Clinical Radiology

Accuracy of Contemporary Oesophageal Cancer Lymph Node Staging with Radiological-Pathological Correlation

--Manuscript Draft--

Manuscript Number:	CRAD-D-16-00762R1
Full Title:	Accuracy of Contemporary Oesophageal Cancer Lymph Node Staging with Radiological-Pathological Correlation
Article Type:	Original Paper
Corresponding Author:	Kieran George Foley, MBBCh FRCR Cardiff University Cardiff, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Cardiff University
Corresponding Author's Secondary Institution:	
First Author:	Kieran George Foley, MBBCh FRCR
First Author Secondary Information:	
Order of Authors:	Kieran George Foley, MBBCh FRCR
	Adam Christian
	Patrick Fielding
	Wyn G Lewis
	Stuart Ashley Roberts
Order of Authors Secondary Information:	
Abstract:	Aim Accurate lymph node staging is vital to inform optimum treatment decisions in patients with oesophageal cancer. This study evaluates the accuracy of contemporary N-staging and provides radiological-pathological correlation in patients with lymph node metastases (LNMs) that were radiologically staged N0. Materials and Methods One hundred and twelve patients were included who underwent surgery alone (n=41) or had neo-adjuvant therapy (n=71) between October 2010 and December 2015. Contrast-enhanced CT (CECT), endoscopic ultrasound (EUS) and PET/CT N-stage were compared to pathological N-stage [node-negative (N0) vs node-positive (N+) groups]. Fifty LNMs from 15 patients pre-operatively staged as N0 were measured and the maximum size recorded. Results Accuracy, sensitivity and specificity of N0 vs N+ disease with CECT, EUS and PET/CT was 54.5%, 39.7% and 77.3%, 55.4%, 42.6% and 75.0%, and 57.1% 35.3% and 90.9%, respectively. All modalities were more likely to under-stage nodal disease; CECT (X2 32.890, df 1, p<0.001), EUS (X2 28.471, df 1, p<0.001) and PET/CT (X2 50.790, df 1, p<0.001). PET/CT was more likely to under-stage nodal disease than EUS (p=0.031). Median LNM size was 3 mm, with 41 (82%) of LNMs measuring <6 mm and 22 (44%) classified as micro-metastases (≤2 mm). Conclusion This study has demonstrated poor N-staging accuracy in the modern era of radiological staging. Eighty-two percent of LNMs measured <6mm, making direct identification extremely challenging on medical imaging. Future research should focus on investigating and developing alternative surrogate markers to predict the likelihood of

	LNMs.

Accuracy of Contemporary Oesophageal Cancer Lymph Node Staging with Radiological-Pathological Correlation

Authors

Kieran G. Foley[a], Adam Christian[b], Patrick Fielding[c], Wyn G. Lewis[d], S. Ashley Roberts[e]

a. Division of Cancer & Genetics, Cardiff University.
b. Department of Pathology, University Hospital of Wales, Cardiff
c. Wales Research & Diagnostic PET Imaging Centre, Cardiff.
d. Department of Upper GI Surgery, University Hospital of Wales, Cardiff.
e. Department of Clinical Radiology, University Hospital of Wales, Cardiff.

Institution from which work originated:

Division of Cancer & Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff, Wales, UK, CF14 4XN

Corresponding Author:

Dr K G Foley, Division of Cancer & Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff, Wales, UK, CF14 4XN
Tel: +442920 747747
Fax: +442920743029
foleykg@cardiff.ac.uk

Funding Information:
KF received funding from Tenovus Cancer Care, UK (Grant reference TIG2016/04). We also acknowledge the members of the South East Wales Upper GI cancer MDT.

Author Contributions

1 guarantor of integrity of the entire study	SAR
2 study concepts and design	KF SAR
3 literature research	KF AC
4 clinical studies	AC PF WGL SAR
5 experimental studies / data analysis	N/A
6 statistical analysis	KF
7 manuscript preparation	KF AC PF SAR
8 manuscript editing	KF AC PF WGL SAR

Dear Editor,

On behalf of the authors, I wish to thank you for accepting our manuscript for publication in Clinical Radiology.

Please find our responses to the reviewers' comments below.

Reviewer #1

Major comments: none

Minor comments:

Page 5, line 80: It would be worth describing here the criteria used to define positive nodes at CT.

A sentence describing the criteria used has been included.

Page 6, line 108: which criteria do you adopted to define positive nodes at PET? Please state.

Our criteria for defining positive lymph nodes on PET have been included.

Figures: authors could add two figures showing 1) a true positive nodal case and 2) a false negative nodal case, each showing CT, ultrasound, PET and if possible pathology.

We have included a single figure (Figure 1) showing CT, PET, fused PET/CT images and the pathology slide for a 'false negative' case. After discussion, we decided not to include a 'true positive' case. The authors felt this would take up valuable space without adding much value because the general radiological community are likely to recognise a pathological lymph node.

Reviewer #2

1. the length of time between imaging and surgery/pathological assessment, which has an unknown impact on how severely the various imaging modalities understage. This is mentioned by the authors as a weakness and cannot be rectified; such is the nature of retrospective studies.

   This limitation has not been changed.

2. The small proportion of pathological specimen available for retrospective analysis. This is not seem to be discussed by the authors as a weakness. It is a shame since the part of the manuscript dealing with size measurement of the proven metastases is very interesting, but the fact that it is only a small subgroup makes it less valuable. The authors should at least mention why this was and whether anything linked those specimen that could be analysed (as a smaller point in this section please explicitly state that node measurements represent long axis).

   We have expanded the discussion regarding the availability of resection specimens for analysis. This can be found in the histopathological methods of the materials and methods section.

We hope you find our responses satisfactory and accept the manuscript for publication.

Kind Regards,

The Authors.

Abstract

Aim

Accurate lymph node staging is vital to inform optimum treatment decisions in patients with oesophageal cancer. This study evaluates the accuracy of contemporary N-staging and provides radiological-pathological correlation in patients with lymph node metastases (LNMs) that were radiologically staged N0.

Materials and Methods

One hundred and twelve patients were included who underwent surgery alone (n=41) or had neo-adjuvant therapy (n=71) between October 2010 and December 2015. Contrast-enhanced CT (CECT), endoscopic ultrasound (EUS) and PET/CT N-stage were compared to pathological N-stage [node-negative (N0) vs node-positive (N+) groups]. Fifty LNMs from 15 patients pre-operatively staged as N0 were measured and the maximum size recorded.

Results

Accuracy, sensitivity and specificity of N0 vs N+ disease with CECT, EUS and PET/CT was 54.5%, 39.7% and 77.3%, 55.4%, 42.6% and 75.0%, and 57.1% 35.3% and 90.9%, respectively. All modalities were more likely to under-stage nodal disease; CECT (X^2 32.890, df 1, $p<0.001$), EUS (X^2 28.471, df 1, $p<0.001$) and PET/CT (X^2 50.790, df 1, $p<0.001$). PET/CT was more likely to under-stage nodal

disease than EUS (p=0.031). Median LNM size was 3 mm, with 41 (82%) of LNMs measuring <6 mm and 22 (44%) classified as micro-metastases (≤2 mm).

Conclusion

This study has demonstrated poor N-staging accuracy in the modern era of radiological staging. Eighty-two percent of LNMs measured <6mm, making direct identification extremely challenging on medical imaging. Future research should focus on investigating and developing alternative surrogate markers to predict the likelihood of LNMs.

Accuracy of Contemporary Oesophageal Cancer Lymph Node Staging with Radiological-Pathological Correlation

Introduction

Contemporary radiological staging of oesophageal cancer (OC) involves a multi-modality approach. In the UK, patients have initial contrast-enhanced computed tomography (CECT) of the thorax and abdomen following histological confirmation to assess the potential resectability of the tumour, or any distant metastatic disease which may preclude radical therapy.

If the patient is deemed suitable for radical treatment, either in the form of definitive chemo-radiotherapy (dCRT) or surgery (+/- neo-adjuvant therapy), positron emission tomography combined with computed tomography (PET/CT) and endoscopic ultrasound (EUS) are performed for a more detailed assessment of disease stage. (1) PET/CT has greater sensitivity for distant metastatic disease than CECT (2), whereas EUS is regarded as the 'gold-standard' investigation for defining T- and N-stage, whilst also assisting surgical and radiotherapy planning. (3)

This staging process is complex and time-consuming but necessary, because each modality has limitations for lymph node staging. CECT provides anatomical information only, relies on size criteria and involves radiation. PET/CT also involves radiation but provides additional functional metabolic data and improves the positive predictive value (PPV) of lymph node metastases (LNMs). (4) The differentiation of

peri-tumoural LNMs from adjacent avid tumour can be challenging on PET images. (5) This may increase 'false-negative' rates therefore under-staging the extent of nodal disease. EUS has better sensitivity compared to CECT and PET/CT due to its superior contrast resolution.

The prognosis of OC is poor, with 5-year survival approximately 13%. (6) Many patients present with advanced disease and the incidence is increasing. (7) The presence of LNMs is a major prognostic indicator, therefore it is vital to stage nodal disease accurately. (8) Accurate staging optimises management plans and provides the best chance of survival for patients with potentially curable disease. If the multi-disciplinary team (MDT) decide upon surgical management and radiological staging is ≥T3 or ≥N1, two cycles of neo-adjuvant chemotherapy (NACT) are given prior to resection. This is currently considered best practice in the UK, because overall survival was shown to improve compared to surgery alone. (9)

Management decisions are influenced by results of lymph node assessment based on findings of radiological staging investigations. Differentiation of node-negative (N0) from node-positive (N+) disease is important, because this should ensure that patients avoid unnecessary chemotherapy if over-staged, and are not denied potentially beneficial neo-adjuvant chemotherapy if under-staged.

However, the existence of small LNMs (<6 mm), which cannot be directly visualised on any imaging modality, are likely to cause inaccurate staging and progress, with a subsequent detrimental effect on patient outcome. (10)

Therefore, we aim to define the accuracy of CECT, EUS and PET/CT N-stage in the modern era of radiological OC staging. We will also investigate the prevalence of micro-metastases and size of LNMs in patients radiologically staged N0 but pathologically node-positive (pN+), by providing radiological-pathological correlation.

Materials and Methods

This retrospective cohort study includes consecutive patients who underwent surgical resection of an oesophageal or gastro-oesophageal (GOJ) tumour, over a 5-year period (November 2010 – December 2015) within a centralised service. Radiological and pathological staging data was obtained from the *blinded* database (*blinded*) following Regional Upper Gastrointestinal (GI) Cancer MDT discussion. Institutional Review Board (IRB) approval was granted (ref no. 14/WA/1208). The requirement for informed consent was waived.

Inclusion criteria were a previously untreated, biopsy-proven oesophageal or GOJ tumour in patients who underwent surgery alone, or had a poor Mandard tumour regression grade (TRG 4) or no response (TRG 5) following either NACT or neo-adjuvant chemo-radiotherapy (NACRT). (11) All patients had fully completed CECT, EUS and PET/CT staging investigations and were classified according to the International Union Against Cancer (UICC) Tumour Node Metastasis (TNM) 7th edition. (12) All patients also had a full pathological N-stage (pN), also defined by the TNM 7th edition.

Patients with tumours that showed complete pathological response (pCR, TRG 1) or tumours with some response (TRG 2 & 3) following NACT or NACRT were excluded because the final pathology is not likely to be representative of pre-operative status. Incomplete radiological staging investigations in particular, EUS examinations, in which the operator was unable to traverse a stenotic tumour in order to fully classify N-stage, were excluded. Patients that underwent an 'open-and-close' procedure due to irresectable disease at the time of operation, were also excluded.

CECT Acquisition Protocol

CECT was performed either in the host institution of the centralised service (*blinded*) or in local referring hospitals prior to surgery, according to Royal College of Radiologists guidelines. (1) All CECT examinations were reviewed at the Regional Upper GI MDT, and deemed to be of a satisfactory technical standard. The technique used at the host institution is as follows: GE HD 750 Discovery 64-slice scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK); helical acquisition with collimation of 40mm, pitch 0.984:1 and tube rotation speed of 0.4 seconds; tube output of 120kVp with smart mA dose modulation between 60-600mA; slice thickness of 0.625mm; up to 500ml of water orally and 100-150mls of Niopam 300 intravenously with bolus tracking. Lymph nodes were considered involved on CECT if the short axis measurement was 1 cm or greater, located in the expected distribution of disease, round with loss of fatty hilum and demonstrated altered density or enhancement.

EUS Protocol

All EUS examinations were performed in 3 centres by 4 endosonographers. 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 <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. The primary

oesophageal tumour was assessed, together with an evaluation of peri-oesophageal and peri-gastric structures as described previously. (13) The criteria for malignant lymphadenopathy specified a hypo-echoic pattern, spherical contour, distinct border, and short axis diameter of 6 mm or more.

PET/CT Acquisition 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 prior to proceeding with imaging. Patients received a dose of 4 MBq of ^{18}F-FDG per kilogram of body weight. Uptake time was 90 minutes, which is standard at our institution. ^{18}F-FDG PET/CT imaging was performed with a GE 690 PET/CT scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK). 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 50cm 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. Nodes were classed as involved on PET/CT if identified on the CT component and showed FDG-uptake appreciably higher than background values. No specific standardised uptake value was used for the inclusion of regional nodes. Lymph nodes considered physiological or related to an alternative aetiology were excluded from the N-stage.

Histopathological Methods

Histopathological reporting of OC specimens was performed according to minimum requirements defined by the Royal College of Pathologists (RCPath). (14) All lymph nodes identified in the resection specimen were prepared in 3 mm slices for pathological evaluation. N-stage was then assigned depending on the number of LNMs identified. TRG of the primary tumour was assigned according to the degree of fibrosis compared to residual tumour cells. (11) In discordant cases, all available resection specimens that were radiologically staged N0 but pathologically N+ were further evaluated. All available specimens were retrieved and reviewed from the archive. Due to the retrospective nature of analysis, some of the older cases were archived off-site, and were unavailable at the time of evaluation. The maximum size (long axis) of both involved lymph nodes and metastases within those lymph nodes, were retrospectively recorded. Maximum size was defined as the largest dimension on the glass slide measured by a Consultant Pathologist. A micro-metastasis is defined as tumour deposit measuring ≤2 mm. (15) Furthermore, a metastasis to lymph node ratio was calculated.

Statistical Analysis

Descriptive statistics are used to describe categorical and continuous variables. In this study, N-stage is separated into negative (N0) and N+ (N1, N2 or N3) groups. Accuracy is defined as number of correct investigations divided by total number of investigations. Sensitivity and specificity of N+ disease are calculated for each modality. A Chi-square test assessed significant differences in under- or over-staging for each modality. Significant differences in under-staging between

modalities was assessed with McNemar's test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS v23 (IBM, Chicago, IL).

Results

A total of 190 patients were considered for inclusion in the study. Seventy-eight patients (41.1%) were excluded from the study; 22 were 'open-and-close' procedures, 16 were TRG 1, 13 were TRG 2, 13 were TRG 3 following neo-adjuvant treatment, and 14 had incomplete EUS staging.

Following exclusions, 112 patients were included in the study. The median age was 65 years (range 24-78) and the male: female ratio was 92 (82.1%): 20 (17.9%). Fifty-nine tumours (52.7%) were located in the oesophagus; 10 in the mid oesophagus and 49 in the distal oesophagus. Fifty-three tumours (47.3%) were located at the GOJ; 19 Siewert (Sw) type I, 15 Sw type II and 19 Sw type III.

One hundred tumours (89.3%) were adenocarcinoma, with 11 SCC (9.8%) and 1 neuroendocrine (0.9%). Forty-one patients (36.6%) were treated with surgery alone, 67 (59.8%) treated with NACT and 4 (3.6%) treated with NACRT. Of the 71 treated with neo-adjuvant therapy, 42 were TRG 4 and 29 were TRG 5.

For CECT, 75 patients (67.0%) were staged N0 and 37 (33.0%) were N+. For EUS, 72 patients (64.3%) were staged N0 and 40 (35.7%) were N+. For PET/CT, 84 (75.1%) were staged N0 and 28 (24.9%) were staged N+. Table 1 compares the frequency of radiological and pathological N-stages for CECT, EUS and PET/CT.

Overall, median time between radiological staging and surgery was 3 months (range 1-9 months), 1 month (range 0-3 months) in patients undergoing surgery alone and 4 months (range 3-4 months) in patients receiving NACT.

Accuracy, Sensitivity and Specificity of CECT, EUS and PET/CT N-stage

N0 vs N+ disease was correctly identified with CECT, EUS and PET/CT in 61 cases (54.5%), 62 (55.4%) and 64 (57.1%), respectively. There was no significant difference between CECT, EUS and PET/CT for detecting N+ disease (X^2 0.169, df 2, p=0.919). The sensitivity and specificity for identifying N0 vs N+ disease with CECT, EUS and PET/CT was 39.7% and 77.3%, 42.6% and 75.0%, and 35.3% and 90.9%, respectively.

Under-staging vs Over-staging

All modalities were significantly more likely to under-stage nodal disease; CECT (X^2 32.890, df 1, p<0.001), EUS (X^2 28.471, df 1, p<0.001) and PET/CT (X^2 50.790, df 1, p<0.001). Comparing modalities, there was a borderline significant difference in under-staging between CECT and EUS (p=0.063) but no difference between CECT and PET/CT (p=1.000). However, there was a statistically significant between both EUS with PET/CT (p=0.031), suggesting PET/CT may further under-stage nodal disease.

Pathological Lymph Node Measurement

Fifteen archived resection specimens in patients pre-operatively staged N0 were available for retrospective measurement of the lymph nodes and their respective metastases. In total, 50 involved lymph nodes were assessed. (Table 2) The median

size of involved lymph nodes was 6 mm (range 2-15 mm) and the median metastasis size was 3 mm (0.5-13.5 mm). Twenty-two (44%) LNMs measured ≤2 mm, which are defined as micro-metastases. (Fig. 1) Forty-one (82%) LNMs were ≤6 mm and 46 (92%) LNMs were ≤10 mm. A metastasis to lymph node size ratio was calculated. Thirty-one (62%) of the lymph nodes examined were replaced with ≥50% metastatic deposit, 19 (38%) were replaced with <50% metastatic deposit, with 12 (24%) replaced with <25% metastatic deposit, using maximum size criteria.

Discussion

This study has found poor N-stage accuracy with CECT, EUS and PET/CT. In general, all modalities were more likely to under-stage nodal disease, with PET/CT more likely to under-stage than EUS. Another important finding, is the prevalence of small LNMs (<6 mm) in the resection specimens of patients radiologically staged N0. Micro-metastases have been found in lymph nodes of early oesophageal tumours (16) but little has been published with radiological correlation. Studies investigating lung cancer have detected micro-metastases in patients radiologically staged N0 (17), although evidence in OC is lacking.

The majority of LNMs (82%) were <6 mm, which makes direct visualisation extremely challenging on current medical imaging techniques and is likely to be the main reason for discrepancy between radiological and pathological staging. In addition, traditional radiological measurement of lymph nodes is taken in the short-axis (18), which further reduces the likelihood that LNMs are diagnosed. Even with the improved contrast resolution of EUS compared to cross-sectional imaging, it is unlikely that a lymph node of this size would confidently be classified as involved. (13) Similarly, there was a relatively high prevalence of micro-metastases (44%).

These results have significant implications for treatment decision-making processes and demonstrate that contemporary radiology techniques are inadequate for N-staging. Numerous studies have demonstrated the importance of LNMs, which have a significant effect on overall survival. (8) Better evidence is required to understand the prognostic significance of micro-metastases, but they are generally felt to confer a worse prognosis. (19, 20)

There is evidence that a significant proportion of surgical patients have systemic micro-metastases at the time of resection. In one study, micro-metastases were detected in the resected rib in 53.7% to 78% of cases, and was dependent on the histological technique used. (21) This is a higher detection rate than our study, but the results are comparable due to different techniques and tissues used between the studies. The high rate of micro-metastases may be a reason that our results show significant under-staging of nodal disease, and perhaps clinicians could consider lowering the threshold for treating patients with systemic neo-adjuvant therapy.

Previously published research from our institution has shown the prognostic significance of N-stage, LNM count and volume of nodal disease in patients with OC. (22, 23) Nodal disease in these studies probably continues to be an important prognostic indicator, but the radiological staging is likely to have under-estimated the total nodal disease burden in those patient cohorts. Results of staging performance have also been published from our institution. These studies compared CECT and EUS with pN-staging. Blackshaw et al focused on accuracy of N-staging in GOJ tumours and found significant differences in agreement, sensitivity and specificity between Siewert type II and type III tumours. (24) Weaver et al found agreement, sensitivity and specificity of N-staging was 0.603, 79% and 84% for CECT and 0.610, 91% and 68% for EUS. (13) The results of the current study show poorer agreement and sensitivity. There are a number of reasons for these findings, including disease evolution, greater inter-observer variability between reporters, and fewer, but more specialised upper GI cancer pathologists reporting the resection specimens, with possibly higher rates of LNM detection. (15)

Accuracy of diagnosing N+ disease with CECT, EUS and PET/CT was 54.5%, 55.4% and 57.1%, respectively. In a clinical context, these results are unsatisfactory given that the presence of LNMs is such a major prognostic indicator. (8) The sensitivity and specificity for identifying N0 vs N+ disease with CECT, EUS and PET/CT was 39.7% and 77.3%, 42.6% and 75.0%, and 35.3% and 90.9%. Specificity results are comparable with past meta-analyses but sensitivity results are lower for all modalities. Previously published literature states sensitivity for N-staging of EUS, CECT and PET/CT is 80%, 50 % and 57%, and specificity is 70%, 83% and 85%, respectively. (2) However, this meta-analysis was conducted prior to this centralisation of many upper GI cancer services. The reduced sensitivity of staging investigations is supported by our results, which demonstrate that under-staging is more common for all modalities.

As current investigations are unreliable for differentiating N0 from N+ disease, future research should focus on investigating and developing new methods of predicting the likelihood of lymph node involvement. Surrogate markers of LNMs, such as texture analysis of the primary tumour and other non-invasive quantitative imaging techniques, may allow better risk stratification of patients, provide more powerful prognostic data and further inform optimum treatment decisions. (25, 26) MRI may provide an alternative staging modality. Research studies have demonstrated variable diagnostic ability, with sensitivity, specificity and accuracy ranging between 38-62%, 68-85% and 64-77%, respectively. These current results are comparable to CT, EUS and PET/CT but continuing improvements in functional MRI scanner technology may yield further developments. (27, 28)

Strengths of Study

This study provides radiological-pathological correlation in a group of OC patients with discordant nodal staging. Radiological-pathological correlation is essential for understanding limitations of staging techniques and identifies areas requiring further research. All patients were discussed at the Regional MDT and the management plan for each individual was decided upon by consensus. The Regional MDT covers a large population of over 1.4 million people and is highly experienced in the management of OC. Histopathological examination was performed by consultant GI pathologists according the guidelines defined by the RCPath. (14) We implemented strict criteria to control the selection of patients for this study, which compares imaging findings to 'gold-standard' pathological staging. The majority of patients received neo-adjuvant therapy, which can alter the stage of disease between pre-treatment imaging and surgical resection. To control for this, only patients with Mandard TRG 4 or 5 were included, which should allow a more direct comparison with the final pathological resection specimen. The majority of patients tend to have a TRG 4 or 5 response. (29)

Limitations

As a result of neo-adjuvant therapy, there is a time-lag between radiological staging and surgical resection, which could allow for tumour progression and LNM development. However, the median time period in this study was 3 months. In addition, patients with an 'open-and-close' procedure were excluded, which further demonstrates radiological disease under-staging. There are also known limitations of pathological lymph node examination. Approximately 3 mm sections are taken through lymph nodes once they are mounted in a cassette, but this may be performed with varying skill and consistency. Micro-metastases may be missed if

not bisected during preparation, and this suggests that the true incidence of micro-metastases in this cohort of patients may be even greater. Although the RCPath define the minimum requirements for pathological reporting, there is no recommended, standardised method for lymph node preparation and assessment in OC, at present. The centralised upper GI cancer service is referred patients from several local NHS trusts. As a result, multiple readers from different hospitals report the staging CECT examinations. During this period, 3 endosonographers performed the EUS examinations in 2 different hospitals. All PET/CT scans were performed using the same scanner and protocol and were reported by 4 different consultant radiologists. However, all staging was performed according to the TNM 7th edition.

Conclusion

In conclusion, this evaluation of contemporary staging performance over a 5-year period in a centralised upper GI cancer service has shown poor N-staging accuracy for CECT, EUS and PET/CT. Radiological-pathological correlation in patients staged N0 has shown a large number of small LNMs (<6 mm) that are extremely challenging to diagnose directly from medical imaging. The findings of this study have significant implications for patient care, because radiological staging results largely influence treatment decisions made by the MDT. Future research should focus on prediction of the likelihood of lymph node involvement as current lymph node imaging is inadequate.

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Figure Legends

Figure 1. CT (with calipers), PET and fused PET/CT images of a 'false-negative' left gastric lymph node in a patient with junctional adenocarcinoma. A low-power magnification of the lymph node shows a micro-metastasis. For reference, the lymph node measured 5 mm in maximum size and the micro-metastasis (highlighted with yellow outline) measured 1.2 mm.

Table 1

Table 1. Comparison of N-stage frequency classified by CECT, EUS, PET/CT and pathology.

CECT N-stage					
Frequency (%)	N0	N1	N2	N3	Total
pN0	34 (30.4)	8 (7.1)	2 (1.7)	0 (0.0)	44 (39.3)
pN1	21 (18.8)	4 (3.6)	2 (1.7)	0 (0.0)	27 (24.1)
pN2	16 (14.3)	10 (8.9)	1 (0.9)	0 (0.0)	27 (24.1)
pN3	4 (3.6)	7 (6.3)	3 (2.7)	0 (0.0)	14 (12.5)
Total	75 (67.0)	29 (25.9)	8 (7.1)	0 (0.0)	112 (100.0)
EUS N-Stage					
Frequency (%)	N0	N1	N2	N3	Total
pN0	33 (29.5)	9 (8.0)	1 (0.9)	1 (0.9)	44 (39.3)
pN1	20 (17.9)	7 (6.3)	0 (0.0)	0 (0.0)	27 (24.1)
pN2	13 (11.6)	10 (8.9)	4 (3.6)	0 (0.0)	27 (24.1)
pN3	6 (5.4)	6 (5.4)	1 (0.9)	1 (0.9)	14 (12.5)
Total	72 (64.3)	32 (28.6)	6 (5.4)	2 (1.7)	112 (100.0)
PET/CT N-stage					
Frequency (%)	N0	N1	N2	N3	Total
pN0	40 (35.8)	4 (3.6)	0 (0.0)	0 (0.0)	44 (39.4)
pN1	23 (20.5)	4 (3.6)	0 (0.0)	0 (0.0)	27 (24.1)
pN2	15 (13.4)	10 (8.9)	2 (1.7)	0 (0.0)	27 (24.1)
pN3	6 (5.4)	6 (5.4)	2 (1.7)	0 (0.0)	14 (12.5)
Total	84 (75.1)	24 (21.4)	4 (3.6)	0 (0.0)	112 (100.0)

406 **Table 2**

407 Table 2. Frequency of and distribution of lymph node and metastasis size when
408 separated in groups of 2 mm for descriptive purposes.

Frequency (%)	Maximum Size (mm)							
	0-2	2.1-4	4.1-6	6.1-8	8.1-10	10.1-12	12.1-14	14.1-16
Lymph Node	3 (6.0)	11 (22.0)	13 (26.0)	12 (24.0)	4 (8.0)	3 (6.0)	3 (6.0)	1 (2.0)
Metastasis	22 (44.0)	9 (18.0)	10 (20.0)	3 (6.0)	2 (4.0)	2 (4.0)	2 (4.0)	0 (0.0)

409

Revised Figure

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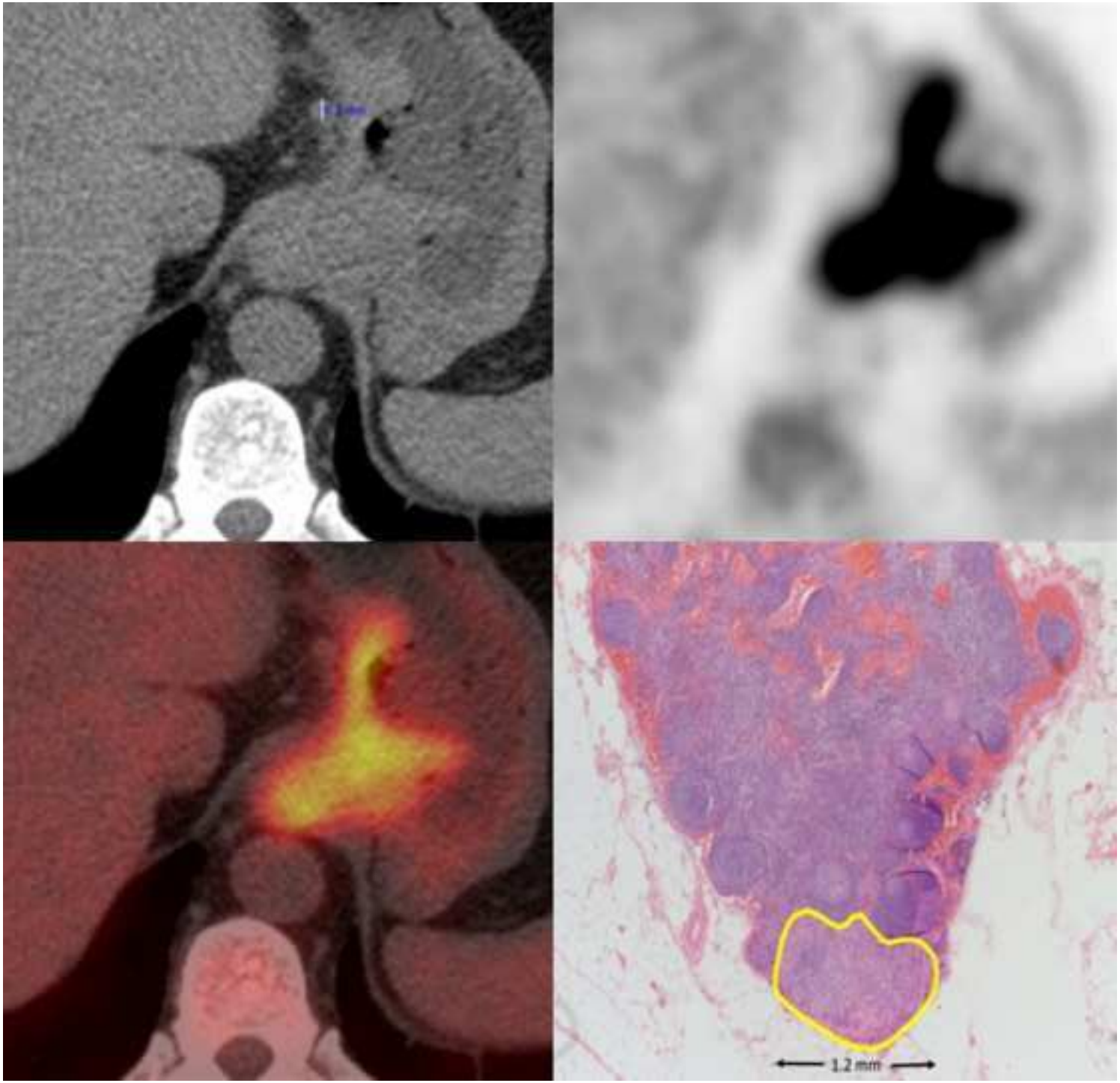

Highlights

1. CT, EUS and PET/CT N-staging accuracy is poor in oesophageal cancer.

2. CT, EUS and PET/CT are all more likely to under-stage nodal disease.

3. Many lymph node metastases are too small to be identified with direct imaging.