. meta-Analysis as topic.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. meta analysis.pt.
3. (meta analy$ or metaanalys$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. \ (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. \ random allocation/ or double blind method/ or single blind method/
18. \ (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. \ or/15-18
20. \ (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trials as topic/
21. \ (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. \ (20 or 21) and random$.tw.
23. \ (clinical$ adj trial$1).tw.
24. \ ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. \ placebos/
26. \ (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. \ (allocated adj2 random).tw.
28. \ or/23-27
29. \ practice guidelines/
30. \ practice guideline?.tw.
31. \ practice guideline.pt.
32. \ or/29-31
33. \ 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. \ (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. \ 33 not 34
36. \ limit 35 to english
37. \ limit 36 to human
38. \ exp bladder neoplasms/
40. \ Urinary Bladder/
41. \ 39 and 40
42. \ 38 or 41
43. \ exp transitional cell carcinoma/
44. \ 42 and 43
45. \ neoadjuvant chemotherapy.tw.
46. \ 44 and 45
47. \ (200403$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
48. \ 46 and 47

Embase
49. exp meta analysis/ or exp systematic review/  
50. \ (meta analy$ or metaanaly$).tw.
51. \ (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
52. \ (systematic adj (review$ or overview?)).tw.
53. exp review/ or review.pt.
54. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
55. (study adj selection).ab.
56. 5 and (6 or 7)
57. or/1-4,8
58. (cochrane or embase or psychlit or psyclit or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
59. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
60. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
61. randomization/ or single blind procedure/ or double blind procedure/
62. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
63. or/12-14
64. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
65. 16 and random$tw.
66. (clinic$ adj trial$1).tw.
67. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
68. placebo/
69. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
70. (allocated adj 2 random).tw.
71. or/18-22
72. practice guidelines/
73. practice guideline?.tw.
74. practice guideline.pt.
75. or/24-26
76. 9 or 10 or 11 or 15 or 17 or 23 or 27
77. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
78. 28 not 29
79. limit 30 to english
80. limit 31 to human
81. exp bladder neoplasms/
82. (cancer? or carcinoma? or neoplasm? or tumo$r).tw.
83. bladder.tw.
84. 34 and 35
85. 33 or 36
86. exp transitional cell carcinoma/
87. 37 and 38
88. neoadjuvant chemotherapy.tw.
89. 39 and 40
90. (2004$03 or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ew.
91. 41 and 42

ASCO Annual Meeting - searched http://www.ascopubs.org/search with keywords: neoadjuvant AND (bladder cancer)

Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?
6. No
If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.

7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:
7. New data supports existing recommendations but the recommendations do not cover all relevant areas.
I suggest amalgamation of the adjuvant and neo-adjuvant guidelines to create a more comprehensive perioperative guideline.
If Yes, the document can be ENDORSED. If No, go to 8.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

8. Not applicable

If Yes, a WARNING note will be placed on the web site. If No, go to 9.

9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

9. Not applicable

If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.

10. An update should be initiated as soon as possible. List the expected date of completion of the update:

10. Not applicable

An UPDATE will be posted on the website, indicating an update is in progress.

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

DSG Approval Date: 24 October 2012
Comments from DSG members:

OUTCOMES DEFINITIONS

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY - A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.