A large series, resection controlled study to assess the value of radial EUS in restaging gastroesophageal cancer following neoadjuvant chemotherapy

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SUMMARY. The true value of endoscopic ultrasound (EUS) post-neoadjuvant chemotherapy for esophageal carcinoma is not established. Superior loco-regional detail may yield useful staging and prognostic information but information on its accuracy, as compared with computed tomography (CT), remains undefined and limited by small study size. We prospectively studied 109 patients with gastroesophageal cancer; 99 of whom were undergoing surgery. All had EUS and helical CT imaging before and after neoadjuvant chemotherapy and the results were compared with pathological staging of resected specimens. Tumor response was assessed by the reduction in maximal tumor depth at EUS and correlated with patient survival. There was no difference in T and N stage accuracies between EUS and CT following neoadjuvant chemotherapy. MANOVA showed a reduction in maximal tumor depth by > 50% at EUS to be associated with longer survival (relative risk = 0.48, P < 0.05). EUS responders had a median survival of 38 months compared to 30 months for non-responders (P < 0.05). The identification of lymphadenopathy at radial EUS was not predictive of survival. This large series study demonstrates the staging accuracy of CT and non-biopsy EUS in the setting of neoadjuvant chemotherapy for gastroesophageal cancer to be equivalent and poor. An endosonography may contribute useful clinical information in respect of potential survival. It is questionable whether radial EUS should be included in protocols for restaging.

KEY WORDS: cancer, chemotherapy, endoscopic ultrasound, esophagus, staging.

INTRODUCTION

Esophageal carcinoma is a significant cause of mortality.¹ Although the prognosis of this condition is poor, the clinical benefit of neoadjuvant chemoradiation and chemotherapy is widely, albeit not universally, accepted.²⁻⁵ The use of neoadjuvant chemotherapy implies a need for restaging information. Given current technologies, this is problematic.

Endoscopic ultrasound (EUS) is superior to computed tomography (CT) for the initial loco-regional T and N staging of esophageal cancer, but its utility following neoadjuvant therapy is not well established.⁶⁻⁸ Published studies cannot be definitive, being limited by size, and have reported widely variable T and N stage accuracies; most intimate questionable clinical value.⁹⁻¹¹ Such imperfect accuracy is largely because the inflammation and fibrosis induced by neoadjuvant therapy makes identification of residual tumor by EUS difficult.

The depth of tumor infiltration and lymphatic spread are important determinants of resectability and survival.¹²⁻¹³ With improvements to CT technology it might be a moot point whether non-biopsy EUS can contribute any additional information to the staging of esophageal tumors following neoadjuvant therapy. Yet, the detail offered by EUS is impressive, both in terms of morphology and accurate measurement of change. If this obvious strength of EUS is to be harnessed, it must be done so in a practical way. Whereas assessing morphological detail is general, the measurement of changes in tumor volume, 3D estimates and so on, is more difficult, and certainly not universally available on all EUS platforms.¹⁴

The aims of this large, post-surgical study were twofold: to compare post-chemotherapy EUS T...
and N stage accuracy with that of CT, using pathology from surgically resected specimens as a gold standard and also to determine whether EUS measurement of maximal tumor depth can assess the response to neoadjuvant therapy and predict survival.

MATERIALS AND METHODS

This study was a prospective analysis of patients with carcinoma of the esophagus or gastric cardia. The following patient inclusion criteria were applied: (i) histologically proven esophageal or gastric cardiac cancer (adenocarcinomas or squamous cell carcinomas); (ii) physical fitness for surgery; (iii) successful completion of a planned course of preoperative chemotherapy, with a view to curative surgical resection thereafter; and (iv) had undergone endosonographic evaluation prior to and following the completion of neoadjuvant chemotherapy.

Before initiating neoadjuvant chemotherapy, a multidisciplinary team determined whether the primary tumor was potentially resectable and whether the patient was fit to undergo chemotherapy. The tumor was considered non-resectable if there was malignant supra-clavicular and celiac adenopathy, the presence of distant metastasis (for example, lung, bone, liver), a malignant pleural effusion and invasion of the tracheo-bronchial tree.

Treatment decisions were made independent of study enrolment and written informed consent was obtained from all eligible patients. This study was approved by the institutional review board of Guy’s and St Thomas’ Hospital.

Staging

Both pre- and post-chemotherapy radial EUS was performed under conscious sedation with either a standard echo endoscope (GF-UM20/GF-UM200, Olympus KeyMed, Southend-on-Sea, UK) or a non-optical wire-guided slim-probe (Olympus MH-908, Olympus KeyMed) by one of two experienced endosonographers (JM, LD). The decision to use the wire-guided echo endoscope was made if the patient had significant dysphagia or if the standard diagnostic echo endoscope failed to traverse the malignant stricture. Any patient who failed complete evaluation either at pre or post-chemotherapy EUS was excluded from the study. None of the patients were subjected to prior esophageal dilatation before EUS. T and N stages were determined by endosonography according to the TNM classification. Patients with a tumor stage of T1N0 and T2N0 were excluded from this study, as they had curative surgery without prior neoadjuvant therapy.

A lymph node was considered malignant if at least three of these criteria were present: hypoechoic internal echo pattern, sharp borders, rounded shape, diameter > 10 mm (pre-chemotherapy) or 5 mm (post-chemotherapy EUS). The 5-mm cut-off value was adopted based on observations from two previous studies.

The maximal depth of the tumor (Tmax) was measured at the maximal thickness of the tumor mass at endosonography prior to initiation of chemotherapy and at a repeat examination performed at least 2 weeks after the last dose of chemotherapy (Fig. 1). Patients with a > 50% reduction in Tmax were classified as EUS responders.

Chemotherapy

All patients received preoperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (three cycles over a 9-week period). If necessary, the dosage and/or timing of the chemotherapy was adjusted for renal, hematological or gastrointestinal toxicity. Surgery was performed 4–6 weeks after completion of chemotherapy.
Pathology

The depth of tumor invasion and presence of lymph node involvement were determined by the pathologic assessment of resected specimens. Cancers were staged according to the TNM classification and T0N0 was considered devoid of identifiable tumor cells.

Survival

Follow-up data were obtained from hospital records and telephone communication with primary physicians. The date of death and cause of death were recorded. Survival was calculated from the date of diagnosis. The median follow up for all patients was 21.0 months (range 5 months to 64 months). The survival studies only included patients who were followed up for at least 12 months or until the death of the patient. Patients who were alive and followed up for less than a year were excluded from survival analysis (Fig. 1).

Statistics

The McNemar test was used to compare the accuracy of EUS and CT staging using pathological staging as the gold standard.

For survival analysis, the patients were separated into EUS responders and non-responders. The two groups were compared in terms of clinical characteristics using the Wilcoxon two-sample test for continuous variables and the $\chi^2$ test or the Fisher's exact test for categorical variables. Median survival was estimated using the Kaplan–Meier method and differences in survival among groups were assessed using the log–rank test. MANOVA Cox regression analysis was done to determine the influence of co-variables on survival.

All tests of significance were two-tailed and statistical significance was accepted as $P < 0.05$. For statistical calculations, the SPSS package version 12.0 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

A total of 109 patients who had completed the prescribed course of chemotherapy were enrolled. Of these, 102 patients were followed up for at least one year or until death and were entered into the survival study (Fig. 1).

Post-chemotherapy EUS and CT staging accuracy

A total of 99 patients completed neoadjuvant chemotherapy followed by surgery. In 10 patients there was no surgery due to the decision of the physician ($n = 8$) or the patient ($n = 2$). The eight patients not offered surgery were staged as T4 both before and after chemotherapy (T4 crus, $n = 4$; T4 pleura, $n = 2$, with development of malignant pleural effusion and T4 pericardium, $n = 2$). Table 1 compares post-chemotherapy EUS and CT staging of the gastroesophageal tumors, with the pathologic tumor staging of the resected specimens.

There was no significant difference in post-chemotherapy T stage accuracy between EUS (66.7%) and CT (57.6%) ($P = 0.151$). Following chemotherapy, both EUS and CT tended to over-stage cancers at EUS: 19 patients were over-staged and 14 under-staged whereas CT over-staged 25 and under-staged 17 patients.

Fifteen of 35 patients without enlarged lymph nodes on post-chemotherapy EUS had true N0 disease. The negative predictive value (NPV) of the absence of enlarged lymph nodes for ruling out residual tumor in lymph nodes (i.e. pathN0 disease) was 42.3%. However, the positive predictive value of identifying pathN1 disease by the visualization of enlarged lymph nodes on post-chemotherapy EUS was 67.2%. The sensitivity of post-chemotherapy EUS in being able to identify persistent malignant lymphadenopathy was 68.3%. The overall N stage accuracy of post-chemotherapy EUS (60%), as compared to CT (52%), was not statistically different ($P = 0.256$).

The operating characteristics of radial EUS and CT in the re-assessment of gastroesophageal tumors following neoadjuvant chemotherapy are given in Table 2. Endosonography tended to over-stage and under-stage at either end of the T-stage spectrum (T0 and T4), respectively.

A complete pathologic response (absence of residual tumor cells or pathologic T0N0) was seen in eight patients who underwent surgery (8%). Only two of these patients were identified on post-chemotherapy EUS. However, all eight patients were in the post-chemotherapy EUS responder group.

Conversely, 10 patients (10%) were T4 at surgery; post-chemotherapy EUS identified only two of these. The sensitivity, specificity, positive predictive

<table>
<thead>
<tr>
<th>Stage</th>
<th>Post-chemotherapy EUS ($n$)</th>
<th>Post-chemotherapy CT ($n$)</th>
<th>Pathologic tumor staging ($n$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>T1</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>T2</td>
<td>22 (22)</td>
<td>25 (25)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>T3</td>
<td>65 (66)</td>
<td>69 (70)</td>
<td>53 (54)</td>
</tr>
<tr>
<td>T4</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>N0</td>
<td>35 (35)</td>
<td>32 (33)</td>
<td>36 (36)</td>
</tr>
<tr>
<td>N1</td>
<td>64 (65)</td>
<td>47 (48)</td>
<td>63 (64)</td>
</tr>
</tbody>
</table>

Table 1 The T and N stage of esophageal cancers as assessed by radial endoscopic ultrasound (EUS) and computed tomography (CT) ($n = 99$) compared to post-surgical pathology
value (PPV) and NPV of post-chemotherapy EUS in detecting T4 disease was 20%, 97.8%, 50% and 91.6%, respectively. Nine of these patients were in the post-chemotherapy EUS non-responder group (Table 2).

### Survival study

There were 102 patients in this survival study and all were followed for a minimum of 12 months or until death: the median survival was 22.5 months. Ninety-two patients had surgery. Endosonography measured a positive response (i.e. more than 50% reduction in the Tmax) in 42 patients (42.2%). Forty-six patients (45%) died, 43 from disease-related causes. There were no significant differences in the patient characteristics or baseline staging between the EUS responder and non-responder groups (Table 3).

The baseline Tmax for the pre-treatment EUS was not significantly different in the EUS responder group (15.6 mm ± 4.2 mm, mean ± SD) from that in the EUS non-responder group (15.2 mm ± 3.0 mm). However, the post-chemotherapy EUS Tmax in the EUS responder group (6.4 mm ± 2.2 mm) versus the EUS non-responder group (12.3 mm ± 4.0 mm) was significantly different (P < 0.05).

Clinical factors included in a Cox proportional hazards model are shown in Table 4. Tmax reduction by 50% at EUS was the only variable that predicted survival time in MANOVA (relative hazard = 0.48, P < 0.05). Survival in the EUS responder group was significantly longer than that in the non-responder group (median survival 38 months vs 30 months, P < 0.05) (Fig. 2).

Kaplan–Meier survival estimates for patients predicted by radial EUS to have N0 or N1 disease following chemotherapy showed no demonstrable difference (Fig. 3).

### Table 2 The T and N staging accuracy of endoscopic ultrasound (EUS) and computed tomography (CT) in the assessment of esophageal cancer post-chemotherapy; n = 99

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EUS (%)</th>
<th>CT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0-T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97.8</td>
<td>98.9</td>
</tr>
<tr>
<td>Specificity</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>NPV</td>
<td>91.6</td>
<td>90.7</td>
</tr>
<tr>
<td>PPV</td>
<td>97.3</td>
<td>98.9</td>
</tr>
<tr>
<td>Accuracy</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.8</td>
<td>98.9</td>
</tr>
<tr>
<td>NPV</td>
<td>91.6</td>
<td>90.7</td>
</tr>
<tr>
<td>PPV</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Accuracy</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>N-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>68.3</td>
<td>53.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>41.7</td>
<td>51.4</td>
</tr>
<tr>
<td>NPV</td>
<td>42.3</td>
<td>37.5</td>
</tr>
<tr>
<td>PPV</td>
<td>67.2</td>
<td>66.7</td>
</tr>
<tr>
<td>Accuracy</td>
<td>59.6</td>
<td>51.5</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.

### Table 4 Predictors of survival

<table>
<thead>
<tr>
<th>Clinical factor</th>
<th>Risk ratio</th>
<th>Cox regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology (tumor type)</td>
<td>1.31</td>
<td>P = 0.79</td>
</tr>
<tr>
<td>Location of tumor (proximal versus distal)</td>
<td>0.79</td>
<td>P = 0.85</td>
</tr>
<tr>
<td>Initial T-stage on endoscopic ultrasound (EUS) (T2 versus T3 or T4)</td>
<td>0.65</td>
<td>P = 0.31</td>
</tr>
<tr>
<td>Initial N classification on EUS (N1 versus N0)</td>
<td>1.12</td>
<td>P = 0.76</td>
</tr>
<tr>
<td>EUS measurement of maximal tumor depth; responders (&gt; 50% decrease) versus non-responders</td>
<td>0.48</td>
<td>P = 0.03</td>
</tr>
</tbody>
</table>

Fig. 2 Survival in months when divided into two groups on the basis of tumor response to neoadjuvant chemotherapy. Responders showed a decrease in maximal tumor depth of at least 50% at endoscopic ultrasound, compared with the baseline study.
DISCUSSION

Neoadjuvant chemoradiotherapy for gastroesophageal cancer offers some clinical benefit. Assessing tumor response and suitability for subsequent surgery however, is problematic, with no clear guide as to the best method, previously reported accuracy for imaging in this situation being inconclusive mainly on account of the study size. This large study shows EUS to be no more accurate than CT in predicting either resectability/non-resectability or the presence of residual tumor deposits, nodal or otherwise. Change in a readily available EUS measurement, simple cross-sectional tumor depth, however, is predictive of patient survival.

The recognized merits of EUS for initial loco-regional staging do not extrapolate well to the post-neoadjuvant setting, as inflammation and fibrosis cannot be differentiated from a residual tumor. Previous evaluation of the utility of EUS for this purpose reports T-stage accuracy to range from 27% to 82%, with the accuracy of N ranging from 38% to 94%. This study shows post-chemotherapy EUS T and N stage accuracies to be 66.7% and 59.6%, respectively. Importantly, no advantage in these terms can be shown for EUS over post-chemotherapy CT; EUS tending to over-stage. The importance of this current work is that a large cohort has been studied and that operative staging has been used as the gold standard.

Pathological tumor response correlates with increased survival for patients with esophageal carcinoma receiving multimodality therapy. To assess the utility of post-chemotherapy EUS in terms of T/N staging alone would be to underplay its greatest strength: high resolution views of abnormal tissue. However, baseline EUS assessment of tumors cannot identify those who will have a complete response to neoadjuvant chemotherapy, so more subtle measurements are required. Maximal tumor area can be measured at EUS and patients with a 50% or greater reduction in this index following chemoradiation are more likely to show tumor regression and lesions confined to the esophagus at the time of resection, in addition to having a survival advantage. Studies detailing this criterion, however, have been small. The current work uses a simple, universally applicable measure of tumor response and has demonstrated survival benefit amongst responders as compared to non-responders.

Measurement of the maximal tumor depth provides a simple indicator of pathologic response and survival with no requirement for specialized software. In attempting to optimize the measurement of the tumor response, the post-chemotherapy EUS was performed at least 2 weeks following chemotherapy, permitting some degree of subsidence in local inflammation. This delay might also explain why the reported T-stage accuracy was better than that of some other studies addressing this subject.

The presence of residual tumor in lymph nodes after preoperative chemoradiation is known to be an important determinant of postoperative survival. Not surprisingly, we noted a marked difference in cumulative survival between patients with pathN0 (median survival 44 months) and pathN1 (28 months, \(P < 0.005\)). Our data, however, failed to show survival benefit in those patients with post-chemotherapy N0 versus N1 disease, as defined by EUS imaging (median survival of 38 months versus 30 months, \(P = 0.87\)). Radial EUS following neoadjuvant therapy cannot reliably distinguish benign from malignant lymph nodes using solely morphological criteria (hypoechoic internal echoes, rounded shape, sharp borders and size). Although the PPV of EUS for identifying malignant lymphadenopathy was 67% and the sensitivity 68%, the NPV for pathN0 disease was only 42%. It could be suggested that endoscopic ultrasonography-fine-needle aspiration (EUS-FNA) or positron emission tomography would be useful adjuncts in this situation, but the case remains unproved. Furthermore, the question remains as to what role surgery truly plays in the face of persistent local nodes.

There is a survival benefit for patients with complete pathological response (pathCR) following neoadjuvant therapy but the reliable identification of such a response remains elusive. The total restitution of normal EUS esophageal layers with no residual abnormality of any kind is suggested to
predict a complete pathologic response.\textsuperscript{10,14} In the current study, post-chemotherapy EUS identified only two of eight patients with pathCR and a single patient had complete restitution of normal esophageal layers.

The more important corollary to the identification of patients with a complete response to neoadjuvant chemotherapy is to identify those with T4 disease and who thus remain inoperable. Although we identified only two of 10 patients with T4 disease who had chemotherapy followed by surgery, giving a sensitivity of 20% and a PPV of 50%, there were eight patients with T4 disease who were not subjected to surgery following a repeat EUS after chemotherapy (physician decision, with details given in the results section). If these patients had proceeded onto surgery, the sensitivity and PPV of post-chemotherapy EUS in our study would have most likely improved.

In conclusion, this study is of sufficient size to define the accuracy for T and N restaging of post-chemotherapy radial EUS and CT as being equivalent. Endosonographic assessment of change to tumor depth is predictive of improved survival when regression as measured by maximal tumor depth is at least 50%.

References