The Effectiveness of Off-Protocol Adjuvant Chemotherapy for Patients with Urothelial Carcinoma of the Urinary Bladder


Abstract

Purpose: The role of adjuvant chemotherapy for patients with high-risk urothelial carcinoma of the bladder (UCB) is not well defined. Here we address the value of adjuvant chemotherapy in patients undergoing radical cystectomy for UCB in an off-protocol routine clinical setting.

Experimental Design: We collected and analyzed data from 11 centers contributing retrospective cohorts of patients with UCB treated with radical cystectomy without neoadjuvant chemotherapy. Patients were grouped into quintiles based on their risk of disease progression using estimates from a fitted multivariable Cox proportional hazards model. The association of adjuvant chemotherapy with survival was explored across separate quintiles.

Results: The cohort consisted of 3,947 patients, 932 (23.6%) of whom received adjuvant chemotherapy. Adjuvant chemotherapy was independently associated with improved survival (hazard ratio, 0.83; 95% confidence interval, 0.72-0.97, P = 0.017). However, the effect of adjuvant chemotherapy was significantly modified by the individual's risk of disease progression such that an increasing benefit from adjuvant chemotherapy was seen across higher-risk subgroups (P < 0.001). There was a significant improvement in survival between the treated and nontreated patients in the highest-risk quintile (hazard ratio, 0.75; 95% confidence interval, 0.62-0.90; P = 0.002). This group was characterized by an estimated 32.8% 5-year probability of cancer-specific survival, with 86.6% of patients having both advanced pathologic stage (≥T3) and nodal involvement.

Conclusion: Adjuvant chemotherapy is associated with a significant improvement in survival for patients treated in an off-protocol clinical setting. Selective administration in patients at the highest risk for disease progression, such as those with advanced pathologic stage and nodal involvement, may optimize the therapeutic benefit of adjuvant chemotherapy.

Urothelial carcinoma of the bladder (UCB) is the 4th most common cancer in men in the United States (1). Radical cystectomy and pelvic lymphadenectomy is the gold standard treatment for those patients with muscle-invasive or high-risk nonmuscle invasive disease (2). This operation provides local cancer control and improves long-term survival (3, 4). Unfortunately, however, disease recurrence is observed in 30% to 56% of patients undergoing surgery, most often the result of occult metastatic disease (4, 5). The prognosis for patients with disease recurrence following cystectomy is poor. As a result, systemic perioperative chemotherapy has been explored as an adjuvant to surgery in both neoadjuvant (preoperative) and adjuvant (postoperative) settings.

Cisplatin-based combination neoadjuvant chemotherapy renders a 5% to 7% absolute survival benefit for patients...
undergoing radical cystectomy has not been widely adopted. Several reasons have been cited for this situation, including concerns over unnecessarily treating patients who may not benefit from neoadjuvant chemotherapy and over disease progression that may arise from delays in surgery caused by chemotherapy, especially in cases involving inefficacy, as well as the belief that adjuvant chemotherapy may be as effective as neoadjuvant chemotherapy if the former is administered selectively based on adverse pathologic characteristics (8).

A number of randomized controlled trials have evaluated the benefit of adjuvant chemotherapy. Some studies have shown a treatment benefit, whereas others have not (9–15). A recent meta-analysis of individual patient data from available trials reported a 25% relative reduction in the risk of death for those receiving adjuvant chemotherapy compared with those undergoing surgery without adjuvant chemotherapy (16). In addition, a benefit of adjuvant chemotherapy was also supported in the findings of a pooled analysis of phase III trials (8). Nevertheless, the conclusions drawn from these studies are limited due to individual trial method flaws and insufficient patients and events. As a result, the routine use of adjuvant chemotherapy for patients undergoing radical cystectomy has not gained widespread acceptance. Moreover, these trials were carried out in highly selected patients and under favorable protocol conditions. The results of these trials are difficult to apply to patients in everyday practice who may be older, have increased comorbidities, and may receive suboptimal chemotherapy regimens or doses (17, 18).

Table 1. Baseline characteristics of the cohort (n = 3,947)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>833 (21.1)</td>
</tr>
<tr>
<td>Male</td>
<td>3,114 (78.9)</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
</tr>
<tr>
<td>pT0</td>
<td>225 (5.8)</td>
</tr>
<tr>
<td>pTa</td>
<td>118 (3.0)</td>
</tr>
<tr>
<td>pTis</td>
<td>410 (10.5)</td>
</tr>
<tr>
<td>pT1</td>
<td>507 (13.0)</td>
</tr>
<tr>
<td>pT2</td>
<td>918 (23.6)</td>
</tr>
<tr>
<td>pT3</td>
<td>1,211 (31.1)</td>
</tr>
<tr>
<td>pT4</td>
<td>502 (12.9)</td>
</tr>
<tr>
<td>Pathologic grade</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>225 (5.8)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>71 (1.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1,669 (42.9)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1,926 (49.5)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>1,305 (33.5)</td>
</tr>
<tr>
<td>Soft tissue surgical margin positivity</td>
<td>233 (6.0)</td>
</tr>
<tr>
<td>Concomitant carcinoma in-situ</td>
<td>1,974 (50.7)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>996 (25.6)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>926 (23.8)</td>
</tr>
</tbody>
</table>

Materials and Methods

Patient selection and data collection

We retrospectively analyzed the clinical and demographic information of patients with a diagnosis of transitional cell carcinoma of the bladder treated with radical cystectomy and lymphadenectomy at 11 institutions (see note) from 1979 to 2008. Patient information was collected in a database approved by the Institutional Review Board at each individual institution. The data from each individual site were then combined into a single database for analysis. All variables were systematically evaluated for inconsistencies and data integrity. All inconsistencies were resolved by the members at each individual site prior to the final data analysis.
The study cohort was composed of 4,201 patients with sufficient data for review. Patients from one center were excluded because none of the patients at that center received adjuvant therapy. This left 3,947 patients from 11 centers for analysis. None of the patients received neoadjuvant chemotherapy. Adjuvant chemotherapy was defined as chemotherapy given within 90 days following radical cystectomy in patients without evidence of disease recurrence. Indication, selection, and regimen type were at the investigator's discretion and were based on patient tumor stage and overall health status. The adjuvant chemotherapy regimen and number of cycles for each patient were not specified.

Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures, and all slides were reviewed by genitourinary pathologists according to 1973 WHO grading and 2002 American Joint Committee on Cancer tumor-node-metastasis (TNM) staging. Concomitant urothelial carcinoma in situ (CIS) was defined as the presence of CIS in conjunction with another pathologic T-stage other than CIS alone. Soft tissue surgical margin status was determined by the presence of disease at nonurothelial margins. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular

| Table 2. Univariate and multivariate Cox proportional hazards model for the association between clinical and pathologic characteristics and cancer-specific mortality |
|---------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                | Univariate                                      | Multivariate                                    |
|                                | HR (95% CI)                                     | P                                               | HR (95% CI)                                     | P                                               |
| Age                            | 1.02 (1.01-1.03)                                | <0.001                                          | 1.02 (1.01-1.02)                                | <0.001                                          |
| Male gender                    | 0.79 (0.69-0.90)                                | 0.001                                           | 0.81 (0.70-0.93)                                | 0.003                                           |
| Pathologic stage               | 1.73 (1.64-1.82)                                | <0.001                                          | 1.42 (1.34-1.52)                                | <0.001                                          |
| Grade                          |                                                 |                                                 |                                                 |                                                 |
| 0-1                            | Ref                                             | —                                               | —                                               | —                                               |
| 2                              | 4.73 (3.14-7.12)                                | <0.001                                          | 0.98 (0.63-1.54)                                | 0.94                                            |
| 3                              | 4.49 (2.98-6.76)                                | <0.001                                          | 0.90 (0.57-1.41)                                | 0.65                                            |
| Positive surgical margin       | 4.16 (3.50-4.94)                                | <0.001                                          | 1.78 (1.48-2.15)                                | <0.001                                          |
| Lymphovascular invasion        | 3.04 (2.70-3.42)                                | <0.001                                          | 1.47 (1.28-1.68)                                | <0.001                                          |
| Concomitant CIS                | 0.92 (0.82-1.03)                                | 0.149                                           | 0.99 (0.87-1.12)                                | 0.85                                            |
| Pathologic nodal involvement   | 4.00 (3.56-4.51)                                | <0.001                                          | 2.50 (2.14-2.90)                                | <0.001                                          |
| Adjuvant radiotherapy          | 3.51 (2.41-5.11)                                | <0.001                                          | 1.81 (1.22-2.67)                                | 0.003                                           |
| Adjuvant chemotherapy          | 2.15 (1.91-2.43)                                | <0.001                                          | 0.83 (0.72-0.97)                                | 0.017                                           |
| HR* (SE)                       | 0.05 (0.29)                                     | <0.001                                          |                                                 |                                                 |

*HR corresponds to the value of θ for the shared frailty survival model.

Table 3. Association of adjuvant chemotherapy and cancer-specific mortality using a Cox proportional hazards model stratified by quintiles of estimated probability of death from bladder cancer

<table>
<thead>
<tr>
<th>5-year estimated probability of DSS (95%CI)*</th>
<th>No. of patients receiving adjuvant chemotherapy (%)</th>
<th>HR† (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>94.2 (92.0-95.9)</td>
<td>33 of 775 (4.4%)</td>
<td>6.21 (2.89-13.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>81.3 (78.0-84.2)</td>
<td>79 of 774 (11.4%)</td>
<td>2.20 (1.43-3.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>71.1 (67.3-74.5)</td>
<td>156 of 776 (25.2%)</td>
<td>1.10 (0.79-1.53)</td>
<td>0.592</td>
</tr>
<tr>
<td>58.6 (54.6-62.4)</td>
<td>262 of 773 (51.3%)</td>
<td>1.06 (0.84-1.35)</td>
<td>0.619</td>
</tr>
<tr>
<td>32.8 (29.3-36.4)</td>
<td>396 of 774 (51.2%)</td>
<td>0.75 (0.62-0.90)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Abbreviation: DSS, disease-specific survival.

*Quintiles created using individuals’ estimated prediction of the fitted multivariate Cox proportional hazards model (see Table 2).
†Log-rank test for trend <0.001.
walls. Pelvic lymph node dissections were examined grossly and all lymphoid tissue was submitted for histologic examination.

Follow-up
Follow-up was done according to institutional protocols. Patients generally were seen postoperatively at least every three to four months for the first year, semiannually for the second year and annually thereafter. Follow-up visits consisted of a physical examination and serum chemistry evaluation, including liver function and alkaline phosphatase tests. Diagnostic imaging of the upper tracts (e.g., ultrasonography and/or i.v. pyelography, computerized tomography abdomen/pelvis with i.v. contrast) and chest radiography were done at least annually or when clinically indicated. Additional radiographic evaluation, such as bone scan and/or computerized tomography, was done at the discretion of the treating physician. Detection of cancer in the ureter and/or urethra was coded as a second (metachronous) primary and not as local or distant recurrence. When patients died, the cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of bladder cancer had progressive, widely disseminated, and often highly symptomatic metastases at the time of death.

Data analysis
The log-rank test statistic was used to compare estimated survival probabilities between groups. Univariable and multivariable Cox proportional hazards regression models addressed time to recurrence and time to cancer-specific mortality after radical cystectomy. Although lymph node density was significantly associated with cancer-specific mortality, it was excluded from the analysis to avoid model overfitting due to the strong direct correlation with pathologic nodal status. A shared-frailty survival model was used to account for heterogeneity and random effects based among the 11 centers. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test. To determine if the effect of adjuvant chemotherapy was modified by disease risk, estimates from the fitted multivariable Cox proportional hazards regression model were generated.

Then patients were grouped into five equal-numbered quintiles on the basis of their disease risk estimate. The association of adjuvant chemotherapy with cancer-specific mortality across the five quintiles was then assessed using a univariable Cox proportional hazards regression model. Formal test for trend was conducted using the log-rank test for equality of survivor functions. For all statistical analyses, \( P < 0.05 \) was considered significant and all \( P \) values were two-sided. Statistical tests were carried out with Stata/IC 10.0.

Results
The clinical and pathologic characteristics of the study cohort are shown in Table 1. The median follow-up time was 32 months [interquartile range (IQR), 13.3-72.1 months]. Median overall survival for the entire cohort was 6.6 years [95% confidence interval (95% CI), 6.0-7.1 years]. Median cancer-specific survival was not reached. The 5-year and 10-year cancer-specific survival estimates for the entire cohort were 66.7% (95% CI, 65.0-68.3%) and 60.3% (95% CI, 58.3-62.3%), respectively. The 5-year and 10-year recurrence-free survival estimates for the entire cohort were 59.2% (95% CI, 57.5-60.9%) and 55.3% (95% CI, 53.4-57.2%), respectively. A total of 932 (23.6%) patients received adjuvant chemotherapy.

The association between clinical-pathologic features and cancer-specific mortality is shown in Table 2. In the multivariable model, adjuvant chemotherapy was associated with an improved survival [hazard ratio (HR), 0.83; 95% CI, 0.72-0.97; \( P = 0.017 \)]. In addition, pathologic stage, gender, LVI, surgical margin status, adjuvant radiation therapy, and nodal status were significantly associated with survival (Table 2).

We carried out additional analyses to test the hypothesis that the effectiveness of adjuvant chemotherapy is dependent on disease risk. Table 3 shows the results of the association of adjuvant chemotherapy with cancer-specific mortality across the quintiles based on predicted probabilities of cancer-specific survival. Patients in the 1st and 2nd quintiles represented the lowest risk for death from disease, with 5-year probability of disease-specific survival of 94.2% and 81.3%, respectively. Within these two quintiles, adjuvant chemotherapy was associated with decreased

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**Table 4. Selected pathologic characteristics of patients within quintiles based on disease risk**

<table>
<thead>
<tr>
<th>Quintile*</th>
<th>5-y predicted DSS (95% CI)</th>
<th>pT1</th>
<th>pT2</th>
<th>pT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94.2 (92.0-95.9)</td>
<td>772 (99.6%)</td>
<td>3 (0.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2</td>
<td>81.3 (78.0-84.2)</td>
<td>406 (52.5%)</td>
<td>337 (43.5%)</td>
<td>31 (4.0%)</td>
</tr>
<tr>
<td>3</td>
<td>71.1 (67.3-74.5)</td>
<td>44 (5.7%)</td>
<td>371 (47.8%)</td>
<td>336 (43.3%)</td>
</tr>
<tr>
<td>4</td>
<td>58.6 (54.6-62.4)</td>
<td>19 (2.5%)</td>
<td>172 (22.3%)</td>
<td>424 (54.9%)</td>
</tr>
<tr>
<td>5</td>
<td>32.8 (29.3-36.4)</td>
<td>1 (0.13%)</td>
<td>34 (4.4%)</td>
<td>411 (53.1%)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Off-Protocol Adjuvant Chemotherapy for Bladder Cancer

Table 4. Selected pathologic characteristics of patients within quintiles based on disease risk (Cont’d)

<table>
<thead>
<tr>
<th>pT4</th>
<th>Lymph node metastasis</th>
<th>≥T3 or lymph node metastasis</th>
<th>≥T3 and lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (0%)</td>
<td>9 (0.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>0 (0%)</td>
<td>18 (1.8%)</td>
<td>49 (6.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>25 (3.2%)</td>
<td>30 (3.0%)</td>
<td>390 (50.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>158 (20.4%)</td>
<td>229 (23.1%)</td>
<td>714 (92.4%)</td>
<td>97 (12.5%)</td>
</tr>
<tr>
<td>328 (42.4%)</td>
<td>705 (71.1%)</td>
<td>774 (100%)</td>
<td>670 (86.6%)</td>
</tr>
</tbody>
</table>

*Quintiles created using individuals’ estimated prediction of the fitted multivariate Cox proportional hazards model (see Table 2).

Discussion

We evaluated the effect of off-protocol adjuvant chemotherapy on survival using a large international cohort of patients treated with radical cystectomy and lymphadenectomy for UCB. We found that the effect of adjuvant chemotherapy on survival was contingent on the severity of the disease. Administration of adjuvant chemotherapy resulted in a significant survival benefit in patients with high-risk characteristics, particularly those with advanced pathologic stage and node-positive disease, as these patients seem to derive the most benefit from adjuvant chemotherapy. Well-designed adjuvant trials from Italy and Spain failed to reach planned accrual and were consequently underpowered to detect a benefit from adjuvant chemotherapy (11, 20). Additional randomized clinical trials evaluating this approach have been widely criticized for inadequate sample size, poor reporting, and/or method flaws (7, 8, 21). A pooled analysis of randomized studies favored a benefit from adjuvant chemotherapy, but with only 5 trials and 350 patients covered in the analysis, the authors indicated the need for larger studies to determine the role of adjuvant chemotherapy (8). In addition, a well-designed meta-analysis of 491 individual patient data from 6 available randomized controlled trials was unable to draw any definitive conclusions due to the limited number of patients and events. Despite these limitations, the available evidence from randomized trials would indicate that some patients derive benefit from adjuvant chemotherapy.

The results of the previous randomized trials for adjuvant chemotherapy in bladder cancer may be difficult to generalize to patients in everyday practice. Because of the advanced age and high prevalence of tobacco exposure in this population, patients with invasive bladder cancer regularly have comorbid conditions that limit their ability to receive optimal chemotherapy. The results of this observational trial support the activity of adjuvant chemotherapy in an off-protocol population treated in routine clinical practice. Moreover, our findings may help explain the lack of benefit observed in some previous adjuvant chemotherapy trials and may aid in the design of future studies. Our findings indicate that the direction and magnitude of the therapeutic effect of adjuvant chemotherapy is heavily influenced by the number of patients with combined advanced pathologic stage and nodal involvement as these patients seem to derive the most benefit from adjuvant chemotherapy based on our analysis. Although the presence of nodal involvement is the single most important prognostic feature for patients undergoing radical cystectomy with lymphadenectomy, the outcome for patients with nodal involvement is variable and dependent on additional prognostic features. Indeed, patients with node-positive disease and advanced pathologic stage (≥T3) have a significantly higher likelihood of disease recurrence and death compared with patients with node-positive disease and pathologic stage ≤T2 disease (4).
A subset of patients with less advanced disease may derive therapeutic benefit from adjuvant chemotherapy. Although pelvic nodal involvement and advanced pathologic stage are highly correlated with disease recurrence, some patients without these features will still experience relapse following surgery. Our findings do not support routine administration of adjuvant chemotherapy to patients with pathologic T3, node-negative disease, but we recognize that a benefit from adjuvant chemotherapy for this subgroup of patients may require a larger number of patients and events. In our cohort, 26% of patients with pathologic T2 disease and without nodal involvement experienced disease recurrence and 20% died from UCB. Clearly there is a subset of patients with pathologic T2 and node-negative disease who have occult metastasis at the time of surgery and may derive benefit from adjuvant chemotherapy. To this end, enrollment in trials such as the p53 trial, which tested the utility of adjuvant chemotherapy in patients with organ-confined (pT1–T2) high-risk UCB based on p53 status, is strongly recommended as molecular stratification, pharmacogenetics, and/or improved imaging modalities will be necessary to tailor adjuvant therapy for these patients.

We recognize the limitation of our study as a result of residual confounding not adjusted for in our analyses. Residual confounding is anticipated as many patients undergoing radical cystectomy have significant age-related and/or smoking-related comorbidities that influence their ability to be selected for and/or tolerate adjuvant chemotherapy and are usually related to the outcome. Unfortunately, the comorbidity status of patients was not collected during data acquisition, and it is expected that the absence of this information would systematically bias the results in favor of adjuvant chemotherapy because healthier patients are more likely to receive adjuvant chemotherapy.

We acknowledge additional limitations of this study. First, although the cooperation of multiple centers in this project increased the generalizability of our findings and the robustness of our estimates, these advantages may be at least partially offset by lack of control over data quality and homogeneity. For example, potentially meaningful characteristics such as pathologic T3a versus T3b, the presence of hydronephrosis, or regimen and number of cycles of chemotherapy were not included. We did, however, consider differences among the 11 centers by using a shared-frailty survival model. This allowed for within- and between-center variability to diminish the influence of center-related differences on our estimates.

Second, our estimates for the effect of adjuvant chemotherapy in the low-risk subgroup were underpowered because of the lack of events in this population, and we acknowledge that no conclusions can be made with respect to the benefit or harm of adjuvant chemotherapy for this population. Indeed the imprecision of the estimates is reflected by the wide confidence intervals. Third, we acknowledge that the cohort in this study underwent radical cystectomy by multiple surgeons and had their specimens evaluated by multiple pathologists. However, all surgeons operated at selected academic centers with significant experience in UCB management, which might increase the generalizability of the results, compared with the single-center single-surgeon setting. In addition, all specimens were examined by dedicated genitourinary pathologists at each center.

In conclusion, adjuvant chemotherapy in this study was associated with a significant improvement in survival among a large international cohort of patients treated in an off-protocol clinical setting. However, the benefit of adjuvant chemotherapy was principally dependent on the individual's disease risk. Selective administration in patients at the highest risk of disease progression, such as those with advanced pathologic stage and nodal involvement, may optimize the therapeutic benefit of adjuvant chemotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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