Results of POUT - A phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

Abstract: MP18-03

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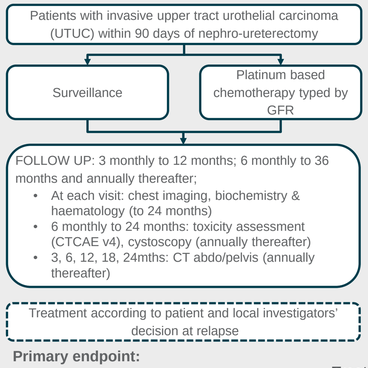
Background

- Upper Tract Urothelial Carcinoma (UTUC) is rare with around 1400 new UK diagnoses per year and 240 deaths[1]
  - Local and metastatic recurrence rate is approx. 50%[2]
  - 60% of UTUC is invasive at diagnosis[3]
  - Standard treatment: nephro-ureterectomy followed by surveillance
- Insufficient evidence to recommend adjuvant systemic chemotherapy for invasive UTUC[4] and no international consensus on systemic treatment
- Previous studies of systemic chemotherapy in locally advanced UTUC were limited, mostly retrospective reviews with small sample sizes[5]
- UTUC shares similar aetiology with muscle invasive bladder cancer (MIBC)
- MIBC is chemosensitive, trials of neoadjuvant and adjuvant chemotherapy have shown benefit in Disease Free Survival (DFS)[6] and Progression Free Survival (PFS)[7]
- Literature on Quality of Life (QoL) in UTUC is limited with no data related to mode of therapy[8]
- POUT aims to determine if adjuvant chemotherapy improves DFS for patients with confirmed invasive or node positive UTUC

Methods: Trial design

Trial schema



- Participants were randomised into POUT between May 2012 and Nov 2017 by 57 UK centres
- Eligible patients had histologically confirmed TCC pT2-pT4 pN0-3 M0 or pTany N1-3 M0, WHO PS 0-1, and were fit to receive chemotherapy
- Concurrent MIBC was excluded, however, concurrent Non Muscle Invasive Bladder Cancer (NMIBC) was acceptable
- QoL was assessed using EORTC QLQ-C30 and EQ5D questionnaires at baseline, pre-cycle 3/week 7 and 3, 6, 12 and 24 months

Primary endpoint:

- Disease free survival (DFS)

Secondary endpoints:

- Metastasis free survival (MFS); Acute and late toxicity (CTCAE v4); Treatment compliance; Feasibility of recruitment; Overall survival; Incidence of contralateral primary tumours; Incidence of bladder and second primary tumours; QoL

Quality of Life sub-study primary endpoint:

- EORTC QLQ-C30 Global health status / quality of life subscale

Treatment regimen:

Four 21 day cycles:

- **Gemcitabine** 1000mg/m^2 day 1 & 8
  With
- **Cisplatin** 70mg/m^2 day 1 if GFR ≥ 50 ml/min
  OR
- **Carboplatin*** AUC 4.5/AUC 5 day 1 if GFR 30-49ml/min
  *only permitted for impaired renal function
- Supportive care according to local practice

Methods: Statistical design

- 3 year DFS in the control arm assumed to be 40%
- Trial powered to detect a 15% improvement in 3 year DFS (HR=0.65)
- Planned sample size – 345 patients including inflation for drop out; 172 events required for 80% power, 2-sided 5% significance level
- Monitoring of safety and efficacy by an Independent Data Monitoring Committee (IDMC), with defined Peto-Haybittle stopping rule (p<0.001) for efficacy / inefficacy
- QoL assessed using a 2-sided 5% significance level there is a 87% power to detect an 8 point difference
- In Nov 2017, the IDMC recommended early closure to recruitment as the stopping rule had been met
- Time to event outcomes compared via log-rank test with HR & 95% CI reported from a Cox proportional hazard (PH) model (PH assumptions held)

Results: Baseline characteristics

- 261 participants were randomised of whom;
  - 1 withdrew consent and is excluded from analysis
  - **131 allocated chemotherapy**; 124 received chemotherapy, 7 declined/clinical decision
  - **129 allocated surveillance**; 2 received chemotherapy following IDMC decision, 1 ineligible
- Snapshot 2nd Jan 2018
- Median follow-up 19.3 months (IQR: 9.5-35.6)

		Surveillance N=129		Chemotherapy N=131		Total N=260	
		N	%	N	%	N	%
Sex	Male	83	64.3%	93	71.0%	176	67.7%
	Female	46	35.7%	38	29.0%	84	32.3%
Age group (years)	<50	5	3.9%	5	3.8%	10	3.8%
	50-59	24	18.6%	19	14.5%	43	16.5%
	60-69	52	40.3%	50	38.2%	102	39.2%
	70-79	40	31.0%	51	38.9%	91	35.0%
	≥80	8	6.2%	6	4.6%	14	5.4%
	Median (IQR)	66.5	(61.5, 73.3)	69.2	(62.5, 75.0)	68.5	(62.0, 74.1)
Pathological stage	pT2	30	23.3%	45	34.4%	75	28.8%
	pT3	88	68.2%	82	62.6%	170	65.4%
	pT4	11	8.5%	4	3.1%	15	5.8%
Nodal involvement*	N0	117	90.7%	119	90.8%	236	90.8%
	N1	8	6.2%	7	5.3%	15	5.8%
	N2	4	3.1%	4	3.1%	8	3.1%
	N3	0	0.0%	1	0.8%	1	0.4%
Microscopic margin status*	Positive	14	10.9%	17	13.0%	31	11.9%
	Negative	115	89.1%	114	87.0%	229	88.1%
Planned chemotherapy type*	Gem-cis	85	65.9%	81	61.8%	166	63.8%
	Gem-carb	44	34.1%	50	38.2%	94	36.2%

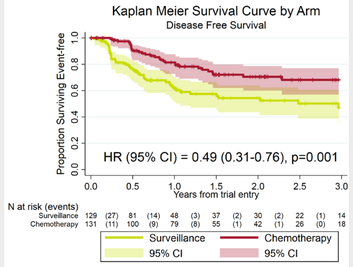
*Balancing factors for minimisation

Results: Treatment compliance

Number of cycles of chemotherapy received	Treatment on-going N=4		No further treatment expected N=127		Total N=131	
	N	%	N	%	N	%
0	2	50	7	6	9	7
1	0	0	12	9	12	9
2	1	25	7	6	8	6
3	1	25	10	8	11	8
4 (max)	0	0	91	72	91	69

- 9/70 (12.9%) participants who received Gem-Cis at the start of treatment switched to Gem-Carb for remaining treatment cycles

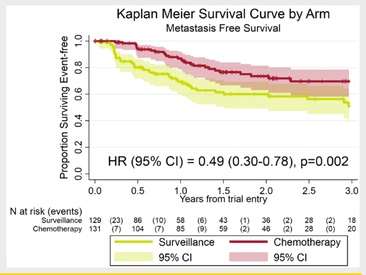
Results: Disease free survival



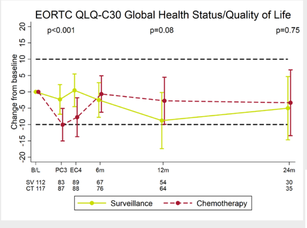
- DFS defined as time from randomisation to first of death from any cause, metastases or any ureteric or renal bed recurrence
- Proportion of people alive and relapse free at 2 years:
  Chemotherapy:
  0.71 (95% CI: 0.60, 0.79)
  Surveillance:
  0.54 (95% CI: 0.43, 0.64)
- After adjustment for stratification factors: HR (95% CI) = 0.47 (0.30-0.74); p=0.001

Results: Metastasis free survival

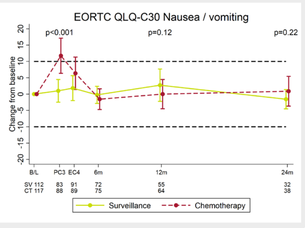
- MFS defined as time from randomisation to first distant recurrence or death from any cause
- Proportion of people alive and metastasis free at 2 years:
  Chemotherapy:
  0.74 (95% CI: 0.63, 0.81)
  Surveillance:
  0.60 (95% CI: 0.49, 0.69)



Results: Quality of Life

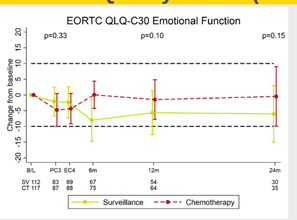


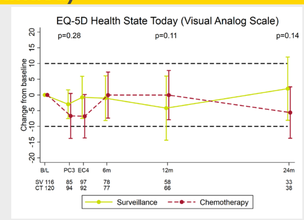
- 252/260 (96%) participants entered the optional QoL sub-study (123/129 surveillance, 129/131 chemotherapy)
- Baseline questionnaires available for 232/252 (92%) participants



- Figures display mean change from baseline and 99% CI
- p-values from ANCOVA models at pre-specified time-points are presented
- p<0.01 considered statistically significant to account for multiple testing

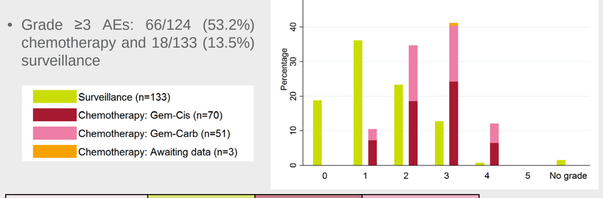
Results: Quality of Life (continued)





Results: Adverse events (AE) during treatment period

- Toxicity data available for 257 participants
- Grade ≥3 AEs: 66/124 (53.2%) chemotherapy and 18/133 (13.5%) surveillance



Most frequent ≥ grade 3 AEs	Surveillance (n=133)		Chemotherapy received at C1: Gem-Cis (n=70)*		Chemotherapy received at C1: Gem-Carbo (n=51)	
Neutrophil count decreased	0	0.0%	17	24.3%	19	37.3%
Hypertension	8	6.0%	2	2.9%	1	2.0%
Platelet count decreased	0	0.0%	5	7.1%	6	11.8%
Febrile neutropenia	0	0.0%	4	5.7%	4	7.8%
Hearing impairment**	3	2.3%	0	0.0%	3	5.9%
Nausea	0	0.0%	2	2.9%	4	7.8%
Vomiting	0	0.0%	1	1.4%	5	9.8%
Pulmonary embolism	0	0.0%	4	5.7%	1	2.0%
Anaemia	0	0.0%	3	4.3%	1	2.0%
Dyspnoea	0	0.0%	1	1.4%	2	3.9%

*Cycle 1 chemotherapy type pending for 3 participants ** Includes tinnitus

- Most common grade ≥3 AE for chemotherapy was neutropenia 36/124 (29%) and for surveillance was hypertension 8/133 (6%)

Conclusions

- POUT was closed to recruitment early as the protocol defined early stopping rule for efficacy was met in favour of chemotherapy
- Adjuvant platinum based chemotherapy within 90 days following nephro-ureterectomy improved disease free survival and metastasis free survival in UTUC
- Patients randomised to chemotherapy had lower global health status during chemotherapy, a result of nausea & vomiting and fatigue, but no evidence of a difference at 12 and 24 months
- Follow up for overall survival is ongoing
- Based on these results, adjuvant platinum based chemotherapy should be considered a new standard of care in these patients

Contact

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