Chemotherapy for Bladder Cancer: Treatment Guidelines for Neoadjuvant Chemotherapy, Bladder Preservation, Adjuvant Chemotherapy, and Metastatic Cancer


To determine the optimal use of chemotherapy in the neoadjuvant, adjuvant, and metastatic setting in patients with advanced urothelial cell carcinoma, a consensus conference was convened by the World Health Organization (WHO) and the Société Internationale d’Urologie (SIU) to critically review the published literature on chemotherapy for patients with locally advanced bladder cancer. This article reports the development of international guidelines for the treatment of patients with locally advanced bladder cancer with neoadjuvant and adjuvant chemotherapy. Bladder preservation is also discussed, as is chemotherapy for patients with metastatic urothelial cancer. The conference panel consisted of 10 medical oncologists and urologists from 3 continents who are experts in this field and who reviewed the English-language literature through October 2004. Relevant English-language literature was identified with the use of Medline; additional cited works not detected on the initial search regarding neoadjuvant chemotherapy, bladder preservation, adjuvant chemotherapy, and chemotherapy for patients with metastatic urothelial cancer were reviewed. Evidence-based recommendations for diagnosis and management of the disease were made with reference to a 4-point scale. Results of the authors’ deliberations are presented as a consensus document. Meta-analysis of randomized trials on cisplatin-containing combination neoadjuvant chemotherapy revealed a 5% difference in favor of neoadjuvant chemotherapy. No randomized trials have yet compared survival with transurethral resection of bladder tumor alone versus cystectomy for the management of patients with muscle-invasive disease. Collaborative international adjuvant chemotherapy trials are needed to assist researchers in assessing the true value of adjuvant chemotherapy. Systemic cisplatin–based combination chemotherapy is the only current modality that has been shown in phase 3 trials to improve survival in responsive patients with advanced urothelial cancer. A panel of international experts has formulated grade A through D recommendations for the management of patients with locally advanced and metastatic urothelial cancer on the basis of level 1 to 3 evidence and the findings of phase 2 trials, prospective randomized clinical trials, and meta-analyses. UROLOGY 69 (Suppl 1A): 62–79, 2007. © 2007 Elsevier Inc.

Muscle-invasive bladder cancer is one of the most aggressive epithelial tumors, with a high rate of early systemic dissemination; 5-year survival rates depend principally on pathologic stage and nodal status. With increasing T stage, especially when cancer extends outside the bladder wall, the prognosis worsens. Failure is usually owing to occult metastatic disease that is present at the time of initial diagnosis.

NEOADJUVANT CHEMOTHERAPY

A description of the grades and levels of evidence referred to throughout this article is provided in Table 1.¹

What Do We Know About Survival From Cystectomy Series?

Cystectomy is considered to be the “gold standard” of treatment for patients with clinically localized muscle-invasive bladder cancer. This idea has been fortress through the widespread practice of orthotopic bladder

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substitutions. The 5-year survival rate after cystectomy, however, is at best 65% (including patients with pT2), and, in major series from the University of Padua, Memorial Sloan-Kettering Cancer Center, and the University of Southern California, ranges from 36% to 48% (level 3).2–5 High-risk patients with pathologic stage T3 to T4 and/or positive nodes have an even worse 5-year survival rate that is somewhere between 25% and 35%.

Advantages and Disadvantages of Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is intended for patients with operable clinical stage T2–T4a muscle-invasive disease. The rationale for giving chemotherapy before cystectomy or full-dose radiation therapy (RT) is based on the intent to treat micrometastatic disease that is present at diagnosis.

In this way, systemic chemotherapy is delivered very early when the burden of metastatic disease is minimal. The indications for neoadjuvant chemotherapy have additionally evolved to include programs in which bladder preservation is planned.6 Therapy is tolerated better before surgery or RT than afterward (level 4). Toxicity is usually less than that seen in patients with metastatic disease, in that subjects with localized disease usually have a better performance status (level 4).

Patients are clinically staged, which may lead to some difficulties in assessing response to therapy. A discrepancy between clinical and pathologic staging can be expected in some 30% of cases (level 3).7,8 Also, cystectomy or RT may be delayed during neoadjuvant chemotherapy administration. This may have a negative effect on those patients who do not respond to chemotherapy. In some series, an interval >12 weeks between diagnosis of muscle invasion and performance of cystectomy is associated with a worse outcome (level 3).9,10

It is unknown whether 3 or 4 cycles of therapy are needed because this question has never been systematically evaluated. Toxicity in the neoadjuvant setting can be assessed through 2 large cooperative group randomized trials. In the European Organization for Research and Treatment of Cancer/Medical Research Council (EORTC/MRC) trial of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy, a 1% mortality rate was attributed to CMV.11 In the American Intergroup Trial coordinated by the Southwest Oncology Group (SWOG), no deaths were owing to chemotherapy with methotrexate, vinblastine, doxorubicin [Adriamycin; Bedford Laboratories, Bedford, OH], and cisplatin (M-VAC) (level 1).12

Urologists are sometimes reluctant to pursue neoadjuvant chemotherapy because they fear that it may increase the incidence of perioperative morbidity. Very few trials have been undertaken to study this possibility.13,14 In a comparative study of neoadjuvant and adjuvant chemotherapy from the M. D. Anderson Cancer Center (Houston, TX); neoadjuvant chemotherapy did not increase perioperative morbidity (level 1).13

Randomized Trials: Does Neoadjuvant Chemotherapy Improve Survival?

Neoadjuvant chemotherapy theoretically should provide benefit to patients, whether it is given before cystectomy or before RT. In the United States and in most of Europe, radical cystectomy is preferred for patients who have a good performance status.

Randomized trials have evaluated whether neoadjuvant chemotherapy improves survival. Initial studies explored the use of single-agent cisplatin, but more recent trials have used cisplatin-containing combination chemotherapy. These latter trials have shown a trend toward a small benefit or no survival benefit. What has occurred is that most trials probably did not enroll sufficient numbers of patients to allow detection of differences in survival. The results of randomized trials are presented in Table 2.11,15–24

Results from the intergroup trial initiated by SWOG have been published in the New England Journal of Medicine.12 Patients with cT2 to cT4a urothelial carcinoma of the bladder (transitional cell carcinoma [TCC]) were randomly assigned between 3 cycles of M-VAC chemotherapy followed by cystectomy or cystectomy alone. Enrollment took place over an 11-year period at 126 institutions, and patients were stratified according to age (<65 years or ≥65 years) and stage (cT2 vs cT3 or cT4a). Of 317 patients enrolled, 307 were eligible. Only

<table>
<thead>
<tr>
<th>Table 1. Summary of International Consultation on Urological Diseases (ICUD) modified Oxford Center for Evidence-Based Medicine grading system for guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Levels of evidence</td>
</tr>
<tr>
<td>— Level 1</td>
</tr>
<tr>
<td>— Level 2</td>
</tr>
<tr>
<td>— Level 3</td>
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<tr>
<td>— Level 4</td>
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<tr>
<td>● Grades of recommendation</td>
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<tr>
<td>— Grade A</td>
</tr>
<tr>
<td>— Grade B</td>
</tr>
<tr>
<td>— Grade C</td>
</tr>
<tr>
<td>— Grade D</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial.
Adapted with permission from Incontinence.2
A trend toward improved survival favored M-VAC—therefore, the relevance of this approach cannot be ruled out. A 5.5% benefit favored patients treated with CMV chemotherapy. 25 Survival at 5 years was 50% with CMV compared with 44% with RT; at 8 years, it was 43% with CMV and 37% with RT. Although Hall25 concluded that no change in absolute benefit had occurred, patients treated with CMV had a consistent survival benefit that was maintained over time (level 1).

A trial that was almost identical to the SWOG study was performed by the Gruppo Uro-Oncologico Nord Est (GUONE) cooperative group in Italy. Over a 6.5-year period, 206 patients were randomly assigned to neoadjuvant M-VAC before cystectomy or to cystectomy alone.15 No clear differences in survival were demonstrated, as 3-year survival was 62% for the M-VAC–treated patients and 68% for patients in the cystectomy-alone arm (level 2).

The Nordic cystectomy I trial evaluated neoadjuvant doxorubicin, cisplatin, and preoperative RT before cystectomy versus preoperative RT and cystectomy alone. A 15% survival difference in favor of patients treated with chemotherapy was seen in only a subset analysis of patients with T3 or T4 disease.24 Investigators were unable to confirm this survival advantage in the subsequent Nordic cystectomy II trial, in which 317 patients were randomly assigned cystectomy or cystectomy preceded by methotrexate and cisplatin (without RT).16 However, combining the 2 trials provided positive results in favor of neoadjuvant chemotherapy (level 2).26

What is the value of neoadjuvant chemotherapy?27 Although >2000 patients were evaluated in neoadjuvant chemotherapy randomized trials, the real value of neoadjuvant chemotherapy in terms of survival has not been clarified. For this reason, a meta-analysis of 10 neoadjuvant chemotherapy trials was performed.28 Unfortunately, original data from the SWOG trial were not available. Overall survival for the whole group and for a subgroup of patients treated with single-agent cisplatin was not affected by neoadjuvant chemotherapy. In a subset of patients treated with cisplatin-

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**Table 2. Randomized phase 3 trials of neoadjuvant chemotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>Patients (N)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin chemotherapy</td>
<td>Cis/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td>Australia/UK17</td>
<td>Cis/RT or preop RT+cytectomy</td>
<td>RT or preop RT+cytectomy</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td>Canada/NCI18</td>
<td>Cis/cystectomy</td>
<td>Cystectomy</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td>Spain (CUETO)19</td>
<td>CMV/cystectomy</td>
<td>Cystectomy</td>
<td>976</td>
<td>5.5% difference in favor of CMV (P = 0.06)</td>
</tr>
<tr>
<td>Nordic II16</td>
<td>MTX/Cis/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td>Abol-Enein et al.23</td>
<td>CarboMV/cystectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with CarboMV</td>
</tr>
<tr>
<td>Nordic cystectomy I trial</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Italy (GUONE)25</td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td>Italy (GISTV)21</td>
<td>M-VEC/cystectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td>Genoa22</td>
<td>Cis/5-FU/RT/cystectomy</td>
<td>Cystectomy</td>
<td>311</td>
<td>No difference, 15% benefit with ADM + Cis in T3–T4a</td>
</tr>
<tr>
<td>Nordic cystectomy II trial</td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>298</td>
<td>Benefit with M-VAC</td>
</tr>
<tr>
<td>SWOG Intergroup20</td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td>Nordic II trial</td>
<td>MTX/Cis/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
</tbody>
</table>

ADM = doxorubicin (Adriamycin; Bedford Laboratories, Bedford, OH); CarboMV = carboplatin, methotrexate, and vinblastine; cis = cisplatin; CMV = cisplatin, methotrexate, and vinblastine; CUETO = Club Eurologico Espa˜nol de Tratamiento Oncologico; EORTC/MRC = European Organization for Research and Treatment of Cancer/Medical Research Council; 5-FU = 5-fluorouracil; GIST-V = Gruppo Italiano per lo Studio dei Tumori della Vescica; GUONE = Gruppo Uro-Oncologico del Nord Est; MTX = methotrexate; M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin; M-VEC = methotrexate, vinblastine, epirubicin, and cisplatin; NCI = National Cancer Institute; preop = preoperative; RT = radiation therapy; SWOG = Southwest Oncology Group; UK = United Kingdom.
containing combination chemotherapy, a 5% difference (P = 0.016; 95% confidence interval [CI], 1% to 9%) in favor of neoadjuvant chemotherapy was demonstrated. This reflected a change in survival from 45% to 50%, which is also consistent with only a 1% to 7% difference in survival. Most patients were from the EORTC/MRC trial; thus, the results are similar to those from that trial (level 2).

A very similar meta-analysis of neoadjuvant randomized controlled trials was conducted in Canada.29 A total of 16 eligible trials that included 3315 patients were identified, and 2605 patients provided data suitable for a meta-analysis of overall survival. The pooled HR was 0.90 (95% CI, 82% to 99%; P = 0.02). Eight trials used cisplatin-based combination chemotherapy, and the pooled HR was 0.87 (95% CI, 78% to 96%; P = 0.006), consistent with an absolute overall survival benefit of 6.5% from 50% to 56.5% (95% CI, 2% to 11%). A major pathologic response was associated with improved overall survival in 4 trials. Neoadjuvant cisplatin–based chemotherapy improved overall survival in muscle-invasive urothelial carcinoma, but the size of the effect was modest (level 2).

Surgical factors were evaluated in 268 patients with muscle-invasive bladder cancer who underwent radical cystectomy in the SWOG Intergroup Trial.30 Cystectomies were performed by 106 surgeons at 109 institutions. Half of the patients received neoadjuvant M-VAC. The 5-year postcystectomy survival and local recurrence rates in all patients who underwent cystectomy were 54% and 15%, respectively. Surgical variables associated with longer postcystectomy survival were negative margins (HR, 0.37; P = 0.0007) and removal of ≥10 nodes (HR, 0.51; P = 0.0001). These associations did not differ by treatment arm (P >0.21 for all tests of interactions between treatment and surgical variables). Predictors of local recurrence were positive margins (odds ratio [OR], 11.2; P = 0.0001) and removal of <10 nodes (OR, 5.1; P = 0.002). The quality of surgery was an independent prognostic factor for outcome after adjustments were made for pathologic factors and neoadjuvant chemotherapy usage (level 2).

Available data suggest that for “average risk” cT2 patients, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers (level 2).

Furthermore, in cases in which small differences in survival are observed, it is always regrettable that data on quality of life are inadequate.

Summary. Cystectomy is considered to be the “gold standard” of treatment for patients with localized muscle-invasive bladder cancer. Neoadjuvant chemotherapy was intended for patients with operable clinical stage T2 to T4a muscle-invasive disease. The rationale for giving chemotherapy before cystectomy or full-dose RT is based on the intent to treat micrometastatic disease present at diagnosis. A discrepancy between clinical and pathologic staging can be expected. Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable. Available data suggest that for “average-risk” patients with cT2 cancer, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers. The quality of the surgery is a confounding factor in these studies. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a 5% difference in favor of neoadjuvant chemotherapy. Unfortunately, in this case, in which small differences in survival can be seen, it is regrettable that the data on quality of life are inadequate.

BLADDER PRESERVATION

Muscle-Invasive Bladder Cancer: Can Bladder Preservation Achieve Survival Equivalent to Radical Cystectomy?

The goal of any organ-preservation strategy should be to achieve cancer survival equivalent to extirpative surgery, while maintaining quality of life in the patient. Improvement in surgical techniques and the development of continent urinary diversions have resulted in decreased morbidity and better postoperative quality of life for patients undergoing radical cystectomy for muscle-invasive bladder cancer,31 leading some to suggest that bladder preservation is not necessary.

Although mortality rates with radical cystectomy have decreased by 50% since the 1990s, survival rates with surgery alone have remained steady, with 5-year survival rates of 66% reported for pathologic stage T2, 35% for pT3, and 27% for pT4 disease (Table 3)2,3,12,32–43 (level 3). In addition, up to 15% of patients with muscle-invasive disease have no pathologic residual disease at the time of cystectomy, indicating the potential curability of select patients with transurethral resection alone. These findings suggest that although bladder preservation may be a viable alternative to radical cystectomy in selected patients, transurethral resection alone is successful in only a small percentage of patients. The risk of clinical understaging in 30% to 50% of patients (level 3),44–46 the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapies have resulted in a multidisciplinary approach to bladder preservation.

Before effective chemotherapy became available, early attempts at bladder preservation included the use of transurethral resection of bladder tumors (TURBT) or partial cystectomy alone for solitary tumors amenable to complete surgical resection. No randomized trials compared survival with TURBT alone versus cystectomy for the management of muscle-invasive disease. The 5-year overall survival rates in case series from 1951 to 1988 in which TURBT alone was performed were 61% for T2a disease and 36% for T2b disease (Table 4),47–53 similar to findings of radical cystectomy series reported during the
same period (Table 3) (level 3). Two large series have now reported similar long-term 10-year survival rates that indicate that TURBT alone may be an effective bladder-sparing technique in selected patients with small tumors. In 1998, Solsona et al. reported 10-year follow-up results in 176 patients with muscle-invasive disease who were treated with transurethral resection alone compared with 76 patients with node-negative muscle-invasive disease who underwent radical cystectomy during the same period. Disease-specific survival rates in patients treated with TURBT alone were 81% at 5 years and 75% at 10 years, with 83% maintaining their native bladder at 5 years and 80% at 10 years (level 3). Of note, all patients treated with TURBT alone in this series had a negative restaging TURBT. Herr reported 10-year follow-up data on 99 patients who underwent TURBT alone for muscle-invasive bladder cancer versus 52 patients who underwent immediate cystectomy. The 10-year disease-specific survival rate for patients treated with TURBT alone was 76%, with 56% maintaining their native bladder, compared with 71% disease-specific survival in patients undergoing immediate radical cystectomy. It is interesting to note that 73 patients (74%) in the TURBT-alone group had no residual tumor on their restaging TURBT and enjoyed an 82% 10-year survival rate, compared with a 57% 10-year survival rate in 26 patients with residual T1 tumor on their restaging TURBT (level 3).

These data denote the therapeutic importance that TURBT can have in multimodality bladder preservation strategies and the difficulty involved in interpreting the contribution of each component to survival in a multimodality bladder-sparing reported series. Restaging of TURBT has not been performed as standard practice in all combined modality series; therefore, it is difficult to know the impact that TURBT alone may have had on survival. One would expect patients who have been rendered clinical pT0 by TURBT alone or TURBT plus chemotherapy before radiation or cystectomy to have better long-term survival, and this has been demonstrated in several prospective case series (Table 5) (level 3). The clinical factors in these studies that were associated with a better chance of complete clinical response to TURBT alone or TURBT plus chemotherapy and thus better survival are (1) clinical stage (organ-confined), (2) tumor size < 3 to 5 cm, (3) absence of hydronephrosis, (4) absence of a palpable mass, and (5) unifocal disease. However, none of these factors has been prospectively verified in a randomized trial.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>No Residual Disease at Cystectomy (%)</th>
<th>Operative Mortality (%)</th>
<th>Survival by Pathologic Stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchie et al. (1975)</td>
<td>134</td>
<td>8</td>
<td>8.5</td>
<td>40 20 —</td>
</tr>
<tr>
<td>Bredael et al. (1980)</td>
<td>174</td>
<td>—</td>
<td>4</td>
<td>51 25 18</td>
</tr>
<tr>
<td>Mathur et al. (1981)</td>
<td>58</td>
<td>7</td>
<td>3.4</td>
<td>77 33 29</td>
</tr>
<tr>
<td>Skinner and Lieskovsky (1984)</td>
<td>197</td>
<td>10</td>
<td>2</td>
<td>64 44 36</td>
</tr>
<tr>
<td>Montie et al. (1984)</td>
<td>99</td>
<td>10</td>
<td>9</td>
<td>69 57 —</td>
</tr>
<tr>
<td>Giuliani et al. (1985)</td>
<td>202</td>
<td>—</td>
<td>12</td>
<td>56 19 0</td>
</tr>
<tr>
<td>Roehrborn et al. (1991)</td>
<td>280</td>
<td>—</td>
<td>2.1</td>
<td>63 36 24</td>
</tr>
<tr>
<td>Pagano et al. (1991)</td>
<td>261</td>
<td>9</td>
<td>1.8</td>
<td>57 15 21</td>
</tr>
<tr>
<td>Wishnow and Tenney (1991)</td>
<td>188</td>
<td>5</td>
<td>1.1</td>
<td>79 46 33</td>
</tr>
<tr>
<td>Waehre et al. (1993)</td>
<td>227</td>
<td>25</td>
<td>—</td>
<td>61 36 29</td>
</tr>
<tr>
<td>Vieweg et al. (1999)</td>
<td>686</td>
<td>—</td>
<td>—</td>
<td>58 22 15</td>
</tr>
<tr>
<td>Stein et al. (2001)</td>
<td>633</td>
<td>6</td>
<td>3</td>
<td>72 48 33</td>
</tr>
<tr>
<td>Dalbagni et al. (2001)</td>
<td>284</td>
<td>10.7</td>
<td>—</td>
<td>59 25 29</td>
</tr>
<tr>
<td>Madersbacher et al. (2003)</td>
<td>507</td>
<td>—</td>
<td>4.5</td>
<td>74 52 36</td>
</tr>
<tr>
<td>Grossman et al. (2003)</td>
<td>154</td>
<td>15</td>
<td>0.6</td>
<td>75 — 24*</td>
</tr>
</tbody>
</table>

* Southwest Oncology Group (SWOG) 8710 trial cystectomy-alone arm.
† Pathologic stage T3 and T4a combined.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>B1 (T2a)*</th>
<th>B2 (T2b)*</th>
<th>5-Year Overall Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flocks (1951)</td>
<td>142</td>
<td>56%</td>
<td>43%</td>
<td>47%</td>
</tr>
<tr>
<td>Milner (1954)</td>
<td>88</td>
<td>57%</td>
<td>23%</td>
<td>53%</td>
</tr>
<tr>
<td>Barnes et al. (1967)</td>
<td>114</td>
<td>—</td>
<td>—</td>
<td>40%</td>
</tr>
<tr>
<td>O’Flynn et al. (1975)</td>
<td>123</td>
<td>59%</td>
<td>20%</td>
<td>53%</td>
</tr>
<tr>
<td>Barnes et al. (1977)</td>
<td>75</td>
<td>—</td>
<td>—</td>
<td>31%</td>
</tr>
<tr>
<td>Herr (1987)</td>
<td>44</td>
<td>70%</td>
<td>57%</td>
<td>68%</td>
</tr>
<tr>
<td>Henry et al. (1988)</td>
<td>43</td>
<td>63%</td>
<td>38%</td>
<td>—</td>
</tr>
<tr>
<td>Totals</td>
<td>629</td>
<td>61%</td>
<td>36%</td>
<td>49%</td>
</tr>
</tbody>
</table>

* Marshall-Jewett (comparable TNM) clinical stage.
Table 5. Partial cystectomy/transurethral resection of the bladder tumor (TURBT) + neoadjuvant chemotherapy for stage T2–T4a

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, N (Surgery Type)</th>
<th>Chemotherapy</th>
<th>% Clinical CR (n)</th>
<th>% Survival (n)</th>
<th>% Alive with Bladder (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al. (1984)</td>
<td>57 (54 TURBT/3 PC)</td>
<td>M</td>
<td>58 (33/57)</td>
<td>59 (31/54)/2 yr</td>
<td>79 (19/24)/2 yr</td>
</tr>
<tr>
<td>Srougi and Simon (1994)</td>
<td>36 (30 completed; 4 PC/12 RC)</td>
<td>M-VAC</td>
<td>47 (14/30)</td>
<td>78 (7/9)/3 yr</td>
<td>20/5 yr</td>
</tr>
<tr>
<td>Herr et al. (1998)</td>
<td>60/111 (15 PC/28 TURBT/17 RC)</td>
<td>M-VAC</td>
<td>54 (60/111)</td>
<td>50/5 yr</td>
<td>58 (25/43)/10 yr</td>
</tr>
<tr>
<td>Thomas et al. (1999)</td>
<td>50 (44 TURBT/6 PC)</td>
<td>CM</td>
<td>76 (38/50)</td>
<td>74 (32/43)/10 yr</td>
<td>60/4 yr</td>
</tr>
<tr>
<td>Angulo et al. (1996)</td>
<td>71 (TURBT)</td>
<td>CMV</td>
<td>33 (20/61)</td>
<td>47/5 yr</td>
<td>55 (11/20) of CRs and 0 of PRs/3 yr</td>
</tr>
<tr>
<td>Sternberg et al. (1999)</td>
<td>87 TURBT/PC/RC 28 PC</td>
<td>M-VAC</td>
<td>51 (40/87)</td>
<td>59/5 yr</td>
<td>18 (11/61) overall/3 yr</td>
</tr>
<tr>
<td>de la Rosa et al. (2002)</td>
<td>40 (TURBT)</td>
<td>CMV</td>
<td>53 (21/40)</td>
<td>75/3 yr</td>
<td>57 (24/87)/4.5 yr</td>
</tr>
<tr>
<td>Sternberg et al. (2003)</td>
<td>104 (52 TURBT/13 PC/39 RC)</td>
<td>M-VAC</td>
<td>47 (49/104)</td>
<td>35/7 yr</td>
<td>28 overall/7 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 (31/52)/5 yr</td>
<td>44 (23/52)/5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69 PC/7 yr</td>
<td>31 (4/13)/7 yr</td>
</tr>
</tbody>
</table>

CM = cisplatin and methotrexate; CMV = cisplatin, methotrexate, and vinblastine; CR = complete response; M = methotrexate; M-VAC = methotrexate, vinblastine, doxorubicin (Adriamycin; Bedford Laboratories, Bedford, OH), and cisplatin; PC = partial cystectomy; PR = partial response; RC = radical cystectomy.
On the basis of phase 2 trials, bladder preservation may be possible in selected patients who respond to neoadjuvant chemotherapy (level 3).\textsuperscript{7,58,64} The question is, Can we preserve the bladder and achieve the same survival as with radical cystectomy? Response to chemotherapy is clearly an important prognostic factor.\textsuperscript{6,7,12,24} However, this may represent patient selection, as it is possible that patients who do well have characteristics that would make them survive longer, whether or not they were treated with chemoradiotherapy. In the EORTC and SWOG trials, improved survival was clearly shown in patients who were pT0 at cystectomy. These may be the same patients who would have benefited from a bladder preservation strategy.

In the SWOG trial, the pT0 rate in patients who received M-VAC was 38%, compared with 15% for those who underwent cystectomy alone ($P<0.001$). The pT0 rate after CMV in the EORTC/MRC trial was similarly 33%. After 2 cycles of neoadjuvant M-VAC chemotherapy, the pT0 rate was 40% in the M. D. Anderson trial of M-VAC given both before and after cystectomy (neoadjuvant and adjuvant) versus adjuvant chemotherapy alone.\textsuperscript{13}

In Rome, 104 patients with clinical T2–T4N0M0 tumor of the bladder were treated with neoadjuvant M-VAC.\textsuperscript{7} After clinical restaging, 52 patients underwent TURBT alone, 13 patients had a partial cystectomy, and 39 patients had a radical cystectomy. Median survival for the entire group was 7.49 years (95% CI, 4.86 to 10.00 years). At TURBT after administration of M-VAC, 49 patients (49%) were T0. Responding patients underwent TURBT or partial cystectomy alone after chemotherapy. In all, 60% of those who had M-VAC and TURBT alone were alive at a median follow-up time of 56 months (range, 10 to 160 months). A total of 44% of patients in the TURBT group maintained an intact bladder. Among responding patients with monofocal lesions who underwent partial cystectomy, only 1 required salvage cystectomy, and the 5-year survival rate was 69%.

Of note, in 77 patients whose disease was downstaged to T0 or superficial disease, the 5-year survival rate was 69%. This contrasts with a 5-year survival rate of only 26% in 27 patients who failed to respond, and whose disease was staged as T2 or greater after chemotherapy. Median survival for 27 patients >70 years of age (median, 73 years; range, 70 to 82 years) was surprisingly long, at 90 months (ie, 7.5 years). For elderly patients who underwent TURBT and partial cystectomy, the 5-year survival rate was 67%, with a median survival time of 9 years. In 47% of patients, the bladder was preserved.

Patients who undergo neoadjuvant chemotherapy and bladder preservation should be highly informed, willing to undergo frequent follow-up and multiple cystoscopies, and aware of the possibility that cystectomy may become necessary. For patients with residual disease at first cystoscopy (within 3 months) after TURBT alone or neoadjuvant chemotherapy plus TURBT, we must critically assess the effectiveness of combined modality approaches compared with immediate radical cystectomy.

**What Can Be Attained By Adding Radiation Therapy to Neoadjuvant Chemotherapy?**

Combining systemic chemotherapy with radiation therapy may allow bladder preservation while sensitizing the tumor to radiation therapy and also treating occult metastases. Trials of combined neoadjuvant chemotherapy and radiation therapy are shown in Table 6.\textsuperscript{65–72} This approach has been used by the Radiation Therapy Oncology Group (RTOG) at Massachusetts General Hospital,\textsuperscript{64} as well as by investigators in Erlangen and Paris.\textsuperscript{65,66} Selection criteria for chemoradiation are similar to those that predict a good prognosis after cystectomy. Patients with small T2 or T3 lesions without hydronephrosis who undergo a thorough TURBT tend to fare best (level 3).

Most patients undergo TURBT followed by chemoradiation, restaging TURBT, and consolidative RT in responding patients, and cystectomy in nonresponders; 5-year survival rates ranging from 42% to 63%, with organ preservation in approximately 40% of patients, have been reported. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy may be significant.

The use of newer active chemotherapeutic agents such as gemcitabine and the taxanes in the neoadjuvant setting or as concomitant therapy with radiation remains experimental, but it is being incorporated into treatment protocols. Neoadjuvant gemcitabine, paclitaxel, and carboplatin followed by observation or immediate cystectomy is under study by SWOG. Molecular markers, recurrence rates, and cystectomy-free survival rates are currently being evaluated.

As in the case with neoadjuvant chemotherapy alone, patients should be highly motivated to preserve their bladders and understand the possible adverse effects of combined therapy.

**Summary.** The goal of any organ-preservation strategy should be to achieve cancer survival equivalent to that attained with extirpative surgery, while maintaining quality of life in the patient. The risk of clinical understaging in 30% to 50% of patients, the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy have led to a multidisciplinary approach to bladder preservation. No randomized trials have compared survival with TURBT alone versus cystectomy for the management of muscle-invasive disease. Clinical factors associated with a better chance of complete clinical response to TURBT alone or TURBT plus chemotherapy and thus better survival include (1) clinical stage (organ-confined), (2) tumor size <3 cm, (3) absence of hydronephrosis, (4) absence of a palpable mass, and (5) unifocal disease. Patients with residual disease at first cystoscopy (within 3 months) after
TURBT alone or neoadjuvant chemotherapy plus TURBT are those in whom we must critically assess the effectiveness of combined modality approaches compared with immediate radical cystectomy. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and RT may be significant.

ADJUVANT CHEMOTHERAPY

Advantages and Disadvantages of Adjuvant Chemotherapy

Adjuvant chemotherapy is widely used after cystectomy in patients with pt3–pt4a and/or pn + mo disease in an effort to delay recurrence and prolong survival. This approach of administering chemotherapy after local treatment has led to increased survival in patients with several other solid tumors.6,71,74

The rationale for giving adjuvant chemotherapy is that local treatment is performed immediately. Treatment decisions are based on pathologic criteria after the cystectomy specimen has been carefully examined. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage. Surgery is not delayed, and no time is wasted in those patients who would not respond to chemotherapy. If micrometastases are present, they are treated when their volume is low, rather than after waiting for overt metastatic disease.

The advent of orthotopic bladder substitutions and the decreased morbidity of cystectomy have increased the tendency of urologists to operate early, await the pathologic stage, and then consider adjuvant chemotherapy. A major disadvantage is that the bladder is not preserved; also, the start of systemic therapy for occult metastases is delayed while focus is placed first on the primary tumor. Response cannot be easily evaluated, and the only clinical end point that can be assessed is time to tumor recurrence. An additional disadvantage is the difficulty involved in administering chemotherapy to patients after cystectomy.

Despite its appeal, very few randomized trials have evaluated adjuvant chemotherapy (Table 7).75–81 Two studies have received attention. In an American phase 3 prospective trial, Skinner et al.75 showed a significant increase in time to progression and survival in patients randomly assigned to receive chemotherapy after undergoing cystectomy. This study has been criticized for its methods. Specifically, only a small percentage of potentially eligible patients were entered into the study, therapy varied and changed during the course of the study.

Table 6. Trials of combined chemotherapy and radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Chemotherapy</th>
<th>5-Year Survival (%)</th>
<th>5-Year Survival with Intact Bladder (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG study 85-12 (1993)67</td>
<td>42</td>
<td>DDP</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>RTOG study 88-02 (1996)68</td>
<td>91</td>
<td>MCV + RT and DDP</td>
<td>62*</td>
<td>44</td>
</tr>
<tr>
<td>RTOG study 89-03 (1998)69</td>
<td>123</td>
<td>MCV + RT and DDP</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>University of Erlangen (2001)75,70</td>
<td>199</td>
<td>DDP or Carbo</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td>University of Paris (2001)66,71</td>
<td>120</td>
<td>DDP/5-FU</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Massachusetts General (2002)72</td>
<td>190</td>
<td>MCV or DDP/5-FU</td>
<td>54</td>
<td>46</td>
</tr>
</tbody>
</table>

Carbo = carboplatin; DDP = cisplatin; 5-FU = 5-fluorouracil; MCV = methotrexate, cisplatin, and vinblastine; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group.

* 4-year survival data.

Table 7. Adjuvant chemotherapy after cystectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Chemotherapy</th>
<th>No Chemotherapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logothetis et al. (1988)81</td>
<td>CISCA</td>
<td>62</td>
<td>71</td>
<td>Benefit, but not randomized</td>
</tr>
<tr>
<td>Skinner et al. (1991)75</td>
<td>CAP</td>
<td>47</td>
<td>44</td>
<td>Benefit, few patients received therapy</td>
</tr>
<tr>
<td>Stockle et al. (1992)76</td>
<td>M-VAC/M-VEC</td>
<td>26</td>
<td>23</td>
<td>Benefit, few patients, no treatment at relapse</td>
</tr>
<tr>
<td>Studer et al. (1994)77</td>
<td>DDP</td>
<td>40</td>
<td>37</td>
<td>No benefit, DDP alone inadequate</td>
</tr>
<tr>
<td>Bono et al. (1997)78</td>
<td>CM</td>
<td>48</td>
<td>35</td>
<td>No benefit for NOM0</td>
</tr>
<tr>
<td>Freiha et al. (1996)79</td>
<td>CMV</td>
<td>25</td>
<td>25</td>
<td>Benefit in relapse-free survival only</td>
</tr>
<tr>
<td>Otto et al. (2001)80</td>
<td>M-VEC</td>
<td>55</td>
<td>53</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

CAP = cyclophosphamide, doxorubicin (Adriamycin); Bedford Laboratories, Bedford, OH, and cisplatin; CISCA = cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); CM = cisplatin and methotrexate; CMV = cisplatin, methotrexate, and vinblastine; DDP = cisplatin; M-VAC = methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; M-VEC = methotrexate, vinblastine, epirubicin, and cisplatin.
and the primary benefit was attained by a subgroup not prospectively identified in the study plan (level 2).

Another adjuvant chemotherapy trial conducted in Germany was published by Stockle et al.\textsuperscript{76,82} Patients were randomly assigned to cystectomy or cystectomy followed by M-VAC or methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC). Patients had poor risk factors; 60% had positive nodes, most of which were stage T4. The study was prematurely discontinued with only small patient numbers after an interim analysis showed a benefit for patients randomly assigned to chemotherapy. Reported progression rates were 27% in treated patients versus 82% in controls. Survival was different between the 2 groups as well. The 5-year progression-free survival rate was 59% after chemotherapy was recommended versus 13% after the recommendation was made to undergo cystectomy alone (level 2).\textsuperscript{82} Biases introduced by early cessation of nonblinded phase 3 trials have been well recognized. In addition, and contrary to current standard practice, investigators did not offer chemotherapy to patients in the observation group at the time of recurrence. Whether this had an effect on the observed survival advantage remains an open question. Of note, in a more recent German series in which M-VEC was compared with observation after cystectomy, no difference in survival was confirmed (level 2).\textsuperscript{80}

Because of the difficulty associated with interpretation of these adjuvant chemotherapy trials, a systematic review of published randomized trials of adjuvant cisplatin-containing combination chemotherapy in locally advanced bladder cancer was undertaken. A difference in favor of adjuvant chemotherapy was suggested, but serious methodologic flaws were found in all studies. Major deficiencies included insufficient sample size, inappropriate early cessation of patient entry, inappropriate statistical analyses, and insufficient reporting of results, all of which led to poorly substantiated and supported conclusions (level 2).\textsuperscript{83} More specifically, it was concluded that the available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice.

To address these questions, 2 separate adjuvant studies have been initiated. The EORTC, together with other international cooperative groups, has begun a large randomized adjuvant trial in patients at high risk for recurrence. This patient population was chosen on the basis that chemotherapy is commonly administered to these patients already and the fact that generally fewer patients are present, these are treated when at a low volume, rather than waiting for overt metastatic disease.

The advent of orthotopic bladder substitutions and the decreased morbidity associated with cystectomy have increased the tendency of urologists to operate early and then to consider adjuvant chemotherapy. Although it is common for patients to be selected for adjuvant therapy on the basis of risk for recurrence, this does not necessarily imply that these patients are the most likely to benefit from administered therapy. Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice. The results of larger collaborative international adjuvant chemotherapy trials will be needed for the true value of adjuvant chemotherapy to be assessed.

**Chemotherapy in Metastatic Disease**

Systemic chemotherapy is the only modality that has been shown in phase 3 trials to improve survival in responding patients with advanced bladder cancer (level 1).\textsuperscript{37,88} The M-VAC regimen, first reported in 1985 by investigators from Memorial Sloan-Kettering Cancer Center, revealed that urothelial carcinoma was sensitive to chemotherapy.\textsuperscript{89} Patients with measurable lesions were found to have a remarkably high response rate of 72%, and 36% attained complete response.\textsuperscript{84} Long-term survival was achieved in patients who attained complete response. In addition, patients who achieved a complete response. In addition, patients who achieved a complete response.
response with the combination of chemotherapy and surgery had twice the survival of patients who had only a partial response to chemotherapy and no further surgery (level 3).³⁴ The median overall survival time for the whole group was 13.1 months. Chemotherapy was more effective in patients with nodal disease only compared with patients who had visceral metastases.³⁴,³⁸

In an update of these results, a retrospective analysis of 5 different M-VAC trials encompassing 203 patients from Memorial Sloan-Kettering Cancer Center was reported. Among 194 evaluable patients, 46 patients achieved a complete response (24%) and 84 patients a partial response (43%), yielding an overall response rate of 67%. The median survival time for all 203 patients was 14.8 months, with a 5-year survival rate of 17% (level 3).³⁰ The 5-year survival rate for the 46 patients with a complete response after chemotherapy alone was 40%. An additional 30 patients achieved complete response after chemotherapy followed by surgery, with a 5-year survival rate of 33% (level 3).³¹

Prognostic factors were predictive of response and survival in these patients. A total of 3 risk categories were established on the basis of Karnofsky performance status (KPS) and the presence or absence of visceral metastases. There were 2 factors that had an independent prognosis: KPS <80% and visceral (lung, liver, or bone) metastasis. Median survival times for patients who had 0, 1, or 2 risk factors were 33, 13.4, and 9.3 months, respectively (P = 0.0001). The median survival time of patient cohorts could vary from 9 to 26 months simply by altering the proportion of patients from different risk categories.³²

Prior M-VAC prognostic models for predicting increased toxicity and poor overall survival included the presence of visceral metastases, the presence of abnormal levels of alkaline phosphatase, and a low KPS (level 2).³⁷,³³,³⁹ Similar findings regarding prognostic factors, risk categories, and survival have been seen when using the new agents in triple-combination regimens (level 2).³⁴ Prognostic factors in patients with metastatic disease in phase 2 trials can be as important as the therapy actually given to the patients and can be a determinant of both response and survival (level 2). Randomized trials in the 1990s showed that M-VAC was superior to single-agent cisplatin (level 1)³⁷ and to the CISCA (cisplatin, cyclophosphamide, and doxorubicin [Adriamycin]) combination regimen (level 1).³⁸ Although M-VAC was found superior to single-agent cisplatin,³⁷ long-term survival of the patients receiving M-VAC was poor.³² In the years since M-VAC was developed, it has been considered the standard therapy for “fit” patients with advanced disease. In the Memorial Sloan-Kettering Cancer Center experience, M-VAC has been associated with severe toxicity and long-term survival in only 15% of patients with visceral metastases and in 30% of patients with nodal disease. The need for improved efficacy and reduced toxicity has led investigators to continue to seek less toxic and more effective regimens.

Other extensively studied combination regimens in metastatic urothelial carcinoma are cisplatin and methotrexate (CM) and CMV (level 3).³⁵–³⁷ CMV has been shown to be superior to methotrexate and vinblastine (MV) in a randomized study of 214 patients undertaken by the MRC (level 1).³⁸ The median survival time was 7 months with CMV versus 4.5 months with MV, and the 1-year survival rate was 29% with CMV versus 16% with MV. The HR for overall survival was 0.48 in favor of CMV. This study demonstrated the significant survival impact of cisplatin and has helped to justify the routine use of cisplatin-based combination chemotherapy. Although CM, CMV, and M-VAC have never been compared in randomized studies, most centers have considered M-VAC to be the standard regimen.

More recent combination regimens have shown better survival results than were observed in the original M-VAC series (in the range of 14 to 15 months) (level 3)³⁹–⁴³ (Table 8).³⁵–³⁸,³⁰⁴. This may be owing to multiple reasons, including case selection, stage migration (patients with locally advanced disease mixed with patients with advanced metastatic disease), better radiologic techniques, increased patient awareness, increased use of postchemotherapy surgery, and newer active agents.³⁴–³⁷

### Single Agents

Antitumor activity has been demonstrated with several single agents, although these drugs have rarely produced an improvement in survival (level 3).³⁰–³² The response rate to single agent cisplatin is 17% (12% in phase 3 trials).³⁷ Carboplatin has also been widely used because of its ease of outpatient administration and its milder toxicity profile. Phase 2 studies in advanced urothelial cancer have shown a 12% to 14% response rate.³⁸,³⁹

Several other novel chemotherapeutic agents have activity in urothelial carcinoma, including gemcitabine, the taxanes (paclitaxel and docetaxel), pemetrexed, the epothilones, and vinflunine.³⁴–³⁷,³⁹–³⁰ Gemcitabine is usually given on a 4-week schedule, with the drug administered weekly for 3 weeks, followed by a 1-week rest. When gemcitabine is administered as a single agent, response rates of 23% to 28% have been obtained in both pretreated patients and in those who have not had prior therapy.³⁹,³⁴,³⁵,³⁹

Following several phase 2 studies,³⁵,³⁸ a randomized international trial compared GC with M-VAC. Eligibility criteria included patients with T4b, N2 or N3, or M1 disease. The trial revealed a similar efficacy with respect to response, time to progressive disease, and survival between the 2 treatment arms, whereas GC was significantly less toxic than M-VAC.³³ The median survival time was 13.8 months for GC-treated patients and 14.8 months for M-VAC–treated patients, with an HR of 1.04, but the study did not include enough patients (N = 405) to prove that the 2 regimens had equivalent efficacy. However, based on the favorable balance in the risk–benefit ratio in favor of GC (level 2), GC is now...
considered an alternative to M-VAC as a standard of care in patients with locally advanced and metastatic urothelial cancer.

The 5-year update of the randomized GC versus M-VAC trial is awaited. However, to look for the first possible long-term results after treatment with GC, the data from the first 3 phase 2 studies114,115,116 on GC, which included a total number of 121 patients, have been pooled. The median survival time for all patients was 13.2 months, with an estimated 4-year survival rate of 13%. In patients without visceral metastases, the estimated median overall survival time of 9 months.123 In untreated patients with response rates that are similar to M-VAC, a recent randomized study reported by the Hellenic Group has shown inferior activity of the docetaxel and cisplatin (DC) combination compared with classic M-VAC. Although this study was designed to detect a survival advantage for DC, the investigators instead observed that survival was inferior for patients treated with DC. Because performance status was not used in this trial as a prospective stratification variable, the treatment arms were not appropriately balanced. After adjusting for prognostic factors, difference in time to progression remained significant (HR, 1.61; P = 0.005), whereas survival difference was not significant at the 5% level (HR, 1.31; P = 0.089) (level 2).104

### Dose Intensification

In a phase 3 EORTC Genitourinary Group trial, high-dose M-VAC given every 2 weeks with granulocyte/colony-stimulating factor (G-CSF) was compared with M-VAC.85 It was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time if G-CSF was routinely added. This trial revealed less toxicity with high-dose M-VAC owing to the addition of G-CSF. Although there was not a significant difference found in median survival (>14 months in both arms), there was a significant difference in favor of high-dose M-VAC in response rate and complete response rate. The 2-year survival rate was 35% with high-dose M-VAC compared with 25% with M-VAC (level 1). One could conjecture that this regimen might be useful in the neoadjuvant or adjuvant setting because the cycle length is much shorter and it is delivered in half the time of traditional M-VAC (level 4).

### Reducing Toxicity in Unfit or Elderly Patients

Strategies have been developed to minimize toxicity in patients who are unfit, elderly, or who have compromised renal function.128 Unfortunately, there is no general consensus as to how to define who is considered “unfit.” The EORTC is evaluating the combination of gemcitabine and carboplatin compared with methotrexate, carboplatin, and vinblastine in patients ineligible for platinum-based chemotherapy.129

Cisplatin-related toxicity is not inconsequential in elderly patients. Renal insufficiency limits wide applicability, and long-term survival remains poor. These protocols seek less-toxic treatments for patients who cannot undergo cisplatin-based regimens, primarily for medical reasons. One major problem is that “unfit” or “poor performance status” patients are often mixed or confused with “elderly” and “renally impaired” patients. Performance status–2 patients

### Table 8. Phase 3 randomized trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Patients (N)</th>
<th>Response Rate</th>
<th>Median Survival (mo)</th>
<th>Best Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehrer et al.</td>
<td>M-VAC</td>
<td>126</td>
<td>39%</td>
<td>12.5</td>
<td>M-VAC</td>
</tr>
<tr>
<td></td>
<td>DDP</td>
<td>120</td>
<td>12%</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Logothetis et al.</td>
<td>M-VAC</td>
<td>65</td>
<td>65%</td>
<td>12.6</td>
<td>M-VAC</td>
</tr>
<tr>
<td></td>
<td>CISCA</td>
<td>55</td>
<td>46%</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>von der Maase et al.</td>
<td>M-VAC</td>
<td>202</td>
<td>46%</td>
<td>14.8</td>
<td>M-VAC ~ GC</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>203</td>
<td>49%</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Sternberg et al.</td>
<td>HD-M-VAC</td>
<td>134</td>
<td>62%</td>
<td>14.5</td>
<td>HD-M-VAC ~ M-VAC</td>
</tr>
<tr>
<td></td>
<td>M-VAC</td>
<td>129</td>
<td>50%</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>Bamias et al.</td>
<td>M-VAC</td>
<td>109</td>
<td>54%</td>
<td>14.2</td>
<td>M-VAC</td>
</tr>
<tr>
<td></td>
<td>DC-DPP</td>
<td>111</td>
<td>37%</td>
<td>9.3</td>
<td></td>
</tr>
</tbody>
</table>

CISCA = cisplatin, doxorubicin (Adriamycin; Bedford Laboratories, Bedford, OH), and cyclophosphamide; DC = docetaxel and cisplatin; DDP = cisplatin; GC = gemcitabine-cisplatin; HD-M-VAC = high-dose M-VAC; M-VAC = methotrexate, vinblastine, doxorubicin, and cisplatin; ~ = similar to.
Constitute a group with very poor prognosis group, but they may still respond to chemotherapy. Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Efficacy data on the use of chemotherapeutic combinations as effective and safe palliative therapy in clearly defined "unfit" patients are still scant. Outside of a clinical trial, methotrexate, carboplatin, vinblastine (M-CAVI), carboplatin-gemcitabine, carboplatin-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, carboplatin, or a taxane can be considered for "unfit" patients on an individual basis (level 3).

The combination of gemcitabine and carboplatin has been evaluated in predefined "unfit" patients with bladder cancer in a dose-finding study (performance status ≥2 and or creatinine clearance <60 mL/min). Using this combination, investigators reported an overall response rate of 43.5%, with a median survival time of 14.4 months in 16 patients ineligible for the cisplatin-based regimen ("unfit" patient population). The preliminary results found in this phase 2 trial using the carboplatin-gemcitabine combination therapy prompted an EORTC randomized phase 2/3 trial comparing carboplatin-gemcitabine with M-CAVI in patients ineligible for cisplatin-based chemotherapy; this trial is ongoing.

### Dual-Combination Chemotherapy

Paclitaxel and carboplatin combination chemotherapy regimens have been routinely used in advanced urothelial carcinoma. Several studies with carboplatin (area under the curve 5 to 6) and paclitaxel (150 to 225 mg/m²) have reported response rates ranging from 21% to 63%, although many of the responses were only partial. In the SWOG study, the response rate was only 14%, with a very poor median survival time of only 9 months. This may have been owing to a predominance of patients with poor performance status and with visceral metastases, suggesting that the regimen was not necessarily to blame for the poor results. Nonetheless, a number of investigators now question whether or not it is ethical to give "fit" patients this combination.

Because no phase 3 trials have compared carboplatin and paclitaxel with the standard regimens of M-VAC or GC (the ECOG trial of M-VAC versus carboplatin and paclitaxel was closed early because of poor accrual), it is probably best not to use this regimen except in patients with extremely poor renal function who cannot tolerate cisplatin (level 3).

Trials of carboplatin-based combinations reported in the 1990s (the combination of carboplatin with methotrexate and vinblastine [CarboMV134 and M-CAVI108]) showed response rates of 30% to 40% and median survival times of 8 to 10 months108,134, these results were, again, inferior to those obtained with M-VAC. Two additional underpowered randomized studies also suggested the suboptimal efficacy of carboplatin-based chemotherapy (level 3).135,136

The platinum-free combination of gemcitabine and paclitaxel chemotherapy has been evaluated in several studies, with favorable results demonstrated even in pretreated patients.137–142 In a phase 2 Italian and Israeli study, 40 patients who had been pretreated with M-VAC had a 60% overall response rate (28% complete response and 33% partial response) when treated with paclitaxel 150 mg/m² and gemcitabine 2500 to 3000 mg/m² every 2 weeks on an outpatient basis. Of note, the response rate was 27% in patients who had failed prior chemotherapy for metastatic disease within the last year, as compared with 80% for patients who received prior neo-adjuvant or adjuvant M-VAC. The median survival time for all patients was 14.4 months, which was equal to that seen in another American study.138

Of concern was the pulmonary toxicity observed by the Hoosier group. In that study, a weekly regimen of combination gemcitabine 1000 mg/m² and paclitaxel 110 mg/m², given on days 1, 8, and 15 every 4 weeks, was used in patients who were not pretreated.139

The combination of docetaxel 40 mg/m² and gemcitabine 800 mg/m² on days 1 and 8 every 3 weeks has been evaluated in pretreated patients by ECOG. Of 29 patients, 25 were evaluable for response. The authors concluded that this regimen was active, with 5 patients attaining a partial response (20% overall response rate) and 10 having stable disease. A combination of doxorubicin and gemcitabine has been reported to lead to a 36% complete response rate, but this has not been confirmed.

The combination of gemcitabine and a taxane is active and well tolerated as first- or second-line treatment in patients with advanced urothelial carcinoma, as well as in patients with compromised renal function (level 3).

### Triple-Combination Chemotherapy

Other combinations using the taxanes and gemcitabine have been put forth as possible alternatives to M-VAC. Both gemcitabine and paclitaxel have been incorporated into multiagent chemotherapy combinations with cisplatin or carboplatin. Phase 2 data from 2 gemcitabine-based triple-combination drug trials are currently available.

The Spanish regimen of gemcitabine, cisplatin, and paclitaxel has led to a very high response rate of approximately 78% (complete response, 28%; partial response, 50%). In the first report from the phase 1 trial, the investigators cited a mean survival time of 24 months, probably owing to patient selection. In the multicenter phase 2 study, the median survival time was 15.6 months, which is more consistent with other currently available regimens. In an American study, the combination regimen of gemcitabine, paclitaxel, and carboplatin (instead of cisplatin) compared favorably with the Spanish regimen, with a reported 14.7-month median survival time and 1-year survival rate of 59%. The overall response rate was 68% (complete response, 32%; partial response, 36%). In a third study from Memorial Sloan-Kettering Cancer Center, triple-combination ifosfamide, paclitaxel (Taxol; Bristol-Myers Squibb Co., Princeton, NJ), and cisplatin (Platinol-AQ; Bristol-Myers Squibb) therapy...
revealed a 68% overall response rate (complete response, 23%; partial response, 45%). Median survival time was 20 months in this single-center study.\textsuperscript{147} The results of ongoing phase 3 trials will determine whether the use of these new triple-combination regimens really results in improved survival.

Summary. Rarely has the use of single-agent chemotherapy produced improvement in survival. Systemic cisplatin-based combination chemotherapy is the only current modality that has been shown to improve survival in responding patients with advanced bladder cancer in randomized phase 3 trials. Prognostic factors of patients with metastatic disease in phase 2 trials can be as important as the therapy actually given to the patients and can be determinants of both response and survival. The randomized study comparing GC and M-VAC did not include enough patients to prove equivalency, but, based on the similar efficacy of GC compared with M-VAC, as well as a favorable risk–benefit ratio, GC is now considered a standard-of-care alternative to M-VAC in patients with locally advanced and metastatic urothelial cancer.

Phase 2 studies of dual-drug combinations of paclitaxel or docetaxel with cisplatin have shown activity in untreated patients, with response rates similar to those reported with M-VAC. However, in 1 randomized trial (where treatment arms were not appropriately balanced), M-VAC has proved to be superior in terms of time to progression. When high-dose intensity M-VAC (HD-M-VAC)—given every 2 weeks with G-CSF—was compared with M-VAC, it was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time, with a significant difference in favor of HD-M-VAC in overall response rate and complete response rate but without a significant survival difference. Strategies have been developed to minimize toxicity in patients who are considered “unfit” or “elderly” or who have “compromised renal function.” Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Outside of a clinical trial, M-CAVI, carboplatin-gemcitabine, carboplatin-paclitaxel, gemcitabine-taxane, or monotherapy with gemcitabine, carboplatin, or a taxane could be used in “unfit” patients on an individual basis. Because no phase 3 trials have compared carboplatin and paclitaxel with M-VAC or to GC, this regimen should not be used in “fit” patients. The findings of 2 small randomized studies using “classic” agents have suggested the suboptimal efficacy of carboplatin-based combination chemotherapy compared with M-VAC. Even with the incorporation of the “new” agents, carboplatin-based regimens should not be used in “fit” patients outside of a clinical trial. The combination of gemcitabine and a taxane is active and well tolerated as first- or second-line treatment of patients with advanced urothelial carcinoma and in patients with compromised renal function. Whether or not newer triple-combination regimens can improve survival remains to be determined in ongoing phase 3 trials.

RECOMMENDATIONS

Neoadjuvant Chemotherapy

1. Cystectomy is considered the gold standard of treatment for localized muscle-invasive bladder cancer (grade B).
2. When neoadjuvant chemotherapy is considered, a discrepancy between clinical and pathologic staging can be expected (grade B).
3. Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable (grade B). However, few data on quality of life are available.
4. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a modest difference in favor of neoadjuvant chemotherapy (grade B).
5. Available data suggest that for “average-risk” cancer patients with cT2, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers (grade B).
6. The quality of the surgery is a confounding factor in these studies (grade B).

Bladder Preservation

1. The goal of any organ-preservation strategy should be to achieve cancer survival equivalent to that of extirpative surgery, while maintaining quality of life in the individual patient (grade D).
2. The risk of clinical understaging in 30% to 50% of patients and the advent of more effective combination chemotherapy have led to a multidisciplinary approach to bladder preservation (grade C).
3. No randomized trials have compared bladder-sparing approaches versus radical cystectomy (grade D).
4. Clinical factors associated with a better prognosis with TURBT with or without chemotherapy include clinical stage (organ confined), tumor size <3 to 5 cm, absence of hydronephrosis, unifocal disease, and absence of carcinoma in situ (grade C).
5. After TURBT alone or chemotherapy plus TURBT, if residual disease is found at the first cystoscopy (within 3 months), patients with muscle-invasive cancer should be considered for immediate radical cystectomy (grade C).
6. Although survival is similar to that in contemporary cystectomy series, the combined morbidity of chemotherapy and radiation therapy may be significant (grade C).
7. Patients who undergo bladder preservation approaches should be highly motivated to preserve their bladders and understand the possible adverse effects of combined therapy and the burden of long-term follow-up (grade C).
Adjuvant Chemotherapy

1. The advent of orthotopic bladder substitutions and the decreased morbidity of cystectomy have increased the tendency of urologists to operate early and then consider adjuvant chemotherapy (grade C).

2. With adjuvant chemotherapy after cystectomy, local treatment is performed immediately, and treatment decisions may be based on pathologic criteria. The availability of sufficient tissue for increasingly sophisticated analysis of putative molecular prognostic and predictive markers is also an advantage (grade D).

3. Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice (grade B).

4. Results of larger collaborative international adjuvant chemotherapy trials will be needed before the true value of adjuvant chemotherapy can be assessed (grade D).

Chemotherapy in Metastatic Disease

1. Single-agent chemotherapy has rarely produced improvement in survival (grade A).

2. Systemic cisplatin-based combination chemotherapy is the only current modality that has been shown to improve survival in responsive patients with advanced bladder cancer in phase 3 trials (grade A).

3. Prognostic factors of patients with metastatic disease in phase 2 trials may be as important as the therapy actually given to patients and can be the determinant of both response and survival (grade B).

4. The randomized study comparing GC and M-VAC did not include enough patients to prove equivalency, but, on the basis of a similar efficacy of GC compared with M-VAC and a favorable risk–benefit ratio, GC is now considered an alternative to M-VAC as a standard of care in patients with metastatic urothelial cancer (grade B).

5. Phase 2 studies of 2 drug combinations of paclitaxel or docetaxel with cisplatin have shown activity in untreated patients with RRs similar to M-VAC, but in 1 randomized trial, in which treatment arms may not have been perfectly balanced, M-VAC was superior (grade C).

6. When HD–M-VAC (given every 2 weeks with G-CSF) was compared with M-VAC, it was found that it was possible to deliver twice the dose of cisplatin and doxorubicin with less toxicity, fewer dose delays, and in half the time, with a significant difference in favor of HD–M-VAC in overall response rate and complete response rate, but without a significant survival difference (grade B).

7. Strategies have been developed to minimize toxicity in patients who are considered “unfit” or “elderly,” or who have “compromised renal function.” Clinical trials should be designed to clearly distinguish among these 3 groups of patients. Low-morbidity regimens are being developed for “unfit” patients (grade C).

8. Because no phase 3 trials have compared carboplatin and paclitaxel with M-VAC or GC, this regimen should not be used in “fit” patients (grade C).

9. Routine use of carboplatin is not supported in “fit” patients with good creatinine clearance (grade C).

10. Whether or not we can improve survival with newer triple drug combination regimens will depend on the results of ongoing phase 3 trials (grade D).

References


