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


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Statement of Translational Relevance

The role of adjuvant chemotherapy for patients undergoing radical cystectomy for bladder cancer remains unresolved. Using a large international collaborative dataset this study evaluated the benefit of adjuvant chemotherapy among a unique group of patients who did not receive chemotherapy prior to surgery. The study utilizes a shared-frailty survival model to address the systematic bias associated with center based differences. In addition, we examined the association of adjuvant chemotherapy over a spectrum of disease risk by generating estimates of disease progression based on our multivariable regression model. Our observations indicate that selective use of adjuvant chemotherapy will provide benefit for approximately 20% of patients. Based on our findings, these patients can be identified based on the pathologic stage of their disease and the extent of nodal involvement. These findings have important implications in the practice of administration of adjuvant chemotherapy and in the design of adjuvant chemotherapy trials.
**Purpose:** The role of adjuvant chemotherapy (AC) for patients with high-risk urothelial carcinoma of the bladder (UCB) is not well defined. Here we address the value of AC in patients undergoing radical cystectomy for UCB in an off-protocol routine clinic 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 AC with survival was explored across separate quintiles.

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

**Conclusion:** AC 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 AC.
Introduction

Urothelial carcinoma of the bladder (UCB) is the 4th most common cancer in men in the U.S(1). Radical cystectomy (RC) and pelvic lymphadenectomy is the gold standard treatment for those patients with muscle-invasive or high-risk non–muscle-invasive disease(2). This operation provides local cancer control and improves long-term survival(3, 4). Unfortunately, however, disease recurrence is observed in 30-56% 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 adjunct to surgery in both neoadjuvant (preoperative) and adjuvant (postoperative) settings.

Cisplatin-based combination neoAC (neoAC) renders a 5-7% absolute survival benefit for patients undergoing cystectomy for UCB(6, 7). However, administration of neoAC for all patients undergoing radical cystectomy has not been widely adopted for several reasons: "(1) concerns that a substantial number of patients who do not benefit from neoAC will be treated unnecessarily; (2) in cases of inefficacy, chemotherapy delays time to surgery resulting in disease progression; and (3) the perception that selective administration of AC (AC), based on adverse pathologic characteristics, may be as effective as neoAC"(8).

A number of randomized controlled trials have evaluated the benefit of AC. Some studies have demonstrated a treatment benefit, while 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 AC compared to those undergoing surgery without AC(16). In addition, a benefit of AC 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 AC 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). As a result, the efficacy of AC observed in the meta-analysis may not be as great as the value in the off-protocol setting.

The purpose of this observational study is to determine the activity of AC in the off-protocol setting across an international cohort of patients undergoing radical cystectomy with lymphadectomy for bladder cancer. We hypothesize that AC is associated with a survival beneficial for a patients when used in routine clinical practice.

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 was 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 neoAC. AC 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 based on patient tumor stage and overall health status. The AC regimen and number of cycles for each patient were not specified.

**Pathologic evaluation**

All surgical specimens were processed according to standard pathological procedures and all slides were reviewed by genitourinary pathologists according to 1973 WHO grading and 2002 AJCC 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 (STSM) status was determined by the presence of disease at non-urothelial margins. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls. Pelvic lymph node dissections were examined grossly and all lymphoid tissue was submitted for histological examination.

**Follow-up**

Follow-up was performed according to institutional protocols. Patients generally were seen post-operatively 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 tests and alkaline phosphatase. Diagnostic imaging of the upper tracts (e.g., ultrasonography and/or intravenous pyelography, CT abdomen/pelvis with IV contrast) and chest radiography were performed at least annually or when clinically indicated. Additional radiographic evaluation, such as bone scan and/or computerized tomography, was performed 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 in order 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 AC was modified by disease risk, estimates from the fitted multivariable Cox proportional hazards regression model were generated. Then patients were grouped into 5 equal numbered quintiles on the basis of their disease risk estimate. The association of AC with cancer-specific mortality across the 5 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, a p-value of <0.05 was considered significant and all p-values were two-sided. Statistical tests were performed with Stata/IC 10.0 (College Station, Texas).

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

The association between clinical-pathologic features and cancer-specific mortality is shown in Table 2. In the multivariable model, AC was associated with an improved survival (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 performed additional analyses to test the hypothesis that the effectiveness of AC is dependent on disease risk. Table 3 shows the results of the association of AC 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 (5-yr probability of DSS of 94.2% and 81.3%, respectively). Within these two quintiles, AC was associated with a decreased survival (HR 6.21 and HR 2.20, respectively, P<0.001). AC was not associated with survival for patients in the 3rd and 4th quintiles (P>0.5). Patients in the 5th quintile (32.8% 5-yr probability of DSS) experienced a significant benefit from AC (HR 0.75, 95%CI 0.62-0.90, P=0.002). The median survival was 25 weeks (22.3-29.3 weeks) for patients receiving AC and 19.2 weeks (14-23.1 weeks) for patients not receiving chemo, a difference of 5.8 weeks (P<0.001).

To illustrate key differences among the patients from the various quintiles, selected pathologic characteristics of patients within each quintile are shown in Table 4. Patients in the first two quintiles had predominately low pathologic
stage and node negative disease; less than 10% of patients in these quintiles had advanced pathologic stage (≥T3) or node positive disease. The 3rd quintile represents an intermediate-risk group with 53.8% having ≤T2 and most patients without node positive disease. Although more than 90% of patients in the 4th and 5th quintile had either advanced pathologic stage (≥T3) or node positive disease, only 12.5% of patients in the 4th quintile had advanced pathologic stage and node positive disease compared to 86.6% of patients in the 5th quintile.

Discussion

We evaluated the effect of off-protocol AC on survival using a large international cohort of patients treated with radical cystectomy and lymphadenectomy for UCB. We found that the effect of AC on survival was contingent on the severity of the disease. Administration of AC resulted in a significant survival benefit in the patients at highest risk of death from disease but no definitive association between AC and survival was observed for a majority of patients.

The role of AC for patients undergoing radical cystectomy with lymphadenectomy remains unresolved. The p53 trial failed to show a survival benefit for AC in patients with high risk organ-confined disease but the study’s power was limited by the lower than expected event rate and failure of some patients to receive the assigned therapy(19) Well designed adjuvant trials from Italy and Spain failed to reach planned accrual and were consequently underpowered to detect a benefit for AC(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 AC, but with only 5 trials and 350 patients, the authors concluded that "larger studies are needed to identify the role of AC…”(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 AC.

The results of the previous randomized trials for AC in bladder cancer may
be difficult to generalize to patients in everyday practice. Because of the
advanced age and high prevalence of tobacco exposure among this population,
patients with invasive bladder cancer regularly have comorbid conditions which
limit their ability to receive optimal chemotherapy. The results of this
observational trial support the activity of AC in an off-protocol population treated
in routine clinical practice. Moreover, our findings may help explain the lack of
benefit observed in some previous AC trials and may aid in the design of future
studies. Our findings indicate that the direction and magnitude of the therapeutic
effect of AC 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 AC 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 (\( \geq T3 \)) have a significantly higher likelihood of disease recurrence and death
compared to patients with node-positive disease and pathologic stage \( \leq T2 \)
disease(4).

A subset of patients with less advanced disease may derive therapeutic
benefit from AC. 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 AC to patients with pathologic T2, node
negative disease, but we recognize that a benefit from AC 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 a subset of patients with pathologic T2 and node negative disease have occult metastasis at the time of surgery and may derive benefit from AC. To this end, enrollment in trials such as the p53 trial, which tested the utility of AC in patients with organ-confined (pT1-T2) high-risk UCB based on p53 status, are strongly recommended as molecular stratification, pharmacogenetics, and/or improved imaging modalities will be necessary to tailor adjuvant therapy for these patients (22).

We recognize the limitation of our study as a result of residual confounding not adjusted for in our analyses (23, 24). Residual confounding is anticipated as many patients undergoing radical cystectomy have significant age-related and/or smoking-related comorbidities which influence their ability to be selected for and/or tolerate AC and are casually related to the outcome (25). Unfortunately, patients’ comorbidity status was not collected during data acquisition and it is expected that the absence of this information would systematically bias the results in favor of AC because healthier patients are more likely to receive AC.

We acknowledge additional limitations of this study. First, while 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, 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 AC in the low-risk subgroup were underpowered due to the lack of events in this population and we acknowledge
that no conclusions can be made with respect to the benefit or harm of AC 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 to the single-center single-surgeon setting. In addition, all specimens were examined by dedicated genitourinary pathologists at each center.

**Conclusion**

In this study, AC 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 AC was principally dependent on the individual's disease risk. 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 AC.
Note: List of contributing institutions

Baylor College of Medicine, Houston, Texas, USA
John Hopkins University, Baltimore, Maryland, USA
Laval University, Québec City, Québec, Canada
Ludwig-Maximilians-Universität München, Klinikum Grosshadern, Munich, Germany
McGill University Health Centre, Montréal, Quebec, Canada
University of Padua, Padua, Italy
University of Regensburg, Regensburg, Germany
University of Southern California, Los Angeles, California, USA
University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA,
University of Texas Southwestern Medical Center, Dallas, Texas, USA
University of Western Ontario, London, Ontario, Canada
REFERENCES

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>66 (23-94)</td>
</tr>
<tr>
<td>Median no. lymph nodes removed (IQR)</td>
<td>18 (11-31)</td>
</tr>
<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>
Table 2. Univariate and multivariate cox proportional hazards model for the association between clinical and pathologic characteristics and cancer-specific mortality

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01-1.03</td>
<td>&lt;0.001</td>
<td>1.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.79</td>
<td>0.69-0.90</td>
<td>0.001</td>
<td>0.81</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td>1.73</td>
<td>1.64-1.82</td>
<td>&lt;0.001</td>
<td>1.42</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.73</td>
<td>3.14-7.12</td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>4.49</td>
<td>2.98-6.76</td>
<td>&lt;0.001</td>
<td>0.90</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td>4.16</td>
<td>3.50-4.94</td>
<td>&lt;0.001</td>
<td>1.78</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>3.04</td>
<td>2.70-3.42</td>
<td>&lt;0.001</td>
<td>1.47</td>
</tr>
<tr>
<td>Concomitant CIS</td>
<td>0.92</td>
<td>0.82-1.03</td>
<td>0.149</td>
<td>0.99</td>
</tr>
<tr>
<td>Pathologic nodal involvement</td>
<td>4.00</td>
<td>3.56-4.51</td>
<td>&lt;0.001</td>
<td>2.50</td>
</tr>
<tr>
<td>Adjuvant Radiotherapy</td>
<td>3.51</td>
<td>2.41-5.11</td>
<td>&lt;0.001</td>
<td>1.81</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td>2.15</td>
<td>1.91-2.43</td>
<td>&lt;0.001</td>
<td>0.83</td>
</tr>
</tbody>
</table>

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

†Quintiles created using individuals’ estimated prediction of the fitted multivariate cox proportional hazards model (see table 2).

*Log-rank test for trend <0.001

DSS – Disease-specific survival
Table 4. Selected pathologic characteristics of patients within quintiles based on disease risk.

<table>
<thead>
<tr>
<th>Quintile*</th>
<th>5-yr predicted DSS</th>
<th>≤pT1</th>
<th>pT2</th>
<th>pT3</th>
<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>1</td>
<td>94.2 (92.0-95.9)</td>
<td>772 (99.6%)</td>
<td>3 (0.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>9 (.9%)</td>
<td>0 (0%)</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>
<td>0 (0%)</td>
<td>18 (1.8%)</td>
<td>49 (6.2%)</td>
<td>0 (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>
<td>25 (3.2%)</td>
<td>30 (3.0%)</td>
<td>390 (50.3%)</td>
<td>1 (0.1%)</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>
<td>158 (20.4%)</td>
<td>229 (23.1%)</td>
<td>714 (92.4%)</td>
<td>97 (12.5%)</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>
<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).