Adjuvant chemotherapy in upper tract urothelial carcinoma: results of the POUT phase III randomised controlled trial

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Summary

Background

Urothelial carcinomas of the upper urinary tract (UTUC) are rare, with poorer stage-for-stage prognosis than urothelial carcinoma of the urinary bladder. No international consensus exists on the benefit of adjuvant chemotherapy for UTUC patients following nephro-ureterectomy with curative intent; the POUT trial (NCT01993979) aimed to assess the efficacy of systemic platinum-based chemotherapy

Methods

This phase III randomised controlled open-label trial recruited UTUC patients following nephro-ureterectomy staged as pT2-pT4 pN0-3 M0, or pTany N1-3 M0 at 71 UK hospitals. Participants were centrally assigned (1:1) to surveillance or to four 21-day cycles of intravenous chemotherapy using a minimisation algorithm with a random element. Chemotherapy was either cisplatin (70mg/m^2) or carboplatin (AUC4.5/AUC5, for reduced GFR (<50mL/min) only) given on day 1 and gemcitabine (1000mg/m^2) on days 1 and 8 initiated within 90 days of surgery. Follow-up included standard cystoscopic, radiological and clinical assessments. The primary endpoint was disease-free survival analysed by intention to treat with a Peto-Haybittle stopping rule for (in)efficacy.

Findings

A pre-planned interim analysis met the efficacy criterion for early closure, after recruitment of 261 participants (132 chemotherapy, 129 surveillance). Participants were enrolled between 19/06/2012 and 08/11/2017 from 56/71 opened sites. One participant withdrew consent for data usage and is excluded from analyses. Chemotherapy significantly improved disease-free survival (hazard ratio 0·45; 95% CI: 0·30-0·68; p=0.00017) at a median follow up of 30·3 months (IQR: 18·0-47·5). Three-year event-free estimates were 71% (95% CI: 61-78) and 46% (95% CI: 36-56) for chemotherapy and surveillance respectively. Acute grade≥3 emergent adverse events were experienced by 44% (55/126) participants who started chemotherapy and 4% (5/129) managed by surveillance. There were no treatment related deaths.

Interpretation

Adjuvant platinum-based chemotherapy should be considered a new standard of care following nephro-ureterectomy for patients with locally advanced UTUC.

Funding

POUT was funded by Cancer Research UK (CRUK/11/027).

Research in Context

Evidence before this study

Prior to this study, there was little previous research evaluating the efficacy of systemic chemotherapy for locally advanced upper tract urothelial carcinoma (UTUC), partly due to the rarity of the disease. Undersized or retrospective studies had not demonstrated a survival benefit for chemotherapy convincingly. International guidelines therefore recommended nephro-ureterectomy followed by surveillance as the standard-of-care.

The majority of urothelial carcinomas in both UTUC and bladder cancer originate in the transitional epithelium (transitional cell carcinoma). It is logical therefore to consider data from trials of systemic bladder cancer therapy for signals to indicate whether chemotherapy may be efficacious in UTUC. Studies of peri-operative chemotherapy for primary UC of the bladder suggested localised UC was chemosensitive, with, on meta-analysis, cisplatin-based neoadjuvant chemotherapy demonstrating an absolute improvement of 5% in overall survival at 5 years (hazard ratio=0·86 95% CI: 0·77-0·95, p=<0.003). A comparable trial in UTUC was therefore justified, especially in view of the inferior stage-for-stage outcomes in UTUC when compared to bladder UC.

Challenges of obtaining definitive histology and accurate staging for UTUC prior to nephro-ureterectomy risk either under- or over-treatment with neoadjuvant therapy. The POUT trial was therefore designed as a phase III randomised trial of adjuvant platinum-based chemotherapy, intended to provide, for the first time, robust evidence regarding its efficacy in UTUC.

Added value of this study

To our knowledge this is the largest randomised controlled clinical trial conducted exclusively in upper tract urothelial carcinoma world-wide.

Implications of all available evidence

We have demonstrated that giving adjuvant platinum-based chemotherapy within 90 days following nephro-ureterectomy reduces subsequent rates of disease recurrence.

Our data therefore suggest that adjuvant platinum-based chemotherapy should be recommended as a new standard of care following nephro-ureterectomy for all patients with locally advanced upper tract urothelial carcinoma in whom there are no definitive contra-indications to chemotherapy.

Introduction

Upper tract urothelial carcinoma (UTUC; transitional cell carcinoma of the ureter or renal pelvis) is rare, occurring in around 2 per 100,000 people in the western world. A lack of symptoms and delayed diagnosis mean that tumours are often muscle-invasive or locally advanced at presentation (56%), resulting in worse survival figures than for urothelial carcinoma of the urinary bladder. More than 50% of patients diagnosed with UTUC die as a result of their disease, despite systemic platinum-based chemotherapy following local or metastatic recurrence.[1] Improved management of early stage disease therefore has the potential to save lives. At the inception of this study, there was no proven role for systemic treatment for locally-advanced UTUC. Nephro-ureterectomy followed by surveillance has remained the routine treatment for localised UTUC.[1]

UTUC shares several clinico-pathological features with muscle invasive urothelial (transitional cell) carcinoma of the bladder. Robust survival improvements are seen with platinum-based chemotherapy in urothelial bladder cancer, in both the neoadjuvant and metastatic settings.[2-4] Similar benefits of platinum-based palliative chemotherapy have been seen for UTUC and urothelial bladder cancer in the advanced stages.[5] There is thus a clear rationale for investigating peri-operative, platinum-based chemotherapy in UTUC patients.

Due to the strength of evidence demonstrating survival gain, neoadjuvant chemotherapy is the accepted standard of care for muscle-invasive bladder cancer. Although a neoadjuvant approach is attractive for patients with UTUC, particularly when the loss of renal function associated with nephrectomy is considered, the unreliability of pre-operative UTUC staging and histopathology would likely result in over-treatment for some patients and under-treatment for others.[6] Previous studies of adjuvant chemotherapy in UTUC are largely retrospective, with limited statistical power and conflicting conclusions,[7-9] providing insufficient evidence to recommend peri-operative chemotherapy. Thus, for many patients with muscle invasive UTUC, surgery alone is considered the standard approach.

Patient reported outcome data for this rare patient group is also lacking, with the majority available in the literature at the outset of this trial focusing on short term outcomes following nephro-ureterectomy, and none collected within the context of randomised controlled trials.

POUT aimed to prospectively assess the impact of adjuvant platinum-based chemotherapy on survival, safety, and quality of life in locally advanced UTUC.

Methods

Study design

POUT was a phase III randomised controlled parallel group open-label trial (ISRCTN98387754, NCT01993979, CRUK/11/027), investigating the impact of adjuvant, platinum-based chemotherapy on disease free survival, overall survival, safety, and quality of life following radical nephro-ureterectomy for locally advanced UTUC. An intervention was included to understand and then support recruitment to the trial[10]. The trial was conducted in 71 National Health Service hospitals in the United Kingdom.

Regulatory approvals were obtained prior to trial activation from the Medicines and Healthcare Products Regulatory Authority and the North West – Greater Manchester South Research Ethics Committee (11/NW/0782). POUT was sponsored by The Institute of Cancer Research and conducted according to the principles of Good Clinical Practice. The Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU) coordinated the trial, carried out central statistical data monitoring, and conducted all analyses. The trial management group was overseen by independent data monitoring and trial steering committees. The full study protocol is available as part of the supplementary materials.

Participants

Eligible patients were aged at least 16 years, had received en-bloc radical nephro-ureterectomy for UTUC (including resection of all radiologically/macroscopically abnormal nodes) and were: (i) post-operatively staged as muscle-invasive (pT2-pT4, Nany) and/or lymph node-positive (pTany, N1-3)

disease; (ii) metastasis free (M0); (iii) had predominantly transitional cell carcinoma histology (iv) fit to receive adjuvant chemotherapy within 90 days following surgery.

Formal extended lymph node dissection was not mandated. Participants with lymph node involvement identified on pre-operative imaging or during surgery had all grossly abnormal nodes resected. Post-operative imaging was mandated for these patients prior to randomisation; those with residual lymphadenopathy as determined by the local investigator were excluded. Participants had satisfactory haematological and biochemical blood profiles, and a glomerular filtration rate (GFR) ≥30 mL/min.

Participants were recruited by their clinical care teams and provided written informed consent prior to enrollment.

Randomisation and masking

Treatment allocation was conducted centrally by ICR-CTSU, using a minimisation algorithm incorporating a random element. Balancing factors were planned platinum agent (cisplatin vs. carboplatin), pre-operative radiologically and/or pathologically assessed nodal involvement (N0 vs. N1 vs. N2 vs. N3), status of microscopic surgical margins (positive vs. negative), and treating centre. Participants were randomised 1:1 to either surveillance or chemotherapy. Treatment allocation was not blinded.

Procedures

Participants allocated to chemotherapy received four 21-day cycles of platinum-based combination chemotherapy, to commence within 14 days following randomisation. Gemcitabine 1000mg/m^2 was given on days 1 and 8 of each cycle. Either cisplatin 70mg/m^2 or carboplatin (AUC 4.5 or AUC5, according to local practice, pre-specified for each treatment centre) was given on day 1. Impaired renal function (GFR ≥30 and <50 mL/min) was the only permitted reason to give carboplatin rather than cisplatin. The protocol recommended calculation of GFR by the Cockcroft and Gault method, however use of the Wright formula or estimation by radioisotope clearance were also permitted. Participating sites prespecified their intended assessment method prior to

activation and were requested to use the same GFR assessment method for a participant throughout the study. Patients otherwise unsuitable to receive cisplatin were not permitted to join the trial to minimise the potential confounding effects of frailty and co-morbidity.

Use of generic agents was permitted, no recommended manufacturer was specified. Hydration and infusion rates were in accordance with local practice. Protocol-specified recommendations were for chemotherapy to commence within 90 days of nephro-ureterectomy, for gemcitabine to be given as a 30-minute intravenous infusion in 500ml sodium chloride, cisplatin as a 4-hour intravenous infusion in 1L sodium chloride, and carboplatin as a 1-hour intravenous infusion.

All participants receiving chemotherapy had assessment of haematology and serum biochemistry, estimation of GFR and calculation of body surface area prior to each cycle of chemotherapy.

Adverse events during each chemotherapy cycle were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Participants allocated to the surveillance group underwent adverse event assessment every three weeks following randomisation to mirror the assessment schedule of participants allocated to receive chemotherapy. Protocol-specified dose modifications were permitted for CTCAE grade ≥3 toxicity. Patients intended to receive cisplatin were to switch to carboplatin if the estimated GFR fell to between 30 – 49ml/min. If the GFR fell from ≥70 ml/min to 50 – 69 ml/min then it was permitted for the cisplatin dose to be split across two consecutive days.

Participants in both groups were followed up at 3, 6, 9, and 12 months, then six-monthly to 36 months from randomisation regardless of whether or not chemotherapy was complete, and annually thereafter. Assessment of disease recurrence included either plain film X-ray or cross-sectional imaging (computerised tomography, CT) of the thorax plus CT of abdomen and pelvis at 3, 6, 9*, 12, 18, 24, 30*, and 36 months then annually to 60 months (*imaging of the thorax only at these timepoints). Cystoscopy was performed 6-monthly to 24 months, then annually to 60 months to detect recurrence in the lower urinary tract. Follow up assessments were conducted in accordance with the standard practice in the UK at time.

Assessment of adverse events was conducted at each follow-up visit to 24 months. Participants in the optional patient reported quality of life sub-study were asked to complete the EORTC QLQ-C30 and EQ-5D-5L questionnaires on paper at baseline, pre-cycle 3/week 7 and 3 months, then 6, 12, and 24 months post randomisation.

Participants in both groups who experienced disease recurrence were permitted to receive any appropriate further treatment as clinically indicated, including platinum-gemcitabine chemotherapy.

Outcomes

The primary endpoint was disease-free survival according to local assessment. This was defined as time from randomisation to the first of: recurrence in the tumour bed; metastasis; or death from any cause. Recurrence and/or metastasis could be determined either radiologically or pathologically. Patients were censored at date of diagnosis of second primary cancer (including muscle invasive bladder cancer and contralateral UTUC). New non-muscle invasive bladder cancer was not regarded as an event or a reason to censor although such events were recorded for future analysis.

Secondary endpoints included metastasis-free and overall survival, treatment compliance, acute and late toxicity, patient reported quality of life.

Statistical analysis

The trial was designed to detect a hazard ratio of 0·65 in favour of chemotherapy, equivalent to a 15% absolute improvement in 3-year disease-free survival (from 40% to 55%; chosen to correspond with the magnitude of benefit observed for chemotherapy in muscle invasive bladder cancer), with a 2-sided significance of 5% and 80% power. On this basis, target recruitment was 345 participants (172 events), including a 2% inflation for loss to follow-up.

Time-to-event endpoints were analysed according to the intention to treat principle using the logrank test and are presented using Kaplan-Meier plots. Estimates of treatment effect (with 95% confidence intervals [CI]) were made using unadjusted and adjusted Cox regression models, with a hazard ratio (HR) <1 favouring chemotherapy. Adjusted models included planned chemotherapy

type, nodal status and microscopic margin status (balancing factors) and pathological stage. Pre-specified subgroup analysis was conducted for the adjustment factors. The proportional hazards assumption of the Cox model held when tested with Schoenfeld residuals. Two-sided p values <0·05 were considered statistically significant.

Incidence of acute treatment-emergent adverse events, defined for both groups as an increase in grade of any adverse event from baseline up to the 3-month time point, was compared by treatment received using Wilcoxon rank-sum (worst grade) and chi-squared (proportion grade ≥3) tests.

Adverse events reported by more than 10% of participants in either group, or with significant differences between groups using the Wilcoxon rank-sum test with a 1% significance level (to make some adjustment for multiple testing) were considered meaningful. Toxicity and treatment compliance data are reported by treatment received at cycle one. Treatment compliance was assessed in the safety population, which includes all participants allocated to receive chemotherapy who had at least one dose of gemcitabine, cisplatin or carboplatin. Comparisons of the frequency of each adverse event type excluded participants who were not assessed for that adverse event type in the first 3 months of treatment (or equivalent time points for the surveillance group).

The global health score of the EORTC QLQ-C30 reported up to 12 months was summarised according to randomised allocation on an intention to treat basis. Data were analysed in accordance with the QLQ-C30 scoring manual. Change from baseline was compared between randomised groups using analysis of covariance model, adjusting for baseline score. Allowance for multiple testing was made by assessing at 3 and 12 months only, with p-values <0·01 considered statistically significant; consequently 99% confidence intervals were used.

Accumulating safety and efficacy data were reviewed in confidence annually throughout the trial by an independent data monitoring committee. A Peto-Haybittle stopping rule (p<0·001) addressed both efficacy and inefficacy in disease-free survival.

Analyses are based on a snapshot of data taken on 7th November 2018 and include data from all follow-up visits up to and including 31st May 2018. This snapshot supersedes that used for the interim analysis which led to the decision to close the trial early, in order that complete treatment and three month toxicity data could be reported. Analyses were conducted using STATA version 15·1 (StataCorp LP; 2015).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Seventy-one UK hospitals opened the study. Between 19th June 2012 and 8th November 2017, 261 participants (132 chemotherapy, 129 surveillance) were recruited from 56 of the 71 sites (supplementary table 1).

Recruitment closed early on the recommendation of the independent data monitoring committee, having met the early stopping criterion for efficacy. At the point of trial closure, the independent data monitoring committee recommended that all participants who were still within the 90 day window from nephro-ureterectomy should be offered chemotherapy. The two participants randomised to surveillance and still within this timeframe crossed over to receive chemotherapy but were included in the surveillance group for ITT analysis. Figure 1 shows the participant flow through the trial. Two-hundred and sixty participants were included in the intention to treat population; one participant withdrew consent for data usage following randomisation and is not included in any analyses.

Median age was 68·5 years (interquartile range (IQR): 62.0-74.1), 245/260 participants (94%) were staged pT2/pT3 and of these 223/245 (91%) were also staged N0, 166/260 (64%) had GFR ≥ 50mL/min (Table 1, supplementary table 2). Median follow-up was 30·3 months (IQR: 18·0-47·5).

Ninety-five of 126 participants (75%) who started chemotherapy received all four planned cycles (52 gemcitabine-cisplatin; 43 gemcitabine-carboplatin). Thirty-one participants discontinued chemotherapy early (clinician decision (n=11), toxicity (n=10), patient choice (n=8) or other, unspecified (n=2)). There was no evidence of a difference in the proportion of patients who completed four cycles of chemotherapy by planned platinum agent (gemcitabine-cisplatin: 70% [57/81]; gemcitabine-carboplatin: 73% [38/52], chi-squared p=0.74). Forty-one of 71 (58%) patients who started cisplatin completed four cycles of cisplatin. 198/218 (91%) cycles of gemcitabine-cisplatin and 186/223 (83%) cycles of gemcitabine-carboplatin were delivered without a dose reduction (Figure 1). Sixteen of 76 (21%) participants intended for cisplatin switched to carboplatin due to post-randomisation drop in GFR. Six participants switched prior to start of treatment and a further ten patients changed chemotherapy regimen from gemcitabine-cisplatin to gemcitabine-carboplatin at cycle 2 or later; of these, six were due to a reduction in GFR, as per protocol, two were due to suspected renal impairment and two were due to grade 3 toxicity (joint pain, tinnitus). One of 50 participants planned to receive carboplatin switched to cisplatin due to a post-randomisation increase in GFR prior to treatment initiation.

Fewer disease related events contributing to the primary endpoint were reported in participants randomised to chemotherapy (35/131, 27%) than in participants randomised to surveillance (60/129, 47%). Chemotherapy conferred a 55% reduction in relative risk of disease recurrence or death (HR 0·45; 95% CI: 0·30-0·68, log-rank p=0·00011; Figure 2A). Three-year disease-free survival estimates were 71% (95% CI: 61%-78%) in the chemotherapy group and 46% (95% CI: 36%-56%) in the surveillance group, with an estimated absolute difference of 25% (95% CI: 11%-38%). Median disease-free survival in the surveillance group was 29.8 months (IQR: 6.3-not reached; 95% CI: 13.6-incalculable), and not reached in the chemotherapy group. The benefit of chemotherapy was largely unchanged after adjustment for known prognostic factors (HR 0·46; 95% CI: 0·30 – 0·71, p=0·00036; supplementary table 3). Sensitivity analyses including second primary muscle invasive bladder cancers as recurrence events gave similar results (supplementary table 4). There was no evidence of heterogeneity of disease-free survival treatment effect by pre-specified balancing factors or tumour stage (Figure 3).

Participants randomised to chemotherapy also had a lower risk of metastasis (hazard ratio 0·48; 95% CI: 0·31-0·74, log-rank p=0·00072; Figure 2B). Three-year event free rates were 71% (95% CI: 60% - 79%) in the chemotherapy group and 53% (95% CI: 42% - 63%) in the surveillance group, with an estimated absolute difference of 17% (95% CI: 4%-31%). Results were similar in multivariable analyses (supplementary table 3).

Analysis of overall survival is planned once 88 deaths have occurred or all participants have at least 2 years of follow-up (whichever occurs first). There have been 62 deaths to date (24 chemotherapy; 38 surveillance). Of these, 49 were attributed to UTUC, four to bladder cancer, one to other malignancy, and eight to other causes. There were no treatment related deaths.

Grade ≥3 acute treatment emergent adverse events were reported for 44% (55/126) participants; 31/71 (44%) who started gemcitabine-cisplatin and 24/55 (44%) who started gemcitabine-carboplatin, compared to 4% (5/129) managed by surveillance (p<0·0001). For each chemotherapy regimen, adverse events were consistent with those commonly seen in routine clinical practice (supplementary table 5). Patients who received chemotherapy were more likely than those on surveillance to experience grade ≥3 neutrophil (45/126 [36%]) and platelet count decreases (13/126 [10%]), nausea (8/126 [6%]), febrile neutropaenia (8/126 [6%]), and vomiting (7/126 [6%]). Fifty-four serious adverse events were reported for 42/131 participants allocated chemotherapy; 39 of these events were related to treatment. Analysis of late toxicity is planned once two-year data are available for all participants.

Two-hundred and fifty-six of 261 (98%) participants consented to the patient reported quality of life study, including one participant who withdrew consent to use data following randomisation. There was no difference in return rates by randomised group at any timepoint. Questionnaires were returned by 243/255 (95%) participants at baseline (119/125 [95%] surveillance and 124/130 [95%] chemotherapy), 208/255 (82%) at 3 months (101/125 [81%] surveillance and 107/130 [82%] chemotherapy) and 166/237 (70%) at 12 months (78/112 [70%] surveillance and 88/125 [70%] chemotherapy). Mean overall global health status score at baseline was 77% (standard deviation 19%) for the chemotherapy group and 76% (standard deviation 19%) for the surveillance group.

Overall global health status was lower during chemotherapy (pre-cycle 3) and immediately afterwards (3 months) in participants randomised to chemotherapy versus surveillance. This difference had resolved by six months (Figure 4). Full quality of life data analysis is planned once two-year data are available for all participants.

Discussion

To our knowledge, this is the largest trial ever reported in this patient population. We have demonstrated that gemcitabine-platinum combination chemotherapy initiated within 90 days following nephro-ureterectomy significantly improves disease-free survival in locally advanced UTUC. Chemotherapy was also associated with improved metastasis-free survival, with acceptable acute toxicities consistent with existing data,[11] and with no more than transient impact on patient-reported quality of life.

The relative impact on survival of carboplatin and cisplatin remains unclear in urothelial carcinoma in the absence of sufficient data from clinical trials incorporating a direct, randomised comparison between the two agents. A meta-analysis of outcomes of patients with advanced urothelial carcinoma treated with platinum-based chemotherapy showed superior tumour response rates in trials of cisplatin compared to those of carboplatin.[12] In POUT, a GFR of >50 mL/min was deliberately selected as the criterion for cisplatin delivery. The appropriate selection of the cisplatin eligible population was a critical consideration during development of the POUT trial, with input sought from potential investigators. Whilst we acknowledge that a GFR of <60 mL/min forms part of the Galsky definition of “cisplatin unfit”, the routine practice in UK treatment of patients with non-UTUC tumours is to use a cut point of GFR>50 mL/min. Given UK oncologists’ experience and familiarity with use of cisplatin in non-UTUC patients and our wish not to exclude patients in the rare UTUC setting for whom cisplatin may be a feasible treatment, it was considered appropriate to set the criterion for switching to carboplatin at a GFR of < 50mL/min.

Acknowledging limited power for formal statistical testing, our analysis found no apparent heterogeneity of treatment effect and results were consistent across pre-specified subgroups, including planned platinum agent. POUT trial data therefore support the use of adjuvant platinum-

based chemotherapy in all patients who have undergone nephro-ureterectomy with curative intent. Whilst cisplatin should be the preferred agent where possible, our results suggest those for whom cisplatin is contraindicated due to poor renal function may still derive benefit from the alternative gemcitabine-carboplatin regimen. Those with resected nodal disease and those with microscopically positive margins at surgery should also be offered adjuvant platinum-based chemotherapy, subject to their fitness for systemic treatment.

The limitations of our study largely relate to pragmatic decisions taken during study development to enable successful recruitment to this trial in a rare patient population whilst preserving our ability to address the primary endpoint.

At time of study development, a feasibility survey across all UK sites confirmed that a formal nodal dissection was not part of standard care, nor were there strong supportive data, therefore it was deemed inappropriate to mandate this in the protocol. On-going debate around the survival benefits of extended abdominal lymph node dissection (ELND) in UTUC[13] meant that this procedure was only required for patients with observable lymphadenopathy on baseline imaging. As the majority of participants had limited lymph node dissection it is possible that occult metastases were overlooked in some patients categorised as N0, as a proportion were likely to have been microscopically node positive. As there was a clear benefit from adjuvant chemotherapy in the N0 group of patients, it is uncertain whether standard use of nodal dissection would offer additional benefit. The role of ELND in N0 disease therefore remains a subject for future studies.

We acknowledge that disease free survival (DFS) is not considered a fully validated surrogate of overall survival following nephro-ureterectomy for UTUC.[13] However, in a rare disease such as this, a suitably powered trial with overall survival as the primary endpoint was not considered feasible. It was not deemed appropriate to use a placebo control arm; the use of identical follow-up procedures in both arms of the trial aimed to minimize the risk of assessment bias. Whilst mature survival data, as a secondary endpoint, are not yet available, the large improvement in DFS we observed for the primary endpoint, together with the improved metastasis free survival observed as a secondary endpoint, strongly suggest that patients have better outcomes with chemotherapy

than without. Given the rarity of UTUC and the urgent need to improve outcomes we believe that there is now sufficient evidence to advocate use of gemcitabine-platinum combination chemotherapy as a standard of care.

It remains contentious whether peri-operative systemic therapy would be most effective for UTUC in the neoadjuvant or adjuvant setting. Meaningful pathological complete response rates[14] and, in retrospective case series, survival benefits,[15] suggest similar potential advantages with neoadjuvant therapy in UTUC to those seen in bladder cancer. Furthermore, potentially nephrotoxic, cisplatin-based chemotherapy may be safer and more feasible for UTUC if given prior to nephro-ureterectomy, when patients retain maximal renal function. It is likely that some patients were excluded from POUT (and may be similarly excluded from adjuvant chemotherapy in real life practice) due to insufficient recovery after surgery. These patients may be better served with neoadjuvant chemotherapy, albeit with the risk that chemotherapy toxicity may prevent some from proceeding with curative surgery. As noted above, we had considered a trial of neoadjuvant chemotherapy when developing the POUT concept; however there were, and remain, concerns regarding the reliability of pre-operative staging and histology in muscle-invasive UTUC.[6] Prior to POUT opening, a feasibility survey was conducted across all potential UK investigators which strongly supported an adjuvant rather than a neoadjuvant study for the reasons we have outlined. Two patient focus groups conducted during study development explored the different approaches and their feedback favoured an adjuvant trial. An exploration of the relative feasibility of adjuvant and neoadjuvant cytotoxic chemotherapy in UTUC is under way (NCT02969083). Whilst POUT has demonstrated superiority of adjuvant chemotherapy over surgery alone, it is not clear that patients previously planned for neoadjuvant chemotherapy should now defer treatment until surgery is complete. However until further robust evidence becomes available, we propose that adjuvant treatment should be considered the preferred setting for future trials of peri-operative chemotherapy in UTUC.

Previous studies adding a third agent to gemcitabine-platinum combinations have met with limited success in advanced disease,[16-18] partly due to the high burden of toxicity. However, more recent data suggest potential benefits from two new classes of agents – fibroblast growth factor receptor

inhibitors (FGFR) and immune checkpoint therapeutics. Increased understanding of the biology of UTUC suggests that there are distinct molecular differences between UTUC and bladder urothelial carcinomas.[19] Higher proportions of FGFR alterations and luminal-like urothelial cancer signatures have been observed in UTUC[20] than in bladder cancer.[21] As the former molecular type is associated with high response rates to FGFR inhibitors and the latter with lower response rates to chemotherapy in advanced urothelial cancers, there may be particular value in exploring the orally-bioavailable FGFR inhibitors such as erdafitinib alone or in combination with gemcitabine-platinum regimens in molecularly-selected patient cohorts.[22-25] Efficacy of checkpoint inhibitors such as pembrolizumab and atezolizumab in advanced urothelial carcinoma[26-28] has prompted trials of immunotherapy into the peri-operative setting as monotherapy, and in combination with cytotoxic chemotherapy for UC bladder (e.g. NCT02365766; NCT03661320). Although the adjuvant trials have included pre-planned cohorts of patients with UTUC, there are no current phase III trials addressing the role of immunotherapy in the adjuvant treatment of UTUC alone. Both FGFR inhibitors and immune checkpoint inhibitors might therefore be suitable additions to chemotherapy in future phase III trials which specifically address optimisation of peri-operative therapy in UTUC.

We conclude that adjuvant platinum-based chemotherapy should be adopted as a new standard of care for patients with locally-advanced UTUC for whom systemic chemotherapy is not contraindicated. It should be routinely considered for all patients in this group and future studies should focus on combinations with novel agents in the adjuvant setting, which may further improve the prognosis for locally advanced UTUC.

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Contributors

AB is the POUT trial Chief Investigator and EH is the methodological lead. Both led study design and acquired funding for the trial.

AB, MJ, JC, RJ, RB, CH, AW, JWFC, JLD, AF, FXK, RK, TP, CW, RL and EH are members of the POUT Trial Management Group which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation and manuscript preparation.

PC, PAE, SJ and JW were involved in recruitment and treatment of participants and contributed to data collection and manuscript preparation.

EH oversaw statistical analyses and was responsible for central management of the trial at ICR-CTSU, with RL's support.

RT conducted central study management at ICR-CTSU and contributed to data acquisition, interpretation and manuscript writing.

DD and BJ conducted statistical analyses at ICR-CTSU and contributed to data interpretation and manuscript writing.

All authors reviewed and approved the manuscript.

Declaration of interests

J. Chester reports personal fees and non-financial support from MSD, UK (Pembrolizumab), outside the submitted work. R Jones reports non-financial support from NHS Greater Glasgow and Clyde Health Board, grants from Chief scientist office, Scotland during the conduct of the study; grants and personal fees from Roche, personal fees and non-financial support from MSD, personal fees from Merck Serono, personal fees and non-financial support from BMS, grants and personal fees from AstraZeneca, personal fees and non-financial support from Janssen, grants and personal fees from Astellas, personal fees and non-financial support from Ipsen, grants and personal fees from Exilixis, grants and personal fees from Clovis, grants, personal fees and non-financial support from Bayer outside the submitted work. D Dolling reports grants from Cancer Research UK, grants from Prostate Cancer UK during the conduct of the study. R Bryan reports a patent issued (RT Bryan & DG Ward, Bladder cancer prognosis, WO/2016/083832) and has previously contributed to advisory boards for Olympus Medical Systems and Janssen. J Catto reports personal fees from Astra Zeneca, personal fees from Janssen, personal fees from Roche, personal fees from Ferring, personal fees from MSD, personal fees from Bristol-Myers Squibb during the conduct of the study. J Donovan reports grants from Cancer Research UK during the conduct of the study. S Jagdev reports personal fees from Janssen, grants from Ipsen, grants from Astellas, personal fees from Novartis outside the submitted work. T Powles reports other from

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Data sharing statement

Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to others upon request. The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements.

Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required. Restrictions

relating to patient confidentiality and consent will be limited by aggregating and anonymizing identifiable patient data. Additionally, all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

Tables and Figures

Figure 1 – Trial profile

Table 1 – Participant and tumour characteristics at trial entry

Figure 2 – Kaplan Meier estimates of disease-free and metastasis-free survival

Figure 3 – Subgroup analysis of disease-free survival

Figure 4 - Patient reported quality of life – global health status EORTC QLQ-C30

Supplementary material (web appendix):

Protocol

Supplementary table 1 – POUT centres and recruitment

Supplementary table 2 – Combined pathological tumour stage and nodal stage by treatment arm

Supplementary table 3 – Multivariable Cox models for disease-free survival and metastasis-free survival

Supplementary table 4 – Sensitivity analyses of multivariable Cox models for disease-free survival and metastasis-free survival

Supplementary table 5 – Acute treatment emergent toxicity

621 **Table 1: Participant and tumour characteristics at trial entry**

		Surveillance N=129		Chemotherapy N=131		Total N=260	
		N	%	N	%	N	%
Sex	Male	83	64	93	71	176	68
	Female	46	36	38	29	84	32
Age group (years)	<50	5	4	5	4	10	4
	50-59	24	19	19	15	43	17
	60-69	52	40	50	38	102	39
	70-79	40	31	51	39	91	35
	80+	8	6	6	5	14	5
	Median (inter-quartile range)	66·5	(61·5, 73·3)	69·2	(57·8, 75·0)	68·5	(62·0, 74·1)
WHO performance status	0	85	66	90	69	175	67
	1	43	33	40	31	83	32
	Missing	1	1	1	1	2	1
Smoking status	Current	14	11	13	10	27	10
	Previous	67	52	70	53	137	53
	Never	47	36	48	37	95	37
	Missing	1	1	0	0	1	0
Concomitant medication	No	27	21	25	19	52	20
	Missing	0	0	1	1	1	0
	Yes	102	79	105	80	207	80
	Antihypertensives	*51*	40	*60*	46	*111*	43
	Analgesics	*30*	23	*21*	16	*51*	20
	Antidiabetic	*11*	9	*15*	11	*26*	10
	Anticoagulants	*19*	15	*9*	7	*28*	11
	Antianginals	*7*	5	*7*	5	*14*	5
	Other	*80*	62	*77*	59	*157*	60
Pathological T stage	pT2	30	23	44	34	74	28
	pT3	88	68	83	63	171	66
	pT4	11	9	4	3	15	6
Nodal stage**	N0	118	91	118	90	236	91
	N1	7	5	8	6	15	6
	N2	4	3	4	3	8	3
	N3	0	0	1	1	1	0
GFR (ml/min)	30-49	45	35	49	37	94	36
	≥50	84	65	82	63	166	64
Site of tumour	Renal pelvis	44	34	47	36	91	35
	Ureter	42	33	47	36	89	34

	Both	40	31	37	28	77	30
	Missing	3	2	0	0	3	1
Type of surgery	Open	17	13	21	16	38	15
	Laparoscopic	104	81	109	83	213	82
	Robotic	4	3	1	1	5	2
	Other*	1	1	0	0	1	0
	Missing	3	2	0	0	3	1
Microscopic margin status	Positive	14	11	17	13	31	12
	Negative	115	89	114	87	229	88
Number of lymph nodes dissected	0	92	71	86	66	178	68
	1-3	21	16	25	19	46	18
	4-9	6	5	6	5	12	5
	≥10	6	5	3	2	9	3
	Missing	4	3	11	8	15	6

622 *Kidney and ureter freed laparoscopically and removed through open incision at iliac fossa·

623 ** Nodal stage was determined radiologically where pathological staging was not available.