Neoadjuvant Chemotherapy for Bladder Cancer

By Guru Sonpavde, MD [2] and Seth P. Lerner, MD [3]

Occult distant micrometastasis at the time of radical cystectomy leads predominantly to distant failures in patients with locally advanced muscle-invasive transitional cell carcinoma of the bladder. Cisplatin-based combination chemotherapy enhances survival in patients with metastatic urothelial cancer. Studies evaluating adjuvant chemotherapy have been limited by inadequate statistical power. However, randomized clinical trials have demonstrated a survival benefit for neoadjuvant cisplatin-based combination chemotherapy, which should be considered a standard of care. In addition, neoadjuvant therapy may assist in the rapid development of novel systemic therapy regimens, since pathologic complete remission appears to be a powerful prognostic factor for long-term outcomes. Patients who are either unfit for or refuse radical cystectomy may benefit from neoadjuvant chemotherapy with or without radiation to enable bladder preservation.

An estimated 67,160 cases of bladder cancer (~25% of which are muscle-invasive) and 13,750 deaths from this disease are predicted for 2007 in the United States.[1] Radical cystectomy achieves excellent long-term outcomes in muscle-invasive transitional cell carcinoma (TCC) of the bladder (Table 1). The overall long-term progression-free survival (PFS) rate is 60% to 70% in large retrospective reports from the University of Southern California (USC), Germany, Switzerland, and the Bladder Cancer Research Consortium.[2-7] Extravesical disease confers a relatively poor PFS of 40% to 60%, whereas lymph node involvement is associated with a PFS of 15% to 35%.

### Table 1

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of Patients</th>
<th>Median Follow-up</th>
<th>Perioperative Chemotherapy</th>
<th>Muscle-Invasive Cancer</th>
<th>Organ-Confinned Disease</th>
<th>Extravesical Disease</th>
<th>Lymph Node-Positive Disease</th>
<th>Overall Distant Failure</th>
<th>Overall Local Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>USC[2]</td>
<td>1,054</td>
<td>10.2 yr</td>
<td>27%</td>
<td>63%</td>
<td>76%–78%</td>
<td>45%–61%</td>
<td>34%</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Uln[5]</td>
<td>788</td>
<td>2.9 yr</td>
<td>0%</td>
<td>74%</td>
<td>69%–91%</td>
<td>45%–81%</td>
<td>14%</td>
<td>9.5%</td>
<td>4%–20%</td>
</tr>
<tr>
<td>Bern[6]</td>
<td>507</td>
<td>3.75 yr</td>
<td>0%</td>
<td>82%</td>
<td>73%–85%</td>
<td>56%–67%</td>
<td>33%</td>
<td>25%–51%</td>
<td>3%–13%</td>
</tr>
<tr>
<td>BCRC[7]</td>
<td>888</td>
<td>3.25 yr</td>
<td>31%</td>
<td>78%</td>
<td>63%–87%</td>
<td>19%–38%</td>
<td>16%</td>
<td>22%</td>
<td>—</td>
</tr>
</tbody>
</table>

BCRC = Bladder Cancer Research Consortium; PFS = progression-free survival; USC = University of Southern California.

### Risk Factors for Recurrence Following Radical Cystectomy

A postoperative nomogram was developed by the International Bladder Cancer Nomogram Consortium, based on > 9,000 postoperative patients and including age, sex, time from diagnosis to surgery, pathologic tumor stage and grade, tumor histologic subtype, and regional lymph node status.[8] The predictive accuracy of the nomogram (concordance index = 0.75) was significantly better than standard staging (concordance index = 0.68; P < .001) or standard pathologic subgroupings (concordance index = 0.62; P < .001).

The quality of radical cystectomy appears to have a major impact. Extended pelvic lymph node dissection (regardless of pathologic tumor involvement) up to the aortic bifurcation (as opposed to the iliac bifurcation or inferior mesenteric artery), lymph node density (number of pathologically positive lymph nodes/total number of lymph nodes removed), and margin status each appear to have a significant impact on outcome.[9-11] The total number of lymph nodes involved, pathologic stage of the primary tumor, and adjuvant chemotherapy also appear to be risk factors. The majority of bladder cancer recurrences are distant (Table 1). The high incidence of distant recurrence implies the frequent presence of distant micrometastasis (especially in those with pathologic extravesical and lymph node–positive disease), which perioperative systemic chemotherapy may eradicate and thereby enhance survival. Perioperative radiotherapy is likely to
play a smaller role in enhancing outcome since local recurrences are less common.

**Systemic Chemotherapy for Metastatic Urothelial Cancer**

Randomized trials have demonstrated significantly improved outcomes with MVAC (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin) compared to single-agent cisplatin, CISCA (cisplatin, cyclophosphamide, doxorubicin), or cisplatin/docetaxel (Table 2).[12-14] The median PFS and overall survival (OS) for MVAC are 8 and 14 months, respectively. However, MVAC largely remains a palliative regimen producing a suboptimal long-term survival rate of 4% to 15%.

Conventional MVAC compared with dose-dense MVAC (DD-MVAC) every 2 weeks with recombinant human granulocyte colony-stimulating factor (G-CSF, Neupogen) demonstrated nearly identical median survivals (15.1 vs 14.9 months), while the 5-year survival rate was superior for DD-MVAC (21.8% vs 13.5%, P = .042).[15] DD-MVAC was also superior for overall response rate (RR = 72% vs 58%, P = .016) and complete response (CR) rate (25% vs 11%, P = .006) (Table 2). Owing to the modest size of this trial, it is suggestive but cannot be considered definitive for the superiority of DD-MVAC.

A European randomized trial that accrued 405 patients compared GC (gemcitabine [Gemzar], cisplatin) with MVAC.[16] The median survival (13.8 months for GC vs 14.8 months for MVAC), RR (49% for GC vs 46% for MVAC) and time to progression (7.4 months for both GC and MVAC) were similar. The toxicity profile favored GC, with a significant reduction in the incidence of grade 3/4 mucositis (1% vs 22%), neutropenic sepsis (1% vs 12%), neutropenic fever (2% vs 14%), and alopecia (11% vs 55%). Although the median survivals were similar, the study was underpowered to detect equivalence. However, given the significantly better toxicity profile for GC and the superimposed survival curves, GC has been recognized as an acceptable new standard for metastatic TCC.

A recently reported randomized trial did not demonstrate an improved OS with the addition of paclitaxel to GC.[17] The median survival (12.8 vs 15.7 months, P = .1) and progression-free survival (7.7 vs 8.8 months, P = .109) were not statistically different for GC and PCG (paclitaxel/cisplatin/gemcitabine). The RR was superior for PCG compared to GC (57% vs 46%, P = .02). PCG was more toxic, producing a greater incidence of neutropenic fevers (12.5% vs 3.8%), diarrhea (18.9% vs 8.9%), and alopecia (50.6% vs 15.6%). However, thrombocytopenic hemorrhage was less common with PCG (6.8% vs 11.4%). PCG has not replaced GC as a standard, owing to the lack of survival improvement. Thus, front-line chemotherapy for advanced urothelial cancer can be chosen la carte from MVAC, DD-MVAC, and GC.

A phase III trial planned by the Cancer and Leukemia Group B (CALGB) will examine the benefit of combining GC and bevacizumab (Avastin). Ongoing early phase I/II trials are evaluating novel chemotherapeutic (vinflunine, nab-paclitaxel [Abraxane], E7389) and biologic agents (sunitinib [Sutent], sorafenib [Nexavar], vandetanib, pazopanib, lapatinib [Tykerb], cetuximab [Erbitux], trastuzumab [Herceptin], VEGF Trap), alone or in combination therapy.

**Renal Dysfunction**

Renal dysfunction, usually defined as a calculated creatinine clearance (CrCl) of < 60 mL/min by the Cockcroft-Gault (CG) equation, appears to be quite common in patients with urothelial carcinoma and
renders patients ineligible for cisplatin therapy. Renal dysfunction may be attributable to advanced age, comorbidities, or ureteric obstruction. In a retrospective study, the probability of ineligibility for cisplatin increased with age, with > 40% of postoperative patients aged > 70 years found ineligible for cisplatin by the CG equation.[18] However, current formulas may underestimate CrCl, especially in those over 65.[19] Both carboplatin-based and nonplatinum regimens have been employed in patients with renal dysfunction or poor performance status. However, small randomized trials suggest that carboplatin regimens are inferior to cisplatin regimens.[20-22] Therefore, patients ineligible for treatment with cisplatin require a special focus.

**Adjuvant Chemotherapy for Bladder Cancer**

Studies employing adjuvant chemotherapy were conducted in muscle-invasive and locally advanced bladder cancer before neoadjuvant or preoperative chemotherapy was studied (Table 3). All of the patients in these studies were pathologically staged since they had undergone radical cystectomy and pelvic lymph node dissection. Problems in the interpretation of these trials include the lack of statistical power due to their small size, as well as early termination.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Standard Arm</th>
<th>Experimental Arm</th>
<th>PFS Benefit</th>
<th>Survival Benefit</th>
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<tbody>
<tr>
<td>USC[23]</td>
<td>91</td>
<td>Observation</td>
<td>CISCA, others</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>German[24]</td>
<td>49</td>
<td>Observation</td>
<td>MVAC, MVEC</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Stanford[25]</td>
<td>55</td>
<td>Observation</td>
<td>CM</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Swiss[26]</td>
<td>77</td>
<td>Observation</td>
<td>Cisplatin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>German[27]</td>
<td>327</td>
<td>MVAC, MVEC</td>
<td>CM</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ABC Meta-analysis[28]</td>
<td>491</td>
<td>Observation</td>
<td>Cisplatin-based chemotherapy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The single largest published randomized clinical trial enrolled 91 patients at USC.[23] Patients with deeply muscle-invasive and/or node-positive disease were randomized to observation or chemotherapy including a CISCA-like regimen, single-agent cisplatin, and regimens selected by clonal assays. The median survival was significantly improved in the chemotherapy arm (4.3 vs 2.4 years, P = .0062), but the 3-year survival rate was not statistically superior (66% vs 50%, P = .09). Of the 44 patients randomized to chemotherapy, 11 refused treatment. Accrual of patients was extremely slow, with the study taking 8 years to accrue 91 patients. The trial also employed Wilcoxon statistics for analysis, which emphasize early, but often nonsustained, differences. A German randomized trial of 49 patients included those with extravesical and/or node-positive disease.[24] Patients received observation or adjuvant MVAC or MVEC (methotrexate, vinblastine, epirubicin [Ellence], cisplatin). A significant improvement in relapse-free survival (P = .0012) was observed without a difference in overall survival. The cystectomy-alone arm fared worse than expected, with 18 of 23 patients exhibiting progression. Most patients who progressed in the cystectomy group did not receive chemotherapy on progression. Of the 26 patients in the chemotherapy group, 8 did not receive it. Other small prospective randomized trials from Stanford and Switzerland evaluated CMV (cisplatin, methotrexate, vinblastine) or high-dose cisplatin, respectively, and did not demonstrate improved survival.[25,26] The German multicenter trial AUO-AB 5/95 randomized 327 patients with extravesical and/or lymph node–positive disease to adjuvant CM (cisplatin/methotrexate) or MVEC, with the goal of proving noninferiority of CM.[27] The hazard ratio (HR) for PFS (1.13) supported the noninferiority of CM. The 5-year progression-free, disease-specific, and overall survival rates were
similar. Grade 3/4 leukopenia occurred in 7% of patients treated with CM and 22.2% of patients treated with MVEC (P < .0001). However, in the absence of definitive data supporting adjuvant chemotherapy, an arm receiving no adjuvant therapy compared to MVEC may have been the optimal design.

The Advanced Bladder Cancer Meta-analysis Collaboration analyzed 491 patients from six trials, representing 90% of all patients randomized in cisplatin-based combination chemotherapy trials and 66% of patients from all eligible trials.[28] The overall HR for survival of 0.75 suggests a 25% relative reduction in the risk of death for chemotherapy compared to the control group. However, this meta-analysis is clearly flawed due to the inclusion of poorly conducted trials.

Ongoing Large Cooperative Group Trials of Adjuvant Chemotherapy

The major advantage of adjuvant therapy is that it treats a population of patients whose risk of relapse is clearly defined by their pathologic stage at cystectomy. Ideally, a large, adequately powered, and well-designed study is necessary to definitively prove the efficacy of adjuvant chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) is currently conducting a prospective randomized study comparing adjuvant chemotherapy with delayed chemotherapy at clinical relapse. Eligibility includes extravesical disease with or without lymph node involvement. The chemotherapy regimens allowed are MVAC, DD-MVAC, or GC. Unfortunately, many physicians appear to have already concluded that adjuvant chemotherapy does have a real impact on survival, and consider further randomized comparisons of adjuvant chemotherapy with observation to be inappropriate. Selection of candidates for adjuvant chemotherapy based on molecular factors is being explored.

Overexpression of p53 appears to correlate with an increased risk of progression as well as chemosensitivity.[29] The Southwest Oncology Group (SWOG) has just closed a prospective randomized trial to assess adjuvant MVAC in patients with p53-overexpressing T1 and T2 (invasion of the lamina propria or muscle layer) bladder cancer.

The Cancer and Leukemia Group B (CALGB) and Eastern Cooperative Oncology Group (ECOG) have accepted adjuvant GC as standard, and an Intergroup study was planned to enroll 800 patients with extravesical or node-positive TCC at cystectomy to GC or dose-dense AG (doxorubicin/gemcitabine) followed by PC (paclitaxel/cisplatin). Unfortunately, this trial closed prematurely due to poor accrual.

Neoadjuvant Chemotherapy for Bladder Cancer

In comparison with trials of adjuvant chemotherapy, large randomized trials of neoadjuvant chemotherapy have been completed (Table 4). The patients in these trials were clinically staged before they received chemotherapy and were eligible if they had muscle-invasive and locally advanced but operable disease.
MSKCC Retrospective Experience
A total of 111 patients with clinical T2–4, N0, M0 (muscle-invasive and extravesical) operable bladder cancer treated with neoadjuvant MVAC at Memorial Sloan-Kettering Cancer Center (MSKCC) were assessed.[30] Postchemotherapy surgery was performed in 81 patients. Prechemotherapy T stage and postchemotherapy pathologic stage were the only factors with independent prognostic value. An association between pathologic downstaging and survival was found in patients with initial extravesical disease (5-year survival was 54% with downstaging vs 12% without downstaging), but not for those with bladder-confined disease. In a separate report, p53 overexpression was a negative prognostic factor for survival (P = .001).[31]

Nordic Cystectomy Trials
The Nordic Cooperative Bladder Cancer Study Group conducted a randomized phase III study (Nordic Cystectomy trial I) to assess the benefit of neoadjuvant chemotherapy in patients with bladder cancer scheduled to undergo local therapy with radical cystectomy after brief radiation therapy (4 Gy daily for 5 consecutive days).[32] A total of 325 patients with T1 grade 3 and T2–4a, Nx, M0 bladder cancer were randomized to local therapy with or without two cycles of neoadjuvant cisplatin plus doxorubicin. The 5-year overall survival was similar in both groups (59% vs 51%, P = .1). In the subset of patients with extravesical disease, the 5-year survival was significantly better for neoadjuvant chemotherapy (52% vs 37%, P = .03), although this finding is only hypothesis generating.

As a follow-up to the Nordic Cystectomy trial I, the Nordic Cystectomy trial II evaluated neoadjuvant chemotherapy alone without preoperative radiation.[33] A total of 317 patients with clinical stages T2–4a, Nx, M0 underwent radical cystectomy with or without three cycles of neoadjuvant cisplatin. However, chemotherapy was administered according to protocol in only 74% of patients. The 5-year survival rates were similar (53% with chemotherapy and 46% in the control group, P = .2375). A pathologic complete response (pCR) was observed in 26.4% of patients in the chemotherapy group compared to 11.5% in the control group (P = .001). Therefore, despite substantial pathologic downstaging, no improvement in survival was demonstrated with neoadjuvant chemotherapy.

MDACC Perioperative Chemotherapy Trial
A total of 140 patients at M.D. Anderson Cancer Center (MDACC) were randomized to receive two cycles of MVAC before and three cycles after radical cystectomy, or five cycles of MVAC after initial radical cystectomy.[34] Eligible patients had TCC with extravesical disease or muscle-invasive disease with vascular invasion.

<table>
<thead>
<tr>
<th>Table 4</th>
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</thead>
<tbody>
<tr>
<td>Randomized Trials of Neoadjuvant Chemotherapy</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Standard Regimen</th>
<th>Chemotherapy Regimen</th>
<th>Survival Benefit</th>
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<tbody>
<tr>
<td>Nordic Cystectomy I[32]</td>
<td>325</td>
<td>Observation</td>
<td>Cisplatin + doxorubicin</td>
<td>No</td>
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<td>Nordic Cystectomy II[33]</td>
<td>317</td>
<td>Observation</td>
<td>Cisplatin + methotrexate</td>
<td>No</td>
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<tr>
<td>MDACC[34]</td>
<td></td>
<td>Adjuvant MVAC × 5</td>
<td>MVAC × 2 → Cystectomy → MVAC × 3</td>
<td>No</td>
</tr>
<tr>
<td>International collaboration[35,36]</td>
<td>976</td>
<td>Observation</td>
<td>CMV</td>
<td>Yes</td>
</tr>
<tr>
<td>US Intergroup[37]</td>
<td>317</td>
<td>Observation</td>
<td>MVAC</td>
<td>Yes</td>
</tr>
<tr>
<td>ABC Meta-analysis[39]</td>
<td>2688</td>
<td>Observation</td>
<td>Cisplatin alone, cisplatin combination regimens</td>
<td>Yes for cisplatin combination regimens</td>
</tr>
</tbody>
</table>

ABC Meta-analysis = Advanced Bladder Cancer Meta-analysis; CMV = cisplatin/methotrexate/vinblastine; MDACC = M.D. Anderson Cancer Center; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin.
Survival was approximately 60% at 31.7 months for both groups. Neoadjuvant chemotherapy achieved pCR in 37% of patients compared to 4% for radical cystectomy before chemotherapy (P = .00006). Neoadjuvant MVAC was feasible, lowered the positive surgical margin rate (2% vs 11%) and was not accompanied by increased postoperative morbidities. However, this trial was designed to detect a 20% difference in outcomes, and was not powered to confirm equivalence of the two approaches.

International Collaboration of Trialists Study

This is the single largest trial of neoadjuvant chemotherapy for bladder cancer, with an accrual of 976 patients.[35] Eligible patients included those with T2 grade 3, T3, or T4a disease who were candidates for local therapy with radical cystectomy or external-beam irradiation. Patients were randomized to local therapy with or without three cycles of neoadjuvant CMV. The study was designed to detect an absolute improvement in survival of 10% (from 50% to 60%). During the initial report, the difference between the 3-year survival rates with neoadjuvant chemotherapy and local therapy alone approached, but did not reach statistical significance (55.5% vs 50%, P = .075). The median survival for chemotherapy was 44 months vs 37.5 months for the local therapy–alone group. After a longer median follow-up of 7 years, the difference achieved statistical significance (P < .05).[36] The 3-year disease-free survival was significantly longer with neoadjuvant chemotherapy (46% vs 39%, P = .019). Following neoadjuvant chemotherapy, pCR was found in 32.5%. Chemotherapy-related mortality was 1%, and postoperative complications did not increase.

The chemotherapeutic regimen used in this study is not considered standard, and CMV has never been compared with MVAC. Although the improvement in survival was less than originally sought, the trial is nevertheless considered positive, with results favoring neoadjuvant CMV.

Intergroup Trial

A total of 317 patients with operable T2, N0, M0 to T4a, N0, M0 disease were enrolled in an Intergroup trial reported in 2003.[37] The patients were stratified for age and stage and randomized to radical cystectomy alone or three cycles of MVAC before radical cystectomy. At 5 years, 57% of patients in the neoadjuvant chemotherapy group were alive compared to 43% of those in the cystectomy-alone group (two-sided P = .06). The median survival was 77 months for the neoadjuvant chemotherapy group and 46 months for the cystectomy-alone group. Improved survival was associated with pCR, defined as absence of residual muscle-invasive tumor. The 5-year survival for all patients with a pCR was an impressive 85%. The neoadjuvant chemotherapy group displayed a significantly higher pCR rate (38% vs 15%, P < .001).

The planned radical cystectomy was performed in 82% of patients in the neoadjuvant chemotherapy group compared to 81% of patients in the radical cystectomy–alone group. Reasons for not performing cystectomy (n = 39) were aborted surgery at time of exploration due to unresectability or positive nodes, patient refusal, and progression of malignancy. Approximately 87% of patients in the chemotherapy group received at least one cycle of MVAC. Chemotherapy-induced grade 4 neutropenia occurred in 33%, and grade 3 gastrointestinal toxicities occurred in 17%. However, no life-threatening toxicities or deaths occurred from chemotherapy, and no increase in postoperative complications was observed.

Although the two-sided P value of .06 did not indicate a statistically significant difference between the study groups, the original goal for significance—a one-sided P < .05—was achieved. Survival was associated with neoadjuvant chemotherapy (HR = 1.39, P = .06), completion of radical cystectomy (HR = 2.88, P < .001), and ≥ 10 pelvic lymph nodes removed (HR = 2.38, P < .001).[38] Five-year survival and freedom from local relapse were 81% and 91% in patients who had neoadjuvant chemotherapy/radical cystectomy/≥ 10 lymph nodes removed (n = 66), 66% and 90% in patients with radical cystectomy/≥ 10 lymph nodes removed (n = 60), 55% and 73% in chemotherapy/radical cystectomy/≤ 10 lymph nodes removed (n = 49), and 39% and 66% in radical cystectomy/≤ 10 lymph nodes removed (n = 44). The 5-year survival rate in patients with positive surgical margins (n = 25) and those who did not undergo radical cystectomy (n = 39) was dismal at 0% and 11%, respectively. Therefore, both the quality of surgery and neoadjuvant chemotherapy appear to impact favorably and independently on outcomes.

Advanced Bladder Cancer Meta-analysis Collaboration

A meta-analysis was initiated by the Medical Research Council (UK) Clinical Trials Unit and reported by the Advanced Bladder Cancer Meta-analysis Collaboration.[39] A total of 2,688 patients were analyzed from 10 trials, and information for individual patients was updated. Groups were defined according to the type of chemotherapy regimen (cisplatin alone or platinum-based combination) and local therapy (cystectomy, radiation therapy, or preoperative radiation followed by cystectomy).
Platinum-based combination chemotherapy significantly improved 5-year OS compared to local therapy alone (50% vs 45%, P = .016, HR = 0.87). Combination chemotherapy also displayed an improvement in disease-free survival (P = .0001), locoregional disease-free survival (P = .012), and metastasis-free survival (P = .001). Single agent cisplatin chemotherapy did not demonstrate an improvement in survival (P = .26) or any of the other endpoints. Additionally, combination chemotherapy yielded significantly improved survival (P = .044) and disease-free survival (P = .046) compared to cisplatin alone.

Therefore, the meta-analysis supports platinum-based combination neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer. Since all platinum-based combination trials were analyzed as a group, it is not possible to discern from this meta-analysis the best combination for use in neoadjuvant therapy.

**Neoadjuvant vs Adjuvant Chemotherapy for Bladder Cancer**

Based on the above studies, neoadjuvant cisplatin-based combination chemotherapy is accepted as a standard of care, whereas data are not definitive for adjuvant chemotherapy. Recent retrospective data from MSKCC also reveal that the GC regimen yields a pCR rate of 35%, which appears similar to MVAC/CMV.[40] Trials have not addressed neoadjuvant strategies for patients who are ineligible for cisplatin therapy. Neoadjuvant chemotherapy permits the in vivo assessment of tumor response and pathologic downstaging. It can provide a powerful prognostic assessment since pCR correlates with prolonged survival.

The neoadjuvant paradigm may also accelerate the pace of development of novel systemic agents. Since pathologic response can be rapidly determined after cystectomy, the efficacy of a regimen is evident before long-term follow-up. Owing to the availability of tissue before and after chemotherapy, it may be possible to determine molecular and biologic characteristics that predict for chemosensitivity. Several novel agents and regimens are being evaluated in the neoadjuvant setting (Table 5). Other potential but unproven advantages of neoadjuvant treatment include earlier therapy for micrometastases before development of drug resistance and superior efficacy compared to adjuvant chemotherapy owing to an intact tumor vascular bed.
On the other hand, since pathologic stage is not determined before cystectomy, some early-stage low-risk patients may receive neoadjuvant chemotherapy unnecessarily. For example, patients with small muscle-invasive T2 tumors who bear no residual disease in the cystectomy specimen (owing to complete resection during the preceding cystoscopic biopsy) and have no accompanying hydronephrosis or carcinoma in situ have an excellent long-term disease-free survival (~85%) with radical cystectomy alone and may not warrant perioperative chemotherapy.

The adjuvant chemotherapy model provides precise pathologic data before systemic therapy that can be utilized to determine prognosis. Prompt surgical resection may allay patient anxiety, whereas in the neoadjuvant model, the patient bears the tumor for several weeks or months until surgery. The primary disadvantage of the adjuvant chemotherapy paradigm may be the lack of feasibility of adjuvant chemotherapy in an undefined proportion of patients after radical cystectomy.

**Neoadjuvant Concurrent Chemotherapy and Radiation**

The National Cancer Institute of Canada (NCIC) has conducted the only randomized prospective trial of neoadjuvant concurrent chemoradiation.[41] The goal of the study was to determine the value of concurrent cisplatin (three cycles of cisplatin at 100 mg/m² given every 2 weeks) to preoperative or definitive radiation in patients with muscle-invasive bladder cancer. A total of 99 patients with clinical T2-4b TCC of the bladder were enrolled.

The investigators found no difference in the rate of distant metastasis and survival. However, first recurrence in the pelvis occurred in 25 of 48 control patients compared to 15 of 51 cisplatin-treated patients (P = .038). Therefore, the investigators concluded that concurrent neoadjuvant
chemoradiation might improve pelvic control without appreciable control of distant metastasis. Unfortunately, the small size of this trial prevents a definitive conclusion regarding the utility of concurrent chemoradiation before definitive local therapy.

Neoadjuvant Chemotherapy for Bladder Preservation

Neoadjuvant chemotherapy with or without radiation therapy has been administered for muscle-invasive bladder cancer as a bladder-preserving strategy. The common theme in all of these studies has been to select patients with a pCR to chemotherapy or chemoradiation for bladder preservation. Although this strategy appears promising, bladder preservation protocols have not been compared with radical cystectomy in randomized studies. Therefore, this strategy can be currently applied only in patients who are either poor candidates for or refuse radical cystectomy. The MSKCC has reported their experience with neoadjuvant MVAC followed by bladder-sparing surgery for patients with muscle-invasive T2–3, N0, M0 bladder cancer.[42] A total of 111 patients underwent neoadjuvant MVAC followed by transurethral resection (TUR) of the primary tumor site. Of these 111 patients, 60 (54%) demonstrated a pCR. Of these 60 patients, 28 underwent follow-up with TUR alone, 15 underwent partial cystectomy, and 17 elected radical cystectomy. After a median follow-up of 10 years, among the 43 patients who had bladder-sparing surgery, 32 (74%) were alive, including 25 (58%) with an intact functioning bladder. Of these 43 patients, 24 (56%) developed recurrences, which were invasive in 13 (30%) and superficial in 11 (26%). Thus, the majority of patients who achieved pCR after TUR and neoadjuvant chemotherapy demonstrated long-term survival with preservation of the bladder.

An Italian study of 104 patients with clinical T2–4, N0, M0 TCC of the bladder were treated with three cycles of neoadjuvant MVAC followed by TUR.[43,44] A total of 49 patients (49%) attained pCR at the time of TUR. Following chemotherapy, 52 patients underwent TUR alone, 13 underwent partial cystectomy, and 39 underwent radical cystectomy. Of the 52 patients who underwent TUR alone, 31 (60%) are alive at a median follow-up of 56+ months and 23 (44%) have maintained an intact bladder. Of the 13 patients who underwent partial cystectomy, 4 (31%) were alive with functioning bladders at a median follow-up of 88+ months. In the radical cystectomy group, 38% of patients were alive after a median follow-up of 45 months. Patients who attained pCR demonstrated a 5-year survival rate of 69%, while those without pCR had a survival of only 26%.

Neoadjuvant Chemoradiation for Bladder Preservation

Based on the Harvard experience of 190 patients with muscle-invasive stage T2–4a bladder cancer, investigators reported outcomes with chemoradiation for bladder conservation.[45] In 144 of these patients, radiotherapy (4,000 cGy) was administered with two cycles of concurrent cisplatin. Those who attained a complete clinical response were selected for additional radiation (2,480 cGy) and one additional cycle of cisplatin, while those with persistent disease underwent radical cystectomy. In 98 of these 144 patients, two courses of neoadjuvant CMV preceded the chemoradiation. Subsequent protocols included the administration of both cisplatin and fluorouracil (5-FU) concurrent with accelerated twice-daily irradiation in 29 patients. In another 17 patients, concurrent cisplatin with twice-daily irradiation was followed by three cycles of adjuvant CMV chemotherapy.

The 10-year actuarial overall survival rate was 36%, and the 10-year disease-specific survival for patients with an intact bladder was 45%. One-third of patients treated with the goal of bladder-sparing ultimately required a cystectomy, and no patient required cystectomy because of bladder morbidity. The absence of initial hydronephrosis predicted for a significantly better outcome. Therefore, the authors recommended against a bladder-preserving chemoradiation approach in patients with hydronephrosis. Normally functioning bladders were found in 24 of 32 disease-free patients evaluated with a urodynamic study.[46]

A total of 415 patients at the University of Erlangen were treated with radiotherapy (126 patients) or chemoradiation (289 patients), and patients attaining pCR were selected for bladder conservation.[47] Chemotherapy regimens during the first and fifth week of radiation included cisplatin alone, carboplatin alone, or cisplatin plus 5-FU. A pCR was observed in 72% of patients. The 10-year overall and disease-specific survival rates were 31% and 42%, and more than 80% of survivors had preserved bladders. Of the patients who achieved pCR, local control without muscle-invasive relapse was maintained in 64%. Chemoradiation appeared to produce better pCR rates compared to radiation alone (CR = 61% for radiation, 66% for radiation plus carboplatin, 82% for radiation plus cisplatin, and 87% for radiation plus 5-FU/cisplatin).

The Radiation Therapy Oncology Group (RTOG) reported a randomized study of 123 patients evaluating two cycles of neoadjuvant CMV before concurrent cisplatin plus radiation.[48] Those who achieved a clinical complete response received an additional 25.2 Gy of radiation plus one additional concurrent cycle of cisplatin. Neoadjuvant CMV did not produce an improvement in 5-year survival.
(48% vs 49%) or survival with preserved bladders (36% vs 40%). However, only 67% of patients assigned to neoadjuvant CMV completed the protocol compared to 81% in the chemoradiation-alone group.

An inordinately unfavorable toxicity profile was observed with neoadjuvant CMV chemotherapy; 10 patients developed neutropenic sepsis, 3 of whom died. Moreover, the study did not complete the planned accrual of 174 patients to detect a 20% difference in bladder-intact survival, and lacked statistical power. On subgroup analysis, patients without hydronephrosis displayed a statistically superior complete response rate (64% vs 38%, P = .02) and a trend toward improved overall (54% vs 33%, P = .06) and bladder-intact survival (43% vs 26%, P = .06).

An ongoing phase II RTOG trial is evaluating concurrent radiation plus paclitaxel with or without trastuzumab.

**Conclusions**

Neoadjuvant cisplatin-based combination chemotherapy preceding radical cystectomy should be considered a standard of care for muscle-invasive and operable bladder cancer. In contrast, definitive data supporting adjuvant chemotherapy are lacking, but an ongoing European randomized trial is attempting to definitively answer this question. Neoadjuvant and adjuvant chemotherapy may have a similar efficacy, although there are no randomized studies comparing these approaches. pCR after neoadjuvant chemotherapy is a powerful prognostic factor for outcomes, and the neoadjuvant chemotherapy paradigm may provide the means by which systemic therapy can be rapidly developed. Neoadjuvant therapy for patients who are not candidates for cisplatin has not been studied and needs a special focus. Chemotherapy with or without radiation also offers a viable bladder-conserving strategy in selected patients. Further advances require close multidisciplinary collaboration between oncologists, urologists, and radiation therapists.

**Disclosures:**

Dr. Sonpavde is a member of the speakers bureau for Sanofi-Aventis, Pfizer, and Novartis, and has received research support from Pfizer, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, and CytoGen. Dr. Lerner has received research support from Pfizer, Eli Lilly, Bristol-Myers Squibb, CytoGen, Photocure, and Cell Genesys.

**References:**


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