**The Impact of Endoscopic Ultrasound on the Management and Outcome of Patients with Oesophageal Cancer: an Update of a Systematic Review**

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**Abstract**

Objectives

Oesophageal cancer staging relies on a multi-modal approach due to limitations of individual radiological investigations. With adoption of positron emission tomography (PET) for staging and treatment planning, the role of endoscopic ultrasound (EUS) in these patients has been questioned. This study updated a systematic review concerning the impact of EUS in the modern era of oesophageal cancer staging.

Methods

To update the previous systematic review, we searched databases including MEDLINE and Embase, selecting studies published from 2005 onwards. Studies reporting primary data in patients with oesophageal or gastro-oesophageal junction cancer who underwent radiological staging and treatment, regardless of intent, were included. The primary outcome was the reported change in management after EUS. Secondary outcomes were recurrence rate and overall survival. Two reviewers extracted data from included articles. This study was registered with PROSPERO (*blinded*).

Results

Eighteen studies with 11,836 patients were included. 2,805 patients (23.7%) underwent EUS compared to 9,031 (76.3%) without EUS. Reported change of management varied widely from 0% to 56.0%. When used, EUS fine-needle aspiration (FNA) precluded curative treatment in 37.5% to 71.4%. Overall survival improvements ranged between 121 and 639 days following EUS intervention compared to patients without EUS. Smaller effect sizes were observed in a randomised controlled trial, compared to larger differences reported in observational studies.

Conclusion

Current evidence for the effectiveness of EUS in oesophageal cancer pathways is conflicting and of limited quality. In particular, the extent to which EUS adds value to contemporary cross-sectional imaging techniques is unclear and requires formal re-evaluation.

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**Introduction**

Oesophageal cancer diagnosis, staging and treatment planning relies on a multi-modal, multi-disciplinary approach [1]. Endoscopic, radiological, and laparoscopic techniques can all be used to decide upon the best management strategy. Amongst these modalities, the accuracy of local tumour (T-) and nodal (N-) staging by endoscopic ultrasound (EUS) has historically been reported as superior to the non-invasive, cross-sectional techniques of computed tomography (CT) and 18F-fluorodeoxyglucose positron-emission tomography (PET) [2,3]; however, none of these three modalities are perfectly accurate [4].

Modern diagnostic pathways have recently become more reliant on cross-sectional techniques when staging and planning optimal treatments for patients with oesophageal cancer [5,6]. In particular, PET-CT is now widely used to stage potentially curable patients due to its higher sensitivity for detecting distant metastases [2], resulting in fewer patients undergoing futile surgical resection only to experience progressive disease soon afterward [7]. Subsequently, a trend towards more selective use of EUS following CT and PET-CT staging has emerged. The National Institute for Health and Clinical Excellence (NICE) guidelines now recommend EUS only be used when supporting ongoing management decisions [8]. However, this guidance can be interpreted differently, which has contributed to considerable variation in clinical practice [9]. As such, the best strategy for incorporating EUS in contemporary oesophageal cancer staging pathways is unclear.

A systematic review published by Dyer et al [10] in 2008 synthesised the evidence concerning the impact of EUS on the management of oesophageal cancer. This systematic review identified few high-quality studies but signalled that EUS changed management in a significant number of patients, which improved patient selection for radical treatment by identifying patients with undetected metastases on cross-sectional imaging and subsequently resulted in improved survival. However, many of the evaluated studies lacked a comparison group to allow for meaningful comparisons of changes in management and patient outcomes, and did not routinely use staging PET-CT.

Given recent advances in cross-sectional staging approaches for oesophageal cancer, we updated the systematic review by Dyer et al [10]. Specifically, we aimed to re-evaluate the impact of EUS by updating the literature concerning the management and outcome of patients with oesophageal cancer in the context of the contemporary oesophageal cancer staging pathway.

**Materials and Methods**

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [11] and Synthesis Without Meta-Analysis (SWiM) [12] guidelines, and was prospectively registered with PROSPERO (*blinded*).

*Search strategy and selection criteria*

A systematic search of MEDLINE, Embase, Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, and ClinicalTrials.gov was undertaken up to 2nd February 2021. Search terms relating to oesophageal cancer and EUS were devised using Medical Subject Headings (MeSH). (Supplementary material 1) The search was limited to articles published in the English language and records with a publication date of 2005 onwards were selected to update the search performed in Dyer et al [10]. Study filters for randomised control trials and observational study types were applied. Reference lists of all eligible studies were checked and underwent citation tracking for additional eligible studies. A search of the grey literature was not performed.

Inclusion criteria for the systematic review were (i) studies reporting primary data in patients with confirmed oesophageal or gastro-oesophageal junction cancer (adenocarcinoma or squamous cell carcinoma (SCC)), (ii) patients who underwent radiological staging, and (iii) patients who received treatment for their oesophageal cancer (including treatment delivered with non-curative intent).

Exclusion criteria were (i) studies not containing any primary data, (ii) studies recruiting fewer than 10 patients, (iii) studies investigating catheter probe or intra-operative EUS, and (iv) studies not meeting the primary or secondary outcomes of the review.

*Data collection and extraction*

The title and abstracts of studies retrieved during the search process were screened by two reviewers for relevance. Studies that met the eligibility criteria were included in the systematic review. Relevant data were extracted from the final set of eligible articles. (Supplementary material 2) Data were inputted into a spreadsheet (Microsoft Excel 365) designed specifically for this review. To maximise efficiency, one reviewer extracted the relevant data from the articles, which was then checked and confirmed by a second reviewer. In cases of disagreement, a third author was asked to review the article and decided upon the data to be recorded.

*Risk of bias assessment*

The methodological quality of eligible studies was assessed using the Newcastle-Ottawa Scale (NOS) [13]. The overall components of the quality assessment for each study were reported using the star-rating system of the NOS.

*Outcomes*

The primary outcome of this systematic review was the impact of EUS on the management plan, defined as the percentage of cases in which EUS changed management. For example, EUS may have changed a patient from planned primary surgical resection to neo-adjuvant treatment and surgery, or to non-curative intent after upstaging local disease to metastatic. The secondary outcomes were the rates of biopsy-confirmed local recurrence and overall survival, defined as the length of time between diagnosis and death, or the date of last follow-up.

*Data Analysis*

As originally planned, meta-analysis was not performed in this systematic review. We anticipated that few articles with sufficient quality to allow appropriate meta-analysis would be retrieved. This finding was observed in the original systematic review by Dyer et al [10].

Evidence was synthesised for both primary and secondary outcomes. The results of primary and secondary outcomes of each individual study were used to summarise the range and distribution of observed effect estimates across the cohorts of oesophageal cancer patients.

Standardised metrics were used during evidence synthesis and are presented in tables. The standardised metrics were the percentage change in management using EUS for the primary outcome, and the percentage difference in recurrence rates and absolute difference in overall survival for secondary outcomes. Survival times were transformed to days if provided in months or years.

No studies were prioritised ahead of others. Heterogeneity and limitations of studies were highlighted within tables of evidence. The strength of the overall weight of evidence for both primary and secondary outcomes was judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology [14].

**Results**

The search identified 6,795 studies, of which 73 were duplicates. The titles and abstracts of 2,159 articles were screened, after which 2,117 records were excluded, leaving 42 full-text articles for review.

Twenty-four full-text articles were excluded because the eligibility for primary or secondary outcomes of the systematic review were not met [5,15-23], the study investigated diagnostic accuracy [24-28], the included patient cohort was not relevant [29,30], the article was a review or correspondence [31-33], no primary EUS data was included [34], the article was published in abstract format only [35], for study registration only [36], or the full manuscript was not available despite searching multiple sources [37]. (Fig. 1)

Overall, 11,836 patients from 18 studies [38-55] published since 2005 were included in this review. Important characteristics of the included studies are detailed in Table 1. In total, 2,805 patients (23.7%) received EUS compared to 9,031 (76.3%) who did not receive EUS.

Seventeen studies [23,38-55] reported that EUS was performed for disease staging purposes, with two also specifying treatment planning [42,43]. Two studies [48,52] evaluated EUS staging in early oesophageal tumours. One study did not specify the clinical indication for EUS [39]. Six studies investigated the impact of EUS-FNA [38,42,44,46,52,53]. Six studies [40,43,47,49,53,55] reported that in all, or a proportion, of patients who underwent a PET-CT, EUS reportedly changed management in 11.0% [40] to 28.7% [43], with EUS-FNA changing management in 63.8% patients in one study [53].

Table 2 details the proportion of cases in which EUS or EUS-FNA changed management and summarises the quality of evidence for each study. Reported change in management following EUS use varied widely from 0% to 56.0%. When used, EUS-FNA use changed treatment intent to non-curative in 37.5% to 71.4% of cases. Seven studies reported that EUS upstaged disease, resulting in the provision of neo-adjuvant therapy [39,41,45-47,50,52]. Six studies reported how EUS changed patient management from curative intent to non-curative [38,40,41,46,50,54], two studies described how EUS impacted radiotherapy planning [43,53], and one study described how EUS findings changed the operative approach [44].

Two studies reported recurrence rates in the absence of comparison groups. Pouw et al [48] reported that 10/53 (18.9%) of patients with early neoplasia developed recurrence, however there were no cases where EUS alone diagnosed these. Shimodaira et al [53] reported that 28/37 (75.7%) patients with EUS-FNA positive lymph nodes developed recurrence at last follow-up. All these patients also received a PET-CT. Russell et al [50] described fewer recurrences in patients with EUS who eventually received surgery or EMR compared to no EUS, although no data were provided in the published report.

Studies, with and without comparison groups, reporting overall survival rates are listed in Table 3. Three studies [39,50,55] including a non-EUS comparison group reported improved survival after EUS was used in the pathway. In contrast, Schrager et al [51] found no survival advantage after EUS.

Three studies [39,51,55] with a non-EUS comparison group included a small percentage of patients with early disease, with two reporting a survival improvement after EUS. Das et al [39] and Wani et al [55] found that EUS use in patients with carcinoma in-situ was associated with a survival increase of 299 and 263 days, respectively. The latter study included 853/6436 (13.2%) patients who also received a PET-CT. No other studies investigated outcomes in patients who underwent PET-CT, with or without EUS.

**Discussion**

Survival from oesophageal cancer remains poor despite the use of intensive multi-modal treatment approaches [56]. Many patients present with advanced disease, but for the minority who proceed to curative treatment, overall survival remains approximately 45-50% at 5 years [57]. Enhanced radiological staging with EUS could improve the outcomes of radical treatment by optimising patient selection and treatment.

This systematic review has comprehensively summarised the latest evidence regarding the impact of EUS on the management and outcomes in patients with oesophageal and junctional cancers. Since the previous review in 2008, the Cancer of Oesophagus or Gastricus - New Assessment of Technology of Endosonography (COGNATE) trial [50], the only randomised controlled trial identified, reported that patients randomised to EUS intervention had their management changed in 26.6% of cases. However, 24.5% of patients were also reported to have changed from their initial treatment plan in the non-EUS group, suggesting that the observed improved survival may not have been entirely associated with the addition of EUS intervention. The remaining recent evidence concerning the impact of EUS on management described changes ranging from 0% to 56.0% in studies of generally low quality. These data add to studies included in the 2008 systematic review by Dyer et al [10]. The first study, by Chong et al [58], reported that EUS staging changed management in 15/51 (29.4%) of patients. The second study, by Nickl et al [59] in 1996, reported EUS changed management in 10/41 (24.0%) patients. Neither study reported the number of cases in which futile surgery was avoided following EUS staging. Overall, the evidence for EUS impacting on treatment decisions remains limited.

Studies investigating EUS-FNA found a change in management of up to 70%, mainly used to confirm metastatic disease that would preclude radical therapy. Five prior studies identified in Dyer et al [10] investigated how EUS-FNA impacted on patient management, and also reported substantial changes to the original treatment plan [60,61]. Parmar et al [61] reported that the results of EUS-FNA meant 78% of patients avoided futile surgery in the context of previously undetected metastatic disease. However, original management plans were under-reported, and patients referred for EUS-FNA were a highly selected group. It is unclear how EUS-FNA benefits patients in the setting of routine PET-CT.

Few studies have investigated the impact that EUS had on recurrence and survival rates. Whilst a staging investigation alone is unlikely to directly influence overall survival, the use of that test during the staging pathway could improve the selection of patients for radical curative treatments. The COGNATE randomised interventional trial [50] demonstrated improved quality-adjusted survival in patients staged with EUS compared to CT alone. The use of EUS was associated with improved survival adjusted for generic quality of life with a hazard ratio of 0.705 (95% CI 0.499-0.995), and crude survival with a hazard ratio of 0.706 (95% CI 0.501-0.996) compared to CT alone. Further new studies also found improved survival associated with EUS use across different disease stages [39,51,55]. Two new studies described recurrence rates in different patient groups, but neither of these had a non-EUS comparison group [48,53]. These data add to previous studies investigating clinical outcomes associated with EUS [10]. Harewood and Kumar [62] found that EUS was associated with reduced the recurrence rate (adjusted hazard ratio 0.63 (95% CI 0.43-0.87, p=0.004), and increased survival (adjusted hazard ratio 0.66 (95% CI 0.47-0.90, p=0.008), after increasing the number of patients for neo-adjuvant chemotherapy (32.7% vs 15.0%). Conversely, van Westreenen et al [63] found no survival benefit for patients that underwent EUS, but only reported data for patients that underwent surgical resection. Both studies were retrospective with historical comparison groups and had high risk of bias.

Very few studies have investigated the impact that EUS had on management decisions and patient outcomes in the modern era of radiological staging with PET-CT. These studies were considered low quality because of their retrospective nature, lack of document management plans, and absence of non-EUS comparison group. EUS has the potential to further improve treatment outcomes after routine PET-CT staging [43,55]. Although PET-CT has greater accuracy for distant metastases compared to CT alone, the sensitivity of regional lymph node metastases remains poor at 35-55% [2,4]. Reliance on cross-sectional imaging alone could underestimate lymph node metastases which may increase the likelihood of recurrence and reduce survival. Despite this, Findlay et al [40] have previously suggested that the risks of using EUS may outweigh the benefits. In a large, single-centre study of more than 900 oesophageal cancer patients, of which 798 underwent EUS, probability thresholds of altering management were calculated. EUS utility in the 71.8% of patients with T2-T4a disease was minimal (0.4%), with the associated risk exceeding its benefit. High-quality evidence concerning the role of EUS in the modern era of PET-CT staging is needed to formally re-evaluate its role.

Optimising patient selection for oesophageal cancer surgery is vital to improve overall survival rates and to spare patients the profound quality of life changes attributable to surgery where it is unlikely to be effective for cancer control. Identification of tumour and nodal metastases not detected on CT or PET-CT, particularly the proximal extent of disease and invasion into adjacent organs, may influence the choice of operation [44]. EUS has the potential to achieve improved selection, with its superior contrast resolution allowing better differentiation of tumour from normal oesophagus, and thus greater T-stage accuracy [3] and definition of disease length. The latter point is particularly relevant when planning radiotherapy. If a tumour is non- or poorly-FDG avid on PET-CT [6], and not visualised on CT, then EUS may detect submucosal disease which would alter the gross tumour volume (GTV) [64]. Hence, EUS may still contribute towards a personalised approach to patient selection for radical treatment.

In contrast, EUS remains relatively inaccurate for nodal staging, but does facilitate fine needle aspiration (FNA) of lymph nodes that are suspicious for involvement. Lymph node metastases appear hypoechoic and round with loss of the normal hilum, and a cut-off size threshold of 6 mm is commonly used [65]. However, recent data has questioned the accuracy of this size criterion. In a single-centre study of 112 patients, radiological-pathological correlation revealed that 82% of lymph node metastases measured less than 6 mm, reducing the sensitivity of CT, PET-CT and EUS to 39.7%, 42.6% and 35.3%, respectively [4].

Recent national data has shown considerable widespread variation in EUS use across the United Kingdom (UK) [9]. A cross-sectional survey was distributed to all multi-disciplinary team (MDT) chairs who diagnose and treat patients with oesophageal cancer. The results, provided from 88.7% of National Health Service (NHS) Trusts in the UK, showed that 63% and 43% of centres routinely used EUS for radiotherapy and surgical planning, respectively. The indications for EUS varied widely, were mainly applied on a case-by-case basis, and the data reported from each examination varied depending on the operator. This survey highlights the lack of high-quality evidence concerning EUS, and that a uniform approach to EUS is needed allowing equal access for all oesophageal cancer patients. Significant advances in diagnostics and therapeutics, including the recent recommendation of adjuvant immunotherapy after neo-adjuvant chemoradiotherapy in patients with residual pathological disease [66], have been made since the COGNATE study was published. There is an urgent need to conduct well-designed studies formally re-evaluating the role of EUS in oesophageal cancer staging pathways to provide an evidence base and harmonise EUS use. The feasibility of randomised trials of EUS should be explored, and high-quality prospective cohort studies investigating how EUS changes management should be supported.

This systematic review has updated the literature concerning the impact of EUS in modern radiological staging pathways, using robust methodology. However, this study also has limitations. Study design and methodology were often poorly reported. It is possible that the search strategy missed studies that focussed on CT and PET-CT and did not explicitly describe EUS in the title or abstract. We amended the search strategy used by Dyer et al [10] in attempt to improve search efficiency and relevance. Meta-analysis was not attempted and was never planned. This was appropriate because the review confirmed a low number of suitable low-quality studies existed that described heterogeneous results which were mostly poorly reported. We included studies with and without a comparison group to present all published data, but there were few studies without significant risk of bias from which to draw strong conclusions about the impact of EUS on recurrence and survival rates [67]. Lastly, we could not evaluate publication bias, but we assume that the estimates of effect size reported here are likely to be at the higher end of those observed in routine clinical practice.

In conclusion, this systematic review has comprehensively updated the literature concerning the impact of EUS in modern radiological staging pathways. Using robust methodology, we have shown that few good quality studies exist that evaluate the impact of EUS in oesophageal cancer patients, with even fewer data available in the context of contemporary PET-CT staging. This review identifies an important gap in the evidence where future high-quality research should be planned to evaluate the clinical and cost-effectiveness of EUS staging and treatment planning.

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**Figure Legends**

Figure 1. Study selection process.