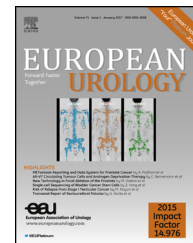


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Brief Correspondence

Efficacy of Systemic Chemotherapy Plus Radical Nephroureterectomy for Metastatic Upper Tract Urothelial Carcinoma

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Abstract

Given the growing body of evidence supporting the benefit of primary tumor control for a wide range of metastatic malignancies, we hypothesized that chemotherapy plus radical nephroureterectomy (RNU) is associated with an overall survival (OS) benefit compared to chemotherapy alone for metastatic upper tract urothelial carcinoma (mUTUC). Within the National Cancer Data Base (2004–2012), we identified 398 (38.4%) and 637 (61.6%) patients who received chemotherapy plus RNU and chemotherapy alone, respectively. Inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier curves showed that 3-yr OS was 16.2% (95% confidence interval [CI] 12.1–20.3) for chemotherapy plus RNU and 6.4% (95%CI 4.1–8.7) for chemotherapy alone ($p < 0.001$). In IPTW-adjusted Cox regression analysis, chemotherapy plus RNU was associated with a significant OS benefit (hazard ratio 0.70, 95% CI 0.61–0.80; $p < 0.001$). Despite the usual biases related to the observational study design, our findings show a net OS benefit for fit patients who received chemotherapy plus RNU for mUTUC relative to their counterparts treated with chemotherapy alone.

Patient summary: We examined the role of radical nephroureterectomy in addition to systemic chemotherapy for metastatic upper tract urothelial carcinoma. We found that such treatment may be associated with an overall survival benefit compared to chemotherapy alone in fit patients.

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Approximately 10% of patients with upper tract urothelial carcinoma (UTUC) present with involvement of extraregional lymph nodes and/or other distant sites at initial diagnosis [1]. Although it can vary tremendously according to baseline characteristics [2], prognosis for these individuals

is ominous, as 3-yr overall survival (OS) rates for metastatic UTUC (mUTUC) do not exceed 10% [1].

Cisplatin-based combination chemotherapy alone is currently considered the standard of care for fit patients with mUTUC [3]. Nonetheless, the paradigm for treating

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metastatic tumors is continuously evolving, with increasing evidence supporting the benefit of controlling the primary focus, notably for metastatic urothelial carcinoma of the bladder [4]. However, to date, there are no data available on the role of radical nephroureterectomy (RNU) in the treatment of mUTUC.

Thus, our objective was to test the impact of RNU on OS in a select cohort of patients from the National Cancer Data Base, who were deemed fit to receive systemic chemotherapy for mUTUC. We hypothesized that for these individuals, chemotherapy plus RNU is associated with an OS benefit compared to chemotherapy alone.

From a population of 43 431 men and women diagnosed with ureter or renal pelvis tumor between 2004 and 2012 (ICD-O-3 codes C65.9–C66.9), we identified 1182 individuals who received multiple-agent systemic chemotherapy for unilateral mUTUC at presentation. Further exclusion criteria are presented in Supplementary Fig. 1. Our final study population included 1035 individuals, who were dichotomized into a chemotherapy plus RNU group and a chemotherapy-alone group.

To account for potential selection bias, observed differences in baseline characteristics between patients who received chemotherapy plus RNU and those who received chemotherapy alone were controlled for with an inverse probability of treatment weighting (IPTW)-adjusted analysis [5]. Balance in covariates between treatment groups before and after IPTW adjustment was assessed using the standardized difference approach. IPTW-adjusted Kaplan-Meier curves and log-rank test were used to compare OS between patients who received chemotherapy plus RNU and those who received chemotherapy alone [6]. In addition, we performed multivariable Cox regression

analysis to estimate the corresponding IPTW-adjusted hazard ratio (HR) [5].

Given the prognostic value of metastases locations for mUTUC, we calculated separate IPTW-adjusted HRs for chemotherapy plus RNU versus chemotherapy alone in subgroups of patients with positive extraregional lymph nodes only and bone/visceral involvement at initial diagnosis by using interaction terms in the multivariable Cox model. Finally, we assessed the impact of baseline characteristics on the treatment effect by conducting a locally weighted regression.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Two-sided statistical significance was defined as $p < 0.05$. An institutional review board waiver was obtained before the study was conducted.

Overall, 398 patients with mUTUC received chemotherapy plus RNU (38.4%) and 637 (61.6%) received chemotherapy alone (Supplementary Fig. 1). In the chemotherapy plus RNU group, 357 (89.7%) and 41 (10.3%) patients received surgery before and after chemotherapy, respectively.

Unweighted and weighted baseline characteristics of eligible patients, stratified according to treatment group, are reported in Table 1. Results of multivariable logistic regression analysis predicting receipt of chemotherapy plus RNU versus chemotherapy alone are reported in Supplementary Table 1. Following IPTW adjustment, all standardized differences were $< 10\%$, indicating that the treatment groups were comparable (Supplementary Fig. 2).

The median follow-up was 25.0 mo (interquartile range 11.4–52.2). IPTW-adjusted Kaplan-Meier curves (Fig. 1) showed that 3-yr OS was 16.2% (95% confidence interval [CI] 12.1–20.3) for chemotherapy plus RNU and 6.4% (95% CI 4.1–8.7) for chemotherapy alone ($p < 0.001$). In

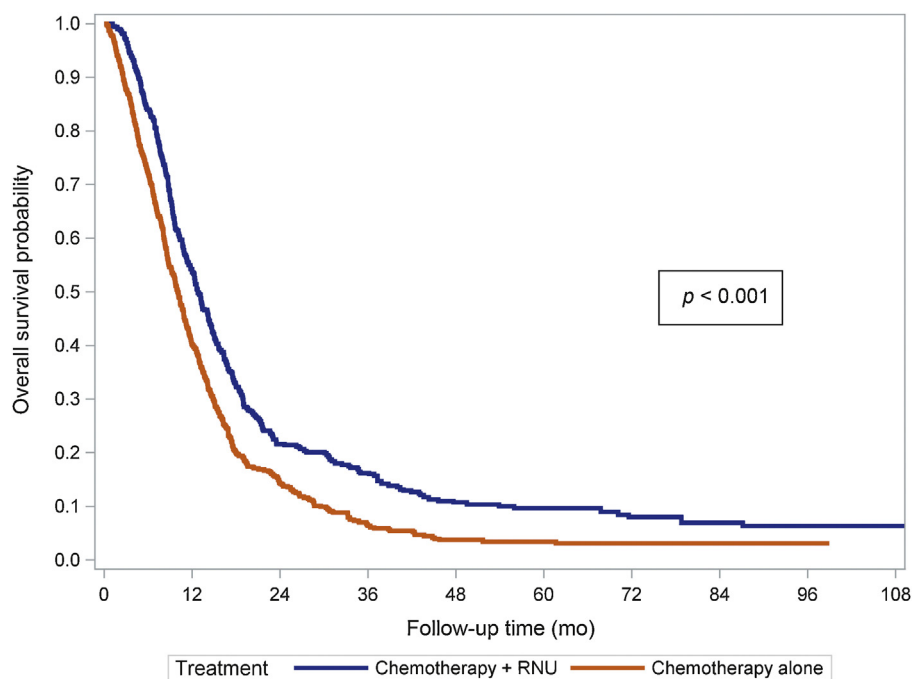


Fig. 1 – Inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier analysis of overall survival among patients who received chemotherapy plus radical nephroureterectomy (RNU) versus chemotherapy alone for metastatic upper tract urothelial carcinoma.

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