16 PET Imaging in Oncology

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Introduction

Positron emission tomography (PET) is an imaging technique that provides *in vivo* measurements in absolute units of a radioactive tracer. One of the attractive aspects of PET is that the radioactive tracer can be labelled with short-lived radioisotopes of the natural elements of the biochemical constituents of the body. This provides PET with a unique ability to detect and quantify physiologic and receptor processes in the body, particularly in cancer cells, that is not possible by any other imaging technique.

The clinical role of PET has evolved considerably over the last decade. From its first applications principally in neurology and cardiology, the evaluation of oncology patients has become a pre-eminent clinical role for PET worldwide. Oncology PET studies now represent almost 90% of clinical studies performed in clinical PET Centres worldwide[1–5]. The dramatic rise in the number of PET oncology studies performed is related both to recent reimbursement approvals (particularly in the USA), as well as the increasing evidence for the role of PET in the staging, monitoring treatment response and biologic characterisation of tumours.

PET Radionuclides in Oncology

The short-lived radionuclides (radioisotopes) required for PET are produced in cyclotrons. In PET oncology clinical applications, the most commonly used positron-emitting tracer is ^{18}F-fluoro-2-deoxy-glucose, or [^{18}F]-FDG [6]. The unique versatility of PET lies in the ability to study numerous physiologic and biochemical processes *in vivo*. The measurement of tissue blood flow, oxygen metabolism, glucose metabolism, amino acid and protein synthesis and nucleic acid metabolism have all been demonstrated in PET oncology clinical studies [6–9]. To exploit these physiologic and molecular targets, there are a number of positron emitting radiopharmaceuticals that have been used in clinical oncology studies to date (Table 16.1). Labelling of a large array of other compounds including hypoxic markers, amino acids, DNA proliferation markers and chemotherapy drugs with ^{11}C and ^{18}F have also been studied in clinical trials [3, 7, 8, 10].

The Evidence for Clinical Use of PET in Oncology

The experience over the last decade is that the most important clinical role of [^{18}F]-FDG PET is in oncology. In many cancers, [^{18}F]-FDG PET has been shown to be the most accurate non-invasive method to detect and

Table 16.1. Positron-emitting radionuclides used in oncology clinical studies (see appendix for further radionuclide information).

Radionuclide	Half-Life
^{15}O	122 seconds
^{13}N	9.97 minutes
^{11}C	20.4 minutes
^{18}F	109.8 minutes
^{124}I	4.17 days
^{86}Y	14.7 hours
^{64}Cu	12.8 hours

stage tumours [1–5, 7–9, 11–21]. This has major implications in terms of improving the planning of treatment and avoiding unnecessary treatment and its associated morbidity and cost. Evaluation of the evidence for [^{18}F]-FDG PET in clinical oncology practice has been complicated by the inherent diagnostic nature of this imaging technique. While standard evidence-based approaches to treatment require randomised controlled trials to establish the appropriate outcome or efficacy measures for assessment, imaging techniques provide information which is commonly used as only a part of the management paradigm of most patients. As such, the practical and ethical issues surrounding this make randomised controlled trials for PET extremely difficult to perform or inappropriate in the majority of clinical scenarios [5, 22]. The establishment of diagnostic accuracy, and impact on patient management (including cost), are therefore the most appropriate levels of evidence that can be accurately obtained for PET in clinical practice [5, 22].

Brain Tumours

Brain tumours are a common and often devastating malignancy that impacts on both paediatric and adult populations. In adults, brain tumours are the leading cause of death for males aged 15 to 34 years, and are the fourth commonest cause of cancer death in females of this age group. Paediatric brain tumours are the second commonest cancer, and the second leading cause of death from cancer, in that age group [23, 24]. The evaluation of brain tumours with [^{18}F]-FDG PET is the longest established oncologic application of PET. Tumour grade can be assessed accurately and non-invasively by [^{18}F]-FDG PET, as the rate of glucose utilisation is directly proportional to the degree of malignancy [25]. This can be used in the planning of biopsies, and in monitoring high grade recurrence, particularly in patients with low grade glioma. Increased [^{18}F]-FDG uptake is seen in high grade glial tumours, as well as in primary cerebral lymphomas, pilocytic astrocytomas, and some unusual tumours (e.g., pleomorphic xanthoastrocytoma. Low grade gliomas) (Fig. 16.1) and other primary brain tumours (e.g., meningiomas) do not usually show increased [^{18}F]-FDG uptake except in more aggressive tumours and in post-radiation meningiomas.

Cerebral metastases occur in 20 to 40% of systemic malignancies, and may be the initial presentation of malignancy in 16 to 35% of cases. [^{18}F]-FDG PET has been extensively studied in patients with cerebral metastases, and has been shown to have a sensitivity ranging from 68 to 79% [26]. The principal issue with

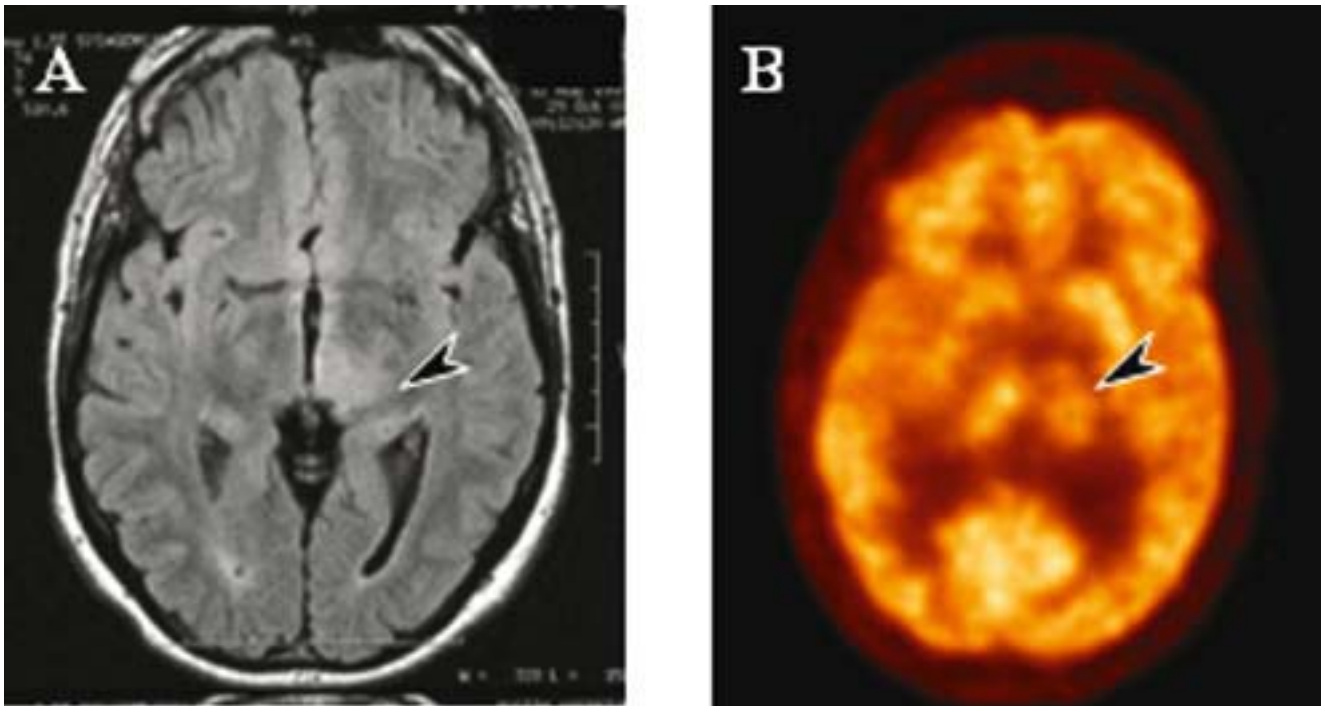

Figure 16.1. (A) MRI scan, and (B) corresponding transaxial [^{18}F]-FDG PET scan of a 53-year-old patient with bilateral hearing loss. A lesion in the left thalamus (arrow) is hypometabolic on [^{18}F]-FDG PET scan. This was subsequently demonstrated to be a low grade glioma.

FDG PET in this setting is the frequent hypometabolic nature of cerebral metastases, and in addition, metastatic lesions are often small (<1 cm in size), and because metastases most often occur at the interface between grey and white matter, identification of lesions can be problematic.

An important role of [^{18}F]-FDG PET is in the assessment of tumour recurrence compared to radiation necrosis, factors critical to the management of these patients and often impossible to determine accurately by CT or MRI (27). The uptake of [^{18}F]-FDG in normal grey matter may make evaluation of tumour recurrence difficult in some cases, and care is required in order to interpret PET scans in these patients.

Patient prognosis may also be evaluated by the presence and degree of uptake of [^{18}F]-FDG [28]. While the evaluation of disease recurrence may also be evaluated with other techniques including ^{201}Tl SPECT, which is more readily available, the problems of blood-brain barrier disruption and mixed grade tumour assessment with ^{201}Tl SPECT may be more accurately assessed with [^{18}F]-FDG PET. Incorporating [^{18}F]-FDG PET into radiotherapy treatment planning, and in monitoring response to therapy, has also emerged as important applications of PET in brain tumours.

A range of other PET tracers have been studied in brain tumours, examining DNA proliferation, protein expression, hypoxia and even gene reporter expression [29, 30]. The most commonly studied tracer is [^{11}C]-methionine PET, which has some advantages in detecting low grade gliomas, although the ability to discriminate between high grade and low grade tumours may be less accurate with [^{11}C]-methionine PET compared to [^{18}F]-FDG PET [31]. In summary, PET studies are an established part of the management of patients with brain tumours in major neuro-oncology centres.

Lung Carcinoma

Solitary Pulmonary Nodules

There have been numerous studies examining the accuracy of [^{18}F]-FDG PET in evaluating solitary pulmonary nodules [32, 33]. Analysis of the published data has shown a high sensitivity (average 96%) and accuracy (average 94%) for determining malignancy (Figs. 16.2 and 16.3 [2, 8, 34]. The specificity is also high but the variation is slightly greater and is dependent on the local prevalence of the known causes of false positive cases, particularly granulomatous diseases such as tuberculosis and histoplasmosis. False negative results may arise where small lesions are present (<0.6 cm), due to the resolution limitations of PET scanners and respiratory motion over the acquisition period, and also with certain types of lung cancer such as bronchoalveolar and carcinoid. The use of [^{18}F]-FDG PET for solitary pulmonary nodules is often reserved for those cases where fine needle aspiration is technically difficult in view of the superior diagnostic yield of this technique.

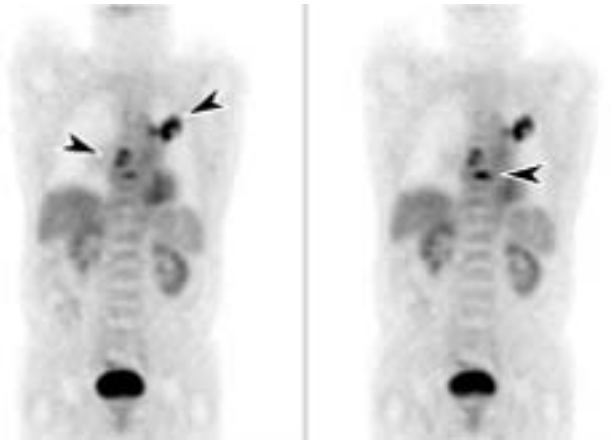

Figure 16.2. Coronal sections of a [^{18}F]-FDG PET scan performed in a 72-year-old man with a left lung carcinoma. Uptake of [^{18}F]-FDG in the primary lung cancer (arrow) and lymph nodes (arrow) is seen, as well as an unsuspected metastasis in a thoracic vertebrae (arrow).

Staging of Non-Small Cell Lung Carcinoma

In patients with known non-small cell lung carcinoma (NSCLC), the results of staging both within and outside the thorax are key in determining operability. Demonstration of unilateral hilar adenopathy is not a contra-indication to surgery if the nodes can be resected with the primary tumour. Conversely, extensive mediastinal involvement, involvement of contralateral lymph nodes, as well as pleural or distant metastases should contra-indicate surgery given the high surgical morbidity and the poor prognosis. The relatively suboptimal sensitivity, specificity and accuracy of conventional imaging techniques, including CT and MRI, for staging of lung carcinoma has been demonstrated repeatedly [35].

Numerous studies have evaluated the role of [^{18}F]-FDG PET for staging NSCLC [11, 17, 18, 35–38]. The reported sensitivity for lymph node staging in non-small

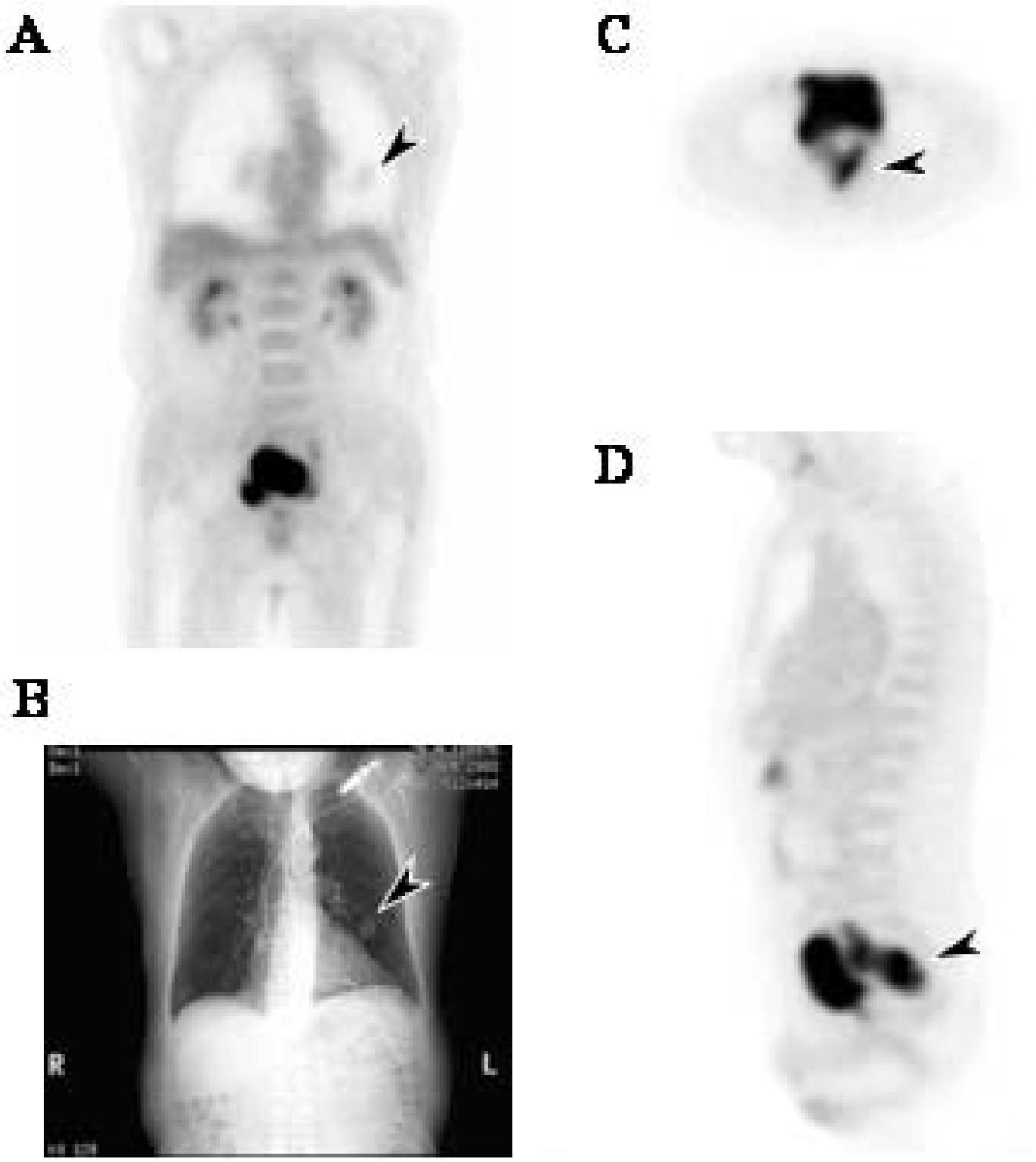

Figure 16.3. (A) Coronal section of a [^{18}F]-FDG PET scan performed in a 76 yr old man with left lower lobe lung nodule (arrow), seen also in (B) CXR. The lesion was hypometabolic on [^{18}F]-FDG PET scan, and was non-malignant. An incidental finding of increased [^{18}F]-FDG uptake in the rectum, seen on (C) transaxial and (D) sagittal images (arrow) was due to a non-diagnosed rectal cancer.

cell lung carcinoma varies from 82 to 100% and the specificity from 73 to 100% [11, 16, 36, 37, 39, 40]. In all series, [^{18}F]-FDG PET has been shown to outperform CT in staging lymph node spread of disease, and has been shown to correctly stage disease over CT scan results in up to 24% of patients (Fig. 16.2) (37). In a recent randomised controlled trial of [^{18}F]-FDG PET in staging patients with newly diagnosed NSCLC, the inclusion of [^{18}F]-FDG PET in diagnostic work up reduced futile thoracotomies by half, indicating the important role of [^{18}F]-FDG PET in this staging process (18). The negative predictive value of [^{18}F]-FDG PET is sufficiently high that a negative mediastinum on [^{18}F]-FDG PET scanning may preclude mediastinoscopy in patient work-up, and a positive mediastinum on [^{18}F]-FDG PET should always be further assessed to exclude false positive results (e.g., sarcoid) [5, 38]. In addition, studies utilising whole body scanning have reported unsuspected metastatic disease in up to 15% of patients (Fig. 16.2) [39]. This is particularly relevant for adrenal lesions, where benign enlargement is common, and [^{18}F]-FDG PET is highly accurate in identifying metastatic involvement [16]. Through correct staging by [^{18}F]-FDG PET, therapy has been shown to be changed in >40% of patients, mainly by obviating unnecessary surgery [40]. [^{18}F]-FDG PET has emerged as a standard pre-operative assessment test in patients with NSCLC.

Recurrent Lung Carcinoma and Response to Therapy Assessment

The ability to accurately evaluate residual masses following surgery or radiotherapy for lung cancer is essential in many patients. Post treatment fibrosis and scarring is common, and [^{18}F]-FDG PET has been shown in a number of small series to be accurate in detecting residual tumour, which allows treatment planning decisions to be reliably made [15]. The potential role of [^{18}F]-FDG PET in treatment planning for radiotherapy of unresectable lung cancer has also been explored, and may provide improved treatment with a reduced incidence of relapse outside the radiotherapy field [41]. In addition, in patients with NSCLC undergoing radical radiotherapy or chemoradiotherapy, [^{18}F]-FDG PET performed soon after therapy has been shown to be a superior predictor of survival than CT response, stage, or pre-treatment performance status [42].

Colorectal Carcinoma

Staging of Primary Colorectal Cancer

The diagnosis of colorectal cancer is principally based on colonoscopy and biopsy, with imaging being performed primarily to assist in initial surgical planning. There have been a number of studies examining the utility of PET for staging primary colorectal carcinoma. In one study of 16 patients with known or suspected primary or recurrent colon and rectal cancer studied with [^{18}F]-FDG PET and CT scans, PET detected all 12 sites of disease in bowel, whereas CT only detected 6 [43]. Other small studies have confirmed these results, although lymphatic spread of tumour was poorly detected with [^{18}F]-FDG PET due to the small size of involved lymph nodes in many cases [44]. Primary colorectal cancers occasionally present as an incidental finding on [^{18}F]-FDG PET (Fig. 16.3), and [^{18}F]-FDG uptake has been reported in adenomatous polyps, a pre-cursor for colon cancer [45]. However, the presence of physiological gut uptake of FDG combined with false positive uptake in inflammatory disease along with low sensitivity to lesions less than 1 cm precludes a significant role for FDG PET in primary diagnosis or screening [46]. The role of PET in primary colon cancer remains limited, and should be reserved for clinical situations where resection of metastatic disease requires accurate staging of distant spread. This is in contrast to advanced rectal cancer, where [^{18}F]-FDG PET has been shown to have a significant impact on management in up to one third of patients planned for preoperative adjuvant treatment (chemoradiation), indicating the potential role of [^{18}F]-FDG PET in this clinical setting [47].

Staging of Metastatic Colon Cancer

Hepatic Metastases

Clinical studies have shown [^{18}F]-FDG PET to be a highly sensitive technique for the detection of hepatic metastases of colorectal cancer. In published series the accuracy of [^{18}F]-FDG PET in identifying metastatic colorectal carcinoma in the liver has ranged from 90 to 98% [8]. The role of PET in this clinical setting appears to be complementary to CT scan and CT portography [48–50]. Mucinous adenocarcinoma may have a lower sensitivity for detection [51]. Importantly, [^{18}F]-FDG

PET has been shown to identify previously unsuspected extrahepatic disease in patients with liver metastases in up to 20% of patients, and can change management in reported series in up to 35% of patients [12, 52].

Extrahepatic Metastases

The detection of extrahepatic metastases of colorectal carcinoma remains a difficult clinical problem. While CT scans are sensitive for hepatic metastases, they are less sensitive for detecting extrahepatic disease [12, 53]. MRI, while as accurate as CT for detecting hepatic metastases of colorectal carcinoma, remains less sensitive in extrahepatic intra-abdominal disease [54]. This is of particular importance in patients considered for surgery for metastatic disease, in view of the high prevalence of undiagnosed sites of extrahepatic disease which results from conventional techniques preoperatively.

Studies examining the accuracy of PET in extrahepatic metastases of colorectal carcinoma have demonstrated higher accuracy than conventional scanning techniques (including CT scan) [12, 52]. Extrahepatic disease has been detected with [^{18}F]-FDG PET with an accuracy of 92 to 93% in recent series. In

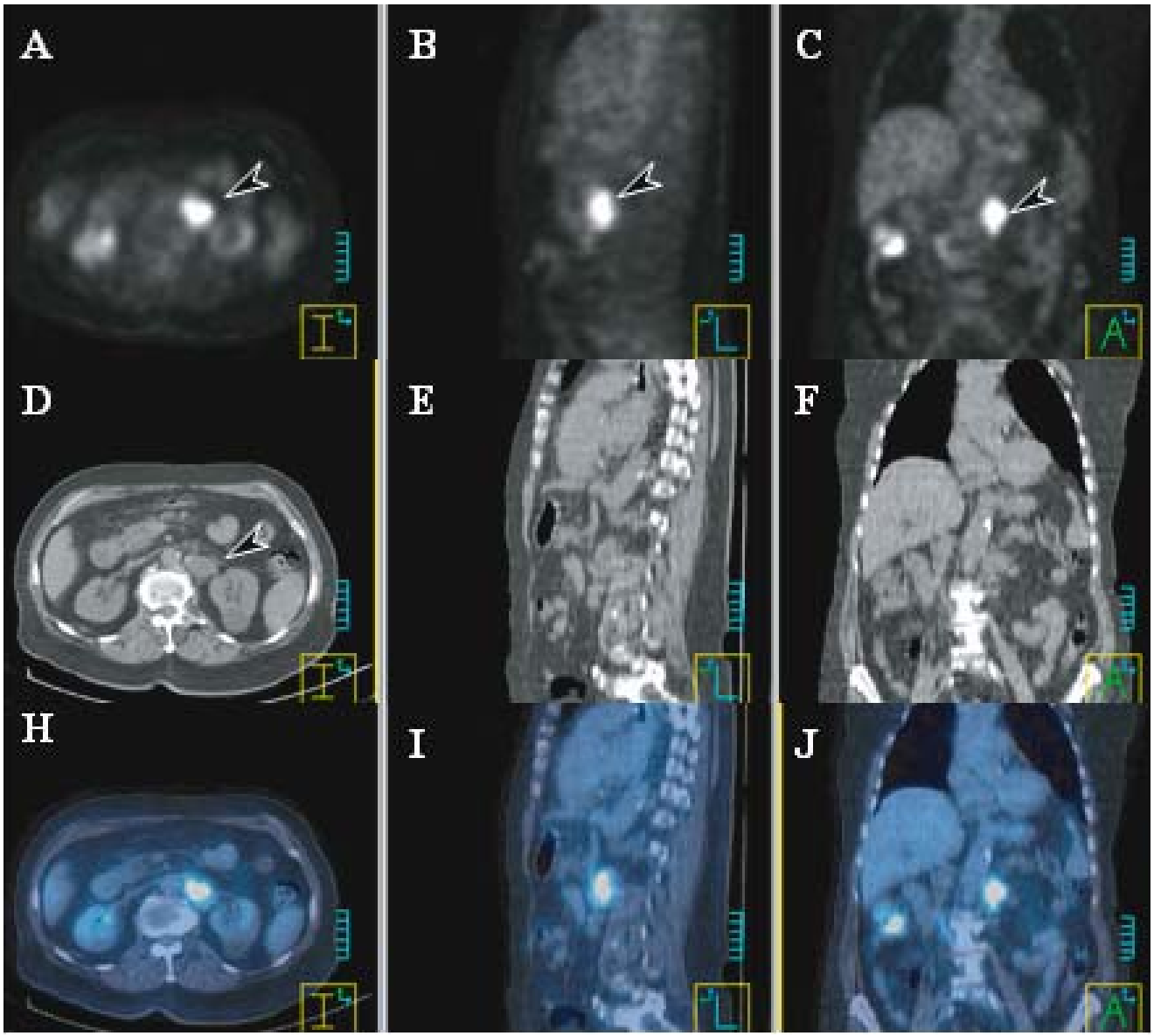

Figure 16.4. An 83-year-old woman with a history of colon cancer and a rising CEA underwent a combined PET/CT scan for staging. (A) transaxial, (B) sagittal and (C) coronal images show a focal area of abnormal [^{18}F]-FDG uptake (arrow), corresponding to a retroperitoneal lymph node region on corresponding CT slices [(D), (E) and (F)]. Co-registered [^{18}F]-FDG PET/CT images [(G), (H) and (I)] show precise localisation of the recurrent colon cancer in the retroperitoneum.

patients with elevated serum CEA markers, occult disease (often extrahepatic recurrence) has been identified accurately with [18F]-FDG PET (Fig. 16.4) [12, 52]. These results have been confirmed in a recent meta-analysis of whole-body [18F]-FDG PET studies in patients with colorectal carcinoma, where the sensitivity and specificity of [18F]-FDG PET in detecting tumour was 97% and 76% respectively, and the change in management was calculated to be 29%, both by upstaging and downstaging disease [55].

Rectal Carcinoma Recurrence

Recurrent colorectal (pelvic) cancer has been reported to occur in 20 to 40% of patients within two years after potentially curative surgery [56]. Both CT and MRI, however, have significant difficulties in reliably distinguishing local spread of disease, and recurrence of rectal cancer from post surgical change [53]. There have been a number of extremely promising clinical studies with [18F]-FDG PET in the evaluation of possible rectal carcinoma recurrence. In one study of 37 patients with suspected rectal carcinoma recurrence, 32/32 patients with recurrent rectal carcinoma were correctly identified with [18F]-FDG PET [57]. The accuracy of [18F]-FDG PET in this setting has also been demonstrated in other published clinical studies [8].

Management Impact of PET and Response to Therapy Assessment

The management impact of [18F]-FDG PET in recurrent colorectal carcinoma has been clearly demonstrated [58, 59]. Studies of [18F]-FDG PET post therapy (chemo/radiotherapy) have also demonstrated a potential role of [18F]-FDG PET in this setting [13, 60, 61]. Based on available evidence, [18F]-FDG PET should be used in the detection of advanced or metastatic colorectal cancer where management will be altered by disease presence and extent.

Lymphoma

The ability of whole body [18F]-FDG PET to accurately stage lymphoma has emerged as an important role of PET in patient management. In the staging of Hodgkins Disease and non-Hodgkins lymphoma (NHL) the sensitivity and specificity of [18F]-FDG PET in detecting sites of disease has been reported as 86–90% and 93–96% respectively, and superior to CT scan [2, 8, 62]. Compared to conventional imaging (e.g., CT scans) [18F]-FDG PET is more sensitive in identifying extra-nodal sites of disease. [18F]-FDG PET has been shown to change management in up to 40% of patients undergoing staging at initial diagnosis [21, 63–65]. In comparison to 67Ga scans, [18F]-FDG PET has been shown to have a greater sensitivity for disease detection (particularly spleen), and in view of the potential advantage of a same day procedure has supplanted 67Ga scans in many oncology centres [66]. In some cases of low grade lymphoma [18F]-FDG uptake may not be high, however this is dependent on histologic subtype, and high sensitivity for disease sites has been reported for follicular and marginal zone low grade lymphoma, and with management change reported in up to 34% of patients (Fig. 16.5) [64, 67].

[18F]-FDG PET has also been shown to have superior accuracy compared to conventional imaging in the restaging of lymphoma patients, particularly where residual masses are present [68, 69]. In comparison to 67Gallium scans, [18F]-FDG PET has been shown to be more accurate in identifying active disease in residual masses (66, 70). [18F]-FDG PET performed as part of the assessment of treatment response for NHL has also been shown to be superior to conventional imaging and to be a strong prognostic indicator of response and progression free survival [68, 71]. [18F]-FDG PET therefore has a major role in both the initial staging, and restaging/therapy response assessment of patients with lymphoma.

Melanoma

The role of [18F]-FDG PET in the initial staging of low-risk (<1 mm thickness) and intermediate-risk (1–3 mm thickness) melanoma is limited, due to the low prevalence of metastatic disease (particularly in low-risk melanoma), and the often small size of metastatic deposits in nodes involved with metastatic spread [72, 73].

Malignant melanoma can spread widely and unpredictably throughout the body, and median survival after the appearance of distant metastases is approximately six months [74]. The accuracy of [18F]-FDG PET in detecting metastatic melanoma has been reported to range from 81 to 100%, and in one series of 100 patients demonstrated a sensitivity of 93% [14]. [18F]-FDG PET has been shown to be particularly sensitive in detecting subcutaneous and visceral metastases

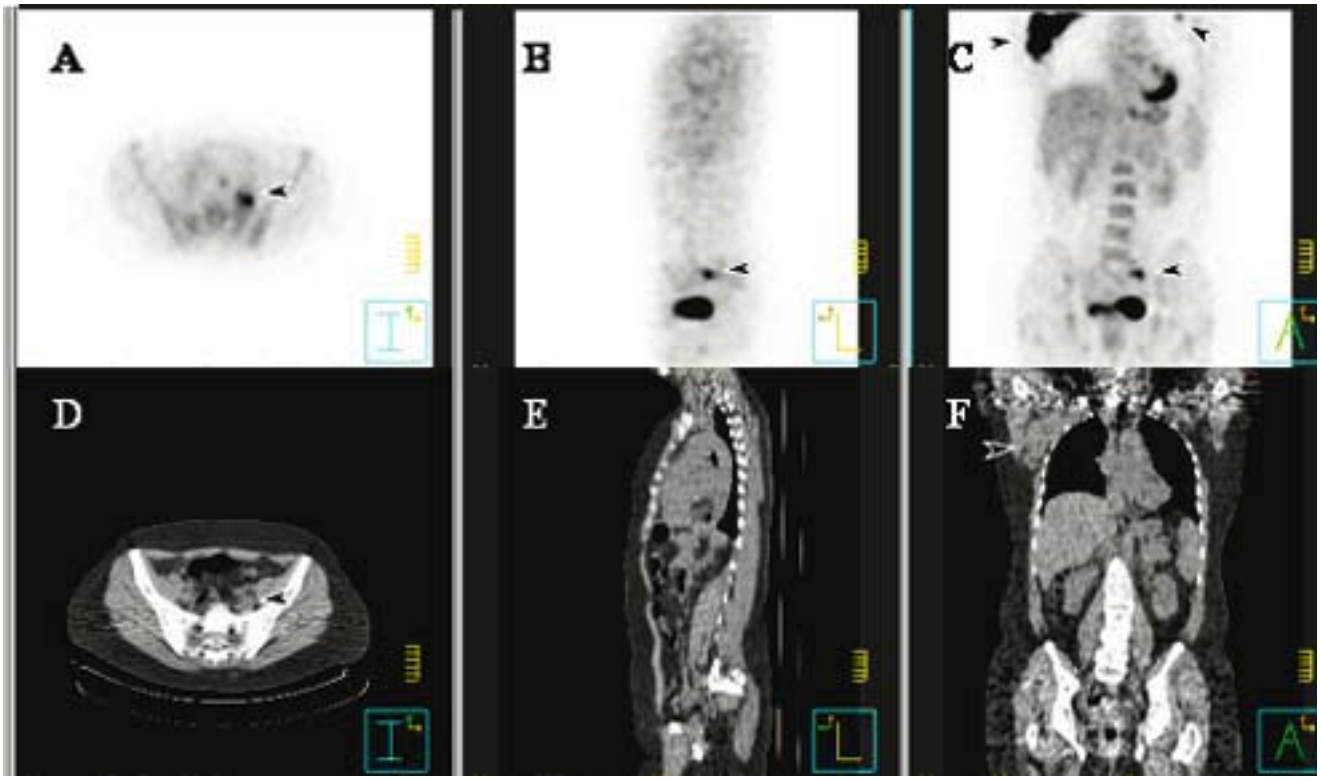

Figure 16.5. A 48-year-old woman with Follicular lymphoma of the right axilla underwent a staging [^{18}F]-FDG PET/CT scan prior to planned radiotherapy. (A) transaxial, (B) sagittal and (C) coronal whole body staging [^{18}F]-FDG PET images show lymphoma in right axillary lymph nodes (arrow), as well as additional lymphoma sites in the left axilla and left illiac nodes (arrows). Corresponding CT scan images [(D), (E) and (F)] show right axillary node enlargement only. The [^{18}F]-FDG PET results upstaged the patient from Stage I to Stage III.

(Fig. 16.6). In published studies and meta-analyses of the literature, [^{18}F]-FDG PET has been demonstrated to detect disease up to six months earlier than conventional techniques, and alter management in 22 to 32% of patients, principally by altering plans for surgical resection of metastatic disease [14, 75–77]. As approximately one quarter of all melanoma patients with metastatic disease are potential candidates for surgical resection, and long disease-free intervals are possible in patients rendered clinically disease free by the surgery, [^{18}F]-FDG PET has a clear role in this clinical setting [5, 78].

[^{18}F]-FDG PET has also been compared to other staging investigations for metastatic melanoma. In a series of 121 patients with metastatic melanoma where [^{18}F]-FDG PET was compared to ^{67}Ga scintigraphy, PET was more accurate and provided incremental and clinically important information in 10% of patients, and at a lower cost [79]. The role of [^{18}F]-FDG PET in melanoma is therefore principally in the evaluation of extent of metastatic disease, the accurate assessment of which can alter patient management particularly where surgery is planned.

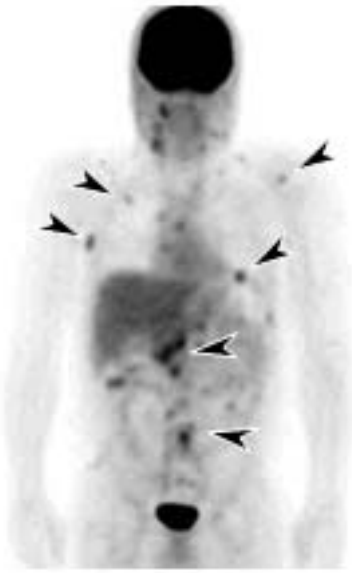

Figure 16.6. A 45-year-old woman with a history of right postauricular melanoma and previous resection of metastases in the right parotid and ipsilateral cervical lymph nodes, was referred for a restaging [^{18}F]-FDG PET scan prior to possible radiotherapy to the operative sites. A coronal whole body image shows multiple metastatic lesions in subcutaneous, lymph node, lung and visceral sites (arrows) throughout the body.

Head and Neck Tumours

The presence of lymph node spread of head and neck tumours is associated with substantially worse prognosis, and clinical examination and imaging techniques (CT and MRI) detect fewer than 50% of involved lymph nodes, which may result in unnecessary neck surgery. In patients with head and neck tumours studied prior to initial surgery, the sensitivity and specificity of [^{18}F]-FDG PET in detecting nodal metastases has been reported ranging from 71 to 91%, and 88-100%, respectively (Fig. 16.7) [8, 80–83]. Metastatic disease outside the neck can also be identified with [^{18}F]-FDG PET scans [84]. Primary tumours can also be detected with a similar sensitivity to CT/MRI. In patients studied after initial treatment of metastatic nodal disease with radiotherapy, [^{18}F]-FDG PET is often accurate only after a three month period [20, 85–87]. This has been shown to be due to the effects of stunning of tumour cells, where the metabolic rate and proliferation of cancer cells may be suppressed after radiotherapy, as well as the possible presence of microscopic disease only after radiotherapy treatment which is below the resolution of the PET camera. In both patient groups, the accuracy of [^{18}F]-FDG PET has the potential to direct surgeons to otherwise unknown sites of metastatic disease, as well as avoiding surgery in areas of the neck where [^{18}F]-FDG PET scans show negative results. [^{18}F]-FDG PET has also been shown to be a prognostic factor for radiotherapy response [88]. In patients with advanced loco-regional head and neck cancer, radiotherapy treatment planning incorporating [^{18}F]-FDG PET information has emerged as an exciting new method of potentially improving response rates.

Breast Carcinoma

The use of [^{18}F]-FDG PET in breast carcinoma has been evaluated in the initial assessment and staging of disease, and in monitoring response to therapy. In

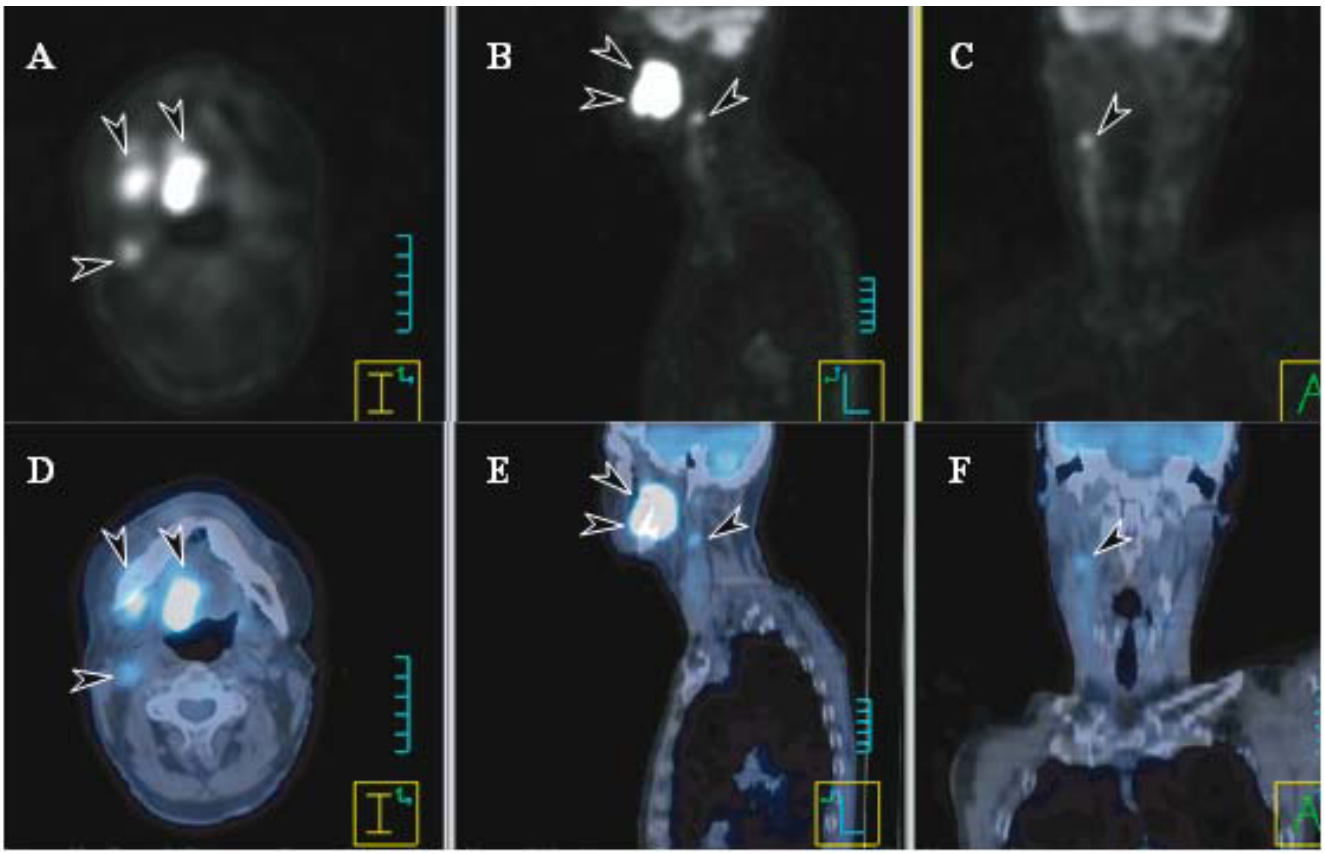

Figure 16.7. (A) transaxial, (B) sagittal and (C) coronal [^{18}F]-FDG PET scan images of a 60 yr old man with carcinoma of the right tonsil and base of tongue (arrows). A previously undiagnosed lymph node metastasis is also seen (arrow). Co-registered [^{18}F]-FDG PET/CT images on corresponding images [(D), (E) and (F)] show the precise localisation of sites of tumour.

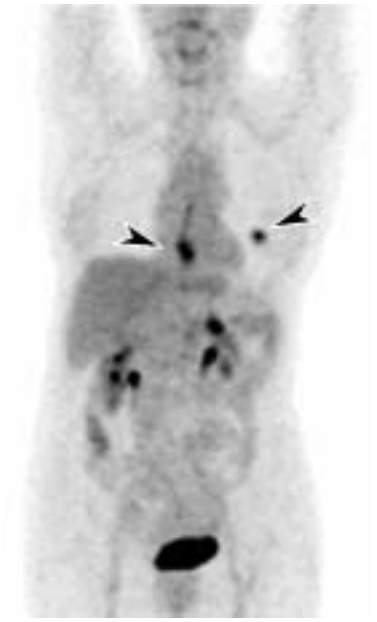

Figure 16.8. Whole body 3D coronal [^{18}F]-FDG PET image of an 81-year-old woman with an oesophageal carcinoma (arrow). A previously undiagnosed left breast carcinoma was also identified (arrow), subsequently confirmed on biopsy. Normal excretion of [^{18}F]-FDG from kidneys, and in bladder, and normal uptake of [^{18}F]-FDG in ascending colon, is also evident.

primary breast tumours, [^{18}F]-FDG PET has been shown to have a mean sensitivity and specificity for tumour detection of 88 and 79% respectively in a recent meta-analysis (Fig. 16.8) [89]. Axillary nodal involvement is a critical issue in the management of patients with breast carcinoma, and [^{18}F]-FDG PET has been shown to have a sensitivity ranging from 57 to 100% and specificity of 66 to 100% across reported series [8]. In a recent prospective study of 360 patients, [^{18}F]-FDG PET was shown to have moderate accuracy in detecting axillary metastases, but often missed small or few nodal metastases [90]. [^{18}F]-FDG PET is therefore not routinely recommended for the axillary staging of breast cancer patients.

One potential area where [^{18}F]-FDG PET has shown great promise is in whole body staging of metastatic breast cancer, where the accuracy of [^{18}F]-FDG PET has been shown to be higher than conventional staging techniques [91, 92]. [^{18}F]-FDG PET has also been evaluated for assessment of tumour response to therapy [61, 93]. Further evaluation in monitoring response to chemotherapy is warranted before the true role of [^{18}F]-FDG PET in this setting can be determined.

Gastric and Oesophageal Tumours

Although the detection of primary gastric and oesophageal tumours with [^{18}F]-FDG PET has been reported to be excellent, the identification of regional nodal metastases has been restricted by the presence of small volume disease in some lymph nodes (Fig. 16.8) [32]. Unsuspected distant disease may be detected by [^{18}F]-FDG PET in up to 20% of cases, and recurrent disease may also be evaluated more accurately than CT scan, which may represent the more appropriate clinical utility of this technique [32].

[^{18}F]-FDG PET has been shown to significantly improve detection of haematogenous and distant lymphatic metastasis in carcinoma of the oesophagus and gastro-oesophageal junction (GEJ) [32, 94–96]. There is no difference in accuracy in detecting squamous cell carcinoma or adenocarcinoma of the oesophagus with [^{18}F]-FDG PET. [^{18}F]-FDG PET may not be as accurate as EUS or CT in determining wall invasion or close lymph node spread of disease, however the diagnostic specificity of lymph node involvement is greatly improved with [^{18}F]-FDG PET [95]. [^{18}F]-FDG PET is more accurate in detecting distant disease, and is also highly accurate in the diagnosis of recurrent disease [94–97]. In assessing response of induction therapy (chemotherapy – radiotherapy) in locally advanced disease, [^{18}F]-FDG PET also appears to be of high value in predicting response [98].

Ovarian Carcinoma

Ovarian carcinoma is the leading cause of death among gynaecological tumours [99]. The treatment of ovarian carcinoma primarily consists of surgical resection followed by chemotherapy and/or radiotherapy. Accurate staging is essential, particularly in the restaging of patients with elevated serum markers (CA-125). [^{18}F]-FDG PET has been shown to have high accuracy in detecting in ovarian carcinoma lesions greater than 1 cm in size, but the detection of micrometastatic disease (one of the most important issues in this disease) has been difficult [100–102]. In several series, [^{18}F]-FDG PET has been shown to be accurate in restaging patients with ovarian cancer, and may be better than CA-125 in this clinical setting [100, 101]. The role of [^{18}F]-FDG PET in the management of ovarian carcinoma remains to be clearly defined, but may princi-

pally be in the evaluation of recurrent masses following therapy, or distant disease.

Germ Cell, Renal Cell and Other Tumours

Studies of [^{18}F]-FDG PET in germ cell tumours and in bone and soft tissue sarcomas have shown high accuracy in detecting metastatic disease and monitoring response to therapy, although reported patient numbers are small [102, 103]. Renal cell carcinoma may also be accurately staged with [^{18}F]-FDG PET, and is particularly useful for the detection of metastatic disease, while false negative primary tumours are occasionally observed [19, 104, 105]. The role of [^{18}F]-FDG PET in tumours such as hepatoma has been limited, due to the low grade nature of these tumours and the poor uptake of [^{18}F]-FDG in clinical studies [2]. In cervical carcinoma, recent reports have shown that [^{18}F]-FDG PET has a high positive predictive value for the detection of metastatic nodes in the pelvis and para-aortic regions, which may assist with surgical planning or possibly indicate cases where chemoradiotherapy may be the most appropriate therapy (Fig. 16.9) [106]. An important emerging role of [^{18}F]-FDG PET is in the detection of metastatic thyroid carcinoma (particularly where ^{131}I scan is negative and serum thyroglobulin levels are elevated), and evaluation of medullary thyroid carcinoma. The application of [^{18}F]-FDG PET in detecting sites of disease for many other less common malignant tumours is the subject of continuing clinical review.

Monitoring Response of Tumour to Therapy

An emerging area of clinical utility of PET is in the monitoring of tumour response to therapy, principally with [^{18}F]-FDG. Accurate evaluation of response to both chemotherapy and radiation therapy, often prior to CT scan changes, have been reported in glioma, colorectal, NSCLC, lymphoma, head and neck tumours, and soft tissue sarcomas [2, 8, 16, 17, 42, 61, 107]. The timing and reliability of [^{18}F]-FDG PET studies in predicting tumour response is the subject of numerous prospective studies. The implications of this approach are significant in terms of optimising treatments, minimising unnecessary morbidity, and reducing costs.

Perhaps the most potentially important clinical use of PET can be found in the ability to label with positron emitters compounds that are either physiologic targets or therapeutics used in cancer therapy. This enables the development of novel compounds, either therapy compounds themselves (e.g., ^{18}F-Fluorouracil), or tracers that measure physiologic events (e.g. ^{18}F-fluoromisonidazole for hypoxia, and $H_2{}^{15}O$ for perfusion), that can predict the success of a therapeutic approach [3, 5, 108, 109]. The pharmacokinetics and pharmacodynamics of therapeutics, measurements of biologic change (e.g., DNA proliferation, signalling events, oxygen metabolism, protein synthesis), or success of treatment *e.g.*, gene therapy, can be accurately evaluated by PET, and may enable more scientific decisions to be made as to treatment efficacy, and how improvements in effect can be achieved [5, 29, 110–114]. These "surrogate markers" for tumour biology provide a unique link between the molecular

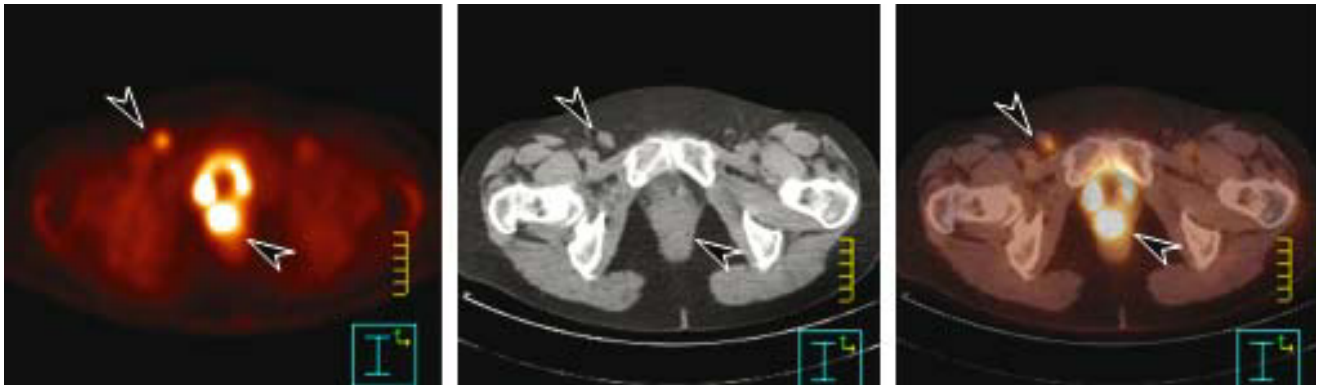

Figure 16.9. A 71-year-old woman with a cervical carcinoma underwent a PET/CT scan for staging. Transaxial (A) [^{18}F]-FDG PET image shows a large primary tumour (arrow) posterior to the bladder, as well as a right groin lymph node (arrow). (B) CT image, and (C) co-registered [^{18}F]-FDG PET/CT scan show the location of the primary and metastatic tumour.

events associated with cancer to the biology of tumour cells, and will dramatically assist in the development of innovative approaches to cancer therapy .

PET/CT scanners in Oncology

The development of combined PET/CT scanners has dramatically changed the approach to PET image interpretation, as the seamless integration of anatomic and PET images allows more accurate determination of abnormal sites and potential clinical relevance [115]. The superior accuracy of this approach in the assessment of many cancers including NSCLC, colorectal cancer, lymphoma and melanoma has been reported [116, 117]. Further assessment of this technology, including the ability to integrate PET/CT data in radiotherapy treatment planning, is an area of significant importance for the management of oncology patients in the future.

Conclusions

PET has emerged as a powerful diagnostic tool in the management of patients with cancer. The published literature has provided evidence of the superior utility over conventional imaging methods of the principal PET tracer [^{18}F]-FDG in the staging of a range of cancers, in monitoring disease recurrence, and in changing patient management to more appropriate therapy. Emerging new PET tracers that can quantitate non-invasively biologic processes within tumours, and the introduction of PET/CT into routine clinical practice, are further enhancing the role of PET in oncology. PET has the potential to dramatically improve our ability to manage patients with cancer, and is making major contributions to our understanding of cancer biology and in developing new therapies.

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