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Received: 10 October 2017 Revised: 09 December Accepted: 11 December 2017 2018 The Authors. Published by the British Institute of Radiology

Cite this article as:

Pencharz D, Nathan M, Wagner TL. Evidence-based management of incidental focal uptake of fluorodeoxyglucose on PET-CT. *Br J Radiol* 2018; **91**: 20170774.

GUIDELINES & RECOMMENDATIONS

Evidence-based management of incidental focal uptake of fluorodeoxyglucose on PET-CT

¹DEBORAH PENCHARZ, BMBS, MSc, FRCP, ²MALAVIKA NATHAN, MBBS, MSc, FRCR and ²THOMAS L WAGNER, MD

¹Department of Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, East Sussex, UK ²Department of Nuclear Medicine, Royal Free Hospital NHS Foundation Trust, London, UK

Address correspondence to: **Dr Deborah Pencharz** E-mail: *deborah.pencharz@bsuh.nhs.uk*

ABSTRACT

Focal incidental uptake, with or without CT abnormalities, is a common finding on fluorodeoxyglucose PET/CT and evidence-based management for this type of uptake is lacking. This article reviews the evidence on focal incidental uptake including the incidence of malignancy, differential diagnosis and imaging criteria which can be used to further characterize it. The article focusses on PET rather than CT criteria. The strength of the evidence base is highly variable ranging from systematic reviews and meta-analyses to a virtual absence of evidence. Caution needs to be used when using standard-ized uptake values (SUVs) reported in other studies due to interpatient and institution observed variation in SUVs. There is sufficient evidence to permit specific suggestions on how to interpret the foci and recommend further management in the: pituitary (investigate when SUVmax >4.1), thyroid (investigate all), breast (investigate all), lung parenchyma (if focus of fluorodeoxyglucose without a CT nodule, no further investigations), colon (investigate all foci with SUVmax >5.9, urgently if SUVmax >11.4), adrenals (criteria depend on if patient has cancer) and prostate gland (investigate in males aged >50 years or >40 years if peripheral uptake or patient has other risk factors). There is some evidence to guide further management for the parotid gland, naso-orophaynx, oesophagus, pancreas, uterus and ovaries. There is insufficient evidence to guide management for the liver, spleen, kidneys, gallbladder, testis and bone, for these organs patient characteristics and other guidelines will likely be of more use in determining further management.

INTRODUCTION

Incidental abnormalities on ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT have been reported in 6.7^{1} – $12\%^{2}$ of scans.

Accurate interpretation of incidental focal uptake and knowing when to suggest further investigations therefore requires knowledge of its differential diagnosis, the incidence of malignancy and any PET/CT criteria which can be used to further characterize it. In this article, we have, therefore, reviewed the evidence on incidental, focal uptake on FDG PET/CT and used it to suggest guidelines for further management. We have chosen not to discuss diffuse uptake as it is usually ascribed to physiological or inflammatory causes.

With some exceptions, we have chosen not to discuss the CT appearances associated with the incidental FDG focus. This is in the interest of article length and because useful diagnostic CT criteria of incidental findings have been described in multiple other publications and comprehensively covered in the American College of Radiology (ACR) white papers.

Where there were multiple studies examining the significance of an incidental focus, we have included the studies we consider to be most useful or accurate, e.g. those looking at the largest cohort of patients, those with the highest rates of follow up or meta-analyses. It should be noted that in almost all the studies which directly investigated the significance of incidental focal uptake, only a minority of foci have a final diagnosis. It is reasonable to assume that there was a selection bias with the most suspicious foci being further evaluated. Therefore, it is likely the incidence of malignancy reported in these papers is higher than the true incidence of malignancy of all foci. We considered ascribing a level of evidence to each recommendation. However the "question" being addressed (how to manage incidentally identified abnormalities) does not fit into classic evidence-based questions, as it is not a question specifically about diagnostic accuracy or of an intervention. Additionally, in general, the quality of the evidence was low (retrospective, observational studies with low rates of follow up and systematic reviews of these observational studies). Therefore, as an alternative, we have summarized the relevant articles in sufficient detail to allow readers to assess the quality of the evidence for themselves and understand the rationale behind the recommendation. It is important to be aware that multiple factors affect standardized uptake value (SUV) measurements. Under carefully controlled conditions, the SUVs in the same patient can normally vary by up to 10% but this increases to >20% in less well controlled conditions.^{3,4} The introduction of newer scanners and reconstruction techniques such as point spread function, time of flight⁵ and algorithms which allow fully convergent PET image reconstruction but without excessive noise⁶ have been shown to increase SUVs and SUVmax. Despite this limitations, using evidence on published SUVs as a guide to managing incidental focal FDG uptake is preferable to non-evidence-based decisions.

For each organ, we have, therefore, summarized the relevant articles in sufficient detail to allow readers to assess the quality of the evidence for themselves and understand the rationale behind the suggested management. There are summary tables for each section for ease of future reference.

Finally, any suggestions for further management should be made in the context of the patient's individual circumstances and choice. In particular, if the patient has known serious comorbidities which would limit life more than the pathology of any incidental findings, then the risks and benefits of further investigations should be carefully evaluated.

HEAD AND NECK

Pituitary

A study of 13,145 consecutive subjects⁷ found that 0.8% demonstrated incidental pituitary uptake. In 29 of 71 subjects with the final diagnosis, the pituitary uptake was pathological: macroadenomas (n = 21), microadenomas (n = 5) and malignancy (n = 3). When SUVmax >4.1 was used as an optimal criterion for detecting pathologic uptake, the diagnostic sensitivity, specificity and accuracy were 97, 88, and 92%, respectively.

Summary and suggestion

Incidental, focal, pituitary uptake with SUVmax >4.1 should be further investigated with pituitary MRI and/or testing of hormonal levels or endocrinology review.

Naso- oropharynx

There is useful evidence on interpreting focal incidental uptake in the pirform fossa, palatine tonsils and nasopharynx which is described below. Evidence for interpreting potential incidental uptake elsewhere (*e.g.* the floor of mouth and base of tongue) is scarce and a single study without easily adaptable conclusions is outlined at the end of the section.

Within the piriform fossa, Cho et al⁸ found that 0.05% of 56,585 PET/CTs had incidental, focal uptake. There was a final diagnosis of malignancy in 10.3% (n = 29) and benign causes in 76.5% (n = 215). Malignant lesions had significantly higher SUVmax ($9.1 \pm 3.6 vs \ 3.5 \pm 1.0$) and ipsilateral to contralateral SUVmax ratio (SUVmax_I:SUVmax_C) ($4.2 \pm 1.8 vs \ 1.5 \pm 0.4$) compared to benign causes. Lesion SUVmax ≥ 4.2 identified malignancy with a sensitivity of 93% and specificity of 87%. SUVmax_I: SUVmax_C \geq 1.8 had a sensitivity of 100% and specificity of 90% for the detection of malignancy.

Davison et al⁹ compared the SUVmax ratio in patients with and without (n = 26 each) palatine tonsillar squamous cell carcinoma (SCC). When an SUVmax ratio cut-off of 1.48 was used the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis was 1.0, *i.e.* 100% sensitivity and specificity. Lee et al¹⁰ reported that the SUVmax ratio (mean, range) of patients with early pT stage tonsillar SCC was (2.5, 1.0–5.4),occult tonsillar SCC found at surgery (1.7, 0.85–3.8). in patients with cervical metastases of SCC of unknown primary without tonsillar primaries (1.1, 0.86–1.3) and in healthy controls (1.2, 1.0–1.5).

Lee et al¹¹ compared patterns of benign (n = 177) and malignant (n = 48) nasopharyngeal FDG uptake and found that uptake was significantly more intense in the malignant group (SUVmax 10.4 ± 4.6) than the benign group (3.9 ± 1.4) p < 0.001; however, asymmetry of uptake was not: 68% in the benign group *vs* 90% in the malignant group. When SUVmax of 6.0 was used as cut-off for detection of malignant nasopharyngeal uptake, the AUC of the ROC was 0.93 [95% CI (0.88–0.98)] with a sensitivity of 88% and a specificity of 92%.

Heusner et al¹² studied 590 patients to assess for qualitatively increased or asymmetric uptake within the head and neck without a corresponding CT abnormality with a mean follow up of 2.5 years. Of 87 patients with asymmetric uptake within Waldeyer's ring, 1 developed palatine carcinoma (SUVmax 3.2); of 98 patients with asymmetric uptake in the oral floor one developed carcinoma (SUVmax 3.7) and of 72 with asymmetric laryngeal uptake none developed carcinoma.

Summary and suggestions

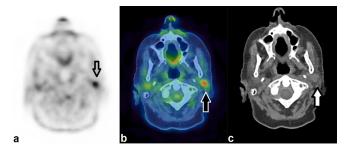
- Intensity of FDG uptake is significantly associated with malignancy.^{8,11} SUVmax \geq 4.2 in the piriform fossa⁸ and SUVmax \geq 6.0 in the nasopharynx¹¹.
- When comparing known benign and malignant uptake SUVmax_I:SUVmax_C >1.8 in the piriform fossa⁸ and SUVmax_I:SUVmax_C >1.48 in the palatine tonsils⁹ are highly suspicious for SCC.

Based on this, we suggest that patients with the above findings should be referred to ear, nose and throat (ENT) for direct visualization. In patients with incidental focal uptake not meeting the criteria above, there is inadequate evidence to formulate guidelines and decisions should be made in individually. Knowledge of if the patient has any important risk factors for head and neck cancer: smoking, alcohol, human papillomavirus and Epstein–Barr virus infection¹³ might be helpful. It should also be remembered that asymmetrical uptake is frequently observed in patients without head and neck cancer.¹²

Parotid

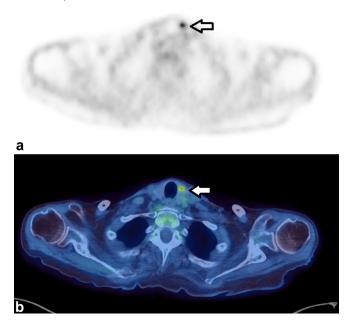
Mabray et al¹⁴ analysed 38,302 PET studies and identified 73 incidental foci of uptake within the parotid which had a follow up diagnosis. 33/73 were manifestations of the patient's known malignancy (26 metastases, 7 lymphomas), 25/73 were benign

Figure 1. Incidental focal uptake in the parotid gland. A 71-yearold female had a PET/CT for further characterization of CT abnormalities identified during follow up for previous TCC of the ureter. Focal uptake of FDG (SUVmax 6.0) demonstrated by the arrow on the axial PET only image (a) localizes to the left parotid gland. On the CT only image (c) a soft tissue density nodule is demonstrated in the parotid. This was thought to be incidental rather than related to the TCC and histology from ultrasound-guided biopsy demonstrated a pleomorphic adenoma. FDG, fluorodeoxyglucose; PET, positron emission tomography; TCC, transitional cell carcinoma.



primary parotid tumours (14 Warthins, 7 benign pleomorphic adenomas, 4 oncocytomas) and 15/73 non-neoplastic causes (lymphatic tissue or inflammation). No malignant primary parotid tumours were identified. In patients with head and neck pathology, there were higher odds ratios (ORs) that focal parotid

Figure 2. Axial images of a 71-year-old female who had a PET/CT to assess for possible malignancy as a paraneoplastic cause of her necrotizing autoimmune myopathy. A focus of increased uptake (SUVmax 6.1) (a) localized to the thyroid gland (b) Fine-needle aspiration showed blood and clumps of colloid and clusters of crowded epithelial cells with enlarged nuclei, the appearances were suspicious of papillary carcinoma. Although the study was performed to look for malignancy, this finding was not thought to be the cause of her myopathy. PET, positron emission tomography; SUV, standardized uptake value.



uptake was a metastasis [OR = 24.6, p < 0.01 for cancer/melanoma, OR = 7.2, p = 0.02 for lymphoma and OR = 3.6, p = 0.07 for FDG-avid cervical lymph node(s)]. Mean SUVmax of the lesions which were manifestation of the patient's known malignancy was 8.4 *vs* 10.3 for benign parotid lesions.

Makis et al¹⁵ found that, of 7,252 oncologic PET/CT studies, FDG incidental parotid uptake occurred in 0.4% (n = 29) of scans of which only 1 (4%) was malignant: follicular lymphoma (FL) in a patient with a previous history of follicular lymphoma. The commonest histology was Warthin's tumour. PET/CT was unable to differentiate benign from malignant parotid lesions based on SUVmax alone.

Park et al¹⁶ examined PET and CT criteria in 272 patients who exhibited focal parotid uptake, 68 had pathological confirmation. There were 32 malignant lesions: 11 metastatic carcinoma, 8 primary salivary malignancies/other. The benign lesions included 24 Warthins tumours, 4 pleomorphic adenomas and "other" in 8. There were no significant differences in SUVmax, size or Hounsfield Unit (HU) max between benign and malignant lesions. Malignant lesions were significantly more likely to have heterogeneous uptake and ill-defined margins on CT.

Figure 1 demonstrates an incidental focus of uptake within the parotid gland.

Summary and suggestions

SUVmax cannot distinguish between benign and malignant causes of uptake. Warthin's tumour followed by pleomorphic adenoma are the commonest incidental findings which, although benign, when they present with a mass or other symptoms, are typically managed surgically.^{17,18} Some incidental malignant lesions were also detected. Therefore, it is reasonable to refer patients without a known malignancy with incidental focal parotid uptake for further evaluation, either to ENT or with imaging such as parotid ultrasound or MRI.

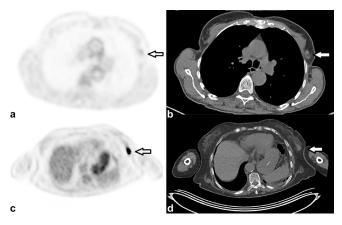
In patients with a known malignancy, particularly within the head and neck, the uptake is much more likely to represent either a metastasis or a benign lesion than a primary malignant parotid lesion. The benefit of further assessment should, therefore, be balanced against the prognosis of the known malignancy

Thyroid

Focal thyroidal uptake can represent benign or malignant pathologies, Barrio et al¹⁹ listed over 20 different histopathology descriptions following thyroidal FNA of focal hypermetabolic thyroid lesions. Benign lesions included benign colloid nodule, benign follicular nodule and adenomatoid nodule. Malignant pathologies included follicular cell neoplasm, Hurthle cell neoplasm and papillary carcinoma. Diffuse uptake is usually ascribed to Graves disease, chronic thyroiditis and hypothyroidism.²⁰

Soelberg et al²¹ performed a systematic review on the risk of malignancy in incidental thyroidal uptake. Out of 125,754 subjects, 1994 (1.6%) had unexpected focal activity, 1051 of these had a final diagnosis of whom 366 (34.8%) had thyroid

Figure 3. Two cases demonstrating how incidental breast uptake, which were both later proven to be carcinoma, can have highly variable FDG uptake. (a, b) are axial PET and CT images respectively from a 69-year-old female who had a PET/CT as part of staging for a previously removed melanoma. No other sites of melanoma were identified; however; there was low-grade uptake (SUVmax 1.8) in the axillary tail of the left breast (arrow) in (a) which localized to a soft-tissue nodule, on the CT (b). This was confirmed as invasive ductal adenocarcinoma on histology. In contrast, there was very intense uptake (SUVmax 19.1), axial PET only image, (c) in the breast of a 73-year-old female who had a PET/CT for potential myeloma. This localized to a breast soft-tissue lesion demonstrated on the CT only image, (d) which was also later confirmed as primary breast carcinoma. FDG, fluodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value.



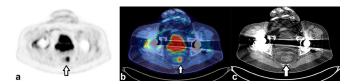
malignancy. In the eight studies reporting individual SUVmax, the mean SUVmax was 4.8 (standard deviation 3.1) in benign and 6.9 (standard deviation 4.7) in malignant lesions (p < 0.001). More recent, smaller, single site studies found a malignancy rate of 23% (7 patients),²² 19% (9 patients)²³ and 23% (19 patients)²⁴ who received final diagnoses. All three studies found the mean SUVmax of the malignant group was higher than the benign group but with large overlap in the range between the groups.

Kim et al²⁵ analysed the use of the unenhanced CT in further characterizing incidental thyroidal uptake in 82 patients. They

Figure 4. Axial-fused PET/CT images of a 66-year-old female who had a PET/CT for further characterization of a right lower lobe lung nodule. The nodule was intensely FDG avid (SUV-max 6.4) (a) and (b) and was shown to be lung cancer on biopsy. She had a further focus of FDG (SUVmax 4.0), arrow in (c) in the contralateral lung which was not associated with a nodule on CT (d) This was assumed to be a microembolus of FDG and chest X-ray 20 months later showed no abnormality at this site. FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value.



Figure 5. Axial images of a 74-year-old male who had a PET/CT for staging of melanoma with a presumed single metastasis to lung. A focus of uptake in the rectosigmoid junction (SUV-max 9.8) (a) appeared to localize to abnormal soft tissue on the fused (b) and CT-only (c) images. The patient went on to have a sigmoidoscopy which demonstrated an 18-mm polyp, he was referred for endoscopic mucosal resection. PET, positron emission tomography; SUV, standardized uptake value.



found that the ratio of the HU of the thyroid nodule to the contralateral thyroid lobe (T/B_{HU}) in predicting malignancy had an AUC of the ROC of 0.94 when a cut off T/B_{HU} \leq 0.68 was used. The sensitivity, specificity, and accuracy of T/B_{HU} was 100, 80 and 87% respectively.

Figure 2 demonstrates an incidental focus in the thyroid gland.

Summary and suggestions

Incidental, focal, thyroidal uptake should have ultrasound scan \pm fine-needle aspiration. The same recommendation was made by the American Thyroid Association²⁶ and the ACR white paper.²⁷ In future, the T/B_{HU} may help differentiate which patients require further investigation.

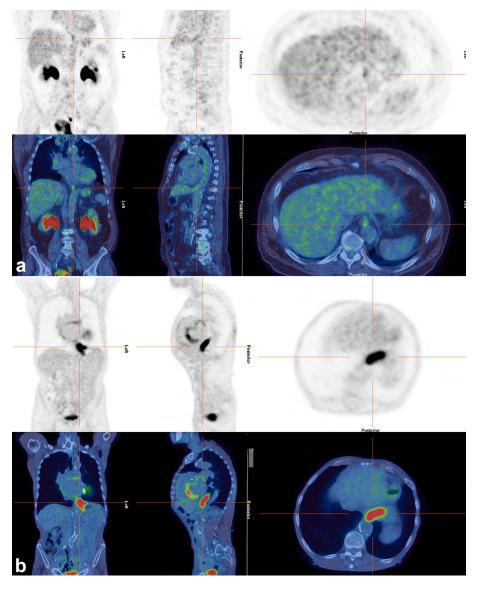
Table 1 for a summary of the evidence and suggestions regarding incidental FDG uptake in the head and neck.

THORAX

Breast

ThoraxBreastThBShin et al²⁸ identified incidental focal uptake in the breast in 1.0% of 21,224 females who underwent PET/ CT.91 lesions had sufficient histological or imaging follow-up for a diagnosis of which 30% were malignant, these pathologies included invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ and secondary deposits from other malignancies. In order of most frequent, the benign pathologies were fibroadenoma, intraductal papilloma, fibrocystic change, sclerosing adenosis and other rarer causes. Multivariate analysis found that none of patient's age, SUVmax or lesion size was useful in distinguishing between benign and malignant causes.Chae et al²⁹ found that incidental focal FDG uptake within the breast occurred in 0.40% of 32,988 patients who had PET/CTs. Of these, 72 had either sufficient histological or imaging follow up to establish a diagnosis of which 45% had a malignant cause. SUVmax and lesion size was larger in the malignant than benign lesions but there was significant overlap in the confidence intervals for both.

Figure 6. Axial, coronal and sagittal PET/CT images (a) of a 73-year-old male with recurrent bladder cancer and faint foci at his GOJ which were presumed to be physiological. This contrasts with (b) which shows a known oesophageal tumour extending to the GOJ. GOJ, gastro-oesophageal junction; PET, positron emission tomography.



CT appearances of breast lesions should also be considered: a spiculated and irregular margin (and rim enhancement for contrast enhanced) is the most accurate sign for malignancy.³⁰ Due to lobular carcinoma's more infiltrative pattern of growth CT findings may be non-specific: appearing as an asymmetric soft-tissue density with or without associated skin thickening or as a mass. A discrete mass is also often absent in inflammatory carcinoma, but with marked skin thickening. Benign breast fibroadenomas appear as well circumscribed round or oval masses which may have popcorn calcifications, fibroadenolipoma often contains fat and glandular tissue. Fat necrosis can have a range of appearances including mimicking malignancy. Despite these recognized CT appearances, a systematic review of incidental breast lesions detected on CT found that benign and malignant breast lesions cannot be safely distinguished from each other on standard chest CT.³¹ Additionally, many benign breast lesions, including those described above, can show increased FDG uptake.³²

Figure 3 demonstrates two different incidental findings within the breast, their differing PET/CT appearances and histologies.

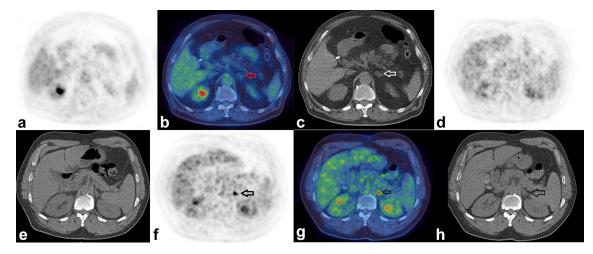
Summary and suggestions

Focal incidental breast uptake, irrespective of the CT appearances requires further evaluation, we recommend by referral to the breast team for triple assessment.

Lung

Focal uptake within the lung, without a corresponding nodule assuming there is no misregistration, was reported to occur in 0.15% of 10,500 patients.³³ In this paper, and in another reported series,³⁴ some of the patients were rescanned a few days later with FDG PET/CT and the foci had disappeared or they were followed up with contrast enhanced CT and no abnormality developed. A different paper reported focal pulmonary FDG

Figure 7. Benign and malignant adrenal nodules. Figure shows the PET-only (a) fused (b) and CT-only (c) images respectively of a 72-year-old male who had a PET/CT to assess for possible large vessel vasculitis. There was no evidence for vasculitis, however there was a 1.5 cm low attenuation nodule (HU -30) in the left adrenal demonstrating only low-grade FDG uptake (SUVmax 1.5). Based on the presence of macroscopic fat, this was presumed to be an adrenal myelolipoma. Figures (d, e) show PET- and CT-only images respectively in a 68-year-old male who had a PET/CT to further characterize persistent consolidation in his lung, the adrenals look normal. A PET/CT repeated 9 months later (f, g, h) now shows an intense focus of FDG uptake in the left adrenal gland with SUVmax 7.3 (SUVmax of liver 4.1, HU of the adrenal 28). This was assumed to be an adrenal metastasis from his lung cancer which had also progressed elsewhere. FDG, fluorodeoxyglucose; HU, Hounsfield unit; PET, positron emission tomography; SUV, standardized uptake value.



without a corresponding CT abnormality in four patients who had all received a paravenous injection of FDG.

This finding has been described as the: "hot-clot artefact", where there is agglutination of FDG by erythrocytes during FDG injection. This causes occlusive plugs/microemboli in the pulmonary arterial system and create focal FDG uptake with high SUVs. Microemboli can occur from blood aspiration into the injector, paravenous injection and possibly high speed injection. They are typically peripheral with visually and quantitatively high FDG uptake.³⁵

Due to the nature of the hot-clot artefact, these papers have concluded these foci do not require further follow up.

FDG uptake within CT evident solitary pulmonary nodule (as defined on page ii5 of British Thoracic Society guidelines)³⁶ has been discussed in published guidelines, with increasing intensity of uptake increasing the likelihood of malignancy.^{36,37} The Herder risk prediction model³⁸ could be used (*e.g.* with online tools)³⁹ to further evaluate its risk of malignancy.

Figure 4 demonstrates an FDG avid lung nodule and a pulmonary focus of FDG without CT correlate.

Summary and suggestions

Incidental foci of FDG in the lungs without a CT correlate can be assumed to be a microembolus of FDG and do not require follow up.

An incidental (*i.e.* highly unlikely to be metastatic) pulmonary nodule associated with increased FDG uptake could be referred to a lung MDT or followed up with CT depending on its probability of malignancy as predicted by the Herder prediction model.

Oesophagus and Gastro-Oesophageal junction

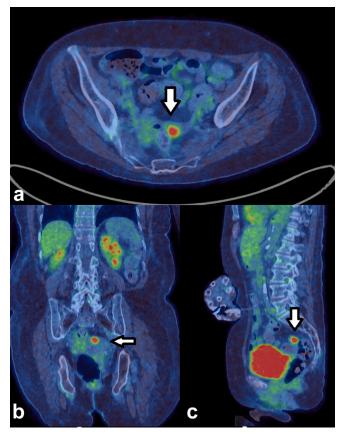
There are no relevant studies looking at incidental uptake within the oesophagus; however; physiological increased uptake at the gastro-oesophageal junction (GOJ) is well-recognized and differentiating benign from malignant uptake at this site can be difficult.⁴⁰ Knowledge of the normal range of uptake can be helpful which has been reported as SUVmax of 1.0–8.4 in 546 patients without CT abnormalities who did not develop GOJ cancer.⁴¹ It should be noted that patients in this paper were scanned from 2002 to 2004 and so the normal range of SUVmax may now be higher.

Stagg et al⁴² compared the uptake at the GOJ with the results of endoscopy performed within 6 months. They found the mean SUVmax in patients with normal findings at endoscopy (n = 151) was 2.1 vs 6.7 for those with oesophageal malignancy (n = 34), 2.5 for those with oesophagitis (n = 21), 2.4 for those with Barrett's oesophagus (n = 8) and 3.5 for those with other non-malignant disorders (n = 5). They determined that a SUVmax \geq 3.5 predicted a necessity for endoscopy with a positive-predicted value (PPV) of 79% and a SUVmax \leq 2.2 had a negative-predicted value (NPV) of 86%.

A different study⁴³ compared the characteristics of early malignant (Barrett's oesophagus, Tis, T1 and T2 adenocarcinomas) and benign oesophageal lesions. This found early malignant lesions had significantly higher FDG uptake on visual scoring, eccentricity and focality compared with benign lesions and that eccentricity and focality were better predictors than intensity.

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Figure 8. Incidental uptake in the endometrium. An 80-year-old female had a PET/CT to investigate for a paraneoplastic cause of her large fibre sensory neuropathy. Intensely increased uptake (SUVmax 12.4) was present in the endometrial cavity, shown on the axial (a) coronal (b) and sagittal images (c) which was shown to be grade 1 endometrioid endometrial carcinoma on biopsy. Although this was thought unlikely to be inducing a paraneoplastic neuropathy, the patient had a hysterectomy but without any improvement in her symptoms, it was, therefore, an incidental finding. PET, positron emission tomography; SUV, standardized uptake value.



Summary and suggestions

There is evidence that when uptake is more eccentric and focal⁴³ and more intense at the GOJ (*e.g.* SUVmax >6)⁴² it is more likely to be malignant. Foci with these characteristics should, therefore, be routinely referred for endoscopy.

Figure 5 demonstrates presumed physiological uptake at the GOJ *vs* an oesophageal cancer extending to the GOJ.

See Table 2 for a summary of the evidence and suggestions regarding incidental FDG uptake in the thorax.

ABDOMEN AND PELVIS

Stomach

Similar to oesophagus, there were no studies directly analysing the significance of focal incidental gastric uptake. However, Le Roux et al⁴⁴ assessed the diagnostic utility of gastric distension in FDG PET/CT in 39 patients with previously identified suspicious incidental,

focal, gastric uptake. Of these, 14 patients had persistent suspicious uptake, of these 10 had cancer (6 lymphoma, 2 melanoma metastases, a pancreatic serosal metastasis and a primary gastric adenocarcinoma) and the remaining 4 had benign pathology. Incidental focal gastric uptake has, therefore, been shown to represent gastric cancer⁴⁴ but the true incidence is unknown. Providing evidencebased suggestions for incidental uptake within the stomach is, therefore, not possible.

Colon

A systematic review and meta-analysis of incidental focal colonic uptake⁴⁵ found that, of 89,061 patients evaluated by FDG PET or PET/CT, the pooled prevalence of incidental colonic uptake was 3.6%. Of these, approximately one-third (n = 1044) underwent colonoscopy or histological examination (a presumed selection bias of more suspicious appearing foci). The pooled risk of malignant or premalignant lesions was 68% [95% CI (60–75%)]. There was a significant overlap in average SUV between malignant, premalignant and benign focal uptake.

The largest single-site study published to date⁴⁶ of 7300 patients found a prevalence of incidental focal colonic uptake of 5.5%. Of these, 60% went on to have colonoscopy. The authors listed reasons why patients did not have colonoscopy of which 14% were because the uptake was described as "probably physiological". 53% of patients had a benign cause for the uptake, 37% had an adenoma and 10% adenocarcinoma. The median SUVmax (and interquartile range) for the benign group was 8.2 (5.9–10.1), for the advanced adenomas 9.7 (7.2–12.6), the non-advanced adenomas 8.3 (6.1– 10.5) and the adenocarcinomas 16.6 (12–20.8). Using an SUVmax >11.4 as a cut off to distinguish adenocarcinoma from other aetiologies, the AUC of the ROC was 0.868 with a sensitivity of 80%, specificity of 82%, PPV 34% and NPV 98%.

Figure 6 demonstrates an incidental focus of FDG within the sigmoid colon.

Summary and suggestions

Focal colonic uptake represents adenoma or adenocarcinoma in up to 47^{46} –68%⁴⁵ of patients with significant overlap in the range of SUVmax between the different aetiologies. Based on this, we recommend that all patients with focal colonic uptake and SUVmax >5.9 have colonoscopy or virtual colonoscopy unless there is sufficient reason not to such as advanced illness or recent colonoscopy. This should be performed urgently if SUVmax >11.4 as the likelihood of malignancy is higher. There is no good evidence on the significance of focal colonic uptake with SUVmax <5.9 and, for these foci, decisions should be made on a case by case basis.

Pancreas

We could find only one publication on incidental pancreatic uptake, a letter to the editor.⁴⁷ This reported incidental pancreatic uptake in 14 of 2868 patients (0.49%), of whom 11 had widespread FDG avid lesions in liver, bone, lungs and lymph nodes from lymphoma or metastases. Pancreatic cancer was diagnosed in two and unclear in one patient. Within the pancreas, intensity of FDG uptake cannot reliably distinguish between different pancreatic pathologies.⁴⁸

Site of focal uptake	Evidence/when to further evaluate	Recommended form of evaluation
Pituitary gland	Foci with SUVmax > 4.1^7	Pituitary MRI and/or hormonal testing
Piriform fossa	Foci with SUVmax $\ge 4.2^8$	Referral to ENT for direct visualization
	Foci with SUVmax _I : SUVmax _C ≥ 1.8	
Palatine tonsils	Foci with SUVmax ratio between tonsils $> 1.5^{9,10}$	-
Nasopharynx	Foci with SUVmax $> 6.0^{11}$	
Oro and nasopharynx not specified above	Inadequate evidence for foci not meeting the above criteria.	
Parotid: patients without cancer	Consider referring all foci, as common benign causes usually require further evaluation and some incidental malignancies occur.	Ultrasound, MRI or referral to ENT
Parotid: patients with head and neck malignancy	Focus is much more likely to be either a metastasis from the known cancer or benign. ¹⁴ Further evaluation may well be unnecessary	
Thyroid	All foci	Ultrasound ± FNA

Table 1. Summary of evidence-based suggestions for further evaluation of incidental FDG uptake in the head and neck^a

^aLimitations in SUV reproducibility and individual patient characteristics, particularly other life-limiting comorbidities and patient choice, should be taken into account when using this evidence.

ENT, ear, nose and throat; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; SUV, standardized uptake value.

Summary and suggestions

From the limited data, we, therefore, recommend that foci which are not most likely part of a more widespread disease process (*e.g.* lymphoma or metastatic cancer) are further investigated, with either CT or MRI.

Liver

We could find no articles assessing the significance of focal incidental hepatic uptake, although there was an article on the use of FDG PET/CT to help characterize incidental hepatic abnormalities identified via other imaging.⁴⁹ The intensity of FDG uptake is variable in both benign (*e.g.* adenomas, haemangioendotheliomas and abscesses) and malignant aetiologies (metastases and primary hepatic malignancies)^{50,51} and cannot be used to distinguish between them. Hepatocellular carcinoma in particular frequently does not demonstrate significantly increased FDG uptake ⁵⁰ but should clearly be considered as a cause of the uptake if there are signs of chronic liver disease.

Gallbladder

We could find no papers discussing incidental focal uptake in the gallbladder. Gallbladder carcinoma 52 and benign causes

(focal adenomyomatosis⁵³ and xanthogranulomatous cholecystitis)⁵⁴ have all been shown to be FDG avid. A study of 34 patients with gallbladder malignancy⁵² reported a wide variation in the SUVmax of lesions (mean SUVmax 7.92 \pm 6.25). In addition, a meta-analysis⁵⁵ showed marked heterogeneity in different studies' abilities to distinguish benign from malignant uptake.

Spleen

We could find no papers discussing incidental uptake in the spleen although temporary, focal, non-pathological FDG retention in the spleen has been described.⁵⁶ There are multiple published case reports of FDG uptake in benign splenic lesions (*e.g.* hamartoma,⁵⁷ epidermoid cyst with haemorrhage,⁵⁸ lymphangioma⁵⁹ and inflammatory pseudotumour-like follicular dendritic cell tumour⁶⁰) Lymphomatous or metastatic splenic involvement is also possible.

Kidney

We could find no papers focussing on incidental renal uptake of FDG. However, Kochhar et al wrote a paper on the role of FDG PET/CT in imaging of renal lesions.⁶¹ Useful conclusions from this paper are that angiomyolipomas, oncocytomas and renal cell

Table 2. Summary of evidence-based suggestions for further evaluation of incidental FDG uptake in the thorax^a

Site of focal uptake	Evidence/when to further evaluate	Recommended form of evaluation
Breast	All foci	Referral to the breast team
Lung	Incidental foci without a CT correlate can be assumed to be a microembolus of FDG^{33}	No follow up required
	CT nodules demonstrating increased FDG uptake have a higher risk of malignancy ³⁷	Refer to lung MDT/lung cancer specialist or follow up with CT depending on the risk of malignancy
Oesophagus and GOJ	Foci with the following characteristics are associated with malignancy: increased focality, eccentricity ⁴³ and increased intensity of uptake (SUVmax > 6) ⁴²	Routinely refer foci with these characteristics for endoscopy

^aLimitations in SUV reproducibility and individual patient characteristics, particularly other life-limiting comorbidities and patient choice, should be taken into account when using this evidence.

FDG, fluorodeoxyglucose; GOJ, gastro-oesophageal junction; MDT, multidisciplinary team; SUV, standardized uptake value.

Site of focal uptake	Evidence/when to further evaluate	Recommended form of evaluation
Stomach	Insufficient evidence	
Colon	Refer focal colonic uptake with SUVmax > 5.9 Urgent referral if SUVmax > 11.4 ⁴⁶ No good evidence on the significance of focal colonic uptake with SUVmax < 5.9	Colonoscopy or virtual colonoscopy
Pancreas	Investigate foci which are not most likely part of a more widespread disease process, <i>e.g.</i> lymphoma or metastatic cancer	MRI or CT
Liver, gallbladder, spleen and kidney	Inadequate evidence, benign and malignant causes can be avid. Take into account patient characteristics, CT appearances and publications on CT features. ⁶²⁻⁶⁴	Ultrasound, CT or MRI
Adrenal: patients without known cancer or hormonal hypersecretion ^b	Evaluate nodules with a nodule:liver SUV max ratio > 1.8 . ⁶⁷ Consider following up other patients, <i>e.g.</i> if the SUVmax ratio is close to 1.8 or the CT features are non diagnostic.	Adrenal CT or MRI
Adrenal: patients with cancer ^b	The combination of FDG uptake ≤ liver or CT criteria: HU < 10 or macroscopic fat is highly accurate in distinguishing benign nodules from metastases ⁶⁸ An SUVmax ratio (adrenal:liver) of > 2.5 had been shown to exclude all benign nodules. ⁷⁰ Nodules not characterized by the above criteria require further evaluation	Adrenal CT or MRI
Prostate	Test all males aged > 50 Test males aged 40–50 years if the focus is peripheral, they are of black ethnicity or have affected first degree relatives.	PSA testing
Ovaries	Post-menopausal females: refer increased ovarian/adnexal uptake. Pre-menopausal females: refer ovarian uptake which is <i>not</i> occurring around midcycleor uptake at these times which is associated with concerning CT features.	Pelvic ultrasound
Uterus	Post-menopausal: refer endometrial uptake unless it has typical appearances of fibroids with low grade uptake. Pre-menopausal: Uptake occurring outside of midcycle or menstruation or fibroid related FDG uptake significantly above liver ^{79,82} should be considered for further evaluation	Pelvic ultrasound
Testis	Insufficient evidence	
Bone	Foci without CT abnormalities: insufficient evidence for patients without cancer. Consider focus as suspicious for a metastasis in patients with cancer	Consider MRI

Table 3. Summary of evidence-based suggestions for further evaluation of incidental FDG uptake in the abdomen and pelvis and bone^a

^aLimitations in SUV reproducibility and individual patient characteristics, particularly other life-limiting comorbidities and patient choice, should be taken into account when using this evidence.

^bUsing PET-CT to characterize nodules < 1 cm should be done with caution.

FDG, fluorodeoxyglucose; PSA, prostate specific antigen; SUV, standardized uptake value.

carcinoma (RCC) can all display variable FDG avidity (simple cysts are photopenic). Renal metastases are typically FDG avid.

Summary and suggestions for liver, gallbladder, spleen and kidney

There is inadequate evidence for these organs and decisions on when to further investigate will be have to be made individually depending on patient characteristics and the guidelines from the ACR white papers.^{62–64}

Adrenal

Due to adrenal morphology and the resolution of PET, identifying incidental focal adrenal uptake without an associated CT nodule is unlikely and consequently, there were no studies examining this. However, the detection of incidental adrenal nodules is common (occurring in 1.5% of CT studies performed as part of screening)⁶⁵, as is their frequency as a site of metastases. Therefore, using published evidence to help characterize, and so distinguish, incidental adrenal nodules from more significant pathology is useful. A meta-analysis revealed that FDG PET has 97% sensitivity and 91% specificity in the differentiation between malignant and benign adrenal disease (using a variety of diagnostic criteria).⁶⁶ It also stated that the specificity of FDG PET for characterizing adrenal lesions smaller than 10 mm should be considered with caution.

Tessonnier et al⁶⁷ evaluated FDG PET/CT in distinguishing benign from malignant uptake in patients with known adrenal nodules without evidence of hormonal hypersecretion or active cancer and when CT or MRI had been inconclusive. They reported that the use of 1.8 as the threshold for nodule/liver SUVmax ratio demonstrated 100% sensitivity and specificity in 41 adrenal masses of which there were 12 malignant tumours, 17 benign tumours and 12 tumours classified as benign on follow-up.

Boland et al⁶⁸ reported that qualitative FDG uptake was the most accurate way to distinguish benign from malignant nodules in 165 adrenal lesions in 150 patients with known cancer when uptake moderately or significantly increased compared to liver was considered malignant and uptake less than or equal to liver was considered benign. They also incorporated CT appearances where an unenhanced HU of <10 (previously shown to be a useful cut-off)⁶⁹ or the presence of macroscopic fat (to identify myelolipomas) was used to establish benignity. By combining unenhanced and qualitative CT and PET data, the analysis vielded a sensitivity of 100% for the detection of malignancy, a specificity of 99%, a PPV of 93%, a NPV of 100% and an accuracy of 99%. Conversely, for the detection of benignity, the sensitivity, specificity, PPV, NPV and accuracy were 99, 100, 100, 93 and 99%, respectively. However, some benign nodules are known to be moderately FDG avid and Brady et al⁷⁰ investigated patients with known or suspected lung cancer and found that SUVmax ratio (adrenal:liver) of >2.5 excluded all FDG avid benign adrenal nodules.

Figure 7 demonstrates a presumed benign small adrenal myelolipoma and a presumed early adrenal metastasis from lung cancer.

Summary and suggestions for distinguishing benign and malignant adrenal nodules

Patients without known cancer or hormonal hypersecretion: a nodule:liver SUVmax ratio >1.8 should have further evaluation either with CT or MRI. Given the small sample size of the study from which this recommendation is taken,⁶⁷ it would be reasonable to follow up other patients with interval imaging, *e.g.* if the SUVmax ratio is close to 1.8 and the CT features cannot diagnose an adenoma or myelolipoma.

Patients with cancer: the combination of PET (uptake less than or equal to liver) or CT criteria (HU <10 or macroscopic fat) to identify benign nodules had excellent diagnostic accuracy⁶⁸ but not 100% sensitivity or PPV. An SUVmax ratio (adrenal:liver) of >2.5⁷⁰ excluded all benign nodules.

Using PET/CT to characterize nodules <1 cm should be done with caution.

Prostate

A systematic review and meta-analysis of incidental focal prostatic uptake included 47,925 patients.⁷¹ The prevalence of incidental prostatic uptake was 1.8%, of these 444 were further evaluated and 17% had malignancy. There was a trend to higher SUVmax in the malignant group but this was not statistically significant. Peripheral uptake but not presence or absence of calcification was a predictor of malignancy. The predictive nature of peripheral uptake is to be expected because prostate cancer is more likely to arise in the peripheral zone and because a central focus could represent urine in the urethra. A more recent study⁷² of 20,422 patients found 1.4% of scans had focal prostatic uptake. Only 22.5% of these patients had further investigations of which 55% had malignancy, again SUVmax between benign and malignant uptake was not statistically significantly different. It should also be noted that prostate cancer is very strongly correlated with age, in the UK, the age-specific incidence rates were 3/100,000 for males aged 40-44 years, 17/100,000 for males aged 45-49 years and with a rapid increase in rates with increasing age over 50 years.⁷³ Other important risk factors for prostate cancer are being of black ethnicity^{74,75} and having one or more first degree relatives affected.⁷⁶

Summary and suggestions

From the evidence above, males aged >50 years with focal prostatic uptake should have PSA testing and males aged 40–50 years should have PSA testing if the focus is peripheral, they are of black ethnicity or have affected first degree relatives.

Uterus and ovaries

Interpreting the significance of possible incidental ovarian and uterine uptake requires an understanding of normal physiological uptake. In pre-menopausal females, there is increased physiological ovarian and endometrial uptake during the late follicular and early luteal phase of the menstrual cycle and slightly more intense physiological endometrial uptake in the first few days of the menstrual cycle.^{77,78} Increased physiological uptake does not occur in post-menopausal females,^{77,78} the mean endometrial SUV in postmenopausal patients not receiving hormonal therapy was 1.7.⁷⁸

Uterine leiomyomas (fibroids) are present in 25-30% of pre-menopausal females,^{79,80} therefore an understanding of normal fibroid uptake is also required. They have been reported as showing increased FDG uptake in 10.4% of pre-menopausal females and in 1.2% of post-menopausal females.⁸¹ In females who had more than one PET scan, uptake within the leiomyoma disappeared or newly appeared, therefore newly emerging uptake does not necessarily mean malignant transformation. In pre-menopausal females, uptake is usually at a similar level to liver, however, in 3 out of 22 proven leiomyomas uptake was greater than liver.⁷⁹ Kitajima et al reported the SUVmax of 61 leiomyomas as 2.34 (range 1.59–5.15)⁸² and that the SUVmax of degenerated leiomyomas (mean 2.89, range 1.59-5.15) was significantly higher than that of non-degenerated leiomyomas (mean 2.17, range 1.61-4.44). Zhao et al⁸³ showed that FDG uptake is significantly higher in uterine sarcomas than leiomyomas with an SUVmean of 2.5 (range 1.0-5.8) in leiomyomas (n = 33) and 5.5 (range 1.8–12) in sarcomas (n = 14), they did not report on SUVmax. Their study only analysed females with suspicious uterine findings, either clinically or on MRI/ultrasound scan, which likely explains the higher SUV in the leiomyomas than that reported in the other study.

In terms of interpreting incidental uptake, we could find no studies that examined the significance of uptake which was neither physiological nor fibroid related. FDG PET/CT cannot accurately discriminate between benign and malignant ovarian and uterine pathologies.^{78,84,85} It is also worth noting that that the incidence of uterine cancers significantly increases with age, occurring at a rate of less than 7/100,000 in females under 45 but rising relatively steeply after that.⁸⁶

BJR

Figure 8 demonstrates incidental uptake within the endometrium of a post-menopausal female.

Summary and suggestions

- Post-menopausal females: increased ovarian/adnexal uptake or uterine uptake which does not have PET/CT findings consistent with leiomyomas, should be further evaluated with pelvic ultrasound scan or MRI.
- Pre-menopausal females:
- Ovarian uptake which is not occurring around midcycle should be further imaged with ultrasound.
 - Endometrial uptake in a normal-sized uterus at midcycle or menstruation should be considered physiological. Leiomyomas are common and usually show intensity of FDG uptake similar to liver.^{79,82} Uterine FDG uptake above this level or occurring outside of midcycle or menstruation should be considered for further imaging, although uterine malignancies in females under 45 are rare.

Testis

We could find no studies which examined the significance of incidental, non-physiological testicular uptake, although abnormal increased uptake within the testicles due to lymphoma has been shown to not always be associated with CT abnormalities.⁸⁷ There is, therefore, insufficient data to make evidence-based suggestions. If testicular pathology is suspected it should be further evaluated with testicular ultrasound.

Bone

We could find no studies that analysed incidental, focal skeletal uptake without associated CT abnormalities. However, it should be noted that FDG PET/CT has a high sensitivity for the diagnosis of bone metastases, reported as 89.7%, similar to MRI and better than CT and bone scintigraphy.⁸⁸ It has also been shown that, of 31 lesions with positive findings at PET and negative findings at CT, 19 were malignant giving a PPV of 61%.⁸⁹

Summary and suggestions

Focal uptake within bone, without CT abnormalities, in patients with known cancer should be considered suspicious for a bone metastasis. Due to the lack of evidence, we are unable to suggest evidence-based guidelines for focal skeletal FDG uptake without a CT abnormality in patients without a known cancer. In this circumstance, MRI may be helpful to evaluate for the presence and nature of soft-tissue abnormalities within the bone. Bone single photon emission CT-CT is less likely to be helpful if there are no detectable abnormalities on CT to aid the interpretation of the aetiology of bone tracer uptake.

See Table 3 for a summary of the evidence and suggestions regarding incidental FDG uptake in the abdomen, pelvis and bone.

CONCLUSION

Interpreting incidental FDG uptake on PET/CT can be challenging, However there is published evidence about its aetiology; parameters to distinguish different causes of uptake and the CT can provide further useful diagnostic information. These findings, together with knowledge of the patient's risk factors, allows evidence-based suggestions to be made and is likely to lead to improved patient management. However, SUVs can vary between patient, institution and over time and this needs to be taken into account when using the evidence. Finally, for some organs, there is very little evidence on the significance of incidental uptake and these areas would benefit from further research.

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