Radiological Prediction of Positive Circumferential Resection Margin in Oesophageal Cancer

Abstract

Purpose

A positive circumferential resection margin (CRM) is regarded as a poor prognostic indicator in oesophageal cancer (OC) but its prediction can be challenging. MRI is used to predict a threatened CRM in rectal cancer but is not commonly performed in OC unlike PET/CT, which is now routinely used. Therefore, this study assessed the additional predictive value of PET-defined tumour variables compared with EUS and CT T-stage. The prognostic significance of CRM status was also assessed.

Materials and Methods

This retrospective study included 117 consecutive patients [median age 64.0 (range 24-78), 102 males, 110 adenocarcinomas, 6 squamous cell carcinoma (SCC), 1 neuro-endocrine] treated between 1st March 2012 and 31st July 2015. A binary logistic regression model tested 5 staging variables; EUS T-stage (≤T2 vs ≥T3), CT T-stage (≤T2 vs ≥T3), PET metabolic tumour length (MTL), PET metabolic tumour width (MTW) and the maximum standardised uptake value (SUV_{max}).

Results

The CRM was positive in 43.6%. Sixty-seven (57.3%) patients received neo-adjuvant chemotherapy (NACT), 31 patients (26.5%) underwent surgery alone and 19 patients (16.2%) had neo-adjuvant chemo-radiotherapy (NACRT). Median overall survival (OS) was 36.0 months (95% confidence interval (CI) 24.1-47.9) and the 2-year OS was 55.4%. A binary logistic regression model showed EUS ≥T3 tumours were independently and significantly more likely to have a positive CRM than EUS ≤T2 tumours (HR 5.188, 95% CI 1.265-21.273, p=0.022). CT T-stage, PET MTL, PET MTW and SUV_{max} were not significantly associated with CRM status (p=0.783, 0.852, 0.605 and 0.413, respectively). There was a significant difference in OS between CRM positive and negative groups (X^2 4.920, df 1, p=0.027).

Conclusion

Advanced EUS T-stage is associated with a positive CRM, but PET-defined tumour variables are unlikely to provide additional predictive information. This study demonstrates the continued benefit of EUS as part of a multi-modality OC staging pathway.

Introduction

The impact of circumferential resection margin (CRM) involvement on patient outcome in oesophageal cancer (OC) has been widely reported. [1-3] Although some studies have failed to demonstrate the prognostic significance of an involved or threatened CRM [4, 5], it is now widely accepted that a positive resection margin is important. [6] Analysis from the USA Intergroup 113 trial investigated the effect of CRM status on survival. [7] Thirty-two percent of patients with a R0 resection were alive and disease-free at 5 years, compared to only 5% survival in those with a R1 resection.

Prediction of pathological CRM involvement could influence treatment selection, potentially improving overall survival (OS) and recurrence rates. Clinicians may have a lower threshold for offering neo-adjuvant therapy to patients at risk. In general, fit patients with tumours of stage T3/T4a, N0/N1, or T1/T2 N1, are considered for neo-adjuvant therapy. Following publication of MRC OE02, the current standard treatment in the UK is neo-adjuvant chemotherapy (NACT) followed by surgery, although neo-adjuvant chemoradiotherapy (NACRT) is gaining support and may eventually become standard of care. [8-10]

In the UK, patients with OC are initially staged with contrast-enhanced computed tomography (CT) to exclude unresectable disease or distant metastases. Patients with potentially curable disease then routinely undergo

EUS and positron emission tomography (PET) combined with CT (PET/CT) for more detailed staging. [11] PET/CT is predominately used to exclude distant metastases not demonstrated on CT, and for treatment planning. Image features including metabolic tumour length (MTL), metabolic tumour width (MTW) and the maximum standardised uptake value (SUV_{max}) are prognostic indicators of survival and treatment response. [12, 13]

There is currently limited evidence investigating the association between PET-defined tumour variables and a threatened CRM. MRI accurately predicts a positive CRM in rectal cancer [14], however early MRI studies in OC encountered initial difficulties because the examination is technically challenging. [15] Alternative methods are required to improve CRM prediction in OC. PET-defined tumour variables may provide additional predictive value when assessing the CRM.

Therefore, this study investigated the additional value of PET-defined tumour variables (MTL, MTW and SUV_{max}) compared with EUS and CT T-stage, to predict a threatened CRM. The prognostic significance of a positive CRM was also assessed.

Methods and Materials

Patient Cohort

A retrospective cohort study was conducted in consecutive patients with biopsy-proven OC treated between 1st March 2012 and 31st July 2015. Patients with gastro-oesophageal junction (GOJ) tumours were included. Clinical, radiological, surgical and pathological data were reviewed from a prospectively maintained surgical upper gastro-intestinal (GI) cancer database in a University teaching hospital.

Patients were identified for inclusion at the centralised Regional Upper GI Cancer MDT and deemed to have potentially curable disease following clinical examination, upper GI endoscopy and radiological staging investigations. All patients underwent PET/CT examination in the same institution using the same scanner and protocol and had surgical resection (with or without neo-adjuvant therapy) in the centralised regional service. Institutional review board granted approval for the study (13//DMD5769). Patients were excluded from the study if the patient had incomplete staging, salvage oesophagectomy after radical radiotherapy or an 'open-and-close' procedure (aborted resection). Following exclusions, 117 patients were included in the study.

Radiological Staging

Radiological staging was classified according to International Union Against Cancer (UICC) Tumour Node Metastasis (TNM) 7th edition. [16] PET/CT examinations were reported by Consultant Radiologists with minimum of 5 years' experience. EUS was performed in 3 centres by 4 experienced endosonographers.

CT Protocol

CT was performed either in the host institution of the centralised service, or in the local referring hospitals, according to Royal College of Radiologists guidelines. [11] All CT examinations were reviewed at the Regional Upper GI MDT, and deemed to be of a satisfactory technical standard. At the host institution, CT was performed with a GE HD 750 Discovery 64-slice scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK). CT images were acquired by a helical acquisition with collimation of 40mm, pitch 0.984:1 and tube rotation speed of 0.4 s. Tube output was 120 kVp with smart mA dose modulation between 60-600 mA. Slice thickness was 0.625 mm with acquisition of images on soft and lung algorithms with 3 mm reconstructions. Approximately 500 ml of water was given orally. Between 100-150 ml of Niopam 300 was given intravenously.

EUS Technique

At the host institution, an initial endoscopic examination was performed using a 9 mm diameter Olympus Paediatric gastroscope (Olympus, Southend, UK) to assess the degree of oesophageal luminal stenosis. Patients with an estimated oesophageal luminal diameter of less than 15 mm underwent examination using the smaller-diameter MH-908 oesophagoprobe, and where there was no luminal stenosis, the standard UM-2000 echoendoscope was used (Olympus, Southend, UK). The type of echoendoscope used was at the discretion of the endoscopist. No significant difference in accuracy exists between the 2 echoendoscopes. [17] The primary oesophageal tumour was assessed, together with an evaluation of the para-oesophageal anatomical structures as described previously. [18]

PET/CT Protocol

Patients were fasted for at least 6 hours prior to tracer administration. Serum glucose levels were routinely checked and confirmed to be less than 7.0 mmol/L. Patients received a dose of 4 MBq of ^{18}F-FDG per kilogram of body weight. Uptake time was 90 minutes. ^{18}F-FDG PET/CT imaging was performed with a GE 690 PET/CT scanner (GE Healthcare, Buckinghamshire, UK). CT images were acquired in a helical acquisition with a pitch of 0.98 and a tube rotation speed of 0.5 s. Tube output was 120 kVp with output modulation between 20 and 200 mA. Matrix size for the CT acquisition was 512 x 512 pixels with a 50 cm field of view. No oral or intravenous contrast was administered. PET images were acquired at 3 minutes per field of view. The

length of the axial field of view was 15.7 cm. Images were reconstructed with the ordered subset expectation maximisation algorithm, with 24 subsets and 2 iterations. Matrix size was 256 x 256 pixels, using the VUE Point ™ time of flight algorithm. (Fig. 1)

PET-Defined Tumour Variables

PET MTL is defined as the maximum perceived cranio-caudal length of primary tumour and was measured on a GE advantage windows 4.5 reporting workstation (GE healthcare, Buckinghamshire, UK) by a single observer with 5-years' experience of PET research. The observer was blinded to the histopathological results and used consistent methodology. The maximum intensity projection images were rotated to visualise the greatest length of tumour and MTL was measured in mm. MTW is defined as the maximum perceived width of primary tumour perpendicular to the MTL and was measured in mm. The SUV_{max} of the primary tumour represents the voxel with the highest FDG-uptake value and is automatically returned by the software, based on an adaptive threshold method of 42%. Non-avid tumours were recorded as a value of 0.0.

Clinical Management

Administration of neo-adjuvant therapy was dependent on radiological stage of disease, regional MDT discussion, perceived medical fitness and patient

wishes. Most patients received NACT, usually by two cycles of 80mg/m^2 cisplatin and 1000 mg/m^2 of 5-fluorouracil (5-FU) for 4 days. A minority received four cycles of epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) and 5-FU (200 mg/m^2). For NACT, patients typically receive 2 cycles of oxaliplatin (130 mg/m^2) and capecitabine (625mg/m^2) as induction NACT followed by 45 Gy of radiotherapy administered in 25 fractions over a 5-week period with concurrent chemotherapy. All surgery was performed by specialist upper GI surgeons in a centralised tertiary referral unit. Trans-hiatal surgery was selected for patients with tumours of the distal oesophagus, in whom it was considered that a thoracotomy may carry an unacceptable risk of respiratory complications due to poor performance status.

Histopathological Analysis

Histopathological examination of the resection specimen was performed by a Consultant Histopathologist with a special interest in Upper GI malignancy. The primary outcome of the study was a positive CRM. There are two widely agreed definitions of CRM status. The Royal College of Pathologists (RCPath) define a positive (or threatened) CRM as tumour within 1 mm of the resection margin. [19] (Fig. 2) The College of American Pathologists (CAP) define tumour at the cut margin of the resection as positive. [20] Only the RCP definition is used in the UK, and a comparison between the two is not performed in this study. Tumour Regression Grade (TRG) was assigned according to the Mandard Classification in patients who received neo-adjuvant therapy. [21]

Survival Data

The secondary outcome of the study was OS, defined in months, measured from the date of diagnosis. Survival data was obtained from the Cancer Network Information Service Cymru (CaNISC, Velindre NHS Trust, Wales). Each patient was followed up 3-monthly in the first year and 6-monthly thereafter, until either 5 years or death.

Statistical analysis

Categorical variables are summarised as frequency (percentage) and continuous variables as median (range). Chi-square tests assessed differences between EUS T-stage, CT T-stage, TRG and treatment type with CRM status. EUS and CT T-stage was separated into ≤T2 vs ≥T3 prior to analysis given that relatively few patients present with T1 and T2 tumours. The agreement between EUS and CT T-stage was assessed with the weighted kappa statistic (Kw). [22] Mann-Whitney U tests assessed differences between PET MTL, PET MTW and SUV_{max} with CRM status. Multi-variate analysis was performed by entering the 5 variables into binary logistic regression model. The model was powered using an event per variable (EPV) ratio of at least 10, with an event defined as a positive CRM. [23] A log-rank test assessed differences in OS between CRM status. A p-value of <0.05 was considered

statistically significant. Data analysis was performed using SPSS version 23 (IBM, Chicago, IL, USA).

Results

Patient characteristics are detailed in Table 1. The median age of the cohort was 64.0 years (range 24-78). Median survival was 36.0 months (95% confidence interval (CI) 24.1-47.9) and 2-year OS was 55.4%. The radiological and pathological TN classification of disease is detailed in Table 2. No patients in the cohort were classified as having distant metastatic (M1) disease following radiological staging investigations.

The positive CRM rate in patients treated with NACT, surgery alone and NACRT was 50.7%, 38.7% and 26.3%, respectively. There was no significant difference in positive CRM rates between these treatments (X^2 4.001, df 2, p=0.135).

Most tumours were staged ≥T3 by EUS and CT (78.6% and 70.9%, respectively) with relatively few early cancers (T1 & T2). (Table 2) There was relatively weak agreement between EUS and CT T-stage (Kw 0.424, 95% CI 0.273-0.575, p<0.001). The median PET MTL was 48.1 mm (range 0.0-88.0), the median PET MTW was 23.5 mm (0.0-47.8) and the median SUV_{max} was 11.1 (0.0-70.9).

A chi-square test demonstrated EUS ≥T3 tumours were more likely to have a positive CRM than EUS ≤T2 tumours (X^2 4.962, df 1, p=0.026). (Table 3) CT T-stage, PET MTL, PET MTW and SUV_{max} were not significantly associated with CRM status (p=0.161, 0.852, 0.605 and 0.413, respectively). In addition,

the TRG was significantly associated with CRM status (X^2 14.042, df 4, p=0.007).

EUS ≤T2 vs ≥T3, CT ≤T2 vs ≥T3, MTL and MTW and SUV_{max} were entered into a binary logistic regression model. (Table 4) The EPV ratio was 10.2. EUS ≤T2 vs ≥T3 was significantly and independently associated with CRM involvement (HR 5.188, 95% CI 1.265-21.273, p=0.022).

There was a significant difference in OS for CRM status (X^2 4.920, df 1, p=0.027). (Fig. 3) The mean OS for patients with negative CRM resections was 39.6 months (95% CI 34.5-44.7) compared to 30.9 months (25.6-36.2) for those with a positive CRM.

Discussion

This study has shown that EUS ≥T3 is a significant, independent predictor of a positive CRM but PET-defined tumour variables may not have any additional value for predicting pathological CRM involvement. These results highlight the continued benefit of EUS in the OC staging pathway and validate previous results from our centre, which demonstrated that EUS ≥T3 has an increased risk of CRM involvement compared to tumours ≤T2. [24] Studies investigating the association of radiological staging investigations and CRM are limited in frequency.

Reid et al found a positive CRM to be independently and significantly associated with OS for all pT-stages. [24] Advanced endoscopic ultrasound (EUS) T-stage was independently associated with a positive CRM, with an almost 25-fold increased risk of a threatened CRM, once a tumour was classified T3 or greater. The recruitment period for Reid et al ended in February 2012, therefore these results provide some internal validation in a new, independent cohort of patients.

Sagar et al produced the first major paper that described the prognostic effect of CRM involvement in OC. [2] A systematic review and meta-analysis by Chan et al found significant 5-year survival differences in patients with a positive CRM. [1] The overall 5-year mortality rate was significantly different according to both criteria (odds ratio 4.02 and 2.52, respectively). Our study

also shows a significant difference in OS between positive and negative CRM groups. Chan et al highlighted differences between the American and British definitions of CRM involvement. Rates of involvement were 15.3% according to the CAP definition, and 36.5% according to the RCP definition. Only the RCPath definition is used in this current study.

EUS provides the most accurate T-stage assessment. [25] Pooled sensitivities of 82-92% and an accuracy of 83% are described. [26, 27] This modality benefits from superior contrast resolution compared to PET and CT. PET variables are unlikely to provide sufficiently detailed anatomy to predict CRM involvement, due to its inherently limited spatial resolution. [28] Similarly, CT is poor at differentiating individual layers of the oesophageal wall making it inferior to EUS. There was relatively weak agreement between EUS and CT T-stage, which confirms this finding. CT T-stage was not significantly associated with CRM status in this study.

Identification of a threatened CRM from radiological staging investigations is likely to benefit patient outcome. In the UK, PET/CT and EUS are generally only performed prior to treatment initiation and are not repeated post-neo-adjuvant therapy, as in other countries including the USA. Two strategies for individualising treatment exist; the first is the decision to use neo-adjuvant therapy if the CRM is threatened and the second is the decision to operate post-neo-adjuvant therapy. One study did not show any benefit when surgical resection was performed following a complete response on PET/CT. [29] The

former strategy of predicting CRM involvement prior to treatment initiation is more suited to the UK staging pathway, given that PET/CT and EUS are not repeated. Furthermore, results of this study have shown that patients with a good response are significantly less likely to have a positive CRM following resection.

Treatment selection can influence the positive CRM rate. NACRT may improve the number of R0 resections (a microscopically margin-negative resection) compared to NACT, with R0 rates of between 87.5% and 92.0% described in the literature. [24, 30] This current study did not demonstrate a significantly different positive CRM rate between treatments, but there were small numbers of patients in the NACRT group.

The positive CRM rate in this patient cohort is high but comparable to those quoted in the National Oesophago-Gastric Cancer Audit. [31] A trans-hiatal approach was employed in 47.9% of patients in this cohort. This is significantly higher than the national rate of 4%, which could in turn explain the relatively high positive CRM rate. The surgeons in our institution employ this technique because the population of patients on which they operate tend to have significant co-morbidities attributable to the effects of poor lifestyle and deprivation. [32] Morbidity rates are reduced following trans-hiatal resection compared to a trans-thoracic approach. [33]

Strengths of Study

All patients with OC in this study were managed by an experienced MDT, serving a stable population of approximately 1.5 million. The staging pathway has not altered during the study period therefore all patients have been staged consistently. All PET/CT examinations were performed using the same scanner and protocol. Operations were all performed as part of a centralised service by Upper GI cancer surgeons. Oesophageal resection specimens were assessed and reported by a Consultant Histopathologist with an interest in upper GI cancer, and findings routinely discussed at MDT. The study is powered according to the EPV and the results of the uni-variate analysis did not affect variable selection for the multi-variate regression model, thus preventing an over-fitted model. [34]

Limitations

A confounding factor in this analysis is the technique of the surgeon and the approach employed. The surgical approach used was considered the best for the patient and most likely to result in a positive outcome. In line with national data, the two most common types of oesophagectomy were used; trans-thoracic (Ivor-Lewis) and trans-hiatal. The surgeons work together within a centralised system so their techniques are likely to be similar. This patient cohort is relatively heterogeneous. Patients with differing stage of disease,

treatment type, histology and response to treatment were included. In general, OC patients are a heterogeneous cohort and introduction of some sample heterogeneity into research studies can be unavoidable. This reflects the intention-to-treat basis of clinical research, but can introduce potential bias into the results. Three treatment types are included in this study, which have differing effects on CRM status, as evidenced by the CROSS trial. [30] However, only 19 patients had a complete (TRG 1, n=9) or excellent (TRG 2, n=10) response to neo-adjuvant therapy, which suggests that the disease did not change significantly in the majority of cases. EUS examinations were performed by different endosonographers, which may cause variability in T-stage accuracy, but again adds weight to the generalisability of the results.

Conclusion

A positive CRM is an important prognostic indicator of survival. Prior knowledge of a threatened CRM would assist clinicians with management decisions. This study has shown that EUS ≥T3 is a significant independent predictor of a positive CRM, but PET-defined tumour variables are unlikely to add additional predictive value regarding CRM status.

References

1. Chan DS, Reid TD, Howell I, Lewis WG. Systematic review and meta-analysis of the influence of circumferential resection margin involvement on survival in patients with operable oesophageal cancer. Br J Surg. 2013;100(4):456-64.
2. Sagar PM, Johnston D, McMahon MJ, Dixon MF, Quirke P. Significance of circumferential resection margin involvement after oesophagectomy for cancer. Br J Surg. 1993;80(11):1386-88.
3. Salih T, Jose P, Mehta SP, Mirza A, Udall G, Pritchard SA, et al. Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy. Eur J Cardiothorac Surg. 2013;43(3):562-7.
4. Harvin JA, Lahat G, Correa AM, Lee J, Maru D, Ajani J, et al. Neoadjuvant chemoradiotherapy followed by surgery for esophageal adenocarcinoma: significance of microscopically positive circumferential radial margins. J Thorac Cardiovasc Surg. 2012;143(2):412-20.
5. Pultrum BB, Honing J, Smit JK, van Dullemen HM, van Dam GM, Groen H, et al. A critical appraisal of circumferential resection margins in esophageal carcinoma. Ann Surg Oncol. 2010;17(3):812-20.
6. Okada N, Fujii S, Fujita T, Kanamori J, Kojima T, Hayashi R, et al. The prognostic significance of the positive circumferential resection margin in pathologic T3 squamous cell carcinoma of the esophagus with or without neoadjuvant chemotherapy. Surgery. 2016;159(2):441-50.
7. Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007;25(24):3719-25.
8. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727-33.
9. Mukherjee S, Hurt CN, Gwynne S, Bateman A, Gollins S, Radhakrishna G, et al. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. BMC Cancer. 2015;15:48.
10. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-8.
11. Roberts SA, Kay C. Oesophagus and stomach cancers. In: Nicholson T, editor. Recommendations for cross-sectional imaging in cancer management. 2nd ed. London: Royal College of Radiologists; 2014.
12. Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C. Prognostic value of 18F-FDG PET image-based parameters in oesophageal

cancer and impact of tumour delineation methodology. Eur J Nucl Med Mol Imaging. 2011;38(7):1191-202.
13. Roedl JB, Halpern EF, Colen RR, Sahani DV, Fischman AJ, Blake MA. Metabolic tumor width parameters as determined on PET/CT predict disease-free survival and treatment response in squamous cell carcinoma of the esophagus. Mol Imaging Biol. 2009;11(1):54-60.
14. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. Br J Surg. 2003;90(3):355-64.
15. Riddell AM, Richardson C, Scurr E, Brown G. The development and optimization of high spatial resolution MRI for imaging the oesophagus using an external surface coil. Br J Radiol. 2006;79(947):873-9.
16. Sobin LH, Gospodarowicz MK, Wittekind CH. UICC TNM Classification of Malignant Tumours. 7th ed. New York: Wiley, 2009.
17. Twine CP, Lewis WG, Escofet X, Bosanquet D, Ashley Roberts S. Prospective comparison of optic versus blind endoscopic ultrasound in staging esophageal cancer. Surg Endosc. 2009;23(12):2778-84.
18. Weaver SR, Blackshaw GRJC, Lewis WG, Edwards P, Roberts SA, Thomas GV, et al. Comparison of special interest computed tomography, endosonography and histopathological stage of oesophageal cancer. Clin Radiol. 2004;59(6):499-504.
19. Mapstone N. Dataset for the Histopathological Reporting of Oesophageal Carcinoma. 2nd ed. London: Royal College of Pathologists, 2007.
20. College of American Pathologists. Surgical Pathology Cancer Case Summary: Esophagus. Northfield: College of American Pathologists, 2005.
21. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73(11):2680-6.
22. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.
23. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
24. Reid TD, Chan DS, Roberts SA, Crosby TD, Williams GT, Lewis WG. Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer and the predictive role of endoluminal ultrasonography. Br J Cancer. 2012;107(12):1925-31.
25. Tangoku A, Yamamoto Y, Furukita Y, Goto M, Morimoto M. The new era of staging as a key for an appropriate treatment for esophageal cancer. Ann Thorac Cardiovasc Surg. 2012;18(3):190-9.
26. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008;14(10):1479-90.
27. van Vliet EP, Eijkemans MJ, Kuipers EJ, Poley JW, Steyerberg EW, Siersema PD. Publication bias does not play a role in the reporting of the

results of endoscopic ultrasound staging of upper gastrointestinal cancers. Endoscopy. 2007;39(4):325-32.
28. Kinahan PE, Fletcher JW. Positron emission tomography-computed tomography standardized uptake values in clinical practice and assessing response to therapy. Semin Ultrasound CT MR. 2010;31(6):496-505.
29. Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, et al. Outcomes of patients with esophageal cancer staged with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol. 2010;28(31):4714-21.
30. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
31. National Oesophago-Gastric Cancer Audit. An Audit of the Care Received by People with Oesophago-Gastric Cancer in England and Wales Annual Report.2016: Available from: http://content.digital.nhs.uk/og.
32. Blake PA, Karran AL, Chan DSY, White C, Lewis WG. Prognostic Significance of Deprivation in Upper Gastrointestinal Cancer. Gastrointestinal Cancer: Research & Therapy. 2017;2(2):1018.
33. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-9.
34. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ. 2009;338:b375.

Figure Legends

Figure 1. Axial fused PET/CT image of a distal oesophageal adenocarcinoma which had a positive CRM following surgical resection.

Figure 2. A selected radial EUS image of the distal oesophageal adenocarcinoma (T, calipers), in close proximity to the descending thoracic aorta (AO). A corresponding medium-power magnification of the tumour demonstrates a positive CRM (white arrow), with stained tumour cells at the cut resection margin.

Figure 3. Kaplan-Meier plot demonstrates a significant difference in overall survival between CRM status (X^2 4.920, df 1, p=0.027). Patients with a positive CRM have worse OS.

Table 1. Characteristics of Patient Cohort

Demographic	Frequency (%)
Gender	
Male	102 (87.2)
Female	15 (12.8)
Histology	
Adenocarcinoma	110 (94.0)
Squamous Cell Carcinoma	6 (5.1)
Neuro-endocrine	1 (0.9)
Degree of Differentiation	
Well	13 (11.1)
Moderate	40 (34.2)
Poor	57 (48.7)
GX	7 (6.0)
Radiological T-stage	
T1	12 (10.3)
T2	13 (11.1)
T3	83 (70.9)
T4a	9 (7.7)
Radiological N-stage	
N0	58 (49.6)
N1	41 (35.0)
N2	14 (12.0)
N3	4 (3.4)
Treatment Type	
NACT	67 (57.3)
Surgery Alone	31 (26.5)
NACRT	19 (16.2)
Tumour Regression Grade	
TRG 1	9 (10.5)
TRG 2	10 (11.6)
TRG 3	11 (12.8)
TRG 4	32 (37.2)
TRG 5	24 (27.9)

Operation Type	
Trans-hiatal oesophagectomy	56 (47.9)
Ivor-Lewis oesophagectomy	35 (29.9)
Total gastrectomy	22 (18.8)
3-stage oesophagectomy	3 (2.5)
Oesophago-gastrectomy	1 (0.9)
Circumferential Resection Margin	
Negative	66 (56.4)
Positive	51 (43.6)

GX unable to be assessed; NACT neo-adjuvant chemotherapy; NACRT neo-adjuvant chemo-radiotherapy

Table 2. Radiological and Pathological TN Staging Classification

Frequency (%)	CECT	EUS	PET/CT	Pathology
T0	0 (0.0)	0 (0.0)	0 (0.0)	9 (7.7)
T1	12 (10.3)	12 (10.3)	0 (0.0)	18 (15.4)
T2	22 (18.8)	13 (11.1)	0 (0.0)	9 (7.7)
T3	73 (62.4)	83 (70.9)	0 (0.0)	71 (60.7)
T4a	10 (8.5)	9 (7.7)	0 (0.0)	10 (8.5)
TX	0 (0.0)	0 (0.0)	117 (100.0)	0 (0.0)
Total	117 (100.0)	117 (100.0)	117 (100.0)	117 (100.0)
N0	70 (59.8)	67 (53.7)	81 (69.2)	48 (41.0)
N1	31 (26.5)	36 (30.8)	27 (23.1)	26 (22.2)
N2	12 (10.3)	12 (10.3)	8 (6.8)	30 (25.6)
N3	2 (1.7)	2 (1.7)	1 (0.9)	13 (11.1)
NX	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Total	117 (100.0)	117 (100.0)	117 (100.0)	117 (100.0)

TX/NX unable to be assessed

Table 3. Association of EUS T-stage Groups and CRM involvement

Frequency (%)	CRM negative	CRM positive	Total
EUS ≤T2	19 (16.2)	6 (5.1)	25 (21.4)
EUS ≥T3	47 (40.3)	45 (38.4)	92 (78.6)
Total	66 (56.4)	51 (43.6)	117 (100.0)

Table 4. Results of Multi-Variate Binary Logistic Regression Model

Variable	Hazard Ratio (95% CI)	p-value
EUS ≤T2 vs ≥T3	5.188 (1.265-21.273)	0.022
CT ≤T2 vs ≥T3	1.163 (0.398-3.397)	0.783
PET MTL	0.633 (0.684-1.273)	0.652
PET MTW	0.836 (0.445-1.570)	0.578
SUV_{max}	0.989 (0.940-1.040)	0.655

HR hazard ratio, CI confidence interval, MTL metabolic tumour length, MTW metabolic tumour width