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Impact of integrated PET/CT in the staging of oesophageal cancer—a UK population-based cohort study

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AIM: To document the impact of integrated positron-emission tomography and computed tomography (PET/CT) on the management of a cohort of UK patients undergoing PET/CT as part of their staging investigations for potentially curable oesophageal cancer.

MATERIALS AND METHODS: A multicentre, prospective study of newly diagnosed patients with oesophageal cancer undergoing PET/CT was set up across five cancer networks covering a total population of 6.6 million. Data were prospectively collected for cases diagnosed between 1 November 2006 and 31 October 2007.

RESULTS: One hundred and ninety-one patients underwent PET/CT, with 31 (16%) positive for possible metastatic disease. Amongst the 31 positive examinations, 18 (9.4%) were confirmed to have metastatic disease, and 13 (6.5%) patients had no subsequent evidence of metastatic disease, although in three (1.6%) of these a second previously unsuspected pathology was diagnosed. Two patients had false-negative PET/CT and were found to have metastatic disease. The results of the PET/CT examination down-staged 10 (5%) patients thought to have coeliac/M1a node involvement on CT. Fifteen of 110 (13%) patients with stage 3 or 4 disease at CT and endoscopic ultrasound (EUS) had confirmed metastatic disease at PET/CT, compared with none of 18 with stage 2b, three of 52 (6%) with stage 2a, and none of 10 with stage 1 disease.

CONCLUSION: This study confirms the role of PET/CT in a multicentre UK setting in the management of patients with potentially curable carcinoma of the oesophagus, improving the accuracy of pre-treatment staging compared with CT and EUS alone. Early tumours infrequently show evidence of metastasis on PET/CT, although further data are required to confidently determine the stage of tumours where PET/CT has no additional value.

Introduction

The incidence of oesophageal carcinoma has dramatically increased over the last two decades[1–3] and the prognosis remains poor, with an overall 5-year survival rate of 7%. Oesophagectomy is generally recognized as offering the best prospect of long-term cure, but is a major procedure with perioperative mortality in modern series of 2–10% and significant morbidity in up to 60% of patients.[4] Postoperative quality of life is significantly compromised for 3–6 months and never returns in those who develop early postoperative recurrence or metastatic disease.[5] Poor long-term survival for patients who appear to have complete tumour resection appears to be, in part, due to a failure to detect distant metastases at or before the time of surgery.[6,7] Accurate preoperative staging

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is thus essential in providing informed treatment choices for these patients.

Conventional imaging used for staging oesophageal cancer in the UK includes contrast-enhanced computed tomography (CT) of the chest and abdomen with positive or negative oral contrast medium load, and endoscopic ultrasound (EUS), techniques that provide high-quality anatomical information. EUS enables accurate assessment of the depth of invasion (T stage) together with accurate information regarding local nodal involvement (N stage). Recently preoperative imaging has variably included the use of integrated positron-emission tomography and CT (PET/CT). PET detects metabolically active tissue based on the metabolism of glucose.[8] Studies have reported that metastases missed at CT were subsequently identified using PET in more than 10% of patients with oesophageal cancer.[9–11] Combined PET/CT imaging facilitates the separation of normal physiological uptake from pathological uptake, and enables accurate anatomical localization of functional abnormalities. PET/CT combines both multisection CT and PET capabilities in two sequential scans, avoiding the need for patient motion between the CT and PET components of the study, thereby leading to more accurate co-registration of the CT and PET data.[12] The use of PET/CT is likely to add accuracy over PET alone by enabling morphological and metabolic information to be gained in one sitting allowing more precise interpretation. Use of PET/CT in routine clinical practice in the UK has been variable and dependent largely on availability of this imaging technique.

The aim of this study was to establish the effect of combined PET/CT on the management of a prospective cohort of patients with newly diagnosed oesophageal cancer across five cancer networks in England.

Materials and methods

A multicentre prospective study was undertaken of patients with newly diagnosed oesophageal cancer who underwent PET/CT imaging. This study was supported and sponsored by the upper GI tumour panel of the South West Cancer Intelligence Service (SWCIS), a cancer registry encompassing a population of 6.6 million, across five cancer networks covering the south and southwest of England. The study included patients from 12 NHS trusts. Ethical approval was not required for this study as this was an audit of patients undergoing PET/CT. One of the remits of SWCIS is to conduct audits to improve services to cancer patients and this audit was within this remit.

Patients

Patients with histologically confirmed oesophageal cancer either confined to the oesophagus or involving the oesophagogastric junction diagnosed between 1 October 2006 and 30 September 2007 were included. All patients included in this study were, at the time of their PET/CT, candidates for potentially curative treatment of their tumours. This included a small number of patients with disease staged as potentially inoperable by CT and EUS, but where the multidisciplinary team (MDT) still thought that surgery may be an appropriate management plan.

Imaging

All CT examinations were undertaken on current generation multidetector CT machines and with thin-section acquisitions as optimized according to local practice. An oral load of positive or negative (water) contrast medium was administered prior to CT and images obtained during the administration of intravenous contrast medium (volume generally 100–150 ml dictated by local practice). Images were viewed according to local practice and the final local radiological report was taken to be definitive.

EUS, where possible, was performed according to locally agreed protocols and the operator's report used as an end-point.

PET/CT was obtained at a variety of sites according to local arrangements with both fixed-site machines and mobile units being utilized. All studies were integrated PET/CT without intravenous contrast medium for the CT examination. Although there may have been some minor variation in local practice, PET/CT was generally undertaken after a 6 h fast. A standard dose of 400 MBq of 2- [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) was administered and imaging commenced after a 45 min uptake period. Blood glucose of $\leq$10 mmol/l was considered acceptable. Results were recorded at local MDT meetings.

PET/CT examinations were reported as positive if there were areas of non-physiological uptake of tracer away from the primary tumour, suggesting the possibility of metastasis and negative if there were no areas of positive uptake outside the tumour (no metastases).

All preoperative imaging was completed within a 4-week time period.

Patient management

The CT and EUS findings, together with all other preoperative staging investigations, were

reviewed and correlated at 12 local MDT meetings involving upper gastrointestinal surgeons, thoracic surgeons, medical oncologists, pathologists, radiation oncologists, and radiologists with PET/CT training. The tumour-node-metastasis classification (fifth edition) proposed by the International Union Against Cancer was used for staging.[13]

Data

Data were prospectively collected by means of proforma to include demographics, preoperative staging with and without PET/CT, histological staging, PET/CT baseline practice, and effect on MDT management decision. Data were entered into an Excel (Microsoft) spreadsheet and analysed.

Results

A total of 191 (149 male, 42 female) patients of median age 66 years underwent PET/CT (Table 1). The findings of the PET/CT examinations are summarized in Fig. 1 indicating the distribution of PET/CT examinations that were positive and negative. True-positive results were those that identified metastases and synchronous pathology not detected by CT and EUS, in contrast to false-positive results that were later shown to have incorrectly suggested the presence of metastases not detected by CT and EUS.

Thirty-one (16%) patients had positive examinations consistent with distant metastases. Eighteen (9.4%) patients were subsequently upstaged and had distant metastases identified, including extensive lymph node involvement ($n = 11$), bone ($n = 7$), liver ($n = 3$), cervical lymph node ($n = 1$), and lung ($n = 1$). Preoperative CT did not involve the neck in 92 (48%) patients, but did include the neck in the one case where PET/CT identified an additional cervical node metastasis. The patients whose cancers were upstaged after PET/CT were initially staged with combined CT and EUS as IIa in three (6%) patients, III in 13 (13%) patients, and IV in two (20%) patients (Table 2). The patients with true-positive results were confirmed by biopsy ($n = 11$), and by subsequent clinical course, and further imaging ($n = 10$). Three (1.6%) patients had unexpected synchronous pathology discovered during PET/CT. These lesions were a colonic adenoma, primary lung neoplasm, and carcinoid tumour of the lung.

Table 1 Demographics and pathological characteristics of patients undergoing integrated positron-emission tomography and computed tomography (PET/CT).

	No. of patients $N = 191$ [n(%)]
Age group (years)	
36–54	23 (12)
55–64	61 (32)
65–74	69 (36)
75+	38 (20)
Histology	
Adenocarcinoma	133 (70)
Squamous cell carcinoma	49 (26)
Other	9 (4)
Site	
Upper	3 (2)
Middle	26 (13)
Middle/lower	11 (6)
Lower	105 (55)
Junctional	46 (24)

The 10 (5%) patients with false-positive PET/CT results were from increased uptake in the liver ($n = 4$), kidney ($n = 1$), adrenal ($n = 1$), bone ($n = 1$), colon ($n = 1$), thyroid ($n = 1$), and mesentery ($n = 1$). These were confirmed as negative by appropriate negative investigations shown in Table 3.

Negative PET/CT was reported in 160 (84%) patients with 158 (83%) patients having true-negative results with eight (4%) being down-staged in the MDT meeting. Coeliac/M1a node involvement was excluded at PET/CT in seven patients and liver metastases were excluded in one patient. These findings were confirmed at operation and histologically in five cases, but three did not proceed to resection. Two patients decided not to proceed with surgery and one who tolerated neo-adjuvant chemotherapy poorly was subsequently deemed unfit for surgery.

The other 150 (79%) that were negative were also negative for distant metastases on combined CT and EUS. The primary tumour was not detected by PET/CT in 10 patients, seven (70%) of these cases were staged as T1 or T2 by combined CT and EUS. Two (1%) patients had false-negative PET/CT for distant metastases. In these cases conventional preoperative imaging was also negative for distant metastases. One patient was found to have metastasis in the peritoneum at operation, and the other in a neck lymph node, which became evident at preoperative clinical examination. Both false-negative PET/CT results were positive for primary tumour uptake and were classified as T3 by CT and EUS. These two false-negative cases were both reviewed by the MDT and by an independent radiologist retrospectively and no change was made to the initial report of the PET/CT.

PET/CT was found to be helpful in planning management in 174 cases (91%), changed staging in 65 cases (34%), and management in 50 cases (26%). The overall sensitivity of PET/CT in detecting

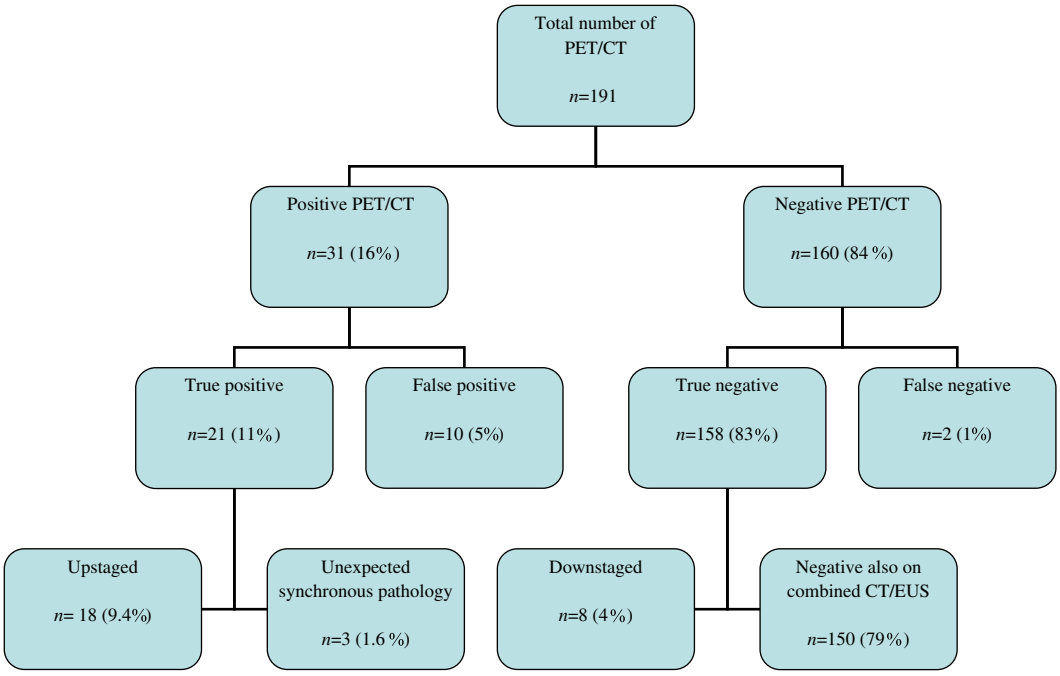

Figure 1 Chart illustrating the results of PET/CT for distant metastases.

distant metastases was 91% and its specificity was 94%. The pathological stage at resection is summarized in Table 4.

CT was performed in every patient and EUS was performed in 132 patients (69%). PET/CT was performed routinely in 167 (87%) and selectively in 24 cases (13%) to assist with preoperative staging. Amongst those having PET/CT selectively, nine out of the 24 (38%) cases were shown to be truly positive for metastatic disease compared with nine out of 167 (5%) for those carried out routinely. The wait for PET/CT was reported to be less than 2 weeks in 10 out of the 12 centres in this study.

One hundred and seventy-three patients were deemed eligible for potentially curative resection after preoperative staging including PET/CT. One hundred and ten patients went on to have curative resection after two further patients were found to have distant metastases (false negative). PET/CT was positive for primary tumour uptake for all 110 patients that went on to have resection. The four patients subsequently shown to have stage 0 disease received neo-adjuvant chemoradiotherapy. Sixty-one patients did not go on to have oesophageal resection because of patient choice ($n = 10$), fitness for surgery post-neo-adjuvant chemoradiotherapy ($n = 11$), tumour progression ($n = 18$), death ($n = 2$), and unknown ($n = 20$).

Table 2 Distribution of integrated positron-emission tomography and computed tomography (PET/CT) positive results for distant metastases by conventional staging with CT and endoscopic ultrasound (EUS).

Stage at CT and EUS	TNM	No. of cases [*n* (%)]	Distant metastases on PET/CT [*n* (%)]
I	T1, N0, M0	9 (5)	0
IIa	T2 or 3, N0, M0	52 (27)	3 (6)
IIb	T1 or 2, N1, M0	20 (11)	0
III	T3 N1 or T4 any N, M0	100 (52)	13 (13)
IV	Any T, any N, M1	10 (5)	2 (20)

Discussion

This is the first UK multicentre study to review the impact of PET/CT on patients thought to be candidates for curative treatment based on CT/EUS.

Table 3 Investigations confirming false-positive integrated positron-emission tomography and computed tomography (PET/CT) results.

Investigation confirming false-positive PET/CT results	Anatomical site
Fine needle aspiration	Thyroid $n = 1$
Magnetic resonance imaging	Bone $n = 1$, liver $n = 1$
Biopsy	Kidney $n = 1$, adrenal $n = 1$
Colonoscopy	Colon $n = 1$
Laparoscopy	Liver $n = 4$, mesentery $n = 1$

Table 4 Pathological stage post-resection for patients who had negative integrated positron-emission tomography and computed tomography (PET/CT) results for metastatic disease.

Pathological stage post-resection for patients who had negative PET/CT for metastatic disease	Number of patients
0	4
I	14
IIa	32
IIb	11
III	49
IV	0
Unresected	61

PET/CT suggested distant metastases in 16% of patients and these metastases were confirmed in 9%. This is consistent with previous single-centre series where 10% or more of patients have been found to have previously unsuspected metastatic disease in oesophageal cancer after PET/CT.[14,15,16] As well as contributing to pre-treatment staging, unexpected synchronous disease, such as colonic adenoma, primary lung neoplasm, and carcinoid, was found at PET/CT in a small number of cases, as previously reported in other series.[16,17,18] It is, thus, important to critically analyse the results of PET/CT for distant metastases before they are accepted. This study found a false-positive rate of 5% ($n = 10$) and false-negative rate of 1% ($n = 2$). The findings of synchronous disease and false-positive PET/CT highlight the importance of precise determination of the cause of areas of uptake before they are attributed to metastatic disease, in order to avoid denying potentially curative treatment to patients who do not have metastatic disease. Other authors have highlighted this. Taira et al.[19] evaluated PET/CT with regard to the identification of bone metastases in a variety of malignancies, and found very high positive predictive values (PPV, 98%) when both PET and CT portions of the examination were in concordance. However, PET and CT examinations appear to be discordant relatively frequently, and the PPV is then reduced significantly (PPV, 61% for PET versus 17% for CT; negative predictive value, 83% for PET versus 39% for CT). Furthermore, in patients with solitary bone lesions for which the PET and CT findings are discordant, the PPV for integrated PET/CT is particularly low at 43% suggesting that this finding should be interpreted with great care to avoid denying potentially curative treatment.[19] Recent review has found PET/CT to be unhelpful in differentiating (1) inflammatory changes and neoplastic processes in lymph node stations or lymphatic tissues (Waldeyer ring or appendix); (2) residual tumour and post-therapy changes immediately after surgery or radiation therapy; (3) benign thyroid adenoma and thyroid cancer; (4) focal physiological bowel uptake and large or small bowel malignancies; or (5) focal physiological uptake in the uterus during menstruation and uterine cancer.[20] This has important implications for radiology workload in terms of validating areas of non-physiological uptake on PET/CT by other imaging techniques or biopsy. With more experience and recognition of common patterns of spread, the need for confirmatory biopsy may be reduced when positive PET/CT findings are considered typical of metastatic disease.

It has been suggested that PET/CT had limited additional value and that it should be used selectively in advanced tumours.[21–23] In one institution-based study only 6.6% of stage III–IV oesophageal cancer had previously undetected metastatic disease.[21] This multicentre study found metastatic disease in 13% of stage III/IV disease by conventional staging, and 6% of patients with stage IIa oesophageal cancer. PET/CT was used selectively in 13% ($n = 24$) of cases possibly introducing a small selection bias towards greater identification of undetected distant metastases in more advanced stage disease by conventional imaging. A strength of this study is that it reflects the impact of PET/CT in current clinical practice, within which there is often a degree of uncertainty. PET/CT is used mainly in stage II/III disease and where doubt exists after conventional imaging, in those thought to have stage IV disease. Where doubt arose following conventional imaging of stage IV disease, eight out of the 10 were subsequently shown to be PET/CT negative for distant metastases, with two out of the 10 showing further metastases not already detected. The role of PET/CT is thus confirmed in advanced disease, although the available data are not yet sufficiently robust to define the role of PET/CT in early-stage disease. A recent review in this journal discussed further potential for PET/CT in assessing the effect of neoadjuvant therapy, and potentially in determining the need for adjuvant treatment. Further applications that require investigation include its role as a prognostic marker for patient outcome and as an aid to intensity modulated radiation therapy.[24]

Quality control of images and their interpretation is an important issue in a cancer registry population-based study and a potential weakness of such a study is the lack of quality control with regards to the interpretation of images. Thus this study includes results from a heterogeneous group of operators and radiologists with different levels of experience. However, it reflects current

ongoing clinical practice. The PET/CT centres used for imaging patients in this study were also part of the National Health Service (NHS) southern sector national contract and so subject to independent audit of reporting. The population included in this study is managed according to improving outcomes guidance,[25] with review of cases taking place in specialist centres according to network agreed protocols, which provides a good level of quality assurance. That the findings are similar to other single-centre studies also provides a good degree of assurance that quality control was appropriate.

Imaging the neck as part of routine CT with or without ultrasound examination has been suggested to increase sensitivity for detection of metastatic disease[26] and the neck was not routinely imaged using CT in 50% of patients in this study. The only patient with a solitary neck node in this study found on PET/CT had previously undergone CT of his neck, which failed to diagnose this metastasis. Although there is good evidence for routine staging CT to include the neck, the present data do not suggest that this should substitute for PET/CT imaging.

MDTs themselves found PET/CT imaging to be helpful in management of patients with management changes occurring in 50 (26%) patients. The complex nature of patients' clinical course of treatment is evident by the fact that of 191 patients who were found to have disease potentially amenable to curative treatment, only 110 patients eventually went on to have resection. In this cohort of patients PET/CT has provided valuable true-negative data for over 80% of patients, with this finding apparently validated by pathological stage at resection and patients' early subsequent progress. The most important role of PET/CT potentially lies in reducing the chance of early recurrence post-resection. This role is not yet confirmed, and it is essential to carefully follow up this and other cohorts of patients having had PET/CT, in order to define the impact of PET/CT on early recurrence of disease.

References

1. Bosetti C, Levi F, Ferlay J, et al. Trends in oesophageal cancer incidence and mortality in Europe. *Int J Cancer* 2008; **122**:1118—29.
2. Forman D. Oesophago-gastric adenocarcinoma—an epidemiological perspective. *Aliment Pharmacol Ther* 2004; **20**(Suppl. 5):55—60. discussion 61—62.
3. Office for National Statistics. Registrations of cancer diagnosed in 1993—96, England and Wales. *Health Stat Q* 1999;**4**:59—70.
4. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. *Br J Surg* 1998;**85**: 840—4.
5. Blazeby JM, Farndon JR, Donovan J, et al. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. *Cancer* 2000;**88**: 1781—7.
6. Roth JA, Putnam Jr JB, Lichter AS, et al. Cancer of the esophagus. In: Devita Jr VT, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology*. 4th ed. Philadelphia: Lippincott; 1993. p. 776—817.
7. Anderson LL, Lad TE. Autopsy findings in squamous-cell carcinoma of the esophagus. *Cancer* 1982;**50**:1587—90.
8. Wren SM, Stijns P, Srinivas S. Positron emission tomography in the initial staging of esophageal cancer. *Arch Surg* 2002; **137**:1001—7.
9. Flanagan FL, Dehdashti F, Siegel BA, et al. Staging of oesophageal cancer with 18-F-fluorodeoxyglucose positron emission tomography. *AJR Am J Roentgenol* 1997;**168**: 417—24.
10. Luketich JD, Friedman DM, Weige TL, et al. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg* 1999;**68**:1133—7.
11. Block MI, Patterson GA, Sundaresan RS, et al. Improvement in staging of esophageal cancer with the addition of positron emission tomography. *Ann Thorac Surg* 1997;**64**: 770—6.
12. Bruzzi JF, Munden RF, Truong MT, et al. PET/CT of esophageal cancer: its role in clinical management. *RadioGraphics* 2007;**27**:1635—52.
13. Sobin LH, Wittekind C. *TNM classification of malignant tumors*. 6th ed. New York: Wiley-Liss; 2002.
14. van Westreenen HL, Heeren PA, van Dullemen HM, et al. Positron emission tomography with F-18-fluorodeoxyglucose in a combined staging strategy for esophageal cancer prevents unnecessary surgical explorations. *J Gastrointest Surg* 2005;**9**:54—61.
15. Ott K, Weber W, Siewert JR. The importance of PET in the diagnosis and response evaluation of esophageal cancer. *Dis Esophagus* 2006;**19**:433—42.
16. Salahudeen HM, Balan A, Naik K, Mirsadree S, Scarsbrook AF. Impact of the introduction of integrated PET-CT into the preoperative staging pathway of patients with potentially operable oesophageal carcinoma. *Clin Radiol* 2008;**63**:765—73.
17. Bruzzi JF, Truong MT, Macapinlac H, et al. Integrated CT-PET imaging of esophageal cancer: unexpected and unusual distribution of distant organ metastases. *Curr Probl Diagn Radiol* 2007;**36**:21—9.
18. Kneist W, Schreckenberger M, Bartenstein P, et al. Prospective evaluation of positron emission tomography in the preoperative staging of esophageal carcinoma. *Arch Surg* 2004; **139**:1043—9.
19. Taira AV, Herfkens RJ, Gambhir SS, et al. Detection of bone metastases: assessment of integrated FDG PET/CT imaging. *Radiology* 2007;**243**:204—11.
20. Kostakoglu L, Hardoff R, Mirtcheva R, et al. PET-CT fusion imaging in differentiating physiologic from pathologic FDG uptake. *Radiographics* 2004;**24**:1411—31.
21. van Westreenen HL, Westerterp M, Sloof GW, et al. Limited additional value of positron emission tomography in staging oesophageal cancer. *Br J Surg* 2007;**94**: 1515—20.
22. Duong CP, Demitriou H, Weih L, et al. Significant clinical impact and prognostic stratification provided by FDG-PET

in the staging of oesophageal cancer. *Eur J Nucl Med Mol Imaging* 2006;**33**:759—69.
23. Heeren PA, Jager PL, Bongaerts F, et al. Detection of distant metastases in oesophageal cancer with (18-F)-FDG PET. *J Nucl Med* 2004;**45**:980—7.
24. Chowdury FU, Bradley KM, Gleeson FV. The role of ^{18}F-FFDG PET/CT in the evaluation of oesophageal carcinoma. *Clinical Radiology* 2008;**63**:1297—309.
25. National Cancer Action Team. *Guidance on commissioning cancer services: improving outcomes in upper gastro-intestinal cancers the manual*. London. Department of Health. 2004.
26. van Vliet EP, van der Lugt A, Kuipers EJ, et al. Ultrasound, computed tomography, or the combination for the detection of supraclavicular lymph nodes in patients with esophageal or gastric cardia cancer: a comparative study. *J Surg Oncol* 2007;**96**:192—3.