Comparison of Adjuvant Chemotherapy for Upper Tract versus Lower Tract Urothelial Carcinoma: A Systematic Review and Meta-Analysis

Seyed B. Jazayeria, Jennifer S. Liu, Brittany Weissman, Janice Lester, David B. Samadi, Michael A. Feuerstein

Department of Urology, Lenox Hill Hospital, Northwell School of Medicine, New York, NY; Health Science Library, Northwell Health, Long Island Jewish Medical Center, New Hyde Park, NY, USA

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Abstract
Introduction: Principles of management for upper tract urothelial carcinoma (UTUC) are mostly derived from knowledge of lower tract urothelial carcinoma (LTUC), however recent research indicates that these may be disparate diseases. In this review, we sought to compare the responsiveness of these tumors to similar treatment, platinum-based chemotherapy used in the adjuvant setting. Materials and Methods: PubMed, EMBASE, and Web of Science were searched using a systematic search strategy. Disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS) in patients with LTUC and UTUC treated with adjuvant chemotherapy were compared. Review Manager V 5.3 was used for meta-analyses. Results: Adjuvant chemotherapy was associated with improved DFS (HR 0.41, 95%CI 0.31–0.54), CSS (HR 0.29, 95%CI 0.17–0.50) and OS (HR 0.51, 95%CI 0.38–0.70) rates in LTUC. The effectiveness of adjuvant chemotherapy in UTUC was less pronounced with respect to DFS (HR 0.61, 95%CI 0.1–0.93) and CSS (HR 0.70, 95%CI 0.56–0.90) rates, and there was no effect on OS (HR 0.87, 95%CI 0.69–1.10). Differences in CSS and OS were significant (p < 0.0001) in favor of adjuvant chemotherapy for LTUC versus UTUC. Conclusion: Despite similar histology, we found significant differences in responsiveness to adjuvant chemotherapy between LTUC and UTUC. This may add to the already growing knowledge that these are disparate diseases. Newer systemic treatments for urothelial carcinoma may prove more effective than platinum-based chemotherapy in the adjuvant setting for UTUC.

Introduction
Urothelial carcinoma (UC) is the second most common genitourinary cancer worldwide [1]. Lower tract urothelial carcinoma (LTUC) is the most common form of UC and accounts for more than 90% of all UC cases. On the other hand, upper tract urothelial carcinoma (UTUC) is a rare and less understood malignancy with an incidence of 2 cases per 100,000 individuals [2]. The low incidence of UTUC has led to the limited literature on the management of UTUC. While randomized clinical level I data exists for systemic treatment of advanced LTUC, our understanding of the UTUC is largely limited to retrospective analyses [3]. Therefore, in practice, management of patients with UTUC is largely guided by understanding principles of LTUC [4].

Despite similarities in age, gender, pathology and risk factors, LTUC and UTUC have been considered 2 different diseases [5]. It is important to consider that the 2 portions of the urinary tract arise from different embryological structures [6]. Although the genomic profiles of LTUC and UTUC have many similarities, there may be subtle differences that may impact response to systemic
treatment [7, 8]. In addition, the systemic treatment of UC is rapidly changing with several checkpoint inhibitors now FDA approved for treatment of metastatic disease [9]. In lieu of these recent findings, we aimed to compare the responses of LTUC and UTUC to the standard platinum-based adjuvant chemotherapy (AC). With a paucity of data for neoadjuvant chemotherapy (NAC) in UTUC, we focused this study on response to AC.

**Methods**

PubMed, EMBASE, and Web of Science were searched on September 12, 2016 using the keywords bladder, upper tract, calic*, pyelocalyc*, calyx, transitional, urotheli*, cancer, malignanc*, tumor* and carcinoma*. The keywords were arranged in a search strategy format which was used in the search process. Results were limited to literature published after 1985. Search results were imported into an EndNote X7 library, and 2 researchers (S.B.J., B.W.) independently reviewed titles, abstracts, and full-texts of the papers to select the literature. The inclusion criteria to select a paper was based on the following: 1. Reporting the results on at least 40 subjects; 2. The use of platinum-based chemotherapy regimens; 3. Performing partial or radical cystectomy in LTUC or nephroureterectomy in UTUC (papers which included patients treated with transurethral, intravesical, percutaneous techniques or radiation at any time were excluded) and 4. Reporting data on oncologic outcomes of treatment. Papers which included cases rather than UC, i.e. squamous cell carcinoma, were excluded. In the event of an inconsistency between the 2 investigators, a discussion with a third researcher (J.L.) would occur, and a decision to include or exclude the paper was made. Full-texts of the selected papers were then reviewed, and results were summarized. References of the selected articles were also hand searched to find additional evidence. An updated search was performed on June 30, 2017 and all new search results were reviewed. The primary outcomes of interest were disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS). Data were then entered into Review Manager V. 5.3 [10] for meta-analysis. In papers where individual hazard ratio (HR) data was not provided, we followed the methods described by Guyot et al. [11] to derive HRs from reported Kaplan-Meier graphs.

**Results**

Primary search results are shown in figure 1. Overall 3,257 initial records were identified. After an abstract and full-text review, 14 articles met the inclusion criteria of the study. An updated search in PubMed resulted in the selection of 1 additional paper. After a hand-search of the references, we included 5 more articles that met our inclusion criteria. Of the total 20 papers, 14 reported outcomes comparing AC to no AC groups in UTUC or LTUC were reviewed and 4 papers were excluded for further meta-analysis. In addition to not having suitable data for meta-analysis, Dorff et al. [12] compared AC medication regimens. Park et al. [13] did not report HR data for meta-analyses in addition to not providing Kaplan–Meier curves to estimate HRs. Song et al. [14] compared AC treatment between LTUC and UTUC and Zargar-Shoshtari et al. [15] evaluated AC treatment in patients who had NAC prior to surgery, which was an exclusion criterion of several other papers included in this review. Lucca et al. [16, 17] only reported outcomes on lymph-node positive patients. Tsai et al. [18] compared NAC and AC treatments in UTUC. Youssef et al. [19] and Gallagher et al. [20] compared chemotherapy to patients without chemotherapy, but made no differentiation in their survival analyses on the type of chemotherapy treatment that was administered (NAC or AC). Table 1 provides an overview of individual study characteristics. Table 2 is an overview of all survival outcomes reported in the selected papers. The risk of bias table is presented in supplement 1.

**AC in LTUC**

Eight studies [13, 17, 21–26] reported survival outcomes on the role of AC for LTUC (table 1), including 4 randomized controlled trials and 4 retrospective studies with a total of 1,098 patients treated with platinum-based AC and 855 patients who received surgery alone. Che-
**Table 1. Overview of study characteristics**

| Study | Comparison | AC regimen | Study eligibility criteria | Accrual period | Study type | Median follow-up, months | Total patients |
|-------|------------|------------|-----------------------------|----------------|------------|-------------------------|----------------|
|       |            |            |                             |                |            | AC                      | No-AC          |
| UTUC  |            |            |                             |                |            |                         | 421            |
| Hellenthal et al., 2009 | Mix vs. no-AC | 5% patients with carboplatin; 95% with cisplatin; 60% MVAC; 20% GC | pT3N0, pT4N0 and/or N+ | 1992–2006 | retrospective multicenter | 26 | 121 | 421 |
| Kim et al., 2013 | GCarbo vs. no-AC | MVAC, GC | pT3 or pT4 or pT1–2N1–3 | 2000–2013 | retrospective single center | 34 | 36 | 29 |
| Kawashima et al., 2012 | Mix vs. no-AC | 2 patients with carboplatin; 38 cisplatin-based | pT3N0/x | 1999–2009 | retrospective multicenter | not reported | 38 | 55 |
| Ku et al., 2011 | Mix vs. no-AC | MVAC, GC, cisplatin, cyclophosphamide, and doxorubicin (CISCA) | pT1–4 | 1991–2006 | retrospective single center | 38 | 48 | 116 |
| Lee et al., 2015 | Mix vs. no-AC | MVAC/MVEC | T2/N0 and LVI+ | 1986–2013 | retrospective single center | 54 | 64 | 280 |
| Lucca et al., 2015 | Mix vs. no-AC | MVAC, GC, MVEC | T1–4 and N+ | 1987–2012 | retrospective multicenter | 35 | 107 | 156 |
| Total |            |            |                             |                |            |                         |                |
| LTUC  |            |            |                             |                |            |                         | 1057           |
| Bono et al., 1997 | Mix vs. no-AC | cisplatin, MTX | T2–4a and N0 | 1984–1987 | prospective multicenter | 69 (mean) | 43 | 47 |
| Freiha et al., 1996 | MVAC vs. no-AC | cisplatin, methotrexate and vinblastine (CMV) | pT3–4; N0 or N+ | 1986–1993 | prospective single center | 62 | 27 | 28 |
| Kanatani et al., 2015 | Mix vs. no-AC | MVAC/GC | pT3–4 or pN1–3 or both | 1990–2012 | retrospective single center | 29 | 39 | 22 |
| Lehmann et al., 2006 | MVAC/MVEC vs. no-AC | MVAC/MVEC | pT3, pT4a, and/or pN+ | 1987–1990 | prospective multicenter | 28 | 26 | 23 |
| Lucca et al., 2015 | Mix vs. no-AC | MVAC, MVEC, GC | T1–4 and N+ | 1979–2012 | retrospective multicenter | 160 | 874 | 649 |
| Park et al., 2007 | Mix vs. no-AC | MVAC or GC | T3–4N0 or N+ | 1989–2004 | retrospective single center | 34 | 60 | 200 |
| Paz-Ares et al., 2010 | Mix vs. no-AC | paclitaxel, gemcitabine, cisplatin | pT2G3 (N0–2), or pT3–4 (N0–2) any G, or pN1–2, any T, any G | 2000–2007 | prospective multicenter | 30 | 68 | 74 |
| Waki et al., 1990 | MVAC vs. no-AC | MVAC or CAP | pT2–4 | 1979–1988 | retrospective single center | not reported | 21 | 12 |
| Total |            |            |                             |                |            |                         | 1098           |

CAP = Cyclophosphamide, doxorubicin, cisplatin; GC = gemcitabine, cisplatin; MTX = methotrexate; MVAC = methotrexate, vinblastine, Adriamycin, and cisplatin; MVEC = methotrexate, vinblastine, epirubicin, and cisplatinum; Mix = patient treated with a mixed-medication AC.
### Table 2: Overview of study survival outcomes

| Study                        | Oncologic outcomes | Comment |
|------------------------------|--------------------|---------|
| **AC in UTUC**               |                    |         |
| Hellenthau et al., 2009      |                    |         |
| AC in UTUC                   | DFS                 | adjusted HR 0.79 (95% CI 0.58–1.08) | raw numbers are not mentioned in reference paper but study reports p values for log-rank tests from Kaplan-Meier analyses (defined DFS as bladder recurrence-free survival)
|                              | CSS                 | median OS 24 vs. 26 months (p = ns) adjusted HR 0.94 (95% CI 0.71–1.25) |
| Kim et al., 2013             |                    | CSS log-rank test, p = 0.47 adjusted HR 0.52 (95% CI 0.17–1.67) estimated HR 0.66 (95% CI 0.30–1.43) |
| Kawashima et al., 2012       |                    | 5-year CSS rate 81 vs. 64% (p = 0.09) adjusted HR 0.21 (95% CI 0.06–0.66, p = 0.01) estimated HR 0.43 (95% CI 0.18–1.02) |
| Ku et al., 2011              |                    | DFS log-rank test, p = 0.049 Adjusted HR 0.25 (95% CI 0.11–0.56, p < 0.01) |
| Lee et al., 2015             |                    | adjusted SHR 0.83 (CI not reported, p = 0.22) estimated SHR 0.54–1.06 adjusted SHR 0.59 (95% CI 0.43–0.80) |
| Lucca et al., 2015           |                    | adjusted SHR 0.83 (CI not reported, p = 0.22) estimated SHR 0.54–1.06 adjusted SHR 0.59 (95% CI 0.43–0.80) |
| **AC in LTUC**               |                    |         |
| Bono et al., 1997            |                    | adjusted HR 0.75 (95% CI 0.41–1.4) |
| Freiha et al., 1996          |                    | adjusted HR 0.74 (95% CI 0.49–1.11) |
| Kanatani et al., 2015        |                    | median DFS 37 vs. 12 months (p = 0.01) Estimated HR 0.43 (95% CI 0.21–0.87, p = 0.02) |
| Lucca et al., 2015           |                    | median CSS 57 vs. 18 month (p = 0.01) univariate HR 0.41 (95% CI 0.21–0.81, p = 0.01) adjusted HR 0.19 (95% CI 0.08–0.43, p = 0.0001) |
| Lehmann et al., 2006         |                    | adjusted SHR 0.83 (95% CI 0.71–0.97, p = 0.02) estimated HR 0.84 (95% CI 0.73–0.96, p = 0.012) |
| Park et al., 2007            |                    | adjusted HR 0.35 (95% CI 0.18–0.69, p = 0.003) |
| Paz-Ares et al., 2010        |                    | adjusted HR 0.40 (95% CI 0.20–0.78, p < 0.01) |
| Waki et al., 1990            |                    | adjusted HR 0.38 (95% CI 0.25–0.58, p < 0.001) |

**GC** = Gemcitabine-cisplatin; **GCcarbo** = gemcitabine-carboplatin; **MVAC** = methotrexate, vinblastine, adriamycin and cisplatin; **CI** = confidence interval; **SHR** = sub-hazard ratio (Fine-Gray competing-risk model); **ns** = not significant.

**Mix** Patient treated with a mixed-medication AC; **Adjusted HRs** multivariate HRs reported by the paper; **Univariate HRs** univariate HRs reported by the paper; **Estimated HRs** were calculated from estimating primary data from Kaplan-Meier curves provided by papers.

*Study reported as AC compared with no AC unless noted otherwise.*
motherapy regimens most commonly included methotrexate, vinblastine, adriamycin, cisplatin or gemcitabine, cisplatin. The range of median follow-up among the 8 studies was 11 to 160 months. There appeared to be a consistent benefit in median and 5-year DFS, CSS, or OS rates from patients with AC compared with those who received surgery alone (table 2).

**AC in UTUC**

No randomized trials investigated the role of AC in UTUC. We found 6 retrospective studies [16, 19, 27–30] with a total of 414 patients treated with platinum-based (cisplatin or non-cisplatin) AC and 1,057 patients who received surgery alone. The range of median follow-up time from the 6 studies was 26 to 54 months. There did not appear to be a benefit in median and 5-year DFS, CSS, and OS rates from patients with AC compared with those who received surgery alone (table 2).

### Meta-Analyses Comparing AC Responses

In LTUC, a total of 224 patients who underwent AC and 206 patients who underwent surgery alone were included in the meta-analysis. For UTUC, a total of 307 AC patients and 901 no-AC patients were included. Figures 2 and 3 show forest plot results from the papers eligible for meta-analysis. Forest plot results from univariate survival outcomes are included in supplement 2.

**DFS** Five studies evaluated DFS in LTUC [21–24, 26], four of which were clinical trials, and the remaining used multivariate analyses (fig. 2a). The pooled HR among the 5 studies was 0.41, 95% CI 0.31–0.54, p < 0.0001, representing a 59% survival benefit in patients treated with AC.

For DFS in UTUC (fig. 3a), 2 studies [28, 29] had sufficient data for meta-analysis. Survival data from these 2 studies were estimated by extracting primary data from Kaplan-Meier curves. The pooled univariate HR of 0.61,

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|-------------------|----|--------|--------------|--------------|
| Bone 1997         | -0.26769          | 0.19562 | 10.9% | 0.75 [0.40, 1.40] | |
| Freiha 1996       | -1.12303          | 0.404246 | 11.8% | 0.33 [0.16, 0.72] | |
| Kanetani 2015     | -1.12303          | 0.404246 | 11.8% | 0.32 [0.16, 0.72] | |
| Lehmann 2006      | -1.12303          | 0.404246 | 11.8% | 0.32 [0.16, 0.72] | |
| Paz-Ares 2010     | -0.96759          | 0.214686 | 41.0% | 0.30 [0.25, 0.58] | |
| Total (95% CI)    | 1.35000            | 0.41 [0.31, 0.54] | |

Test for overall effect: Z = 6.40 (p < 0.00001)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|-------------------|----|--------|--------------|--------------|
| Kanetani 2015     | -1.68201          | 0.42902 | 36.6% | 0.19 [0.08, 0.43] | |
| Lehmann 2006      | -0.92426          | 0.347086 | 60.4% | 0.40 [0.20, 0.76] | |
| Total (95% CI)    | 1.00000            | 0.29 [0.17, 0.50] | |

Test for overall effect: Z = 4.54 (p = 0.00001)

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|-------------------|----|--------|--------------|--------------|
| Bone 1997         | -0.43078          | 0.32313 | 23.0% | 0.65 [0.34, 1.25] | |
| Freiha 1996       | -0.40034          | 0.37796 | 17.7% | 0.67 [0.32, 1.44] | |
| Lehmann 2006      | -0.56217          | 0.311218 | 36.1% | 0.57 [0.31, 1.06] | |
| Paz-Ares 2010     | -1.04982          | 0.278363 | 33.2% | 0.35 [0.20, 0.66] | |
| Total (95% CI)    | 1.00000            | 0.51 [0.38, 0.70] | |

Test for overall effect: Z = 4.18 (p = 0.00001)

FIG. 2. a Multivariate DFS outcomes. b Multivariate CSS Outcomes. c Multivariate OS outcomes. Disease-free survival (a), cancer-specific survival (b), and overall survival (c) hazard ratios of studies investigating platinum-based adjuvant chemotherapy treatments for lower tract urothelial carcinoma. Fixed-effects models were used for studies with an I2 heterogeneity value of 75% or less. Random-effects models were used for studies with an I2 value over 75%.

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95% CI 0.40–0.93, p = 0.02, suggesting a 39% DFS benefit for patients treated with platinum-based AC. The univariate HR was reported as no multivariate data was found.

CSS For CSS in LTUC (fig. 2b), only 2 studies [23, 24] had sufficient data for meta-analysis, with a pooled HR 0.29, 95% CI 0.17–0.50, p < 0.00001. Between-study heterogeneity was not significant based on the Cochran Q statistic (0.17) and I^2 = 47%, so a fixed-effects model was used in analyses.

For CSS in UTUC, there were 4 studies [27, 28, 30, 31] with sufficient data for meta-analysis (fig. 3b). The pooled HR across the 4 studies was 0.70, 95% CI 0.56–0.90, p = 0.004. Between-study heterogeneity was not significant based on the Cochran Q statistic (0.16) and I^2 = 41%, so a fixed-effects model was used in analyses.

OS Four clinical trials [21, 22, 24, 26] found a highly significant OS benefit in patients treated with AC in the lower tract (fig. 2c) with a pooled HR of 0.51, 95% CI 0.38–0.70, p < 0.0001.

Conversely, 2 studies reported OS outcomes for the upper tract [27, 30], both of which evaluated multi-agent cisplatin-based treatments (fig. 3c). No significant survival benefit was found based on the pooled multivariate HR of 0.87, 95% CI 0.69–1.10, p = 0.24.

Discussion

In this study, we reviewed the available literature to compare the responses to AC of LTUC and UTUC. The purpose of this study was to determine if clinical responses to the same systemic therapy differ between these 2 histologically similar cancers. We acknowledge that evidence supports the use of NAC for LTUC, and that evidence is weaker for AC for LTUC [32]. However, due to the paucity of data of NAC for UTUC, this study focused on AC.
Our pooled analyses showed a strong benefit for AC in terms of CSS in LTUC and UTUC, but we found that the overall effect was significantly stronger in LTUC. The pooled HR calculated in our study also suggested a higher impact of AC on OS in LTUC.

Leow et al. [33] conducted a meta-analysis, on AC for LTUC using available randomized controlled trials. In the current meta-analysis, our inclusion criteria was more stringent as we excluded papers with mixed pathology or fewer than 40 enrollees. We did not have access to patient level data, and all HRs were derived either directly from the manuscript or were computed using reported Kaplan-Meier curves. Similar to our findings, Leow et al. [34] did not find a significant benefit in favor of AC in OS of patients with UTUC.

Differences in survival between LTUC and UTUC can be partly explained by the accuracy of pre-surgery staging in treatment selection [5]. UTUC are often diagnosed at a higher stage at the time of diagnosis [35]. Transurethral resection of bladder tumor allows precise staging of the primary tumor, however accurate biopsy and staging of UTUC remains challenging. While radical cystectomy may be recommended in non-muscle invasive LTUC with certain aggressive features, nephroureterectomy is often recommended at earlier stages of disease. This might cause a lead-time bias in which UTUC is treated more aggressively at earlier stages of the disease.

Recent genomic data suggests that subtle differences in gene expression may account for different treatment approaches [8]. Sfakianos et al. [7] compared the genomic profile of high-grade UTUC and LTUC. This study showed that although UTUC and LTUC contain alterations in similar genes, the frequency of gene alterations is different. Compared to high-grade LTUC cases, patients with high-grade UTUC have more frequent alterations in the FGFR3, HRAS genes, and fewer alterations in TP53 and RB1. In a study of cell cycle markers, LTUC and UTUC were found to have similar genomic profiles across all stages of the disease. However, in the subset of lymph node positive patients, UTUC patients had a higher alteration rate in Cyclin E. Moreover, node positive UTUC patients were also reported to harbor higher number of altered mutations in cell cycle markers overall [8]. These studies suggest a biological theory for differences in efficacy for systemic treatment. Similarly, it will be important to investigate differences in expression of PDL-1 and PD-1 inhibitors between UTUC and LTUC.

One limitation of this review is the relatively poor quality of primary data from the selected studies. We did not have access to patient level data to exclude patients with UC with variant histology or patients receiving NAC. There were 4 randomized controlled trials out of the 10 studies eligible for meta-analyses, and the remaining studies were nearly all retrospective in design, which is not ideal for studying survival time. Furthermore, seven of our studies were single-institution studies that lacked well-standardized methodology, including consistency in reporting data as well as in statistical methods.

Results from Kaplan-Meier methods should be interpreted with caution as this method of evaluating survival is a crude analysis and consequently does not adjust for multiple confounders. A Cox hazard ratio is a much more statistically meaningful measure of effect to interpret primary data than outcomes estimated by Kaplan-Meier survival curves. The majority of our studies were able to conduct more rigorous multivariate Cox proportional hazard models, controlling for important variables such as lymphovascular invasion, nodal status, and stage. However, within these papers, many reported on different survival outcome types and therefore made it difficult to make uniform conclusions from our meta-analysis results. For example, some studies only measured CSS and OS, but not DFS, and in others, only DFS was reported. Additionally, DFS definition was not universal among the studies. Some studies defined DFS by the time of surgery as reference point, while others used the randomization date. These differences may cause minimal changes in time to recurrence calculation. To accommodate for this discrepancy in the reported data, we only pooled HR of randomized controlled trials or HR derived from multivariate analyses together and reported multivariate and univariate results separately. We also pooled HRs from Kaplan-Meier survival curves together with HRs from univariate analyses.

While this review showed no significant OS benefit with AC in UTUC, it is important to interpret our results while considering the several limitations associated with nonrandomized retrospective studies. Selection bias may have affected results from our selected reports in the following ways: the proportion of patients with AC in some studies were significantly smaller, sometimes by 3- or 4-fold than the proportion of patients treated with surgery alone. Furthermore, in some studies, the number of patients within gender and lymph node status was much larger or smaller than those without chemotherapy treatment. Due to the inability to adjust for certain contributing factors of selection bias, our review may not fully...
capture the efficacy of AC within the selected papers. In the study of Leow et al. [34], the authors determined that many of the studies selected were affected by negative selection bias, creating an underestimation of many of the studies’ reported outcomes.

Many retrospective studies do not specifically evaluate patients at the highest risk of disease. While the large majority of the selected studies examined patients with high-risk conditions and completed sub-analyses evaluating patients with positive lymph node status, only 2 studies specifically evaluated lymph node positive patients. Additionally, it is important to note that papers selected patients based on different patient selection criteria. All but a couple studies had selected patients with advanced cancer, or high-risk conditions, defined at pT3 or pT4, with or without lymph node involvement as their study population. While the heterogeneity of our summarized data was moderately high, one of the major strengths of this review was the robust and comprehensive selection of literature available. We opted a strict inclusion criteria and performed a comprehensive search within multiple available electronic records.

Conclusion

In this meta-analysis, we found that platinum-based AC was more effective in LTUC than UTUC. Our findings support distinct clinical and genomic differences between these cancers, and the need for more effective adjuvant treatment targeting UTUC, perhaps utilizing checkpoint inhibitors.

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Supplement 1  Risk of bias analyses of the select studies in this review.

| Study                | Selection bias | Performance bias | Detection bias | Attribution bias | Reporting bias |
|----------------------|----------------|------------------|----------------|------------------|----------------|
| Bonomi et al., 1997  | ●              | ●                | ○              | ●                | U              |
| Freiha et al., 1996  | ●              | ●                | ○              | U                | ○              |
| Hellenthal et al., 2009 | ●            | ●                | ○              | –                | –              |
| Kanter et al., 2013  | ●              | ●                | ○              | –                | –              |
| Kawashima et al., 2012 | ●          | ●                | ○              | –                | –              |
| Kim et al., 2013     | ●              | ●                | ○              | U                | –              |
| Ku et al., 2011      | ●              | ●                | ○              | U                | –              |
| Lee et al., 2015     | ●              | ●                | ○              | U                | –              |
| Lehmann et al., 2006 | ●              | ●                | ○              | U                | –              |
| Luca et al., 2015    | ●              | ●                | ○              | U                | U              |
| Luca et al., 2013    | ●              | ●                | ○              | U                | U              |
| Park et al., 2007    | ●              | ●                | ○              | U                | U              |
| Paz-Ares et al., 2010| ●              | ●                | ○              | –                | –              |
| Waki et al., 1990    | ●              | ●                | ○              | U                | U              |

Supplement 2

LTUC CSS

| Study or Subgroup | log[Hazard Ratio] | SE     | Weight | IV, Random, 95% CI | Hazard Ratio IV, Random, 95% CI |
|-------------------|------------------|--------|--------|-------------------|---------------------------------|
| Luca 2015         | -0.17435         | 0.06687| 61.1%  | 0.84 [0.73, 0.96]  | 0.64 [0.32, 1.26]               |
| Kanterani 2015    | -0.8916          | 0.344369| 38.9%  | 0.41 [0.21, 0.81]  |                                |
| Total (95% CI)    | 100.0%           |        |        |                   |                                |

Heterogeneity: TAU² = 0.20, Chi² = 4.17, df = 1 (P = 0.04), I² = 76%
Test for overall effect Z = 1.30 (P = 0.19)

LTUC DFS

| Study or Subgroup | log[Hazard Ratio] | SE     | Weight | IV, Fixed, 95% CI | Hazard Ratio IV, Fixed, 95% CI |
|-------------------|------------------|--------|--------|-------------------|---------------------------------|
| Freiha 1996       | -0.84397         | 0.362598 | 45.2%  | 0.43 [0.21, 0.86]  |                                |
| Kanterani 2015    | -0.48204         | 0.329339| 54.8%  | 0.83 [0.33, 1.20]  |                                |
| Total (95% CI)    | 100.0%           |        |        |                   |                                |

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.44); I² = 0%
Test for overall effect Z = 2.58 (P = 0.009)
