World Journal of Urology (2019) 37:1329–1337
https://doi.org/10.1007/s00345-018-2516-z

ORIGINAL ARTICLE

Survival effect of perioperative systemic chemotherapy on overall mortality in locally advanced and/or positive regional lymph node non-metastatic urothelial carcinoma of the upper urinary tract

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Received: 9 August 2018 / Accepted: 1 October 2018 / Published online: 8 October 2018

Abstract

Objectives To analyze the potential survival benefit of perioperative chemotherapy (CHT) in patients treated with nephroureterectomy (NU) for non-metastatic locally advanced upper tract urothelial carcinoma.

Methods Within the Surveillance, Epidemiology, and End Results database (2004–2014), we identified 1286 patients with T3 or T4, N 0–3 M0 UTUC. Kaplan–Meier plots, as well as multivariable Cox regression models (MCRMs) relying on inverse probability after treatment weighting (IPTW) and landmark analyses, were used to test the effect of CHT vs no CHT on overall mortality (OM) in the overall population ($n=1286$), as well as after stratification according to lymph node invasion (LNI).

Results Overall, 37.4% patients received CHT. The CHT rate was higher with LNI (62.2% vs 35.2%, $p<0.001$). In MCRMs, testing for OM in the overall population, CHT was associated with lower rates of OM (HR 0.71, CI 0.58–0.87; $p=0.001$). Similarly, in MCRMs testing for OM in patients with LNI, CHT achieved independent predictor status for lower OM (HR 0.61, CI 0.48–0.78; $p<0.001$). Conversely, in MCRMs testing for OM in patients without LNI, no CHT effect was recorded (HR 0.72, CI 0.52–1.01; $p=0.05$). All results were confirmed after IPTW adjustment and in landmark analyses.

Conclusions Our results represent a contemporary North American report indicating lower OM after CHT for patients with locally advanced non-metastatic upper tract urothelial carcinoma, specifically in patients with T3–T4, N1–N3, M0 disease. Validation of the current and of the previous study is required within a randomized prospective design.

Keywords Upper urinary tract · Urothelial carcinoma · Positive lymph nodes · SEER · Chemotherapy

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2516-z) contains supplementary material, which is available to authorized users.

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Introduction

Urothelial carcinoma of the upper urinary tract (UTUC) is a rare entity and accounts for 5–10% of all urothelial malignancies [1]. Among UTUC patients, those with locally advanced T3/T4 with N1–3 or without N0 locoregional disease account for 12.6% of UTUC patients [2]. In those individuals, nephroureterectomy (NU) represents the standard of care [3, 4]. The addition of either neoadjuvant or adjuvant chemotherapy (CHT) has to be considered [4, 5]. However, such indication is based on extrapolation of data from urothelial bladder cancer trials [6, 7]. In the recent POUT trial, the investigators reported a disease-free survival advantage for adjuvant CHT on 345 T2–T4, N0–3, M0 patients. Overall survival data were not yet available [8]. To date, only one North American population-based study that originated from the National Cancer Database (NCDB) demonstrated an association between adjuvant CHT and lower overall mortality (OM) in T3–T4 N0–3 M0 patients [9]. Additionally, one systematic review and meta-analysis, based on Asian institutional studies ($n = 110$) [10–12], also demonstrated lower OM in CHT-exposed patients [13]. However, their findings may not be generalizable to North American patients. Moreover, one European ($n = 627$) [14], one Canadian ($n = 308$) [15] and one large multi-institutional contemporary study ($n = 1544$) [16] also examined the effect of CHT after NU in non-metastatic UTUC (non-mUTUC). However, neither study showed an association with lower OM. Based on very limited North American data suggesting a potential benefit of CHT in the context of NU in non-mUTUC, we decided to revisit this hypothesis in a different population-based analysis within a different patient sample.

Patients and methods

Study population

Within the Surveillance, Epidemiology, and End Results (SEER) database (2004–2014), we identified 1286 patients with histologically confirmed advanced (T3/T4, N0–3, M0) urothelial carcinoma of the renal pelvis or ureter who underwent NU with lymph node dissection. Patients with metastatic disease and patients aged < 18 years were excluded.

Definition of variables for analyses

Patients were stratified according to CHT (yes) or no CHT (no/unknown). Covariates consisted of pathological N-stage (N0, N1–3), pathological T-stage (T3, T4), tumor location (renal pelvis, ureter), laterality (left, right), gender (male, female), age at diagnosis ($75 <, \geq 75$), race (Caucasian, African-American, other), year of diagnosis (2004–2008 and 2009–2014), region of origin (Pacific Coast, East, North and Southwest), socioeconomic status (low, high) and marital status (married, unmarried). Mortality was defined according to the SEER mortality code [17]. All other deaths were considered as other-cause mortality.

Statistical analysis

Descriptive statistics focused on frequencies and proportions for categorical variables. The statistical significance of differences in medians and proportions was tested with the Kruskal–Wallis and Chi square tests. All statistical tests were two-sided with a significance level set at $p < 0.05$. First, we tested the annual CHT rates. The estimated annual percentage changes (EAPCs) were tested with the least squares linear regression. Second, multivariable logistic regression was tested for patients and tumor characteristics associated with CHT delivery. Third, Kaplan–Meier plots illustrated OM rates according to treatment (CHT vs no CHT). Fourth, multivariable Cox regression models tested the effect of CHT on OM in the overall population and according to pathological N-stage status. Here, two separate sets of models tested the effect of CHT in, respectively, N0 and N1–3 patients. Landmark analyses at 2 months tested for immortal time bias [18]. Finally, all analyses were repeated after adjustment according to inverse probability after treatment weighting (IPTW) [9, 19] (Supplementary Fig. 1), to minimize potential differences between CHT and no CHT patients. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project.org/).

Results

General characteristics of the study populations

Of 1286 T3–T4, N0–N3, M0 UTUC patients, the majority were male (57.5%), Caucasian (87.1%) and aged < 75 years (59.6%). The median age was 72 years (interquartile range 64–79 years). 991 patients harbored T3 (77.1%) vs 295 T2 (22.9%) stage. High-grade UTUC was recorded in 89.3% of patients. Tumor location was divided between ureteral (24.5%) and pelvic (75.5%). Overall, 481 patients (37.8%) received CHT (Table 1).

Trend analyses

Chemotherapy administration rates did not change over time in the overall population (EAPC −0.15%; $p = 0.7$). Similarly, no changes were recorded over time after stratification according

Table 1 Baseline characteristics of 1286 surgically treated non-metastatic upper urinary tract urothelial carcinoma patients (Surveillance, Epidemiology, And End Results Registry 2004–2014)

	Overall ($n = 1286$) (%)	No chemotherapy ($n = 805$) (%)	Chemotherapy ($n = 481$) (%)	p value
Age (years)				
Mean	71 (0.3)	73.5 (0.367)	66.9 (0.456)	< 0.001
Median (interquartile range)	72 (64–79)	75 (67–81)	68 (59–74)	< 0.001
N-stage				
N0	704 (54.7)	522 (64.8)	182 (37.8)	< 0.001
N+	582 (45.3)	283 (35.2)	299 (62.2)	
T-stage				
T3	991 (77.1)	639 (79.4)	352 (73.2)	0.01
T4	295 (22.9)	166 (20.6)	129 (26.8)	
Grade				
High grade	1148 (89.3)	715 (88.8)	433 (90)	0.2
Low grade	69 (5.4)	50 (6.2)	19 (4)	
Unknown	69 (5.4)	40 (5)	29 (6)	
Location				
Pelvis	971 (75.5)	612 (76)	359 (74.6)	0.6
Ureter	315 (24.5)	193 (24)	122 (25.4)	
Laterality				
Left	714 (55.5)	439 (54.5)	275 (57.2)	0.4
Right	572 (44.5)	366 (45.5)	206 (42.8)	
Region				
Pacific coast	660 (51.3)	405 (50.3)	255 (53)	0.04
East	451 (35.1)	298 (37)	153 (31.8)	
North	136 (10.6)	74 (9.2)	62 (12.9)	
Southwest	39 (3)	28 (3.5)	11 (2.3)	
Age (categorical) (years)				
<75	766 (59.6)	391 (48.6)	375 (78)	< 0.001
≥75	520 (40.4)	414 (51.4)	106 (22)	
Socioeconomic status				
High	633 (49.2)	409 (50.8)	224 (46.6)	0.2
Low	653 (50.8)	396 (49.2)	257 (53.4)	
Gender				
Female	547 (42.5)	341 (42.4)	206 (42.8)	0.9
Male	739 (57.5)	464 (57.6)	275 (57.2)	
Marital status				
Married	789 (61.4)	463 (57.5)	326 (67.8)	0.001
Unknown	40 (3.1)	28 (3.5)	12 (2.5)	
Unmarried	457 (35.5)	314 (39)	143 (29.7)	
Race				
Caucasian	1120 (87.1)	706 (87.7)	414 (86.1)	0.5
African-American	65 (5.1)	36 (4.5)	29 (6)	
Others	101 (7.9)	63 (7.8)	38 (7.9)	
Year of diagnosis				
2004–2008	665 (51.7)	422 (52.4)	243 (50.5)	0.5
2009–2014	621 (48.3)	383 (47.6)	238 (49.5)	

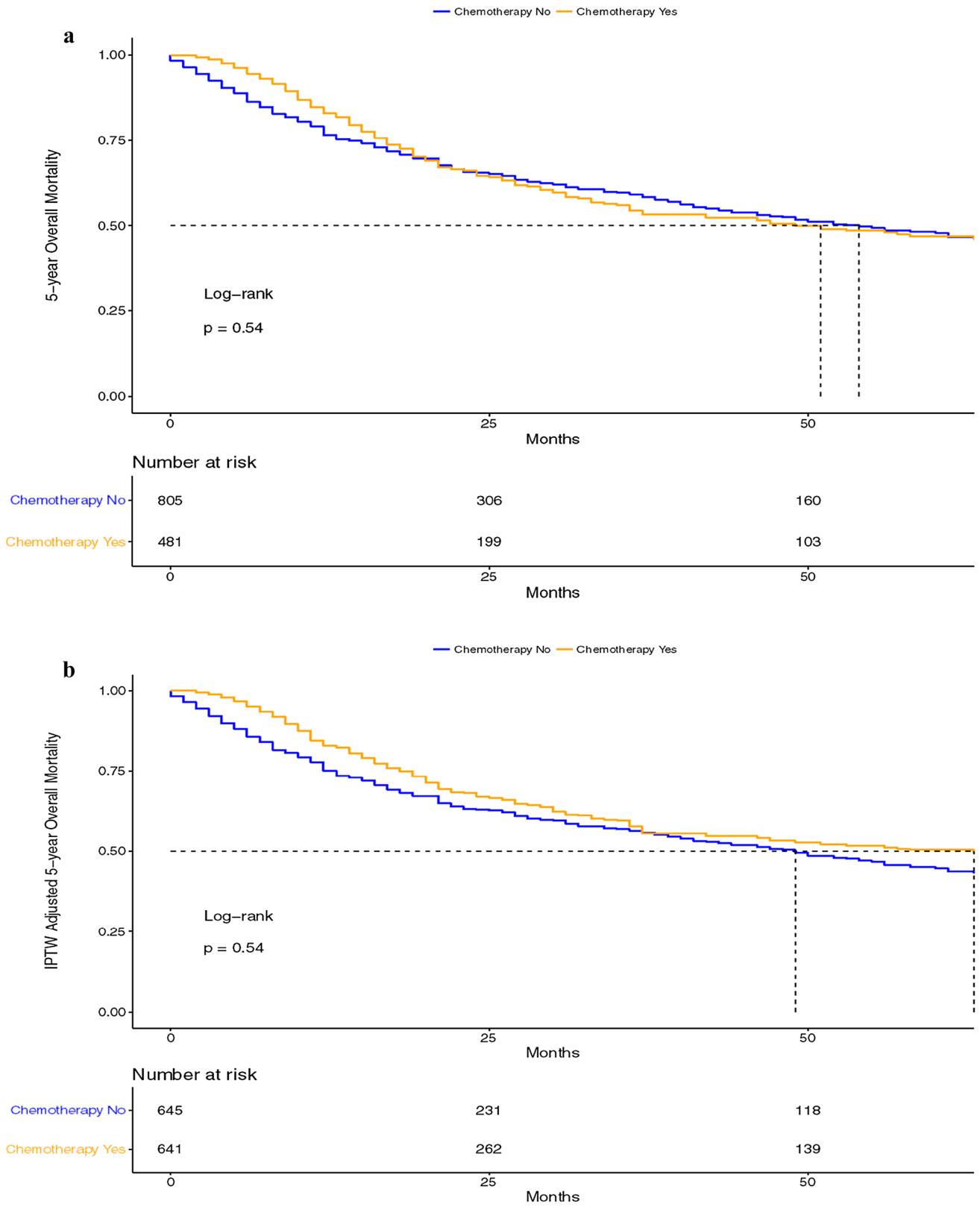

Fig. 1 Kaplan–Meier plots depicting 5-year overall mortality before (**a**) and after inverse probability after treatment weighting (**b**) in 1286 non-metastatic surgically treated upper urinary tract patients according to chemotherapy administration

Table 2 Multivariable Cox regression models predicting overall mortality after inverse probability of treatment weighting and 2-month landmark analyses in 1286 surgically treated non-metastatic upper urinary tract urothelial carcinoma patients (adjusted for tumor grade, tumor location, laterality, race, gender and year of diagnosis)

	Hazard ratio	Confidence interval (95%)	*p* value
Chemotherapy			
No (ref.)			
Yes	0.82	0.67–0.99	0.04
T-stage			
T3 (ref.)			
T4	1.85	1.51–2.27	< 0.001
N-stage			
N0 (ref.)			
N+	2.36	1.94–2.90	< 0.001
Age (years)			
< 75 (ref.)			
≥ 75	1.28	1.05–1.55	0.01

to LNI [N0 (EAPC − 0.06%; $p = 0.9$), N1–3 (EAPC − 0.75%; $p = 0.2$)].

Characteristics associated with chemotherapy administration

In multivariable logistic regression analyses predicting CHT delivery, only LNI (OR 3.47, CI 2.68–4.05; $p < 0.001$) and ureteral vs pelvic location (OR 1.37, CI 1.02–1.83; $p = 0.03$) achieved independent predictor status for higher CHT rates. Conversely, only older age (OR 0.23, CI 0.17–0.30; $p < 0.001$) was associated with lower CHT rates.

Survival analyses

IPTW-adjusted 5-year OM rates were, respectively, 50% (CI 45–55%) for CHT vs 55% (CI 50–60%) for no CHT patients ($p > 0.05$) (Fig. 1a, b). In MCRMs, CHT achieved independent predictor status for lower OM (HR 0.71, CI 0.58–0.87; $p < 0.001$) (Supplementary Table 1). The results were confirmed after IPTW adjustment (HR 0.75, CI 0.63–0.90; $p = 0.002$) and landmark analyses (HR 0.82, CI 0.68–0.99; $p = 0.04$) (Table 2).

In sensitivity analyses performed according to lymph node invasion, IPTW-adjusted 5-year OM rates in N0 patients were 33% (CI 25–38%) for CHT vs 33% (CI 26–39%) for no CHT patients ($p > 0.05$) (Fig. 2a, b). In MCRMs, CHT did not achieve independent predictor status for lower and OM (HR 0.72, CI 0.52–1.00; $p = 0.05$). The results were confirmed after IPTW adjustment (HR 0.85, CI 0.64–1.13; $p = 0.3$) and landmark analyses (HR 0.88, CI 0.66–1.17; $p = 0.4$).

Conversely, 5-year OM rates in N1–3 patients were 66% (CI 58–73%) for CHT vs 78% (CI 67–85%) for no CHT patients ($p < 0.01$) (Fig. 3a, b). In MCRMs, CHT achieved independent predictor status for lower OM (HR 0.61, CI 0.48–0.78; $p < 0.001$).The results were confirmed after IPTW adjustment (HR 0.61, CI 0.48–0.78; $p < 0.001$) and landmark analyses (HR 0.71, CI 0.55–0.91; $p < 0.001$).

Discussion

Non-metastatic locally advanced UTUC represents a rare entity [1, 2], and NU is the standard of care that is applicable to the majority of such patients [3]. Use of neoadjuvant and adjuvant CHT in such individuals is based on data extrapolation from urothelial bladder cancer patients [6, 7], since only one retrospective population-based North American study suggested an OM benefit in this setting [9]. To address the unmet need for additional validation of potential OM CHT benefit, we tested this hypothesis within a different population-based sample and made several noteworthy observations.

First, CHT was administered at a substantially higher rate to T3/4 N1–3 M0 patients than to their T3–T4, N0, M0 counterparts (OR 3.47, CI 2.68–4.05; $p < 0.001$). This observation reflects clinical practice, where salvage CHT is usually administered in the context of metastatic progression in those without LNI. Conversely, the presence of LNI at NU represents a strong indication for CHT in non-mUTUC patients [5]. This practice is consistent with guideline recommendations that indicate a potential for CHT in N1–N3 patients, as well as T3 to T4 patients [4, 5].

Second, we also noted no differences in CHT rates according to geographical region, gender, race and year of diagnosis. Absence of variability according to these variables indicates the absence of significant barriers or selection biases regarding CHT rates. Moreover, absence of annual variability is indicative of similar interest in CHT among clinicians and of similar patient characteristics that determine CHT eligibility. Conversely, lower rates of CHT were recorded in patients ≥ 75 years. This observation is related with increased comorbidities in elderly patients that may lead to CHT ineligibility.

Regarding the association between CHT and OM, we were able to corroborate the findings of Seisen et al. [9] from the NCDB, within the current SEER database population. Specifically, we found a clinically meaningful and highly statistically significant benefit of CHT in patients with T3–T4, N1–3, M0 non-mUTUC treated with NU (HR

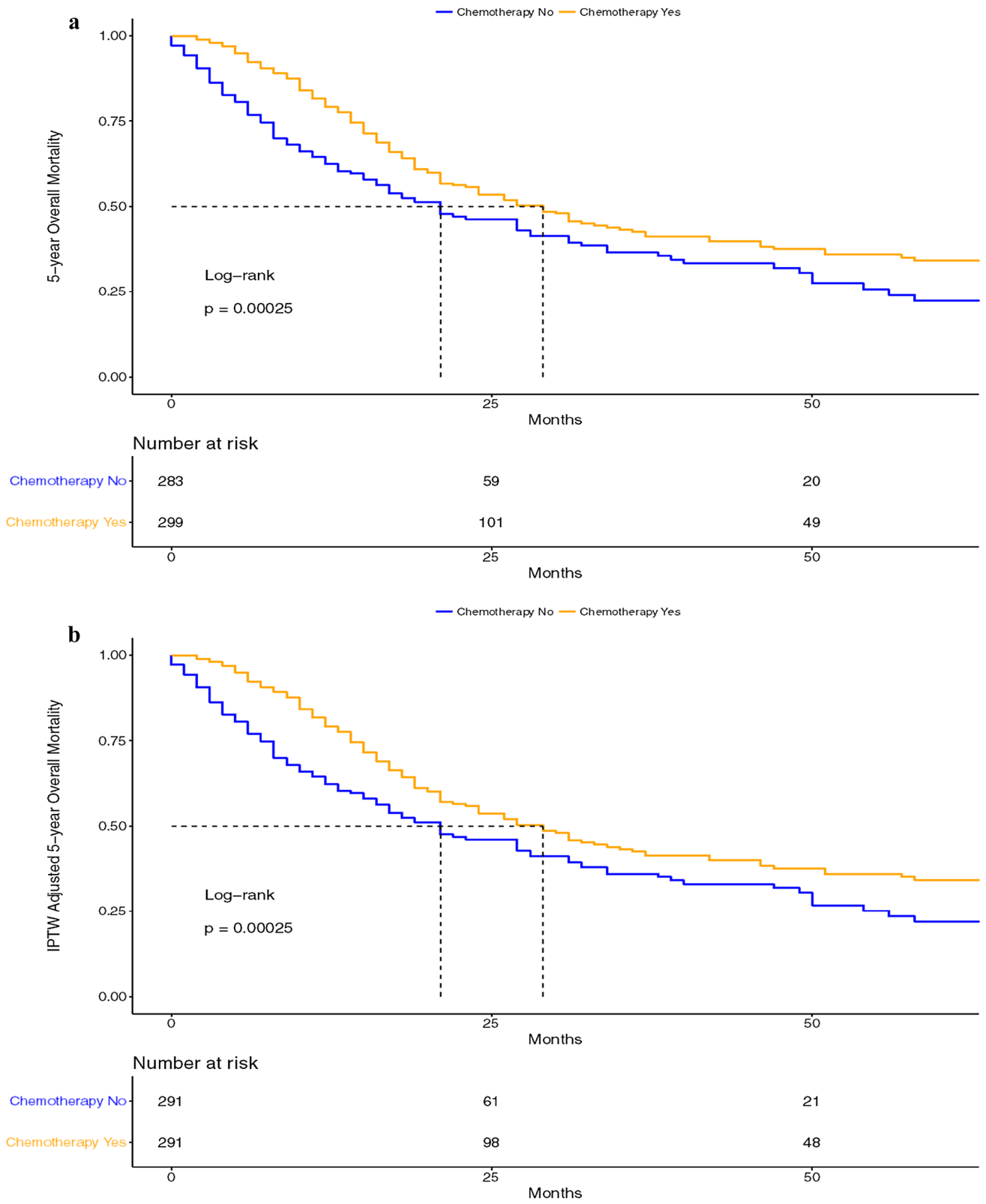

Fig. 2 Kaplan–Meier plots depicting 5-year overall mortality before (**a**) and after inverse probability after treatment weighting (**b**) in 582 non-metastatic surgically treated upper urinary tract patients with lymph node invasion according to chemotherapy administration

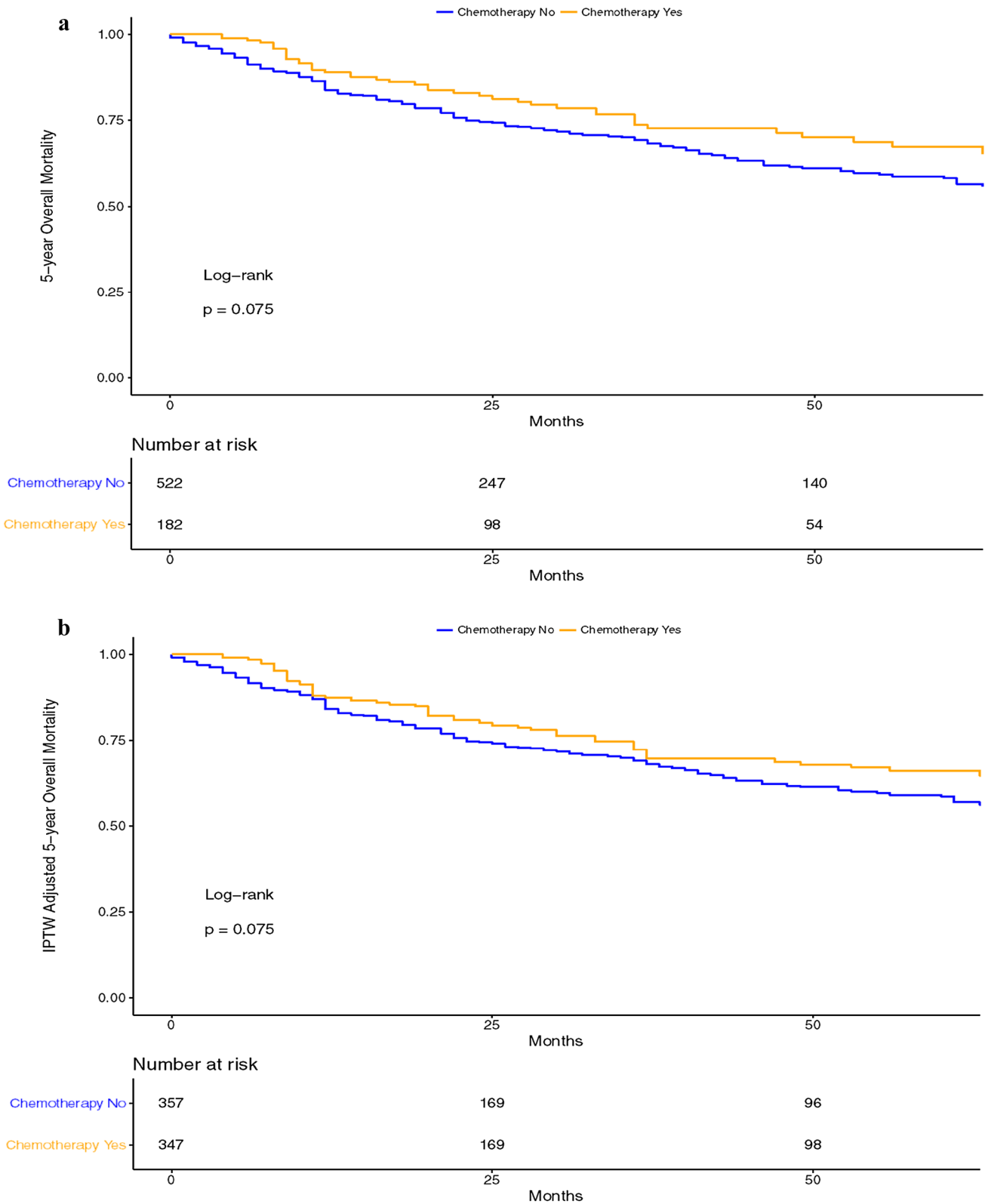

Fig. 3 Kaplan–Meier plots depicting 5-year overall mortality before (**a**) and after inverse probability after treatment weighting (**b**) in 704 non-metastatic surgically treated upper urinary tract patients without lymph node invasion according to chemotherapy administration

0.61, CI 0.48–0.78; $p < 0.001$). Conversely, we found no statistically significant benefit in patients with T3–T4, N0, M0, non-mUTUC (HR 0.72, CI 0.52–1.00; $p = 0.05$). In the overall population, a statistically significant association was identified between CHT and OM (HR 0.71, CI 0.58–0.87; $p < 0.001$). These findings are in agreement with the study of Seisen et al. with respect to the patient population in which the OM benefit was recorded. Moreover in this subset of patients, the magnitude of the OM decrease is concordant between the study of Seisen et al. and our study (overall population HR 0.77 vs 0.71; N1–3 patients HR 0.64 vs 0.61). Additionally, we confirmed the validity of the association between CHT and OM, even in landmark analyses controlling for immortal time bias. Last but not least, in a contemporary analysis of Necchi et al. [16] no advantage of adjuvant CHT was found in pT2-4, N0–N3, M0 patients. It has to be noted that in the cohort of Necchi et al. [16], the percentage of N + patients was only 17.8% vs 45.3% in our cohort. This difference may explain the absence of survival benefit of adjuvant CHT reported by the investigators.

Taken together, these observations indicate that retrospective analyses of CHT in the context of NU for locoregional non-mUTUC might be beneficial, when OS represents the end point of interest. This said, the retrospective nature of both analyses cannot fully eliminate potential selection biases, despite the application of most stringent statistical methodology aimed at eliminating such selection biases. In consequence, validation from within prospective design should ideally be performed. Such studies are ongoing. Specifically, in the POUT trial the investigators recently reported a disease-free survival advantage for adjuvant CHT on 345 T2–T4, N0–3, M0 patients. Overall survival data were not yet available [16].

Our study is not devoid of limitations. First and foremost, the limitation of the current study is the lack of detailed information regarding CHT. Specifically, CHT agents were unavailable. In consequence, a proportion of patients exposed to CHT might have received non-cisplatinum-containing regimens [13]. We believe that this proportion is relatively low, since previous studies showed no survival benefit, when such regimens were used in the setting of UTUC. Based on this observation, exclusion of patients exposed to non-cisplatinum-based regimens could potentially improve the observed OM benefit within our study. It is of note that the same limitation applies to the study of Seisen et al. [9], where specific CHT regimens were also not known. A similar degree of contamination with non-cisplatinum-based regimens probably also occurred, based on virtually the same results that were recorded in Seisen et al.'s study compared to ours. Second, the timing of CHT administration was not known in our study; in consequence, a proportion of patients may have benefited from neoadjuvant CHT in addition to most benefiting from adjuvant CHT [20, 21]. This rationale is based on data reported by Seisen et al. [9], where most patients (> 95%) received adjuvant CHT. The virtual perfect concordance between Seisen et al.'s findings and our findings strongly suggests that a very similar proportion of individuals might have received adjuvant CHT (> 95%). The retrospective nature of the SEER database represents the second most important limitation of the current study. This design type only allows to test the association between CHT and OM, but does not allow to infer causality. The same limitation applies to Seisen et al., based on the same retrospective design consideration as in our study. In consequence, despite the agreement between our study and the one of Seisen et al., our combined findings can only be interpreted as hypothesis generating and require formal validation from within randomized prospective design. Several additional limitations should also be mentioned. Specifically, heterogeneity regarding tumor stage and grade evaluation may be present because no central pathology review was present. Finally, the site of removed lymph nodes was not assessed and no standardized template was used.

Conclusions

Our results represent a contemporary North American report indicating lower OM after CHT for patients with locally advanced non-metastatic upper tract urothelial carcinoma, specifically, in patients with T3–T4, N1–N3, M0 disease. Validation of the current and of the previous study is required within a randomized prospective design.

Author contributions Protocol/project development: SN, FP, EM, PIK. Data collection or management: SN, FP, EM, PIK, ZT. Data analysis: SN, FP, EM, PIK, ZT. Manuscript writing/editing: SN, FAM, SFS, DS, FS, EM, SL, AB, LC and PIK.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Financial disclosures Sebastiano Nazzani certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: none.

Conflict of interest The authors declare that they have no competing interests.

Ethical standards We affirm that all authors have complied with the principles of the World Journal of Urology regarding ethical responsibilities of authors and compliance with ethical standards.

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