A multicentre cohort study to define and validate pathological assessment of response to neoadjuvant therapy in oesophagogastric adenocarcinoma

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Abstract

Background: This multicentre cohort study sought to define a robust pathological indicator of clinically meaningful response to neoadjuvant chemotherapy (NAC) in oesophageal adenocarcinoma (OAC).

Methods: A questionnaire was distributed to 11 UK Upper GI cancer centres to determine the use of NAC response assessment. Records of consecutive patients undergoing oesophagogastric resection at 7 centres between January 2000 and December 2013 were reviewed. Pathological response to NAC was assessed using the Mandard tumour regression grade (TRG) and lymph node down-staging.

Results: TRG (73%, n=8/11) was the most widely used system to assess response to NAC, but there was discordance on how TRG was used in practice.
Of 1392 patients, 1293 had TRG assessment and data were available for clinical and pathological nodal staging (cN and pN) in 981 patients and TRG, cN and pN in 885 patients. There was a significant difference in survival between responders (TRG 1-2: median overall survival (OS) not reached) and non-responders (TRG 3-5: median OS: 2.2 years 95% CI: 1.936-2.505, $p<0.0001$; HR: 2.459 95% CI: 1.222-4.946, $p=0.012$). The presence of lymph node down-staging in local non-responders was associated with significantly improved OS (median not reached) versus those without lymph node down-staging (median OS: 1.919 yrs. 95 % CI: 1.681-2.158, $p<0.0001$).

Conclusion: A clinically meaningful local response to neoadjuvant chemotherapy is restricted to the small minority of patients (15%) graded as TRG 1-2 only. In local non-responders a sub-set of patients (21%) derive benefit from NAC by lymph node down-staging and their survival mirrors that of local responders.

Keywords: oesophageal cancer; gastro-oesophageal cancer; neoadjuvant; regression.

Introduction

Neoadjuvant chemotherapy (NAC) followed by surgery, **along with peri-operative chemotherapy and neoadjuvant chemo-radiotherapy is a standard of care** in the management of patients with locally advanced adenocarcinoma of the oesophagus / oesophagogastric junction (OGJ) in the UK.[1] The potential benefits of NAC include: downstaging of the primary tumour[2] and lymph nodes[3], increased tumour resectability[4], elimination of micrometastases[5] and improved survival.[6] Early assessment of response to NAC may provide information to tailor multimodal therapy.[7]

Both NAC and surgery are associated with considerable morbidity and mortality[8] and evidence remains inconsistent for the survival benefit for patients who undergo NAC.[4, 8, 9] The most recent meta-analysis to compare NAC versus surgery alone in 2062 patients suggests a 5.1% absolute survival advantage at 2 years for patients treated with NAC for adenocarcinoma.[6] This is because only a small minority of patients have a significant pathological response to neoadjuvant therapy and it is these patients who gain a significant survival benefit from NAC.[10-13]

There are numerous methods to assess pathological response to neoadjuvant therapy but no universal measure is used consistently.[10, 14-18] The majority were developed for patients who underwent neoadjuvant chemoradiotherapy and did not differentiate patients based on histology. Few studies have been validated in patients with oesophageal adenocarcinoma undergoing NAC.[2, 19-22] Tumour Regression Grading (TRG) as described by *Mandard et al*[23] is suggested by UK guidelines, although this has not gained universal acceptance, and the guidelines give no detail regarding how TRG should be used to guide therapy decisions.[1, 17] This system is based on the amount of residual tumour and the degree of fibrosis at the primary tumour site on a 5-point scale.[23] Reports from single-centre cohorts [20, 24] or from small sub-sets of larger multi-centre trials[25] have identified a significant survival advantage with Mandard TRG1-2 or TRG1-3, further confusing clinical decision making.

A number of clinically important questions could be addressed by a robust and universally accepted measure of response to neoadjuvant treatment including: the development of biomarkers to accurately predict an individual patient's tumour response to preoperative therapy leading to non-responders proceeding directly to surgery or being considered for alternative neoadjuvant regimes and the identification of patients who are likely to benefit from adjuvant therapy in new stratified trials.

This multicentre cohort study evaluated the current status of neoadjuvant response assessment in multidisciplinary team decision-making via a questionnaire, and aimed to define and validate the pathological assessment of response to neoadjuvant chemotherapy in treated oesophagogastric adenocarcinoma.

The aim was to provide a consistent, simple, robust and universally acceptable method to assess response to neoadjuvant therapy to allow wider application for both clinical use and biomarker discovery.

Methods

Questionnaire

A questionnaire was distributed to 11 Upper GI cancer centres, all part of the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium, to assess the current use of neoadjuvant response assessment in clinical practice (Supplementary Document 1). The OCCAMS consortium is a UK-wide multicentre consortium to facilitate clinical and molecular stratification of oesophagogastric cancer with ethical approval for biological sample collection and analysis in conjunction with detailed clinical annotation (Research Ethics Committee number: 10/H0305/1).

Patients

The records of consecutive patients undergoing oesophagogastric resection (tumours of the oesophagus and gastro-oesophageal junction only were included) treated at the following seven centres: University Hospital Southampton NHS Foundation Trust, Belfast Health and Social Care Trust, University Hospitals Birmingham NHS Foundation Trust, University Hospital Cambridge NHS Foundation Trust, Royal Infirmary of Edinburgh, Portsmouth NHS Trust, Nottingham University Hospitals NHS Trust between January 2000 and December 2013 were reviewed as part of the OCCAMS consortium. All patients were discussed at a specialist multidisciplinary team meeting (MDT). Standard staging investigations included high-resolution computed tomography, endoscopic ultrasonography, and latterly integrated fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) and staging laparoscopy, where indicated. Patients considered suitable for potential surgical resection with tumours staged as cT2NxM0 or cTxN+M0 were considered for NAC based on local practice and national guidelines.[1]

NAC consisted of platinum based triplet therapy: three 21-day cycles of anthracycline, platinum and fluoropyrimidine: ECF (Epirubicin 50mg/m^2, Cisplatin 60mg/m^2, both intravenously on day 1 and protracted venous infusion 5-FU 200mg/m^2 per day) or ECX (Epirubicin 50mg/m^2, Cisplatin 60mg/m^2, both intravenously on day 1 and Capecitabine 625mg/m^2 orally twice daily for 21 days) or EOX (Epirubicin 50 mg/m^2 i.v. bolus and Oxaliplatin 130 mg/m^2 i.v. infusion over 2 hours on day 1, Capecitabine 625 mg/m^2 orally twice daily for 21 days) or two cycles of Cisplatin 80mg/m^2 intravenously on day 1 and intravenous infusion of 5-fluorouracil 1000mg/m^2 over 96 hours.

A repeat CT or PET-CT scan was performed, prior to surgery to assess the response to chemotherapy and disease operability.

Data recorded included demographics, tumour characteristics, resection type, and histopathological analysis of the surgical specimen. TNM-7 was used to report tumour stage after analysis of pathology reports.[26] Pathological tumour clearance ("R"-status) was determined according the Royal College of Pathologists' guidance.

Overall survival (OS) was defined as time from operation to date of death from any cause or date of last review.

Factors analysed

Pathological response to chemotherapy was assessed using the tumour regression grade (TRG) system developed by Mandard *et al* who scored regression based on the degree of fibrosis and residual cancer cells (TRG 1 to 5).[23, 27] TRG was scored by specialist gastrointestinal pathologists blinded to the clinical data at the treating cancer centre and 10% of cases were externally validated by an independent pathologist as part of the OCCAMS/ICGC project[28, 29] with a Kappa value >0.8.

All dissected lymph nodes were stained with hematoxylin and eosin and microscopically analysed for metastatic disease. Lymph node down staging was defined as any regional lymph node positive on clinical staging (cN+) that subsequently had no evidence of pathological regional lymph node disease (cN0), as previously described.[24]

Statistical analysis

Descriptive data are represented as median and range unless indicated with Kruskal-Wallis, Mann Whitney U and Pearson's chi-squared test, which were used as appropriate for comparison. Kaplan-Meier, univariate and multivariate cox logistic regression modelling were used to assess the relationship between pathological response grading systems and OS. All factors that showed statistical significance on univariate analysis were entered to derive the final model. Stratified analyses were performed based on receipt of neoadjuvant chemotherapy, nodal stage and response to chemotherapy. A p value <0.05 was considered statistically significant for all tests. Statistical analysis was performed with SPSS® version 22 (SPSS, Chicago, Illinois, USA).

Results

Assessment of the current clinical use of response assessment to neoadjuvant chemotherapy

The responses from 11 UK cancer centres demonstrated that TRG (73%, n=8/11) is the most widely used system to assess response to NAC and that it is felt to be useful in providing prognostic information for the patient (73%, n=8/11) and to make decisions about the modification of adjuvant therapy (82%, n=9/11). There is **no consensus** on how TRG is being used to influence decision making for individual patients in practice, with centres using different scores to define responders, with most using TRG 1-3 (63%, n=5/8), and a lack of consensus on how adjuvant therapy should be guided by TRG. Some centres would advocate adjuvant therapy based on whether the patient had responded to therapy (n=5/11) whilst others would not use response information (n=6/11) (Supplementary Figure 1).

Study patients

A total of 1392 patients underwent neoadjuvant therapy with attempted curative resection for oesophageal of OGJ adenocarcinoma. Of these, 1293 had TRG assessment and data were available for both clinical and pathological nodal staging (cN and pN) in 981 patients and TRG, cN and pN in 885 patients available (Fig 1).

Patients were predominantly men (n=1181/1392, 85%) and had a median age of 64 years (range: 26-83 years). Resection clearance (R0) as defined by the Royal College of Pathologists was achieved in 67% (913/1371) and the median nodal yield was 23. Detailed patient characteristics and clinical and pathological outcomes are summarised in Table 1.

Chemotherapy was the predominant neoadjuvant treatment, either platinum based triplet (n=1037/1392, 75%) or cisplatin and fluorouracil (n=281/1392, 20%), chemoradiotherapy was used in 3 patients. In 71% (n=912/1293) of patients there were demonstrable signs of local pathological tumour regression (TRG 1-4) with 6% (n=76/1293) exibiting a complete pathological response (TRG 1). Lymph node down-staging (cN1+ to ypN0) was observed in 26% (n=259/981).

Assessment of a clinically meaningful pathological response to NAC in oesophageal adenocarcinoma

Median follow-up for the 1293 patients who underwent NAC with TRG available was 3.6 years (95% CI: 3.183-4.099). There was a clear association between TRG and prognosis across all groups (Figure 2A). A significant difference in OS was observed for the 192 (15%) patients with TRG 1-2 defined as "responders" and the 1101 (85%) patients with TRG 3-5, defined as "non-responders". (Figure 2B, median OS; TRG 1-2: not reached (mean OS: 7.682 years 95% confidence interval (CI): 7.053-8.312) versus median OS TRG 3-5: 2.220 95% CI: 1.936-2.505 (mean OS: 4.055 years 95% CI: 3.781-4.329; $p<0.0001$)). No significant difference in survival was observed between patients graded as TRG 1 compared to TRG 2 (Mean OS; TRG1: 7.462 95% CI: 6.480-8.444 versus TRG 2: 7.632 95% CI: 6.839-8.426; $p=0.911$ (Median OS's: not reached)).

Responders and non-responders had similar preoperative clinical features (age, sex) and clinical stage of disease (cT stage = $p=0.101$ cN stage, $p=0.711$; cM stage, $p=0.109$) yet responders had markedly reduced ypT stage ($p<0.0001$), and ypN stage ($p<0.0001$) and were more likely to nodal down-staging ($p<0.0001$) (Table 2). Complete resection (R0) was achieved in 93% (n=173/187) of responders compared with 62% (n=678//1085) of non-responders and this correlated across the TRG scores from 1 to 5 (supplementary table 1). **Of those patients who underwent an R1 resection, in 92.7% this was at the radial (circumferential) margin, this was not affected by location or type of surgery performed.** There was no significant difference in nodal yield between responders and non-responders ($p=0.437$).

Patients with lymph node down-staging following NAC (n=259/981) had improved OS versus patients without down-staging, (median OS LN down-staged: not reached (mean OS: 7.639 years 95% CI: 7.082-8.196)) versus median OS LN not down-staged: 2.040 95% CI: 1.778-2.301 (mean OS: 3.560 years 95% CI: 3.208-3.991), $p<0.0001$) (Figure 3).

Univariate and multivariate analysis confirmed known predictors of OS in OAC (Table 3). Factors that retained significance for the prediction of worse OS on multivariate analysis were: vascular/lymphatic invasion (HR: 1.607 95% CI: 1.233-2.095, p<0.0001), no significant response to NAC (TRG 3-5) (HR: 2.459 95% CI: 1.222-4.946, $p=0.012$) and ypN stage and ypM stage.

Evaluation of chemotherapy regimen

Patients treated with platinum based triplet chemotherapy had significantly greater response to chemotherapy in the local tumour (TRG) ($p<0.0001$) and regional lymph nodes ($p=0.027$) and were more likely to have an R0 surgical resection ($p=0.004$) when compared to patients who received CF (Table 2 and Supplementary Table 2).

There was no difference in OS between chemotherapy regimens on multivariate analysis although univariate analysis demonstrated greater OS for platinum based triplet therapy

(Table 3 and Supplementary Figure 2), but the study was not specifically powered to address this question.

Evaluation of combined local tumour response (TRG) and lymph node downstaging

In this cohort, 85 (60%) of the 142 local responders to NAC (TRG 1-2) additionally demonstrated down-staging of their regional lymph nodes compared to only 158 (21%) of 743 non-responders (TRG 3-5), $p<0.0001$ (Figure 4).

The presence of lymph node down-staging in local non-responders was associated with significantly improved OS (median OS: not reached (mean OS: 7.241 95% CI: 6.495-7.986)) versus TRG 3-5 & LN not downstaged (median OS: 1.919 95 % CI: 1.681-2.158 (mean OS: 3.286 95 % CI: 2.195-3.658) $p<0.0001$).

Discussion

This multicentre study demonstrates that a clinically meaningful local response to neoadjuvant chemotherapy for adenocarcinomas of the oesophagus and OGJ is restricted to the small minority of patients (15%) graded as TRG 1-2 only. In apparent local non-responders there is a sub-set of patients who appear to derive additional benefit from NAC by lymph node down-staging and their survival mirrors that of local responders.

The difficulties faced by clinicians in routine practice regarding what constitutes a meaningful response to NAC and how this information should be used to tailor subsequent treatment has primarily been caused by the cohort sizes of previous studies. For example, the Mandard system was developed in 1994 in a cohort of 93 French patients (84% squamous cell cancer) treated with cisplatin and radiotherapy, where TRG 1-3 was found to correlate with improved disease free survival.[23] In a subsequent study performed in the UK and Ireland, TRG had no correlation with survival in 43 patients with adenocarcinoma.[30] More recent work from single institutions has demonstrated the validity of the TRG system in patients with oesophageal cancer treated with NAC, but cohort sizes remain small (e.g. Fareed et.al 103 patients, TRG 1-3 associated with disease-specific survival advantage [19]; Noble et.al 136 patients, TRG 1-2 associated with disease-free survival advantage).[24] Larger series have focussed on the role of NAC and tumour stage rather than TRG[31] or mainly included gastric cancers.[25] **In the context of neoadjuvant chemoradiotherapy a three-point scale for TRG using TRG 1 compared with TRG 2/3, and TRG 4/5, was found to be the best discriminant fit of all response measurement modalities in a cohort of 393 patients from a single centre in Ireland [32]. The data presented here does not support this classification and suggests that there may be differences in the histomorphological assessment of response between chemotherapy and chemoradiation.**

The strengths of the current study are its cohort size, length of follow-up and multi-centre nature. This study shows that TRG is a robust measure of local response to NAC in routine clinical practice with excellent correlation between local centre scoring and central validation. The inclusion of the two UK centres (Nottingham[19] and Southampton[24]) to previously publish discordant results regarding the level of TRG associated with "response" adds weight to the finding that only TRG 1-2 represents a true local responder group. This is supported by the use of overall survival as the outcome measure in the current study, and by the similarity between responder and non-responder groups in terms of pre-treatment characteristics.

Contrary to a recent sub-group analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial, where lymph node status was the only independent predictor of survival in patients treated with chemotherapy[25], in the current study non-response to NAC (TRG 3-5) was independently associated with poor overall survival (HR: 2.459 95% CI: 1.222-4.946, *p*=0.012). This probably reflects the relative sizes of the study cohorts (1293 in the current study versus 330 in MAGIC[25]). In this study no attempt was made to assess the utility (or not) of post-operative chemotherapy in either responders or non-responders. In a recent study of 333 patients from a single UK centre only responders to NAC were observed to derive a survival advantage from the adjuvant portion of the MAGIC regime and there was evidence of potential harm for non-responders in terms of chemotherapy morbidity[33]. The question of who should receive adjuvant treatment and what form this treatment should take needs to be urgently addressed in prospective studies so that futile overtreatment with chemotherapy can be avoided and better-targeted therapies can be applied where appropriate. TRG and lymph node down-staging could be used to stratify patients whilst the validation of recently discovered mutational endotypes takes place[28].

This study was not designed to investigate differences in outcome between different chemotherapy regimens. However, the data clearly shows superiority for platinum based triplet chemotherapy, including Epirubicin, over Cisplatin and 5-fluoruracil for local tumour response, but this did not translate into better survival. These findings are in keeping with the results of the MRC OEO5 trial, where 2 cycles of neoadjuvant CF was shown to be equivalent to 4 cycles of ECX for overall survival, with higher chemotherapy related toxicity in the ECX arm[34]. Widely regarded as a negative trial, OEO5 is important because it identifies the requirement of robust markers of patient and tumour stratification to guide precision treatment.

There are clear drawbacks when performing a large multi-centre cohort study over a relatively long time period. This was not a randomised trial and there is missing data, therefore bias cannot be excluded, but the sample size helps to negate this deficiency. Staging modalities, chemotherapy and to a lesser extent surgery will have changed over the time of the study. It is possible that a number of patients who received treatment at the beginning of the study period may have been excluded from treatment had they been staged with modern modalities, leading to a worsened overall survival. It could be presumed that these patients would be in the non-responder group, as there is some evidence to support the association between local tumour response and systemic relapse, but tumour stage after NAC seems to be more important than initial stage at presentation in terms of assessing prognosis.[31] **These drawbacks may also explain the relatively low overall R0 resection rate (67%), but it is important to note that in the majority of R1 resections the circumferential margin was involved and the more stringent Royal College of Pathologists definition of margin involvement was used. No attempt has been made**

to assess the theoretical benefit of using NAC (rather than neoadjuvant chemo-radiotherapy) to treat distant micro-metastatic disease in these patients. On-going randomised studies will hopefully answer this important question.

The finding that a small group (~20%) of apparent primary tumour non-responders have down-staging of local nodes and an associated good long-term survival, similar to that of primary tumour responders, is important both for discussions of prognosis with individual patients and for the design of the next generation of tailored adjuvant treatment trials. The use of cN stage to determine involved nodes pre-operatively compared with ypN stage post-operatively to determine down-staging is open to criticism. In support of this strategy, it has previously been shown that patients with ypN0 disease have worse overall survival than patients with pN0 disease suggesting true nodal involvement[24] and down-staging has been accurately demonstrated in other cohorts.[31] This also reflects current clinical practice in the UK and elsewhere. **However, an alternative interpretation of this data is that it could be consistent with an issue of clinical over-staging rather than down-staging.** A future analysis should consider the pathological assessment of nodal down-staging (is there evidence of fibrosis/previous tumour in the nodes?) and the relationship of this to prognosis. Large-scale collaborations such as the OCCAMS consortium are ideally placed to do this.

As the research community begins to consider the move from binary "one size fits all" treatment and trial designs to more personalised strategies robust markers of treatment response will be required. The findings presented in this study confirm TRG as such a marker and clearly define groups of patients who benefit from NAC. In addition, giving clarity to the assessment of response offers the opportunity to determine biomarkers that may predict response to existing and novel neoadjuvant treatments, whether they are patient, tumour or treatment related.

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Legends to figures and tables

Figure 1. Consort diagram of patients showing contribution of participating centres. Numbers in red boxes were used for all statistical analyses.

Figure 2. Survival analysis of patients grouped according to TRG score.

(A) Kaplan-Meier survival curves according to individual TRG score. (B) Kaplan-Meier survival curves for Responders (TRG 1-2) and Non-Responders (TRG 3-5).

Figure 3. Survival analysis of patients grouped according to lymph node down-staging.

Figure 4. The effect of lymph node down-staging on survival.

(A) Percentage of patients who exhibited lymph node down-staging grouped by TRG. (B) Kaplan-Meier curves for local tumour Responders (TRG 1-2) compared with local tumour Non-Responders divided into those with evidence of lymph node down-staging or no down-staging.

Supplementary Figure 1. Responses to questionnaire sent to 11 UK cancer centres to determine current use of pathological response information in clinical decision making.

Supplementary Figure 2. Kaplan-Meier curves for patients treated with cisplatin and 5-FU or platinum based triplet chemotherapy.

Table 1. Clinical and pathological characteristics of full cohort (n=1392).

Values in parentheses are percentages unless indicated.

Table 2. Clinical and pathological characteristics of patients with TRG available grouped as Responders (TRG 1-2) and Non-Responders (TRG 3-5).

Values in parentheses are percentages unless indicated.

Table 3. Univariate and multivariate Cox regression analysis of patient, treatment and tumour factors associated with overall survival for patients who received neoadjuvant chemotherapy.

Supplementary Table 1. Resection margin involvement by TRG

Supplementary Table 2. Effect of chemotherapy regime on TRG, lymph node down-staging and resection margins.

Figure 1

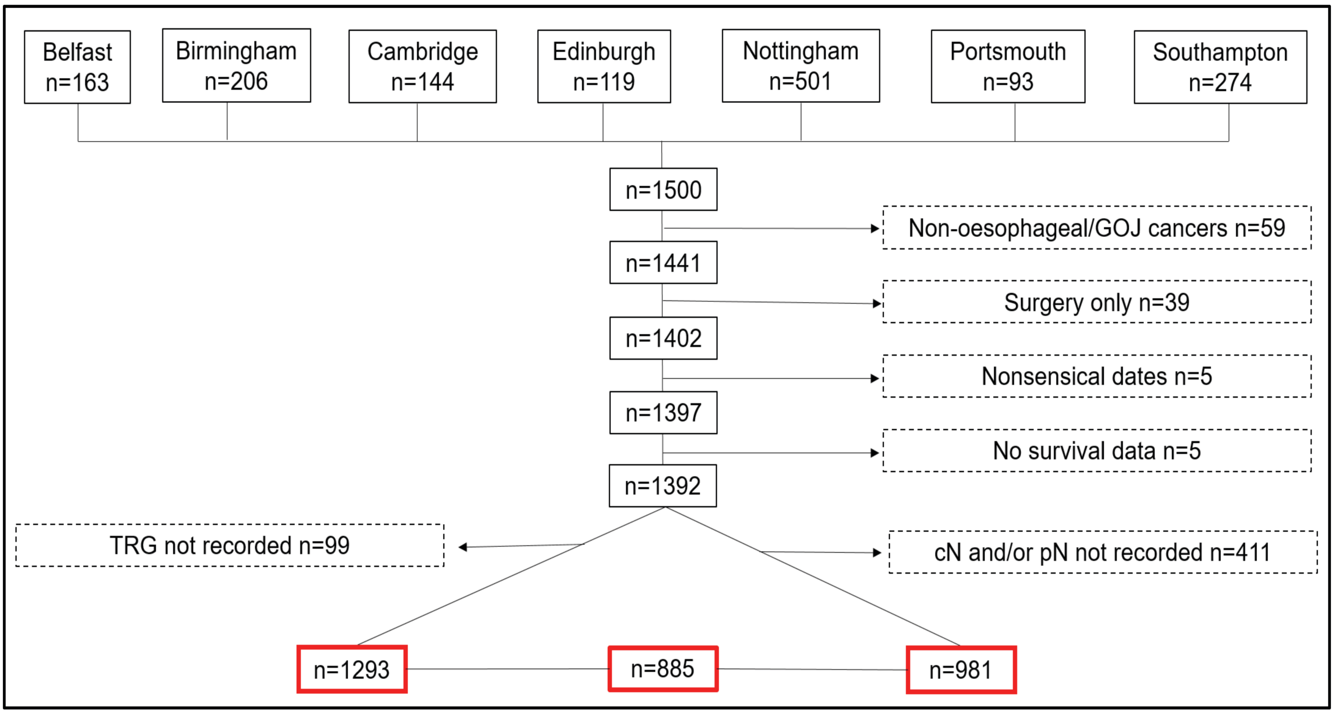
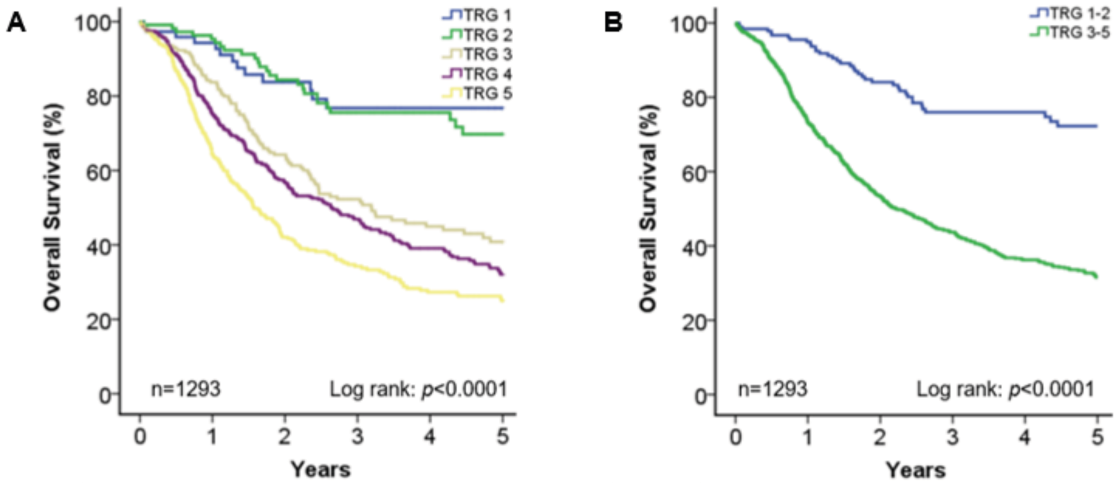

Belfast n=163
Birmingham n=206
Cambridge n=144
Edinburgh n=119
Nottingham n=501
Portsmouth n=93
Southampton n=274
n=1500
Non-oesophageal/GOJ cancers n=59
n=1441
Surgery only n=39
n=1402
Nonsensical dates n=5
n=1397
No survival data n=5
n=1392
TRG not recorded n=99
cN and/or pN not recorded n=411
n=1293
n=885
n=981

Figure 2

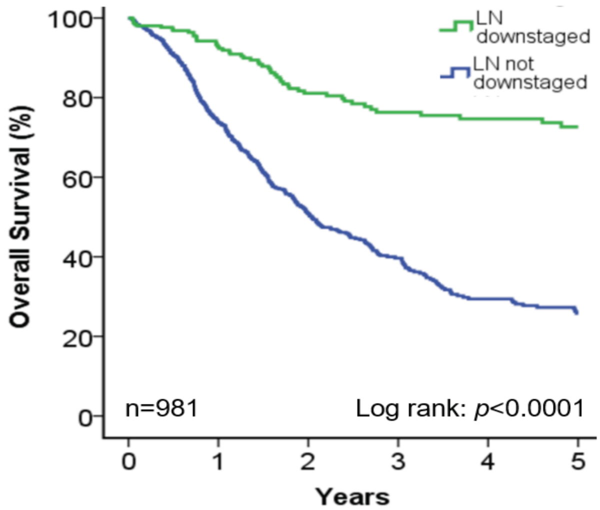


No. at risk						
TRG 1	76	58	40	28	22	16
TRG 2	116	97	70	54	43	32
TRG 3	239	181	111	69	50	34
TRG 4	481	320	198	120	88	57
TRG 5	381	213	111	72	53	42

No. at risk						
TRG 1-2	192	155	110	82	65	48
TRG 3-5	1101	714	420	261	191	133

TRG	Median	95% CI	Mean	95% CI	*p*
1	Not reached	-	7.462	6.480-8.444	<0.0001
2	Not reached	-	7.632	6.839-8.426	
3	3.190	2.161-4.218	4.899	4.274-5.523	
4	2.642	2.145-3.139	4.163	3.745-4.582	
5	1.572	1.287-1.856	3.385	2.955-3.815	
1-2	Not reached	-	7.682	7.053-8.312	<0.0001
3-5	2.220	1.936-2.505	4.055	3.781-4.329	

Figure 3

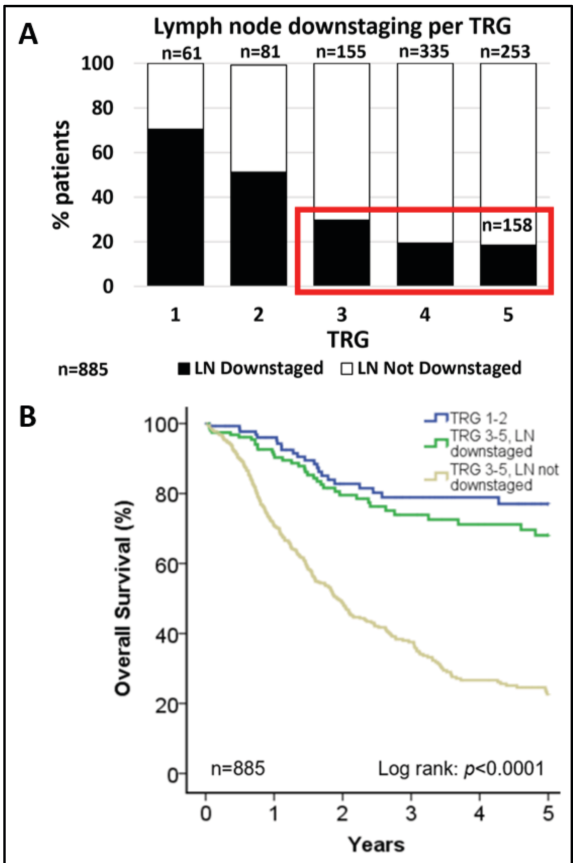


No. at risk

LN downstaged	259	199	132	101	85	67
LN not downstaged	722	451	219	115	73	50

Group	Median survival	95% CI	Mean survival	95% CI	P
LN downstaged	Not reached	-	7.639	7.082-8.196	<0.0001
LN not downstaged	2.040	1.778-2.301	3.560	3.208-3.991	

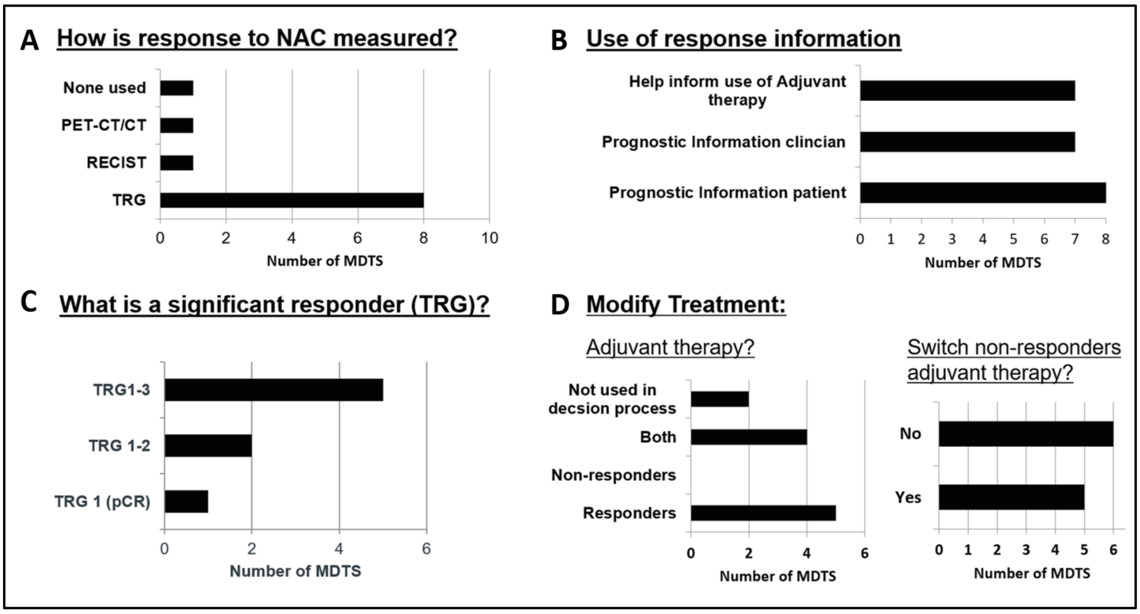
Figure 4



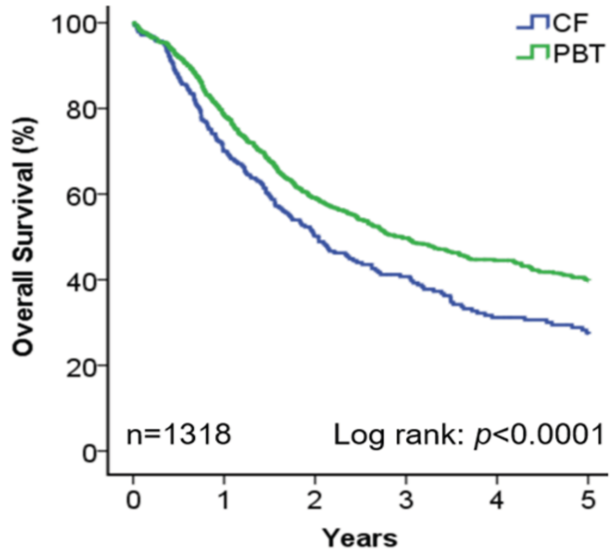
No. at risk						
TRG 1-2	142	109	68	54	44	32
TRG 3-5, LN downstaged	158	118	77	58	50	42
TRG 3-5, LN not downstaged	585	347	169	87	54	36

Group	Median survival	95% CI	Mean survival	95% CI	P
TRG 1-2	Not reached	-	7.770	7.092-8.448	<0.0001
TRG 3-5, LN downstaged	Not reached	-	7.241	6.495-7.986	
TRG 3-5, LN not downstaged	1.919	1.681-2.158	3.286	2.915-3.658	

Supplementary Figure 1



Supplementary Figure 2



No. at risk

CF	281	192	115	84	60	43
PBT	1037	719	438	273	208	147

Regime	Mean survival	95% CI	Median survival	95% CI	P
CF	4.087	3.463-4.711	2.037	1.641-2.433	<0.0001
PBT	5.269	4.992-5.617	2.954	2.520-3.388	

Supplementary Table 1

TRG	Margins Involved (%)	Margins Not Involved (%)	*P*
1	2 (2.7)	71 (97.3)	**<0.0001**
2	12 (10.5)	102 (89.5)	
3	61 (25.5)	178 (74.5)	
4	180 (38.0)	294 (62.0)	
5	166 (44.6)	206 (55.4)	

Supplementary Table 2

	CF (%)	PBT (%)	*P*
TRG			
1	4 (1.6)	65 (6.7)	**<0.0001**
2	10 (4.0)	95 (9.7)	
3	46 (18.4)	182 (18.7)	
4	103 (41.2)	354 (36.3)	
5	87 (34.8)	279 (28.6)	
Lymph Node Downstaged?			
Yes	39 (19.8)	196 (27.6)	**0.027**
No	158 (80.2)	514 (72.4)	
Resection Status			
R0	165 (58.7)	693 (68.0)	**0.004**
R1	116 (41.3)	326 (32.0)	

Table 1

Preoperative Status		
Age (range) yr		63.6 (26-83)
Sex ratio (M:F)		1181 (84.8): 211 (15.2)
cT stage	1	10 (1.0)
	2	136 (13.8)
	3	798 (80.7)
	4	45 (4.6)
	Unknown	403
cN stage	0	235 (23.8)
	1	634 (64.2)
	2	102 (10.3)
	3	16 (1.6)
	Unknown	405
cM stage	0	998 (98.7)
	1	13 (1.3)
	Unknown	381
Tumour site	Oesophagus	445 (32.0)
	Gastroesophageal Junction	947 (68.0)
	Siewert 1	290 (42.0)
	Siewert 2	272 (39.2)
	Siewert 3	130 (18.8)
	Siewert unknown	255
Chemotherapy regime		
Cisplatin + 5-fluorouracil		281 (20.2)
Platinum based triplet therapy		1037 (74.5)
Other/unknown		74 (5.3)
Pathological Outcomes		
yPT	0	65 (4.7)
	1	135 (9.7)
	2	231 (16.6)
	3	867 (62.4)
	4	91 (6.6)
	Unknown	3
yPN	0	514 (37.1)
	1	432 (31.2)
	2	246 (17.7)
	3	194 (14.0)
	Unknown	6
yPM	0	1340 (97.6)
	1	33 (2.4)
	Unknown	19
TRG	1	76 (5.9)
	2	116 (9.0)
	3	239 (18.5)
	4	481 (37.2)
	5	381 (29.5)
	Unknown	99
Nodal Yield (range)		23.2 (0-75)
% Positive Nodes (range)		15.6 (0.0 -100.0)
Lymph nodes downstaged (cN1 to yPN0)		259 (26.4)
Resection clearance	R0	913 (66.6)
	R1	458 (33.4)
	Unknown	21
Vascular/lymphatic invasion	Yes	447 (50.2)
	No	443 (49.8)
	Unknown	502
Differentiation	No residual tumour	8 (0.9)
	G1	57 (6.3)
	G2	327 (36.4)
	G3	429 (47.8)
	G4	77 (8.6)
	Unknown	494

Table 2

		TRG 1-2 N = 192	TRG 3-5 N = 1101	*P* value
Preoperative Status				
Age (range) yr		64.5 (37-79)	63.3 (26-83)	0.089
Sex ratio (M:F)		163 (84.9): 29 (15.1)	938 (85.2): 163 (14.8)	0.914
cT stage	1	3 (2.1)	5 (0.7)	0.101
	2	26 (18.1)	97 (12.8)	
	3	108 (75.0)	625 (82.5)	
	4	7 (4.9)	31 (4.1)	
	Unknown	48	343	
cN stage	0	32 (22.4)	170 (22.7)	0.711
	1	96 (67.1)	480 (64.2)	
	2	14 (9.8)	84 (11.2)	
	3	1 (0.7)	14 (1.9)	
	Unknown	49	353	
cM stage	0	145 (97.3)	755 (99.0)	0.109
	1	4 (2.7)	8 (1.0)	
	Unknown	43	338	
Tumour site	Oesophagus	76 (39.6)	363 (33.0)	0.074
	Gastroesophageal Junction	116 (60.4)	738 (67.0)	
	Siewert 1	35 (40.2)	224 (43.8)	0.617
	Siewert 2	33 (37.9)	198 (38.7)	
	Siewert 3	19 (21.8)	90 (17.6)	
	Siewert unknown	29	226	
Chemotherapy Regime				
Cisplatin + 5-fluorouracil		14 (7.3)	236 (21.4)	**<0.0001**
Platinum based triplet therapy		160 (83.3)	815 (74.0)	
Other/unknown		18 (9.4)	50 (4.5)	
Pathological Outcomes				
ypT	0	64 (33.7)	0 (0)	**<0.0001**
	1	49 (25.8)	74 (6.7)	
	2	33 (17.4)	176 (16.0)	
	3	42 (22.1)	770 (70.0)	
	4	2 (1.1)	80 (7.3)	
	Unknown	2	1	
ypN	0	145 (75.9)	336 (30.7)	**<0.0001**
	1	33 (17.3)	372 (33.9)	
	2	12 (6.3)	213 (19.4)	
	3	1 (0.5)	175 (16.0)	
	Unknown	1	5	
ypM	0	189 (99.0)	1058 (97.3)	0.179
	1	2 (1.0)	29 (2.7)	
	Unknown	1	14	
Nodal Yield (range)		22.30 (3-65)	22.92 (0-75)	0.437
% Positive Nodes (range)		2.94 (0-54.17)	17.91 (0-100)	**<0.0001**
Lymph nodes downstaged (cN1 to ypN0)		85 (59.9)	158 (21.3)	**<0.0001**
Resection clearance	R0	173 (92.5)	678 (62.5)	**<0.0001**
	R1	14 (7.5)	407 (37.5)	
	Unknown	5	16	
Vascular/lymphatic invasion	Yes	15 (11.6)	364 (54.9)	**<0.0001**
	No	114 (88.4)	299 (45.1)	
	Unknown	63	438	
Differentiation	No residual tumour	8 (7.8)	0 (0)	**<0.0001**
	G1	20 (19.4)	34 (4.9)	
	G2	37 (35.9)	263 (37.7)	
	G3	34 (33.0)	332 (47.6)	
	G4	4 (3.9)	69 (9.9)	
	Unknown	89	403	

Table 3

			Univariable			Multivariable	
		HR	**95%CI**	***P* value**	**HR**	**95%CI**	***P* value**
Patient Factors							
Age		1.000	(0.992-1.009)	0.918			
Sex	Female	1.000	Ref				
	Male	1.084	(0.877-1.339)	0.458			
Chemotherapy Regime							
Platinum base triplet		1.000	Ref		1.000	Ref	
Cisplatin + 5-fluorouracil		1.440	(1.219-1.701)	**<0.0001**	1.074	0.816-1.413	0.610
Tumour Response							
TRG	1	1.000	Ref				
	2	1.029	(0.535-1.979)	0.932			
	3	2.803	(1.608-4.887)	**<0.0001**			
	4	3.499	(2.043-5.994)	**<0.0001**			
	5	4.811	(2.806-8.250)	**<0.0001**			
TRG group	1-2	1.000	Ref		1.000	Ref	
	3-5	3.659	(2.645-5.060)	**<0.0001**	2.459	1.222-4.946	**0.012**
Lymph Node Response							
LN downstaged	Yes	1.000	Ref		1.000	Ref	
	No	3.985	(2.975-5.339)	**<0.0001**	1.590	0.846-2.986	0.149
Tumour Factors							
ypT stage	0	1.000	Ref		1.000	Ref	
	1	1.410	(0.693-2.869)	0.343	0.585	0.119-2.885	0.510
	2	2.382	(1.241-4.574)	**0.009**	0.492	0.102-2.382	0.378
	3	4.995	(2.670-9.342)	**<0.0001**	0.674	0.140-3.246	0.623
	4	8.546	(4.350-16.789)	**<0.0001**	0.936	0.183-4.797	0.937
ypN stage	0	1.000	Ref		1.000	Ref	
	1	2.780	(2.257-3.425)	**<0.0001**	1.859	1.035-3.336	**0.038**
	2	3.845	(3.043-4.860)	**<0.0001**	2.495	1.382-4.506	**0.002**
	3	7.724	(6.080-9.811)	**<0.0001**	4.302	2.361-7.839	**<0.0001**
ypM stage	0	1.000	Ref		1.000	Ref	
	1	3.051	(2.101-4.430)	**<0.0001**	2.511	1.485-4.248	**0.001**
Vascular/ lymphatic invasion	No	1.000	Ref		1.000	Ref	
	Yes	2.882	(2.332-3.562)	**<0.0001**	1.607	1.233-2.095	**<0.0001**
Resection clearance	R0	1.000	Ref		1.000	Ref	
	R1	2.298	(1.977-2.670)	**<0.0001**	1.257	0.968-1.632	0.086
Differentiation	G1	1.000	Ref		1.000	Ref	
	G2	1.713	(1.031-2.847)	**0.038**	0.957	0.515-1.777	0.888
	G3	2.759	(1.684-4.521)	**<0.0001**	1.076	0.583-1.988	0.814
	G4	2.713	(1.548-4.758)	**<0.0001**	0.887	0.434-1.811	0.742