PREDICTING PATHOLOGICAL RESPONSE OF ESOPHAGEAL CANCER TO NEOADJUVANT CHEMOTHERAPY: THE IMPLICATIONS OF METABOLIC NODAL RESPONSE FOR PERSONALISED THERAPY

Running title

Predicting esophageal pathological response

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Disclaimers

FVG is a paid consultant to Alliance Medical

MRM is a paid consultant/advisor Amgen, BMS, GSK, Merck, Millennium and has received institutional funding from Amgen, AZ, BMS, Clovis, Eisai, GSK, Immunocore, Johnson & Johnson, Merck, Millennium, Novartis, Pfizer, Roche and Vertex

Financial support

JMF is supported by the NIHR Oxford Biomedical Research Centre

Word count

2405

ABSTRACT

INTRODUCTION

Only a minority of esophageal cancers demonstrates a pathological tumor response (pTR) to neoadjuvant chemotherapy (NAC). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) is often used for restaging after NAC and to assess response. Increasingly, it is used during therapy to identify unresponsive tumors and predict pTR , using avidity of the primary tumor alone. However, definitions of such metabolic tumor response (mTR) vary. We aimed to comprehensively re-evaluate metabolic response assessment using accepted parameters, as well as novel concepts of metabolic nodal stage (mN) and nodal response (mNR).

PATIENTS AND METHODS

This was a single-center retrospective UK cohort study. All patients with esophageal cancer staged before NAC with PET-CT and after with CT or PET-CT and undergoing resection from 2006-2014 were identified. pTR was defined as

Mandard tumor regression grade 1-3; imaging parameters included metrics of tumor avidity (standardized uptake value [SUV]max/mean/peak), composites of avidity and volume (including metabolic tumor volume), nodal SUVmax, and our new concepts of mN stage and mNR.

RESULTS

Eighty-two (27.2%) of 301 patients demonstrated pTR. No pre-NAC PET parameters predicted pTR. In 220 patients re-staged by PET-CT, The optimal tumor ΔSUVmax threshold was a 77.8% reduction. This was as sensitive as the current PET Response Criteria in Solid Tumors (PERCIST) 30% reduction, but more specific with a higher negative predictive value ($p<0.001$). ΔSUVmax and Δlength independently predicted pTR, and composite avidity/spatial metrics outperformed avidity alone. Whilst both mTR and mNR were associated with pTR, in 82 patients with FDG-avid nodes before NAC we observed mNR in 10 (12.2%) not demonstrating mTR.

CONCLUSION

Current definitions of metabolic response are suboptimal and too simplistic. Composite avidity/volume measures improve prediction. mNR may further improve response assessment, by specifically assessing metastatic tumor sub-populations, likely responsible for disease relapse, and should be urgently assessed when considering aborting therapy on the basis of mTR alone.

Keywords

Esophageal cancer; neoadjuvant therapy; positron-emission tomography; precision oncology

INTRODUCTION

In the USA and Europe the mainstay of curative treatment of esophageal cancer is neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACR) followed by surgery (*1,2*). Both confer important survival benefits (*3*); however, up to 60% of tumors show either minimal or no pathological response (pTR) to NAC (*4,5*), and a similarly poor response is seen in 30-40% after NACR*(6)*. For these patients, such, in retrospect, futile therapy delays surgery, potentially allowing disease progression and a worse prognosis (*7*). The ability to predict pTR at the outset would therefore be invaluable, as it would allow personalized therapy, with neoadjuvant therapy being omitted or changed to alternative therapy in those patients unlikely to benefit.

The evidence for the predictive value of baseline molecular markers and positron emission tomography (PET) is insufficiently robust to justify major treatment changes (*8,9*). Interval assessment of response during therapy is, therefore, the next best option for personalizing therapy. Interval tumor metabolic response (mTR) on PET predicts pTR, albeit imperfectly. A 35% reduction in maximum standardized uptake value (SUVmax) is most commonly used during therapy (*10,11*) , and formed the basis of the landmark MUNICON trial, wherein NAC was continued after a single cycle only in patients with a reduction in SUVmax greater than 35% (*12*)*;* the alternative PERCIST criteria recommend a 30% reduction after NAC to define mTR *(13*). However, these thresholds may not be optimal: PERCIST is neither tumor nor context-specific, whilst the MUNICON threshold was derived from just 40 patients; furthermore, SUVmax provides no spatial information. More fundamentally, both assess only the primary tumor; the high rates of disease recurrence seen even in patients with pathologically responsive primary tumors, suggests important unidentified factors, perhaps involving nodal or distant micrometastases—a recent report

described tumor down-staging after NAC (a reduction from pre-treatment clinical to post-treatment pathological stage) to be strongly associated with survival (*14*).

With this in mind, we recently explored the novel concepts of FDG-avid nodal stage (mN stage) and metabolic nodal response (mNR), and demonstrated major clinical implications for identifying disease progression during NAC, independent of primary tumor stage and response (*15*).

In this study we aimed to re-examine comprehensively the utility of PET-CT in predicting pTR to NAC. Firstly, we assessed the predictive ability of clinical, pathological and imaging factors available before NAC. Secondly, we aimed to define and compare optimal thresholds of mTR after NAC and assess, for the first time, the novel concept of mNR. Thirdly, we aimed to generate and validate predictive models that might have clinical utility.

METHODS

Patients and staging protocol

All patients who underwent potentially curative surgical resection of esophageal/gastroesophageal junctional cancer and were staged initially with computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) PET-CT were identified from a departmental database (May 2006-November 2014) (*16*). This included all cell types. The study was approved by the institutional clinical governance department, and the need for written informed consent was waived. Patients were also staged with endoscopic ultrasound, and laparoscopy for tumors extending below the diaphragm as previously described (*16*).

Examinations were reported by a consultant upper gastrointestinal radiologist/gastroenterologist using the contemporary American Joint Committee on Cancer TNM staging manual (6th (*17*) or 7th edition (*18*)).

Neoadjuvant chemotherapy

NAC was considered for all patients with disease more advanced than T1N0. Patients with esophageal and GEJ Siewert 1/2 tumors (*19*) received either: cisplatin and 5-fluorouracil (5-FU; 2 cycles; n=182)(*20*), oxaliplatin and 5-FU (2 cycles; n=46) (*21*), epirubicin, cisplatin and 5-FU (ECF; 3 cycles; n=7), epirubicin, cisplatin and capecitabine (ECX; 3 or 4 cycles; n=22) (*22*), epirubicin, oxaliplatin and capecitabine (EOX; 3 cycles; n=3), cisplatin and etoposide (2 cycles; n=1) or oxaliplatin and capecitabine (2 cycles; n=1). Patients with type 3 GEJ tumors received ECX/EOX/ECF (3 cycles). Some patients (distal esophageal/GEJ) received 3 cycles of ECX pre-and post-operatively with (n=7) or without bevacizumab (n=20) (*23*), or 3 cycles of ECF pre- and post-operatively (n=12) (*24*).

Restaging CT and PET-CT

Patients were re-staged 4-6 weeks after NAC using CT before 2008 and PET-CT afterwards (although a small minority underwent CT due to clinical trial protocols) as previously described (*16*). ^{18}F-FDG PET-CT was performed using one of two scanners. Before 3rd November 2009 scans were performed on a GE Discovery STE (GE Healthcare,Milwaukee, USA) 60 minutes post-injection of 400MBq ^{18}F-fluorodeoxyglucose (FDG). Images were reconstructed using a time of flight ordered subset expectation maximization reconstruction algorithm (two iterations, 20 subsets, 70cm field of view, 128 matrix, voxel size 5.47x5.47x3.3 mm^3). After 3rd November 2009, scans were performed on a GE Discovery 690

(GE Healthcare,Milwaukee, USA) 90 minutes post-injection of 4MBq/Kg FDG. Images were reconstructed using a time of flight ordered subset expectation maximization reconstruction algorithm (two iterations, 24 subsets, 6.4mm Gaussian filter, 70cm field of view, 256 matrix, voxel size 2.73x2.73x3.3 mm^3). Examinations were independently reported by 2 dedicated PET-CT radiologists.

Operations

Surgery was typically performed within 2 weeks of re-staging scan. A minimum two-field lymphadenectomy was performed as standard.

Data and variables

Patient variables included age, gender, and American Society of Anesthesiologists grade (*25*); pre-treatment tumor variables were cell type, grade (*26*), anatomical site, T (7^{th} edition), N stage (6^{th} edition as data were insufficient for conversion to the 7^{th}), and whether the tumor was impassable at esophago-gastroduo-denoscopy. PET-CT variables are described below. NAC variables comprised dual or triple agent regimen (due to large number of regimens and small patient groups), and time (days) from staging to restaging scan and scan to surgery to adjust for delays and number of cycles given. pTR was defined as Mandard Tumor Regression Grade (TRG) ≤3, following dedicated review by a consultant cellular pathologist (*27*). The Mandard TRG was used in preference to alternative TRGs, being the most frequently used TRG for esophageal cancer (*28*), with optimal prediction of survival (*29,30*).

PET-CT variables

Variables comprised primary tumor FDG-avidity (SUVmax and length [cm]), mN stage, mNR and SUVmax of the most FDG-avid node. The development of mN stage and mNR have been described previously (*15*). mN stage (nodes visible discretely from the tumor, within a standard lymphadenectomy territory, with SUVmax>2.5 or background mediastinal blood pool) comprised mN0 (0 avid nodes), mN1 (1-2 nodes) and mN2 (>2 nodes). mNR comprised complete (CMR), or partial metabolic response (PMR; reduction in mN or SUVmax ≥30%), stable (SMD; stable mN or reduction/progression SUVmax <30%) or progressive metabolic disease (PMD; progression of mN or SUVmax ≥30%.

For examinations using the second PET-CT scanner, additional variables were generated by two authors: metabolic tumor volume (MTV), SUVmean, SUVpeak, and tumor glycolytic volume (TGV)mean/max. MTV was measured using a fixed threshold technique (SUV≥4). TGVmean was calculated manually as the product of MTV and SUVmean. TGVmax was calculated as the product of MTV and SUVmax. mTR was quantified using absolute changes (Δ%) and thresholds defined previously (PET Response Criteria in Solid Tumors [PERCIST} and MUNICON criteria; SUVmax) (*13*); additionally, new thresholds were generated by receiver operator characteristics (ROC).

Statistical analysis

Analysis was performed using R v3.0.2 (*31*). Correction for multiple comparisons was performed using the Bonferroni method (*32)* or false discovery rate using FDRtoolv1.2.12 (*33*). For regression continuous variable distribution was assessed using density plots and transformed (age^2; logSUVmax/mean/peak and time to re-staging/surgery). Multivariate analysis included all variables

(including PET-CT scanner) after exclusion of perfect separators. ROC optimal thresholds were calculated and compared with pROC (*34*); 95% confidence intervals (CI) using 200 iterations of 0.632 bootstrapping. Sensitivities and specificities were compared using McNemar's test (DTComPair v1.0.3) (*35*).

Model development, tuning, validation and performance

Three techniques were used as previously described (*16*): logistic regression (backwards stepwise binary logistic), decision tree analysis (recursive partitioning using loss matrices) and artificial neural networks (feed forward back-propagation multilayer perceptron). Models were tuned, generated and validated internally (0.632 bootstrapping) using a development group (patients staged/restaged using the more recent scanner) and validated independently (patients staged/restaged using the earlier scanner; validation group). We partitioned patients in this way to minimize any potential bias, to ascertain immediate clinical utility, and also to assess generalizability to a different scanner system.

RESULTS

Three-hundred-and-two patients underwent resection following NAC. TRG was available for 301 (table 1). pTR was evident in 82 patients (27.2%): TRG 1 in 14 (4.65%); TRG 2 in 13 (4.32%); TRG 3 in 55 (18.3%); TRG 4 in 162 (53.8%); TRG 5 in 67 (22.2%).

Predicting pathological response before NAC

Although there were nominally significant associations between tumor anatomical location and response, on multivariate regression, the only variable

that predicted pTR was the use of a triple agent NAC regimen: OR 5.98 (CI 2.44-14.7; $p=8.94x10^{-5}$; Table 2).

Predicting pathological response after NAC using absolute PET variables

A more FDG-avid primary tumor after NAC, as quantified by all metrics, was negatively associated with pTR: logSUVmax OR $3.84x10^{-4}$ ($1.17x10^{-5}$-$2.00x10^{-3}$; $p=9.89x10^{-6}$ (Table 3; Supplementary Table 1).

Predicting pathological response using metabolic tumor response

mTR predicted pTR (tables 1 and 4; Supplementary Table 2). This was true both for ΔSUVmax and Δlength, independently on regression: logΔSUVmax OR for each % reduction 1.03 (1.01-1.06), $p=3.24x10^{-3}$; Δlength OR=1.02 (1.00-1.03); p=0.019. Interestingly, whilst a PERCIST ≥30% reduction was associated with pTR, the MUNICON ≥35% threshold was not, once adjusted for Δlength. All additional metrics of mTR were associated with pTR.

Predicting pathological response using metabolic nodal response

mNR was associated with pTR using Fisher's exact test (Table 1, but not on multivariate regression (Table 4). Notably, mNR and pTR were discordant in 42/220 (19.1%) patients (Table 5). In 41 cases there was a nodal CMR or PMR without pTR, representing 51.2% of the 82 patients with FDG-avid nodes before NAC (Table 5).

mTR and mNR were also compared (Table 5) and were found to be discordant in 13 (5.90%) cases overall, representing 15.9% of patients with FDG-avid nodes before NAC. Typically discordance arose due to a mNR in the absence of mTR (10 cases; 4.6% and 12.2% respectively).

Defining optimal metabolic response thresholds

The accuracy of each continuous (non-threshold) metric of mTR in predicting pTR is shown in Supplementary Table 3: all were moderately discriminant (80.2-84.4%), with no statistically significant differences.

The optimal thresholds for each metric of mTR were determined (supplementary Table 3), for (a) discrimination (b) sensitivity and (c) specificity. The optimal Δ SUVmax for sensitivity was a 27.4-30.6% reduction, identical to PERCIST (30%) and similar to the MUNICON threshold (35%). However, specificity was minimal: 33.0% (23.8-42.6); 41.8% (32.0-52.2) respectively. By contrast, the optimal ΔSUVmax threshold for balancing sensitivity (73.6% [58.6-82.7]) and specificity (84.5% [78.7-89.1]) was dramatically different: a 77.8% reduction. Rounded down to a more pragmatic 75.0%, sensitivity was identical, whilst specificity reduced slightly to 84.0%.

The ability of each mTR metric to predict pTR is shown in Supplementary Tables 4-6. Overall, ΔSUVmax of 77.8%, was significantly more discriminant, with higher negative predictive value (NPV), than the PERCIST (30%) and MUNICON (35%) thresholds. The same was true for ΔMTV, ΔTGVmax and ΔTGVmean. The highest sensitivities were seen with PERCIST (sensitivity 100%), MUNICON (97.1%), **Δ**MTV (97.1%), ΔTGVmax (97.1%) and ΔTGVmean (94.3%); these were significantly more sensitive than Δlength ($<4.68x10^{-3}$; FDR=0.046), but not

ΔSUVmax of 77.8%. The most specific were ΔSUVmax of 77.8% (81.7% specific) and Δlength of 53.1% (82.7%) ($p<4.11x10^{-4}$).

Performance of predictive models

Models were generated (supplementary table 7) using metrics of mTR/mNR. The most successful was a logistic regression model comprising Δlength + ΔSUVmax; this was highly sensitive (91.4%), moderately specific (71.4%) and discriminant (0.814) and this sensitivity persisted during internal and independent validation (although with relatively poor specificity and discrimination). However, ultimately none of the composite models outperformed individual mTR thresholds (Supplementary Tables 4-7).

DISCUSSION

In this study of 301 patients treated with NAC and surgery—the largest to date in esophageal cancer —we found no baseline clinical, tumor or PET variables associated with pTR. This is perhaps unsurprising, reflecting the daunting complexity involved. 'Chemoresistance' is usually multifactorial and constitutes a spectrum of sensitivity, which depends upon numerous macroscopic, microscopic and molecular factors modulating chemotoxicity (*36,37*). Intratumoral heterogeneity further complicates this, with a number of subclones, potentially demonstrate differential response and baseline characteristics, in addition to heterogeneity between tumor and nodal metastases. In contrast, following NAC, a number of PET variables, including absolute tumor metrics and those assessing either mTR or mNR, were strongly associated with pTR on multivariate analysis, and a number of clinically relevant implications were identified.

Firstly, the identification of a significantly better ΔSUVmax threshold (77.8% reduction) than the generic PERCIST threshold (30%) suggests that the latter should be raised considerably for esophageal cancer to improve stratification of mTR (perhaps to a more pragmatic 75%). This threshold was nominally significantly better than the MUNICON threshold (35%), but as this threshold was originally derived during therapy rather than after therapy (as in our study), the significance of this is uncertain and we are unable to draw further conclusions.

Secondly, rather than considering avidity in isolation, we found evidence that incorporating spatial data improved prediction: Δlength at a most basic level, or ideally a composite metric such as ΔMTV or ΔTGVmax/mean. These outperformed the existing recommended PERCIST threshold of a 30% SUVmax reduction. They were comparably sensitive, but more specific ($p<4.11x10^{-4}$) and discriminant ($p<9.38x10^{-5}$) and were supported by internal (bootstrapping) validation. This suggests that composite metrics may have greater predictive ability in clinical trials than ΔSUVmax alone (such as in the MUNICON trial 35% threshold). In particular, their superior specificity and high NPV (98.5-100%) might identify more non-responders suitable for cessation of therapy. These findings are in keeping with those of recent smaller studies in chemoradiotherapy; in 20 patients using support vectors and logistic regression, Zhang *et al* found mTR quantified using spatial avidity metrics outperformed avidity alone in predicting pTR (*38*); whilst in 37 patients Jayachandran *et al* found MTV to outperform SUVmax (*39*).

Thirdly, this is the first study to assess the novel concept of mNR in association with pTR. We found that the primary tumor and nodal disease often demonstrated a discordant response to NAC, with mNR seen in the absence of mTR or pTR. Using mTR alone (as in the MUNICON trial), this subgroup of

patients would be classed as 'non-responders' and NAC aborted; our findings suggest that in such patients their nodal metastases may in fact be responding to treatment. Nodal metastases by definition contain an aggressive subpopulation of cancer clones originating from the primary tumor, which then evolve differently at a genetic and phenotypic level*(40)*. A crucial such phenotype is chemosensitivity. Whilst clearly mNR is likely an imperfect surrogate of pathological nodal response, no systems for assessing nodal response are in use. Our findings are important, as they offer a vital insight into assessing response in the tumor subclones with proven metastatic behavior, likely to be responsible for local and distant disease relapse.

This study has a number of limitations. Whilst the current gold-standard technique for disease response assessment is direct histopathological examination, this remains imperfect. We used the Mandard classification, which originally described the response of esophageal squamous cell carcinoma to cisplatin-based NACR (*27*). The Mandard TRG has subsequently been validated for esophageal adenocarcinoma (*41*) although a number of other classifications have been described (*42*); all, however, remain relatively subjective, and are tempered by potential inter-observer variability, and intra-tumoral sampling bias (*43*). Ultimately, the Mandard TRG is most frequently used and provides the basis for optimal prediction of survival (*28,30*). An additional limitation of this study is its retrospective design over a long time period, which whilst necessary to generate a sufficient cohort resulted in a change of PET-CT scanner, and the availability of additional metrics for the more recent scanner alone. In addition, we included a range of cell types, rather than restricting our analysis. We sought to mitigate these limitations with dedicated review of TRG by a single expert pathologist, by adjusting analyses for cell type, the scanner used, and by restricting model development to the more recent representative scanner with subsequent validation in the earlier group, in order to minimize any bias. We

also performed a *post hoc* analysis comparing metrics between scanners, demonstrating no significant differences in either metabolic response of the primary or nodal tumor (p=0.109 [Mann-Witney] and 0.068 [Fisher's exact test]). We believe this to be the largest study performed for esophageal cancer and believe that our results are robust—whether they can be extrapolated to NACR is not clear, but we believe warrants urgent assessment. In addition, assessment of a number of textural response parameters, including entropy and run-length matrices, which whilst not routinely used in clinical practice have recently been shown to be associated with pTR following NACR (*44*), and their inclusion in conjunction with volume has been suggested to improve prognostication (*45*). Such metrics may therefore provide complementary predictive data.

In conclusion, we found that the current definitions used for metabolic response assessment after NAC, based solely on ΔSUVmax, are both suboptimal and too simplistic, and that using composite measures of FDG-avidity and volume could significantly improve the predictive ability of PET. The assessment of nodal response, which is often discordant with the primary tumor response, should be urgently studied, as it may offer the potential to further improve response assessment, specifically within tumor populations with proven metastatic behavior.

Table 1: Patient characteristics and management and tumor response

Baseline factor	Overall (n=301)	Pathological response (n=82)	No pathological response (n=219)	p $\alpha=4.55x10^{-3}$ pre-NAC $\alpha=2.63x10^{-3}$ post-NAC
Age *Median; IQR; range*	64.0 (58.0-70.0; 36.0-80.0)	62.5 (57.3-69.0; 36.0-79.0)	64.0 (58.0-70.0; 38.0-80.0)	0.369[a]
Gender *Male* *Female*	 228 (75.7%) 73 (24.3%)	 61 (74.4%) 21 (25.6%)	 167 (76.3%) 52 (23.7%)	0.764[b]
Cell type *AC* *SCC* *AS* *NEC* *SC* *Anaplastic*	 249 (82.7%) 44 (14.6%) 5 (1.66%) 0 (0.00%) 1 (0.33%) 2 (0.66%)	 68 (82.9%) 13 (15.9%) 1 (1.22%) 0 (0.00%) 0 (0.00%) 0 (0.00%)	 181 (82.6%) 31 (14.2%) 4 (1.83%) 0 (0.00%) 1 (0.46%) 2 (0.91%)	0.979 [b]
Grade of differentiation *Well* *Moderate* *Poor* *Undifferentiated*	 28 (9.30%) 128 (42.5%) 140 (46.5%) 5 (1.66%)	 5 (6.10%) 35 (42.7%) 42 (51.2%) 0 (0.00%)	 23 (10.5%) 93 (42.0%) 98 (44.7%) 5 (2.28%)	0.338[b]
Tumor site *Proximal 1/3* *Mid 1/3* *Distal 1/3* *GEJ 1* *GEJ 2* *GEJ 3* *Multifocal*	 0 (0.00%) 18 (5.98%) 52 (17.3%) 72 (23.9%) 107 (35.5%) 51 (16.9%) 1 (0.33%)	 0 (0.00%) 9 (11.0%) 11 (13.4%) 23 (28.0%) 20 (24.4%) 19 (23.2%) 0 (0.00%)	 0 (0.00%) 11 (5.02%) 41 (18.7%) 49 (22.4%) 85 (38.8%) 32 (14.6%) 1 (0.46%)	0.033 [b]
Pre-NAC staging				
T stage *1* *2* *3* *4a* *4b*	 7 (2.33%) 46 (15.3%) 231 (76.7%) 17 (7.76%) 0 (0.00%)	 2 (2.43%) 19 (23.2%) 56 (68.3%) 5 (6.10%) 0 (0.00%)	 5 (2.28%) 27 (12.3%) 175 (79.9%) 12 (35.48%) 0 (0.00%)	0.114 [b]
N stage *0* *1*	 88 (29.3%) 213 (70.7%)	 58 (26.5%) 161 (73.5%)	 30 (36.6%) 52 (63.4%)	0.090 [b]
Initial PET CT *FDG-avid* *FDG-negative*	 290 (96.7%) 11 (3.65%)	 75 (91.5%) 7 (8.54%)	 215 (98.2%) 4 (1.83%)	0.011[b]
Initial PET-CT scanner *1* *2* *NA*	 142 (47.7%) 159 (52.3%) 0 (0.00%)	 38 (46.3%) 44 (55.7%)	 104 (47.5%) 115 (52.5%)	0.897 [b]
Restaging PET-CT scanner *1* *2* *CT*	 62 (20.6%) 158 (52.5%) 81 (26.9%)	 16 (19.5%) 46 (56.1%) 20 (24.4%)	 46 (21.0%) 112 (51.19%) 61 (27.9%)	0.739 [b]
mN stage *0 (0 nodes)* *1 (1-2 avid nodes)* *2 (>2 avid nodes)* *NA*	 209 (69.4%) 54 (17.9%) 38 (12.6%) 0 (0.00%)	 54 (65.9%) 14 (17.1%) 14 (17.1%)	 155 (70.8%) 40 (18.3%) 24 (11.0%)	0.371 [b]
Impassable at EGD? *No* *Yes*	 278 (92.4%) 23 (7.60%)	 77 (93.9%) 5 (6.10%)	 201 (92.8%) 18 (8.20%)	0.633[b]
Surgical approach				
Resection *LTE*	 200 (66.4%)	 12 (14.6%)	 156 (71.3%)	0.003[b]

ILE *3 stage* *THE* *ETG*	46 (15.3%) 10 (3.32%) 1 (0.33%) 44 (14.6%)	44 (53.7%) 5 (6.10%) 1 (1.22%) 20 (24.4%)	34 (15.5%) 5 (2.28%) 0 (0.00%) 24 (11.0%)	
Response to chemotherapy				
Chemotherapy *Dual* *Triple*	 230 (76.4%) 71 (23.6%)	 48 (58.5%) 34 (41.5%)	 182 (83.1%) 37 (16.9%)	$2.69x10^{-5}$ [b]
Days to re-staging scan *Median; IQR; range*	82.0 (71.0-93.0)	88.5 (71.3-106.8; 43.0-167)	82.0 (71.0-91.0; 40.0-165)	0.036 [b]
Days from scan to surgery *Median; IQR; range*	24.0 (17.0-33.0)	23.0 (18.3-31.8; 5.0-52.0)	23.0 (15.0-33; 4.0-72.0)	0.283 [b]
pTR *No* *Yes*	 82 (27.2%) 219 (72.8%)	NA	NA	NA
mTR *Non-avid* *CMR* *PMR* *SMD* *PMD* *NA*	 7 (2.33%) 48 (15.9%) 108 (35.9%) 43 (14.3%) 14 (4.65%) 81 (26.9%)	 5 (8.06%) 33 (53.3%) 20 (32.4%) 4 (1.33%) 0 (0.00%) 20 (NA)	 2 (1.27%) 15 (9.49%) 88 (55.7%) 39 (24.7%) 14 (8.86%) 61 (NA)	$5.38x10^{-13}$ [b]
mNR *No avid nodes* *CMR* *PMR/SMD/PMD* *NA*	 138 (45.8%) 50 (16.6%) 32 (10.6%) 81 (26.9%)	 39 (62.9%) 21 (33.9%) 2 (3.22%) 20 (NA)	 99 (62.6%) 29 (18.4%) 30 (19.0%) 61 (NA)	$1.23x10^{-4}$ [b]

a=Mann-Witney test; b=Fisher's exact test; NA=not applicable; GEJ=gastroesophageal junction; LTE=left thoracoabdominal esophagectomy; ILE=Ivor-Lewis esophagectomy; THE=transhiatal esophagectomy; ETG=extended total gastrectomy; CMR=complete metabolic response; PMR=partial metabolic response; SMD=stable metabolic disease; PMD=progressive metabolic disease; mTR=metabolic tumour response; pTR=pathological tumour response; mNR=metabolic nodal response

Table 2: Baseline factors associated with pathological response to neoadjuvant chemotherapy: univariate and multivariate regression

Factor	Response			
	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Age (Median; IQR)	1.00 (1.00-1.00)	0.536	1.00 (1.00-1.00)	0.949
Sex				
Female	Ref	Ref	Ref	Ref
Male	0.90 (0.50-1.62)	0.722	0.94 (0.45-1.95)	0.859
Cell				
AC	Ref	Ref	Ref	Ref
SCC	1.14 (0.56-2.32)	0.716	0.87 (0.31-2.45)	0.792
AS	NA	NA	NA	
NEC	NA	NA	NA	
SC	NA	NA	NA	
Anaplastic	NA	NA	NA	
Grade				
Well	Ref	Ref	Ref	Ref
Moderate	1.77 (0.62-5.02)	0.284	1.07 (0.33-3.49)	0.906
Poor	1.99 (0.71-5.58)	0.194	1.53 (0.47-4.97)	0.477
Undifferentiated	NA	NA	NA	NA
Site				
Proximal 1/3	NA	NA	NA	NA
Mid 1/3	Ref	Ref	Ref	Ref
Distal 1/3	0.30 (0.10-0.91)	0.034	0.21 (0.05-0.79)	0.021
GOJ 1	0.51 (0.18-1.54)	0.200	0.34 (0.09-1.26)	0.106
GOJ 2	0.28 (0.10-0.78)	0.015	0.17 (0.04-0.69)	0.013
GOJ 3	0.68 (0.23-1.98)	0.480	0.15 (0.03-0.64)	0.020
Multifocal	NA	NA	NA	NA
T stage				
1	Ref	Ref	Ref	Ref
2	1.76 (0.31-10.0)	0.525	2.33 (0.34-16.0)	0.390
3	0.83 (0.16-4.42)	0.830	0.98 (0.15-6.27)	0.986
4a	1.05 (0.15-7.27)	0.967	1.13 (0.13-10.0)	0.916
N stage				
0	Ref	Ref	Ref	Ref
1	0.64 (0.37-1.10)	0.105	0.60 (0.13-1.16)	0.129
Passable at EGD?				
Yes	Ref	Ref	Ref	Ref
No	0.63 (0.20-1.93)	0.416	0.50 (0.13-1.95)	0.317
Chemotherapy				
Chemo				
Dual	Ref	Ref	Ref	Ref
Triple	3.48 (1.97-6.14)	1.76×10^{-5}	5.98 (2.44-14.7)	8.94×10^{-5}
Log time to restaging	63.9 (4.24-964)	2.66×10^{-3}	10.8 (0.42-280)	0.152
Log time to surgery	0.93 (0.31-2.79)	0.896	1.12 (0.29-4.33)	0.873
PET-CT variables				
PET scanner				
1	Ref	Ref	Ref	Ref
2	1.07 (0.64-1.79)	(0.796)	0.69 (0.36-1.32)	0.267
mN stage				
0	Ref	Ref	Ref	Ref
1	0.94 (0.46-1.89)	0.857	1.42 (0.60-3.34)	0.426
2	1.67 (0.80-3.48)	0.720	1.72 (0.67-4.45)	0.261
Log SUVmax	0.43 (0.16-1.11)	0.081	0.54 (0.15-1.92)	0.343

Log FDG-avid length	0.90 (0.81-1.01)	0.070	0.89 (0.77-1.04)	0.145
Subset of patients staged using second PET-CT scanner (n=155)				
SUVmean	1.47 (0.09-23.4)	0.784	1.56 (0.04-65.8)	0.814
SUVpeak	2.53 (0.41-15.8)	0.320	1.85 (0.50-6.77)	0.356
MTV	1.55 (0.79-3.04)	0.203	1.70 (0.66-4.39)	0.276
TGVmax	1.53 (0.84-2.76)	0.163	1.72 (0.74-3.99)	0.230
TGVmean	1.45 (0.86-2.44)	0.164	1.64 (0.78-3.42)	0.189

a=Mann-Witney U Test; b=Fisher's exact test; GEJ=gastroesophageal junction; FDG=flurodeoxyglucose; NA=not applicable; *effect sizes for subgroup with FDG-avid nodes only

Table 3: Post-chemotherapy factors associated with pathological response to neoadjuvant chemotherapy: univariate and multivariate regression – adjusted for baseline variables

Factor	Response			
	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Chemotherapy				
Chemo Dual Triple	 Ref 4.30 (2.16-8.55)	 Ref $3.23x10^{-5}$	 Ref 17.6 (4.39-70.1)	 Ref $5.00x10^{-5}$
Log time to restaging	25.1 (1.10-574)	0.044	0.32 (0.00-69.2)	0.678
Log time to surgery	2.28 (0.57-9.07)	0.241	0.52 (0.06-4.82)	0.567
PET-CT variables				
PET scanner 1 2	 Ref 1.09 (0.58-2.07)	 Ref 0.782	 Ref 0.10 (0.02-0.55)	 Ref 0.008
Restaging PET scanner 1 2	 Ref 1.30 (0.66-2.57)	 Ref 0.446	 Ref 5.24 (0.95-28.9)	 Ref 0.057
Restaging mN stage 0 (0 avid nodes) 1 (1-2 avid nodes) 2 (>2 avid nodes)	 Ref 0.16 (0.02-1.28) 0.16 (0.02-1.28)	 Ref 0.084 0.084	 Ref 1.07 (0.07-16.8) 2.39 (0.18-31.6)	 Ref 0.959 0.509
Restaging log SUVmax	$2.37x10^{-3}$ ($4.21x10^{-4}$-0.01)	$6.93x10^{-12}$	$3.84x10^{-4}$ (1.17x10-5-0.02)	$9.89x10^{-6}$
Restaging log avid length	0.61 (0.51-0.73)	$3.80x10^{-8}$	1.01 (0.76-1.34)	0.951
Restaging log MTL	0.03 (0.01-0.10)	$3.88x10^{-10}$	0.02 ($4.03x10^{-3}$-0.06)	$6.19x10^{-9}$
Subset of patients with FDG-avid nodes (n=30)				
Log nodal SUVmax	8.71 (0.01-5787)	0.514	NA	NA
Subset of patients staged using second PET-CT scanner (n=155)				
Log SUVmean	$1.58x10^{-4}$ ($7.51x10^{-6}$-$3.23x10^{-3}$)	$1.78x10^{-4}$	$1.13x10^{-7}$ ($8.55x10^{-12}$-$1.46x10^{-3}$)	$9.32x10^{-5}$
SUVpeak	$5.05x10^{-3}$ ($1.81x10^{-4}$-0.14)	$1.85x10^{-3}$	0.57 (0.39-0.84)	$3.90x10^{-3}$
Log MTV	0.28 (0.18-0.44)	0.203	0.09 (0.03-0.28)	$2.03x10^{-5}$
Log TGVmax	0.32 (0.21-0.48)	$3.91x10^{-8}$	0.11 (0.04-0.31)	$2.72x10^{-5}$
Log TGVmean	0.30 (0.19-0.46)	$3.27x10^{-8}$	0.10 (0.03-0.29)	$2.29x10^{-5}$

a=Mann-Witney U Test; b=Fisher's exact test; GEJ=gastroosophageal junction; FDG=flurodeoxyglucose; NA=not applicable; *effect sizes for subgroup with FDG-avid nodes only

Table 4: Metabolic response and other factors associated with pathological response to neoadjuvant chemotherapy: univariate and multivariate regression (patients staged and restaged using same PET scanner) – adjusted for baseline variables

Factor	Response			
	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Chemotherapy				
Chemo Dual Triple	 Ref 4.30 (2.16-8.55)	 Ref $3.23x10^{-5}$	 Ref 20.3 (4.50-91.4)	 Ref $8.84x10^{-5}$
Log time to restaging	69.1 (1.86-2571)	0.022	0.22 (0.00-172)	0.658
Log time to surgery	1.75 (0.41-7.44)	0.452	0.70 (0.06-8.36)	0.781
PET-CT variables				
Initial / restaging PET scanner 1 2	 Ref 0.87 (0.40-1.88)	 Ref 0.718	 Ref 0.71 (0.21-2.38)	 Ref 0.580
nMR Negative CMR PMR SMD PMD	 Ref 1.93 (0.93-4.01) 0.45 (0.05-3.87) 0.27 (0.03-2.18) NA (NA)	 Ref 0.076 0.465 0.219 NA	 Ref 2.01 (0.54-7.51) 11.2 (0.64-197.3) 1.15 (0.09-14.4) NA (NA)	 Ref 0.300 0.098 0.911 NA
Reduction logSUVmax (%)	1.04 (1.02-1.05)	$6.65x10^{-8}$	1.03 (1.01-1.06)	$3.24x10^{-3}$
Reduction avid length (%)	1.03 (1.02-1.04)	$9.37x10^{-8}$	1.02 (1.00-1.03)	0.019
Additional metrics in all patients (n=202)				
Reduction MTL (%)	1.05 (1.03-1.07)	$2.86x10^{-6}$	1.11 (1.05-1.16)	$1.16x10^{-5}$
PERCIST (30.0%) CMR PMR S/PMD	 Ref 0.10 (0.04-0.22) 0.04 (0.01-0.14)	 Ref 2.24x10-8 2.18x10-7	 Ref 0.08 (0.02-0.32) 0.06 (0.01-0.49)	 Ref $3.53x10^{-5}$ $8.46x10^{-4}$
MUNICON (35.0%) No response Response	 Ref 5.21 (2.08-13.0)	 Ref 4.22x10-5	 Ref 1.63 (0.41-6.45)	 Ref 0.484
Subset of patients staged using second PET-CT scanner (n=155)				
Reduction SUVmean (%)	1.03 (1.02-1.04)	$2.25x10^{-8}$	1.05 (1.02-1.09)	$1.90x10^{-3}$
Reduction SUVpeak (%)	1.09 (1.03-1.15)	$1.91x10^{-5}$	1.04 (1.02-1.05)	$2.20x10^{-3}$
Reduction MTV (%)	1.44 (1.09-1.92)	$2.70x10^{-5}$	1.16 (1.07-1.25)	0.011
Reduction TGVmax (%)	1.30 (1.12-1.52)	$5.82 x10^{-3}$	2.31 (1.27-4.20)	$2.72x10^{-5}$
Reduction TGVmean (%)	1.23 (1.10-1.37)	$3.91x10^{-8}$	1.87 (1.20-2.90)	$2.29x10^{-5}$

a=Mann-Witney U Test; b=Fisher's exact test; GEJ=gastroesophageal junction; FDG=flurodeoxyglucose; NA=not applicable; *effect sizes for subgroup with FDG-avid nodes only; nMR=metabolic nodal desponse

Table 5: Comparison of tumour and nodal metabolic response

Tumour	mNR

response	NA	CMR	PMR	SMD	PMD
Pathological response					
pTR	39 (17.7%)	21 (9.55%)	1 (0.45%)	1 (0.45%)	0 (0.00%
No pTR	99 (45.0%)	29 (13.2%)	12 (5.45%)	13 (5.91%)	5 (22.7%)
Metabolic response					
NA	6 (2.73%)	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
CMR	32 (14.5%)	14 (1.82%)	1 (0.45%)	1 (0.45%)	0 (0.00%)
PMR	68 (30.9%)	29 (13.2%)1	8 (3.64%)	2 (0.91%)	0 (0.00%)
SMD	22 (9.09%)	5 (2.27%)	4 (1.82%)	10 (4.55%)	3 (1.36%)
PMD	10 (4.55%)	1 (0.45%)	0 (0.00%)	1 (0.45%)	2 (0.91%)

pTR=tumour pathological response; mTR=metabolic tumour response; mNR metabolic nodal response; NA=not applicable; CMR=complete metabolic response

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