

ORIGINAL ARTICLES

Impact of EUS-FNA in the Management of Patients with Oesophageal Cancer

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Abstract

Background and Aim

Endoscopic Ultrasound (EUS) has increased the staging accuracy of oesophageal cancer. The addition of EUS guided fine needle aspiration (EUS-FNA) appears superior to standard EUS for nodal staging. Our aim was to study the impact of EUS-FNA in the management of patients with oesophageal cancer.

Methods

We studied patients undergoing EUS for this indication between May 2003 and May 2006. EUS was performed in patients who were candidates for radical therapy following CT scanning. If suspicious non-peritumoural nodes were seen on EUS, EUS-FNA was undertaken. Further staging was performed as appropriate and all cases were discussed at our multidisciplinary meeting. Results and decisions were prospectively recorded.

Results

One hundred and ninety one patients underwent EUS for staging of oesophageal cancer during this period and 44 EUS-FNA were performed in 42 patients (mean age 62.2 years). Sixty two per cent of patients had adenocarcinoma and 48% sampled nodes were <10mm diameter. Overall, 48% nodes were positive and two "suspicious" for malignancy. Following a positive EUS-FNA and MDM discussions, 15 patients had palliative and two neo-adjuvant therapy. Eleven patients with a negative EUS-FNA underwent radical therapy. Therefore, EUS-FNA appeared to alter management in 28 (67%) patients.

Conclusion

EUS-FNA appears to help direct patients towards appropriate treatment strategies.

Keywords

Oesophageal cancer, endoscopic ultrasonography, EUS-FNA

Introduction

Survival after a diagnosis of oesophageal or gastro-oesophageal junctional cancer depends on the stage at presentation. In addition, staging directs patients towards specific treatment strategies. It is therefore imperative that staging is as accurate as possible in order to deliver appropriate and tailored therapies to individual patients. Appropriate nodal staging in particular prevents patients with incurable disease from undergoing aggressive surgical or oncological therapy with their associated morbidity (and mortality) and reserves radical therapy for suitable individuals. The SAGOC (Scottish Audit of Gastric and Oesophageal Cancer) audit published in 2002, suggested that up to 40% of patients who went for planned curative surgery for oesophageal or junctional cancer subsequently had palliative therapy, and two year survival after surgery was approximately 33%.¹

Staging of upper GI malignancies is based on the American Joint Commission on cancer staging system (last updated 2002) and depends on the TNM classification (see Table I).

Table I: TNM Classification for Oesophageal Cancer (American Joint Committee on Cancer 2002).

Primary tumor (T)

- TX:** Primary tumor cannot be assessed
- T0:** No evidence of primary tumor
- Tis:** Carcinoma in situ
- T1:** Tumor invades lamina propria or submucosa
- T2:** Tumor invades muscularis propria
- T3:** Tumor invades adventitia
- T4:** Tumor invades adjacent structures

Regional lymph nodes (N)

- NX:** Regional lymph nodes cannot be assessed
- N0:** No regional lymph node metastasis
- N1:** Regional lymph node metastasis

Distant metastasis (M)

- MX:** Distant metastasis cannot be assessed
- M0:** No distant metastasis
- M1:** Distant metastasis

Tumors of the lower thoracic esophagus:

- M1a:** Metastasis in coeliac lymph nodes
- M1b:** Other distant metastasis

Tumors of the midthoracic esophagus:

- M1a:** Not applicable
- M1b:** Non-regional lymph node and/or other distant metastasis

Tumors of the upper thoracic esophagus:

- M1a:** Metastasis in cervical nodes
- M1b:** Other distant metastasis

Several studies have demonstrated EUS to be superior to CT in the accuracy of loco-regional staging for both tumour (T) and lymph node (N) stage.^{2,3,4,5} Accepted lymph node characteristics predictive of malignancy on standard EUS are shown in Table II. With all four characteristics, studies have demonstrated 80-100% involvement of lymph nodes by metastases.^{6,7,8} However, most malignant lymph nodes do not meet all these (largely subjective) criteria. Therefore, in many cases it can be difficult to clarify nodal involvement with standard EUS.

Table II: EUS Features Suggestive of Malignant Nodes.

<i>EUS features suggestive of malignant nodes</i>
Size \geq 10mm
Well circumscribed
Circular appearance
Homogeneously hypochoic

The evolution of EUS to encompass guided fine needle aspiration (FNA) of lymph nodes using a linear EUS scope can provide cytological evidence of malignancy. This is superior in accuracy to both CT and to standard EUS features for nodal involvement^{9,10,11} and is a safe procedure with associated low morbidity.^{12,13,14} In addition, the recent SIGN guideline on upper GI cancer suggests that all patients with oesophageal or junctional cancer with potentially curable disease following clinical assessment and CT scanning, should undergo EUS with EUS-FNA if required.¹² The aim of our study was to assess the impact of EUS-FNA in the management of patients with oesophageal and gastro-oesophageal junctional tumours in our unit.

Methods

All patients with oesophageal or gastro-oesophageal junctional tumours referred to our unit who were deemed possible candidates for attempted curative therapy after initial assessment and CT scanning, underwent EUS examination. This was undertaken with a radial echoendoscope (Hitachi-Pentax) and if required, EUS-FNA was performed using a linear echoendoscope (Hitachi-Pentax) to sample suspicious nodes (see Figure 1).

Figure 1: EUS-FNA of Suspicious Subdiaphragmatic Node in Patients with Oesophageal Cancer.



A minimum of three passes were undertaken with a 22-gauge needle (Wilson-Cook) and the EUS-FNA was only undertaken provided the needle would not need to pass through the tumour to sample the node. The samples were transferred to the cytology department in an appropriate preservative and examined by a specialised cytologist. The patients underwent other standard staging procedures as appropriate including laparoscopy for oesophago-gastric junctional tumours.

All cases were discussed at our weekly multidisciplinary meeting (MDM), which included representatives from surgery, gastroenterology, radiology, pathology and oncology, where a decision was made regarding subsequent management. This took into account staging results and the presence of medical co-morbidity. All results and decisions were prospectively entered into a database. We studied the patients who underwent EUS for this indication at our unit between May 2003 and May 2006.

Results

During the study period, 191 patients underwent EUS for staging of oesophageal cancer. Forty four EUS-FNA's were performed in 42 of these patients. Patient and tumour characteristics are shown in Table 3.

Table III: Patient Characteristics, Tumour Type and Location.

Number of patients	42 (32 male)
Mean age (range)	62.2 (40-84) years
Pathology	16 (38%) Squamous
	26 (62%) Adenocarcinoma
Location	Junctional: 6
	Lower third: 24
	Middle third: 10
	Upper third: 2

Eleven (26%) of these patients required dilatation to complete the EUS examination. None had clinical or radiological evidence of a perforation following the procedure.

The diameter of the nodes sampled ranged from 4-25mm, with 21 (48%) of the nodes sampled <10mm in diameter. Twenty of these nodes were in the mediastinum or subcarinal area, 10 at the coeliac axis and 13 in the left gastric or other subdiaphragmatic regions. In addition, one FNA was undertaken of a suspicious left adrenal mass. A total of 23 (53%) of the FNA samples were either positive for malignancy (n=21) or "suspicious for malignancy" (n=2) on cytological assessment. Nineteen samples (in 18 patients) were negative and there was insufficient tissue to achieve a diagnosis in two (4.5%) cases.

Of the 21 nodes less than 10mm diameter, cytology was positive in nine (43%) with two samples insufficient. CT scanning had not revealed any lymph nodes in seven of these nine patients and standard EUS assessment was limited by the small size of the nodes. Of those nodes larger than 10mm, 14 of 23 (61%) were positive on EUS-FNA. CT scanning failed to identify any nodes in three of these fourteen patients, and only a minority of these nodes exhibited all four criteria for malignancy on standard EUS.

On review of the MDM decisions, the result of the EUS-FNA appeared to alter the management in a total of 28 (67%) patients in whom it was undertaken. On the basis of EUS-FNA proven positive nodes and following the MDM discussion, management was altered from a radical to a palliative approach in 15 patients, who had initially been considered for attempted curative therapy. A further two patients underwent neo-adjuvant therapy on the basis of a positive EUS-FNA. In addition, 11 patients with a negative EUS-FNA result (following identification of an indeterminate node on CT or standard EUS) underwent radical therapy after further discussion at the MDM.

Those with no alteration to management included six individuals with a positive and six with a negative EUS-FNA in addition to two patients with insufficient samples on EUS-FNA. In all of these patients a palliative regime was pursued following further assessment and MDM discussion.

The overall one-year survival for EUS-FNA negative and positive patients was 68% and 38% respectively. Of those who were EUS-FNA negative and went on to have surgery, the overall percentage of resected nodes positive for malignancy was 7%. This compares with resected node positivity of 9% and 18% for those with N0 and N1 disease respectively on standard EUS alone.

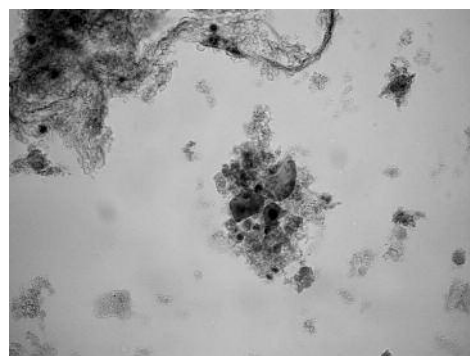
Discussion

Initial studies examining EUS in the staging of oesophageal cancer reported an accuracy of approximately 80% compared with pathologically resected specimens.^{15,16,17} Since then there have been numerous studies comparing standard EUS with CT in staging of this condition, with most showing a superiority of EUS for both T- and N- staging.^{3,4,5,18}

However standard EUS identification of involved nodes can be problematic and is partly subjective. Reports have shown that all four of the classical nodal features of malignancy (Table II) are found in only 25% visible nodes on EUS.⁷ In addition, the only objective measure of tumour involvement on standard EUS is node size, therefore smaller nodes are particularly difficult to assess. One study demonstrated that using size alone as the primary objective measure for identifying malignant nodal involvement resulted in only 69% accuracy with standard EUS for nodes <10mm compared with 92% using EUS-FNA.¹¹ In our study, EUS-FNA was positive for malignancy in 43% of nodes <10mm.

EUS-FNA provides cytological evidence of malignancy (see Figure 2) and improves nodal staging compared with either CT or standard EUS features of nodal involvement.^{9,10,11,19,20,21} These studies have reported that EUS-FNA of nodes including those at the coeliac axis has a sensitivity and specificity of >90% and accuracy of 87%-100%. Positive coeliac nodes indicate M1a disease for lower oesophageal tumours, which often alters management. In addition, oncologists require optimal information regarding tumour extent and involved nodes to help target therapy.

Figure 2: Cytology from EUS-FNA of a Suspicious Node Revealing Evidence of Necrotic Squamous Cancer.



As a result of these data, the recent SIGN guideline on oesophageal and gastric cancer recommended that all patients with oesophageal cancer who are being considered for radical therapy should undergo EUS +/- FNA.¹²

In advanced disease a barrier to accurate staging is stricturing of the tumour which can obstruct passage of the EUS endoscope. Dilatation is required in approximately 30% patients, with 70-80% of strictured tumours at least T3 stage and up to 80% having nodal involvement.²² In our initial cohort of 191 patients, 28% required careful dilatation which allowed passage of the EUS endoscope in all but four who had a very tight structure. Out of our patients undergoing EUS-FNA, 26% required dilatation prior to the procedure with no perforations.

Increased accuracy of staging with EUS and EUS-FNA has had an impact on clinical management, with studies showing alteration in initial proposed therapy in up to 77% of cases following the procedures, usually towards palliative therapy.^{5,10} In our cohort, 67% of individuals undergoing EUS-FNA had their clinical management altered following the procedure, mostly to a palliative approach.

The additional benefit of EUS-FNA over standard EUS is difficult to quantify, however a recent study suggested that a selective EUS-FNA approach (used when a modified standard EUS criteria for nodal involvement was not met) improved accuracy and reduced costs.²³ Another study reported a 13% change in management of patients with oesophageal cancer with the addition of EUS-FNA to the staging protocol in cases where the result would influence clinical management.²⁴ Interestingly, a retrospective analysis suggested that the addition of EUS-FNA appeared to prolong recurrence free survival compared with a cohort who did not undergo the procedure.²⁵ It was suggested that this was a result of more accurate nodal staging and increased use of preoperative neo-adjuvant therapy.

In conclusion, EUS-FNA is a valuable tool for the loco-regional staging of oesophageal cancer and appears to alter management in a significant number of patients. We would suggest that all patients with potentially curable disease after initial assessment and helical CT scanning should undergo EUS with EUS-FNA of suspicious nodes as required. This should optimise staging and direct the patient towards the most appropriate treatment strategy.

References

1. Clinical Resource and Audit Group (CRAG): Scottish Audit of Gastric and Oesophageal Cancer; report 1197-2000. CRAG; Edinburgh 2002. Available from url: <http://www.show.scot.nhs.uk/crag/>.
2. Zeigler K, Sanft C, Zeitz M, et al. Evaluation of endosonography in TN staging in oesophageal cancer. *Gut* 1991;32(1):16-20.
3. Weaver SR, Blackshaw GRJC, Lewis WG, et al. Comparison of special interest computerised tomography, endosonography and histopathological stage of oesophageal cancer. *Clinical Radiology* 2004;59(6):499-504.
4. Kelly S, Harris KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut* 2001;49:534-39.
5. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography in the staging and follow-up of oesophageal cancer. *J Clin Oncol* 2005;23:4483-4489.
6. Catalano MF, Alcocer E, Chak A, et al. Evaluation of metastatic celiac lymph nodes in patients with esophageal carcinoma: accuracy of EUS. *Gastrointest Endosc* 1999;50(3):352-6.
7. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS guided fine needle aspiration for the diagnosis of malignant lymph node invasion. *Gastrointest Endosc* 1997;45(6):474-9.
8. Chen VK, Eloubeidi MA. Endoscopic ultrasound guided fine needle aspiration is superior to lymph node echofeatures: A prospective evaluation of mediastinal and peri-intestinal lymphadenopathy. *Am J Gastro* 2004;99(4): 628-33.
9. Reed CE, Mishra G, Sahai AV, et al. Esophageal cancer staging: improved accuracy by endoscopic ultrasound of celiac lymph nodes. *Ann Thorac Surg* 1999; 67(2):319-21.
10. Vazquez-Sequeiros E, Wiersma MJ, Clain JE, et al. Impact of lymph node staging on therapy of oesophageal carcinoma. *Gastroenterology* 2003;125(6):1883-6.
11. Wiersma M, Vilmann P, Giovanni M, et al. Endosonography-guided aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-95.
12. SIGN Guideline 87: Management of oesophageal and gastric cancer. June 2006. Available from url: <http://www.sign.ac.uk>.
13. Bournet B, Migurese I, Delacrix M, et al. Early morbidity of endoscopic ultrasound: 13 years' experience at a referral center. *Endoscopy* 2006;38(4):349-54.
14. Erickson, RA. EUS-guided FNA. Technological review. *Gastrointest Endosc*. 2004;60 (2), 267-279.
15. Tio TL, Coene PP, Schouwink MH, et al. Esophagogastric carcinoma: preoperative TNM classification with endosonography. *Radiology* 1989;173(2):411-7.
16. Rosch T, Lorenz R, Zenker K, et al. Local staging and assessment of resectability in carcinoma of the esophagus, stomach and duodenum by endoscopic ultrasonography. *Gastrointest Endosc* 1992;38(4): 460-7.
17. Catalano MF, Sivak MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc* 1994;40(4):442-6.
18. Zhang X, Warson DI, Lally C, et al. Endoscopic ultrasound for preoperative staging of oesophageal carcinoma. *Surgical Endoscopy* 2005;19(12):1618-21.
19. Chang KJ, Soetikno RM, Bastas D, et al. Impact of endoscopic ultrasound combined with fine needle aspiration biopsy in the management of esophageal cancer. *Endoscopy* 2003;11:962-65.
20. Giovannini M, Monges G, Seitz JF et al. Distant lymph node metastasis in esophageal cancer: impact of endoscopic ultrasound guided biopsy. *Endoscopy* 1999;31:536-540.
21. Parmar KS, Zwischenberger JB, Reeves AL, et al. Clinical impact of endoscopic ultrasound guided fine needle aspiration of celiac axis lymph nodes (M1a disease) in esophageal cancer. *Ann Thorac Surg* 2002;73:916-21.
22. Wallace MB, Hawes RH, Sahai AV, et al. Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management. *Gastrointestinal Endoscopy*. 2000;51(3):309-13.
23. Vazquez-Sequerios E, Levy MJ, Clain JE et al. Routine versus selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma. *Gastrintest Endosc* 2006;63:204-211.
24. Mortensen MB, Pless T, urup J, et al. Clinical impact of endoscopic ultrasound-guided fine needle aspiration biopsy in patients with upper gastrointestinal tract malignancies. A prospective study. *Endoscopy* 2001;33(6):537-40.
25. Harewood GC, Kumar KS. Assessment of clinical impact of endoscopic ultrasound on oesophageal cancer. *J Gastroenterol Hepatol* 2004;19:433-39.