Clinical significance of incidental findings on staging positron emission tomography for oesophagogastric malignancies

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ABSTRACT

INTRODUCTION The aim of this retrospective study was to determine the clinical significance of incidental findings detected on positron emission tomography (PET) in patients undergoing staging of oesophagogastric malignancies.

METHODS Patients with oesophagogastric malignancies who underwent PET between June 2007 and May 2012 were included in the study. PET was performed according to hospital protocol. All imaging was interpreted by two consultant radiologists in nuclear medicine. Incidental findings that were unrelated to the primary malignancy were recorded and patients were recommended to have further investigations (imaging, endoscopy and biopsy).

RESULTS Overall, 333 patients (240 male, 93 female; mean age: 67 years) with upper gastrointestinal malignancies were eligible for inclusion in the study. Eighty-nine of these patients had PET demonstrating one or more incidental findings. Two patients were found to have a second primary malignancy. One patient had a distant metastasis of his primary cancer and six patients had a premalignant lesion.

CONCLUSIONS In this study, incidental findings were discovered in 26.7% of patients with known oesophagogastric cancer. A second primary cancer or premalignant lesion was found in 8.4% of patients with incidental findings. Patients with these findings should be investigated to rule out further malignancy. There were a high proportion of false positive results in our study. It is recommended that each patient is considered on an individual basis and assessed with simultaneous PET and computed tomography.

KEYWORDS

Positron emission tomography – Incidental finding – Oesophagogastric – Upper gastrointestinal

Accepted 19 November 2013

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Upper gastrointestinal (GI) cancers are becoming more common, especially oesophageal cancer, which is now the seventh and eleventh most common cancer in men and women respectively in England and Wales.^{1–3} The incidence of oesophageal cancer is continuing to rise despite the reduction in tobacco smoking. Suggested causes for this increased incidence include alcohol consumption, nutritional deficiencies and *Helicobacter pylori* infection.^{1–5} Patients presenting with upper GI cancer undergo investigation by computed tomography (CT) and positron emission tomography (PET) with fludeoxyglucose (FDG) to determine the presence of metastatic deposits.^{4–11} PET enhances the identification of recurrent or distant tumour deposits and can also provide information on other biological activity that might be a cause for concern.^{11–15}

Routine interpretation of FDG PET can include the reporting of abnormal incidental foci of uptake, which may be unrelated to the neoplasm for which the patient is being investigated. These incidental findings are often

located in sites distant from the primary tumour, which would not be typical endpoints for metastatic spread. Such findings may require investigation to determine whether they are a second primary malignancy or an unexpected physiological variant.^{5,11} Any cell with increased glucose transport will demonstrate increased uptake of FDG. PET can therefore falsely identify inflammatory, infectious and active granulomatous processes as having a potential malignant aetiology.^{5,10,11} The objective of this retrospective study was to determine the clinical importance of these unexpected incidental findings on FDG PET.

Methods

A total of 333 patients who had histologically proven primary malignant GI lesions and who had undergone whole body FDG PET-CT over a 5-year period were included for analysis retrospectively. Only the first scan was assessed.

FDG PET examinations and interpretation

Whole body imaging was performed at our institution using an integrated PET-CT device (Discovery™ STE; GE Healthcare, Chalfont St Giles, UK). After a six-hour fast (except for water hydration), an intravenous injection of 400MBq of FDG was given. A 45-minute rest period followed, allowing the uptake of FDG, and PET was performed immediately following this. Patients were encouraged to void prior to the imaging to minimise bladder activity.

All PET-CT (transverse, coronal and sagittal planes) was interpreted by two experienced consultant radiologists in nuclear medicine with a GI interest. Areas demonstrating increased FDG uptake were evaluated by comparison with background activity and the presence of morphological alterations on CT. All incidental findings suspicious of malignancy underwent further investigations.

Definition of incidental finding

An incidental finding was defined as any focal accumulation of FDG thought to be unrelated to the primary malignancy. This decision was based on the incidental finding having an atypical location, intensity or pattern for metastasis.¹⁰

Follow-up investigations

Follow-up investigations recommended by the reporting radiologist included tumour markers, magnetic resonance imaging, ultrasonography, mammography, image guided or surgical biopsy and endoscopy. Diagnoses were considered final once the follow-up investigation had been completed.

Incidental findings were deemed clinically significant if the histological diagnosis was malignant or premalignant.

Results

For the 333 patients (240 male, 93 female) included in the study, the mean age at PET was 67 years (range: 28–86 years). The sites of the primary tumours included the oesophagus (*n*=285), the gastro-oesophageal junction (GOJ) (*n*=40) and the stomach (*n*=8). The histological diagnosis of the primary upper GI cancer was most commonly adenocarcinoma (222/333, 66.7%) and squamous cell carcinoma

(85/333, 25.5%). Other subtypes included adenosquamous carcinoma, GI stromal tumour, neuroendocrine carcinoma and Barrett’s oesophagus.

PET demonstrated FDG uptake with increased activity of the upper GI malignancy in 300 of the 333 patients (true positive results). False negative PET was seen in 20 patients (sensitivity 93.8%). These images were reviewed with the corresponding CT. Eight patients still demonstrated no upper GI abnormality. Twelve of the twenty patients with false negative PET were reported to have a thickening of the mucosa suggestive of malignancy, the largest lesion reported as 2.4cm × 5.0cm. The location of the 20 false negative results were the oesophagus (adenocarcinoma *n*=10, squamous cell carcinoma *n*=5) and the GOJ (adenocarcinoma *n*=5).

The specificity of PET in this series was 76.9%, with a positive predictive value of 99% (300/303) (Table 1).

In the 333 FDG PET scans that took place, 95 unexpected abnormal foci of hypermetabolism were identified in 89 patients. The most significant anatomical distribution included (but was not limited to) colorectal (*n*=41), adrenal (*n*=7) and the parotid gland (*n*=5).

Correlative histopathological or endoscopic examinations were completed for 64 (67%) of the 95 incidental findings. While 16 incidental findings (17%) underwent further imaging techniques, the remaining 15 (16%) were investigated using tumour markers and clinical examination.

In the 89 patients with 95 incidental findings, 2 patients were found to have a histologically proven second primary malignancy (1 in the breast, 1 in the colon), 1 patient was found to have a bony metastatic deposit in an unexpected location and 6 patients had premalignant changes in the form of tubular adenoma (*n*=4) and tubulovillous adenoma (*n*=2). The remaining 80 patients had benign lesions or normal findings.

The majority of the incidental findings were of colorectal distribution with FDG uptake described as ‘focal’ in 25 of the 41 colonic incidental findings (61%) and ‘diffuse’ in 3 (7%). The remaining 13 (32%) were reported as ‘physiological’ uptake. The incidental finding demonstrating a colorectal adenocarcinoma was reported as focal uptake of

Table 1 The sensitivity and specificity of positron emission tomography in detecting the original upper gastrointestinal malignancy in the 333 patients included in the study

		Patients with malignancy (confirmed by histology)		
		Positive	Negative	
Uptake of FDG on PET	Positive	TP = 300	FP = 3	PPV = TP / (TP + FP) 99%
	Negative	FN = 20	TN = 10	NPV = TN / (FN + TN) 33%
		Sensitivity = TP / (TP + FN) 93.8%	Specificity = TN / (FP + TN) 76.9%	

FDG = fludeoxyglucose; PET = positron emission tomography; TP = true positive; FP = false positive; PPV = positive predictive value; FN = false negative; TN = true negative; NPV = negative predictive value

FDG on PET while the six premalignant incidental findings were described as focal ($n=5$) and diffuse ($n=1$). Thus, FDG PET was falsely positive for 86 (90%) of the 95 incidental findings suggesting the presence of an unexpected second primary lesion.

Discussion

PET-CT has become an important and valuable resource in the management of cancer patients, superseding the methods of separate CT and PET in the staging of cancers.^{9,14} The sensitivity of PET in detecting upper GI malignancy in this study was 93.8%, which conforms with other studies.^{15–18} However, false negative results continue to be seen; our study demonstrated this in 20/333 patients (6%). False negative FDG uptake on PET has been linked previously to small volume T1 tumours.¹⁸ This is not consistent with the results of our study, in which a larger dimension tumour (2.4cm × 5.0cm) detected on CT was not active metabolically on PET. PET is still fallible despite being sensitive and CT should continue to be reviewed in combination with PET.

CT has a poor sensitivity in detecting a second primary tumour or unexpected metastases when compared with PET-CT.^{9,14} Detection of these incidental findings and their investigation has a significant clinical impact on patients who already have a diagnosis of cancer.⁷ Cancer patients have approximately twice the chance of developing a new primary cancer that is unrelated to the previous diagnosis than a cancer free individual of the same age and sex.^{7,9,19}

Misinterpretation of incidental findings may lead to false upstaging of the primary upper GI malignancy. This may result in patients being told they have metastatic and likely inoperable disease. Additional investigations for the incidental finding are therefore important in aiding therapeutic decisions. One study suggests that the upper GI malignancy determines the prognosis of the patient and, as a result, the verification of benign or premalignant incidental findings is irrelevant.⁸ The investigations suggested are usually histological and, consequently, invasive so benefits must outweigh the associated risks. An algorithm has been designed to aid clinicians in managing incidental findings (Fig 1).

Our study recognises the overall rate of detection of second primary malignancies as 2.1%. This is similar to that described by Ishimori *et al* (1.2%)⁷ and Wang *et al* (0.9%)¹⁰ although other studies have demonstrated a higher incidence of malignant incidental findings, such as that by Beatty *et al*.¹¹ The non-specific accumulation of FDG can make the detection of second primary malignancies very difficult. Inadequate use of histological investigations could explain the low detection rate of second primary malignancies; instead, imaging ($n=16$) and blood markers with clinical examination ($n=15$) were performed. This confirms the importance of histology in the diagnosis of second primary malignancies. The role of histology is now thought to be more important than considered originally in this study, especially as it is not uncommon for the incidental finding to represent cancer.^{5,20–22}

It is important to note that semiquantitative measurement of FDG uptake using the standardised uptake value (SUV) was considered but not included in this study as it was felt not to be of value following previous reports in the literature. The overall view of the literature suggests that the use of SUV remains controversial. Some studies consider SUV as a useful tool for predicting malignancy^{23,24} while other studies demonstrate no statistical difference between the SUV of premalignant, malignant, benign or physiological lesions in unexpected foci of FDG on PET-CT.^{20,22}

Focal and diffuse uptake of FDG is also a preferred method for determining the benign or malignant potential of lesions. Focal distribution is more likely to demonstrate pathological findings, with diffuse FDG uptake being predictive of normal findings at further investigation.²⁵ Focal colonic uptake is reported to be seen in approximately 1–3% of patients.^{6,20,22,26} However, the rate in our study was higher (25/333, 7.5%).

Our study showed a high number of benign incidental findings. In order to reduce the probability of a false positive result, it is important to interpret PET in accordance with other anatomical imaging (CT) and clinical findings. All patients underwent referral to a clinician in the discipline in which their incidental finding was located. In the

majority of cases, this referral resulted in further investigations. Nevertheless, in a few cases, discussion at the specialist multidisciplinary team meeting was deemed sufficient. Other studies such as that by Wang *et al*¹⁰ suggest that unnecessary referral can be avoided when experienced radiologists report incidental findings as most likely benign. Future studies should be completed to determine the number of incidental findings that are falsely reported as benign but that actually have malignant potential.

Conclusions

Despite the potential advantages of detecting second primary cancers at an early stage, erroneous interpretation of incidental findings are likely to have an impact on patient management. Consequences include unnecessary use of invasive techniques to establish a firm diagnosis and increased patient anxiety, having further psychological effects on a patient who already has a diagnosis of cancer. It is therefore important for the timing and route of investigation of the incidental finding to be considered carefully.

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