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Incidence and relevance of clinically indeterminate non-regional lymph nodes in the treatment of oesophageal cancer

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Objectives: Metastatic involvement of non-regional supraclavicular or superior mediastinal lymph nodes in distal oesophageal cancer is rare, but has important implications for prognosis and management. The management of non-regional lymph nodes which appear indeterminate on CT and FDG PET-CT (subcentimetre nodes or those with preserved normal morphology, but increased FDG avidity) can present a diagnostic dilemma. This study investigates the incidence, work-up, and clinical significance of non-regional clinically indeterminate FDG avid lymph nodes.

Methods: A single centre retrospective review of all FDG PET-CT scans conducted over 5 years was conducted. Patients with mid- or distal oesophageal cancer with non-regional FDG avid nodes were identified. Subsequent work-up, management, and outcomes were retrieved from electronic health records.

Results: Reports for 1189 PET-CT scans were reviewed. A total of 79 patients met the inclusion criteria. Of these, 18 (23%) were deemed to have disease and performance status potentially amenable to radical surgery, and underwent further assessment. The indeterminate lymph nodes were successfully sampled via endobronchial ultrasound (EBUS) or ultrasound-guided fine needle aspiration (US-FNA) in 100% of cases. 15/18 (83.3%) of samples were benign and proceeded to surgery. Outcomes for patients who proceeded to surgery were similar to other cohorts. None had pathology suggesting false negative lymph node sampling.

Conclusions: EBUS and US-FNA are effective means of sampling clinically indeterminate non-regional lymph nodes, and can significantly impact prognosis, and management. Further investigations in this context are of value in this cohort and should be pursued.

Advances in knowledge: Non-regional clinically indeterminate lymph nodes represent a diagnostic dilemma in oesophageal cancer staging. Additional investigations in the form of endobronchial ultrasound are effective at providing additional staging information, and can substantially influence patient care.

The management of tumour-distant supraclavicular and superior mediastinal lymph nodes in lower oesophageal cancer is the subject of some controversy. In Asian countries, with high incidences of squamous cell cancer (SCC) and greater proportions of proximal or mid-oesophageal cancers, paratracheal nodal involvement is reported in approximately 30% of patients(1). Paratracheal, and in some cases supraclavicular and cervical(2), nodes are therefore commonly resected as part of a regional radical lymphadenectomy associated with oesophagectomy. In Western countries, with a predominance of distal adenocarcinoma (AC), malignant involvement of these nodes is much less frequent. Owing perhaps partly to a lack of experience, but also the recognition that patients with distant nodal disease have a very poor prognosis(3), most Western centres therefore do not consider such patients as candidates for radical treatment for distal oesophageal cancer.(4) Reports of nodal involvement vary greatly, with some reports suggesting that paratracheal nodal involvement may be present in up to 2-10% of patients(3, 5). It is imperative that superior mediastinal nodes be assessed as part of the staging process, as the identification of potentially involved non-regional lymph nodes can significantly influence patient staging and treatment.

2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) is recommended for all patients with oesophageal cancer who are eligible for radical treatment. Its major role is the detection of distant metastatic disease, that is often occult on conventional contrast-enhanced CT.(6) Although FDG PET-CT is able to contribute to the identification of loco-regional nodal disease, it is limited by moderate sensitivity (57%) albeit with high specificity 91%.(7)

While certain characteristics may allow for a clinical diagnosis, a small proportion of nodes may remain equivocal despite modern imaging modalities; it is these which can present a particular challenge. Options for targeted sampling of tissue with a view to histological confirmation include endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA), endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) and percutaneous US-guided FNA for superficial accessible sites. The sampling efficacy and clinical outcomes for equivocal, FDG avid, tumour-distant lymph nodes in oesophageal cancer is unclear, yet of vital importance to patient staging and management.

This study sought to present the results of an imaging and biopsy-driven approach to staging and management of mid- and distal oesophageal cancer with indeterminate FDG avid non-regional lymph nodes, and corresponding patient outcomes.

Methods

This study was conducted at a high volume tertiary oesophageal cancer centre with a catchment population in excess of 3 million people. This study was registered with and approved by the local institutional review body.

Search and inclusion criteria

FDG PET-CT reports on the local picture archiving communications system (PACS) were free text-searched for the following terms, using wildcard (*) and Boolean operands: oesoph* AND (supraclavicular OR superior mediastinal OR paratracheal OR neck). The returned results were filtered for those requested by appropriate surgical, medical, or oncological teams involved in the management of oesophageal cancer, these were retrieved and individual reports manually screened.

FDG PET-CT scans performed for initial staging of distal or mid-oesophageal cancer, performed between Nov 11, 2015 and Nov 11, 2020 were considered. Proximal tumours were excluded, as superior mediastinal or supraclavicular lymph nodes do not necessarily constitute non-regional spread in this setting, and malignant nodes in these areas can generally be included in a radiotherapy treatment field and thus not affect treatment decisions. Patients with solid organ metastases on FDG PET-CT were excluded.

Patients with non-regional FDG avid lymph nodes, but without other evidence of metastatic spread, were identified and full details retrieved. Regional nodes (i.e. those most commonly included in en-bloc resection of mid- or distal-oesophageal cancer) were defined as inferior mediastinal nodes (stations 7-9) for the purposes of this study. A likely benign node on FDG PET-CT was defined as a node ≤ 10mm in short axis diameter with normal morphology on CT, e.g. ovoid configuration and/or presence of fatty hilum, and without perceptible FDG uptake above surrounding background soft tissue uptake. A likely malignant node was defined as ≥ 10mm in short axis diameter, with loss of benign morphological features on CT, e.g. rounded configuration and/or loss of fatty hilum, and perceptible FDG uptake above background soft tissue uptake, with higher levels of FDG uptake associated with a greater suspicion of malignancy. Nodes classed as indeterminate or suspicious were those with FDG avidity above background soft tissue uptake, with short axis diameter <10mm regardless of morphology, or ≥ 10mm with preserved normal morphological features (smooth outline, ovoid configuration), with absence of any other signs of potential sarcoid or inflammatory reaction. These nodes were considered for further investigation where it was determined that their malignant or benign status would impact on staging and patient management (i.e. non-regional to the primary tumour).

Results of staging investigations, management, and subsequent clinical outcomes were recorded for these patients. As an overall patient denominator, the total number of unique patient identifiers discussed in the multidisciplinary team (MDT) meeting (tumour board) during the study period was also retrieved from the local database.

Patient care pathway

Following initial staging investigation with endoscopy and biopsies, CT, FDG PET-CT, and staging laparoscopy in the case of tumours at or crossing the gastro-oesophageal junction, patients were discussed in the regional oesophago-gastric cancer MDT. Patients who were not considered surgical candidates, generally due to a combination of advanced disease, frailty, or heavy extra-regional nodal burden on CT and/or PET, were referred for definitive or palliative treatment (chemoradiation, chemotherapy, or best supportive care).

Where non-regional FDG avid nodes represented a potential contraindication to curative therapy (in the event of confirmed malignant spread), these were investigated with either EBUS-TBNA or US-FNA. Results were re-reviewed in the MDT meeting; patients suitable for radical surgery were referred for neoadjuvant treatment followed by surgery. Depending on disease type and location, transhiatal, transthoracic, or three-stage oesophagectomy techniques were used.

Results

Following a free-text search of the PACS reporting database, a total of 2404 FDG PET-CT scans containing the target search terms were identified (figure 1). Following further filtering and case-by-case manual review, 79 patients (79 / 1189, 7.0% of examined FDG PET-CT scans; 79 / 3634, 2.3% of overall patients referred to the MDT) with non-metastatic mid- or distal-oesophageal cancer, with FDG avid non-regional (superior mediastinal or supraclavicular) lymph nodes were identified.

Of 79 patients who met the inclusion criteria, 61 / 79 (77%) were deemed not suitable for surgical treatment on account of patient frailty and / or disease burden, and were referred for oncological therapy without further investigation. The remaining 18 patients (18 / 79, 23% of patients with non-regional FDG avid nodes; 18 / 1189, 1.5% of PET scans; 18 / 3634, 0.5% of all patients referred to the MDT) were deemed potentially suitable for radical multimodal therapy in the absence of distant metastases and underwent further investigation. Supraclavicular nodes were sampled with US-FNA,

whereas mediastinal nodes were sampled with EBUS-TBNA. There was a 100% successful rate of both sonographic identification of the lymph nodes in question, and FNA.

In the majority of cases (15 / 18, 83.3%), nodal cytology was non-malignant (containing inflammatory or lymphoid cells) and patients proceeded to have radical treatment (table 1). In squamous cell carcinoma (SCC, 6/18 patients, 33%), this involved definitive platinum-based chemoradiotherapy (CRT) for mid-oesophageal tumours. One patient with distal oesophageal SCC underwent neoadjuvant CRT; following completion of neoadjuvant therapy re-staging scans showed an increase in size an avidity of the suspicious node (station 1R), this was re-biopsied via EBUS, unfortunately demonstrating malignancy which was subsequently managed on a palliative pathway. For adenocarcinoma (AC), patients underwent neoadjuvant chemotherapy followed by surgery. One patient whose lymph node cytology demonstrated metastatic disease underwent FLOT-type chemotherapy, and following a good response (as assessed by CT and PET), proceeded to radical surgery with extended lymphadenectomy but unfortunately suffered early disease recurrence.

Median follow-up for these patients was 18 months (range 3 – 54 months). At time of analysis, 2 / 4 (50%) patients treated with dCRT had suffered recurrence (table 2). One of these had local oesophageal disease recurrence only, attempted salvage oesophagectomy had to be abandoned due to local invasion. The second patient had both local and systemic disease, with hepatic, pulmonary, and nodular disease, but without obvious involvement of the previously sampled lymph node. For patients who underwent surgery, 3 / 8 (36%) had a complete pathological response (CPR). Two patients (25%), both with advanced (T3N3) disease, had positive margins (R1 resection). At time of follow-up, all but one patient were still alive (median overall survival not reached).

Discussion

This study reports the experience of a high-volume tertiary centre in the investigation of non-regional FDG avid nodes in oesophageal cancer. While this can be associated with advanced disease and nodal metastases, the results of this study show that where equipoise exists on imaging, additional investigations in the form of EBUS-TBNA or US-FNA have clear benefit. With appropriate centre experience, these have a very high success rate in identifying and sampling nodes which are positive on FDG PET-CT and as such have potential for malignant involvement. Despite potentially metastatic appearances on staging, the majority of nodes were found to be benign, with patients therefore suitable for radical treatment with curative intent. Where clinical concern exists, repeat biopsy is warranted. While this staging approach applied only to a small number (<1%) of patients in the studied cohort, it had significant implications for their care.

Patients who tolerated neoadjuvant treatment and underwent surgery appeared to have outcomes consistent with those reported in conventional oesophageal cancer cohorts, with a 36% CPR rate(8) and 25% rate of margin positivity(9). Further, these outcomes support that cytology results represented true negatives rather than FNA sampling error. Disease recurrence patterns in those patients who suffered relapse did not include the sampled nodes. A single case of possible false negative initial biopsy was seen in patient 2, highlighting that repeat sampling should therefore be considered where concern exists, such as with progressive lymphadenopathy on re-staging.

Patients who were found to have malignancy in non-regional lymph nodes, conversely, were spared the additional morbidity and mortality risk of radical treatment and surgery. By proceeding without delay to palliative therapy, these patients achieved relatively good outcomes, with survivals of 12 and 43 months. The one patient who did undergo radical treatment despite malignant nodal cytology did so following thorough discussion with the MDT and in the knowledge of a low likelihood of curative outcome, and suffered early disease recurrence.

Limited studies published to date have examined superior mediastinal nodes from varying operative and diagnostic approaches with a focus on nodes potentially resectable as part of an upper paraoesophageal or paratracheal lymphadenectomy. Harada et al reported a single American centre's series of oesophageal AC which included routine surgical resection of paratracheal lymph nodes (stations 1, 2, and 4) when involvement was suspected.(3) This study reported an incidence of positive nodes in junctional AC ranging from 1.2% (Siewert type III tumours) to 7.5% (type I). However, even following surgical resection, in a multivariable adjusted survival analysis, paratracheal nodes were one of the factors most strongly associated with unfavourable outcome, even more so than T or N staging. Poor survival and recurrence rates comparable to cN3-staged disease led authors to question what the best treatment for these patients in future might be; radical surgery in this context exposes patients to major surgery with high morbidity but potentially no survival benefit. To date, no evidence comparing non-surgical therapy versus radical lymphadenectomy for non-regional nodes exists; further research in this area is needed. Even in more proximal tumours, the benefit of surgery for superior mediastinal or supraclavicular nodal disease is unclear, with several studies reporting that such an approach may result in higher complication rates, without significant survival benefit when compared to standard two-field lymphadenectomy.(2, 10, 11)

Considering different approaches to staging non-regional nodes, Shimodaira et al reported the single-centre American results of routine EUS assessment and FNA of paratracheal and supraclavicular nodes for distal (Siewert type I and II) oesophageal cancer(12). This was a safe and effective approach, with no reported complications, and over a third of the 133 included patients had positive EUS-FNA (i.e.

malignant cytology) not demonstrated on FDG PET-CT, i.e. not FDG avid or too small to demonstrate on CT. However, exact locations of the assessed nodes were not reported, and 77.4% of patients with positive EUS-FNA did require adjustment of radiotherapy fields, suggesting the majority of assessed nodes were in fact regional to the tumour and different from the cohort being considered in our study. It remains unlikely, therefore, that routine EUS-FNA represents a realistic or suitable alternative to the approach described in our study.

The results presented here must be considered in the context of their limitations. While it was carried out in a high-volume centre with consistent MDT personnel and approach to patient management throughout the study period, this was a single-centre retrospective study. Owing to limitations of the electronic database and free-text search mechanism, exact denominators for patients treated with curative intent, instead of overall MDT-discussed or PET-scanned patients, could not be given. While in the absence of histopathological confirmation of surgically resected nodes, false negative cytology cannot be excluded, the outcomes for patients were consistent with those for patients without questionable distant nodes.

In summary, FDG avid non-regional nodes in oesophageal cancer can and should be assessed through further investigations such as EBUS-TBNA and US-FNA to procure biopsy or aspirates and determine their benign or malignant nature. With no complications, and a 100% successful node aspiration rate, such an approach is both safe and effective and has potential to significantly impact on patient management. Larger scale studies may in future allow for the identification of radiological parameters to better quantify the nature of such nodes without the need for invasive diagnostics. Patients with benign nodes can proceed with radical treatment, whereas those with metastatic nodes should be given consideration for non-radical or palliative treatment to maximise quality and duration of life.

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Table 1: Pathological details, workup, and subsequent treatment of patients

Patient number	Clinical stage	Nodal CT morphology*	FDG PET SUV_{max}*	Imaging	Nodal station sampled	FNA result
Distal SCC						
1	T3N3	Ovoid 6x7mm	3.6	US-FNA	5	Malignant
2	T4aN2	Round 8x10mm	3.1	EBUS	1 R	Benign
Mid SCC						
3	T1bN0	Ovoid 7x13mm	1.3	EBUS	4R	Benign
4	T3N1	Ovoid 7x9mm	3.5	EBUS	4R, 7	Benign
5	T3N2	Ovoid 4x10mm	2.8	EBUS	3R	Benign
6	T3N3	Ovoid 7x8mm	2.8	EBUS	2R, 4R, 4L, 7	Benign
Distal AC						
7	T2N2	Ovoid 10x14mm	2.6	EBUS	4R, 7	Benign
8	T3N1	Ovoid 10x13mm	8	EBUS	2R, 4L, 7	Benign
9	T3N1	Ovoid 6x17mm	2.9	US-FNA	SCF	Benign
10	T3N1	Ovoid 6x10mm	2.9	US-FNA	SCF	Benign
11	T3N1	Ovoid 11x15mm	3.4	EBUS	3	Malignant
12	T3N2	Ovoid 5x7mm	2.4	EBUS	4R, 7	Benign
13	T2N2	Ovoid 8x13mm	2	EBUS	7, 10R, 11L	Benign
14	T3N2	Ovoid 10x13mm	2.7	EBUS	3R, 7	Benign
15	T3N2	Ovoid 14x16mm	5	EBUS	1L, 4R, 4L, 7	Benign
16	T3N3	Ovoid 7x10mm	1.1	US	SCF	Not biopsied
Mid AC						
17	T3N1	Ovoid 11x14mm	5.2	EBUS	2L	Malignant
18	T3N3	Ovoid 5x11mm	3.1	US-FNA	SCF	Benign

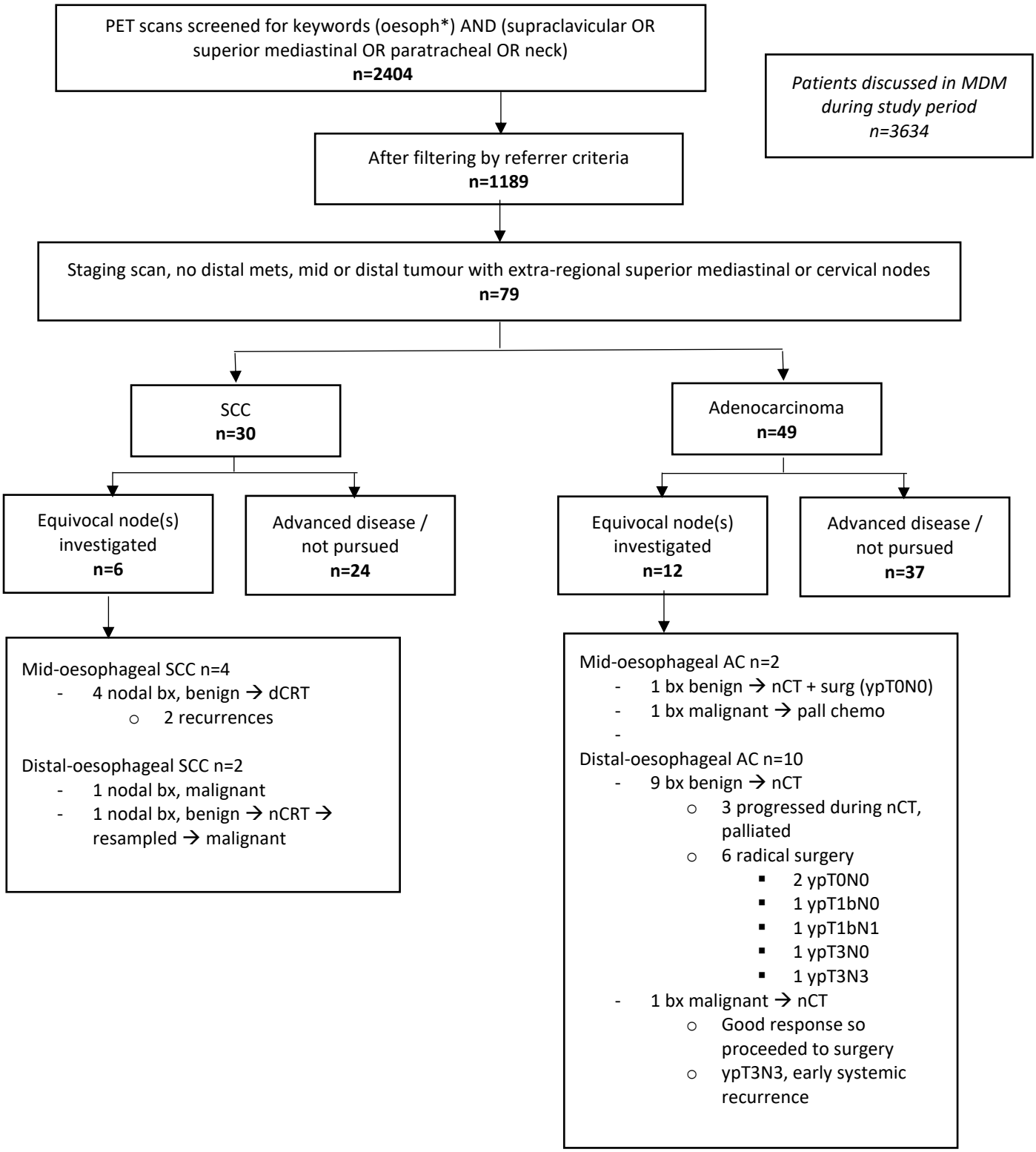
SUV_{max}: maximum standardised uptake value; SCC: squamous cell carcinoma; AC: adenocarcinoma; US-FNA: ultrasound fine needle aspiration; EBUS: endobronchial ultrasound; SCF: supraclavicular fossa; nCRT: neoadjuvant chemoradiotherapy; dCRT: definitive chemoradiotherapy; nCT: neoadjuvant chemotherapy. *: in cases where multiple nodes sampled, reported dimensions and SUVmax relate to most prominent and FDG-avid node

Table 2: Treatment outcomes

Patient number	Clinical stage	Treatment	Outcome	Pathological stage (ypTNM)	Margin	DFS (months)	OS (months)
Distal SCC							
1	T3N3	Palliative CT				n/a	12
2	T4aN2	nCRT	Resampled, malignant			n/r	Alive
Mid SCC							
3	T1bN0	dCRT				n/r	Alive
4	T3N1	dCRT	Local recurrence, attempted salvage surgery abandoned			3	19
5	T3N2	dCRT	Local recurrence, palliative treatment			17	33
6	T3N3	dCRT				n/r	Alive
Distal AC							
7	T2N2	nCT	Systemic progression despite chemo			n/a	6
8	T3N1	ECX	Inoperable at surgery			n/a	10
9	T3N1	ECX		T1bN1 (1/38)	R0	n/r	Alive
10	T3N1	nCT	Died during chemo			n/a	3
11	T3N1	FLOT	Systemic recurrence	T3N3 (18/39)	CRM+	3	3
12	T3N2	FLOT	Systemic recurrence	T1bN0 (0/28)	R0	4	Alive
13	T2N2	FLOT		T0N0 (0/21)	R0	n/r	Alive
14	T3N2	FLOT	Anastomotic and systemic recurrence	T3N3 (12/29)	Proximal margin +	5	Alive
15	T3N2	EOX		T0N0 (0/29)	R0	n/r	Alive
16	T3N3	FLOT		T3N0 (0/22)	R0	n/r	Alive
Mid AC							
17	T3N1	CX + trastuzumab				n/a	43
18	T3N3	nCT		T0N0 (0/20)	R0	n/r	Alive

Figure 1. 1A) Axial CT (A), axial PET (B) and axial fused PET-CT (C) demonstrating a FDG avid (SUV_{max} 3.6) 6 x 7mm ovoid right level 5 cervical node/right supraclavicular fossa (black and white arrows), malignant on cytology. **1B)** Axial CT (A), axial PET (B) and axial fused PET-CT (C) demonstrating a FDG avid (SUV_{max} 3.4) 11 x 14mm ovoid station 3P mediastinal node (black and white arrows), benign on cytology.

Figure 2. Study flow chart


PET scans screened for keywords (oesoph*) AND (supraclavicular OR superior mediastinal OR paratracheal OR neck)
n=2404
Patients discussed in MDM during study period
n=3634
After filtering by referrer criteria
n=1189
Staging scan, no distal mets, mid or distal tumour with extra-regional superior mediastinal or cervical nodes
n=79
SCC
n=30
Adenocarcinoma
n=49
Equivocal node(s) investigated
n=6
Advanced disease / not pursued
n=24
Equivocal node(s) investigated
n=12
Advanced disease / not pursued
n=37
Mid-oesophageal SCC n=4
- 4 nodal bx, benign → dCRT
  - 2 recurrences
Distal-oesophageal SCC n=2
- 1 nodal bx, malignant
- 1 nodal bx, benign → nCRT → resampled → malignant
Mid-oesophageal AC n=2
- 1 bx benign → nCT + surg (ypT0N0)
- 1 bx malignant → pall chemo
-
Distal-oesophageal AC n=10
- 9 bx benign → nCT
  - 3 progressed during nCT, palliated
  - 6 radical surgery
    - 2 ypT0N0
    - 1 ypT1bN0
    - 1 ypT1bN1
    - 1 ypT3N0
    - 1 ypT3N3
- 1 bx malignant → nCT
  - Good response so proceeded to surgery
  - ypT3N3, early systemic recurrence