Clinical Radiology

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

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

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.

1 **Accuracy of Contemporary Oesophageal Cancer Lymph Node Staging with**

2 **Radiological-Pathological Correlation**

3

4 **Introduction**

5 Contemporary radiological staging of oesophageal cancer (OC) involves a multi-

6 modality approach. In the UK, patients have initial contrast-enhanced computed

7 tomography (CECT) of the thorax and abdomen following histological confirmation to

8 assess the potential resectability of the tumour, or any distant metastatic disease

9 which may preclude radical therapy.

10 If the patient is deemed suitable for radical treatment, either in the form of definitive

11 chemo-radiotherapy (dCRT) or surgery (+/- neo-adjuvant therapy), positron emission

12 tomography combined with computed tomography (PET/CT) and endoscopic

13 ultrasound (EUS) are performed for a more detailed assessment of disease stage.

14 (1) PET/CT has greater sensitivity for distant metastatic disease than CECT (2),

15 whereas EUS is regarded as the 'gold-standard' investigation for defining T- and N-

16 stage, whilst also assisting surgical and radiotherapy planning. (3)

17 This staging process is complex and time-consuming but necessary, because each

18 modality has limitations for lymph node staging. CECT provides anatomical

19 information only, relies on size criteria and involves radiation. PET/CT also involves

20 radiation but provides additional functional metabolic data and improves the positive

21 predictive value (PPV) of lymph node metastases (LNMs). (4) The differentiation of

22 peri-tumoural LNMs from adjacent avid tumour can be challenging on PET images.

23 (5) This may increase 'false-negative' rates therefore under-staging the extent of

24 nodal disease. EUS has better sensitivity compared to CECT and PET/CT due to its

25 superior contrast resolution.

26 The prognosis of OC is poor, with 5-year survival approximately 13%. (6) Many

27 patients present with advanced disease and the incidence is increasing. (7) The

28 presence of LNMs is a major prognostic indicator, therefore it is vital to stage nodal

29 disease accurately. (8) Accurate staging optimises management plans and provides

30 the best chance of survival for patients with potentially curable disease. If the multi-

31 disciplinary team (MDT) decide upon surgical management and radiological staging

32 is ≥T3 or ≥N1, two cycles of neo-adjuvant chemotherapy (NACT) are given prior to

33 resection. This is currently considered best practice in the UK, because overall

34 survival was shown to improve compared to surgery alone. (9)

35 Management decisions are influenced by results of lymph node assessment based

36 on findings of radiological staging investigations. Differentiation of node-negative

37 (N0) from node-positive (N+) disease is important, because this should ensure that

38 patients avoid unnecessary chemotherapy if over-staged, and are not denied

39 potentially beneficial neo-adjuvant chemotherapy if under-staged.

40 However, the existence of small LNMs (<6 mm), which cannot be directly visualised

41 on any imaging modality, are likely to cause inaccurate staging and progress, with a

42 subsequent detrimental effect on patient outcome. (10)

43   Therefore, we aim to define the accuracy of CECT, EUS and PET/CT N-stage in the

44   modern era of radiological OC staging. We will also investigate the prevalence of

45   micro-metastases and size of LNMs in patients radiologically staged N0 but

46   pathologically node-positive (pN+), by providing radiological-pathological correlation.

Materials and Methods

48   This retrospective cohort study includes consecutive patients who underwent

49   surgical resection of an oesophageal or gastro-oesophageal (GOJ) tumour, over a 5-

50   year period (November 2010 – December 2015) within a centralised service.

51   Radiological and pathological staging data was obtained from the *blinded* database

52   (*blinded*) following Regional Upper Gastrointestinal (GI) Cancer MDT discussion.

53   Institutional Review Board (IRB) approval was granted (ref no. 14/WA/1208). The

54   requirement for informed consent was waived.

55   Inclusion criteria were a previously untreated, biopsy-proven oesophageal or GOJ

56   tumour in patients who underwent surgery alone, or had a poor Mandard tumour

57   regression grade (TRG 4) or no response (TRG 5) following either NACT or neo-

58   adjuvant chemo-radiotherapy (NACRT). (11) All patients had fully completed CECT,

59   EUS and PET/CT staging investigations and were classified according to the

60   International Union Against Cancer (UICC) Tumour Node Metastasis (TNM) 7th

61   edition. (12) All patients also had a full pathological N-stage (pN), also defined by

62   the TNM 7th edition.

63   Patients with tumours that showed complete pathological response (pCR, TRG 1) or

64   tumours with some response (TRG 2 & 3) following NACT or NACRT were excluded

65   because the final pathology is not likely to be representative of pre-operative status.

66   Incomplete radiological staging investigations in particular, EUS examinations, in

67   which the operator was unable to traverse a stenotic tumour in order to fully classify

68   N-stage, were excluded. Patients that underwent an 'open-and-close' procedure due

69   to irresectable disease at the time of operation, were also excluded.

4

70   CECT Acquisition Protocol

71   CECT was performed either in the host institution of the centralised service (*blinded*)

72   or in local referring hospitals prior to surgery, according to Royal College of

73   Radiologists guidelines. (1) All CECT examinations were reviewed at the Regional

74   Upper GI MDT, and deemed to be of a satisfactory technical standard. The

75   technique used at the host institution is as follows: GE HD 750 Discovery 64-slice

76   scanner (GE Healthcare, Pollards Wood, Buckinghamshire, UK); helical acquisition

77   with collimation of 40mm, pitch 0.984:1 and tube rotation speed of 0.4 seconds; tube

78   output of 120kVp with smart mA dose modulation between 60-600mA; slice

79   thickness of 0.625mm; up to 500ml of water orally and 100-150mls of Niopam 300

80   intravenously with bolus tracking. Lymph nodes were considered involved on CECT

81   if the short axis measurement was 1 cm or greater, located in the expected

82   distribution of disease, round with loss of fatty hilum and demonstrated altered

83   density or enhancement.

84   EUS Protocol

85   All EUS examinations were performed in 3 centres by 4 endosonographers. At the

86   host institution, an initial endoscopic examination was performed using a 9 mm

87   diameter Olympus Paediatric gastroscope (Olympus, Southend, UK) to assess the

88   degree of oesophageal luminal stenosis. Patients with an estimated oesophageal

89   luminal diameter <15 mm underwent examination using the smaller-diameter MH-

90   908 oesophagoprobe, and where there was no luminal stenosis, the standard UM-

91   2000 echoendoscope was used (Olympus, Southend, UK). The type of

92   echoendoscope used was at the discretion of the endoscopist. The primary

93 oesophageal tumour was assessed, together with an evaluation of peri-oesophageal

94 and peri-gastric structures as described previously. (13) The criteria for malignant

95 lymphadenopathy specified a hypo-echoic pattern, spherical contour, distinct border,

96 and short axis diameter of 6 mm or more.

97 PET/CT Acquisition Protocol

98 Patients were fasted for at least 6 hours prior to tracer administration. Serum glucose

99 levels were routinely checked and confirmed to be less than 7.0 mmol/L prior to

100 proceeding with imaging. Patients received a dose of 4 MBq of ^{18}F-FDG per kilogram

101 of body weight. Uptake time was 90 minutes, which is standard at our institution. ^{18}F-

102 FDG PET/CT imaging was performed with a GE 690 PET/CT scanner (GE

103 Healthcare, Pollards Wood, Buckinghamshire, UK). CT images were acquired in a

104 helical acquisition with a pitch of 0.98 and a tube rotation speed of 0.5 seconds.

105 Tube output was 120 kVp with output modulation between 20 and 200 mA. Matrix

106 size for the CT acquisition was 512 x 512 pixels with a 50cm field of view. No oral or

107 intravenous contrast was administered. PET images were acquired at 3 minutes per

108 field of view. The length of the axial field of view was 15.7 cm. Images were

109 reconstructed with the ordered subset expectation maximisation algorithm, with 24

110 subsets and 2 iterations. Matrix size was 256 x 256 pixels, using the VUE Point ™

111 time of flight algorithm. Nodes were classed as involved on PET/CT if identified on

112 the CT component and showed FDG-uptake appreciably higher than background

113 values. No specific standardised uptake value was used for the inclusion of regional

114 nodes. Lymph nodes considered physiological or related to an alternative aetiology

115 were excluded from the N-stage.

116   Histopathological Methods

117   Histopathological reporting of OC specimens was performed according to minimum

118   requirements defined by the Royal College of Pathologists (RCPath). (14) All lymph

119   nodes identified in the resection specimen were prepared in 3 mm slices for

120   pathological evaluation. N-stage was then assigned depending on the number of

121   LNMs identified. TRG of the primary tumour was assigned according to the degree

122   of fibrosis compared to residual tumour cells. (11) In discordant cases, all available

123   resection specimens that were radiologically staged N0 but pathologically N+ were

124   further evaluated. All available specimens were retrieved and reviewed from the

125   archive. Due to the retrospective nature of analysis, some of the older cases were

126   archived off-site, and were unavailable at the time of evaluation. The maximum size

127   (long axis) of both involved lymph nodes and metastases within those lymph nodes,

128   were retrospectively recorded. Maximum size was defined as the largest dimension

129   on the glass slide measured by a Consultant Pathologist. A micro-metastasis is

130   defined as tumour deposit measuring ≤2 mm. (15) Furthermore, a metastasis to

131   lymph node ratio was calculated.

132   Statistical Analysis

133   Descriptive statistics are used to describe categorical and continuous variables. In

134   this study, N-stage is separated into negative (N0) and N+ (N1, N2 or N3) groups.

135   Accuracy is defined as number of correct investigations divided by total number of

136   investigations. Sensitivity and specificity of N+ disease are calculated for each

137   modality. A Chi-square test assessed significant differences in under- or over-

138   staging for each modality. Significant differences in under-staging between

139   modalities was assessed with McNemar's test. A p-value <0.05 was considered

140   statistically significant. Statistical analysis was performed with SPSS v23 (IBM,

141   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.

163

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

165 N0 vs N+ disease was correctly identified with CECT, EUS and PET/CT in 61 cases

166 (54.5%), 62 (55.4%) and 64 (57.1%), respectively. There was no significant

167 difference between CECT, EUS and PET/CT for detecting N+ disease (X^2 0.169, df

168 2, p=0.919). The sensitivity and specificity for identifying N0 vs N+ disease with

169 CECT, EUS and PET/CT was 39.7% and 77.3%, 42.6% and 75.0%, and 35.3% and

170 90.9%, respectively.

171 Under-staging vs Over-staging

172 All modalities were significantly more likely to under-stage nodal disease; CECT (X^2

173 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,

174 p<0.001). Comparing modalities, there was a borderline significant difference in

175 under-staging between CECT and EUS (p=0.063) but no difference between CECT

176 and PET/CT (p=1.000). However, there was a statistically significant between both

177 EUS with PET/CT (p=0.031), suggesting PET/CT may further under-stage nodal

178 disease.

179 Pathological Lymph Node Measurement

180 Fifteen archived resection specimens in patients pre-operatively staged N0 were

181 available for retrospective measurement of the lymph nodes and their respective

182 metastases. In total, 50 involved lymph nodes were assessed. (Table 2) The median

183   size of involved lymph nodes was 6 mm (range 2-15 mm) and the median metastasis

184   size was 3 mm (0.5-13.5 mm). Twenty-two (44%) LNMs measured ≤2 mm, which

185   are defined as micro-metastases. (Fig. 1)   Forty-one (82%) LNMs were ≤6 mm and

186   46 (92%) LNMs were ≤10 mm. A metastasis to lymph node size ratio was

187   calculated. Thirty-one (62%) of the lymph nodes examined were replaced with ≥50%

188   metastatic deposit, 19 (38%) were replaced with <50% metastatic deposit, with 12

189   (24%) replaced with <25% metastatic deposit, using maximum size criteria.

Discussion

191   This study has found poor N-stage accuracy with CECT, EUS and PET/CT. In

192   general, all modalities were more likely to under-stage nodal disease, with PET/CT

193   more likely to under-stage than EUS. Another important finding, is the prevalence of

194   small LNMs (<6 mm) in the resection specimens of patients radiologically staged N0.

195   Micro-metastases have been found in lymph nodes of early oesophageal tumours

196   (16) but little has been published with radiological correlation. Studies investigating

197   lung cancer have detected micro-metastases in patients radiologically staged N0

198   (17), although evidence in OC is lacking.

199   The majority of LNMs (82%) were <6 mm, which makes direct visualisation

200   extremely challenging on current medical imaging techniques and is likely to be the

201   main reason for discrepancy between radiological and pathological staging. In

202   addition, traditional radiological measurement of lymph nodes is taken in the short-

203   axis (18), which further reduces the likelihood that LNMs are diagnosed. Even with

204   the improved contrast resolution of EUS compared to cross-sectional imaging, it is

205   unlikely that a lymph node of this size would confidently be classified as involved.

206   (13) Similarly, there was a relatively high prevalence of micro-metastases (44%).

207   These results have significant implications for treatment decision-making processes

208   and demonstrate that contemporary radiology techniques are inadequate for N-

209   staging. Numerous studies have demonstrated the importance of LNMs, which have

210   a significant effect on overall survival. (8) Better evidence is required to understand

211   the prognostic significance of micro-metastases, but they are generally felt to confer

212   a worse prognosis. (19, 20)

213   There is evidence that a significant proportion of surgical patients have systemic

214   micro-metastases at the time of resection. In one study, micro-metastases were

215   detected in the resected rib in 53.7% to 78% of cases, and was dependent on the

216   histological technique used. (21) This is a higher detection rate than our study, but

217   the results are comparable due to different techniques and tissues used between the

218   studies. The high rate of micro-metastases may be a reason that our results show

219   significant under-staging of nodal disease, and perhaps clinicians could consider

220   lowering the threshold for treating patients with systemic neo-adjuvant therapy.

221   Previously published research from our institution has shown the prognostic

222   significance of N-stage, LNM count and volume of nodal disease in patients with OC.

223   (22, 23) Nodal disease in these studies probably continues to be an important

224   prognostic indicator, but the radiological staging is likely to have under-estimated the

225   total nodal disease burden in those patient cohorts. Results of staging performance

226   have also been published from our institution. These studies compared CECT and

227   EUS with pN-staging. Blackshaw et al focused on accuracy of N-staging in GOJ

228   tumours and found significant differences in agreement, sensitivity and specificity

229   between Siewert type II and type III tumours. (24) Weaver et al found agreement,

230   sensitivity and specificity of N-staging was 0.603, 79% and 84% for CECT and

231   0.610, 91% and 68% for EUS. (13) The results of the current study show poorer

232   agreement and sensitivity. There are a number of reasons for these findings,

233   including disease evolution, greater inter-observer variability between reporters, and

234   fewer, but more specialised upper GI cancer pathologists reporting the resection

235   specimens, with possibly higher rates of LNM detection. (15)

236   Accuracy of diagnosing N+ disease with CECT, EUS and PET/CT was 54.5%,

237   55.4% and 57.1%, respectively. In a clinical context, these results are unsatisfactory

238   given that the presence of LNMs is such a major prognostic indicator. (8) The

239   sensitivity and specificity for identifying N0 vs N+ disease with CECT, EUS and

240   PET/CT was 39.7% and 77.3%, 42.6% and 75.0%, and 35.3% and 90.9%.

241   Specificity results are comparable with past meta-analyses but sensitivity results are

242   lower for all modalities. Previously published literature states sensitivity for N-

243   staging of EUS, CECT and PET/CT is 80%, 50 % and 57%, and specificity is 70%,

244   83% and 85%, respectively. (2) However, this meta-analysis was conducted prior to

245   this centralisation of many upper GI cancer services. The reduced sensitivity of

246   staging investigations is supported by our results, which demonstrate that under-

247   staging is more common for all modalities.

248   As current investigations are unreliable for differentiating N0 from N+ disease, future

249   research should focus on investigating and developing new methods of predicting

250   the likelihood of lymph node involvement. Surrogate markers of LNMs, such as

251   texture analysis of the primary tumour and other non-invasive quantitative imaging

252   techniques, may allow better risk stratification of patients, provide more powerful

253   prognostic data and further inform optimum treatment decisions. (25, 26) MRI may

254   provide an alternative staging modality. Research studies have demonstrated

255   variable diagnostic ability, with sensitivity, specificity and accuracy ranging between

256   38-62%, 68-85% and 64-77%, respectively. These current results are comparable to

257   CT, EUS and PET/CT but continuing improvements in functional MRI scanner

258   technology may yield further developments. (27, 28)

259   Strengths of Study

260   This study provides radiological-pathological correlation in a group of OC patients

261   with discordant nodal staging. Radiological-pathological correlation is essential for

262   understanding limitations of staging techniques and identifies areas requiring further

263   research. All patients were discussed at the Regional MDT and the management

264   plan for each individual was decided upon by consensus. The Regional MDT covers

265   a large population of over 1.4 million people and is highly experienced in the

266   management of OC. Histopathological examination was performed by consultant GI

267   pathologists according the guidelines defined by the RCPath. (14) We implemented

268   strict criteria to control the selection of patients for this study, which compares

269   imaging findings to 'gold-standard' pathological staging. The majority of patients

270   received neo-adjuvant therapy, which can alter the stage of disease between pre-

271   treatment imaging and surgical resection. To control for this, only patients with

272   Mandard TRG 4 or 5 were included, which should allow a more direct comparison

273   with the final pathological resection specimen. The majority of patients tend to have

274   a TRG 4 or 5 response. (29)

275   Limitations

276   As a result of neo-adjuvant therapy, there is a time-lag between radiological staging

277   and surgical resection, which could allow for tumour progression and LNM

278   development. However, the median time period in this study was 3 months. In

279   addition, patients with an 'open-and-close' procedure were excluded, which further

280   demonstrates radiological disease under-staging. There are also known limitations

281   of pathological lymph node examination. Approximately 3 mm sections are taken

282   through lymph nodes once they are mounted in a cassette, but this may be

283   performed with varying skill and consistency. Micro-metastases may be missed if

284   not bisected during preparation, and this suggests that the true incidence of micro-

285   metastases in this cohort of patients may be even greater. Although the RCPath

286   define the minimum requirements for pathological reporting, there is no

287   recommended, standardised method for lymph node preparation and assessment in

288   OC, at present. The centralised upper GI cancer service is referred patients from

289   several local NHS trusts. As a result, multiple readers from different hospitals report

290   the staging CECT examinations. During this period, 3 endosonographers performed

291   the EUS examinations in 2 different hospitals. All PET/CT scans were performed

292   using the same scanner and protocol and were reported by 4 different consultant

293   radiologists. However, all staging was performed according to the TNM 7th edition.

Conclusion

294 **Conclusion**

295   In conclusion, this evaluation of contemporary staging performance over a 5-year

296   period in a centralised upper GI cancer service has shown poor N-staging accuracy

297   for CECT, EUS and PET/CT. Radiological-pathological correlation in patients staged

298   N0 has shown a large number of small LNMs (<6 mm) that are extremely

299   challenging to diagnose directly from medical imaging. The findings of this study

300   have significant implications for patient care, because radiological staging results

301   largely influence treatment decisions made by the MDT. Future research should

302   focus on prediction of the likelihood of lymph node involvement as current lymph

303   node imaging is inadequate.

304 **References**

305 1.   Roberts SA, Kay C. Oesophagus and stomach cancers. In: Nicholson T, ed.

306 Recommendations for cross-sectional imaging in cancer management. 2nd ed.

307 London: Royal College of Radiologists; 2014.

308 2.   van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD.

309 Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer.

310 2008;98(3):547-557.

311 3.   Tangoku A, Yamamoto Y, Furukita Y, Goto M, Morimoto M. The new era of

312 staging as a key for an appropriate treatment for esophageal cancer. Ann Thorac

313 Cardiovasc Surg. 2012;18(3):190-199.

314 4.   Okada M, Murakami T, Kumano S, et al. Integrated FDG-PET/CT compared

315 with intravenous contrast-enhanced CT for evaluation of metastatic regional lymph

316 nodes in patients with resectable early stage esophageal cancer. Ann Nucl Med.

317 2009;23(1):73-80.

318 5.   Foley KG, Lewis WG, Fielding P, et al. N-staging of oesophageal and

319 junctional carcinoma: is there still a role for EUS in patients staged N0 at PET/CT?

320 Clin Radiol. 2014;69(9):959-964.

321 6.   Cancer Research UK. Oesophageal Cancer Statistics. 2016 [Accessed

322 November 22nd 2016]; Available from: http://www.cancerresearchuk.org/health-

323 professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer -

324 heading-Two.

325 7. Cancer Research UK. Oesophageal Cancer Incidence Statistics. 2016

326 [Accessed December 20th 2016]; Available from:

327 http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-

328 cancer-type/oesophageal-cancer/incidence - heading-Three.

329 8. Kayani B, Zacharakis E, Ahmed K, Hanna GB. Lymph node metastases and

330 prognosis in oesophageal carcinoma-a systematic review. Eur J Surg Oncol.

331 2011;37(9):747-753.

332 9. Medical Research Council Oesophageal Cancer Working Group. Surgical

333 resection with or without preoperative chemotherapy in oesophageal cancer: a

334 randomised controlled trial. Lancet. 2002;359(9319):1727-1733.

335 10. Koenig AM, Prenzel KL, Bogoevski D, et al. Strong impact of micrometastatic

336 tumor cell load in patients with esophageal carcinoma. Ann Surg Oncol.

337 2009;16(2):454-462.

338 11. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor

339 regression after preoperative chemoradiotherapy of esophageal carcinoma.

340 Clinicopathologic correlations. Cancer. 1994;73(11):2680-2686.

341 12. Sobin L, Gospodarowicz M, Wittekind C. UICC TNM Classification of

342 Malignant Tumours. 7th ed. New York: Wiley, 2009.

343 13. Weaver SR, Blackshaw GRJC, Lewis WG, et al. Comparison of special

344 interest computed tomography, endosonography and histopathological stage of

345 oesophageal cancer. Clin Radiol. 2004;59(6):499-504.

346   14.   Mapstone N. Dataset for the Histopathological Reporting of Oesophageal

347   Carcinoma. 2nd ed. London: Royal College of Pathologists, 2007.

348   15.   Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer:

349   protocol recommendations and rationale. Mod Pathol. 2010;23 Suppl 2:S26-32.

350   16.   Grotenhuis BA, van Heijl M, Wijnhoven BP, et al. Lymphatic micrometastases

351   in patients with early esophageal adenocarcinoma. J Surg Oncol. 2010;102(7):863-

352   867.

353   17.   Martin LW, D'Cunha J, Wang X, et al. Detection of Occult Micrometastases in

354   Patients With Clinical Stage I Non-Small-Cell Lung Cancer: A Prospective Analysis

355   of Mature Results of CALGB 9761 (Alliance). J Clin Oncol. 2016;34(13):1484-1491.

356   18.   Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation

357   criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer.

358   2009;45(2):228-247.

359   19.   Glickman JN, Torres C, Wang HH, et al. The prognostic significance of lymph

360   node micrometastasis in patients with esophageal carcinoma. Cancer.

361   1999;85(4):769-778.

362   20.   Izbicki JR, Hosch SB, Pichlmeier U, et al. Prognostic value of

363   immunohistochemically identifiable tumor cells in lymph nodes of patients with

364   completely resected esophageal cancer. N Engl J Med. 1997;337(17):1188-1194.

365   21.   Ryan P, McCarthy S, Kelly J, et al. Prevalence of bone marrow

366   micrometastases in esophagogastric cancer patients with and without neoadjuvant

367   chemoradiotherapy. J Surg Res. 2004;117(1):121-126.

368   22.   Chan DS, Fielding P, Roberts SA, Reid TD, Ellis-Owen R, Lewis WG.

369   Prognostic significance of 18-FDG PET/CT and EUS-defined tumour characteristics

370   in patients with oesophageal cancer. Clin Radiol. 2013;68(4):352-357.

371   23.   Foley KG, Fielding P, Lewis WG, et al. Prognostic significance of novel 18F-

372   FDG PET/CT defined tumour variables in patients with oesophageal cancer. Eur J

373   Radiol. 2014;83(7):1069-1073.

374   24.   Blackshaw G, Lewis WG, Hopper AN, et al. Prospective comparison of

375   endosonography, computed tomography, and histopathological stage of junctional

376   oesophagogastric cancer. Clin Radiol. 2008;63(10):1092-1098.

377   25.   Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour

378   heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary

379   evidence of an association with tumour metabolism, stage, and survival. Clin Radiol.

380   2012;67(2):157-164.

381   26.   Dong X, Xing L, Wu P, et al. Three-dimensional positron emission

382   tomography image texture analysis of esophageal squamous cell carcinoma:

383   relationship between tumor 18F-fluorodeoxyglucose uptake heterogeneity, maximum

384   standardized uptake value, and tumor stage. Nucl Med Commun. 2013;34(1):40-46.

385   27.   Wu LF, Wang BZ, Feng JL, et al. Preoperative TN staging of esophageal

386   cancer: comparison of miniprobe ultrasonography, spiral CT and MRI. World J

387   Gastroenterol. 2003;9(2):219-224.

388   28.   Nishimura H, Tanigawa N, Hiramatsu M, Tatsumi Y, Matsuki M, Narabayashi

389   I. Preoperative esophageal cancer staging: magnetic resonance imaging of lymph

390   node with ferumoxtran-10, an ultrasmall superparamagnetic iron oxide. J Am Coll

391   Surg. 2006;202(4):604-611.

392   29.   Noble F, Nolan L, Bateman AC, et al. Refining pathological evaluation of

393   neoadjuvant therapy for adenocarcinoma of the esophagus. World J Gastroenterol.

394   2013;19(48):9282-9293.

395

Figure Legends

397   Figure 1. CT (with calipers), PET and fused PET/CT images of a 'false-negative' left

398   gastric lymph node in a patient with junctional adenocarcinoma. A low-power

399   magnification of the lymph node shows a micro-metastasis. For reference, the

400   lymph node measured 5 mm in maximum size and the micro-metastasis (highlighted

401   with yellow outline) measured 1.2 mm.

Table 1

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

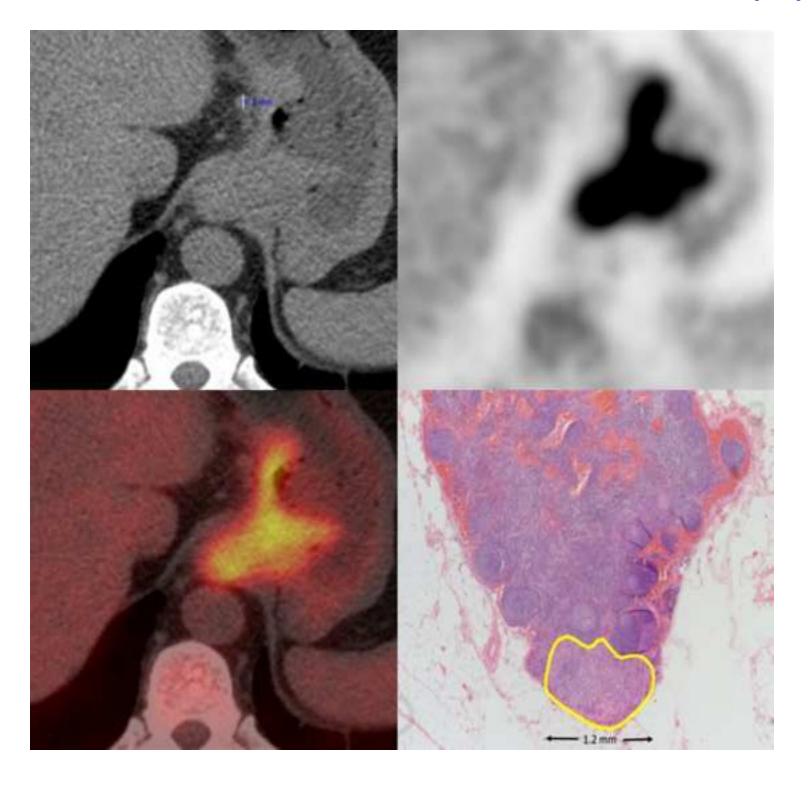| Frequency (%)	CECT N-stage				
	N0	N1	N2	N3	Total
pN0	34 (30.4)	8 (7.1)	2 (1.7)	0 (0.0)	44 (39.3)
pN1	21 (18.8)	4 (3.6)	2 (1.7)	0 (0.0)	27 (24.1)
pN2	16 (14.3)	10 (8.9)	1 (0.9)	0 (0.0)	27 (24.1)
pN3	4 (3.6)	7 (6.3)	3 (2.7)	0 (0.0)	14 (12.5)
Total	75 (67.0)	29 (25.9)	8 (7.1)	0 (0.0)	112 (100.0)
	EUS 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)

405

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

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.