Clinicians' Guides to Radionuclide Hybrid Imaging · PET/CT
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Nagabhushan Seshadri
Chinnamani Eswar *Editors*

PET/CT in Cancer of Unknown Primary

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PET/CT

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PET/CT in Cancer of Unknown Primary

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PET/CT series is dedicated to Prof Ignac Fogelman, Dr Muriel Buxton-Thomas and Prof Ajit K Padhy

Foreword

Clear and concise clinical indications for PET/CT in the management of the oncology patient are presented in this series of 15 separate booklets.

The impact on better staging, tailored management and specific treatment of the patient with cancer has been achieved with the advent of this multimodality imaging technology. Early and accurate diagnosis will always pay, and clear information can be gathered with PET/CT on treatment responses. Prognostic information is gathered and can forward guide additional therapeutic options.

It is a fortunate coincidence that PET/CT was able to derive great benefits from radionuclide-labelled probes, which deliver good and often excellent target to non-target signals. Whilst labelled glucose remains the cornerstone for the clinical benefit achieved, a number of recent probes are definitely adding benefit. PET/CT is hence an evolving technology, extending its applications and indications. Significant advances in the instrumentation and data processing available have also contributed to this technology, which delivers high throughput and a wealth of data, with good patient tolerance and indeed patient and public acceptance. As an example, the role of PET/CT in the evaluation of cardiac disease is also covered, with emphasis on labelled rubidium and labelled glucose studies.

The novel probes of labelled choline, labelled peptides, such as DOTATATE, and, most recently, labelled PSMA (prostate-specific membrane antigen) have gained rapid clinical utility and acceptance, as significant PET/CT tools for the management of neuroendocrine disease and prostate cancer patients, notwithstanding all the advances achieved with other imaging modalities, such as MRI. Hence, a chapter reviewing novel PET tracers forms part of this series.

The oncological community has recognised the value of PET/CT and has delivered advanced diagnostic criteria for some of the most important indications for PET/CT. This includes the recent Deauville criteria for the classification of PET/CT patients with lymphoma—similar criteria are expected to develop for other malignancies, such as head and neck cancer, melanoma and pelvic malignancies. For completion, a separate section covers the role of PET/CT in radiotherapy planning, discussing the indications for planning biological tumour volumes in relevant cancers.

These booklets offer simple, rapid and concise guidelines on the utility of PET/CT in a range of oncological indications. They also deliver a rapid aide memoire on the merits and appropriate indications for PET/CT in oncology.

Peter J. Ell

London, UK

Preface

Hybrid imaging with PET/CT and SPECT/CT combines best of function and structure to provide accurate localisation, characterisation and diagnosis. There is extensive literature and evidence to support PET/CT, which has made a significant impact on oncological imaging and management of patients with cancer. The evidence in favour of SPECT/CT especially in orthopaedic indications is evolving and increasing.

The *Clinicians' Guide to Radionuclide Hybrid Imaging* pocketbook series is specifically aimed at our referring clinicians, nuclear medicine/radiology doctors, radiographers/technologists and nurses who are routinely working in nuclear medicine and participate in multidisciplinary meetings. This series is the joint work of many friends and professionals from different nations who share a common dream and vision towards promoting and supporting nuclear medicine as a useful and important imaging speciality.

We want to thank all those people who have contributed to this work as advisors, authors and reviewers, without whom the book would not have been possible. We want to thank our members from the BNMS (British Nuclear Medicine Society, UK) for their encouragement and support, and we are extremely grateful to Dr Brian Nielly, Charlotte Weston, the BNMS Education Committee and the BNMS council members for their enthusiasm and trust.

Finally, we wish to extend particular gratitude to the industry for their continuous support towards education and training.

Gopinath Gnanasegaran
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London, UK

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1. Cancer of Unknown Primary (CUP)

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1.1 Introduction

The term "cancer of unknown primary" refers to a condition in which a patient has metastatic malignancy without an identified primary source. The majority of patients have malignancy which appears to derive from epithelial cells and hence are regarded as having carcinoma of unknown primary. Cancer of unknown primary (CUP) is diagnosed following histological confirmation of malignancy with no obvious primary after a detailed history, examination and investigations. It occurs in 4–5% of patients presenting with invasive cancer [1].

1.2 Epidemiology

Cancer of unknown primary makes up 3% of all new cancer cases in the UK. It constitutes 3% of total male cancers and 3% of total female cancers. In 2011, there were 9762 new cases of CUP in the UK, 4482 (46%) in men and 5280 (54%) in women, giving a male/female ratio of about 8:10 [2].

The incidence of CUP increases with age, the highest incidence seen in older men and women. In the UK between 2009 and 2011, 55% of cases were

diagnosed in men and women over 75 years of age, and 77% were diagnosed in those over 65 years of age. The age-specific incidence rates rise gradually from age group 25–29 years and then more sharply from age group 70–74 years with the highest incidence being in those above 85 years [2]. CUP incidence rates have decreased in the UK since mid-1990s. The European incidence rates have decreased by 39 and 34% in males and females, respectively. The decrease is a consequence of more unknown cancers having their primary sites identified due to improvements in pathology and immunohistochemistry [3].

CUP represents about 2.2% of all deaths in the UK and is regarded as the fourth common cause of cancer death [2]. The reported overall prognosis of CUP patients is generally very poor with a median survival of 4–12 months, with about 50% of patients alive at 1 year and about 10% at 5 years from diagnosis [4].

1.3 Clinical Presentation/Signs and Symptoms

The clinical presentation of CUP is variable and can either present with general symptoms of advanced malignancy such as tiredness, weight loss and loss of appetite or more specific symptoms due to tumour invasion, e.g. superior vena cava obstruction from a mediastinal mass. It is quite common for patients to present with symptoms due to metastasis in the bone, lung, liver and brain. Sometimes, there are patients with minimal symptoms who are diagnosed following abnormal blood tests such as anaemia, hyponatremia, hypocalcaemia and abnormal liver functions. There are also patients diagnosed after incidental abnormalities noted on radiograph or computed tomography (CT) which they have for other illnesses.

1.4 Diagnosis and Staging Procedures/Investigations

The evaluation of presumed CUP should be systematic and focused. Although the diagnostic algorithm differs depending on the clinico-pathologic presentation, the initial standard workup should include a comprehensive history, physical examination, urinalysis, blood tests and chest X-ray. As long as they are reasonably fit, the patients should also have a CT of the chest and a CT or magnetic resonance imaging (MRI) of the abdomen and pelvis. In addition, women should have pelvic examination and

mammography and in men estimation of prostate-specific antigen (PSA). Some specific symptoms may need certain investigations, e.g. haemoptysis - bronchoscopy; GI bleeding - endoscopy. Further investigations should be considered depending on the histology and after review of initial investigations in a multidisciplinary team (MDT) meeting.

The goals of initial standard workup and biopsy are histological confirmation of the metastatic lesions, identifying the cell lineage (and likely primary sites) of the cancer and guiding further selective tests to identify the favourable or treatable subsets of patients [5].

The next step of workup involves additional selective tests to identify specific subsets of patients, to provide site-specific therapy to the patients who have favourable clinical features or treatable types of tumours [6].

Finally focused immunohistochemistry or molecular-genetic profiling for the choice of treatment may be obtained, which enable and may provide individualized therapy for selected patients to achieve better response to treatment and longer survival gain [7]. However, at present this is offered in selected institutions as molecular profiling is not recommended as part of the routine evaluation as per NCCN Guidelines because more data from prospective clinical trials are necessary to confirm whether molecular profiling can improve the prognosis of patients with CUP [8].

1.5 Prognosis

Few signs and patterns of presentation have been identified to assess prognosis in patients with CUP. Data from the Swedish Cancer Registry revealed that patients with metastases limited to lymph nodes had better prognosis than those with extra nodal disease [9]. Patients with better performance score, low serum lactate dehydrogenase (LDH) and higher serum albumin were identified as favourable prognostic factors as they are more likely to benefit from chemotherapy [10]. Similarly, poor performance status, male gender, elevated LDH levels, metastatic adenocarcinoma involving multiple organs and malignant ascites were identified as adverse prognostic indicators (Table 1.1) [11].

Table 1.1 Investigations to be considered before diagnosis of CUP in patients with suspected CUP

Clinico-pathological data
• Histological confirmation of metastatic cancer

• Detailed medical history • Complete physical (including breast, nodal areas, skin, pelvic and rectal) examination • Histopathology review with specific immunohistochemistry
Laboratory test data for all patients
• Full blood count • Biochemistry • Urinalysis • Testing for occult blood in stools • Chest radiography • CT scan of the thorax, abdomen and pelvis
Laboratory test data for selected patients only
• Mammography (for all women) • Breast MRI • Testicular ultrasonography • PET/CT • Symptom-directed endoscopy • Estimation of serum α-fetoprotein and β-human chorionic gonadotropin • Estimation of serum prostate-specific antigen (in men) • Estimation of serum cancer antigen 125 and cancer antigen 15-3

Key Points

- Cancer of unknown primary (CUP) is diagnosed following histological confirmation of malignancy with no obvious primary after a detailed history, examination and investigations.
- The incidence of CUP increases with age, the highest incidence seen in older men and women.
- Clinical presentation of CUP is variable.
- Evaluation of presumed CUP should be systematic.
- The goals of initial standard workup and biopsy include histological confirmation of the metastatic lesions, identifying the cell lineage of the cancer and guiding further selective tests to identify the favourable or treatable subsets of patients.

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2. An Overview of the Pathology of Cancer of Unknown Primary

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2.1 Introduction

Morphologically, CUP can be classified as (1) well, moderately, or poorly differentiated adenocarcinoma; (2) squamous cell carcinoma; (3) poorly differentiated carcinoma; (4) carcinoma with neuroendocrine differentiation; and (5) undifferentiated cancer. Almost 50% of patients with diagnosed CUP have metastatic adenocarcinoma of well to moderate differentiation, 30% with undifferentiated or poorly differentiated carcinomas, 15% with squamous cell carcinomas, and the remaining 5% will have undifferentiated neoplasms.

Therefore, it is important in the diagnosis of CUP to receive an adequate tumor tissue or properly processed cytological samples. It is also very important for the pathologist to receive as much clinical information to aid his or her assessment.

2.2 Immunohistochemistry

Immunohistochemistry is the only standard test which could be the determining factor in suggesting the primary origin of the lesion. They help pinpoint the site of tumor origin in about 30% of patients [1]. Cytokeratins are intermediate filaments specific to epithelial cells expressed in some normal human tissues, and they have 20 different subunits. Cytokeratin antibody combinations are widely used to predict the anatomical origin of adenocarcinomas. In the diagnostic approach of patients with CUP, clinical features together with morphological characteristics provide a road map to further steps and pathology with immunohistochemistry, which at each step, can give answers leading to the final diagnosis [2].

Several immunohistochemical markers have been proposed to predict the site of the primary tumor. They mainly help determine whether the cancer is a carcinoma, melanoma, lymphoma, or sarcoma. It also helps in subtyping adenocarcinoma; germ cell tumor; hepatocellular, renal, thyroid, neuroendocrine, or squamous carcinoma; and the primary site of adenocarcinoma, i.e., prostate, lung, breast, colon and pancreas, biliary, or ovarian cancer (Table 2.1).

Table 2.1 Summary of stepwise approach of immunohistochemistry markers and their specific tumor types

Immunohistochemistry markers	**Diagnosis**
Step one—Cell lineage	
AE1 or AE3 pan-cytokeratin	Carcinoma
Common leucocyte antigen	Lymphoma
S100; HMB-45	Melanoma
S100; vimentin	Sarcoma
Step two—Subtype of carcinoma	
CK7 or CK20; PSA	Adenocarcinoma
PLAP; OCT4; AFP; HCG	Germ cell tumor
Hepatocyte paraffin 1; canalicular pCEA, CD10, or CD13	Hepatocellular carcinoma
RCC; CD10	Renal cell carcinoma
TTF1; thyroglobulin	Thyroid carcinoma
Chromogranin; synaptophysin; PGP9.5; CD56,	Neuroendocrine
CK5, or CK6; p63	Squamous cell carcinoma
Step three—Primary site of adenocarcinoma	
PSA; PAP	Prostate
TTF1	Lung

GCDFP-15; mammaglobin; estrogen receptor	Breast
CDX2, CK20	Colon
CDX2 (intestinal epithelium); CK20; CK7	Pancreas or biliary
ER; CA-125; mesothelin; WTI	Ovary

2.3 Molecular Diagnosis

Studying for tissue-specific gene expression profile during carcinogenesis can help classify CUP according to the primary site [3]. There are now a number of commercial tests available with accuracy rates of 33–93%. A few examples are the 1550-gene microarray-based Pathwork Tissue of Origin Test, a 92-gene real-time quantitative RT-PCR assay, and the miRview MET test.

2.4 Subsets

Classification of patients with CUP into several clinico-pathological subsets is helpful in investigation and management. This has to be according to age, sex, clinical presentation, histopathology, and organ and site involvement (Table 2.2).

Table 2.2 Metastatic sites and pathological subsets

	Median age (year)	**Male/female (%)**	**Histopathology**
Lymph node sites			
Mediastinal and retroperitoneal	<50	70/30	Undifferentiated or poorly differentiated carcinoma
Axillary	52	0/100	Adenocarcinoma
Cervical	57–60	80/20	Squamous cell carcinoma
Inguinal	58	50/50	Undifferentiated carcinoma, squamous cell carcinoma, mixed squamous and adenocarcinoma
Primary peritoneal in women	55–65	0/100	Adenocarcinoma
Neuroendocrine tumors	63	60/40	Poorly differentiated with neuroendocrine features, low-grade neuroendocrine cancers
Liver	62	61/39	Adenocarcinoma
Lung sites			

Pulmonary metastasis			Adenocarcinoma
Pleural effusion			Adenocarcinoma
Bones			Adenocarcinoma
Brain	51–55	M > F	Adenocarcinoma

Key Points

- Almost 50% of patients with diagnosed CUP have metastatic adenocarcinoma of well to moderate differentiation.
- Immunohistochemistry is the only standard test which could be the determining factor in suggesting the primary origin of the lesion.
- Cytokeratin antibody combinations are widely used to predict the anatomical origin of adenocarcinomas.
- Immunohistochemical markers have been proposed to predict the site of the primary tumor.

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3. An Overview of the Management of Cancer of Unknown Primary

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3.1 Introduction

In CUP, therapy should be tailored on an individual basis according to the clinico-pathological subset of distinct prognosis to which the patient belongs. The management of patients who are confirmed to have favourable subsets or treatable types of CUP after a stepwise diagnostic approach should follow specific guidelines that are based on site-specific therapy or treatment guidelines of metastatic cancer with a known primary tumour. Further, accurate prognostic predictors are potentially of value in clinical decision-making, allowing optimal treatment to be used in those most likely to gain the greatest benefit, whilst avoiding the unnecessary toxicity of futile anticancer treatment in those unlikely to benefit [1].

3.2 Surgical

There has been evidence from a systematic review that in women who present with adenocarcinoma involving axillary nodes, surgery with axillary

lymph node clearance and mastectomy along with local radiotherapy and appropriate systemic chemotherapy gives good results [2]. The standard initial treatment for isolated cervical neck nodal involvement with squamous cell carcinoma has been radical neck dissection. Surgery is also used as a palliative procedure for fixation of long bones to prevent a fracture. In spinal secondaries it is used for spinal stabilisation to prevent or treat spinal cord compression. In patients with oligometastasis in the lung, liver or brain, surgical resection is considered after weighing up other factors.

3.3 Chemotherapy

Chemotherapy has always been the mainstay of treatment in CUP. The decision on the chemotherapy regimen is usually made taking into account the patient-specific and tumour-specific factors. In women with adenocarcinoma involving the peritoneal cavity, platinum and paclitaxel combination chemotherapy is used, similar to treatment of ovarian cancer. The response rates can be as high as 80% with a median survival of 36 months [3]. Patients with poorly differentiated carcinoma with a midline distribution are usually treated like poor prognosis germ cell tumour with platinum-based combination chemotherapy. Patients with poorly differentiated neuroendocrine carcinoma are treated with platinum or platinum and taxane combinations. In isolated adenocarcinoma of axillary nodes after surgery, systemic treatment is used along the lines of breast cancer management. Herceptin and hormonal agents are used according to the receptor status. Sometimes, immune profiling can help in selecting the chemotherapy regimen, e.g: if colonic profile is present, using colorectal chemotherapy regimens. Preliminary data suggest that CUP patients with certain immunohistochemical and/or molecular profile assay diagnoses appear to have improved response rates and survival after site-specific therapies [4]. These data are from small numbers of patients, and additional prospective validation is necessary to substantiate these preliminary findings. Therefore, participation in clinical trials evaluating combinations of cytotoxic compounds with targeted agents or site-specific therapy in patients with putative primary tumour sites highly suspected from immunohistochemical or microarray studies should be strongly encouraged [1].

3.4 Radiotherapy

A radical course of radiotherapy is used after radical neck dissection postoperatively in squamous cell carcinoma of cervical nodes and similarly after lymph node dissection of isolated squamous cell carcinoma of inguinal nodes. In isolated axillary nodes after nodal dissection, breast radiotherapy or mastectomy followed by chest wall radiotherapy is considered. Radiotherapy is more often used for palliation of bone and brain metastasis and for soft tissue invasion or nodal metastasis. Recently, there have been studies investigating SABR (stereotactic ablative body radiotherapy) in patients with oligometastasis [5].

3.5 Supportive Therapies

Patients with CUP also need to be considered for supportive agents such as bisphosphonate in bony metastasis. They may also need adequate management of symptoms with analgesics, antiemetics, etc. and would benefit from good access to palliative care team and psychological medicine if needed.

When deciding on management, multidisciplinary team (MDT) discussion is important with input from the pathologist, radiologist, oncologist, surgeon, specialist nurses and palliative care team. The individual subsets may help to inform us of whether a more radical or palliative approach will be appropriate, but equally important is the information on patient performance status and co-morbidity. Particular unfavourable prognostic groups are those with multiple visceral metastases where response rates from treatment are around 20% with a median survival of 6–7 months [6].

3.6 Management of CUP Patients Who Do Not Fall into Any Specific Subset

The majority of CUP patients (80–85%) do not belong to specific subsets, and their response to treatment is very modest with a median overall survival of less than a year. Two prognostic groups can be identified in this group: those with a good performance status (0–1) and a normal lactate

dehydrogenase (LDH) value, with a median life expectancy of 1 year, and those with either one or both of these prognostic factors, with a median overall survival of only ~4 months [7]. Patients with poor-risk CUP have a poor prognosis even on treatment with a variety of chemotherapeutic combinations. A recent meta-analysis showed no evidence of superior efficacy of any of the administered regimens incorporating platinum salts, taxanes or new-generation cytotoxic compounds (gemcitabine, vinca alkaloids or irinotecan) [8]. A randomised prospective phase III study of 198 patients which compared gemcitabine/irinotecan with paclitaxel/carboplatin/oral etoposide in fit poor-risk patients reported significantly less toxicity with the two-drug regimen and equal survival rates [9]. On the other hand, the efficacy/toxicity ratio of the cisplatin–gemcitabine combination was found to be better than that of the cisplatin–irinotecan regimen in a randomised phase II trial [10]. Modest survival benefit and symptom palliation with preservation of quality of life are the aims of therapy for these patients. Consequently, low-toxicity patient-convenient chemotherapy regimens should be administered to reasonably fit poor-risk CUP patients (Table 3.1).

Table 3.1 Commonly used chemotherapy regimens in various patient subsets

Chemotherapy	Toxicity
Cisplatin gemcitabine	Fit patients, adequate hydration
Cisplatin etoposide	Fit patients with neuroendocrine feature—CUP, adequate hydration
Paclitaxel carboplatin	Convenient outpatient regimen, monitor neurotoxicity
Docetaxel carboplatin	Convenient outpatient regimen, monitor neurotoxicity
Irinotecan oxaliplatin	Outpatient regimen, monitor neurotoxicity and diarrhoea
Oral capecitabine and oxaliplatin	Outpatient regimen, risk for diarrhoea and neurotoxicity
Gemcitabine irinotecan	Convenient outpatient regimen, monitor diarrhoea

Key Points

- Patient management should be tailored on an individual basis according to the clinico-pathological subset.
- Chemotherapy has always been the mainstay of treatment in CUP. The decision on the chemotherapy regimen is usually made taking into account the patient-specific and tumour-specific factors.
- A radical course of radiotherapy is used after radical neck dissection

postoperatively in squamous cell carcinoma of cervical nodes and similarly after lymph node dissection of isolated squamous cell carcinoma of inguinal nodes.

- Multidisciplinary team (MDT) discussion is important in the management.
- The majority of CUP patients (80–85%) do not belong to specific subsets, and their response to treatment is very modest with a median overall survival of less than a year.

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4. Radiological Imaging in Cancer of Unknown Primary

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4.1 Introduction

Imaging plays an important role in CUP, not only as an initial diagnostic screen but also aims to define the primary site and determine whether the malignancy is localised or disseminated. Plain radiographs of the chest and bone have been advocated in the initial workup of these patients. Ultrasound is a fairly quick and easy procedure that does not use radiation, which is why it is often one of the first tests done if an internal mass is suspected. Mammography or breast ultrasound is recommended in women presenting

with axillary or supraclavicular node adenocarcinoma metastases or mediastinal, lung, peritoneal, retroperitoneal, liver, bone or brain metastases if occult breast malignancy needs to be excluded.

Cross-sectional imaging like CT, MRI and PET plays an important role in CUP, because the primary tumour can be located anywhere in the body. In addition, by virtue of their ability to image the entire body, they help detect or exclude additional metastatic sites, which may have important therapeutic or prognostic consequences [1].

4.2 Ultrasound

Abdominal and pelvic ultrasound can be useful to get to a diagnosis in patients who are not fit enough for further imaging. Ultrasonography of the liver and kidneys can help differentiate tumour from benign cysts. Ultrasound can also help in the drainage of fluid collections. Breast and axillary ultrasound can help guide biopsy which is a common procedure to investigate lymph nodes, breast tumours and liver metastasis. More specialised procedures such as endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) help in diagnosing and accurately staging lung and oesophageal cancers and also obtain biopsies.

4.3 Computed Tomography (CT)

During the past 30 years, the accuracy of detecting an unknown primary tumour by CT or MRI has increased from 11–26 to 33–55% [2]. At presentation most patients have a CT scan of the chest, abdomen and pelvis. The CT in addition to helping to get to a diagnosis also helps in planning further investigations such as upper and lower gastrointestinal endoscopy and bronchoscopy and also sometimes to plan a CT-guided biopsy. It helps with the initial multidisciplinary team (MDT) discussion and referral to site-specific clinicians and also decide whether to take a radical or palliative approach. It also helps to identify subsets to plan further specific investigations and provides information to the pathologist. CT scans are also the standard for radiotherapy planning where a scan is taken in the treatment position with adequate immobilisation, and the oncologist outlines the tumour with adequate margins, thus separating normal tissues close to the treatment field. It is the most common imaging modality to assess response to

chemotherapy and radiotherapy by standardised criteria. In a study by Losa Gaspa et al., CT identified a primary tumour in approximately 25% of CUP patients with initial negative investigations [3].

Optimising imaging protocols in CT is very important. For example, in CT, arterial-phase scanning of the chest and upper abdominal organs (liver, pancreas and kidneys) and portal venous-phase scanning of the abdomen and pelvis provide dual-phase abdominal imaging, which is helpful in detection of hyper vascular liver metastases as well as neuroendocrine tumours and renal cell carcinoma.

4.4 MRI

No data is yet available for the validity of whole-body MRI in patients with CUP. However, MRI enables detection of occult primary breast cancers in as many as 70% of cases [4]. MRI is the imaging diagnostic test of choice in a subset of women with isolated axillary nodal adenocarcinoma. MRI is also the imaging of choice in patients presenting with neck nodes to look for primaries in the head and neck region. In patients with solitary brain tumours, it is helpful in the differentiation of primary and secondary lesions and is more sensitive in looking for smaller metastasis in patients with solitary metastasis before proceeding for surgery or stereotactic radiotherapy. In patients with spinal metastasis, it is the investigation of choice to detect suspected spinal cord compression and helps plan surgery or palliative radiotherapy. In prostate, urinary bladder, cervical, uterine and rectal cancers, it helps in accurately staging the local extent of disease and also helps plan radiotherapy. Multiparametric MRI with diffusion weighting, dynamic contrast enhancement and MR spectroscopy is useful in identifying tumour focus and local staging.

4.5 Radionuclide Bone Scan

Bone scintigraphy is usually used to define the extent of bone metastasis particularly in tumours with osteoblastic metastasis, e.g. prostate and breast. They are also useful to detect disease progression and help make decisions of palliative radiotherapy to sites of bone metastasis. A very high PSA with multiple bone metastases on a bone scan by itself can help diagnose prostate cancer in patients presenting with bone metastasis from an unknown primary.

4.6 Limitations of Anatomical Imaging

Cross-sectional radiological modalities like CT and MRI are limited in that they basically only allow for the detection of anatomical abnormalities and abnormal contrast enhancement, as a result of which small lesions and non-enhancing lesions in normal structures may be missed. This may in particular be an issue in CUP, in which the primary tumour may be of small size [5]. These shortcomings may be overcome by the use of hybrid positron emission tomography–computed tomography (PET/CT) imaging.

4.7 Terminology

Patients with cancer of unknown primary have metastatic malignant disease without an identifiable primary site. Understanding and using accurate terminology for these patients are important not only for accurate recording of diagnosis and management but also for audit/research purposes.

A patient who presents with metastatic malignancy identified on clinical examination or by imaging, without an obvious primary site, is regarded as having ‘malignancy of undefined primary origin’ (MUO). ‘Provisional carcinoma of unknown primary origin’ (p-CUP) is used to refer to patients with metastatic malignancy of proven epithelial, neuroendocrine or undifferentiated lineage, after initial, but not exhaustive investigations. Although a primary site will be found in some of these patients, or a non-epithelial malignancy diagnosed, in some patients a primary site will not be found, and a diagnosis of ‘provisional CUP’ will change to a diagnosis of confirmed or c-CUP after all tests are complete [6].

4.8 Multimodality Imaging and Multidisciplinary Team (MDT) Approach

With modern imaging technology including CT, MRI, SPECT–CT and PET/CT, more patients with initial diagnosis of CUP have their primary sites identified facilitating site-specific therapy. Knowledge of specific imaging findings of primary tumours as well as metastatic patterns of primary cancers is very helpful [7].

4.9 Role of Imaging in Investigations and Management

Imaging plays an integral role in the multidisciplinary diagnostic evaluation of patients with CUP. The CUP multidisciplinary team (MDT) generally includes oncologists, pathologists and oncological and palliative care nurses. Most of the patients referred to the CUP MDT would have had some basic investigations including CT scan of the chest, abdomen and pelvis. Careful and methodical second review of the available imaging can in a significant number of patients point to potential sites of primary disease. The immunohistochemistry studies also help in narrowing the possibilities for potential sites of primary. Based on this information and the clinical condition/performance status of the patient, a further plan of investigations can be performed such as targeted endoscopies or biopsies as shown in Table 4.1.

Table 4.1 Role of radiologist in CUP MDT

Investigation
• Excluding mimics of malignancy • Finding potential sites of primary • Recommending safe and least invasive sites for biopsy • Image-guided biopsy • Correlation of imaging findings with clinical features/immunohistochemistry • Imaging and immunohistochemistry correlation may need to targeted specific investigations affecting management • Avoiding unnecessary imaging tests which will not affect management
Management
• Identifying treatable cancers, e.g. lymphoma • Identifying malignancies with more favourable prognosis • Identifying obstructive complications, e.g. bowel/renal/biliary obstruction • Identifying potential for cord compression

If histological confirmation has not yet been obtained, the radiologist should always consider and exclude the possibility of benign pathology masquerading as metastatic malignancy. For example, in multiple lung nodules labelled as metastases without an obvious primary, the possibility of infection mimicking malignancy should be kept in mind and excluded by histology or short-interval follow-up imaging. Similarly, a subset of patients

with bony lesions can be challenging to work up, and some of these may turn out to have a benign diagnosis after a thorough workup. It is very important for the radiologist to have a high index of suspicion so that these patients are identified either by appearances on imaging. Further it is important to identify patients with better prognostic outcome and assist in planning biopsy for confirmation by histology, or immunohistochemistry as these patients can be targeted by tumour-specific therapy rather than sometimes empirical CUP therapy.

4.10 Goals of a Standard CUP Workup

The goals of initial standard workup and biopsy are as follows: histological confirmation that the lesions are indeed metastatic, identifying the cell lineage (and likely primary sites) of the cancer and guiding further selective tests to identify a more favourable or treatable subsets of patients [7, 8] (Table 4.2). The appropriate use of imaging is dependent principally on distribution of lesions and histology of known disease. The distribution of disease can provide clues to the likelihood of the primary site being above or below the diaphragm. For example, lung metastases are twice as common from primary sites ultimately found to be above the diaphragm. Liver metastases are more common from primary disease below the diaphragm [9].

Table 4.2 Imaging identification of tumours—some with more favourable prognostic outcomes or availability of specific treatment

• Lymphoma • Metastatic disease in neck nodes only—head and neck primary • Adenocarcinoma isolated in axillary node—exclude occult/small breast cancer • Liver metastases from occult colonic primary—surgery/RFA—specifically look for potential colonic masses • Peritoneal carcinomatosis—lower GI or ovarian primary—emerging treatments such as cytoreduction and intraperitoneal chemotherapy • Hepatocellular cancer/intrahepatic cholangiocarcinoma • Young men with undifferentiated cancer in retroperitoneum or mediastinum—consider testicular or extragonadal germ cell tumours

After the initial review of clinical, radiological and pathological information by the MDT, it is important to select further targeted tests which have a high likelihood of positive results as nontargeted studies rarely detect the primary site, and confusion can result from false-positive results. It is

therefore important to avoid investigations that do not change management. F-18 FDG PET/CT is currently mainly used in CUP patients presenting with metastatic cervical lymph nodes and unknown primary. There is also an emerging role in problem-solving in challenging patients for identifying suitable sites and guiding biopsy and also for influencing management decisions. This is discussed further in a separate chapter.

Close communication between the pathologist, oncologist and imaging specialists is crucial at this stage. Some clinico-pathologic findings may guide the choice of further imaging studies, and the findings from imaging studies may suggest additional pathologic tests.

4.11 Biopsy and Histology: Important Considerations

Biopsy of a safely accessible lesion is important in obtaining a histological diagnosis. In most patients a site suitable and safe for biopsy can be identified after initial investigations including CT scan of the chest, abdomen and pelvis. This is often the most superficial and least invasively accessible lesion. In some instances, especially in the biopsy of skeletal lesions, CT-guided biopsy may not yield a histological diagnosis of malignancy due to false-negative results. This is usually due to the biopsy being inadvertently obtained in the necrotic regions/non-active parts of the tumour, which may not be obvious on CT unless there is a significant change in density. In such cases functional imaging tools such as PET/CT and to a lesser extent SPECT–CT can be used to guide the biopsy and obtain the correct histological diagnosis. Examples of these are illustrated in the Teaching Cases.

4.12 Pearls and Pitfalls

When evaluating patients, it is important to remember that the pattern of metastatic spread of CUP can be significantly different from that which would be expected from the usual presentation of the same primary tumours if they were not occult. For example, bone metastases are approximately three times more common in pancreatic cancer presenting as occult lesions, but for lung cancer, bone metastases are about 10 times less common. [9] As outlined above, biopsy and histological diagnosis can be challenging due to false-negative results, and it is vital to use all available data from

multimodality imaging for guidance. Finally, it is important to remember benign mimics of malignancy and exclude these to avoid patients erroneously being labelled as metastatic malignancy with associated morbidity.

Emerging treatments and increasing life expectancy for patients with moderately advanced cancer make it imperative for imaging to improve diagnosis of potential sites of primary wherever possible. This often needs multimodality imaging and should always be dealt with a multidisciplinary approach to improve patient benefit. Imaging also plays a vital role in identifying patients with better prognostic subsets and channelising them to appropriate treatment to ensure better treatment and prognostic outcomes.

Key Points

- Imaging plays an important role in CUP.
- Plain radiographs of the chest and bone have been advocated in the initial workup.
- Cross-sectional imaging like CT, MRI and PET plays an important role in CUP.
- During the past 30 years, the accuracy of detecting primary tumour by CT or MRI has increased from 11–26 to 33–55%.
- Multiparametric MRI with diffusion weighting, dynamic contrast enhancement and MR spectroscopy is useful in identifying tumour focus and local staging.
- Bone scintigraphy is usually used to define the extent of bone metastasis particularly in tumours with osteoblastic metastasis.
- Small lesions and non-enhancing lesions in normal structures may be missed in cross-sectional radiological modalities like CT and MRI. This may in particular be an issue in CUP, in which the primary tumour may be of small size.
- Multidisciplinary approach is vital in identifying patients with appropriate prognostic subsets, guiding choice of further imaging studies and channelising them to appropriate treatment to ensure better treatment and prognostic outcomes.

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5. ^{18}F-FDG and Non-FDG PET Radiopharmaceuticals

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5.1 Introduction

Positron emission tomography/computed tomography (PET/CT) is one of the key imaging techniques in oncology. Hybrid PET/CT provides both structural and metabolic information and in general improves sensitivity, specificity and reporter confidence.

Fluorine-18 (^{18}F) is the most commonly used PET-emitting radionuclide label in clinical practice. It is produced using a cyclotron and has a physical half-life of 110 min. The most widely used tracer at present is the glucose analogue, 2-fluoro-2-deoxyglucose (FDG) (Table 5.1).

Table 5.1 Oncology PET radiopharmaceuticals [1–11]

Class	Radiopharmaceutical	Clinical application
Oncology: ^{18}F	Fludeoxyglucose (FDG)	Glucose metabolism
	Fluoride	Bone metabolism
	Fluoro-L-thymidine (FLT)	DNA synthesis

	Fluoromethylcholine (FCH)	Phospholipid synthesis
	Fluoroethylcholine (FEC)	Phospholipid synthesis
	Fluoroethyltyrosine (FET)	Protein synthesis
	Fluoromisonidazole (FMISO)	Hypoxia
	Fluoroazomycin arabinoside (FAZA)	Hypoxia
	Fluoroerythronitroimidazole (FETNIM)	Hypoxia
	Fluciclatide	Angiogenesis
	F-Galacto-RGD	Angiogenesis
	Fluciclovine (FACBC)	Amino acid transport
	ICMT11	Apoptosis
Oncology: ^{11}C	Acetate	Membrane synthesis
	Choline	Phospholipid synthesis
	Methionine	Protein synthesis
Oncology: ^{68}Ga	DOTATOC	Somatostatin receptor
	DOTATATE	Somatostatin receptor
	HA-DOTATATE	Somatostatin receptor
	DOTANOC	Somatostatin receptor
	Somatoscan	Somatostatin receptor
	PSMA	Prostate-specific membrane antigen
	NOTA-RGD	Angiogenesis
Oncology: ^{124}I	Iodide	Sodium iodide symporter
	MIBG	Neuronal activity

Table 5.2 Properties of positron-emitting radionuclides used in clinical practice

Radionuclide	Half-life	Positron energy (max, MeV)	Other emissions	Means of production
Carbon-11	20 min	0.96	–	Cyclotron
Nitrogen-13	10 min	1.20	–	Cyclotron
Oxygen-15	2 min	1.74	–	Cyclotron
Fluorine-18	110 min	0.63	–	Cyclotron
Copper-62	10 min	2.93	–	Generator
Copper-64	13 h	0.65	Beta, gamma	Cyclotron
Gallium-68	68 min	1.83	–	Generator
Rubidium-82	76 s	3.15	–	Generator
Zirconium-89	79 h	0.40	Gamma	Cyclotron
Iodine-124	4.2 days	1.50	Gamma	Cyclotron

5.2 PET Radiopharmaceuticals

5.2.1 ^{18}F-FDG

^{18}F-FDG has a role in localising, characterising, staging and monitoring treatment response and evaluation of recurrent disease in a variety of cancer types. However, increased FDG uptake is not specific to cancer cells. FDG accumulates in cells, in proportion to glucose utilisation [1–5]. In general, increased glucose uptake is a characteristic of most cancers and is in part mediated by overexpression of the GLUT-1 glucose transporter and increased hexokinase activity [1–5]. The net result is an increased accumulation of FDG within tumour cells at a rate greater than in normal tissue. Active inflammatory changes can also result in increased FDG uptake, due to increased glucose utilisation by activated granulocytes and mononuclear cells [1–5] (Tables 5.1– 5.3). The principal route of excretion of FDG from the bloodstream is via the urinary tract. The biodistribution of ^{18}F-FDG varies on several factors such as (a) fasting state, (b) medications, (c) duration of the uptake period post tracer injection, (d) variant metabolism, (e) incidental pathology, etc.

Table 5.3 Common radiopharmaceuticals and their mechanism of uptake [11]

Radiotracer	Mechanism of uptake
^{18}F-Fluorodeoxyglucose (FDG)	Uptake by GLUT-1 transporter followed by phosphorylation by hexokinase
Sodium ^{18}F-fluoride (NaF)	Incorporated within hydroxyapatite in proportion to bone metabolism
^{68}Ga-labelled peptides	Bind to peptide receptor, most commonly somatostatin receptor
^{18}F-Choline (FCH) ^{11}C-Choline	Incorporation into phosphatidylcholine as part of cell wall synthesis
^{11}C-Methionine	Amino acid transport
^{18}F-Fluorothymidine (FLT) ^{11}C-Thymidine	Phosphorylated by thymidine kinase in proliferating cells, FLT not incorporated into DNA
^{82}Rb-Chloride	Transported into myocardial cells by sodium-potassium ATPase in proportion to regional myocardial perfusion

5.2.2 Non-FDG Radiopharmaceuticals

In addition to ^{18}F-FDG, there are several cyclotron- and generator-based radiolabelled molecules used in clinical PET/CT imaging. Sodium fluoride (^{18}F-NaF), ^{68}Ga-labelled peptides, ^{18}F-choline, ^{11}C-choline, etc. each have clinical applications and are discussed in detail in this pocket book series titled 'PET Radiotracers'. While FDG is the workhorse of oncological PET imaging, it is non-specific as it monitors the ubiquitous process of glucose metabolism. Alternative tracers tend to be more specific in their targeting and application. Some attempt to probe the hallmarks of cancer, such as uncontrolled proliferation, angiogenesis, evasion of apoptosis and tissue invasion. Tumour microenvironment, such as hypoxia, has also been probed. However, the tracers which have come into wider use tend to be those which monitor specific features such as membrane synthesis incorporating choline, prostate-specific membrane antigen (PSMA) expression and somatostatin receptor expression.

Conclusion
It is likely that the range of positron-emitting radiopharmaceuticals in routine clinical use will continue to expand in the coming years.

Key Points

- Fluorine-18 (^{18}F) is the most commonly used PET-emitting radionuclide label in clinical practice.
- Fluorine-18 (^{18}F) is produced using a cyclotron and has a physical half-life of 110 min.
- Most widely used tracer at present is the glucose analogue, 2-fluoro-2-deoxyglucose (FDG). FDG is the workhorse of oncological PET imaging.
- FDG is actively transported into the cell mediated by a group of structurally related glucose transport proteins (GLUT).
- Increased FDG uptake is not specific to cancer cells and often will accumulate in areas with increased metabolism and glycolysis.
- The principal route of excretion of FDG from the bloodstream is via the

urinary tract.

- Non-FDG tracers include sodium fluoride (^{18}F-NaF), ^{68}Ga-labelled peptides, ^{18}F-choline and ^{11}C-choline.

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6. Cancer of Unknown Primary: Role of FDG PET/CT

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6.1 Introduction

Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic malignancies for which no primary site of the tumour is found despite extensive diagnostic workup. The patients have malignancy which appears to derive from epithelial cells. CUP accounts for approximately 5% of all cancer diagnoses and is characterised by early dissemination and uncommon metastatic sites and usually carries a poor prognosis [1]. Appropriate treatment strategy is still lacking in this subgroup of patients. Detection of primary tumour in CUP patients may help optimise treatment and thereby improve prognosis.

Conventional diagnostic workup has improved over the years; however, it remains a significant diagnostic challenge to identify the primary tumour site in CUP patients. Cross-sectional imaging techniques scan the entire body, which is important in CUP, because the primary tumour can be located anywhere in the body. Despite advancements in CT and MRI technology,

their utility in CUP is limited. This is largely because these imaging techniques detect predominantly anatomical abnormalities, as a result of which small lesions and non-enhancing lesions, especially with no structural abnormalities, may be missed. This is an issue in CUP, in which the primary tumour may be of small size, and anatomical changes appear much later in the evolution of disease.

Positron emission tomography (PET) provides unique information about the molecular and metabolic changes associated with disease, which can occur in the absence of corresponding anatomical changes. This along with the complimentary anatomic information from computed tomography (CT) provides precise localisation of radiotracer accumulation and thereby improves diagnostic performance. Positron emission tomography/computed tomography (PET/CT) by providing both concurrent anatomical and functional information in a single study has now become an integral part of oncologic imaging and has gained wide acceptance [2]. Because of its high sensitivity for the detection of lesions, combined PET/CT imaging is an attractive tool and is emerging as an excellent alternative to CT alone and conventional magnetic resonance imaging (MRI) in detecting the unknown primary tumour. Its utility is in the search for the primary tumour, evaluate the extent of disease and possible pattern of spread and select amenable biopsy sites.

In CUP the aim of PET/CT is to identify a primary tumour undetected by all previous tests. Identification of an occult primary is presumed to result in improved treatment outcomes as compared with empirical therapy and may optimise treatment planning, which, in turn, may improve patient prognosis. PET/CT may identify additional occult metastases, the knowledge of which may significantly affect management in some situations.

The literature evidence for the use of PET/CT in patients with CUP is largely attributed to the studies with Fluorine-18 labelled fluorodeoxyglucose (F-18 FDG). The rationale for the use of FDG for PET imaging in CUP is due to the fact that the vast majority of malignant cancer phenotypes exhibit increased glucose metabolism [3].

6.2 Evidence for the Use of PET/CT in CUP

Several studies have explored the role of FDG PET/CT in patients with CUP. The evidence is largely from retrospective studies with heterogeneous cohorts

of CUP patients having varying inclusion criteria. Further, some of the earlier studies utilised PET alone, whereas the more recent studies involved combined PET/CT.

A comprehensive review of ten studies, which included three with FDG PET/CT and seven with stand-alone FDG PET, evaluated the efficacy in the detection of primary tumours in patients with CUP after physical examination and conventional workup failed to detect a primary tumour [4]. The study showed that this technique helped detect primary tumours in 41% (range, 24–63%) of the patients that were not apparent after conventional workup. Further, by using this technique, it also led to the detection of previously unrecognised metastases in 37% of patients and altered the clinical management in 34.7% of patients.

In a meta-analyses by Dong et al. [5] involving 21 studies with 480 patients of CUP, 28.5% of primary tumours not apparent on conventional workup were detected on stand-alone FDG PET. Likewise in eight studies with 430 patients, the primary tumour was diagnosed in 31.4% of patients with CUP using the combined FDG PET/CT.

Cervical nodal metastases from an unknown primary tumour constitute 2% of newly diagnosed head and neck cancers [6]. In a comprehensive study by Rushtoven et al., the overall detection rate of FDG PET, based on 20 studies involving a total of 302 patients, was 24.5%. They showed that it also detects additional local and distant metastases in about 27% of patients [7]. Further studies have also shown that in patients with cervical nodal metastases who underwent FDG PET after a negative endoscopy and negative CT and/or MRI, the detection rate for primary tumour was 27% [8].

Moller et al. [9] in a comprehensive literature review of four studies involving 152 CUP patients with extra-cervical metastases, FDG PET/CT detected the primary tumour in 39.5% of patients. In this review, lung was the most commonly detected primary tumour site (50%). The pooled estimates of sensitivity, specificity and accuracy of FDG PET/CT in the detection of the primary tumour site were 87, 88 and 87.5%, respectively.

Further a recent meta-analysis showed that, overall, FDG PET/CT is able to detect 37% of primary tumours in patients with CUP, with both sensitivity and specificity of 84% [10]. The analysis is presented in Table 6.1.

Table 6.1 Diagnostic performance of FDG PET/CT in primary tumour detection [Kwee et al. 10]

Study and year	Primary tumour detection (%)	Sensitivity		Specificity	

		Value	95% CI	Value	95% CI
Freudenberg et al. 2005	57	86	60–96	100	65–100
Nanni et al. 2005	57	100	76–100	89	57–98
Gutzeit et al. 2005	33	88	66–97	89	73–96
Fakhry et al. 2006	32	70	40–89	75	47–91
Pelosi et al. 2006	35	83	66–93	87	73–94
Ambrosini et al. 2006	53	100	84–100	95	76–99
Fencl et al. 2007	22	55	38–70	75	62–85
Bruna et al. 2007	38	93	70–99	77	57–90
Fleming et al. 2007	73	94	73–99	100	61–100
Nassenstein et al. 2007	28	100	74–100	85	69–94
Wartski et al. 2007	34	93	69–99	73	48–89
Pooled estimate	**37**	**84**	**78–88**	**84**	**78–89**

In all these studies, the sites of primary tumour suggested by FDG PET/CT were confirmed by histopathologic analysis of tissues that were obtained by biopsy or surgery; however, imaging procedures or clinical follow-up was accepted if no histopathologic proof could be obtained.

6.3 PET/CT in Response Assessment

There are no large studies available to demonstrate the therapeutic impact of PET/CT specifically in CUP. The National Oncologic PET Registry (NOPR) showed that overall FDG PET/CT changed treatment decisions in 36.5% of all oncology cases [11]. Also there are no studies designed to study the effect of a PET/CT on patients' survival in CUP. However, one study reported that the survival rate of CUP patients with at least one FDG-avid lesion was significantly lower ($p = 0.00001$) than that of the remaining CUP patients [12]. Whereas, another study reported that median overall survival between FDG PET/CT-positive and FDG PET/CT-negative groups was not significantly different [13].

6.4 PET/CT in Radiotherapy Planning

The results of few studies available on the use of FDG PET/CT in patients with cervical CUP for radiotherapy planning indicate that it can modify treatment objective from curative to palliative by detecting distant metastases.

Further, it is shown that incorporation of FDG PET/CT data may significantly alter treatment volumes in patients with cervical CUP [8]. No such studies are available to demonstrate the impact of its use in extra-cervical CUP.

6.5 Stand-Alone PET Versus Combined PET/CT

It is well known that the CT component of a combined PET/CT system allows accurate localisation of sites with FDG uptake and helps discriminate between sites of physiological and pathological FDG uptake, thereby improving diagnostic accuracy.

There are three studies which have directly compared FDG PET/CT to FDG PET alone in CUP. In all three studies, FDG PET/CT was able to detect slightly more primary sites than FDG PET alone, although these differences were not statistically significant [14–16].

Dong et al. in their meta-analyses which included 21 FDG PET and 8 FDG PET/CT studies demonstrated that the pooled accuracy (82.79%), sensitivity (78%) and specificity (83%) of FDG PET/CT evaluations were higher than that by FDG PET alone, which were 78%, 78% and 79%, respectively [5].

A combined PET/CT system does seem to have a clear advantage over a stand-alone PET study in the evaluation of patients with CUP. The pros and cons of F-18 FDG PET/CT in the evaluation of CUP are listed in Table 6.2.

Table 6.2 Pros and cons of FDG PET/CT in the evaluation of CUP

Advantages	Drawbacks
FDG PET/CT is a non-invasive and sensitive imaging modality allowing for detection and staging in a single examination	False negative—Not all malignant lesions are FDG avid. Histology of the primary tumour may influence FDG uptake and identification on PET/CT
FDG PET/CT can explore the whole body in one go and could identify or rule out additional metastatic sites	Small tumours below the spatial resolution of PET may not be reliably detected
Using FDG PET/CT early in the diagnostic workup may reveal useful clinical information and prove beneficial than the current diagnostic strategies	False positive—Inflammation and infection may result in FDG accumulation and mimic malignancy
Early use of FDG PET/CT in the diagnostic pathway has the potential to alter management in extra-cervical CUP	The cost-effectiveness of the use of FDG PET/CT in all patients with CUP is not yet proven

A baseline FDG PET/CT may also play a valuable role for assessment of treatment response following therapeutic intervention	No study has investigated whether the use of FDG PET/CT modified patient outcomes

6.6 PET/CT Protocols

The use of intravenous and oral contrast agents may aid in the evaluation of the CT component of PET/CT study. However, according to the study by Fencl et al., no statistically significant difference was found in the search for a primary tumour or for the presence of any malignant lesion in patients with CUP [13]. Further, a recent meta-analysis showed no beneficial effect of contrast-enhanced CT during PET/CT examination on the diagnostic performance in patients with CUP compared to using no contrast agents at all [10].

Data regarding the influence of different CT protocols on diagnostic performance of FDG PET/CT in CUP are largely lacking; however, it is recommended to use a collimation of less than 2.5 mm, in order to detect small primary lung cancers [16].

Some tumours exhibit a peak FDG uptake well beyond the standard 60 min after FDG administration, while at the same time the surrounding normal tissues show a decline in FDG uptake with time [17–19]. In these subset of patients, additional delayed PET imaging (e.g., 3 h after FDG administration) in order to improve lesion-to-background contrast may be useful [19]. The optimal time for data acquisition has not yet been determined in CUP.

6.7 Limitations

6.7.1 False Positives

FDG is a non-specific radiotracer which can accumulate also in non-malignant areas of increased glycolysis, such as areas of inflammation and infection. The lung has been reported as the most common site of false-positive results using FDG PET/CT in patients with CUP [10]. The false positives could be secondary to iatrogenic pulmonary microembolism due to aspiration of blood during intravenous FDG administration [20], benign inflammatory/infective lesions and pulmonary infarction [15, 21]. Further, frequent overlap between neoplastic and inflammatory/infective causes of FDG uptake in the lung has been reported to impair the diagnostic

performance. Physiological FDG uptake in the lymphoid tissue of the oropharynx can also be misinterpreted as a lesion and may produce false-positive results [22]. This is one of the reasons that the second most common site of false-positive results on FDG PET/CT is the oropharynx [7].

6.7.2 False Negatives

Breast cancer has been reported to be the most common cause of a false-negative FDG PET/CT result in patients with CUP. This is attributable to the small lesion size and low or no FDG uptake. Ovarian cancer has been reported as the second most common cause of false-negative FDG PET/CT result [10].

6.8 Management Impact and Cost-Effectiveness

No study has yet investigated the impact of FDG PET/CT-assisted patient outcomes in CUP. Further the cost-effectiveness of this technique in the evaluation of patients with CUP is not proven. Prospective studies with more uniform inclusion criteria are required to evaluate the exact value of this diagnostic tool.

6.9 Future Directions

The diagnostic challenge for PET/CT is to minimise false-negative results in detecting the primary tumour. A number of radiotracers are under investigation including compounds that can mark hypoxia, angiogenesis and apoptosis in tumours. Advances in PET technology and the integration of PET/MRI as well as improvements in the hardware for data analysis are expected to improve the management of CUP patients.

6.10 Recommendations

The available evidence indicates that FDG PET/CT should be performed as an initial test in CUP patients as it can direct sites of biopsy and could significantly alter treatment objective. It is particularly useful when no primary tumour is identified on conventional imaging and negative endoscopy in this subset of patients. FDG PET/CT is beneficial in the

diagnostic workup of patients with extra-cervical CUP as it has the potential to alter management and should be considered early in the diagnostic algorithm.

Key Points

- PET/CT imaging is an attractive tool and is emerging as an excellent alternative to CT alone and conventional magnetic resonance imaging (MRI) in detecting the unknown primary tumour.
- PET/CT may be useful in detecting the primary tumour, evaluating the extent of disease and possible pattern of spread and selecting amenable biopsy sites.
- PET/CT may identify additional occult metastases, the knowledge of which may significantly affect management in some situations.
- The lung has been reported as the most common site of false-positive results using FDG PET/CT in patients with CUP.
- Physiological FDG uptake in the lymphoid tissue of the oropharynx can also be misinterpreted as a lesion and may produce false-positive results.
- Breast cancer has been reported to be the most common cause of a false-negative FDG PET/CT result in patients with CUP.
- Ovarian cancer has been reported as the second most common cause of false-negative FDG PET/CT result.
- FDG PET/CT should be performed as an initial test in CUP patients as it can direct sites of biopsy and could significantly alter treatment objective.
- PET/CT is particularly useful when no primary tumour is identified on conventional imaging and negative endoscopy in this subset of patients.
- FDG PET/CT is beneficial in the diagnostic workup of patients with extra-cervical CUP as it has the potential to alter management and should be considered early in the diagnostic algorithm.

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7. Pictorial Atlas: Cancer of Unknown Primary

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7.1 Case 1

7.1.1 Clinical Details

A 62-year-old male presented with left-sided neck lump and weight loss. FNAC of the enlarged cervical lymph node was proven to be an adenocarcinoma. Other routine investigations failed to identify the primary tumour. A PET/CT study was performed to search for the unknown primary.

Teaching Points

1. Thyroid nodules found incidentally on 18F-FDG PET are at a relatively high risk of being malignant if uptake is focal (Fig 7.1). The mean incidence of malignancy in thyroid lesions with focal uptake is about 35%. The positive predictive value of focal uptake for malignancy is 39% (Soelberg 2012).

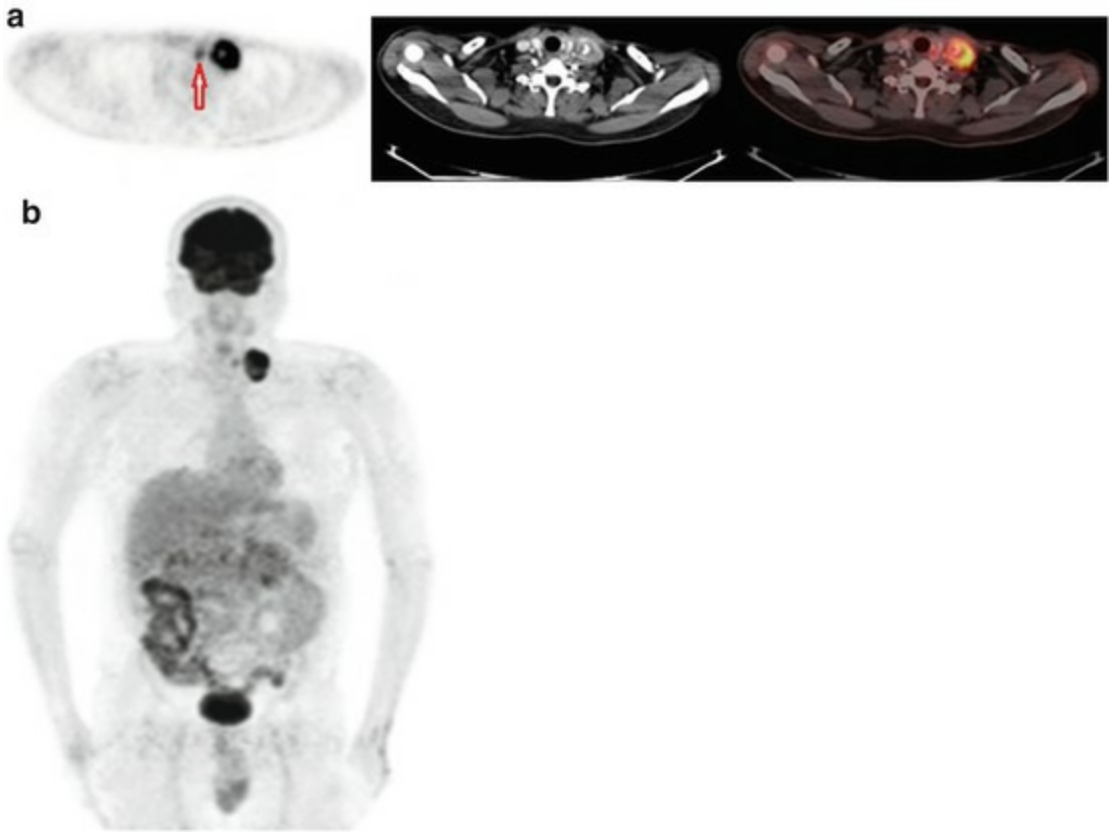

Fig. 7.1 (**a**) PET/CT with intense increased FDG uptake in the enlarged left cervical lymph node. In addition, there is a tiny focus of increased FDG uptake in the left lobe of the thyroid (*red arrow*). FNAC from the metabolically active thyroid nodule revealed papillary carcinoma which was proven on histopathology following total thyroidectomy. (**b**) There is no other abnormal focus of FDG uptake identified elsewhere in the body as demonstrated on MIP images

2. Well-differentiated thyroid cancers are usually radioiodine avid and may display low FDG uptake; in contrast, poorly differentiated thyroid cancers are usually radioiodine negative and FDG positive (Schonberger 2002).

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7.2 Case 2

7.2.1 Clinical Details

A 67-year-old woman presented with pain in the right hip and was detected to have a lytic lesion in the right ischium. Biopsy and histopathology indicated a metastatic carcinoma. FDG PET/CT was undertaken to detect the primary.

Teaching Points

1. The incidence of distant metastases in head and neck squamous cell carcinoma (SCC) is relatively small in comparison to other malignancies. Distant metastases adversely impact survival and management.

2. Pulmonary metastases are the most frequent in head and neck SCC, accounting for 66% of distant metastases. It may be difficult to distinguish pulmonary metastasis from a new primary tumour, particularly if solitary (Fig 7.2). Other metastatic sites include bone (22%), liver (10%), skin, mediastinum and bone marrow (Ferlito 2001).

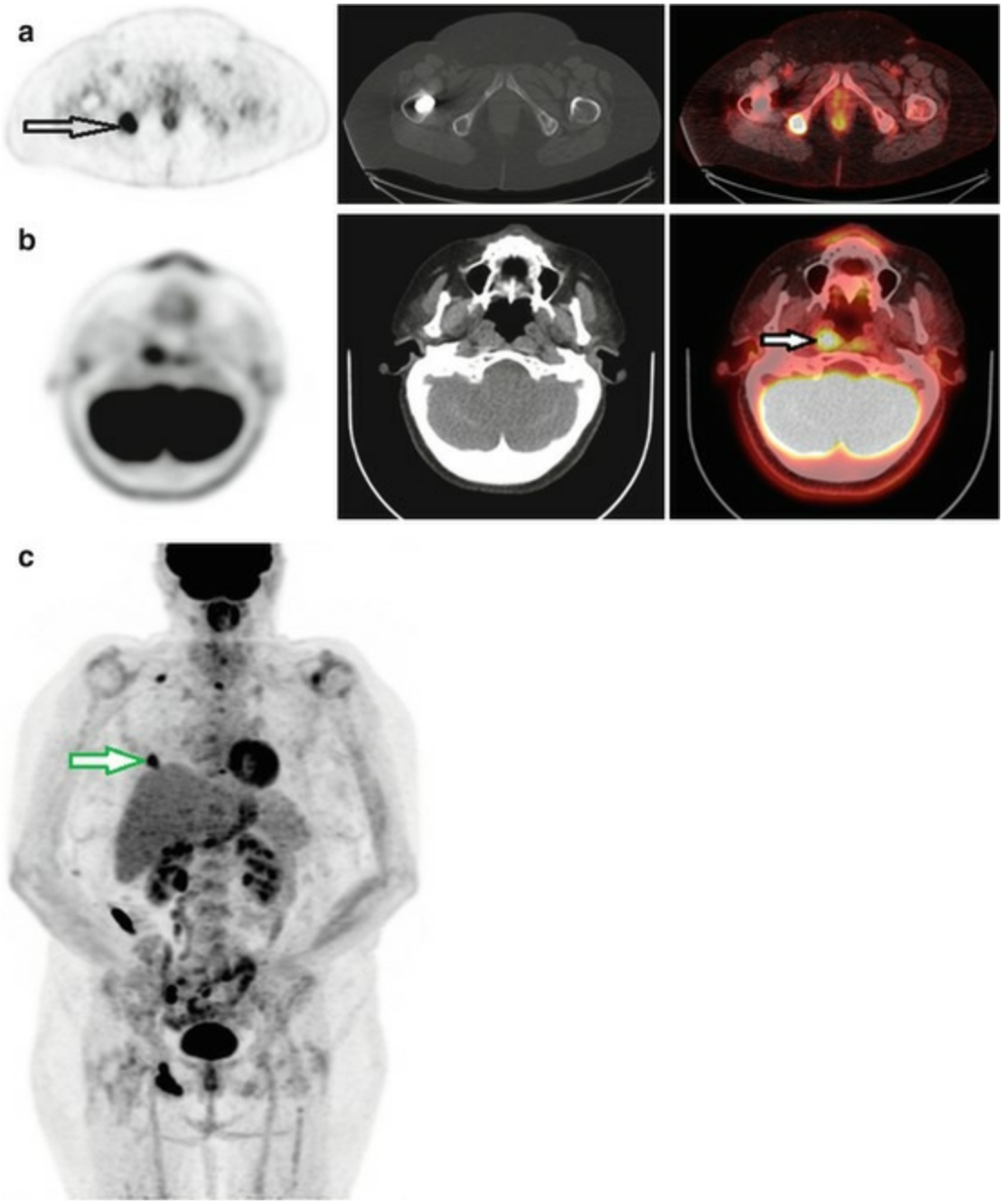

Fig. 7.2 (**a**) PET/CT showed intense FDG uptake corresponding to the lytic lesion (*black arrow*) in the right ischium. (**b**) Axial FDG PET/CT images showed obliteration of the fossa of Rosenmuller on the right with a subtle soft tissue mass with intense FDG uptake suggestive of a primary tumour (*white arrow*). Biopsy and subsequent histopathological examination revealed a squamous cell carcinoma. (**c**) In addition, PET/CT identified a metastasis in the right lung lower lobe (*green arrow*)

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7.3 Case 3

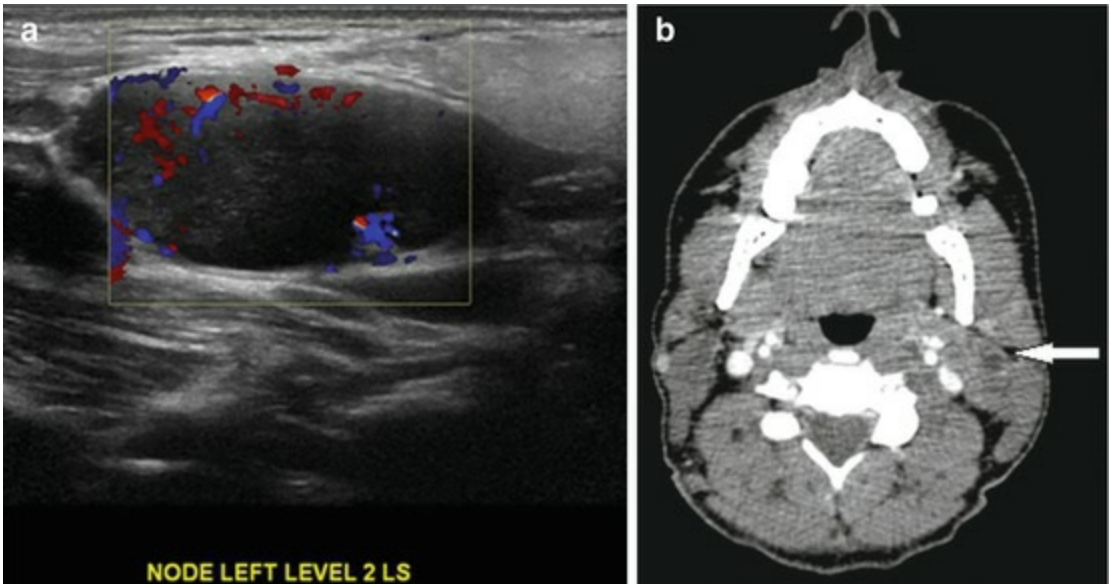
7.3.1 Clinical Details

A 72-year-old male presented with a 2-month history of left-sided neck lump. On palpation, there was an enlarged left cervical lymph node.

Teaching Points

1. Cervical nodal metastases from unknown primary tumour constitute 2% of newly diagnosed head and neck cancers (Grau 2000).

2. The overall detection rate of primary in patients with cervical nodal metastasis on FDG PET is about 25% (Fig 7.3). FDG PET/CT is also shown to detect additional local and distant metastases in about 27% of patients (Rusthoven 2004).



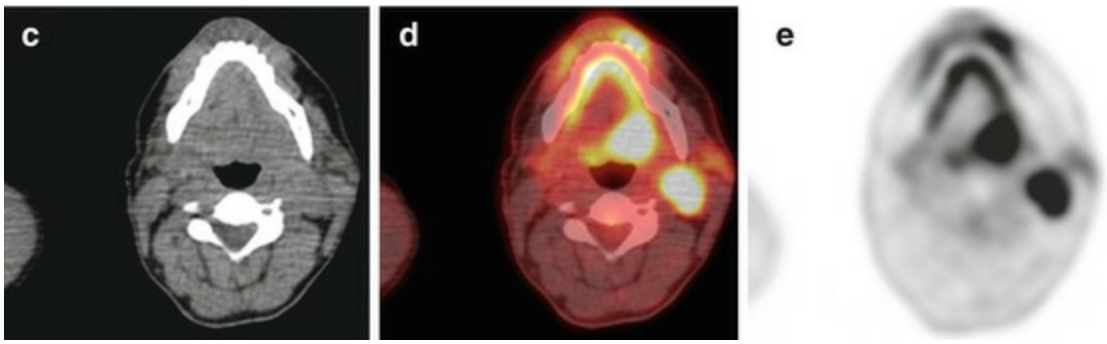


Fig. 7.3 (**a**) An ultrasound scan of the neck showed a 3 cm left level 2 cervical lymph node with a central necrotic area. No other obvious abnormality was identified in the neck. FNAC of the enlarged cervical lymph node showed squamous cell carcinoma. (**b**) As the patient could not tolerate MRI, a contrast-enhanced CT scan of the neck and thorax was undertaken which merely showed a necrotic left level 2 cervical lymph node (*white arrow*). No obvious primary lesion was identified. (**c**–**e**) A PET/CT study was performed to search for unknown primary which showed intense increased FDG uptake in the enlarged left cervical lymph node. In addition, there was a focus of intense in the left tonsil and the adjacent oropharynx which was proven as SCC on histopathology

3. In patients with cervical nodal metastases who undergo FDG PET after a negative endoscopy and negative CT and/or MRI, the detection rate for primary tumour is 27% (Menda 2009).

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7.4 Case 4

7.4.1 Clinical Details

A 35-year old male presented with left-sided neck swelling. Left level 2 node is noted, which on biopsy showed squamous cell carcinoma.

Teaching Points

1. The overall incidence of unknown primary tumours in the head and neck region ranges about 3–7% of all head and neck cancer (Bailet 1992).

2. The sensitivity of FDG PET for detection of primary carcinoma is about 88–100% (Hannah 2002).

3. Scatter (pixel blooming) of focal uptake in primary oropharyngeal tumours, however, can lead to overestimation of the extent of primary disease (Fig 7.4) and not very useful for local (T) staging (Blodgett 2005).

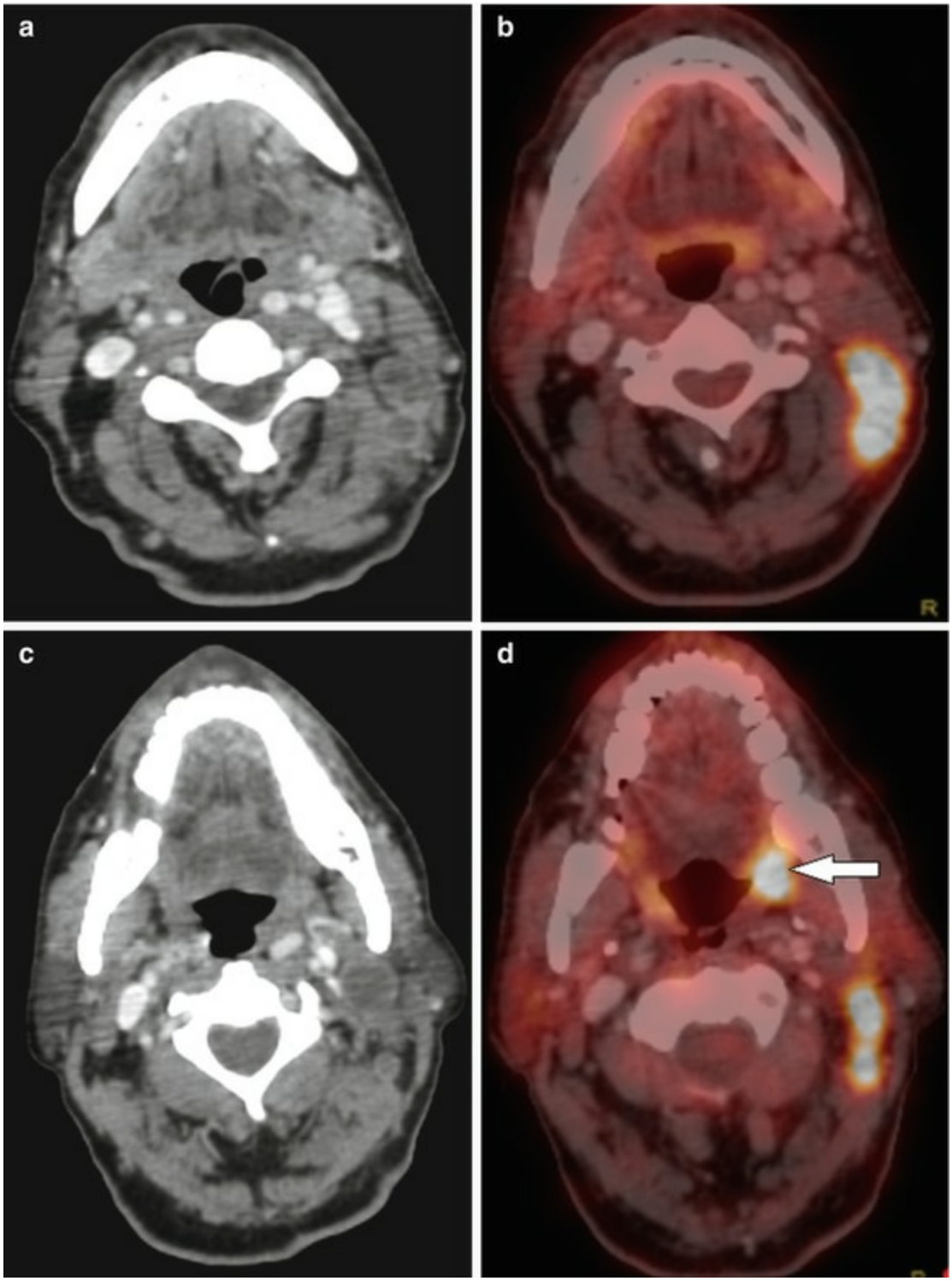

Fig. 7.4 Contrast-enhanced CT (**a**) showed a necrotic left level 2 cervical nodal mass which was intensely FDG avid on PET/CT (**b**). PET/CT (**d**) revealed a focal hypermetabolic lesion in the left gingivo-buccal fold (*white arrow*) which on biopsy was proven to be the primary tumour. No obvious lesion was seen on the diagnostic CT on first read although in retrospect a subtle enhancing lesion is seen at the site (**c**)

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7.5 Case 5

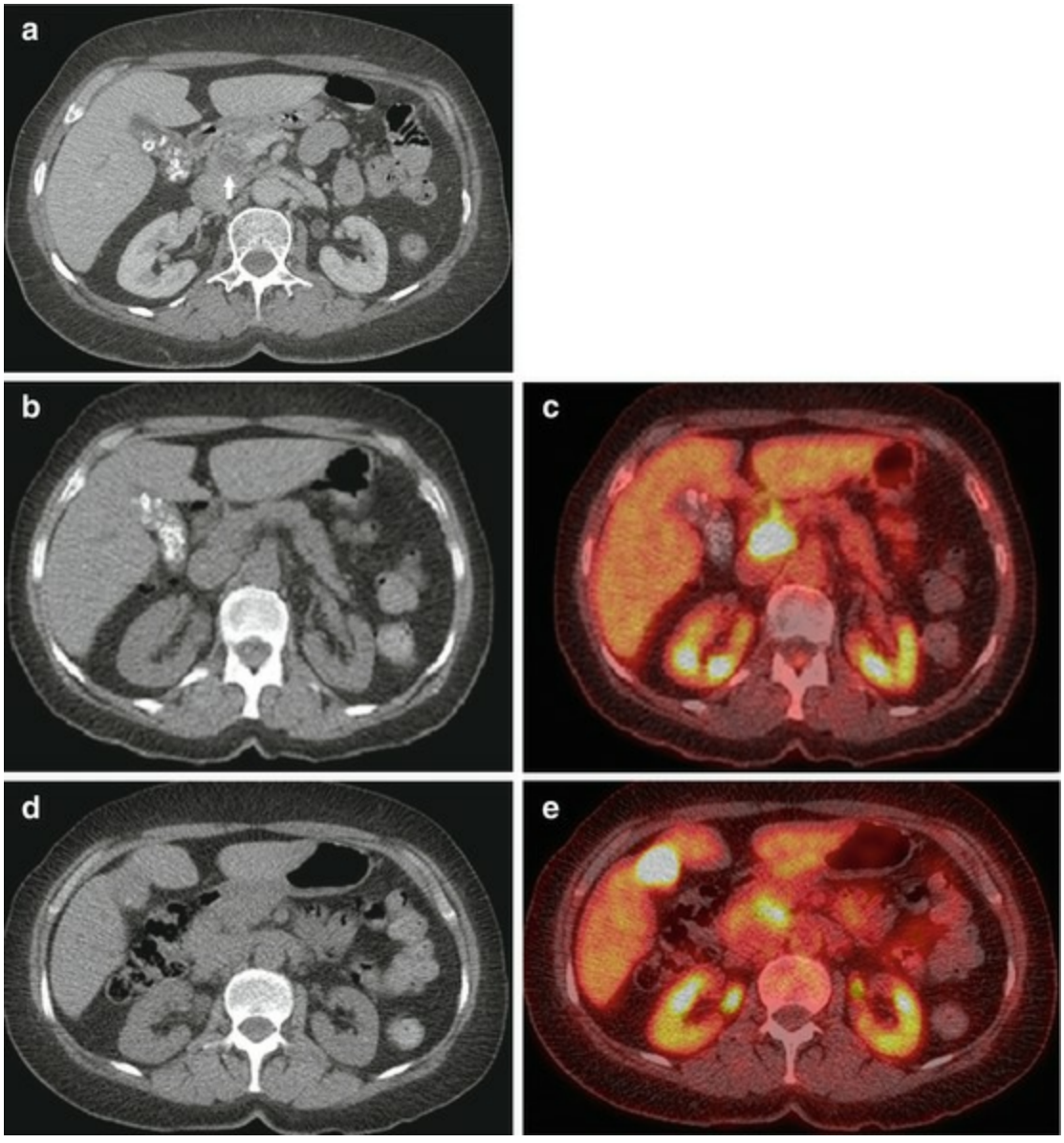
7.5.1 Clinical Details

A 68-year-old woman presented with breathlessness and was diagnosed to have bilateral pulmonary embolism on CT pulmonary angiography. It incidentally revealed a hypodense lesion in the region of the head of pancreas.

Teaching Points

1. Cholangiocarcinoma is the second most common primary hepatic tumour after hepatoma and comprises 10–15% of hepatobiliary malignancies (Nakeeb 1996).

2. It is extremely difficult to detect gall bladder cancer in the early stage (Fig 7.5) with conventional imaging modalities (Shukla 2006).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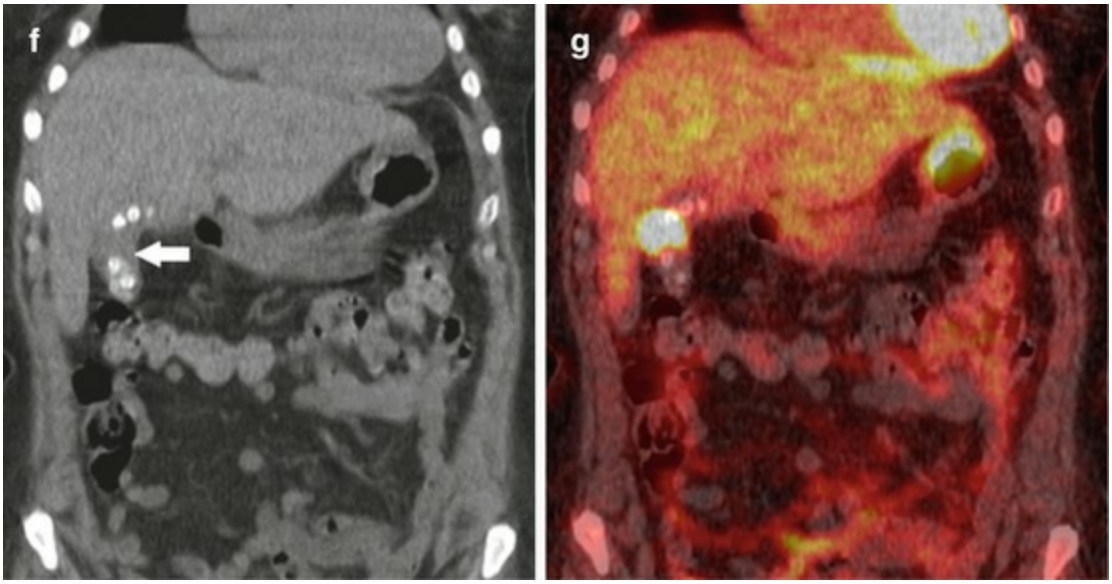

Fig. 7.5 (**a**) A diagnostic CT of the chest, abdomen and pelvis was undertaken in search of underlying malignancy as a cause of pulmonary embolism. This revealed a mass in the region of the head of pancreas (*white arrow*). Incidental gallstones were also seen. Subsequent endoscopic ultrasound and FNAC showed features of an adenocarcinoma with possibility of lymph node metastasis rather than a primary lesion. (**b**, **c**) FDG PET/CT was performed to detect the unknown primary which showed intense metabolic activity in the known lymph node metastasis in the region of the head of pancreas. (**d**, **e**) In addition, there was intense FDG uptake in the gall bladder fundus with a subtle soft tissue density which was difficult to appreciate on the diagnostic CT due to the presence of multiple calculi. (**f**, **g**) The metabolically active lesion in the gall bladder corresponds to a soft tissue density (*white arrow*) on the CT component of the examination as seen on the coronal slices. This was subsequently proven to be adenocarcinoma on histopathology. Further the PET/CT also helped exclude other sites of metastases in this case

3. 18F-FDG PET is extremely useful in the diagnosis and staging of these tumours. It is superior to CT or MR imaging in the detection of LN metastasis; accuracies are 86, 68 and 58%, respectively, in mass-forming intrahepatic cholangiocarcinoma (Seo 2008).

References

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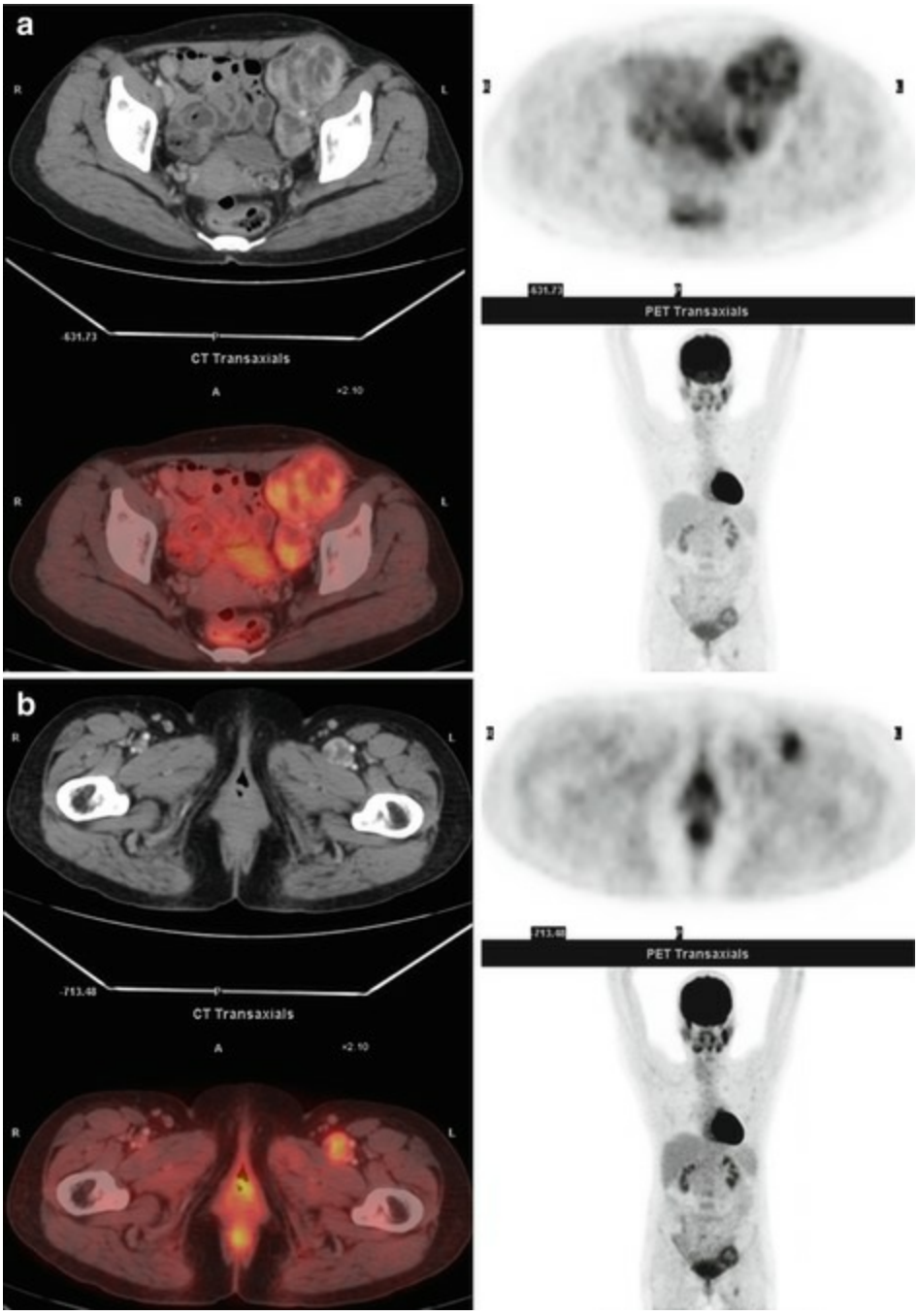
7.6 Case 6

7.6.1 Clinical Details

A 52-year-old woman presented with a lump in the left groin. An ultrasound scan showed an enlarged lymph node mass. Cytologic and immunocytochemical features were suggestive of a sarcoma.

Teaching Points

1. Soft tissue sarcomas are an infrequent group of tumours originating in cells derived from the embryonal mesoderm, representing less than 1% of solid malignant tumours in adults. High-grade sarcomas are generally more FDG-avid than low-grade tumours (Fig 7.6). Low-grade osteosarcomas can produce false-negative results on PET because FDG uptake tends to be low (Dimitrakopoulou-Strauss 2001).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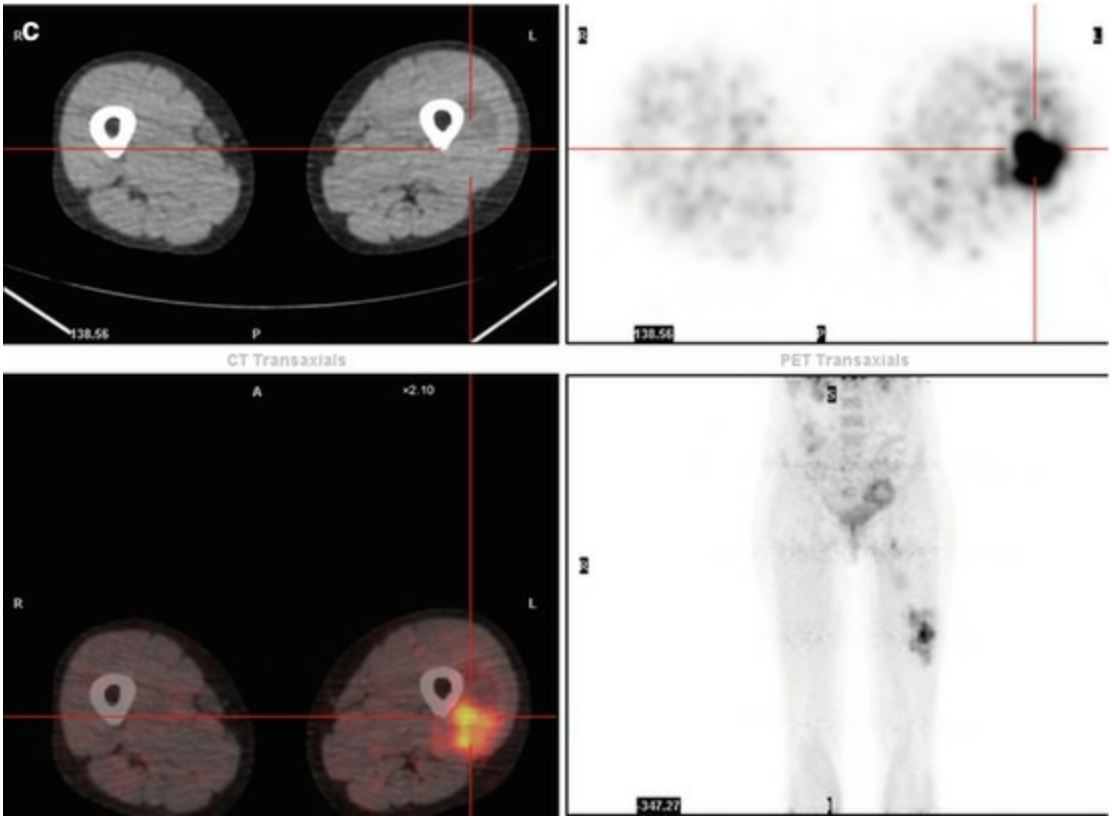

Fig. 7.6 (**a**) An FDG PET/CT examination showed a large necrotic metabolically active left external iliac lymph node mass. (**b**) Enlarged FDG-avid left inguinal lymph node was also noted with no other visible pathology in the pelvis or elsewhere in the upper torso. (**c**) PET/CT images of the lower limbs showed an FDG-avid lesion in the lateral compartment of the left thigh which was barely visible on CECT with some subtle hypodense features. Biopsy confirmed spindle cell sarcoma

2. The sensitivity of FDG PET/CT for the detection of soft tissue tumours is 87% with a specificity of 79%. The positive predictive value for high-grade tumours is higher than that for lower-grade tumours (Ioannidis 2003).

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7.7 Case 7

7.7.1 Clinical Details

A 69-year-old male presented with a lump in the right neck. Ultrasonography revealed bilateral enlarged lymph nodes, and biopsy from the right neck node was proven to be a metastatic squamous cell carcinoma.

Teaching Points

1. In head and neck cancers, SUV of the tumour mass is prognostic for overall survival. SUV of the lymph node is prognostic for extracapsular extension and also for distant metastasis in H & N cancers (Kubicek 2010).

2. Patients with higher lymph node SUVs treated with definitive radiation may warrant higher radiotherapy doses to overcome a greater likelihood of extracapsular extension (Kubicek 2010).

3. Nodal SUV may be used to predict patients who would likely to benefit from induction chemotherapy (Fig 7.7) (Kubicek 2010).

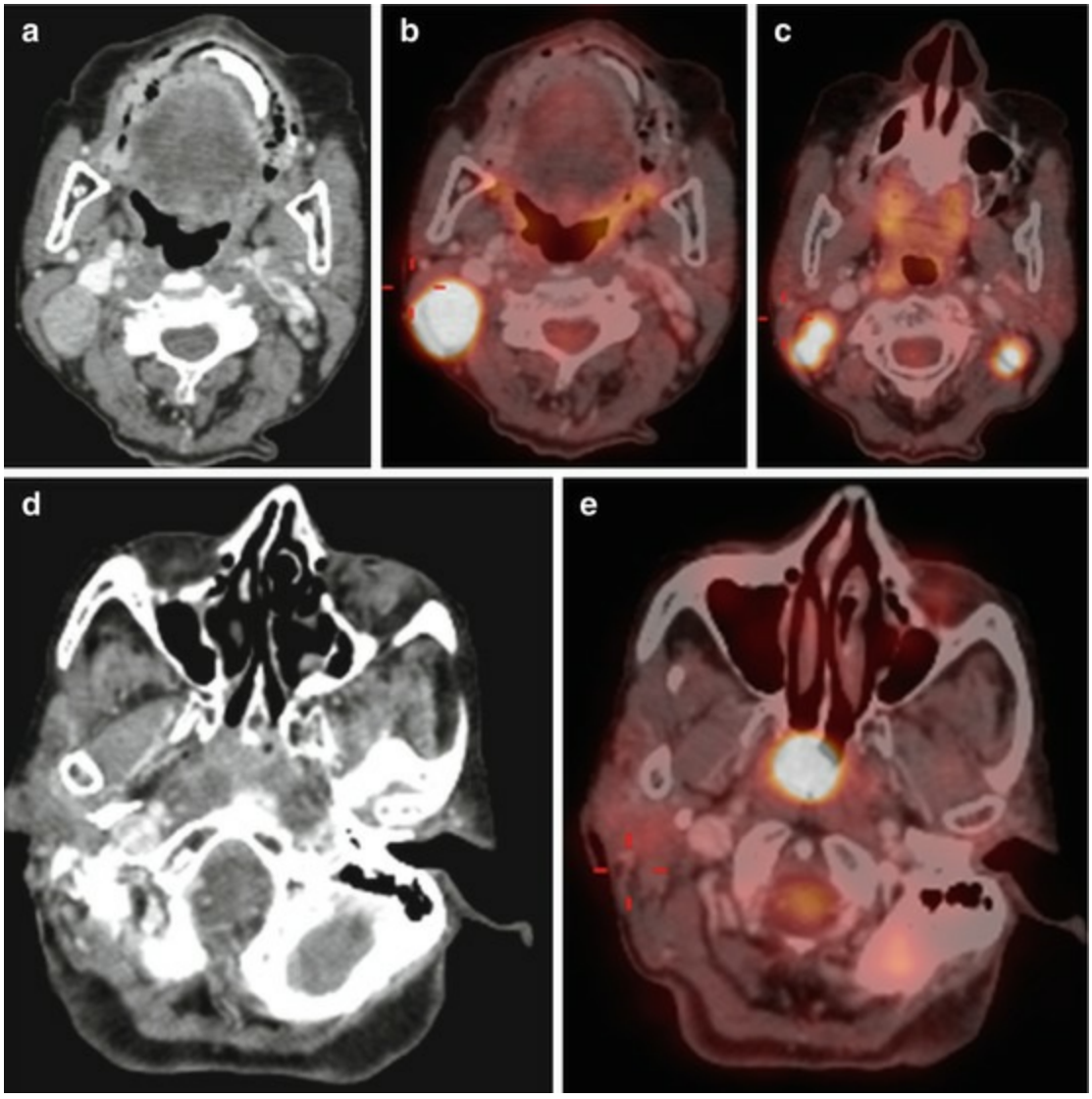

Fig. 7.7 (**a**–**c**) FDG PET/CT showing intense metabolic activity (SUVmax = 21) in the enlarged neck nodes bilaterally compatible with metastasis. There is no easily discernible lesion on CECT (**d**) corresponding to the intense metabolically active (SUVmax = 24) focus in the nasopharynx identified on FDG PET/CT (**e**) which was subsequently confirmed as the primary tumour

Reference

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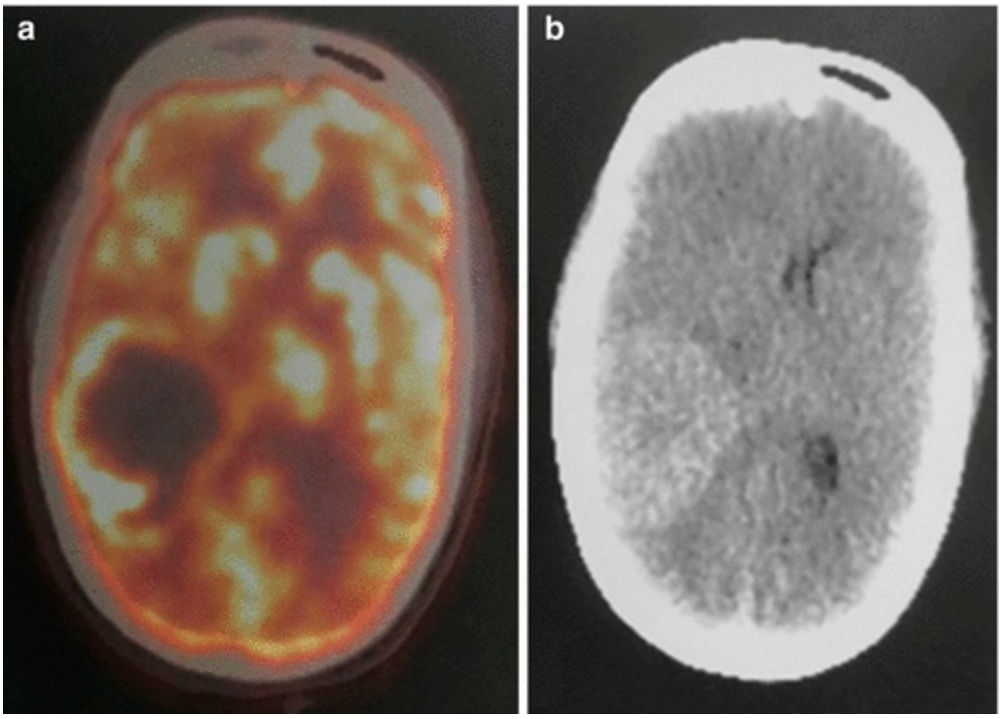
7.8 Case 8

7.8.1 Clinical Details

A 60-year-old female presented with sudden onset seizure and hemiplegia. Diagnostic CT showed a mass lesion in the right temporo-parietal lobe.

Teaching Points

1. Brain metastases are ten times more common than primary brain tumours. Normal brain uses glucose as substrate for metabolism and shows substantial physiological FDG uptake, thus potentially obscuring FDG-avid metastasis (Fig 7.8). Conventional imaging with CT or MRI is the diagnostic imaging of choice (Hagge 2001).



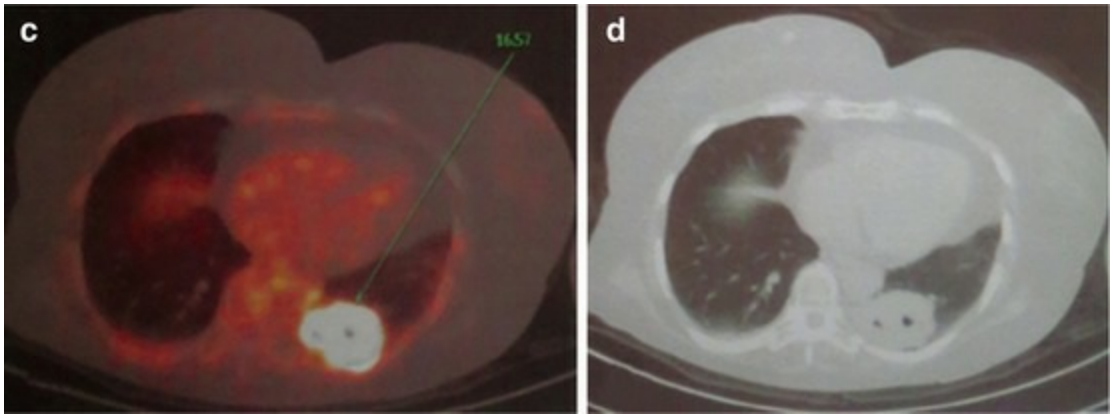


Fig. 7.8 CT head showed a right parieto-temporal mass lesion (**b**). This was largely FDG negative on PET/CT except for a peripheral rim of uptake (**a**). (**c**, **d**) FDG PET/CT showed well-defined cavitary soft tissue mass in the left lower lobe with minimal pleural effusion. This was proven to be a primary adenocarcinoma lung on histopathology

2. The sensitivity of FDG PET/CT for diagnosing lung cancers is 89%, and the specificity is 75% (Deppen 2014).

3. The observation of metastases in patients with non-small cell lung cancer (NSCLC) has major implications on management and prognosis. Forty percent of patients with NSCLC have distant metastases at presentation, most commonly in the adrenal glands, bones, liver or brain (Quint 1996).

4. The use of FDG PET/CT imaging for clinical staging results in a different stage from the one determined by conventional methods in about 27–62% of the patients with NSCLC (Schrevens 2004).

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7.9 Case 9

7.9.1 Clinical Details

A 53-year-old female with low backache and right-sided sciatica was detected to have a large destructive mass lesion in the right sacroiliac region. PET/CT was undertaken to identify the primary tumour.

Teaching Points

1. Eight percent of breast cancer patients present with bony metastases. FDG is sensitive for lytic lesions since the glycolytic rate in lytic metastases is higher (Fig 7.9) (Cook 1998).

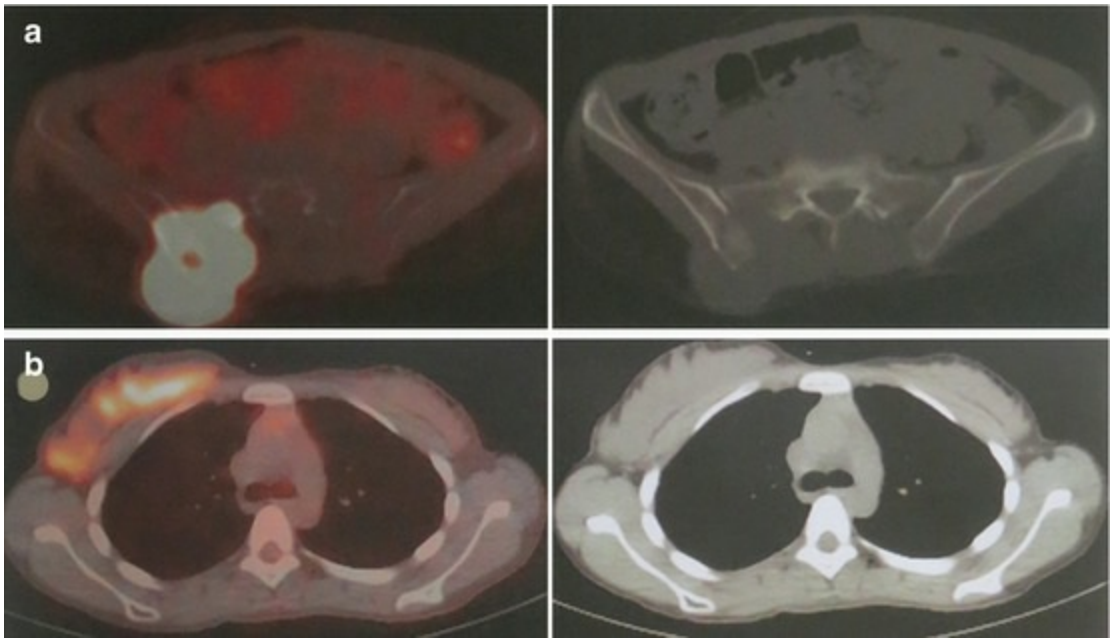

Fig. 7.9 (**a**) FDG PET/CT showed a lytic-sclerotic lesion right sacral ala and adjacent iliac bone with associated soft tissue component involving the gluteus muscle. (**b**) FDG-avid soft tissue mass lesion in the right breast, which was subsequently pathologically proven to be lobular carcinoma of breast

2. FDG PET/CT is not part of current recommendations for initial staging in breast cancer patients; however, there is mounting evidence that, in high-risk patients, results of this examination may be used to modify staging and management in a substantial percentage of patients (Groheux 2013).

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2013;266(2):388–405.

7.10 Case 10

7.10.1 Clinical Details

A 38-year-old male presented with a left supraclavicular lump which on ultrasonography and FNA proved to be metastatic carcinoma. FDG PET/CT was undertaken to identify the primary tumour.

Teaching Points

1. FDG PET/CT has comparable diagnostic performance to CECT in diagnosing primary tumours and regional lymph node metastases in patients with gastric cancers (Fig 7.10) (Kim 2011).

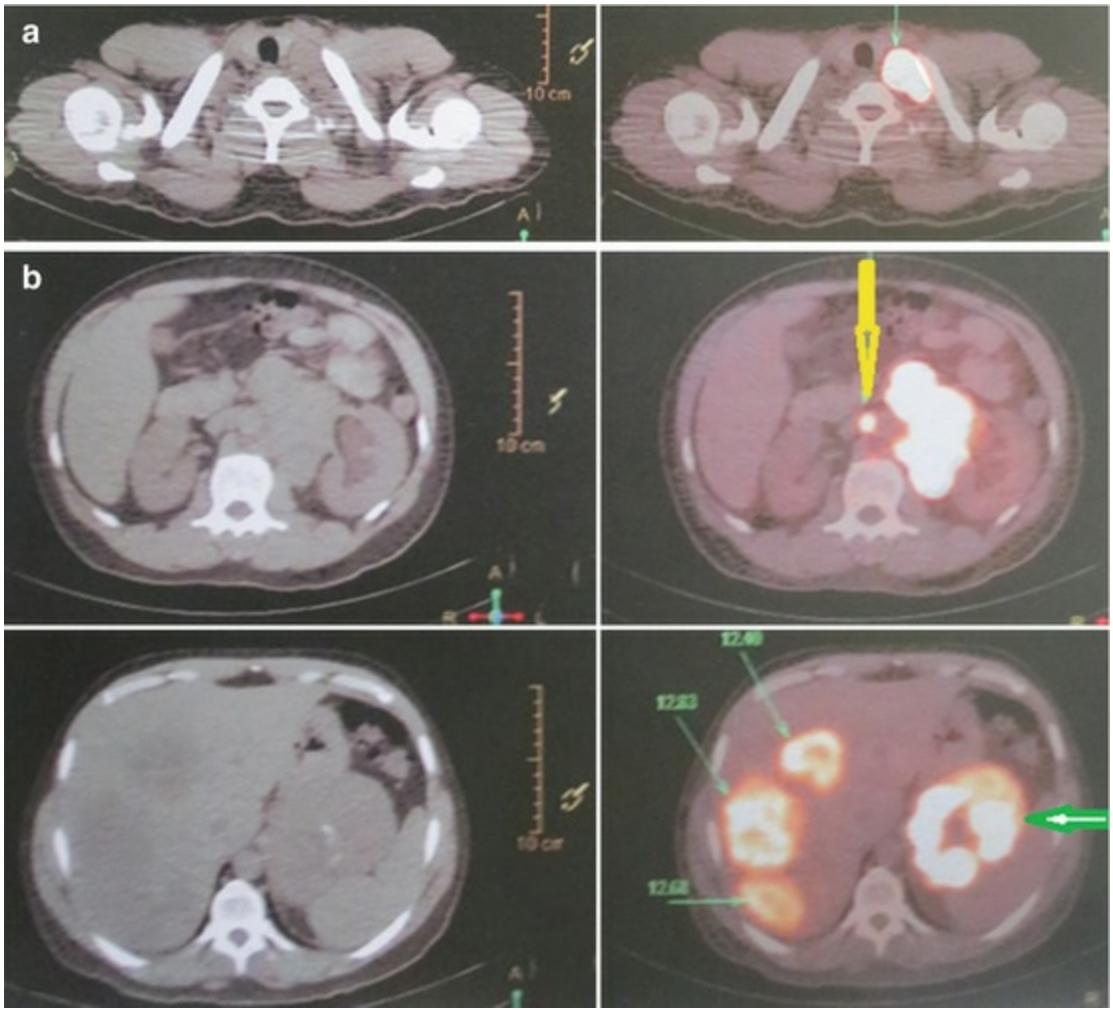

Fig. 7.10 (**a**) PET/CT showed intense FDG uptake in the enlarged left supraclavicular lymph node, confirmed as metastatic carcinoma. (**b**) In addition, there was an FDG-avid mass lesion in the gastric fundus (*solid green arrow*) which on biopsy was proven to be adenocarcinoma with metabolically active upper abdominal lymph node (*yellow arrow*) and multiple liver metastases (*small green arrows*)

2. Solid organ metastasis from the stomach occurs most commonly in the liver via haematogenous dissemination through the portal vein (Miller 1997).

3. The sensitivity of FDG PET/CT to detect certain gastric cancers is low. Mucinous carcinoma, signet ring cell carcinoma and poorly differentiated adenocarcinomas typically have less prominent FDG uptake and may show variable FDG activity (Stahl 2003).

References

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7.11 Case 11

7.11.1 Clinical Details

A 67-year-old male patient presented with low back pain and weight loss. CT and PET/CT images are presented.

Teaching Points

1. As in this case, (Fig 7.11) FDG PET/CT helps target biopsy to the most metabolically active part of the lesion, thus helping obtain a correct diagnosis and leading to prompt treatment (Klaeser 2009).

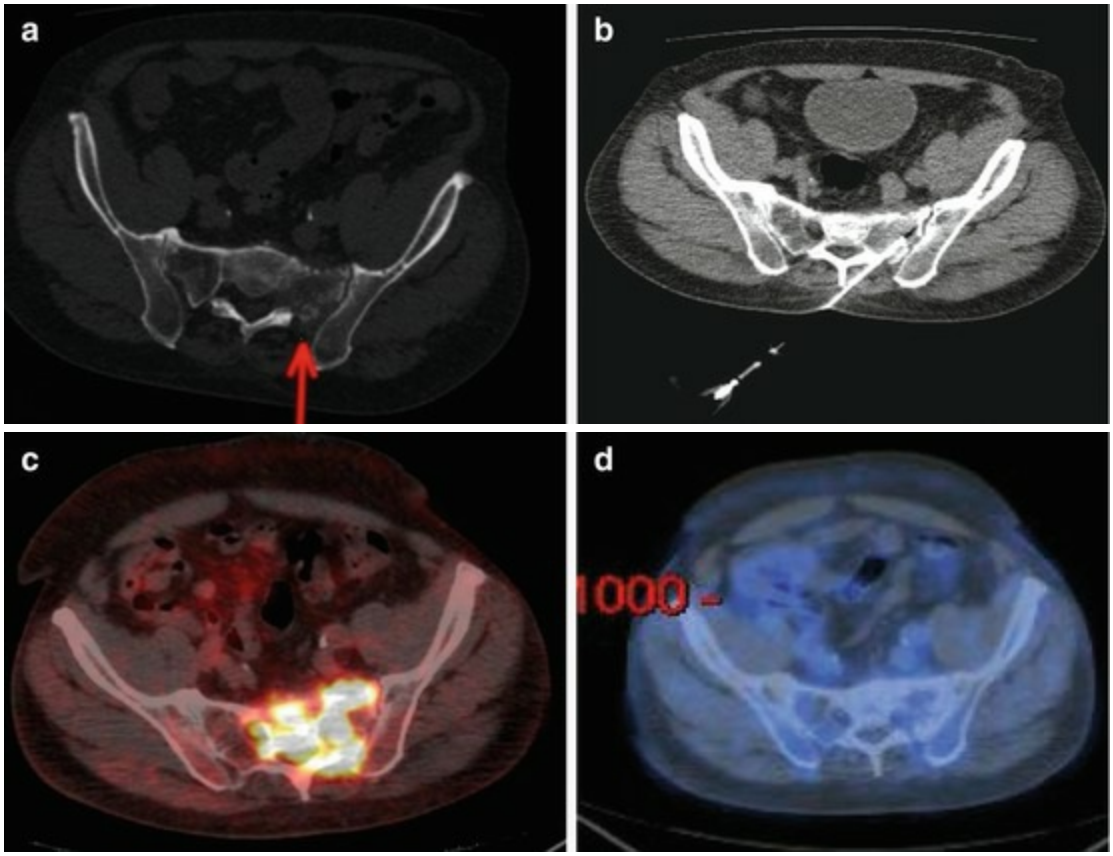

Fig. 7.11 CT pelvis (**a**) demonstrates a mixed sclerotic/lucent lesion in the left side of the sacrum suspicious for a neoplastic pathology—either metastasis or primary bone malignancy. Initial CT-guided bone biopsy (**b**) did not find evidence of malignancy. No other site of primary malignancy or other abnormality was identified on the CT chest, abdomen and pelvis. The patient was referred as a provisional CUP with solitary skeletal metastasis to the MDT for discussion. (**c**) An FDG PET/CT was performed with the aim of identifying any other possible site of primary or secondary malignancy and to guide biopsy. There was intense FDG uptake corresponding to the site of CT abnormality in the sacrum with no evidence of FDG-avid malignancy elsewhere. (**d**) A second biopsy guided by the PET/CT uptake revealed evidence of non-Hodgkin's lymphoma (diffuse large B cell) of the bone. Patient was treated with chemotherapy with good metabolic response on post-treatment PET/CT

2. The first biopsy which was guided by just CT was seen to be inadvertently targeting the least metabolically active area of the lesion which could explain the negative histology. One of the primary reasons for negative biopsy is sampling from necrotic areas of the tumour (Guo 2016).

References

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7.12 Case 12

7.12.1 Clinical Details

A 70-year-old male on presentation was detected to have brain metastasis. Search for a primary revealed a metabolically active mass lesion in the upper pole of the right kidney which was subsequently proven to be renal cell carcinoma.

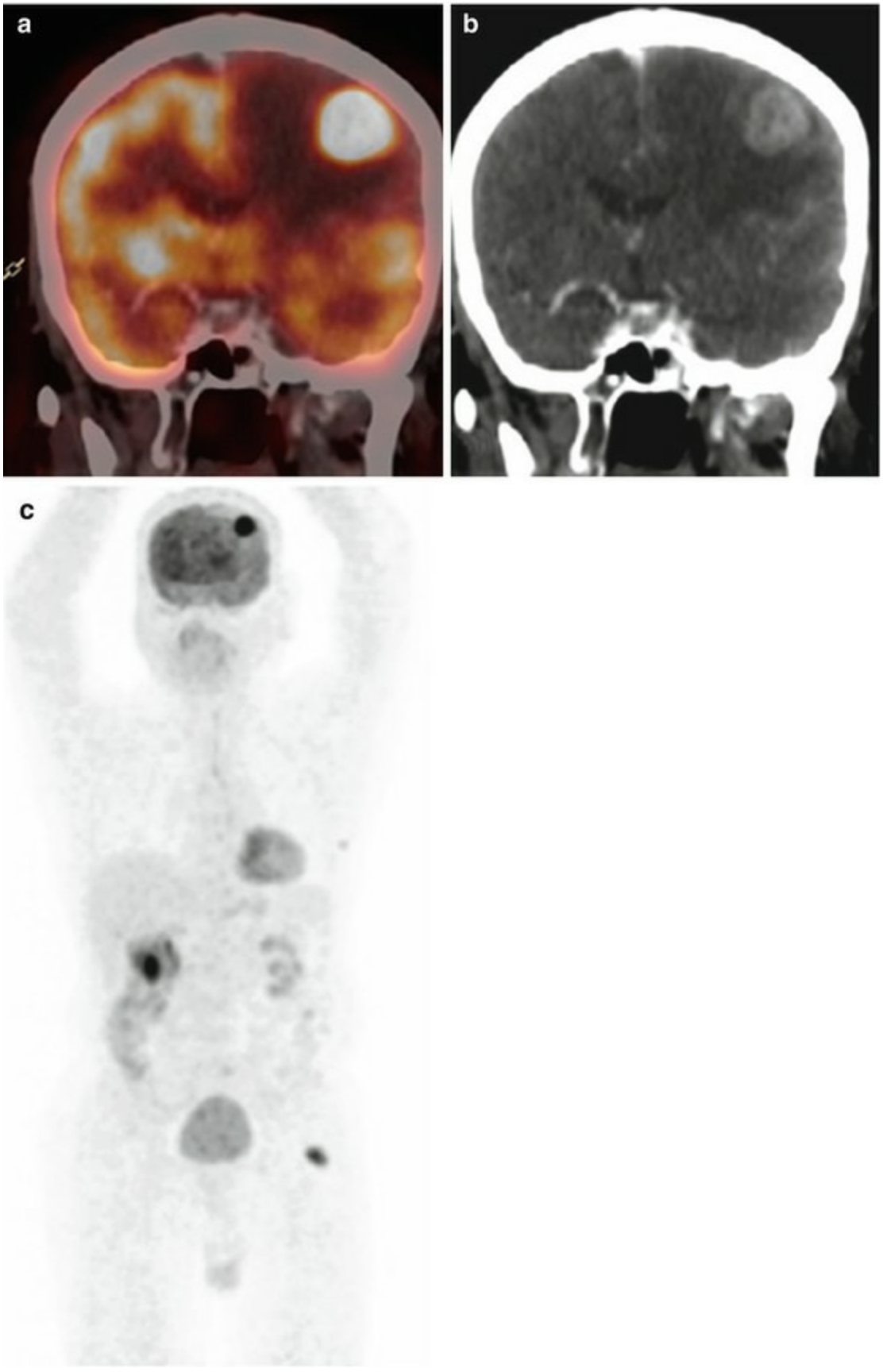
Teaching Points

1. Renal cell carcinoma (RCC) is one of the primary cancers which metastasise to the brain frequently (Posner, 1978). The incidence of brain metastasis in patients with RCC is about 10–20% (Saitoh 1981).

2. Brain metastasis from RCC has the propensity of intratumoural haemorrhage and relatively massive surrounding oedema compared with other metastatic tumours (Kim 2012).

3. FDG PET has a low-negative predictive value in the detection of primary renal tumours with a sensitivity of 60% and specificity of 100% and does not have significant advantage in diagnosis and staging of RCC compared to diagnostic CT and hence not currently recommended for the diagnosis and staging of RCC (Kang 2004).

4. But in FDG-avid RCC, PET/CT (Fig 7.12) can be used to assess therapeutic efficacy and evaluate response to tyrosine kinase inhibitor treatment (Caldarella 2014).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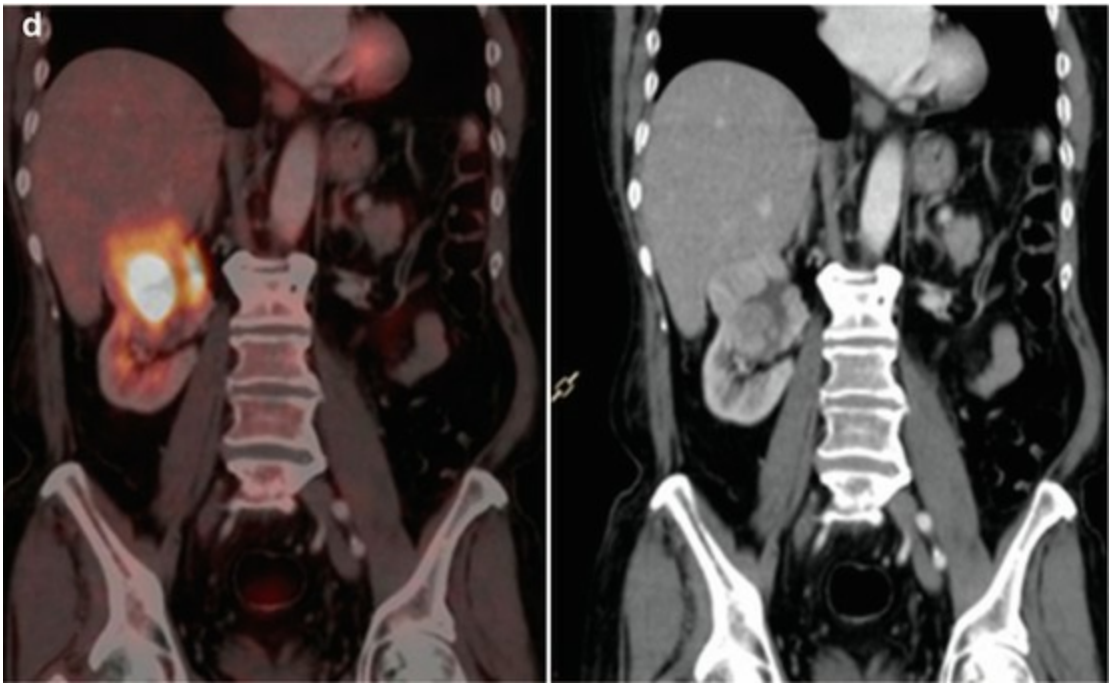

Fig. 7.12 PET/CT showed an FDG-avid lesion in the left parietal lobe (**a**) corresponding to the hyperdense mass lesion with surrounding cerebral oedema and midline shift on the CT component (**b**). Whole-body MIP images (**c**) show a metabolically active lesion in the upper pole of the right kidney which corresponds to an exophytic mass lesion (**d**) compatible with RCC

References

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7.13 Case 13

7.13.1 Clinical Details

A 59-year-old male patient with a history of sciatic pain and lumbar spine disc disease presented with worsening of symptoms. MRI of the spine was performed which showed neoplastic infiltration of L4 vertebra.

Teaching Points

1. FDG PET/CT in this case was used to evaluate indeterminate findings on CT in the chest, abdomen and pelvis and has elegantly demonstrated primary malignancy in the oesophagus and a full spectrum of metastatic disease (Fig 7.13). This led to rapidly establishing the final diagnosis and channelizing the patient towards the correct management pathway (Taylor 2012).

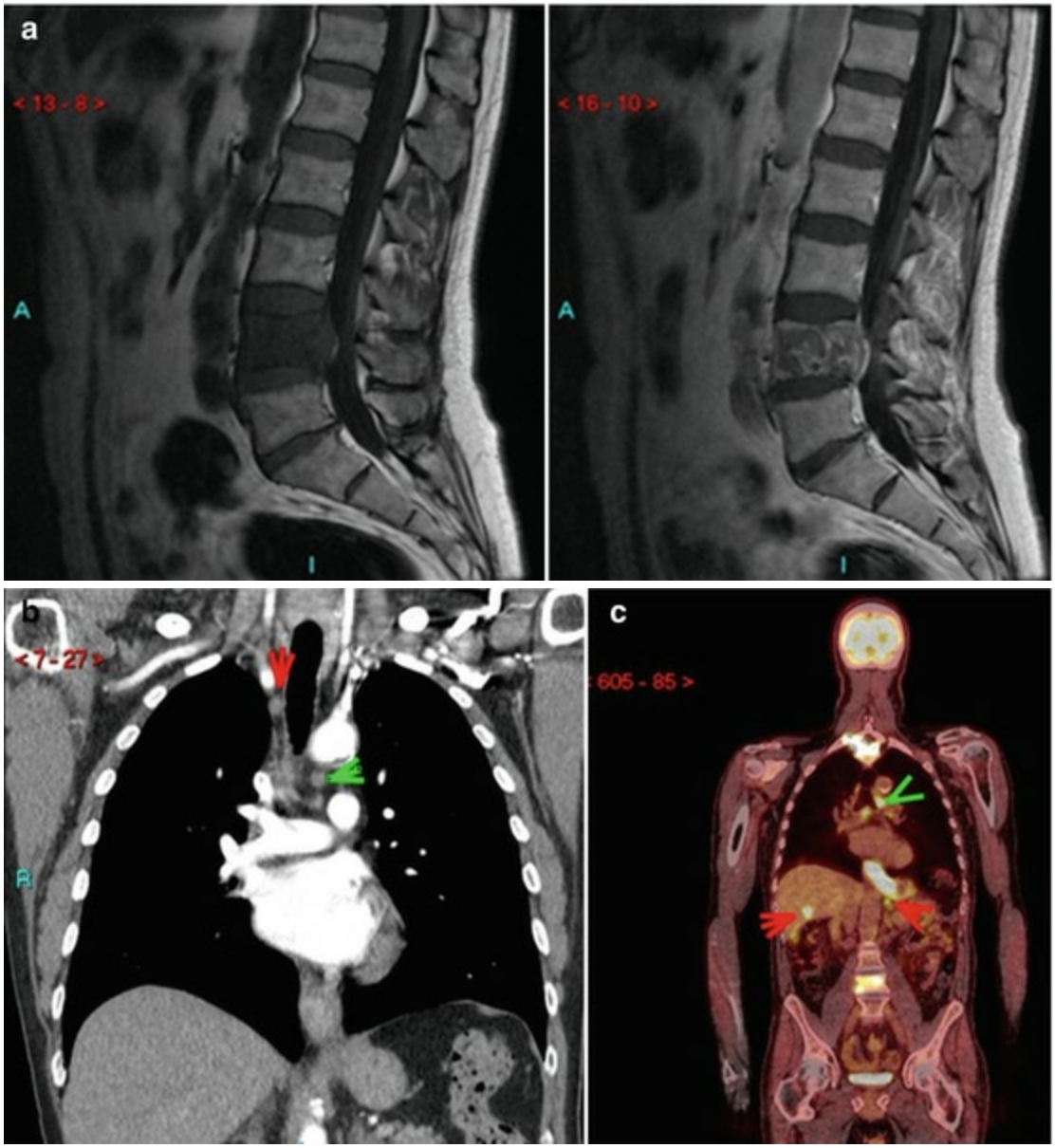

Fig. 7.13 (**a**) MRI of the spine showing abnormal bone marrow signal in the L4 vertebral body, right pedicle and transverse process, together with soft tissue, causing retropulsion of the posterior vertebral body border. The appearances are compatible with neoplastic infiltration with differentials of lymphoma or metastasis. CT-guided vertebral biopsy revealed metastatic adenocarcinoma. (**b**) Subsequent CT in the chest, abdomen and pelvis revealed no definite primary tumour but some rounded borderline-sized mediastinal lymph nodes and non-specific subtle thickening in the lower oesophagus. (**c**) FDG PET/CT fused coronal view shows markedly increased FDG uptake at the gastro-oesophageal junction extending from the distal oesophagus into the cardia of the stomach over a length of approximately 7 cm, appearances compatible with a primary gastro-oesophageal junction tumour. This was subsequently proven to be an adenocarcinoma. PET/CT also showed multiple FDG-avid mediastinal, upper abdominal nodes, small liver lesion and skeletal lesions at T1 and L4 vertebrae in keeping with multiple metastases (*arrow heads*)

2. FDG PET/CT has a defined role in initial staging and continues to be studied in the evaluation of neoadjuvant therapy response and in routine follow-up after definitive therapy. Its use in combination with CT can be used by radiation oncologists in target delineation and planning (Yang 2008).

References

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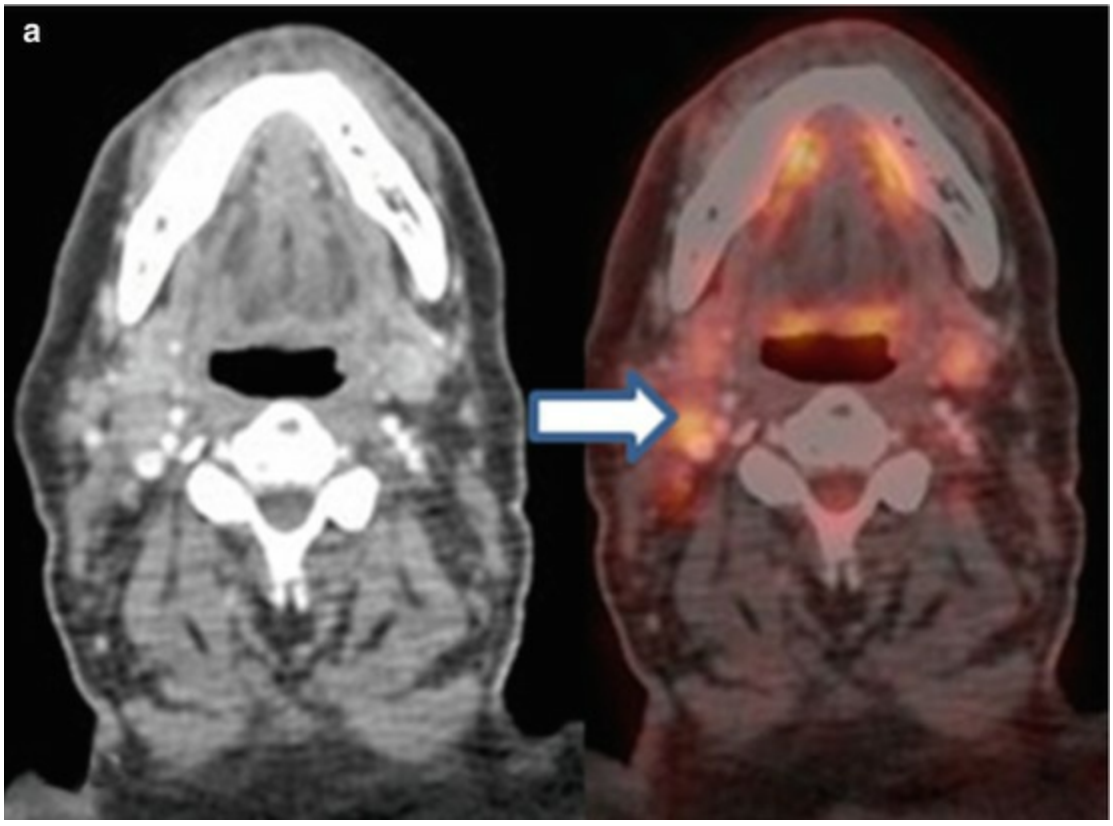
7.14 Case 14

7.14.1 Clinical Details

A patient of CUP presented with a metastatic cervical lymph node. No primary tumour detected on diagnostic CT and negative on triple endoscopy. A diagnostic FDG PET/CT undertaken revealed a primary tumour in the right pyriform sinus with no other FDG-avid lesion elsewhere.

Teaching Points

1. FDG PET/CT is particularly useful not only for the detection of unknown primary but also for staging, restaging and for assessment of treatment response in head and neck cancer patients (Fig 7.14), due to its superior accuracy over clinical examination and conventional anatomic imaging (Castaldi 2013).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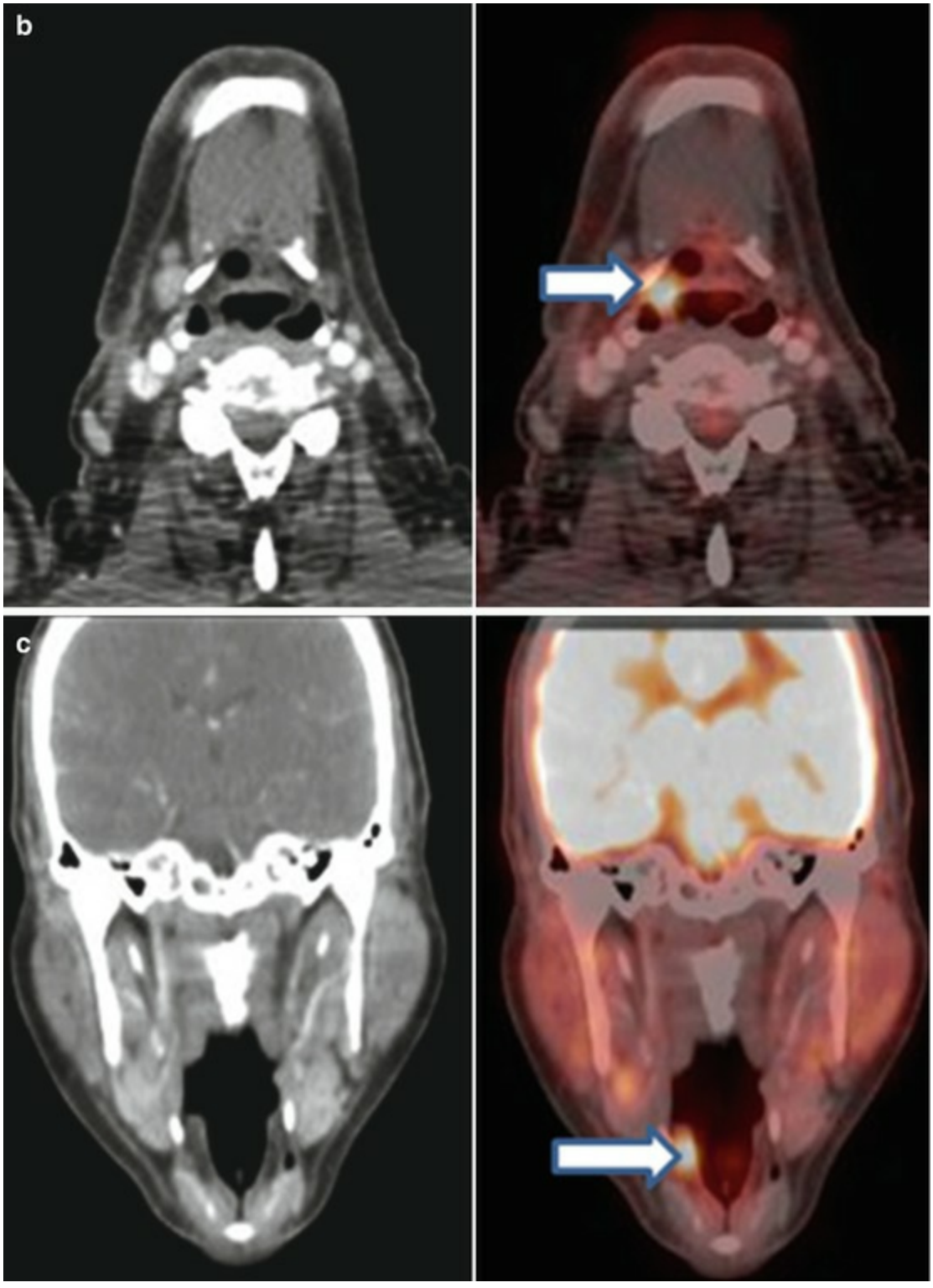
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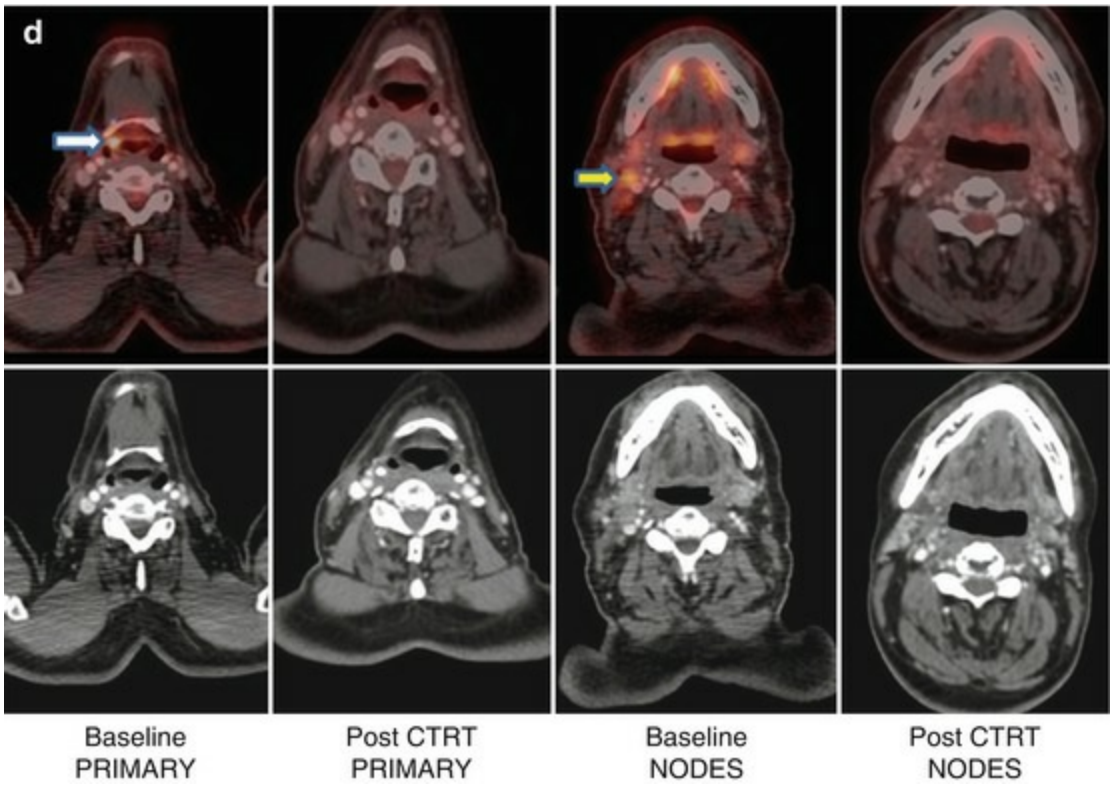

Fig. 7.14 (**a**) Metabolically active metastatic right cervical lymph node (*white arrow*). Transaxial PET/CT slices demonstrate an FDG-avid focus in the right pyriform sinus (*arrow*; **b**) which is better visualized on the coronal slices (**c**) and was proven to be a squamous cell carcinoma. (**d**) FDG PET/CT at baseline and 12-week post-chemoradiotherapy. At baseline, increased FDG uptake is evident in the right pyriform fossa (*white arrow*); after treatment the uptake is no longer visible, suggesting complete metabolic response to treatment. Likewise increased FDG uptake at baseline in the right cervical lymph node (*yellow arrow*) has disappeared on the post-treatment scan, indicating complete metabolic response to treatment

2. FDG PET/CT performed at the end of chemoradiotherapy in head and neck cancers provides prognostic information, as it strongly correlates with local and regional control and survival (Hentschel 2011).

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7.15 Case 15

7.15.1 Clinical Details

An 82-year-old male presented with a pathological fracture of the right humerus. Myeloma screen was negative, and an FDG PET/CT was undertaken to identify the unknown primary.

Teaching Points

1. Lung and pancreatic cancer are the most common primary tumour locations in CUP on autopsy studies (Chevalier 1998).

2. Diagnostic performance of FDG PET/CT is not significantly different between patients presenting with cervical metastases and patients presenting with extracervical metastases, with lung, oropharyngeal and pancreatic cancers reported to be the most frequently detected primary tumours (Kwee 2009).

   In this case FDG PET/CT not only helped identify the unknown primary but also accurately stage disease by identifying additional metastatic sites thus aiding appropriate treatment strategy (Fig 7.15). In selected cases of CUP, FDG PET/CT undertaken upfront in the investigative algorithm helps maximize identification and minimize tests with lower diagnostic yield, thus serving as a one-stop shop.

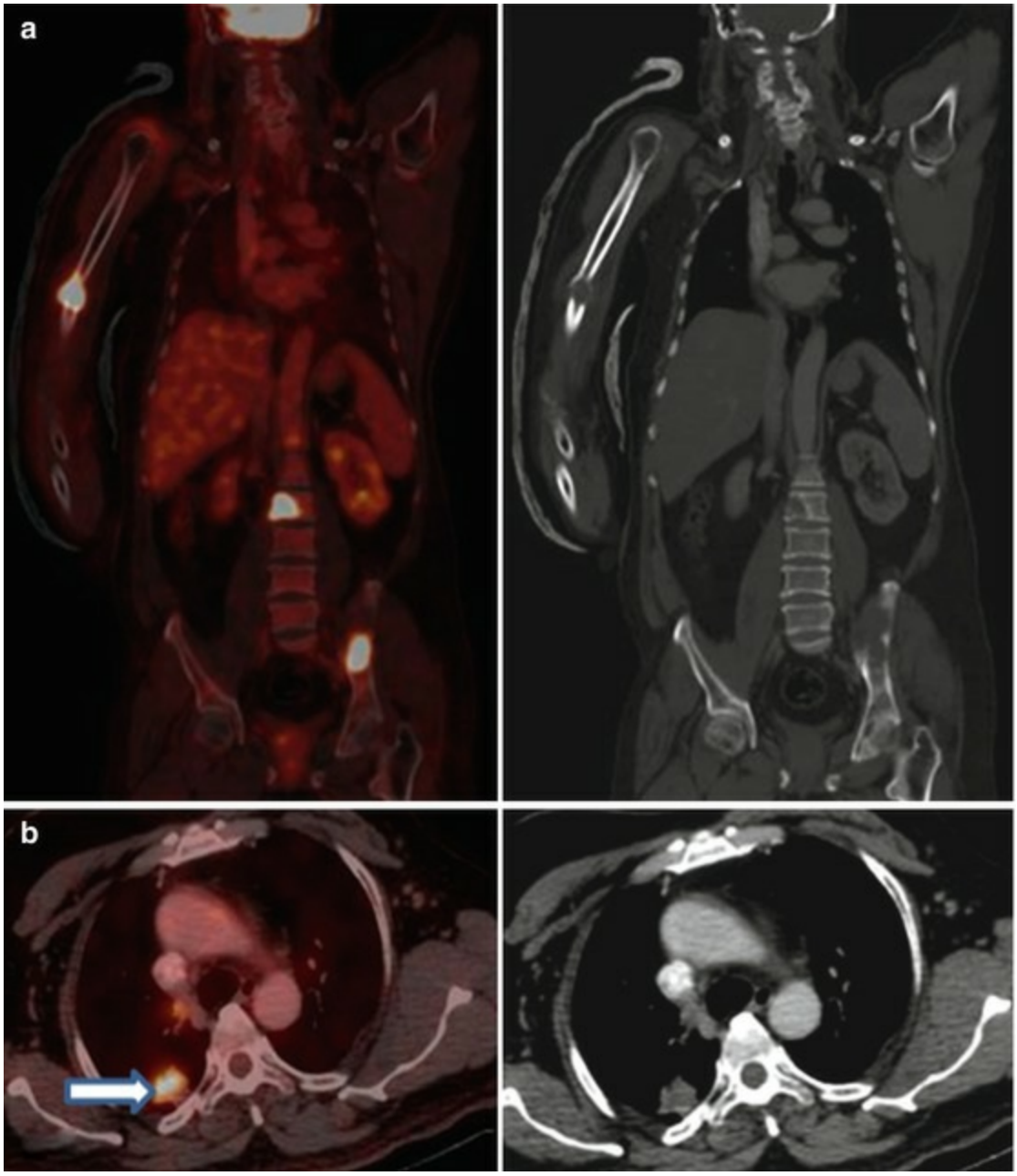

Fig. 7.15 (**a**) PET/CT showed intense FDG uptake at the site of pathological fracture in the right humerus with further focal areas of uptake in the L1 vertebral body and left iliac bone corresponding to lytic metastases. (**b**) Further FDG PET/CT identified a primary lung cancer in the right upper lobe (*arrow*)

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