
Article:
Scarsbrook, AF and Barrington, SF (2016) PET-CT in the UK: Current status and future directions. Clinical Radiology, 71 (7). pp. 673-690. ISSN 0009-9260

https://doi.org/10.1016/j.crad.2016.02.023

PET-CT in the United Kingdom – Current Status & Future Directions

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No grants supported this work

Abstract

Positron emission tomography-computed tomography (PET-CT) has taken the oncological world by storm since being introduced into the clinical domain in the early 21st century and is firmly established in the management pathway of many different tumour types. Non-oncological applications of PET-CT represent a smaller but steadily growing area of interest. PET-CT continues to be the focus of a large number of research studies and keeping up-to-date with the literature is important but represents a challenge. Consequently guidelines recommending PET-CT usage need to be revised regularly to encompass new developments. The purpose of this article is two-fold: firstly it provides a detailed review of the evidence-base underpinning the major uses of PET-CT in clinical practice which may be of value to a wide-range of individuals including those directly involved with PET-CT and to a much larger group with limited exposure but for whom a précis of the current state-of-play may help inform other radiology and multidisciplinary team (MDT) work; the second purpose is as a companion to revised guidelines on Evidence-Based Indications for PET-CT in the UK (being published concurrently) providing a detailed commentary on new indications with a summary of emerging data supporting these additional clinical uses of the technique.

Keywords

Positron emission tomography-computed tomography (PET-CT); Fluorine-18; fluorodexoyglucose (FDG); Non-FDG PET tracers; Gallium-68

Introduction

The introduction of positron emission tomography-computed tomography (PET-CT) into the clinical domain over a decade ago was a technical evolution and rapidly drove an imaging revolution with a proliferation of scanners worldwide over the next few years. In 2005 the Royal College of Radiologists and the Department of Health published a Framework for the Development of Positron Emission Tomography (PET) Services in England which was intended to guide commissioners and potential providers of services on evidence-base, number of scanners likely to be required, workforce and training issues, capital and revenue costs and further research and evaluation[1]. At the time of the publication it was estimated that approximately 11,000 PET-CT scans were being undertaken per annum in England. A subsequent letter was sent to Cancer Network Directors and Specialised Services Commissioners from Professor Sir Mike Richards, National Clinical Director for Cancer and End of Life Care in January 2010 documenting the success of implementation of the framework with a rise in annual demand to approximately 40,000 scans in England equating to about 800 scans per million population. The letter also provided a table listing estimates of likely demand for the key indications and a rise to 1000 scans per million developed by an Expert Consensus Group (UK PET-CT Advisory Board)[2]. This capacity was at the lower end of comparative PET-CT demand in other European countries at the time. Data from the UK and Ireland suggests that PET-CT demand has grown by 14% per annum on average since 2008 but despite this continues to lag behind European comparators for PET-CT scans per million (range in 2012 of 1,257 (England) to 5,144 (Italy) scans per million population)[3].

In England, PET-CT is funded centrally by NHS England and the latest commissioning statement was published in August 2015[4]. This is based on Intercollegiate Evidence Based PET-CT guidelines published by the Royal College of Physicians and Royal College of Radiologists in 2013, which contains a bibliography with supporting evidence for each indication[5]. PET-CT remains the subject of intensive research and the evidence-base continues to expand rapidly. By way of example, a PubMed search for new articles published containing the keyword "positron emission tomography" in the period from early 2013 to late 2015 listed over 6500 abstracts. Accordingly guidelines need updating regularly to incorporate new and emerging clinical applications. This article accompanies a new version of the Intercollegiate PET-CT guidelines, which follows an extensive literature review and incorporates an expanded range of indications supported by recent literature (add ref details once known).

The purpose of this article is to provide a commentary on this important new guidance, review the evidence supporting the more common uses of PET-CT in the UK, highlight new changes since the previous version of the guidelines and discuss the literature underpinning the new indications. It is hoped that this will be helpful not only to those working directly in the PET-CT field but importantly to the many who may not be closely involved in reporting but need working knowledge for general radiological, cancer imaging and multidisciplinary team (MDT) work.

Evidence underpinning common uses of PET-CT

A) Oncology Applications of FDG PET-CT

By far the most commonly used PET tracer in clinical practice is Fluorine-18 fluorodeoxyglucose (FDG). The oncological areas in which FDG PET-CT is currently funded in England comprise a wide-range of clinical indications including staging of patients with potentially radically treatable head and neck, lung, oesophageal, colorectal, hepato-biliary, gynaecological and musculoskeletal cancers. In addition funding is available for selected patients with breast cancer, pleural malignancy, thymic tumours, thyroid carcinoma, bladder, testicular and renal cancers, penile cancer, myeloma, suspected paraneoplastic syndromes, carcinoma of unknown primary and rare childhood tumours. Funding is also available for a wider range of clinical applications in head and neck cancer, lymphoma, hepato-pancreato-biliary cancers, cervical cancer and melanoma. Funding in other countries is variable[6,7,8].

There is strong evidence that PET-CT has superior diagnostic accuracy to conventional imaging in staging and restaging of most cancers[9]. A National Oncologic PET Registry (NOPR) was developed in the United States (US) in 2006 in response to a proposal by US healthcare funders to expand coverage for FDG PET-CT. Funding was obtained if the patient's referring clinician and the scan provider submitted data to a clinical registry to assess the impact of FDG PET-CT on patient management. Data from over 300,000 patients was collated over several years providing evidence for a highly significant impact on patient management across a wide variety of cancers with a management change in 30% of all patients regardless of study indication[10,11]. The NOPR FDG PET-CT registry closed in 2013 due to overwhelming evidence of positive impact on patient management. Recently, a range of randomized controlled trials have evaluated whether treatment stratification based on PET-CT improves patient outcome in lung cancer, lymphoma and colorectal malignancy, a number of ongoing trials are evaluating other tumour types[12]. There is increasing evidence that PET-CT is cost-effective in a variety of different oncological settings by guiding appropriate patient management, which in turn reduces subsequent healthcare expenditure by avoiding futile treatments[8].

Five different cancer types currently form the bulk of oncological FDG PET-CT activity in the UK: non-small cell lung cancer (NSCLC); oesophageal cancer; lymphoma; colorectal cancer; head and neck malignancy. A recent study from America reported that PET-CT use in these 5 malignancies grew rapidly with a 14.6% - 19.9% annual increase in usage of PET-CT imaging depending on cancer type[13]. The major funded indications for use of PET-CT in each of the 5 most common tumour types and key supporting evidence are considered below. Multiple other oncological indications are funded but individually account for relatively small numbers of cases annually in the UK.

Lung Malignancy

The use of FDG PET-CT for staging patients being considered for radical treatment of NSCLC is one of the indications with the strongest evidence-base. A pivotal randomized trial published in 2002, the PLUS study, showed a significant reduction in the number of futile thoracotomies with the addition of FDG PET to the diagnostic

algorithm in patients with potentially operable NSCLC due to the superior diagnostic accuracy of FDG PET and ability to detect occult metastatic disease[14]. Cost-effectiveness of FDG PET has also been demonstrated in this setting[15,16]. The use of FDG PET-CT is now recommended in the staging of patients considered to be candidates for radical treatment options including surgery and radical chemo-radiotherapy. National Institute for Health and Care Excellence (NICE) guidance recommends PET-CT in the assessment of patients with mediastinal nodes <1cm or between 1–2 cm on CT and patients with equivocal lesions that might represent metastases such as adrenal enlargement[17].

The use of FDG PET for assessment of solid solitary pulmonary nodules has also been extensively studied. Two meta-analyses reported a high diagnostic accuracy of FDG PET in this clinical scenario with pooled sensitivity (93.9 – 95%) and specificity (82-85.8%) in a series of almost 1500 nodules[18,19]. Recent British Thoracic Society (BTS) Guidelines on the investigation and management of pulmonary nodules advocate the use of nodule-risk calculators in assessment of solid nodules > 8 mm in diameter[20]. Only patients with nodules with a probability of malignancy >10% using the Brock University calculator[21] are recommended to undergo FDG PET-CT with others undergoing CT surveillance. The BTS guidelines advocate using a four-point qualitative scale to classify nodule FDG uptake ranging from absent through faint (less than or equal to mediastinal blood pool (MBP)) moderate (above MBP) and intense (markedly greater than MBP)[22]. Risk should then be re-assessed using the Herder clinical prediction model[23], which had the highest accuracy in a recent validation study assessing four prediction models of malignancy risk in pulmonary nodules in a UK population[24]. Subsequent patient management is guided by risk with CT surveillance in those with a risk of < 10%, treatment in those with a risk of > 70% and biopsy in those inbetween[20].

There is a paucity of data on the efficacy of FDG PET-CT in the evaluation of sub-centimetre nodules (< 8 mm) and the recent BTS guidelines advocate use of interim CT follow-up in newly detected nodules >5 and < 8 mm as the influence of partial volume effect on FDG uptake is substantial in small nodules and consequently sensitivity is inadequate[20]. FDG PET also has a lower sensitivity and a higher false negative rate in sub-solid nodules[25,26].

Oesophageal Cancer

There is extensive evidence that FDG PET-CT is clinically effective in guiding optimal patient management in potentially resectable oesophageal carcinoma. A large prospective multi-centre trial from Canada evaluated a cohort of 491 patients with potentially operable oesophageal cancer and the use of PET-CT for pre-op staging led to clinically important changes in stage in 188 patients (24%) with the majority (21.8%) being upstaged by detection of unsuspected distant disease[27]. A recent UK study involving over 800 patients undergoing pre-treatment staging with FDG PET-CT reported a similar impact with altered management following PET-CT in 23%[28]. The use of PET-CT in this setting prevents patients with incurable disease receiving futile surgery.

Some oesophageal cancer patients with locally advanced disease derive a survival benefit by undergoing pre-operative neoadjuvant chemotherapy or chemo-

radiotherapy (CRT)[29]. FDG PET-CT can be used as a non-invasive method of assessing therapy response (or lack of) either during or at the end of neoadjuvant treatment[30] (**Figure 1**). A large prospective trial (MUNICON) assessed the use of FDG PET-CT performed after 2 weeks of neoadjuvant chemotherapy for detecting non-responders who then proceeded directly to surgery, responders continued the full course of chemotherapy prior to treatment, median event free survival was significantly higher in the metabolic responder group[31]. A follow-on study (MUNICON II) evaluated if metabolic non-responders had improved outcome with the addition of salvage CRT but event free and overall survival remained significantly lower in this group despite treatment adaption[32]. It is important to note that it can be challenging to accurately interpret studies performed during and shortly after CRT because treatment related oesophagitis or ulceration may mimic viable tumour[33,34]. Use of FDG PET-CT to assess therapy response at the end of neoadjuvant treatment has been more extensively studied and a recent systematic review reported that this was a powerful predictor of subsequent patient outcome[35]. A number of studies have demonstrated that a re-staging FDG PET-CT at the end of neoadjuvant treatment is a prudent approach to avoid non-curative surgery in patients who have developed interim metastatic disease, which can occur in 8-17%[36,37].

A recent meta-analysis has confirmed the superior efficacy of FDG PET-CT compared to conventional imaging in detection of recurrent oesophageal carcinoma with a very low false negative rate[38].

Lymphoma

There is a large body of evidence underpinning the use of FDG PET-CT in the evaluation of patients with lymphoma. Recently international guidelines have been revised to take account of the increasing literature on the efficacy of FDG PET-CT in patients with lymphoma[39]. FDG PET-CT should now be used routinely to stage FDG-avid lymphomas (Hodgkin Lymphoma (HL) and most Non-Hodgkin Lymphoma (NHL)) prior to treatment, as it is more sensitive than CT particularly for detection of extra-nodal disease39. It is not routinely recommended for staging of lymphomas with low-grade FDG avidity but can be useful to determine the extent of disease and identify a suitable biopsy site in patients with low-grade lymphoma with suspected high-grade transformation[40,41].

FDG PET-CT is now also the standard of care for end of treatment remission assessment in FDG-avid lymphoma and classification using an internationally recognized five-point scale (Deauville criteria) should be used for response assessment[42,43,44]. If an interim PET-CT scan has shown complete metabolic response end of treatment scanning is not required.

Interim FDG PET-CT (iPET) to assess treatment response and exclude disease progression is increasingly being used in patients with HL and aggressive NHL and has been used to guide treatment adaption in a range of clinical trials[45,46,47]. The current international imaging guidelines in lymphoma advise against treatment adaptation outside of the clinical trial setting unless interim PET-CT shows clear evidence of disease progression[48]. The field is however rapidly evolving, with two studies, published since the recent guidelines indicating that patients with early stage HL who achieve a complete metabolic response on PET following 2-3 cycles of

ABVD chemotherapy have good outcomes with the use of short-course chemotherapy alone[45,46]. Recent guidelines from the British Committee on Standards in Haematology recommend that in patients with non-bulky stage IA or IIA HL, as there may be longer term risks for some patients treated with radiotherapy (RT), 'clinicians and patients may prefer to treat without radiotherapy' but decision making 'should involve discussion with a radiation oncologist to be aware of the balance of risks between RT and additional cycles of chemotherapy'[49].

In the end-of-treatment setting, a prospective trial from Germany demonstrated that patients with advanced HL and a residual 'PET-negative' mass treated with BEACOPP chemotherapy do not require consolidation radiotherapy[50]. No evidence currently exists to suggest that RT can be safely omitted in advanced stage patients treated with ABVD chemotherapy who have residual tissue on CT that is PET-negative. It is important to note that for these trials exploring the potential to avoid RT, the mediastinal threshold was used for the definition of complete metabolic response (CMR, equivalent to Deauville score 2).

Recently presented data from the UK RATHL trial in advanced HL[51] and the European H10 study in early stage HL[52] suggest that for iPET positive patients treated with ABVD, treatment escalation to BEACOPP may offer survival advantages. The RATHL study also suggested that patients with CMR after 2 cycles of ABVD may have bleomycin safely omitted for subsequent cycles with no adverse impact on outcome and reduction in toxicity. The publication of these data is awaited but is already influencing practice. In these trials, the liver threshold was used for the definition of CMR (equivalent to Deauville score 3).

PET-CT has a valuable role in the assessment of symptomatic patients with suspected relapse of FDG-avid lymphomas but evidence suggests that the routine use of surveillance PET-CT in asymptomatic individuals is not cost-effective and the high false-positive rate may lead to additional unnecessary investigations, radiation exposure and patient anxiety[39,53,54,55]. PET-CT can be used to assess response to second line and subsequent treatments for FDG-avid lymphoma in the same way that it is employed for monitoring efficacy to initial therapy. FDG PET-CT has proven utility in evaluation of patients with relapsed HL[56] and high-grade NHL[57] after salvage chemotherapy and prior to high-dose chemotherapy and autologous stem-cell transplant to assess remission status and residual volume of disease and suitability for transplant.

Colorectal Cancer

The main indications for use of FDG PET-CT in patients with colorectal carcinoma are in staging or re-staging of patients with potentially operable metastatic disease to guide optimal management by identifying patients with more extensive disease who will not benefit from surgery[58] (**Figure 2**) and for detection of recurrent disease[59]. A randomized controlled trial conducted in the Netherlands[60] evaluated the cost-effectiveness of FDG PET-CT in pre-operative assessment of patients with liver metastases being considered for liver resection. 150 patients were studied and 75 underwent FDG PET-CT in additional to conventional imaging work-up. Change in management, futile laparotomy rate and all relevant health care consumption was prospectively evaluated. Diagnostic performance increased and the futile laparotomy

rate reduced by 38% in the PET arm. Additional costs of PET were compensated by a reduction in futile surgery. Net monetary benefit analysis showed savings over a relevant range of willingness to pay for a quality adjusted life year (QALY)[60]. A recent meta-analysis of > 1000 patients with colorectal liver metastases has confirmed that FDG PET-CT is highly accurate in the pre-operative setting and results in a change in patient management in 24% of patients[61].

There are a number of newer applications of FDG PET-CT in colorectal carcinoma, which relate to treatment response assessment and these have been included in the latest version of the guidelines (add ref details once known) and more detail is provided below in the new indications section of this manuscript. Several studies have shown that FDG PET-CT has an accuracy of > 90% in the detection of recurrent colorectal carcinoma[62]. In particular it is more sensitive than CT in detecting lymph node recurrence and may detect occult metastatic disease[63].

Head and Neck Malignancy

FDG PET-CT has a firmly established role in staging of locally advanced head and neck squamous carcinoma (HNSCC) prior to definitive treatment, in the assessment of selected patients with unknown primary head and neck tumours and for evaluation of disease response following (chemo) radiotherapy.

A multi-centre prospective study conducted in Belgium evaluated 233 patients with locally advanced HNSCC who underwent FDG PET-CT in addition to conventional imaging work-up prior to treatment[64]. PET-CT accurately altered staging in 47 patients (20%) mainly nodal staging. In the era of intensity-modulated radiotherapy (IMRT), altered nodal staging would affect delineation of gross tumour volume with subsequent effect on clinical target volume. A subsequent meta-analysis has confirmed the diagnostic accuracy of FDG PET-CT in staging of HNSCC[65].

In the setting of node-positive HNSCC with unknown primary site prospective analysis suggests FDG PET-CT detects the primary site in approximately 30% of cases where CT and/or MRI is negative or inconclusive[66]. As the yield of FDG PET-CT is relatively low a streamlined approach for optimal utility is advocated with cross-sectional imaging review by a subspecialty Head & Neck Radiologist prior to considering FDG PET-CT. A recent study evaluated the cost-effectiveness of FDG PET-CT in the assessment of cancer of unknown primary in the head and neck and found that it was a cost-effective method in patients with nodal disease confined to one side of the neck but the effectiveness was less certain in more extensive nodal disease[67].

There is now extensive evidence supporting the use of FDG PET-CT treatment response assessment in HNSCC and a negative PET-CT performed 3 months following completion of radiotherapy has a very high negative predictive value, is highly suggestive of absence of disease[68] and can reduce the rate of unnecessary neck dissection[69]. Conversely low-grade residual tracer uptake on a post-treatment response assessment scan is more indeterminate and may reflect inflammatory activity or residual disease[70]. An interval PET-CT scan may then assist in differentiating inflammation from residual disease[71] (**Figure 3**). A recent large study of 362 patients from Australia reported the safety and cost-effectiveness of a less

intensive clinical follow-up strategy in patients with complete metabolic response on a 3 month post-treatment PET-CT with reduction in frequency of follow-up from 3 to 6 months with no apparent clinical detriment and reduced costs[72].

B) Non-Oncology Applications of FDG PET-CT

FDG PET-CT is increasingly utilized in selected patients with non-oncological conditions including neurological applications and various inflammatory and infective conditions where conventional imaging has been negative or indeterminate.

Neurological applications

There are two neurological applications of FDG PET-CT funded by NHS England. The first is for pre-surgical assessment of highly selected patients with epilepsy who have medically refractory complex partial seizures and in whom MRI and electroencephalogram (EEG) have not confidently localized the epileptogenic focus. A number of studies have shown that the use of inter-ictal FDG PET-CT in this patient cohort may detect the epileptogenic focus as an area of hypometabolism, which is often spatially concordant with EEG abnormalities[73]. A meta-analysis of published studies[74] and a subsequent cost-effectiveness assessment[75] lend further support to this indication.

The other funded neurological application of FDG PET-CT is for evaluation of carefully selected patients with cognitive impairment and neurological signs suggestive of dementia with diagnostic uncertainty regarding the specific type of dementia following conventional work-up. FDG PET has a reported sensitivity of up to 94% and specificity of up to 86% for diagnosis of Alzheimer's disease (AD) typically manifesting with a characteristic pattern of cortical hypometabolism within the temporal and posterior parietal lobes bilaterally[73] (**Figure 4**). FDG PET has recently been reported to be significantly superior to perfusion SPECT in the differential diagnosis of dementia in a multi-centre trial conducted in the UK[76]. Other frequently encountered disorders including fronto-temporal dementia and dementia with Lewy bodies often have characteristic patterns of altered FDG metabolism although there can be both clinical and radiological overlap[77]. In this scenario, amyloid tracer brain imaging with PET-CT has the potential to distinguish between AD and other dementia sub-types and may influence patient management[78]. Currently NHS England have declined to fund this indication in the UK. A large, prospective, multi-centre trial (Imaging Dementia—Evidence for Amyloid Scanning, IDEAS) is about to start recruitment in the USA and this should help determine the clinical usefulness of Amyloid PET-CT on patient-oriented outcomes[79].

Infection and inflammation applications

FDG uptake is increased at sites of active infection or inflammation as a result of multiple factors in the inflammatory cascade[80]. NHS England currently provides funding for a range of FDG PET-CT indications in selected patients with large vessel vasculitis, sarcoidosis, vascular graft infection and pyrexia of unknown origin[4]. Interested readers are directed to a recent review article, which explores the current and emerging clinical applications of PET-CT in this area in detail and provides an overview of the evidence underpinning these80.

C) Applications of PET-CT using non-FDG tracers

There are limitations to using FDG PET-CT in some tumours either due to lack of reliable FDG uptake (e.g. prostate cancer, well-differentiated neuroendocrine carcinoma) or because the malignancy being evaluated is within an area with avid physiological FDG activity (e.g. brain tumours)[81]. There is funding in England for a range of non-FDG applications including Choline PET-CT in selected patients with prostate (and to a lesser extent hepatocellular) carcinoma, Gallium-68 labelled somatostatin receptor (SSR) PET-CT in neuroendocrine malignancy and Fluoride PET-CT in bone disorders, which are available at an increasing number of centres across the country. In addition a range of other non-FDG scans are provided at a small number of specialist centres including Rubidium-82 Chloride and/or Nitrogen-13 Ammonia PET-CT for assessment of myocardial perfusion, and Fluorine-18 dihydroxyphenylalanine (DOPA) PET-CT for neuroendocrine tumours and Carbon-11 Methionine for assessment of brain tumours and highly selected patients with parathyroid tumours[5]. The evidence underpinning the funded indications for non-FDG PET-CT in more widespread use in England is reviewed below.

Choline PET-CT in Prostatic Malignancy

Carbon-11 and Fluorine-18 labelled Choline are precursors for the biosynthesis of cellular membrane phospholipids and as such are markers of membrane metabolism and turnover, which are increased in certain tumours[82]. The use of Choline PET-CT in the assessment of patients with prostatic malignancy has been extensively studied[83]. The main indication is for assessment of patients with biochemical relapse after prior local treatment with curative intent (radical prostatectomy, radiotherapy or brachytherapy) to differentiate between local, loco-regional and systemic relapse (**Figure 5**). Current European recommendations advocate the use of Choline PET-CT in this clinical scenario if the serum PSA is > 1 ng/mL if the results would influence patient management e.g. salvage radiotherapy or prostatectomy would be performed if localized recurrence is confirmed[84]. A number of studies have evaluated how best to stratify the use of Choline PET-CT in this clinical scenario in order to increase the diagnostic utility of the technique, which even when used optimally has a detection rate of 38% (at best) for patients with a PSA of <2 ng/mL[85]. Specific patient characteristics, which increase the likelihood of a positive Choline PET-CT during the early phase of biochemical relapse include high Gleason score[86], rapid PSA doubling time (< 6 months)[87], increasing PSA level despite androgen deprivation therapy[88] or high PSA nadir after radical prostatectomy. Recent expert opinion suggests that Choline PET-CT might be optimally used to identify patients with biochemical relapse who would benefit from salvage radical prostatectomy and/or salvage lymphadenectomy but is unlikely to be clinically useful in patients with a low PSA following radical prostatectomy[89].

Choline PET-CT also has proven clinical utility for staging of selected untreated patients with prostate carcinoma and high-risk features (e.g. high serum PSA level or Gleason score) with equivocal findings on conventional imaging such as possible nodal disease where confirmation or exclusion of distant disease would directly influence patient management[90].

Gallium-68 labelled somatostatin receptor (SSR) PET-CT

The majority of neuroendocrine tumours (NETs) overexpress somatostatin receptors (SSR) on their cell membrane[91]. Indium-111 DTPA-Octreotide, a radiopharmaceutical with affinity for SSR subtypes 2 and 5 has been in widespread clinical use for imaging of NETs for several years[92]. More recently there has been a rapid growth in interest in PET tracers for evaluating NETs. Gallium-68 is produced from a Germanium-68/Gallium-68 generator and can be readily labelled with somatostatin analogues including DOTA-Tyr-3-Octreotide (DOTATOC), DOTA-NaI-Octreotide (DOTANOC), and DOTA-Octreotate (DOTATATE) with varying affinities for SSR subtypes. A recent meta-analysis reported excellent pooled sensitivity (93%) and specificity (96%) for Gallium-68 labelled SSR PET-CT with detection rates exceeding standard Octreotide scintigraphy for imaging NETs[93] (**Figure 6**).

There has been a paradigm shift where Gallium-68 SSR PET-CT is rapidly evolving as the new gold standard imaging technique for detection and characterization of NETs[94]. There is recent literature demonstrating a substantial impact of Gallium-68 SSR PET-CT on intended patient management[95] and evidence of cost-effectiveness[96]. Despite the obvious strengths, Gallium-68 SSR PET-CT has been slow to be adopted into routine clinical practice in the UK due to a combination of capital and revenue financial considerations, regulatory issues related to good manufacturing practice (GMP) as set out by the Medicines and Healthcare products Regulatory Agency (MHRA), and the relative lack of suitably qualified persons to facilitate pharmaceutical preparation at the local departmental level[97]. Efforts are afoot to address these issues, and it is hoped that in the near future Gallium-68 SSR PET-CT will be more widely available across the UK.

Fluorine-18 Fluoride Bone Imaging

Fluoride PET-CT has been evaluated against Technetium-99m MDP planar and SPECT bone scintigraphy in patients with suspected or known metastatic bone disease and multiple studies show it to be more sensitive and specific than bone scintigraphy, and the addition of CT increases specificity[98,99]. Uptake times are shorter than conventional bone scintigraphy, 15–30 minutes versus 3–4 hours, and imaging times are shorter 15–30 minutes versus 30–60 minutes but the radiation exposure is approximately double with Fluoride PET-CT compared to standard bone scintigraphy[100]. Advances in iterative CT technology may allow dose reduction and recent studies have proposed the use of dual tracer FDG and Fluoride PET-CT in selected patients with malignant disease e.g. breast carcinoma which could facilitate one-stop evaluation with reduced patient inconvenience, lower overall cost and improved scanner efficiency[101]. The main oncological indications for Fluoride PET-CT are identification of bone metastases and/or more accurate assessment of the extent of bony metastatic disease although clinical use remains limited due to the relative paucity of PET-CT scanners compared with gamma cameras, differential cost and lack of validated interpretation criteria[100].

There is established evidence of the superiority of Fluoride PET-CT for assessment of response to treatment of bone metastases in various different tumour types but the inclusion of these in routine clinical practice depends on the establishment of practical

and effective imaging protocols whose costs are acceptable to funding bodies[102]. Data from the United States has shown a significant clinic impact on patient management in the use of Fluoride PET-CT in cancer patients[103]. There is also evidence to support the use of Fluoride PET-CT in various benign applications[100] but there is a lack of cost utility data in this setting and it is likely that with the increased use of multi-slice SPECT-CT there will be an overall improvement in the accuracy of bone scintigraphy for benign disease, in particular this may be of greatest value in the assessment of various musculoskeletal disorders where there is evidence indicating superiority of SPECT-CT over standard bone scintigraphy[104].

New PET-CT Indications

PET-CT remains the subject of intensive research and the evidence base continues to expand with new applications having entered routine clinical practice in other countries since the 2013 version of the UK PET-CT guidelines. Emerging indications, which have been added to the latest guidelines and an overview of the supporting literature are provided below.

Treatment Response in Lung Carcinoma

In selected patients with stage IIIA NSCLC (single primary tumour with loco-regional nodal involvement) neo-adjuvant chemotherapy or CRT followed by surgical resection may be a potentially curative option[105]. The potential role of FDG PET-CT in assessing treatment response after neoadjuvant therapy has been investigated in several studies in variable groups of patients[106]. Despite this, treatment response in NSCLC is still largely assessed with conventional CT. A recent study from Israel evaluating the use of FDG PET-CT to assess the resectability of patients with stage III NSCLC after neoadjuvant therapy reported a very high sensitivity and negative predictive value for detecting responding nodes, which may guide optimal patient selection for curative resection[107]. Another recent study from Korea evaluating a similar patient cohort reported significantly increased relapse-free and overall survival in patients undergoing surgery who showed CMR within mediastinal nodal disease on FDG PET-CT following neoadjuvant treatment compared to incomplete responders[108].

New molecularly targeted chemotherapeutic agents such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) (e.g. Erlotinib, Gefitinib) have been added to the potential treatment options for selected patients with locally advanced NSCLC. Patients with EGFR-mutated tumours are more likely to respond to these agents but it has been reported that patients who do not have EGFR-mutations can also benefit from treatment[109]. Several recent studies have reported the use of FDG PET-CT for early response assessment in patients with NSCLC undergoing EGFR-TKI therapy, which can be performed early in the treatment course and is highly effective in defining patients who are responding to treatment, which correlates with subsequent clinical response and survival and conversely those who are not responding when unnecessary side-effects and further costs can be avoided by stopping treatment[110,111,112].

Treatment Response in Colorectal Carcinoma

For some time there has been interest in the potential use of FDG PET-CT to assess response to neoadjuvant CRT in patients with locally advanced rectal cancer (LARC) in order to stratify patients for further treatment based on whether or not they have had a metabolic response[58]. A prospective study from Spain correlated metabolic response on post treatment FDG PET-CT with tumour regression grade (TRG), disease–free and overall survival, in patients with LARC who underwent neoadjuvant chemotherapy and subsequent total mesorectal excision[113]. The study showed a strong correlation between metabolic response and TRG and a significantly higher 5-year disease-free and overall survival in patients showing > 65% reduction in SUV_{max} on the post-treatment PET-CT (compared to baseline). A large prospective study (n = 181) comparing restaging accuracy of FDG PET-CT and pelvic MRI after neoadjuvant CRT in rectal cancer reported superior accuracy of FDG PET-CT for predicting pathological complete response[114]. These recent studies are supported by a systematic review and meta-analysis including data from over 1500 patients which reported a high pooled accuracy for early PET restaging performed 1-2 weeks after starting CRT (sensitivity 84%, specificity 81%)[115]. It is hoped that future international guidelines on management of rectal cancer will consider emerging evidence and advocate the use of FDG PET-CT in restaging of LARC following neoadjuvant CRT.

The evidence supporting the use of FDG PET-CT in monitoring of treatment response to local ablative therapies in metastatic colorectal cancer including radiofrequency ablation (RFA) for liver/lung metastases and selective internal radiotherapy (SIRT) using Yttrium-90 (Y-90) microspheres for liver metastases has continued to increase over the past few years and has been shown to be more accurate and sensitive in detecting response (or conversely residual viable tumour) than conventional cross-sectional imaging[116,117].

Treatment Response in Cervical Carcinoma

Locally advanced cervical carcinoma is typically treated with CRT but 20-40% of patients will have disease persistence or relapse despite treatment[118]. Pre-existing methods of assessment such as International Federation of Gynaecology and Obstetrics (FIGO) staging criteria do not reliably predict early treatment response or outcome[119]. The development of non-invasive surrogate biomarkers to predict poor response to CRT and guide treatment escalation has been the subject of recent studies. One study evaluated changes in metabolic activity on FDG PET-CT performed during concurrent CRT for cervical carcinoma and reported prognostic value with 4 week SUV_{max} and FDG heterogeneity correlating with subsequent 3 month post treatment PET-CT response[120]. These findings are corroborated by subsequent larger studies, which reported metabolic changes on FDG PET-CT performed during CRT and post completion of CRT were significant predictors of progression free survival[121,122] and that PET-CT was more accurate than MRI for predicting early response during and after CRT[123]. The main value of using FDG PET-CT for response assessment is likely to be to flag patients who have not responded and need treatment escalation (**Figure 7**). A recent study from Turkey reported that 21% of patients with CMR on post-treatment FDG PET CT developed subsequent disease recurrence during a median 28.7 month follow-up period[124].

Multiple Myeloma

Following recommendations by the International Myeloma Working Group (IMWG) a revised International Staging System (R-ISS) for Myeloma was recently published[125]. This provides a simple risk stratification algorithm based on standard "CRAB" features (hyper**C**alcaemia, **R**enal failure, **A**naemia and **B**one lesions) with the addition of validated biomarkers associated with near inevitable progression from smouldering myeloma to multiple myeloma. Smouldering myeloma represents an intermediate (asymptomatic) clinical stage on the spectrum between pre-malignant monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma[126]. In addition the R-ISS now incorporates newer imaging techniques with greater sensitivity for detection of osseous (and extra-medullary) disease than the conventional skeletal survey including CT, MRI and FDG PET-CT[127]. In particular the new guidance recommends the use of one of FDG PET-CT, low-dose whole body CT or MRI (whole body or spine only) in all patients with suspected smouldering myeloma with the imaging modality used being determined by local expertise/scanner availability. One or more areas of osteolytic bone destruction (> 5 mm in size) detected on CT or PET-CT can identify patients with a high risk of progression to multiple myeloma, reported as > 70% within 2 years[128]. Treatment earlier in the course of disease may avoid end organ damage. If lesions are indeterminate, then repeat imaging after an interval is indicated[125].

Several studies have assessed the prognostic value of FDG PET-CT in myeloma but there is currently insufficient evidence to justify the routine use of PET-CT in all cases of newly diagnosed myeloma and selective use in key clinical scenarios is suggested[129]. FDG PET-CT provides incremental value in pre-treatment evaluation of patients with an apparently solitary plasmacytoma since additional unsuspected lesions are detected in up to 40% of patients with a frequent impact on treatment decision[130]. In many patients with myeloma treatment response can be effectively monitored by serum and urine analyses, however in patients with oligo- or non-secretory myeloma this is difficult, conventional imaging assessment may also be challenging e.g. distinguishing between active and inactive bone lesions on CT. Consequently FDG PET-CT can have a valuable role in the assessment of disease extent/activity disease at baseline, following treatment and in the setting of suspected relapse in patients with oligo- or non-secretory myeloma and in patients with predominantly extra-medullary disease[131,132] (**Figure 8**). It also has a role in the assessment of remission status post stem-cell transplantation in selected patients[133].

Rare tumours – Merkel Cell Carcinoma, Adrenocortical Carcinoma, Paediatric sarcoma

Recent publications have reported the utility of FDG PET-CT in rare tumours. Firstly, in Merkel cell carcinoma, a rare neuroendocrine tumour arising from the skin, which has an aggressive nature, a recent meta-analysis reported high sensitivity and specificity[134]. In addition two other groups have recently published data showing that FDG PET-CT has a significant impact on patient management in this patient cohort particularly in restaging post treatment and identifying candidates for salvage therapy[135,136].

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy in which there is recent evidence of the efficacy of FDG PET-CT in patient management. A group from MD Anderson Cancer Center in the USA reported on a large series of patients (n = 106) with ACC and found that in a small but significant proportion of patients PET-CT had a significant impact on patient management particularly in more accurate assessment of response to chemotherapy when CT frequently showed stable disease[137].

Finally, recent literature evaluating the role of FDG PET-CT in paediatric sarcoma including a systematic review of 8 studies in rhadomyosarcoma and a prospective study in Ewing sarcoma and osteosarcoma have documented the superior staging accuracy of the technique compared to conventional imaging specifically in detection of nodal disease and unsuspected metastatic disease[138,139].

Cardiac Implantable Device Infection

There is emerging evidence of the superior utility of FDG PET-CT in the assessment of patients with suspected implanted cardiac device infection. One recent prospective study from Italy documented increased diagnostic accuracy of FDG PET-CT in patients with an implanted cardiac device and associated infective endocarditis[140]. In another study from the UK the use of FDG PET-CT for early and accurate diagnosis of cardiac implantable device generator pocket infection was reported in a cohort of 86 patients[141].

Fluorine-18 Fluoroethyl tyrosine in brain tumours

FDG PET-CT has sub-optimal efficacy in the assessment of brain tumours, particularly in the evaluation of tumour extent and for assessment of suspected recurrence following treatment[142]. Recent meta-analysis data reported only moderate accuracy of FDG PET with a sensitivity of 77% and specificity of 78% for detection of glioma recurrence[143]. There is an increasing body of literature reporting the higher sensitivity and superior accuracy of Fluorine-18 fluoro-ethyl-L-tyrosine (FET) PET-CT in these clinical scenarios[144]. FET is an amino acid analogue and in comparison to FDG has a higher tumour to background contrast, it has been evaluated for assessment of gliomas to guide biopsy and treatment planning, for prognostication in low-grade glioma and for recurrence detection[142]. A recent systematic review has confirmed that FET PET is significantly more accurate than FDG PET for brain tumour diagnosis but that both tracers offer similar performance for grading of tumours[145]. FET PET has comparable accuracy to Carbon-11 methionine PET, an established amino acid tracer with high sensitivity and specificity for evaluation of brain tumours, but FET is advantageous because an on-site cyclotron is not required for production[146]. There are a number of reports suggesting that FET PET may be a cost-effective tool for surgical planning prior to glioma resection, guiding biopsy and in the assessment of treatment response in recurrent high-grade glioma[147,148,149].

Gallium-68 Prostate Specific Membrane Antigen (PSMA) in Prostatic Carcinoma

PSMA is a cell surface protein up-regulated in a range of malignancies, particularly prostate carcinoma, with low expression in normal tissues, which provides a tumour specific imaging target[150]. This has led to the development of PSMA-based ligands

for PET imaging in prostate malignancy over the past few years with Gallium-68 labelled PSMA PET-CT rapidly emerging into routine clinical practice in Europe[151]. Two large retrospective studies have reported the efficacy of the technique in patients with biochemical evidence of recurrent prostate carcinoma following radical treatment with detection rates of up to 96% depending on PSA level and Gleason score[152,153]. It has a significantly higher detection rate in this clinical setting when directly compared to Choline PET-CT particularly in patients with a low PSA level[154,155]. There is growing evidence of superior utility in other clinical scenarios including staging of high-risk patients prior to radical prostatectomy[156] and in guiding radiotherapy planning[157]. This technique is not yet in widespread use in the UK and rapid rollout to many centres may be limited by the complexities of Ga-68 production discussed earlier in this article. Efforts are ongoing to commercially develop a Fluorine-18 labelled PSMA tracer, which is likely to have a more widespread impact if it is shown to be superior to Choline PET-CT. Initial reports suggest this is a highly accurate technique[158,159,160].

Conclusions

The evidence supporting a wide range of PET-CT indications continues to expand year-on-year. The role of FDG PET-CT is firmly established in the management pathways of several different tumour types and recent studies have demonstrated additional applications in assessment of disease response in selected patients with lung, colorectal, haematological and cervical malignancies. Non-oncological uses of FDG PET-CT continue to grow. Non-FDG PET-CT indications are expanding and underpinned by a rapidly expanding literature. Revised Intercollegiate Guidelines encompassing new literature from the past 2 years, provide a comprehensive list of PET-CT indications for routine clinical use.

Figures & Legends

Figure 1: Use of FDG PET-CT to assess treatment response to chemotherapy in oesophageal cancer

A. Axial fused PET-CT image pre-treatment in a patient with a locally advanced oesophago-gastric junction tumour

B. Axial fused PET-CT image performed after completion of chemotherapy showing complete metabolic response within the primary tumour (white arrow)

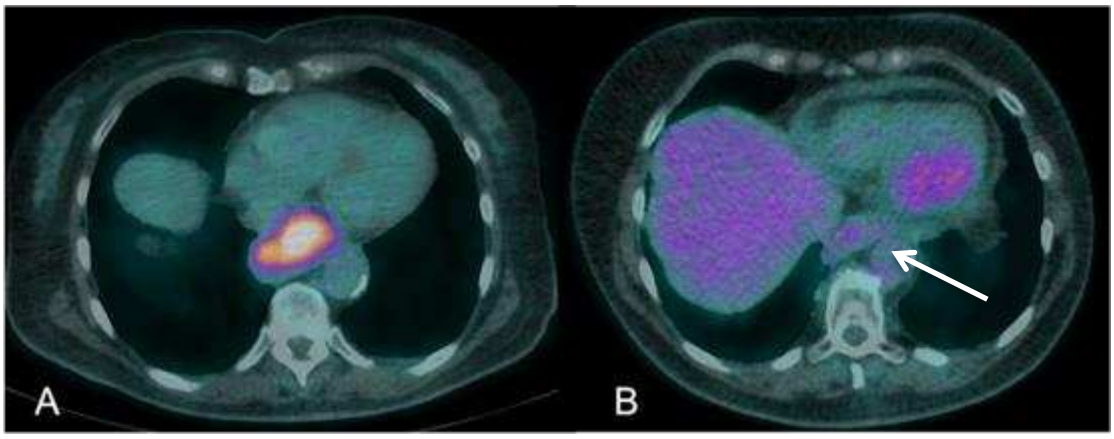


Figure 2: Use of FDG PET-CT to stage potentially operable metastatic colorectal carcinoma

A. Maximum Intensity Projection (MIP) FDG PET image in a patient with previously treated colorectal carcinoma and a new potentially operable pulmonary metastasis

B. Axial fused PET-CT image showing a right lower lobe pulmonary metastasis

C. Axial fused PET-CT image showing an unsuspected left hilar nodal metastasis

D. Axial fused PET-CT image showing an unsuspected bone metastasis within the sacrum

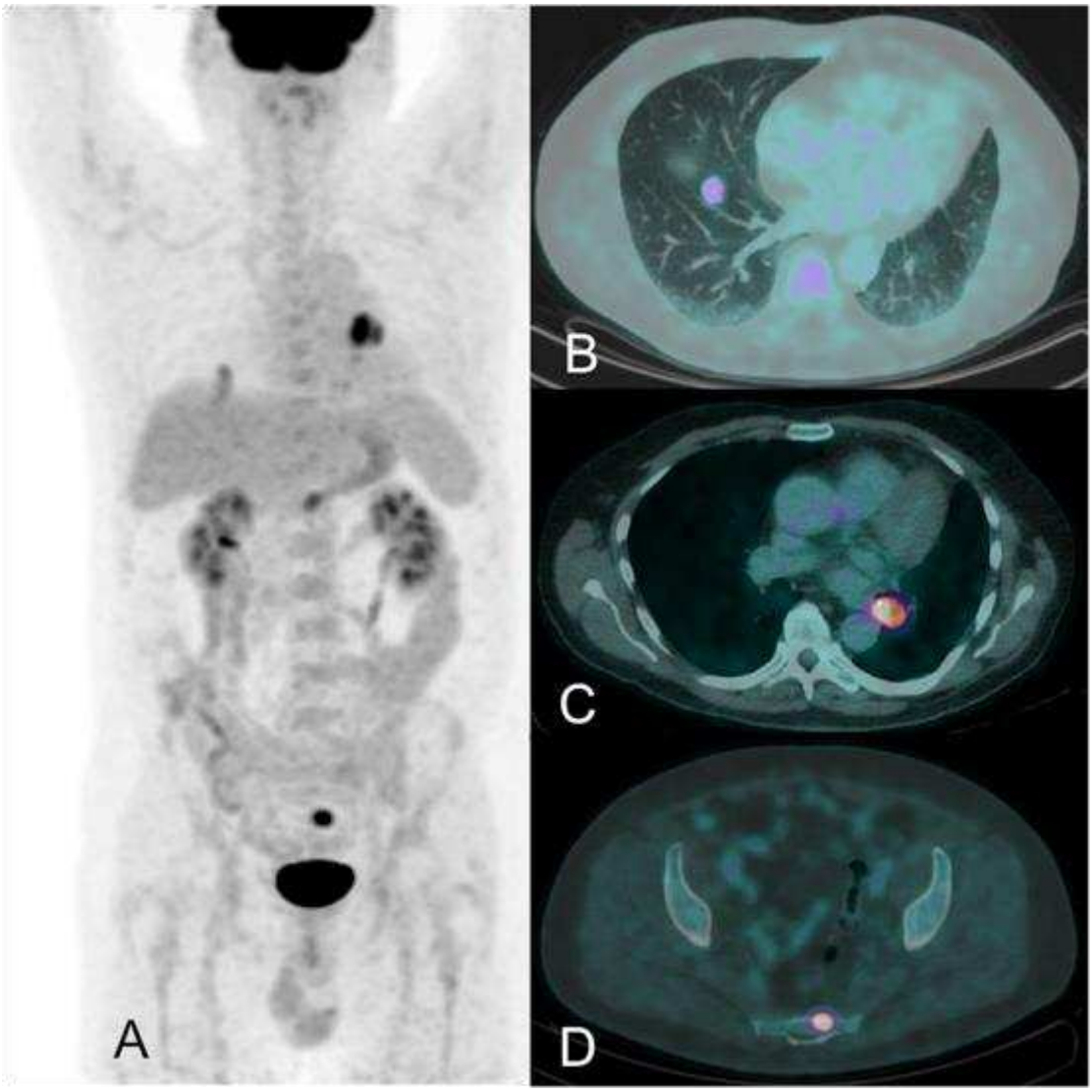


Figure 3: Use of FDG PET-CT in response assessment of head and neck cancer following chemo-radiotherapy

A. Axial fused PET-CT image pre-treatment in a patient with a locally advanced oropharyngeal squamous cell carcinoma involving the base of tongue with bilateral FDG-avid cervical nodal disease

B. Axial fused PET-CT image performed 4 months after completion of chemo-radiotherapy therapy showing complete metabolic response within the nodal disease but indeterminate low-grade residual metabolic activity within the base of tongue. There is also asymmetrical physiological tracer uptake in the right pre-vertebral musculature

C. There was no clinical evidence of residual disease and the patient was managed conservatively and an axial fused PET-CT image performed 3 months later shows resolution of the residual uptake within the tongue base consistent with a complete metabolic response to treatment

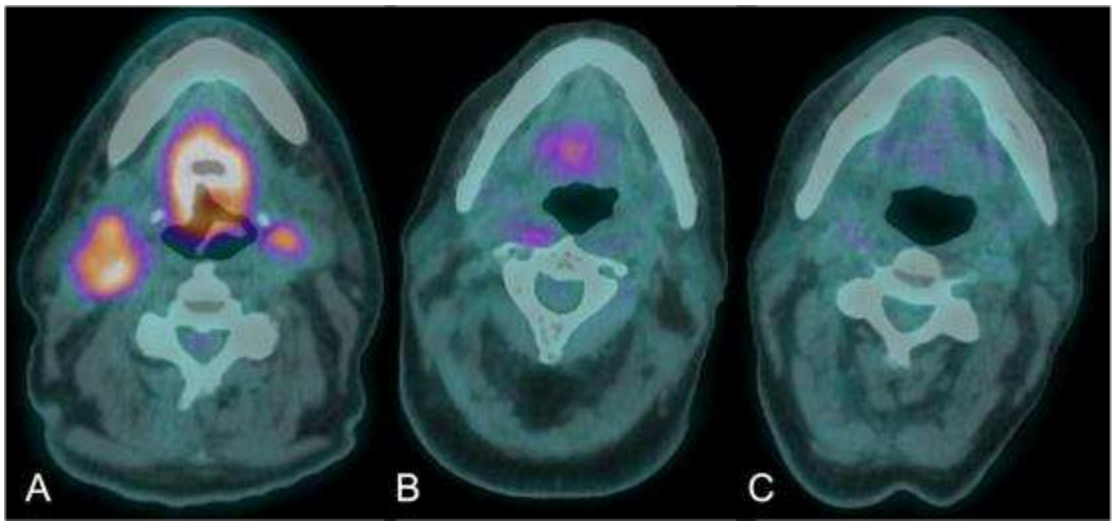


Figure 4: Use of FDG PET-CT in Suspected Dementia

A-B. Axial and sagittal fused PET-CT images of the brain in a 53-year-old male with rapid deterioration in short-term memory showing cerebral hypometabolism in both posterior parietal lobes including the posterior cingulate gyrus and pre-cuneus region and temporal lobes (not shown) typical of Alzheimer's Dementia

C-F. 3D-stereotactic surface projection (3-SSP) z-score maps of the medial and lateral cortices confirm that these regions have significantly reduced metabolism compared with an age-matched normal database (yellow/green colour) (Created using Cortex ID software, GE Healthcare, Amersham, UK)

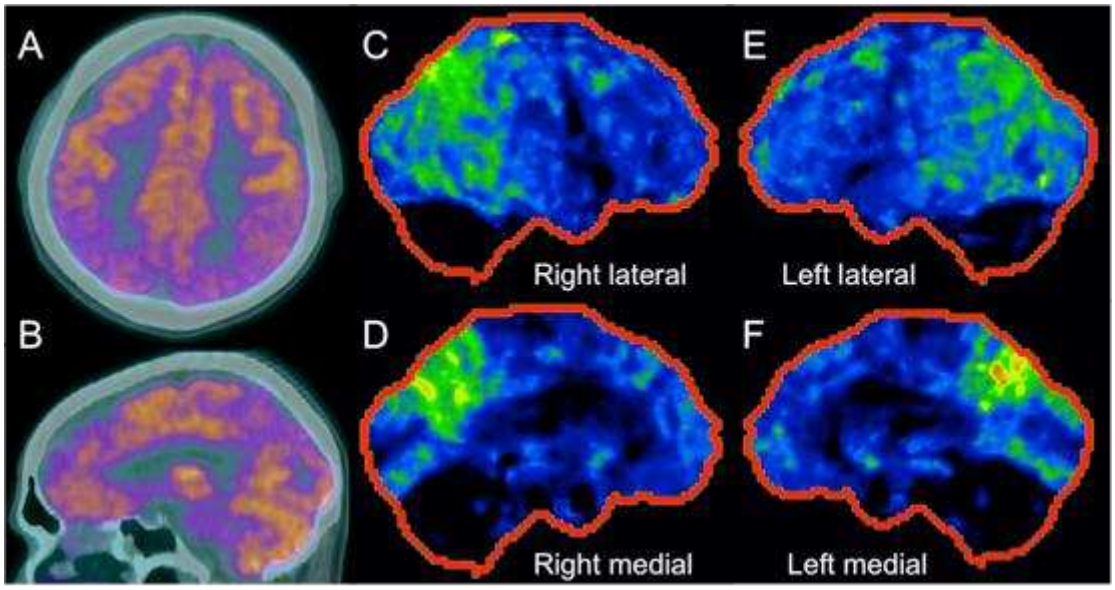


Figure 5: Use of Choline PET-CT in suspected recurrence of prostatic carcinoma

A. Sagittal low-dose CT from a Fluorine-18 Choline PET-CT study in a patient who had previously undergone brachytherapy for localised prostatic carcinoma and had a rising PSA level and suspected recurrence. This shows brachytherapy seeds in situ (green arrow) and a subtle area of mixed lucency/sclerosis within the S1 vertebral body (red arrow)

B. Sagittal fused PET-CT image from the same study showing avid tracer uptake within the S1 vertebral body consistent with a solitary site of metastatic disease (red arrow)

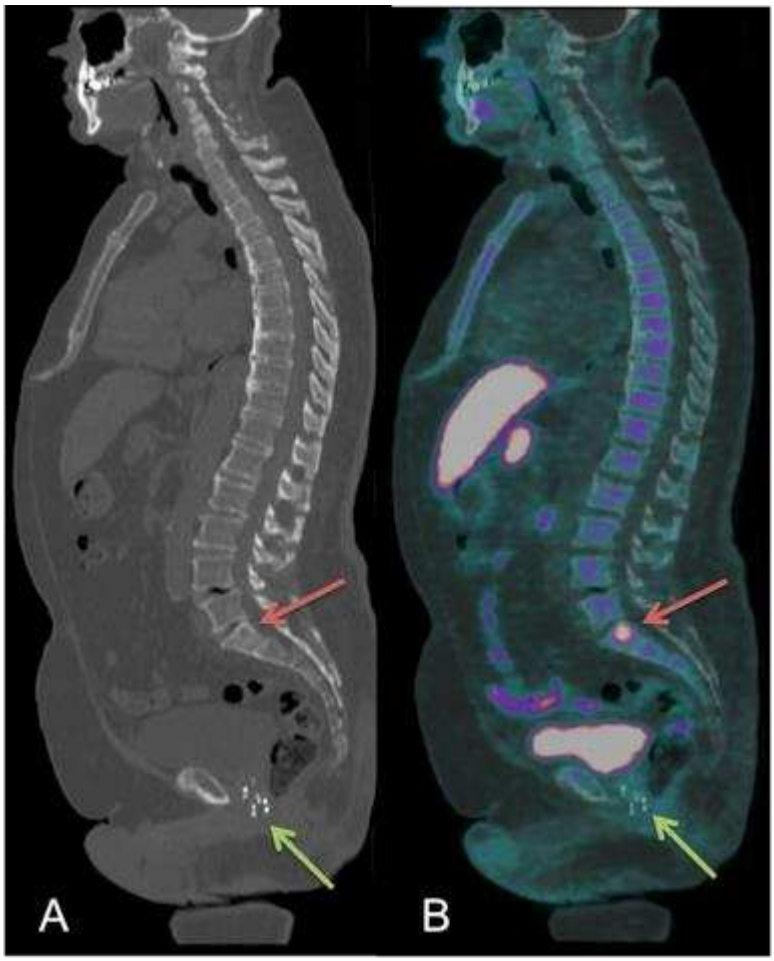


Figure 6: Use of Gallium-68 labelled somatostatin receptor (SSR) PET-CT in neuroendocrine malignancy

A. Anterior planar view from an Indium-111 DTPA-Octreotide scintigram performed in a patient with suspected mid-gut carcinoid showing focally increased tracer activity within the liver and upper abdomen consistent with nodal and liver metastases

B. MIP view from a Gallium-68 DOTA-NaI-Octreotide (DOTANOC) PET-CT study performed one month later as part of work-up for peptide receptor radionuclide therapy which demonstrates greatly superior tumour to background tracer avidity with demonstration of multiple additional abnormal foci within the liver and abdomen. Physiological pituitary gland activity is also present

C. Axial fused PET-CT image showing bi-lobar neuroendocrine liver metastases (white arrows)

D. Axial fused PET-CT image showing retroperitoneal nodal disease (white arrow)

E. Axial fused PET-CT image showing a small peritoneal metastasis in the right iliac fossa (white arrow)

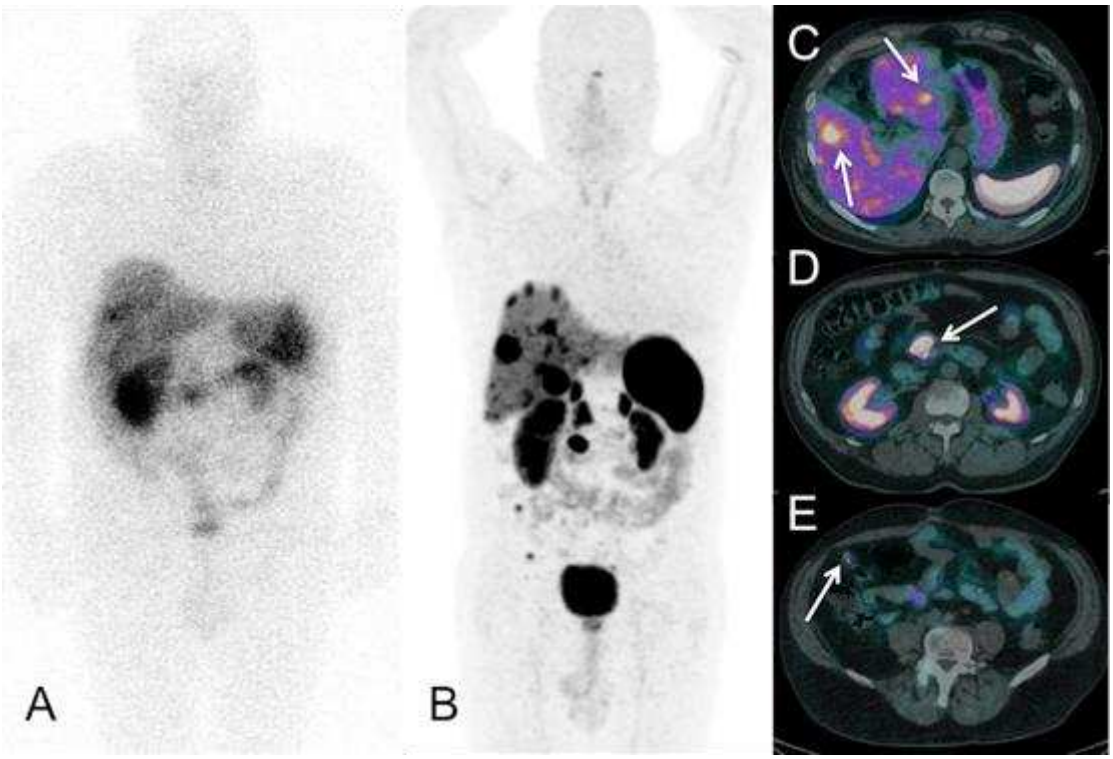


Figure 7: Use of FDG PET-CT for assessment of treatment response following chemo-radiotherapy in locally advanced cervical carcinoma

A. Axial fused PET-CT image pre-treatment in a patient with stage 2B node positive cervical carcinoma showing an FDG avid right pelvic sidewall node. There is also physiological tracer uptake in the left distal ureter

B. Axial fused PET-CT image in the same patient obtained 3 months following completion of chemo-radiotherapy shows residual low-grade tracer activity in the right pelvic sidewall node (white arrow) of uncertain significance

C. Axial fused PET-CT image in the same patient performed 7 months following treatment showing progressive enlargement of the right pelvic sidewall (which arrow) due to residual/relapsed disease

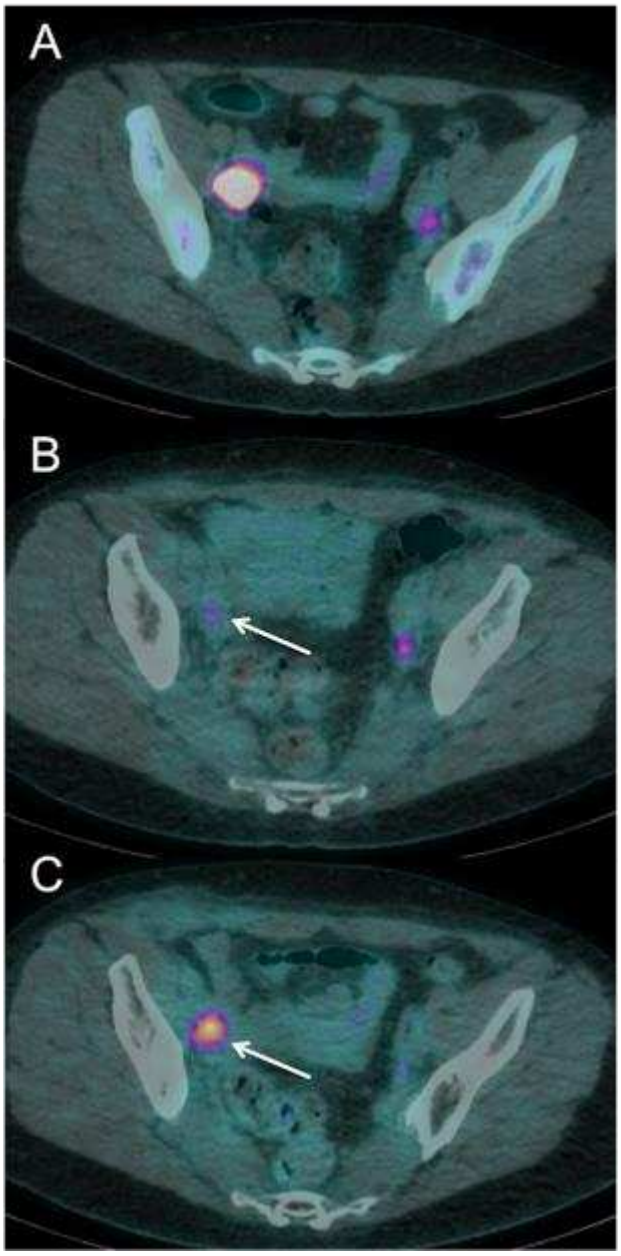
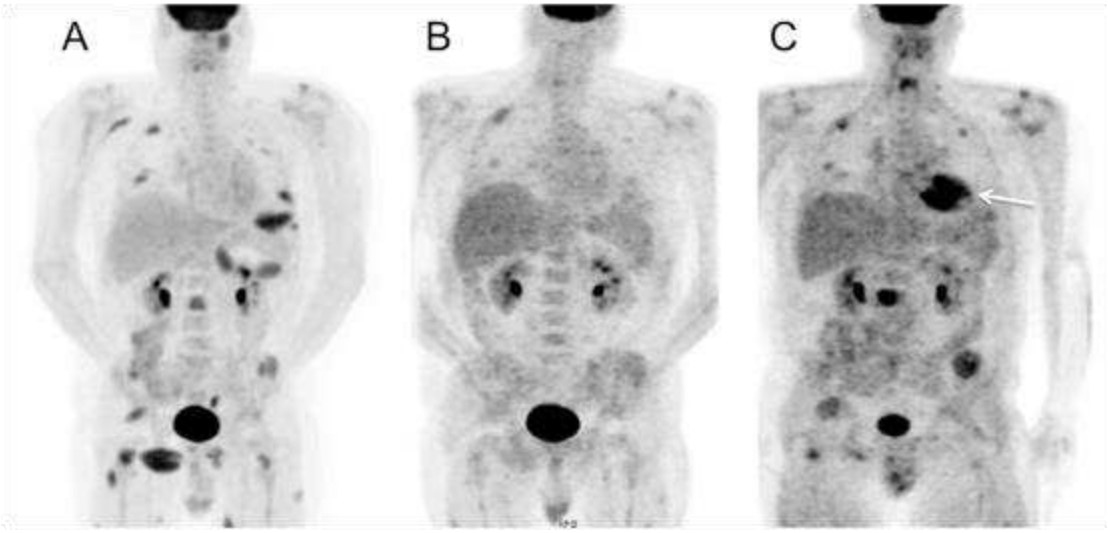


Figure 8: Use of FDG PET-CT in assessment of non-secretory multiple myeloma pre and post treatment

A. MIP image from FDG PET-CT performed in a patient with relapsed non-secretory multiple myeloma after systemic therapy and prior to autologous stem cell transplant confirms multiple sites of soft tissue and bony disease

B. MIP image from a re-staging FDG PET-CT scan performed 3 months post-transplant demonstrates a partial metabolic response to treatment

C. MIP image from a further FDG PET-CT scan performed 3 months later demonstrates multiple sites of bony and soft tissue disease relapse, including an FDG avid pericardial effusion (white arrow), which was aspirated and proven to be malignant



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