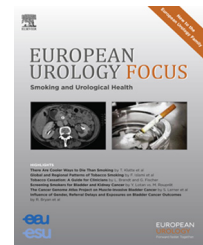


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Bladder Cancer

Effectiveness of Adjuvant Chemotherapy After Radical Cystectomy for Locally Advanced and/or Pelvic Lymph Node–Positive Muscle-invasive Urothelial Carcinoma of the Bladder: A Propensity Score–Weighted Competing Risks Analysis

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Abstract

Background: The benefit of adjuvant chemotherapy (AC) for muscle-invasive urothelial carcinoma of the bladder (UCB) after radical cystectomy (RC) is controversial.

Objective: To assess the effectiveness of AC after RC for muscle-invasive UCB in contemporary European routine practice.

Design, setting, and participants: By using a prospectively collected European multi-center database, we compared survival outcomes between patients who received AC versus observation after RC for locally advanced (pT3/T4) and/or pelvic lymph node–positive (pN+) muscle-invasive UCB in 2011.

Intervention: AC versus observation after RC.

Outcome measurements and statistical analysis: Inverse probability of treatment weighting (IPTW)–adjusted Cox regression and competing risks analyses were performed to compare overall survival (OS) as well as cancer-specific and other-cause mortality between patients who received AC versus observation.

* For the Young Academic Urologists Urothelial Cancer Group.

[†] Collaborators are listed in the Appendix.

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Results and limitations: Overall, 224 patients who received AC ($n = 84$) versus observation ($n = 140$) were included. The rate of 3-yr OS in patients who received AC versus observation was 62.1% versus 40.9%, respectively ($p = 0.014$). In IPTW-adjusted Cox regression analysis, AC versus observation was associated with an OS benefit (hazard ratio: 0.47; 95% confidence interval [CI]: 0.25–0.86; $p = 0.014$). In IPTW-adjusted competing risks analysis, AC versus observation was associated with a decreased risk of cancer-specific mortality (subhazard ratio: 0.51; 95% CI: 0.26–0.98; $p = 0.044$) without any increased risk of other-cause mortality (subhazard ratio: 0.48; 95% CI: 0.14–1.60; $p = 0.233$). Limitations include the relatively small sample size as well as the potential presence of unmeasured confounders related to the observational study design.

Conclusions: We found that AC versus observation was associated with a survival benefit after RC in patients with pT3/T4 and/or pN+ UCB. These results should encourage physicians to deliver AC and researchers to pursue prospective or large observational investigations.

Patient summary: Overall survival and cancer-specific survival benefit was found in patients who received adjuvant chemotherapy relative to observation after radical cystectomy for locally advanced and/or pelvic lymph node-positive bladder cancer.

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1. Introduction

Urothelial carcinoma of the bladder (UCB) is a leading cause of cancer-related mortality in Europe, with an estimated 130 946 new cases and 43 080 deaths in 2015 [1]. Much effort has been devoted to improving oncologic outcomes of radical cystectomy (RC) for patients with localized muscle-invasive disease by using multimodal management, including the delivery of perioperative chemotherapy. Although there is consistent level I evidence supporting the benefit of neoadjuvant chemotherapy [2], the role of selective adjuvant chemotherapy (AC) for patients with locally advanced (pT3/T4) and/or pelvic lymph node-positive (pN+) UCB remains controversial. Specifically, although an updated meta-analysis of nine randomized controlled trials (RCTs) recently demonstrated an overall survival (OS) benefit with the use of immediate postoperative cisplatin-based chemotherapy [3], the latest randomized comparison of AC versus deferred chemotherapy at the time of relapse failed to confirm these results [4]. In addition, several limitations should be considered when analyzing the aforementioned prospective evidence. For example, only a pooled analysis of aggregate data has been performed in the supportive meta-analysis of published and unpublished RCTs, which generally had low statistical power due to poor accrual and early closure.

As such, observational studies have been used to fill this substantial void of prospective evidence [5–8]. A large report recently fueled the controversy by showing that AC was associated with a significant OS benefit in patients with pT3/T4 UCB, although these results may be limited by selection bias [5]. Indeed, the benefit recorded for AC could be related only to a better general condition of individuals included in the intervention arm and, as a consequence, to a decreased risk of other-cause mortality.

To address this limitation, Froehner et al [9] performed a competing risks analysis using a single-institution database, demonstrating a decreased risk of overall and cancer-specific mortality without any significant difference in terms of other-cause mortality between individuals who received AC or observation. While supporting the survival

benefit of AC in the absence of selection bias for a favorable general condition, this approach additionally confirmed that the toxicity profile of cisplatin-based chemotherapy was acceptable, as no significant increased risk of lethal cardiovascular events commonly related to the use of cisplatin-based chemotherapy [9,10] or any other-cause mortality in general was observed. It is noteworthy that no advanced statistical methods were used to account for the residual selection bias that may have interfered with the OS benefit found in this monocentric analysis.

We performed both propensity score-weighted and competing risks analyses of a prospectively collected multicenter database to assess the comparative effectiveness of AC versus observation for postoperative pT3/T4 UCB in a contemporary setting. Based on the available evidence, we hypothesized that AC decreases the risk of overall and cancer-specific mortality without increasing the risk of other-cause mortality.

2. Patients and methods

2.1. Study population

We used the Prospective Multicenter Radical Cystectomy Series 2011 (PROMETRICS 2011), which is a prospectively collected RC data set from 18 tertiary care centers (in Germany, Italy, and Austria). All participating centers provided mandatory data-sharing agreements, as described previously [10], resulting in an institutional review board-approved study. The total cohort consisted of 679 patients undergoing RC for muscle-invasive or high-grade non-muscle-invasive UCB between January 1 and December 31, 2011. Individual eligibility criteria for AC were based on the consensus of an interdisciplinary tumor board at each center. Mirroring the inclusion criteria of RCTs [3,4], we selected only patients with either pT3/T4 or pN+ UCB at the time of RC for final analyses. Patients who received neoadjuvant chemotherapy or any radiation therapy, those with no information on systemic treatment, and those missing follow-up data were excluded from the study. This yielded a final study population of 224 individuals (Fig. 1).

2.2. Data assessment and covariates

Baseline clinical characteristics were assessed preoperatively and documented at the time of admission for RC. Clinical parameters

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