Clinical Trial Update:

Improved Disease Free Survival With Adjuvant Chemotherapy After Nephroureterectomy for Upper Tract Urothelial Cancer. Final Results of the POUT Trial

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Running head: Long-term efficacy results from the POUT trial

Presentation history: Results from this analysis were first presented at ASCO Genitourinary Cancer Symposium 2021 (Birtle AJ, *et al*. Updated outcomes of POUT: A phase III randomized trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). Journal of Clinical Oncology 2021; 39(6_suppl): 455-455.

Abstract

POUT was a phase III, randomised, open-label trial, including 261 patients with muscle-invasive or lymph-node positive, non-metastatic upper tract urothelial cancer (UTUC) randomly assigned following radical nephroureterectomy to platinum-based chemotherapy (132) or surveillance (129). Primary outcome analysis demonstrated that chemotherapy improved disease free survival (DFS). At that time, the planned secondary outcome analysis of overall survival (OS) was immature. By February 2022, 50 and 67 DFS events had occurred in the chemotherapy and surveillance groups respectively, at median follow-up 65 months. Five-year DFS was 62% vs 45%, univariable HR=0.55 (95% CI 0.38-0.80, p=0.001). Restricted mean survival time (RMST) was 18 months longer (95% CI 6-30m) in the chemotherapy arm. There were 46 and 60 deaths in the chemotherapy and control arms respectively. Five-year OS was 66% vs 57%, univariable HR=0.68 (0.46-1.00, p=0.049) and RMST difference 11m (1-21m). Treatment effects were consistent across chemotherapy regimens (carboplatin or cisplatin) and disease stage. Toxicities were similar to those previously reported and there were no clinically relevant differences in quality of life between arms. In summary, although OS was not the primary outcome measure, the updated results add further support for the use of adjuvant chemotherapy in patients with UTUC, suggesting long-term benefits.

INTRODUCTION

Primary analysis of the POUT trial, demonstrating improved disease-free survival (DFS), supports the use of adjuvant gemcitabine:platinum chemotherapy after nephroureterectomy for patients with muscle invasive upper tract urothelial cancer (renal pelvis or ureter, UTUC)[1]. At the time of initial publication, overall survival (OS) data, a key secondary endpoint, were immature. We present updated DFS and a pre-specified final analysis of OS and other secondary endpoints.

PATIENTS & METHODS

Study Design

Trial design details have been published previously[1]. POUT (NCT01993979) was a phase III randomised, open-label trial in which UTUC patients with muscle-invasive (pT2-T4, Nany) or lymph-node positive (pTany, N1-3), non-metastatic disease were randomised following radical nephroureterectomy 1:1 to platinum-based adjuvant chemotherapy or surveillance. Chemotherapy was four 21-day cycles of gemcitabine (1000mg/m^2 day 1 and day 8) and either cisplatin (70mg/m^2) or, if GFR 30-49ml/min, carboplatin (AUC 4.5 or 5) on day 1. The study closed early on advice of the independent data monitoring committee due to superior efficacy in the chemotherapy arm. The trial had ethics approval (11/NW/0782) and participants gave informed consent.

Endpoints

The final OS analysis was planned for when ≥88 deaths had been reported or all participants had been followed up for ≥2 years. OS was defined as time from randomisation to death from any cause (censored at date last known to be alive).

We present updated results for the primary endpoint (DFS) and the secondary endpoints: metastases-free survival (MFS); disease-specific survival (DSS); and quality of life (QoL; EORTC QLQ C30 and EQ-5D at 12 and 24 months). Additionally, time to second primary tumour in the bladder (TSPB) and late toxicity (6-24 months, CTCAE v4, with censoring 3 months prior to recurrence) are reported for the first time and we describe subsequent treatments (exploratory endpoint). TSPB was defined as time from randomisation to date of diagnosis of second bladder primary (muscle-invasive or non-muscle-invasive), censored at diagnosis of other second primary, date last known to be event-free or death).

Statistical analysis

In addition to methods described previously[1], where non-proportional hazards were evident from tests of Schoenfeld residuals[2], restricted mean survival time (RMST) was used to estimate differences between arms in average survival time within a 9-year period without assuming a constant hazard ratio[3]. Analysis was by intention-to-treat with the exception of toxicity (analysed by treatment received).

RESULTS & DISCUSSION

Results

Participants

261 patients (132 chemotherapy; 129 surveillance) were randomised between June 2012 and November 2017 at 57 centres. By February 2022, median follow-up was

65 months (IQR 60-84). One participant (chemotherapy arm) withdrew consent for data use and was excluded from analyses. Table 1 shows baseline characteristics.

Disease events

There were 50 and 67 DFS events in the chemotherapy and surveillance groups, respectively. Risk of recurrence or death was reduced in patients allocated chemotherapy (5-year DFS 62% vs 45%; univariable HR=0.55, 95% CI 0.38-0.80, p=0.001; multivariable HR=0.58, 0.40-0.84, p=0.004, adjusted for nodal status, planned chemotherapy regimen, margin status and pathological stage) (Figure 1A).

Non-proportional hazards were evident and RMST for DFS was 72 and 54 months respectively, an 18-month improvement in the chemotherapy arm (95% CI 6-30, p=0.003). Treatment effect was consistent across subgroups (Figure 2A). MFS and DSS results similarly suggested a benefit of chemotherapy in Cox models (Figure 1B and 1C), and in RMST for MFS where non-proportional hazards were evident (18-month improvement, 95% CI 6-29, p=0.002).

There was no impact of chemotherapy on TSPB (40/131 events vs 37/129 in the surveillance arm; Data Supplement, Figure S1).

Systemic treatment for recurrence was more common in the surveillance arm (45/71, 63% vs 23/47, 49%; Data Supplement, Table S1).

Overall Survival

There were 46 and 60 deaths in the chemotherapy and surveillance groups, respectively, 33/46 (72%) and 48/60 (80%) were due to urothelial cancer (Data Supplement, Table S2). There was a trend towards improved survival in patients allocated chemotherapy (5-year OS 66% vs 57%; univariable HR=0.68, 95% CI

0.46-1.00, p=0.049; multivariable HR=0.76, 0.51-1.12, p=0.17) (Figure 1D). RMST was 78 and 67 months, an 11-month OS improvement with chemotherapy (95% CI 1-21, p=0.036). Treatment effect was consistent across subgroups (Figure 2B).

Adverse Events and QoL

CTCAE grade ≥3 rates between 6-24 months were similar in both groups (40/240, 16.7%, Data Supplement, Table S3). No important differences in QoL were observed (Data Supplement, Table S4).

Discussion

Primary results from POUT have already changed practice on the basis of DFS benefit[4]. The validity of changing practice based on DFS alone has been reaffirmed by recent regulatory approvals for adjuvant nivolumab in invasive urothelial cancer, including UTUC[4]. Although preventing relapse is of likely clinical benefit in its own right, one key purpose of adjuvant therapy is to delay or prevent cancer death. Due to the rarity of UTUC, it was impractical to conduct a trial with OS as a primary endpoint. Furthermore, since POUT was stopped early on the basis of superior DFS with chemotherapy, power for OS analysis was reduced. Nevertheless, a statistically significant OS advantage was seen in univariable analysis (p=0.049) and, although non-significant, multivariable modelling showed a consistent positive trend. The presence of non-proportional hazards may also affect the power of these analyses[3]; RMST results, which account for this, show a statistically significant OS benefit of 11 months over a 9-year period, with the peak benefit between 3-4 years. Combined with improvements in MFS and DSS, these results add weight to the sustained DFS benefit confirmed here.

Although carboplatin is considered by many to be less effective than cisplatin in urothelial cancer[5], nephroureterectomy (by its nature) results in reduced renal function. Hence it was important, for generalisability of results, to include a safe option for delivering platinum-based chemotherapy for those with impaired renal function. Subgroup results from the POUT primary analysis left some uncertainty about the value of carboplatin for those patients[1]. Although not powered for a formal test of interaction, updated HRs (Figure 2) suggest a consistent benefit of chemotherapy, regardless of regimen, supporting inclusion of these patients in the treatment recommendation. Other recent data also suggest that the utility of carboplatin compared with cisplatin in urothelial cancer has been underestimated[6,7].

The POUT primary analysis showed acceptable levels of acute toxicity with chemotherapy, in keeping with previous reports[8]. In the current analysis, data on both clinician-reported toxicity and patient-reported QoL provide reassurance that there are no important long-term adverse impacts which might offset the benefits. Systemic therapy on relapse was less frequent in those who received adjuvant chemotherapy than those in the surveillance group. This may reflect the lack of effective, approved second line therapies in the UK during most of the POUT follow-up period. In contrast, control arm patients could access front-line platinum-based chemotherapy on relapse. We speculate that this difference between arms is unlikely to have had any significant impact on the trial endpoints.

Whilst chemotherapy reduces time to metastasis, it appeared to have no impact on the evolution of second primary formation in the bladder. The extent to which such tumours are clonally-related to UTUC has varied in previous studies[9-12]. The pattern here may suggest that, particularly later forming tumours, could be the result of a

new, *in situ* oncogenic process; notwithstanding, such temporal relationships remain to be fully elucidated.

In summary, updated outcomes from the POUT trial add further support to the value of adjuvant systemic gemcitabine:platinum combination chemotherapy following nephroureterectomy for UTUC.

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Table 1: Participant and tumour characteristics at trial entry

	Surveillance (N=129)	Chemotherapy (N=131)	Total (N=260)
Age (years)			
Median	66	69	68
Range	(43 – 88)	(36 - 85)	(36 - 88)
Sex			
Male	83 (64.3)	93 (71.0)	176 (67.7)
Female	46 (35.7)	38 (29.0)	84 (32.3)
Ethnicity			
British	123	118	241
Irish	0	1	1
Indian	2	1	3
Pakistani	1	0	1
Chinese	0	1	1
Other black background	0	1	1
Other white background	2	5	7
Not specified	1	4	5
Planned chemotherapy regimen[a]			
Gem-cis	82 (63.6)	79 (60.3)	161 (61.9)
Gem-carbo	47 (36.4)	52 (39.7)	99 (38.1)
Nodal Involvement			
N0	118 (91.5)	118 (90.1)	236 (90.8)
N1+	11 (8.5)	13 (9.9)	24 (9.2)
Microscopic surgical margins			
Positive	14 (10.9)	17 (13.0)	31 (11.9)
Negative	115 (89.2)	114 (87.0)	229 (88.1)
Tumor stage			
T2	30 (23.3)	44 (33.6)	74 (28.5)
T3	88 (68.2)	83 (63.4)	171 (65.8)
T4	11 (8.5)	4 (3.1)	15 (5.8)
Primary tumor location			
Ureter	42	47	89
Renal pelvis	45	47	92
Both	41	37	78
Unknown	1	0	1
Number of lesions			
1	112	109	221
>1	13	18	31
Unknown	4	4	8

a. Chemotherapy regimen to be used in the event of randomisation to the chemotherapy arm was specified prior to randomisation

Figure 1: Kaplan-Meier plots with univariable hazard ratios for efficacy analyses (intent-to-treat) showing (A) disease-free survival, (B) metastasis-free survival, (C) disease-specific survival, (D) Overall survival

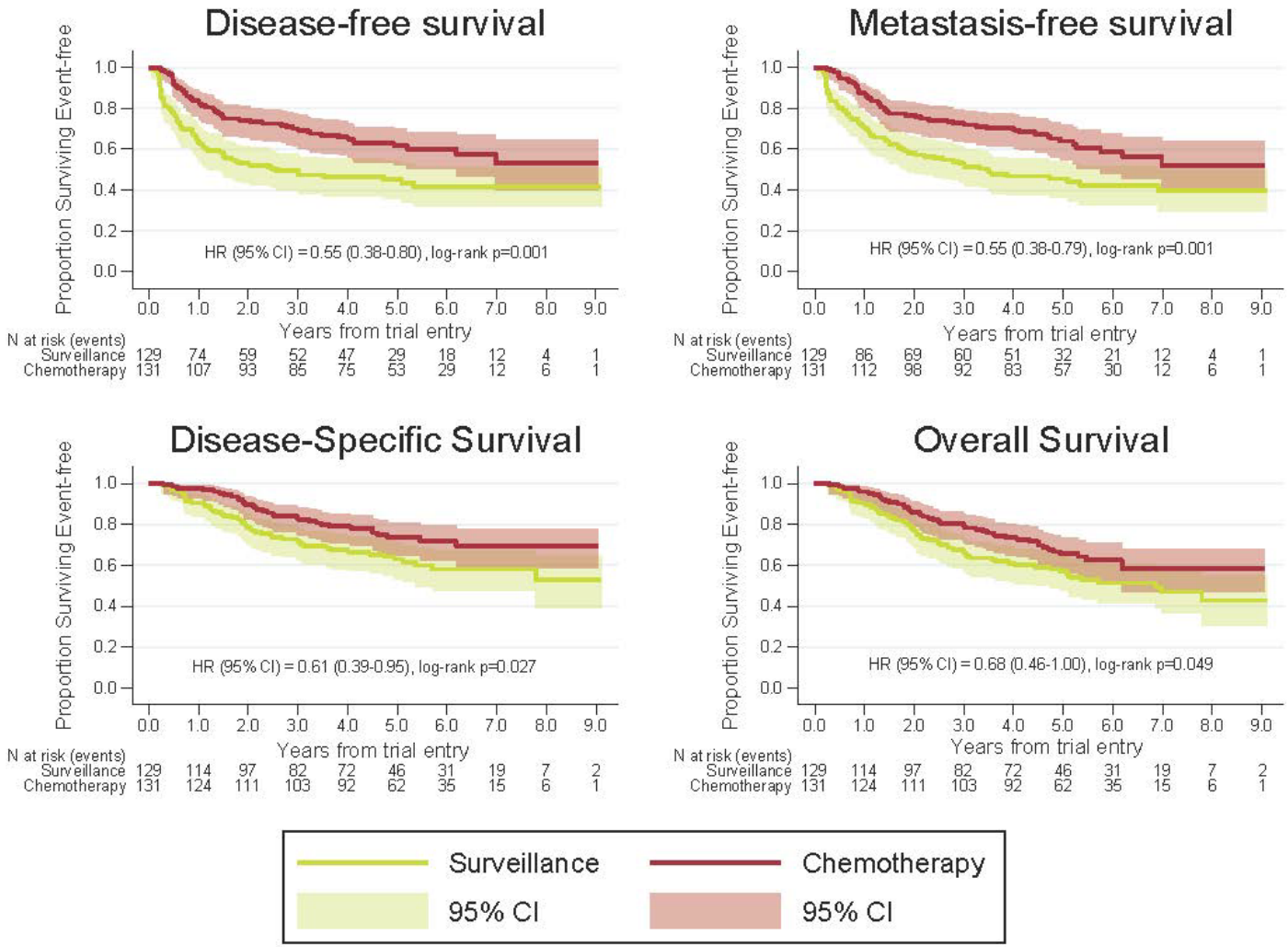
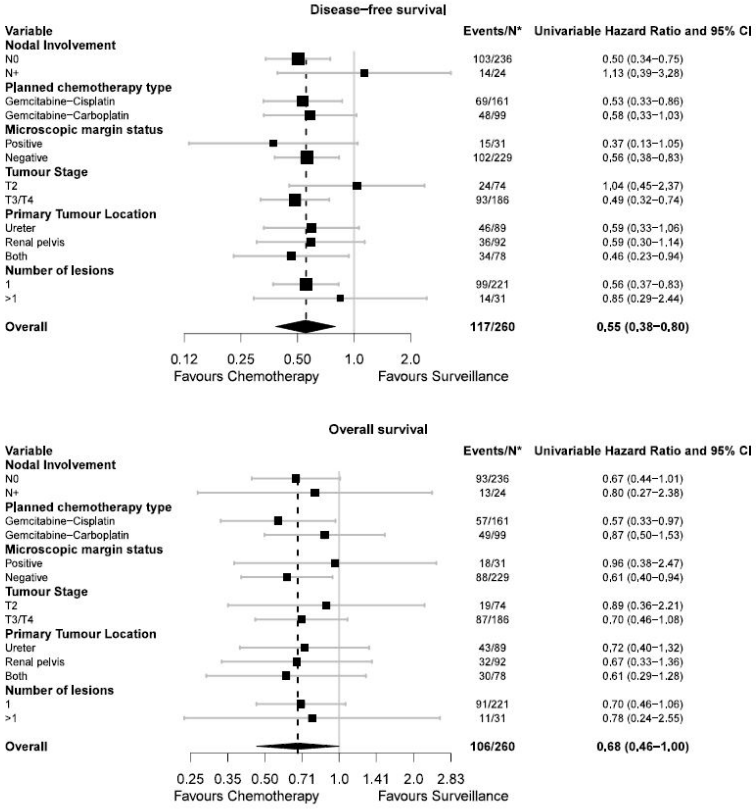


Figure 2: Forest plots showing treatment effects according to key baseline factors and planned chemotherapy regimen for (A) disease-free survival and (B) overall survival



Data Supplement (online only)

Figure S1: Kaplan-Meier plot with univariable hazard ratio for time to second primary in the bladder

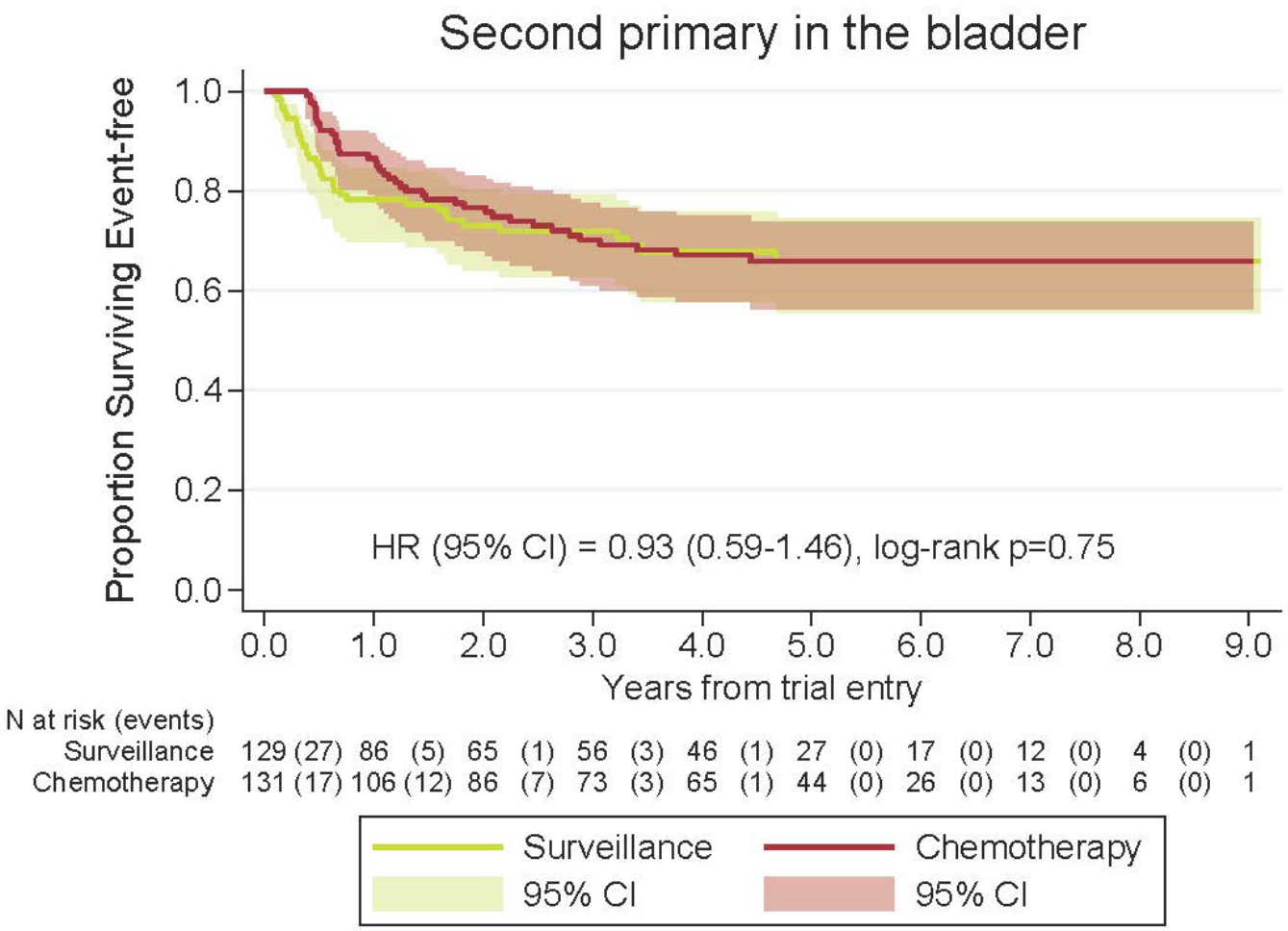


Table S1: Details of treatment for recurrence

	Surveillance		Chemotherapy		Total	
	N	%[a]	N	%[a]	N	%[a]
Patients with a recurrence	71		47		118	
Systemic therapies	45	63.4	23	48.9	68	57.6
Platinum chemotherapy[b]	39	54.9	13	27.7	52	44.1
Non-platinum chemotherapy[b]	1	1.4	3	6.4	4	3.4
Immunotherapy[b]	8	11.3	6	12.8	14	11.9

a. Percentage of patients with a recurrence treated in this way (i.e. denominator is the number of patients who experienced a recurrence of any kind)

b. Categories are not mutually exclusive since patients may have received multiple treatments

Table S2: Causes of death

Cause of death	Surveillance N=60		Chemotherapy N=46		Total N=106	
	N	%	N	%	N	%
UTUC	48	80.0	33	71.7	81	76.4
Bladder cancer	5	8.3	5	10.9	10	9.4
Other malignancy	2[a]	3.3	1[b]	2.2	3	2.8
Myocardial infarction	1	1.7	0	0.0	1	0.9
Respiratory causes	1	1.7	0	0.0	1	0.9
Cardiovascular issues	1	1.7	1	2.2	2	1.9
Infection	1	1.7	4	8.7	5	4.7
Other	0	0.0	1[c]	2.2	1	0.9
Not specified	1	1.7	1	2.2	2	1.9

[a] Small cell carcinoma of left lung (n=1); Colorectal (n=1)

[b] Acute myeloid leukaemia

[c] Gastric bleed (n=1)

Table S3: Late toxicity reported between 6 and 24 months post-randomisation (censored within 3 months of progression)

		Surveillance		Chemotherapy		Total	
	Maximum CTCAE grade reported	**N**	**%**	**N**	**%**	**N**	**%**
Month 6 N=240 Surveillance N=117 Chemotherapy N=123	0	46	39.3	42	34.1	88	36.7
	1	41	35.0	46	37.4	87	36.3
	2	12	10.3	24	19.5	36	15.0
	3	13	11.1	7	5.7	20	8.3
	4	1	0.9	1	0.8	2	0.8
	Missing	2	1.7	3	2.4	5	2.1
	Grade <3	101	86.3	112	91.1	213	88.8
	Grade 3-4	14	12.0	8	6.5	22	9.2
	Missing	2	1.7	3	2.4	5	2.1
Month 12 N=222 Surveillance N=103 Chemotherapy N=119	0	39	37.9	48	40.3	87	39.2
	1	36	35.0	43	36.1	79	35.6
	2	15	14.6	16	13.4	31	14.0
	3	7	6.8	8	6.7	14	6.3
	4	0	0.0	1	0.8	1	0.5
	5	0	0.0	1	0.8	1	0.5
	Missing	6	5.8	2	1.7	8	3.6
	Grade <3	90	87.4	107	89.9	197	88.7
	Grade 3-5	7	6.8	10	8.4	17	7.7
	Missing	6	5.8	2	1.7	8	3.6
Month 18 N=198 Surveillance N=91 Chemotherapy N=107	0	43	47.3	41	38.3	84	42.4
	1	19	20.9	41	38.3	60	30.3
	2	17	18.7	15	14.0	32	16.2
	3	6	6.6	8	7.5	14	7.1
	4	0	0.0	1	0.9	1	0.5
	Missing	6	6.6	2	1.9	8	4.0
	Grade <3	79	86.8	97	90.7	176	88.9
	Grade 3-4	6	6.6	9	8.4	15	7.6
	Missing	6	6.6	1	0.9	7	3.5
Month 24 N=177 Surveillance N=83 Chemotherapy N=94	0	35	42.2	36	38.3	71	40.1
	1	27	32.5	31	33.0	58	32.8
	2	15	18.1	18	19.1	33	18.6
	3	6	7.2	7	7.4	13	7.3
	4	0	0.0	2	2.1	2	1.1
	Grade <3	77	92.8	85	90.4	162	91.5
	Grade 3-4	6	7.2	9	9.6	15	8.5
	0	22	18.8	9	7.3	31	12.9

Maximum overall N=240 Surveillance N=117 Chemotherapy N=123	1	38	32.5	57	46.3	95	39.6
	2	33	28.2	32	26.0	65	27.1
	3	21	17.9	21	17.1	42	17.5
	4	1	0.9	3	2.4	4	1.7
	5[a]	0	0.0	1	0.8	1	0.4
	Grade <3	95	81.2	98	79.7	193	80.4
	Grade 3-5	22	18.8	25	20.3	47	19.6

a. One grade 5: Death due to gastric bleeding

Table S4: Differences between treatment groups in mean functional and symptomatic quality of life scales (EORTC-QLQ-C30) reported at 12 and 24 months post-randomisation

	Item	12 months[a]			24 months[b]		
		Difference[c]	99% CI[d]	p-value[d]	Difference[c]	99% CI[d]	p-value[d]
Functional scales (High scores indicate healthy functioning)	Global health status/QoL	3.99	-4.53 – 12.50	0.22	4.90	-5.14 – 14.94	0.20
	Health state today (EQ-5D)	4.42	-3.93 – 12.78	0.17	-2.41	-11.77 – 6.94	0.50
	Physical functioning	-4.17	-11.35 – 3.01	0.13	-0.60	-8.25 – 7.06	0.84
	Role functioning	-2.27	-13.56 – 9.03	0.60	0.26	-11.73 – 12.25	0.95
	Emotional functioning	4.42	-3.22 – 12.06	0.13	5.64	-3.24 – 14.53	0.10
	Cognitive functioning	-0.81	-8.39 – 6.76	0.78	0.49	-7.72 – 8.69	0.88
	Social functioning	1.43	-10.42 – 13.29	0.75	0.89	-9.64 – 11.42	0.83
Symptomatic scales (High scores indicate high level of symptoms)	Fatigue	-2.71	-11.78 – 6.36	0.44	-7.26	-16.46 – 1.93	0.04
	Nausea and vomiting	-1.97	-7.61 – 3.66	0.36	0.56	-6.87 – 7.98	0.85
	Pain	-2.10	-12.47 – 8.27	0.60	0.64	-10.78 – 12.05	0.88
	Dyspnoea	3.89	-5.68 – 13.46	0.29	6.13	-4.95 – 17.21	0.15
	Insomnia	-4.56	-15.65 – 6.52	0.28	-8.98	-20.65 – 2.69	0.05
	Appetite loss	-3.48	-12.65 – 5.69	0.32	-4.74	-13.79 – 4.32	0.17
	Constipation	-4.41	-15.29 – 6.47	0.29	1.20	-9.15 – 11.54	0.76
	Diarrhoea	-1.15	-7.93 – 5.63	0.66	1.61	-5.30 – 8.53	0.54
	Financial difficulties	-5.71	-14.19 – 2.76	0.08	-1.06	-9.23 – 7.12	0.74

a. Surveillance (N=72), Chemotherapy (N=83)

b. Surveillance (N=59), Chemotherapy (N=73)

c. Differences in mean scores between the trial arms (chemotherapy – surveillance); a difference of >10 points would be considered clinically important, with positive differences indicating an improvement with chemotherapy for functional scales and a detrimental effect of chemotherapy for a symptomatic scale.

d. 99% confidence intervals and p-values from analysis of covariance (ANCOVA) models adjusting for baseline score on the same subscale; p-values of <0.01 were considered statistically significant to allow for multiple testing.