Impact of Positron Emission Tomography and Endoscopic Ultrasound Length of Disease Difference on Treatment Planning in Patients with Oesophageal Cancer

K.G. Foley *, C. Morgan y, S.A. Roberts z, T. Crosby y

* Division of Cancer & Genetics, Cardiff University, Cardiff, UK

y Velindre Cancer Centre, Cardiff, UK

z Department of Radiology, University Hospital of Wales, Cardiff, UK

Abstract

Aims

Treatment decision-making and planning in patients with oesophageal cancer (OC) are guided by radiological measurement of length of disease (LoD). This study aimed to investigate differences in PET and EUS LoD. Their prognostic significance was also assessed.

Materials & Methods

LoD was measured from PET and EUS staging investigations by one observer for each modality. Bland-Altman analysis and Wilcoxon signed rank tests assessed agreement and differences in measurements. In terms of radiotherapy planning, the proportion of cases with a clinically significant difference of more than 2 cm between PET and EUS was also calculated. Univariable and multivariable analysis assessed association with overall survival (OS). A p-value of <0.05 was considered statistically significant.

Results

Consecutive patients (n=160, median age 66.0 years (range 24-83), males=124, adenocarcinomas=115) staged with PET/CT and EUS between 2011 and 2014 were included. PET tended to under-measure compared to EUS. The median PET and EUS LoD was 6.4 and 8.0 cm, respectively. PET and EUS LoD was significantly different ($Z= -7.021$, $p<0.001$). EUS LoD was more than 2 cm longer than PET LoD in 61 cases (38.1%), respectively. In 8 cases (5.0%), PET LoD was more than 2 cm longer than EUS LoD. Both variables had prognostic significance in univariable analysis, but were not independent predictors of OS.

Conclusion

There are significant differences in PET and EUS measurement of LoD. This could impact on clinical decision-making and radiotherapy treatment planning. Clinically significant differences between EUS and PET LoD could lead to a risk of geographical miss in up to 38.1% of cases if the PET/CT measurement alone had been used for radiotherapy planning. These results highlight the continued benefit of EUS in the OC staging and treatment pathway.

Keywords

oesophagus; positron-emission tomography; endosonography; decision making; radiotherapy

Word Count 2,986

Introduction

Oesophageal cancer (OC) staging uses a multi-modality approach including computed tomography (CT), endoscopic ultrasound (EUS) and positron emission tomography (PET). [1] The additional prognostic value of functional imaging means PET/CT is now routinely used in cancer staging pathways for patients considered suitable for radical therapy. [2] The two most common histological cell types are adenocarcinoma and squamous cell carcinoma (SCC), both of which have a high affinity for ^{18}F-fluorodeoxyglucose (^{18}F-FDG), making PET particularly useful in OC.

Primary tumour length is commonly reported following upper gastrointestinal (GI) endoscopy, CT, EUS and PET/CT staging investigations. [3] Of more critical importance is the estimated total length of disease (LoD), defined as the cranio-caudal length of primary tumour plus involved regional lymph nodes. Assessment of treatment options, including suitability for definitive chemo-radiotherapy (dCRT), relies on assessment of LoD at staging. A discrepancy in LoD between imaging modalities could affect clinical decision-making and subsequent treatment planning. Inappropriate radical treatment may be initiated in unsuitable patients, or potentially beneficial therapy could be withheld from those that may respond.

There is now significant interest in the use of PET imaging to assist radiotherapy planning, particularly in OC. [4] Localisation of the gross tumour volume (GTV) in radiotherapy planning relies on accurate localisation of the LoD. Moreover, there has been a decline in EUS use nationally, making delineation of the GTV more reliant on PET and CT alone. [5]

Therefore, this study tested the hypothesis that significant differences exist between PET and EUS LoD. These differences could impact on clinical decision-making and treatment planning, especially in cases where EUS is not performed. The primary aim of this study was to investigate differences in PET and EUS LoD in patients with OC. The secondary aim was to assess the prognostic significance of these measurements.

Materials and Methods

Patient Cohort

Patients staged between January 1st 2011 and December 31st 2014 with biopsy proven oesophageal or gastro-oesophageal junction (GOJ) tumours were considered for this study. All EUS examinations were performed by the same operator. In total, 222 patients were considered for inclusion. Exclusion criteria were a non FDG-avid primary tumour (n=30), a tumour too stenotic to be passed with the endoscope (n=13), LoD not recorded in the EUS report (n=18) and patients lost to follow-up (n=1). Following exclusions, 160 patients were included in the study. The institutional review board gave approval for the study (reference 13//DMD5769). Radiological staging was classified according to the Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) 7th edition. [6]

EUS Technique

All EUS examinations were performed by the same highly experienced operator with a published track-record, to ensure consistency in LoD measurement. [7] 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 if no luminal stenosis, the standard UM-2000 echoendoscope was used (Olympus, Southend, UK). The primary oesophageal tumour was assessed,

together with an evaluation of the para-oesophageal anatomical structures as described previously. [7] EUS LoD was calculated as the length of endoscope insertion relative to the incisors between proximal and distal extent of tumour and lymph node metastases if present, recorded in centimetres (cm). [8] The EUS criteria for malignant lymphadenopathy specified a hypo-echoic pattern, spherical contour, distinct border, and short axis diameter of 6 mm or more.

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. Activity uptake time was 90 minutes. PET/CT imaging was performed with a GE 690 PET/CT scanner (GE Healthcare, Buckinghamshire, UK). 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. CT images were acquired in a helical acquisition with a pitch of 0.98 and a tube rotation speed of 0.5 seconds. 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 Length of Disease Measurement

A single observer (*blinded*) with 4 years' experience of PET/CT interpretation retrospectively measured and recorded PET LoD (cm) whilst blinded to the originally reported PET and EUS LoD. Measurements were performed on a GE Advantage Windows 4.5 reporting workstation (GE Healthcare, Pollards Wood, Buckinghamshire, UK) using the maximum intensity projection (MIP) images in the rotational plane. (Fig. 1) This allowed visualisation of the greatest perceived LoD. Identical viewing settings were used for each case to ensure consistent methodology; the field of view (FOV) was 88.1 cm and the SUV of the MIP display was maintained at 12 g/ml for each case.

Definition of Regional Nodal disease

Regional lymph nodes were defined as any para-oesophageal lymph node from the cervical oesophagus superiorly to the coeliac trunk inferiorly, according to the TNM 7th edition. [6] Nodes were classed as involved on PET/CT if the node was identified on the CT component and showed FDG uptake appreciably higher than background values. No specific SUV_{max} was used for the inclusion of regional nodes. Lymph nodes not meeting these criteria were considered benign. Non-regional lymph nodes were considered metastatic (M1).

Treatment Planning and Selection

An appropriate individual management plan was selected based on radiological stage, patient choice and relevant comorbidity, according to algorithms used by the Regional Upper GI cancer network. [9, 10] In this study, radiotherapy planning was

performed using direct comparison of imaging modalities, considering the maximum LoD recorded. Occasionally, non-deformable fusion of the PET and planning CT was performed, provided the diagnostic PET/CT had been acquired in the radiotherapy planning position to allow accurate fusion.

Survival Data

Overall survival (OS), defined in months survived from the data of diagnosis, was used when assessing the prognostic significance of PET and EUS LoD. Survival data was obtained from the Cancer Network Information Service *blinded* (*blinded*, *blinded*, Wales). All patients were followed up 3-monthly in the first year and 6-monthly thereafter for 5 years, or until death.

Statistical Analysis

Continuous data were expressed as median (range) and categorical data as frequency (percent). A Bland-Altman analysis was used to assess the level of agreement between PET and EUS LoD. [11] The mean difference (PET minus EUS) and 95% limits of agreement (LA) were calculated. A difference of more than 2 cm between PET and EUS is considered clinically significant for radiotherapy planning, therefore the proportion of cases with a clinically significant difference was also calculated. [12] A non-parametric Wilcoxon signed rank test was used to assess differences between PET and EUS LoD. Univariable survival analysis was performed with the log-rank test according to the life-table method of Kaplan-Meier. [13] Multi-variable analysis was performed by entering age (years), stage group (I,

II, III or IV), treatment (curative or palliative) and individual recorded measurement (cm) into a Cox Regression model. [14] All curative treatments were combined into one group in the model rather than entering specific therapies, given the relatively small numbers of patients in some treatment groups. Model power was based on the event per variable (EPV) ratio, recommended as a minimum of 10. [15] A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM, Chicago, USA).

Results

Patient characteristics are detailed in Table 1. The median age of the cohort was 66.0 years (range 24-83). The median OS of the cohort was 20.0 months (95% confidence interval (CI) 16.2-23.8) and median follow-up was 40.0 months (35.1-44.9).

The median PET LoD was 6.4 cm (standard deviation (SD) 4.5, interquartile range (IQR) 4.5-9.4, range 1.0-25.8), respectively. The median EUS LoD was 8.0 cm (SD 5.7, IQR 6.0-12.0, range 1.0-27.0), respectively. PET tended to yield smaller TL and LoD measurements compared to EUS. (Figure 2)

A Wilcoxon signed rank test demonstrated a significant difference between PET and EUS LoD ($Z= -7.021$, $p<0.001$). EUS LoD was more than 2 cm longer than PET LoD in 61 cases (38.1%). In 8 cases (5.0%), PET LoD was more than 2 cm longer than EUS LoD.

Bland-Altman analysis demonstrated substantial variation in measured PET and EUS LoD. (Fig. 3) The mean difference in LoD (PET minus EUS) was -2.2 cm (SD 3.8, 95% LA -9.6 to 5.2). The Bland Altman analysis indicates that the 95% LA between PET and EUS LoD represent a level of disagreement that is potentially clinically significant, suggesting that PET and EUS LoD should not be used inter-changeably. (Fig. 4)

In univariable analysis, PET LoD (Hazard Ratio (HR) 1.076, 95% CI 1.037-1.115, p<0.001) and EUS LoD (HR 1.059, 95% CI 1.028-1.091, p<0.001) were significantly associated with OS. There were significant differences in OS between upper and lower quartiles of PET LoD (13.0 months if >9.4 cm and 29.0 months if <4.5 cm, p<0.001) and EUS LoD (13.0 months if >12.0 cm and 29.0 months if <6.0 cm, p=0.002). However, in multivariable analysis, these variables were not independently associated with OS. (Table 2) The EPV ratio was 22.2.

Discussion

This study has demonstrated significant differences between PET and EUS LoD in patients with OC. Both PET and EUS LoD were significantly associated with OS on univariable analysis, but were not independent predictors. These results are important for treatment option assessment, which can be complex in OC.

Selection of patients for surgical management, neo-adjuvant treatments or dCRT partly relies on accurate assessment of disease extent, often gained from PET/CT and EUS. The LoD is an important measurement that can influence these decisions. These results suggest that PET tends to under-measure LoD compared to EUS.

An accepted maximum LoD for consideration of radiotherapy is 10 cm, as described in the SCOPE trial series protocols (17). There is often more concern about length of irradiated volume in the neo-adjuvant setting, leading to a more conservative approach in this scenario. Inaccuracies in LoD estimation could also affect patient selection for neo-adjuvant chemoradiotherapy. [16]

In terms of radiotherapy planning, a difference of more than 2 cm between PET and EUS is considered clinically significant. [12] Most modern oesophageal radiotherapy planning protocols allow a margin of 2 cm from GTV to clinical target volume (CTV) to allow for microscopic spread along the oesophagus. Differences in LoD of more than 2 cm could lead to a significant risk of a geographical miss if the PET measurement is used alone. In this study, up to 38.1% of cases were at risk of a geographical miss.

Delineation of target volumes for radiotherapy planning is increasingly guided by metabolic activity of the primary tumour and regional nodes on PET/CT. [17] In addition to clinical information, PET images are most commonly viewed alongside the planning CT. The oesophageal GTV can be difficult to define on CT alone because of submucosal spread, the propensity for skip lesions and poor differentiation of tumour from normal oesophagus. Accurate definition of GTV has become even more important given the growing trend for reduced margins combined with increased conformity of treatment volumes and use of advanced techniques such as Volumetric Modulated Arc Therapy (VMAT). Some centres use fusion techniques, but inaccuracies can be introduced if patient positioning differs between diagnostic and planning examinations.

Centres that utilise EUS for radiotherapy planning have reported satisfactory recurrence rates with few edge-of-field relapses. [18] However, EUS is occasionally unavailable at the time of radiotherapy planning, often due to non-traversable tumour, patient choice or increasing service pressures. Limited information can still be acquired from a non-traversable tumour, such as the proximal extent of tumour and assessment of visible lymph nodes, but the maximum LoD may not be fully appreciated in these cases.

If PET alone is relied upon to guide delineation of GTV, all available diagnostic information, including the upper GI endoscopy report, diagnostic CT and PET/CT images, should be used together to plan radiotherapy. The temptation to outline FDG-avid regions of disease alone should be resisted because it is vital to include

disease identified on all available imaging modalities. Usually, the most recent imaging is the radiotherapy planning CT and areas of adjacent, non-avid oesophageal wall thickening should be included in the GTV. This approach is also recommended in the recent SCOPE2 trial radiotherapy planning protocol. [19]

EUS assesses local disease more accurately than PET due to its superior contrast and spatial resolution. Submucosal infiltration is also better assessed with EUS. [20] Physiological FDG-uptake in the oesophagus or stomach is often located adjacent to the tumour, creating an 'avidity gradient' which can cause error in measurement. Another limitation of PET is the suboptimal differentiation of adjacent peri-tumoural lymph node metastases from the primary tumour. [21] However, PET/CT can add useful information in patients with non-traversable tumours, or in cases where there is involvement of the GOJ. Identification of nodal disease distant to the primary tumour can also be assessed. Overall, these results support the combined use of PET and EUS in radiation treatment planning of OC.

It has been suggested that EUS use should be more focused in OC. EUS is an invasive procedure with risk of serious complications and is operator dependent. In many centres, access to EUS is limited, which can impact on patient pathways and time to treatment. This is supported by evidence that EUS use is declining. According to the National Oesophago-Gastric Cancer Audit (NOGCA) data, 47.5% of patients with OC had a staging EUS completed in 2016, compared to 62% reported in 2013. [5] A large single-centre study showed minimal benefit of EUS versus the potential risk of complications in the majority of patients staged T2-T4a on CT. [22] The authors suggested that EUS use should be limited to early stage OC and the

assessment of resectability in more advanced cases. The additional utility of EUS for accurate radiotherapy planning was not discussed in this paper and should be an additional consideration given the increasing use of neo-adjuvant chemoradiotherapy in recent years.

As for other studies investigating imaging measurements, the true pathological length is unknown, making accurate comparison of different modalities difficult. Cancer resections specimens can shrink up to 50% in size which is an important consideration when comparing measurements. [23] Only measurements from single observers for both PET and EUS were analysed in this study, which maintains consistent methodology, but does not allow assessment of inter-observer variability. Future research should focus on the impact of inter-observer variability on treatment decision-making in patients with OC. Identical settings were used when measuring LoD on the PET MIP images. Some tumours with high intensity variation may not have displayed optimally, which potentially introduced error in measurement. However, this methodology was adopted to ensure consistency between patients. In addition, the patient population was relatively heterogeneous, which reflects the observational nature of the study. As a result, the patients included in this study received different treatments. Treatment was included in the multi-variable analysis as curative and palliative groups only. Curative therapies were combined as the numbers in some treatment groups were relatively small.

In conclusion, this retrospective study has demonstrated significant differences in measured PET and EUS LoD from OC staging investigations. These measurements showed prognostic significance on univariable analysis but were not independent

predictors of survival. Differences in these measurements could potentially impact clinical-decision making and radiotherapy treatment planning. In our view, these results highlight the continued benefit of EUS in the OC staging and treatment pathway, particularly adding information in patients requiring radiotherapy.

Acknowledgements

The authors wish to acknowledge the advice of Dr Patrick Fielding, Consultant Radiologist at the Wales Research & Diagnostic Positron Emission Tomography Imaging Centre (PETIC) and all members of the *blinded* Regional Upper GI cancer MDT. *Blinded* also acknowledges the support of the Wales Clinical Academic Training (WCAT) fellowship. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] 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.
- [2] Schmidt T, Lordick F, Herrmann K, Ott K. Value of functional imaging by PET in esophageal cancer. J Natl Compr Canc Netw. 2015;13:239-47.
- [3] Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60:1449-72.
- [4] Ward G, Ramasamy S, Sykes JR, Prestwich R, Chowdhury F, Scarsbrook A, et al. Superiority of Deformable Image Co-registration in the Integration of Diagnostic Positron Emission Tomography-Computed Tomography to the Radiotherapy Treatment Planning Pathway for Oesophageal Carcinoma. Clin Oncol (R Coll Radiol). 2016.
- [5] National Oesophago-Gastric Cancer Audit. An Audit of the Care Received by People with Oesophago-Gastric Cancer in England and Wales Annual Report. 2016.
- [6] Sobin LH, Gospodarowicz MK, Wittekind CH. UICC TNM Classification of Malignant Tumours. 7th ed. New York: Wiley; 2009.
- [7] 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;59:499-504.
- [8] Rice PF, Roberts SA. Discrepancy of echo-endoscopic measurements, which could lead to inaccurate recording of levels during staging of esophageal cancer. Endoscopy. 2003;35:376.
- [9] Karran A, Blake P, Chan D, Reid TD, Davies IL, Kelly M, et al. Propensity score analysis of oesophageal cancer treatment with surgery or definitive chemoradiotherapy. Br J Surg. 2014;101:502-10.
- [10] Gwynne S, Hurt C, Evans M, Holden C, Vout L, Crosby T. Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer. Clin Oncol (R Coll Radiol). 2011;23:182-8.
- [11] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1:307-10.
- [12] Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013;14:627-37.
- [13] Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.
- [14] Cox D. Regression Models and Life-Tables. Journal of the Royal Statistical Society. 1972;34:187-220.
- [15] 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;49:1373-9.
- [16] Hurt CN, Nixon LS, Griffiths GO, Al-Mokhtar R, Gollins S, Staffurth JN, et al. SCOPE1: a randomised phase II/III multicentre clinical trial of definitive

chemoradiation, with or without cetuximab, in carcinoma of the oesophagus. BMC Cancer. 2011;11:466.

- [17] 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.
- [18] Button MR, Morgan CA, Croydon ES, Roberts SA, Crosby TD. Study to determine adequate margins in radiotherapy planning for esophageal carcinoma by detailing patterns of recurrence after definitive chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2009;73:818-23.
- [19] SCOPE2 - A Randomised Phase II/III Trial to Study Radiotherapy Dose Escalation in Patients With Oesophageal Cancer Treated With Definitive Chemo-radiation With an Embedded Phase II Trial for Patients With a Poor Early Response Using Positron Emission Tomography (PET). (2016). Available from: https://clinicaltrials.gov/ct2/show/NCT02741856?term=SCOPE+2&rank=1. (Identifier: NCT02741856).
- [20] Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc. 2012;75:242-53.
- [21] Konski A, Doss M, Milestone B, Haluszka O, Hanlon A, Freedman G, et al. The integration of 18-fluoro-deoxy-glucose positron emission tomography and endoscopic ultrasound in the treatment-planning process for esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2005;61:1123-8.
- [22] Findlay JM, Bradley KM, Maile EJ, Braden B, Maw J, Phillips-Hughes J, et al. Pragmatic staging of oesophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. Br J Surg. 2015;102:1488-99.
- [23] Siu KF, Cheung HC, Wong J. Shrinkage of the esophagus after resection for carcinoma. Ann Surg. 1986;203:173-6.

Figure Legends

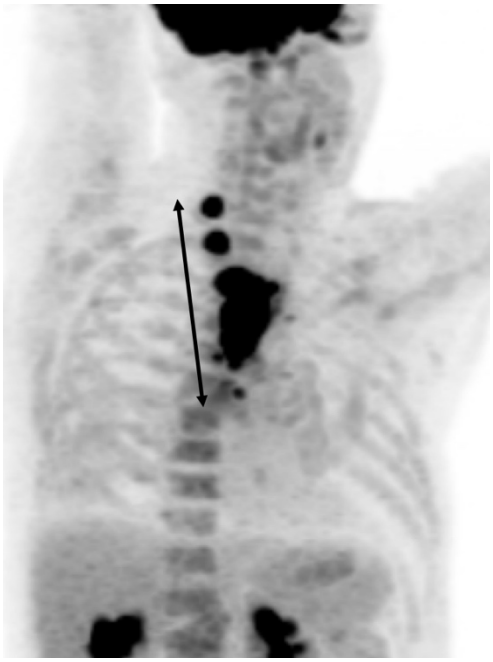

Figure 1. PET maximum intensity projection (MIP) images demonstrating measurement of LoD in a 67-year-old gentleman with a mid-oesophageal SCC and large FDG-avid regional lymph node metastases.

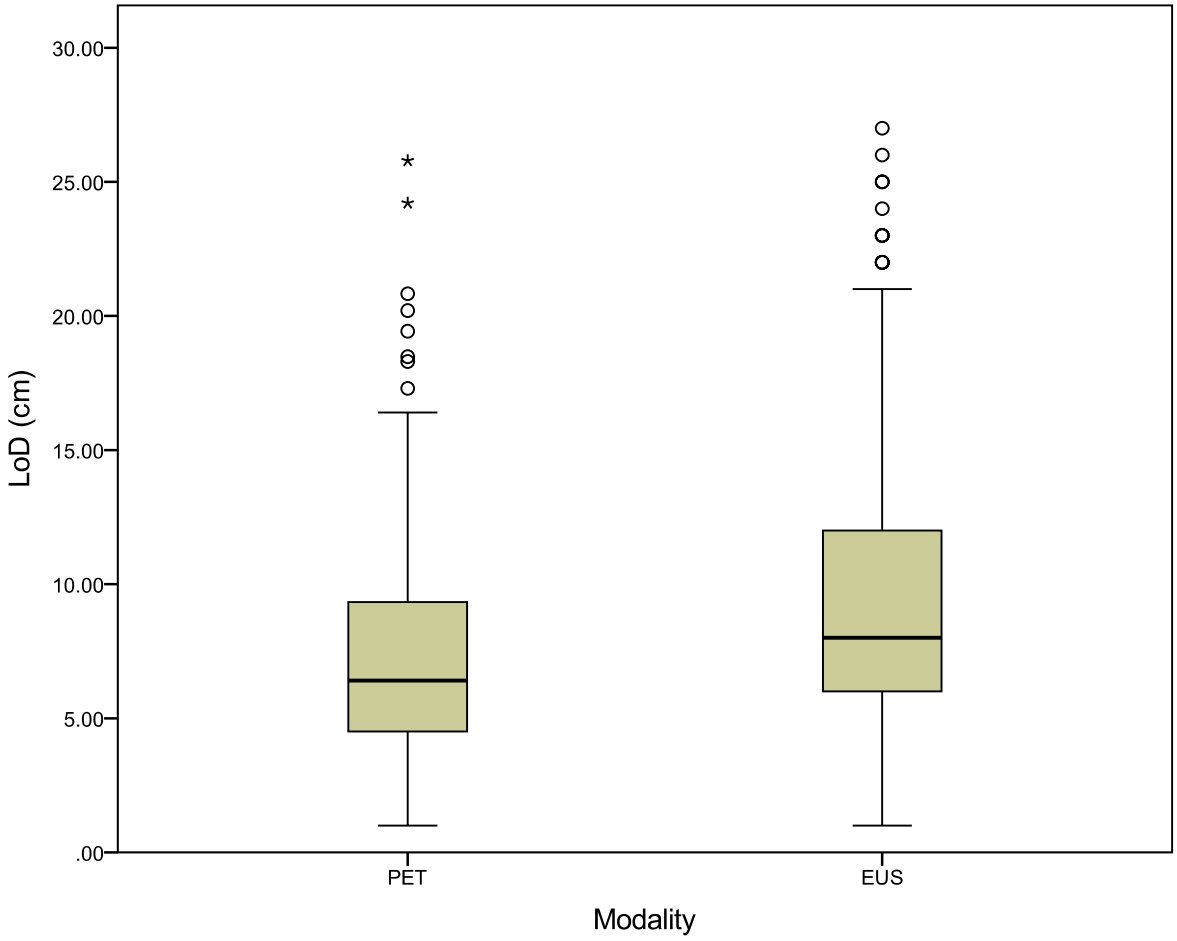

Figure 2. Boxplot representation of measured PET and EUS LoD.

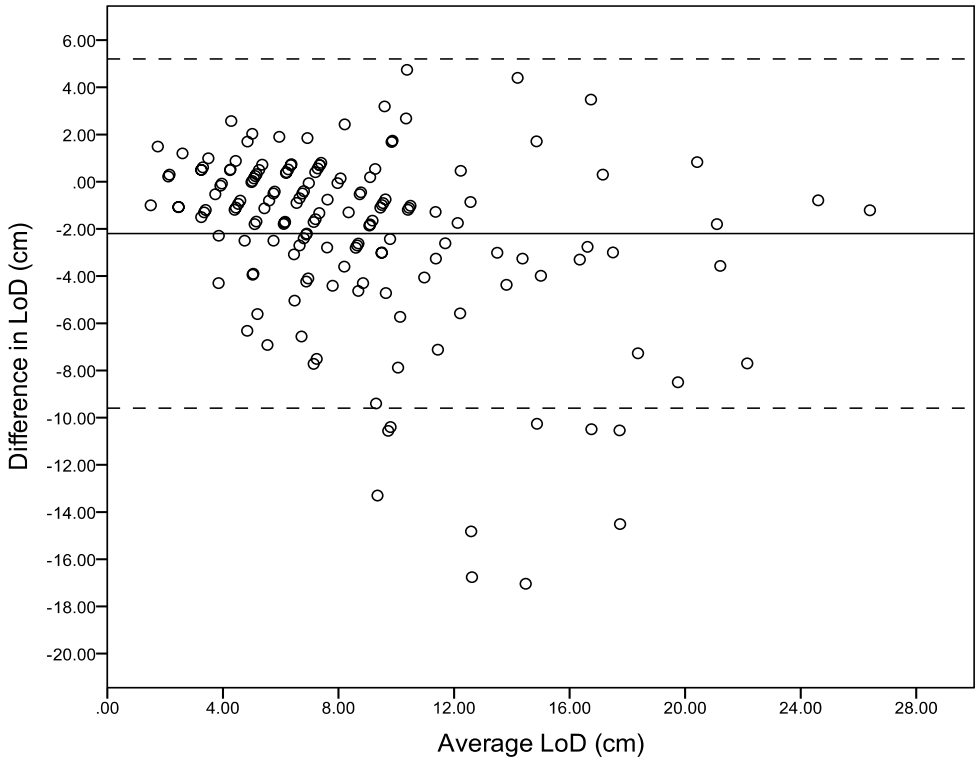

Figure 3. Bland-Altman plot demonstrating limited agreement in measured PET and EUS LoD. The mean difference [PET minus EUS (solid line)] and 95% LA (dashed lines) are displayed.

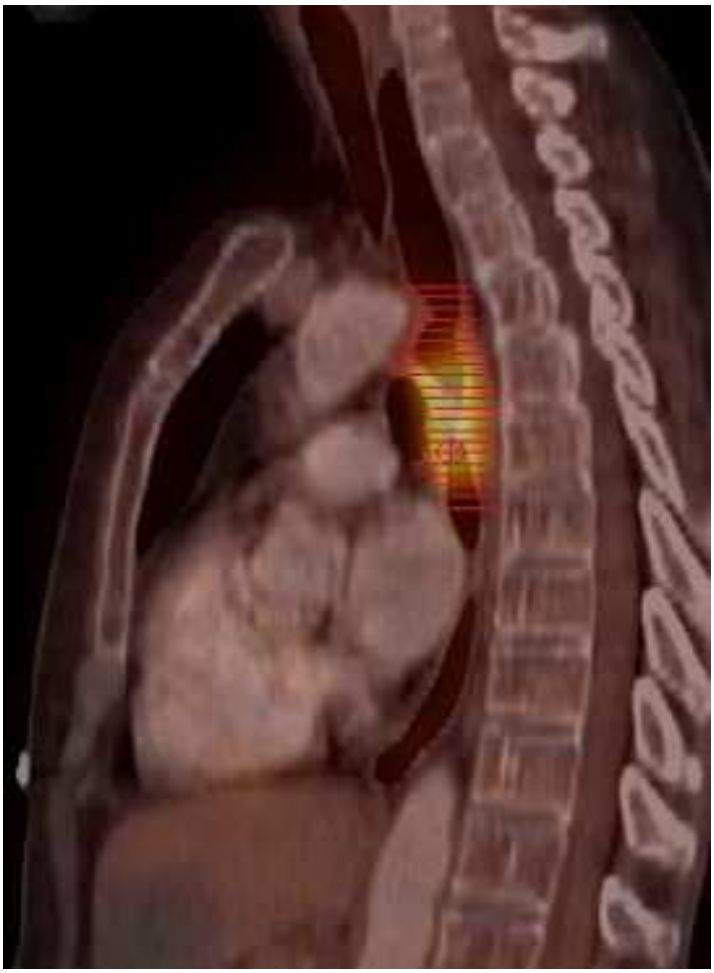

Figure 4. Selected fused sagittal PET/CT radiotherapy planning image demonstrating a FDG-avid mid-oesophageal SCC staged T3 N1 with EUS. The horizontal red lines delineate the GTV incorporating the EUS LoD measurement, with each line representing a 5 mm interval. The PET LoD measured 6.5 cm, whereas the EUS LoD was recorded as 10 cm, indicating non-FDG avid tumour at proximal and distal margins.

Table 1. Baseline Characteristics of Patient Cohort

Patient Characteristic	Frequency (%)
Gender	
Male	124 (77.5)
Female	36 (22.5)
Histology	
Adenocarcinoma	115 (71.9)
Squamous Cell Carcinoma	41 (25.6)
High-grade Dysplasia	2 (1.3)
Neuro-endocrine	1 (0.6)
Undifferentiated	1 (0.6)
Tumour Location	
Oesophagus	96 (60.0)
Gastro-oesophageal junction	64 (40.0)
EUS T-stage	
T1	5 (3.1)
T2	14 (8.8)
T3	97 (60.6)
T4a	33 (20.6)
T4b	11 (6.9)
EUS N-stage	
N0	54 (33.8)
N1	49 (30.6)
N2	35 (21.8)
N3	22 (13.8)
PET/CT N-stage	
N0	81 (50.6)
N1	51 (31.8)
N2	22 (13.8)
N3	6 (3.8)
PET/CT M-stage	
M0	144 (90.0)
M1	14 (8.8)
MX	2 (1.2)
Treatment	
Neo-adjuvant chemotherapy	37 (23.1)
Definitive chemoradiotherapy	35 (21.9)
Surgery alone	17 (10.6)
Neo-adjuvant chemoradiotherapy	14 (8.8)
Endoscopic mucosal resection	1 (0.6)
Palliative	56 (35.0)

Table 2. Results of the Multivariable Cox Regression Model

			95% Confidence Interval	
Variable	p-value	Hazard Ratio	Lower	Upper
Age	0.026	1.024	1.003	1.045
Stage Group	0.002	1.728	1.227	2.433
Treatment	<0.001	0.414	0.265	0.648
PET LoD	0.787	0.992	0.933	1.054
EUS LoD	0.996	1.000	0.950	1.053