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Adjuvant Therapy in the Upper Tract Urothelial Carcinoma: Where are we Standing Now?

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Abstract

Upper tract urothelial carcinomas represent 5-10% of urothelial carcinomas. Given its high recurrence rate, adjuvant therapy became a milestone question. Several studies, especially POUT trial, have succeeded to show a beneficial effect of adjuvant chemotherapy in the high risk UTUC. When it comes to immunotherapy in the adjuvant setting, despite an FDA approved benefit of nivolumab, studies have failed to prove any beneficial effect for UTUC. Other approaches in the adjuvant setting, as targeted therapy or combining chemo-immunotherapy, are still under evaluation.

Keywords: Urothelial Carcinoma, Upper Tract Urothelial Carcinoma, Chemotherapy, Immunotherapy

Introduction

Urothelial carcinomas (UCs) are the fourth most prevalent malignancies in men. Although 90-95% of urothelial carcinomas are located in the lower tract (bladder and urethra), 5-10% of them are located in the pyelocaliceal cavities and ureter and known as upper tract urothelial carcinoma (UTUC) [1].

UTUCs can be classified into low- or high-grade tumors. Low-grade tumors are generally not invasive whereas high grade tumors tend to be aggressive and invasive in the kidney or ureter [34]. At diagnosis, two-thirds of UTUC tend to be invasive while only 15–25% of bladder tumors are invasive [2].

Despite treatment with curative intent, UTUC has a high recurrence risk [3] with five-year cancer specific survival less than 50% for pT2/T3 and less than 10% for pT4 [4].

A retrospective review of the MD Anderson Cancer Center's experience found no improvement in the disease specific survival of UTUC over an 18-years period and suggested a change in the treatment protocol [5]. Thus, improved management of early-stage disease has the potential to save lives [6].

To time, radical nephroureterectomy (RNU) with lymph node dissection remains the current standard of care [3]. However, several studies have showed that kidney-sparing surgery (KSS) was equivalent to radical nephroureterectomy (RNU) in term of CSS (cancer specific survival) in patients with low-risk UTUC [32, 33]. However, radical nephroureterectomy (RNU) remains the standard for high-risk UTUC [34].

In practice, due to the rarity of this entity, there is a lack of high-level evidence-based guidelines and the optimal management of UTUC is based on retrospective limited studies and consisted more probably on extrapolation from bladder cancer approaches which could be not suitable for UTUC [7].

This critical review will summarize the current data on adjuvant therapy in UTUC focusing on the differences between UTUC and bladder cancer and the expected role of immunotherapy.

Adjuvant chemotherapy in bladder cancer

The role of adjuvant chemotherapy in bladder cancer remains a debatable approach and has not been established by a randomized trial. One of the largest randomized trials, the European Organisation for Research and Treatment of Cancer (EORTC) 30994 trial, showed among 284 patients treated with radical cystectomy an improvement in term of five-year PFS (48% versus 32%; HR 0.54, 95% CI 0.40-0.73) but failed to show a significant improvement in overall survival compared to those assigned to observation [five-year OS (54% versus 48%; HR 0.78, 95% CI 0.56-1.08)] [11,12]. However, several studies have shown a benefit of adjuvant chemotherapy in a specific group of patients having a high-risk disease [12,13]. For instance, a prospective study was published by Haquet et al., showed a longer OS in patients with N2-3 disease (17.5 vs. 14.4 months; $p = 0.005$) or with positive surgical margins (16.7 vs. 12.2 months; $p = 0.025$) [12]. Taking all the available data into account, the role of adjuvant chemotherapy in bladder cancer remains unclear. Nevertheless, given its benefits in selected patients, adjuvant chemotherapy can be offered to high-risk bladder cancer patients who did not receive neoadjuvant treatment.

Adjuvant chemotherapy in UTUC

The effectiveness of adjuvant chemotherapy in UTUC seems less controversial compared to the bladder. Several retrospective studies, meta-analyses and one randomized trial had evaluated the benefit of adjuvant chemotherapy in UTUC.
In 2014, in a retrospective study, Yafi et al. showed that adjuvant chemotherapy did not improve survival in UTUC patients. He showed also that 57% of the high-risk patients became ineligible for adjuvant chemotherapy because of poor postoperative renal function. This has led to the use of suboptimal regimen or doses which may explain the negative results [14].

Moreover, in 2017, Necchi et al. conducted a joint study to evaluate the efficacy of adjuvant chemotherapy in UTUC patients. The study results, though not statistically significant, showed shorter OS (HR 1.25, 95% CI 1.02–1.54) in the adjuvant chemotherapy arm. This phenomenon can be explained by the fact that the patients who received adjuvant chemotherapy had a more advanced disease [15].

The effectiveness of adjuvant chemotherapy was compared for the upper tract and lower tract urothelial carcinoma in a meta-analysis published by Jazayeri et al in 2018. The report

showed that adjuvant chemotherapy was more effective in LTUC: 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) versus UTUC: DFS (HR 0.61, 95%CI 0.1–0.93) and CSS (HR 0.70, 95%CI 0.56–0.90) rates, with no effect on OS (HR 0.87, 95%CI 0.69–1.10). Moreover, differences in CSS and OS were significant ($p < 0.0001$) in favor of adjuvant chemotherapy for LTUC versus UTUC [21].

In 2020, a meta-analysis was published by Quhal et al. and showed that adjuvant chemotherapy improved metastasis-free survival and cancer-specific survival in both, localized and locally advanced UTUC. However, in terms of OS, the benefit of adjuvant treatment was only seen among patients with locally advanced UTUC (HR 0.80, 95% CI 0.71–0.90, $p < 0.001$) [16].

However, in contrast to these upper mentioned equivocal results, in 2014, a meta-analysis was published, including one prospective study and nine retrospective studies, with a total of 482 patients receiving adjuvant chemotherapy after nephroureterectomy and 1300 patients treated with nephroureterectomy alone. The pooled evidence showed a benefit of cisplatin-based adjuvant chemotherapy in term of OS and DFS with a respective HR of 0.43 (95% CI, 0.21–0.89; p = 0.023) and 0.49 (95% CI, 0.24–0.99; p = 0.048). No benefit was seen for non-cisplatin-based regimen [17].

Another positive report, a prospective comparative trial on 176 patients (94 patients in the adjuvant chemotherapy group and 82 patients in the observation group), found an improvement of the survival outcome of high-risk UTUC patients. In fact, adjuvant chemotherapy had significantly improved PFS [P = 0.0033, HR = 3.78 (3.13–4.55)], OS [P = 0.0397, HR = 1.39 (1.01–1.75)] and cancer specific survival [P = 0.0255, HR = 1.26 (1.07–1.45)] in this population. In the subgroup analysis, a significant improvement with adjuvant chemotherapy was obtained in the lymph node positive subgroup in term of PFS (11.4 months vs. 31.9 months, P = 0.0018), OS (26.8 months vs. 36.3 months, P = 0.0255) and CSS (28.2 months vs. 39.3 months, P = 0.0197). Similarly, in the T3/4 cohort, adjuvant chemotherapy has improved median PFS (13.9 months vs. 36.3 months, P = 0.0217), OS (20.6 months vs. 32.2 months, P = 0.0183) and CSS (21.9 months vs. 38.4 months, P = 0.0226). [18]

An observational study on 3253 patients, published by Seisen et al in 2017, aimed to evaluate the effectiveness of adjuvant chemotherapy in patients with pT3/T4 and/or pN+ UTUC. Results showed that median OS was significantly longer for adjuvant chemotherapy versus observation (47.41 [interquartile range,19.88 to 112.39] vs 35.78 [interquartile range, 14.09 to 99.22] months; P < .001) [19].

Also, in 2017, a retrospective Japanese study on 449 patients was published to evaluate adjuvant chemotherapy in selected high-risk patients with UTUC. Results showed significant improvement in term of 5-years CSS (p=0.02) in favor of the chemotherapy group compared with the non-chemotherapy group [20].

All these previous studies were limited either by the small numbers or by selection biases from their retrospective nature with low statistical power and conflicting conclusions [15,17,22]. However, in 2020, the results from the prospective randomized POUT trial were published. POUT was a phase 3, open label, randomized controlled trial aiming to evaluate DFS benefit of 4 adjuvant cycles of platinum and gemcitabine versus surveillance in 261 UTUC patients. Adjuvant chemotherapy significantly improved DFS (hazard ratio 0·45, 95% CI 0·30–0·68; p=0·0001). This result was maintained even with additional follow-up, but when it comes to OS, no statistically significant reduction was achieved (HR = 0.72, 95% CI: 0.47-1.08; p = 0.11; adjusted HR = 0.79, 95% CI: 0.52-1.19; p = 0.26). The 3-year event-free estimates were 71% (95% CI 61–78) and 46% (36-56) for adjuvant chemotherapy and surveillance, respectively [23].

Given all this available data and based especially on POUT results, current recommendations consider the option of adjuvant chemotherapy in UTUC as a suitable therapeutic approach.

Adjuvant Immunotherapy

Since 2017, immunotherapy has changed the treatment paradigm of urothelial carcinoma. Three studies have evaluated the adjuvant role of immunotherapy in muscle-invasive bladder cancer including patients with UTUCs.

The first study, the IMvigor 010 trial, was disappointing. 809 patients, with confirmed high-risk muscle invasive urothelial carcinoma treated with radical surgery, were randomly assigned to receive either adjuvant atezolizumab or observation. The trial did not meet its primary endpoint of improved disease-free survival in the atezolizumab group over observation. In the subgroup analysis, median disease free-survival in UTUC patients was 14.2 months (95% CI 5.6-NE) for the atezolizumab group versus 28.1 months (95% CI 6.8-NE) for the observation group [HR1.25 (95% CI 0.57-2.74)] [3].

Few months later, data from CheckMate 274 presented at the 2021 ASCO meeting gave new hopes. In this trial, 709 patients with confirmed high-risk muscle invasive urothelial carcinoma treated with radical surgery, were randomly assigned to receive nivolumab or placebo. Disease-free survival was longer with adjuvant nivolumab than with placebo in the intention-to-treat population [20.8 months ;95% confidence interval [CI], 16.5 to 27.6 versus 10.8 months; 95% CI, 8.3 to 13.9] [24]. On August 19,2021, nivolumab received the FDA approval for adjuvant treatment of patients with high-risk urothelial carcinoma [25]. However, when it came to the subgroup analysis of the 149 patients with UTUC, despite the significant benefit noted in bladder cancer patients [HR 0.63 (95% CI 0.49-0.78)], no benefit was noted in this subgroup, either in renal pelvis located cancer patients [HR 1.23 (CI 95% 0.67-2.23)] nor in ureter located cancer patients [1.56 (CI 95% 0.7-3.48)] [24].

These two studies had provided conflicting results concerning the efficacy of adjuvant immune checkpoint inhibitors (ICIs) in the whole high-risk muscle invasive urothelial cancer population, despite being conducted in similar settings. This divergence could be partially explained by the difference in the control arm where it was observation in IMvigor 010 and placebo in Checkmate 274 leading to a higher dropout with atezolizumab and the sparing of cumulative censoring with nivolumab [26]. However, in both trials, the UTUC subgroups failed to benefit from adjuvant ICIs. Available studies on adjuvant therapies in UTUC are summarized in table 1.

Table 1 : Summary of available studies on adjuvant therapy in UTUC patients

Authors	Objective	Study type	Results
Yafi et al. [14]	Role of adjuvant chemotherapy in patients with UTUC treated by RNU	retrospective	OS: P = 0.8800
Necchi et al. [15]	Analyse the outcomes of adjuvant chemotherapy vs observation after RNU	Joint study	OS (HR 1.25, 95% CI 1.02–1.54)
Jazayeri et al.[21]	Comparison of adjuvant chemotherapy for UTUC versus LTUC	meta-analysis	DFS (HR 0.61, 95%CI 0.1–0.93) CSS (HR 0.70, 95%CI 0.56–0.90) OS (HR 0.87, 95%CI 0.69–1.10)
Quhal et al.[16]	Efficacy of neoadjuvant and adjuvant chemotherapy for UTUC	meta-analysis	MFS (HR 0.65, 95% CI 0.55–0.76, p<0.001) CSS (HR 0.66, 95% CI 0.57–0.77, p<0.001) OS (HR 0.80, 95% CI 0.71–0.90, p < 0.001)
Leow JJ et al.[17]	Role of neoadjuvant and adjuvant chemotherapy for UTUC patients.	meta-analysis	OS HR 0.43 (95% CI, 0.21–0.89; p = 0.023) DFS HR 0.49 (95% CI, 0.24–0.99; p = 0.048)
Luo Y et al.[18]	Outcomes of RNU combined with adjuvant chemotherapy in patients with high risk UTUC	prospective	PFS [P = 0.0033, HR = 3.78 (3.13–4.55)], OS [P = 0.0397, HR = 1.39 (1.01–1.75)] CSS [P = 0.0255, HR = 1.26 (1.07–1.45)]
Seisen et al.[19]	Effectiveness of Adjuvant Chemotherapy After RNU for Locally Advanced and/or Positive Regional Lymph Node UTUC	retrospective	OS (HR, 0.77 [95% CI, 0.68 to 0.88]; P , .001)
Birtle A et al.[23]	Adjuvant chemotherapy in UTUC (the POUT trial)	phase 3, open label, randomized controlled trial	DFS (HR = 0·45, 95% CI 0·30–0·68; p=0·0001) OS (HR = 0.72, 95% CI: 0.47-1.08; p = 0.11)
Bellmunt et al.[3]	Adjuvant atezolizumab high-risk muscle invasive urothelial carcinoma after RNU (IMvigor010)	phase 3, open label, randomized controlled trial	DFS HR = 1.25 (95% CI 0.57-2.74)
Bajorin et al.[24]	Adjuvant nivolumab high-risk muscle invasive urothelial carcinoma after RNU (CheckMate 274)	phase 3, double-blind, randomized controlled trial	For UTUC patients: DFS HR = 1.23 (CI 95% 0.67-2.23)

CI: confidence interval, CSS: cancer-specific survival, DFS: Disease Free-Survival, HR: Hazard Ratio, LTUC: Lower Tract Urothelial Carcinoma, MFS: metastasis Free Survival, OS: Overall Survival, PFS: Progression Free Survival, RNU: Radical Nephroureterectomy, UTUC: Upper Tract Urothelial Carcinoma

Presently, results from AMBASSADOR trial with Pembrolizumab are awaited. In this trial 739 patients with confirmed high-risk muscle invasive urothelial carcinoma treated with radical surgery, were randomly assigned (1:1) to receive pembrolizumab or observation [27].

Other Approaches

To time, no study has evaluated the effect of combining immunotherapy and chemotherapy in the adjuvant setting. A new study, POUT-2, in which the original 75 centers in the POUT trial and international centers will be invited to participate [28], is being developed to compare adjuvant therapy with chemotherapy alone versus chemotherapy/immunotherapy [29].

On the other hand, targeted therapy has emerged as an option in the management of urothelial carcinoma. More specifically, infigratinib (BGJ398), a selective FGFR1–3 inhibitor, has shown promising clinical activity and tolerability in patients with advanced urothelial carcinoma having *FGFR3* alterations [30]. Of note, fibroblast growth factor receptor 3 (FGFR3) genetic alterations occur in up to 70% of UTUC and up to 20% of TTUC (total tract urothelial carcinoma). PROOF 302 was conducted to evaluate the efficacy of infigratinib as adjuvant therapy in patients with high-risk invasive urothelial carcinoma (including UTUC) and FGFR3 alterations. In this trial 208 patients with confirmed high-risk muscle invasive urothelial carcinoma treated with radical surgery, were randomly assigned (1:1) to receive oral infigratinib or placebo. The results are awaited [31].

Conclusion

Adjuvant therapy remains controversial in urothelial carcinoma especially in UTUC. However, adjuvant chemotherapy has succeeded to make its way as a good option in high risk UTUC patients based on the positive results of the POUT phase III trial. But, when it comes to immunotherapy in the adjuvant setting, despite being almost beneficial in bladder cancer patients, at least with nivolumab, it has failed to do so in UTUC patients. Other approaches in the adjuvant setting, as targeted therapy or combining chemo-immunotherapy, are still under evaluation.

References

1. Rouprêt M, Babjuk M, Burger M, et al. (2021) European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020 Update. European Urology 79: 62-79.

2. Margulis V, Shariat SF, Matin SF, et al. (2009) Outcomes of radical nephroureterectomy: A series from the Upper Tract Ur othelial Carcinoma Collaboration. Cancer 115: 1224-1233.

3. J B, M H, Je G, et al. (2021) Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology 22.

4 Y F, Lm K, Tn C, Sl W, V M. (2018) Therapeutic strategies for upper tract urothelial carcinoma. Expert review of anticancer therapy 18.

5 Brown GA, Busby JE, Wood CG, et al. (2006) Nephroureterectomy for treating upper urinary tract transitional cell carcinoma: time to change the treatment paradigm? BJU International 98: 1176-1180.

6 A B, M J, J C, et al. (2020) Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet (London, England) 395: 10232.

7. Campbell MT, Shah AY, Matin SF, Siefker-Radtke AO (2017) Optimizing management of upper tract urothelial carcinoma. Urologic Oncology: Seminars and Original Investigations 35: 492-498.

8. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. (2014) Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 66: 42-54.

9. Kim HS, Jeong CW, Kwak C, Kim HH, Ku JH (2017) Adjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized clinical trials. Oncotarget 8: 81204-81214.

10. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration (2005) Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 48: 189-199.

11. Sternberg CN, Skoneczna I, Kerst JM, et al. (2015) Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. Lancet Oncol 16: 76-86.

12. Haque W, Lewis GD, Verma V, Darcourt JG, Butler EB, Teh BS (2018) The role of adjuvant chemotherapy in locally advanced bladder cancer. Acta Oncol 57: 509-515.

13. Vetterlein MW, Seisen T, May M, et al. (2018) 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. Eur Urol Focus 4: 252-259.

14. Yafi FA, Tanguay S, Rendon R, et al. (2014) Adjuvant chemotherapy for upper-tract urothelial carcinoma treated with nephroureterectomy: assessment of adequate renal function and influence on outcome. Urol Oncol 32: e17-24.

15. Necchi A, Lo Vullo S, Mariani L, et al. (2018) Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: a joint study by the European Association of Urology-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration. BJU Int 121: 252-259.

16. Quhal F, Mori K, Sari Motlagh R, et al. (2020) Efficacy of neoadjuvant and adjuvant chemotherapy for localized and locally advanced upper tract urothelial carcinoma: a systematic review and meta-analysis. Int J Clin Oncol 25: 1037-1054.

17. Leow JJ, Martin-Doyle W, Fay AP, Choueiri TK, Chang SL, Bellmunt J (2014) A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 66: 529-541.

18. Luo Y, Feng BF, Wei DC, et al (2019) [Prospective controlled observation ofeffect of adjuvant chemotherapy onsurvival and prognosis ofhigh-risk upper tract urothelial carcinoma patients underwent radical nephroureterectomy]. Zhonghua Yi Xue Za Zhi 99: 3158-3163.

19. Seisen T, Krasnow RE, Bellmunt J, et al (2017) Effectiveness of Adjuvant Chemotherapy After Radical Nephroureterectomy for Locally Advanced and/or Positive Regional Lymph Node Upper Tract Urothelial Carcinoma. J Clin Oncol 35: 852-860.

20. Ikeda M, Matsumoto K, Hirayama T, et al. (2018) Selected High-Risk Patients with Upper Tract Urothelial Carcinoma Treated with Radical Nephroureterectomy for Adjuvant Chemotherapy: A Multi-Institutional Retrospective Study. Clin Genitourin Cancer 16: e669-e675.

21. Jazayeri SB, Liu JS, Weissman B, Lester J, Samadi DB, Feuerstein MA (2019) Comparison of Adjuvant Chemotherapy for Upper Tract versus Lower Tract Urothelial Carcinoma: A Systematic Review and Meta-Analysis. Curr Urol 12: 177-187.

22. Hellenthal NJ, Shariat SF, Margulis V, et al. (2009) Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. J Urol 182: 900-906.

23. Birtle A, Johnson M, Chester J, et al. (2020) Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet 395: 1268-1277.

24. Bajorin DF, Witjes JA, Gschwend JE et al. (2021) Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine.

25. Research C for DE and FDA approves nivolumab for adjuvant treatment of urothelial carcinoma (2021) FDA.

26. AMBASSADOR Trial to Clearly Define Benefit of Immunotherapy in High-Risk Muscle-Invasive Urothelial Cancer.

27. Alliance A031501: Phase III randomized adjuvant study of MK-3475 (pembrolizumab) in muscle-invasive and locally advanced urothelial carcinoma (MIBC) (AMBASSADOR) versus observation. | Journal of Clinical Oncology.

28. Leow JJ, Chong YL, Chang SL, Valderrama BP, Powles T, Bellmunt J (2021) Neoadjuvant and Adjuvant Chemotherapy for Upper Tract Urothelial Carcinoma: A 2020 Systematic Review and Meta-analysis, and Future Perspectives on Systemic Therapy. Eur Urol 79: 635-654.

29. ESOU 2019: Final Results of the POUT Trial.

30. Pal SK, Rosenberg JE, Hoffman-Censits JH, et al. (2018) Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with FGFR3 Alterations. Cancer Discov 8: 812-821.

31. Pal SK, Daneshmand S, Matin SF, et al. (2020) PROOF 302: A randomized, double-blind, placebo-controlled, phase III trial of infigratinib as adjuvant therapy in patients with invasive urothelial carcinoma harboring FGFR3 alterations. JCO 38(6_suppl), TPS600–TPS600.

32. Cutress ML, Stewart GD, Zakikhani P, Phipps S, Thomas BG, et al. (2012) Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. BJU Int 110: 614-628.

33. Grasso M, Fishman AI, Cohen J, Alexander B (2012) Ureteroscopic and extirpative treatment of upper urinary tract urothelial carcinoma: a 15-year comprehensive review of 160 consecutive patients. BJU Int 110: 1618-1626.

34. Hasan MN, Rouprêt M, Keeley F, Cracco C, Jones R, et al. (2019) Consultation on UTUC, Stockholm 2018 aspects of risk stratification: long-term results and follow-up. World J Urol 37: 2289-2296.