Clinicians' Guides to Radionuclide Hybrid Imaging · PET/CT
Series Editors: Jamshed B. Bomanji · Gopinath Gnanasegaran
Stefano Fanti · Homer A. Macapinlac

Michael S. Hofman
Rodney J. Hicks *Editors*

PET/CT in Melanoma

Clinicians' Guides to Radionuclide Hybrid Imaging

PET/CT

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PET/CT in Melanoma

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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 benefit 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.

London, UK Peter J. Ell, FMedSci, DR HC, AΩA

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 significant impact in 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' Guides 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 Neilly, 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.

London, UK

Gopinath Gnanasegaran
Jamshed Bomanji

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Melanoma

1

John Spillane, Michael Henderson, and Grant A. McArthur

Contents

Melanomas arise from melanocytes located on the basement membrane at the epidermal/dermal junction. The lifetime risk of melanoma has been increasing in recent decades particularly in Caucasians, which is in part due to increased diagnosis of early stage cancer [1]. Rates of melanoma around the world vary from as little as 0.2/100,000 in females in India to 55.8/100,000 in males in northern Australia [2, 3]. Ethnicity influences the rates of melanoma with higher rates in Caucasians in Australia, New Zealand and Europe and lower levels in Asians. Within the USA, there are higher rates in Caucasians, compared to Hispanic and Black communities [2, 3].

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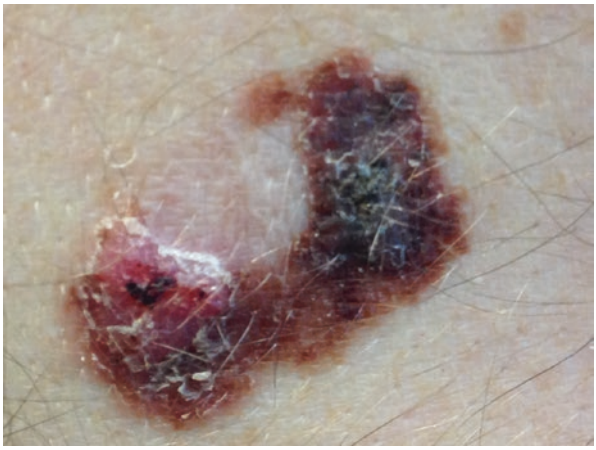

Fig. 1.1 Superficial spreading melanoma

Persons most at risk are fair-skinned individuals with skin that burns easily, a personal or family history of melanoma including the number of cases and age of onset, a history of dysplastic naevi, immunosuppression and a genetic predisposition such as having mutations in CDKN2A (9p21) and the use of sunbeds [2, 4–7]. Intermittent high-dose sun exposure is reported to have a higher rate of melanoma development than chronic sun exposure [4, 8].

1.1 Clinical Features

The commonest presenting symptom of cutaneous melanoma is a visibly changing pigmented skin lesion [5, 9, 10]. The change could be in size, shape, colour or elevation. Although up to one third of melanomas can develop in pre-existing naevi, the majority develop as a distinct lesion. The features of naevi that increase the clinical suspicion of melanoma can be remembered by the acronym ABCDE: A, asymmetry of the lesion; B, border irregularity; C, colour variation; D, diameter; and E, evolution/elevation (see Fig. 1.1) [5, 8, 11]. In contrast, benign pigmented naevi usually have regular borders with a clear demarcation between the naevi and surrounding skin with an even tan or brown colour across the naevi. Elevation is often associated with a vertical growth phase and therefore an increased risk for metastasis. Any evolution of the lesion such as bleeding, ulceration and itch increases the suspicion for melanoma [5].

1.2 Biopsy of the Lesion

Any clinically changing lesion should be further assessed with a biopsy. The recommended method is a complete excision biopsy, with direct closure, [4, 5, 12]. This allows full pathological assessment of the lesion confirming the diagnosis and

providing prognostic information (Breslow thickness, presence of ulceration and mitotic rate) [5]. Wider margins are not recommended as this may interfere with subsequent lymphatic mapping [4, 13].

Partial biopsies, core, superficial or deep shave or incision biopsies may potentially underestimate the lesion leading to inadequate treatment. Difficult lesions such as Spitz tumours, nevoid or desmoplastic melanomas require the entire lesion to be excised to allow the most accurate pathological evaluation of the lesion [5].

Extremity biopsies should be aligned vertically along the limb to minimize the need for skin grafts or flaps [5]. Once the diagnosis has been made, definitive surgery can be undertaken.

1.3 Classification

There are four main types of primary melanoma.

1.3.1 Superficial Spreading Melanoma

It is the most common type of melanoma in Caucasians (see Fig. 1.1). The mean age of diagnosis is 51 years and comprises 40–60% of all melanomas [5, 8]. It frequently arises in a pre-existing naevus. It is often described as a slowly expanding variably pigmented lesion, before a period of rapid clinical change, often just before it is diagnosed [5, 8, 11]. It can occur at any site on the body but more frequently seen on the back in men and lower limbs in women.

1.3.2 Nodular Melanoma

It affects older persons with a mean age of 56 years, men more frequently than women. The overall incidenceis is 10–35% with a higher percentage of thick melanomas [5, 8]. It may develop in normal skin or a pre-existing naevus. They are often described as a rapidly changing lesion and can vary from a pink through to being darkly pigmented. If it lacks pigment it can resemble a vascular lesion. This makes the diagnosis difficult and can cause in a delay in presentation [5].

1.3.3 Lentigo Maligna Melanoma (LMM)

This melanoma classically develops on chronically sun-damaged skin in the elderly usually on the more sun-exposed areas (face and hands). It comprises 10–15% of melanomas [8]. This lesion usually develops from a precursor lesion called lentigo maligna or Hutchinson's melanotic freckle (HMF). There is a 5% lifetime risk of HMF developing into the invasive melanoma without treatment [5, 8]. This is often

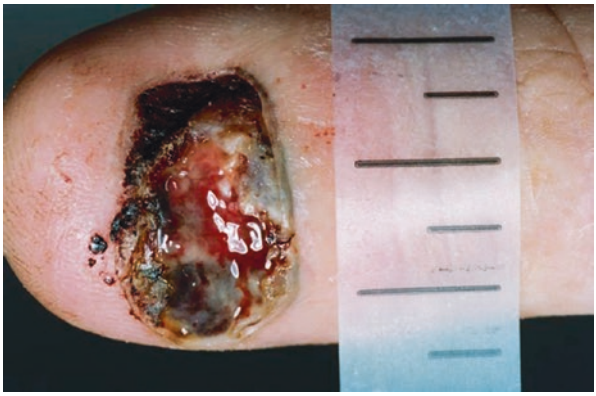

Fig. 1.2 Acral melanoma

associated with a desmoplastic component. Any nodule in an area of HMF should be investigated for LMM. The recurrence rate following standard excision is 8–20% [5, 8, 14–17].

1.3.4 Acrolentiginous Melanoma (ALM)

This type of melanoma develops in the acral skin of the palms and soles (see Fig. 1.2). It represents <5% of melanomas in countries with high rates of melanoma [8]. It is the most common type of melanoma in Blacks and Asian populations, with a mean age of diagnosis of 67 years. It is often light coloured or pink and relatively flat and often diagnosed late [5, 18].

Subungual melanoma is a variant of ALM (Fig. 1.2) arising in the nail matrix and presenting as a brown/black lesion. Both ALM and subungual melanomas may not be related to sun exposure [5].

1.4 Classification/Staging

The eighth addition of the AJCC staging system is due to take effect in 2018 (Table 1.1). Although it is similar to the seventh addition, some changes have been made to the TNM classification. T0- is used when there is no evidence of primary tumour. TX- is used when Breslow thickness cannot be determined. Breslow thickne ss is now measured to the nearest 0.1 mm and not to two decimal points. T1 melanomas are further subcategorised by tumour thickness at a threshold of 0.8 mm. T1a- Is a nonulcerated melanoma <0.8mm. T1b- is between 0.8-1.0mm regardless of ulceration or ulcerated and <0.8mm. Mitotic rate is no longer used in the T category, but remains a major determinant of prognosis across all T categories. Regional lymph nodes and now defined as “clinically occult” or “ clinically detected” rather than microscopic or macroscopic nodal burden. Non-nodal regional disease such as microsatellites, satellites and in-transit metastases and now classified according to

Table 1.1 TNM staging for melanoma based on the AJCC 8th Edition staging sytem (adapted from Amin MB et al. 2017 [22])

T stage	Tumour thickness (mm)
Tx	Thickness unable to be assessed
T0	No evidence of primary tumour
Tis	Melanoma in situ
T1	≤1.0 mm
T1a	<0.8 mm without ulceration
T1b	<0.8 mm with ulceration **or** 0.8–1.0 mm without ulceration
T2	>1.0–2.0 mm T2a—without ulceration T2b—with ulceration
T3	>2.0–4.0 mm T3a—without ulceration, T3b—with ulceration
T4	>4.0 mm T4a—without ulceration T4b—with ulceration
N stage	Number of involved nodes
N0	No nodes detected
N1	1 node involved **or** In-transit, satellite and/or micro satellite metastases with **no** tumour involved nodes
N1a	Clinically *occult* node **&** no in-transit/satellite/microsatellites
N1b	Clinically *detected* node **&** no in-transit/satellite/microsatellites
N1c	**No** regional node disease **and** in-transit/satellite/microsatellite metastases
N2	2 or 3 involved nodes **or** In-transit/satellite/microsatellite metastases with 1 tumour involved node
N2a	2 or 3 positive clinically *occult* nodes **&** *No* in-transit/satellite or microsatellites
N2b	2 or 3 positive nodes (at least 1 clinically *detected*) *& no* intransit/satellite or microsatellites
N2c	1 positive clinically *occult or detected* node **&** in-transit/satellite or microsatellites detected
N3	4 or more positive nodes **or** 2 or more nodes with in-transit/satellite/microsatellite **or** Mattered nodes ± intransit/satellite/microsatellites
N3a	4 or more positive clinically occult nodes **& no** in-transit/satellite/microsatellites
N3b	4 or more positive nodes (at leaset one clinically *detected*) **Or** mattered nodes **& no** in-transit/satellite/microsatellites
N3c	2 or more positive clinically *occult or detected* nodes **&/or** mattered nodes **&** In-transit/satellites/microsatellites
M0	No metastases
M1	Metastatic disease
M1a(0)	Distant skin, soft tissues &/or nonregional lymph nodes **&** LDH not elevated

(continued)

Table 1.1 (continued)

T stage	Tumour thickness (mm)
M1a(1)	Distant skin, soft tissues &/or nonregional lymph nodes **&** LDH elevated
M1b(0)	Lung metastases **&** LDH not elevated
M1b(1)	Lung metastases **&** LDH elevated
M1c(0)	Distant metastases to non-CNS visceral sites & LDH not elevated
M1c(1)	Distant metastases to non-CNS visceral sites & LDH elevated
M1d(0)	Distant metastases to non-CNS visceral sites & LDH not elevated
M1d(1)	Distant metastases to CNS & LDH elevated

Table 1.2 Stage grouping for patients with melanoma (adapted from Amin MB et al. 2017 [22])

TNM classification	Clinical TNM staging	Pathology TNM staging
Tis N0 M0	0	0
T1aN0M0	IA	IA
T1bN0M0	IB	IA
T2a N0 M0	IB	IB
T2b N0 M0	IIA	IIA
T3aN0M0	IIA	IIA
T3b N0 M0	IIB	IIB
T4a N0 M0	IIB	IIB
T4b N0 M0	IIC	IIC
T0 N1b N1c M0	III	IIIB
T0 N2b, N2c, N3b, N3c M0	III	IIIC
T1a/b–T2a N1a, N2a M0	III	IIIA
T1a/b–T2a N1b/c, 2b M0	III	IIIB
T2b/3a N1a–N2b M0	III	IIIB
T1a–T3a N2c or N3a,b,c M0	III	IIIC
T3b/T4a N≥1 M0	III	IIIC
T4b N1a–N2c M0	III	IIIC
T4b N3a, b, c M0	III	IIID
Any T, Any N M1	IV	IV

the number of involved lymph nodes. This is written as N1c, N2c or N3c. Serum lactate dehydrogenase is now classified as "0" when not elevated and "1" when elevated. This classification is attached to each M subgroup and is written in the format M1a(1). Central nervous system disease is classified as a separate new category of M1d. This is regardless of the involvement of other sites with metastatic disease. The AJCC prognostic stage groups are very similar to the seventh addition, however there is subtle differences between clinical TNM (cTNM) and pathological TNM (pTNM) (Table 1.2) [19, 21].

Sentinel lymph node biopsy is an important component of nodal staging and should be discussed with patients particularly those with clinical stage IB or II disease to identify clinical occult stage III disease [19, 21].

Key Points

- Melanomas arise from melanocytes located on the basement membrane at the epidermal/dermal junction.
- Intermittent high-dose sun exposure is reported to have a higher rate of melanoma development than chronic sun exposure.
- The commonest presenting symptom of cutaneous melanoma is a visibly changing pigmented skin lesion.
- The features of naevi that increase the clinical suspicion of melanoma can be remembered by the acronym ABCDE; A, asymmetry of the lesion; B, border irregularity; C, colour variation; D, diameter; and E, evolution/elevation.
- Any clinically changing lesion should be further assessed with a biopsy.
- There are four main types of primary melanoma.
- Superficial spreading melanoma is the most common type of melanoma in Caucasians.
- Nodular melanoma affects older persons with a mean age of 56 years, men more than women.
- Lentigo maligna melanoma classically develops on chronically sun-damaged skin in the elderly usually on the more sun-exposed areas (face and hands).
- Acrolentiginous melanoma (ALM) develops in the acral skin of the palms and soles.
- The important features of the T stage are the Breslow thickness, and ulceration. Clark's level was removed from the 7th and 8th staging system in it's importance for melanoma prognosis in assessing T1 melanomas.

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Pathology of Melanoma

2

Andrew J. Colebatch and Grant A. McArthur

Contents

Melanoma is a malignant proliferation of neoplastic melanocytes. These occur as primary lesions in any region where melanocytes are resident, including the skin, mucosa, uveal tract and meninges. Additionally metastatic melanoma may present without an identified primary lesion. This chapter will concentrate primarily on cutaneous melanoma, which represents around 90% of cases of melanoma in regions with predominant Caucasian populations.

2.1 Histopathology

The microscopic analysis of primary cutaneous melanoma is critical for prognostic assessment as well as evaluation of the completeness of excision. In general, the entire lesion is submitted for histologic analysis, as even minute areas of invasion will significantly affect prognosis. The first critical distinction is between invasive melanoma, which has invaded beyond the basal epidermis, and melanoma in situ, which is confined to the epidermis; it is not uncommon for cutaneous melanoma to

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have both in situ and invasive components, and margins are assessed for each of these. Melanoma in situ lacks metastatic potential, and complete excision is curative.

The three most powerful prognostic microscopic features of invasive melanoma within the primary lesions are the Breslow thickness (defined as the maximum thickness of the melanoma in millimetres measured perpendicular to the skin), presence of ulceration and the presence of mitotic figures; consequently these three features are used in staging melanoma (using the AJCC 7th edition) [1], along with the presence and number of involved lymph nodes and presence and site of distant metastases (see Tables 1.1 and 1.2 in Chap. 1). Together these features provide powerful prognostic information across large patient populations. However, their prognostic utility for individual patients is more limited. With greater understanding of molecular features of melanoma, as discussed below, we are likely to see more sophisticated prognostic algorithms in the future.

2.2 Sentinel Lymph Node Biopsy

In addition, many centres incorporate sentinel lymph node sampling as part of the staging procedure on selected cases. In this procedure the first lymph node draining the lymphatics of the primary tumour is sampled and evaluated histologically. There can be more than one drainage pathway from the primary tumour, resulting in excision and analysis of multiple sentinel nodes. The critical factors recorded are the size of the largest deposit and the presence of extracapsular extension. The measurement and classification of the largest deposit follow the Rotterdam criteria, whereby the single largest cluster is measured and given even if there are multiple positive nodes and is classified as <0.1 mm (sub-micrometastasis), 0.1–1 mm or >1 mm [2].

2.3 Synoptic Reporting of Melanoma

Recent times have seen the adoption of synoptic reporting for melanoma to standardise diagnostic reports, including recommended clinical and histopathologic variables. This includes Breslow thickness, ulceration, level of invasion, mitotic count and margins of invasive and in situ components as essential requirements. In addition, there should be assessment of lymphovascular invasion and neurotropism (perineural or intraneural invasion), presence or absence of satellite lesions (nests of metastatic tumour separated from the primary tumour) and the presence or absence of desmoplastic melanoma; these are shown in Table 2.1. There are, in addition, recommended variables to report, which vary between institutions. These are summarised in Table 2.2 and include the melanoma subtype, presence of regression and presence of tumour infiltrating lymphocytes (TILs). The latter may become particularly relevant in the context of novel immune-modulating therapies.

Metastatic melanoma is one of the great mimics of histopathology and can resemble anaplastic carcinoma, sarcoma or even lymphoma. The use of

Table 2.1 Essential histopathologic features from a synoptic report on melanoma

Essential features	
Ulceration	Present/absent
Breslow thickness	In millimetres
Margin status	Both in situ and invasive components
Mitotic count	Per mm^2
Lymph node status	• Number of sentinel nodes received • Number of positive sentinel nodes • Number of nodes received • Number of positive nodes
Level of invasion (Clark)	I—Confined to epidermis (melanoma in situ) II—Melanoma cells invade but do not fill papillary dermis III—Melanoma cells fill and expand the papillary dermis IV—Melanoma cells infiltrate the reticular dermis V—Melanoma cells invade subcutis

Table 2.2 Recommended other details from a synoptic report on melanoma

Other features	
Tumour-infiltrating lymphocytes	No single system universally in use. System should refer to density and location
Tumour regression	Present/absent. Also should be noted if this extends to margin
Associated melanocytic lesion	An adjacent melanocytic lesion should be recorded
Melanoma subtype	• Superficial spreading melanoma • Nodular melanoma • Lentigo maligna melanoma • Acral lentiginous melanoma • Desmoplastic melanoma • Melanoma arising from blue naevus • Melanoma arising in a giant congenital naevus • Melanoma of childhood • Naevoid melanoma • Melanoma not otherwise classified
Satellite lesions	Present/absent
Lymphovascular invasion	Present/absent
Desmoplastic melanoma component	Present/absent. If present, necessary to determine if melanoma is a ‘pure’ desmoplastic melanoma or ‘mixed’ desmoplastic melanoma. There is improved disease-free survival with pure DM.
Neurotropism	Present/absent

immunohistochemical stains for melanoma antigens such as S100, Melan-A, HMB-45 and Sox10 is of assistance in identifying the lesion as a melanoma.

2.4 Molecular Analysis

The molecular pathology of melanoma has been an area of intense research activity and can be broadly divided into inherited mutations that confer increased susceptibility to melanoma and somatic alterations that occur in established tumours.

Table 2.3 List of common BRAF somatic mutations in cutaneous melanoma along with proportion of cases

BRAF mutation	Proportion of cases (%)
V600E	80
V600K	10–20
V600R	5
K601E	<1
G469A	<1
D594G	<1
V600M	<1
V600 E2	<1
L597V	<1

Approximately 10% of patients with a melanoma demonstrate a family history [3]. 20–40% of these families will have a mutation in *CDKN2A*, which is a locus that codes for two tumour suppressors (p16 and p14ARF) in separate overlapping reading frames. Mutations in *CDK4* and *BAP1* are also high-risk melanoma susceptibility loci.

Numerous studies have investigated recurrent somatic mutations in melanoma. Initial candidate screens identified somatic mutations in *BRAF* and *NRAS* as being common in cutaneous melanoma. *BRAF*, a serine-threonine kinase, is mutated in around 40% of melanomas and shows a mutational hotspot at codon 600, with BRAFV600E mutations (substitution of a valine for a glutamic acid) occurring in between 50 and 80% of *BRAF* mutated melanomas. Additional V600 mutations also occur (V600K, V600R, V600M) as well as mutations in codons 594, 597 and 601 (summarised in Table 2.3). Numerous studies have demonstrated that BRAFV600E has constitutive activity leading to increased signalling through the MAPK pathway with consequent effects a range of cellular properties, including differentiation, proliferation, survival and motility [4, 5]. Of note however, a larger proportion of melanocytic naevi (80%) harbour the same BRAF V600E mutations, demonstrating that this mutation is likely an early event during melanomagenesis, although not sufficient in and of itself [6].

Similarly hotspot mutations in *NRAS* at codons 12, 13 or 61 lead to increased activity and signalling through MAPK. *NRAS* is mutated in approximately 15% of melanomas [7]. These canonical *NRAS* and *BRAF* mutations are mutually exclusive. In addition, recent studies have demonstrated a high rate of *TERT* promoter mutations in melanoma [8, 9]. Melanomas arising in chronically sun-damaged skin, mucosa and acral sites may have mutations in *KIT*, while uveal melanomas show recurrent mutations in *GNAQ* and *GNA11* [10].

The presence of a BRAF V600 mutation in melanoma is critical to evaluate due to the availability of therapy using selective BRAF inhibitors. These drugs lead to rapid responses in almost all cases, but resistant disease emerges at a median time of 6 months after commencing therapy [11]. Newer therapies targeting MEK (also in the MAPK pathway) are emerging and show promising response rates and more favourable side effect profiles [12]. Moreover, new immune checkpoint inhibitors such as anti-CTLA4 and anti-PD1/PDL1 antibodies have shown efficacy in melanoma; however there is need for biomarkers to identify that subset of patients that will benefit from these therapies.

Key Points

- The microscopic analysis of primary cutaneous melanoma is critical for prognostic assessment as well as evaluation of the completeness of excision.
- The entire lesion is submitted for histologic analysis, as even minute areas of invasion will significantly affect prognosis.
- The three most powerful prognostic microscopic features of invasive melanoma within the primary lesions are the Breslow thickness, presence of ulceration and the presence of mitotic figures.
- Metastatic melanoma is one of the great mimics of histopathology and can resemble anaplastic carcinoma, sarcoma or even lymphoma.
- Approximately 10% of patients with a melanoma demonstrate a family history.
- The presence of a BRAF V600 mutation in melanoma is critical to evaluate due to the availability of therapy using selective BRAF inhibitors.

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Management of Melanoma

3

Belinda Lee and Grant A. McArthur

Contents

Until recently, there have been few effective treatment options for patients with metastatic melanoma. A number of targeted therapies and immune-modulating therapies have dramatically improved outcomes and changed paradigms of management. For patients with early stage disease, surgery remains the primary form of management.

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Table 3.1 Recommended excision margins for cutaneous melanoma

T-stage	Breslow thickness	Excision margin	Level and grade of evidence
pTis	In situ melanoma	5 mm	III, B
pT1	<1.0 mm	1 cm	Ib, A
pT2	1.0–2.0 mm	1–2 cm	Ib, A
pT3	2.0–4.0 mm	1–2 cm	Ib, A
pT4	>4.0 mm	2 cm	Ib, B

From the evidence-based practice guidelines for the management of melanoma in Australia and New Zealand [1–5]

3.1 Surgical Management of Primary Melanoma

Lesions should be excised with adequate margins, with recommended radial excision margins outlined in Table 3.1 [1, 6–8]. In the surgical management of acral lentiginous and subungual melanoma, partial amputation incorporating the joint immediately proximal to the melanoma may be necessary [2, 3].

Lesions excised with a margin less than the recommended criteria should be re-excised to achieve these margins. A flap repair or skin graft may be necessary when tissue flexibility is limited to achieving an adequate margin. Referral to a specialist centre should be considered for all cases with melanomas greater than 1 mm thick.

3.2 Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) should be considered in primary melanomas greater than 1.0 mm thick as it provides staging and prognostic information [4, 5, 9, 10]. Patients who have a positive SLNB have tradionally been offered completion lymphadenectomy or referred to a specialist centre to discuss further treatment options [9]. Results from the MSLT-1 study did not demonstrate a significant difference between the 10-year melanoma-specific survival in the SLNB and the observation arms (81.4% versus 78.3%, $p = 0.18$) [11]. Therefore, there is uncertainty about whether routine lymphadenectomy improves outcome, and this is currently being assessed in the MSLT-2 study [9].

3.3 Management of Locoregional Recurrent Melanoma

Surgery is the treatment of choice for single local or regional metastases [12]. In-transit and local metastases can be managed with localised treatment modalities [11, 13]. Isolated limb infusion (ILI) or perfusion (ILP) with melphalan alone or combined with actinomycin-D can be considered for recurrence on a limb with multiple or rapidly progressive deposits unsuitable for local treatments [14]. ILI is less invasive than ILP but may be less effective [15, 16]. Suspected local regional nodal recurrence should be confirmed by fine needle biopsy. Lymph node dissection can be undertaken for clinically involved nodes with no previous dissection [9, 17].

3.4 Radiotherapy

Adjuvant radiotherapy can be considered in selected cases with narrow or positive margins or where re-excision of the primary disease is unsuitable [18]. The use of adjuvant radiotherapy following nodal resection with adverse pathological features can be considered in carefully selected cases but remains controversial. It is associated with reduced lymph node field recurrence but has no impact on relapse-free survival or overall survival. Its benefits must be weighed up against the risk of regional toxicity, lymphedema and reduced quality of life [19]. Concurrent treatment with interferon alpha significantly increases toxicity and should be avoided [20]. Palliative radiotherapy to symptomatic metastatic or unresectable nodal, satellite or in-transit disease may offer some benefit. Stereotactic radiosurgery and/or whole brain radiation therapy either as adjuvant or the primary treatment can be considered in patients with cerebral metastases.

3.5 Adjuvant Systemic Therapy of Melanoma

Patients with resected stage 1–3 melanoma should be followed up by clinical surveillance [21]. Sentinel lymph node biopsy should be considered for disease stratification and is often used to determine eligibility for adjuvant clinical trials. Adjuvant therapy with high-dose interferon alpha can be discussed with patients with stage III, high-risk disease, carefully outlining the risks and benefits associated with this therapy before proceeding [22].

3.6 Management of Metastatic Melanoma

Advanced melanoma should be profiled for the presence of a driving mutation. BRAF V600 mutation is detected in approximately 40% of melanomas [23]. Patients with acral or mucosal melanoma that do not contain a BRAF mutation should be assessed for a KIT mutation.

Treatment with either a targeted therapy or immunotherapy should be considered as first-line therapy depending on the mutational status of the tumour (see Fig. 3.1 and Table 3.2) [24, 25]. Immunotherapy can be used in the first line in both BRAF-mutant and wild-type patients. Cytotoxic chemotherapy can be considered for palliative disease control but has never demonstrated to improve survival [26].

3.6.1 Targeted Systemic Therapy with MAPK Pathway Inhibition

Approximately 40% of metastatic melanomas have a V600 BRAF mutation that activates the MAPK pathway (see Fig. 3.2). Treatment with a BRAF inhibitor can produce rapid tumour regression with significantly improved progression-free survival, overall survival and intracranial activity in BRAF- mutated disease [27]. The median

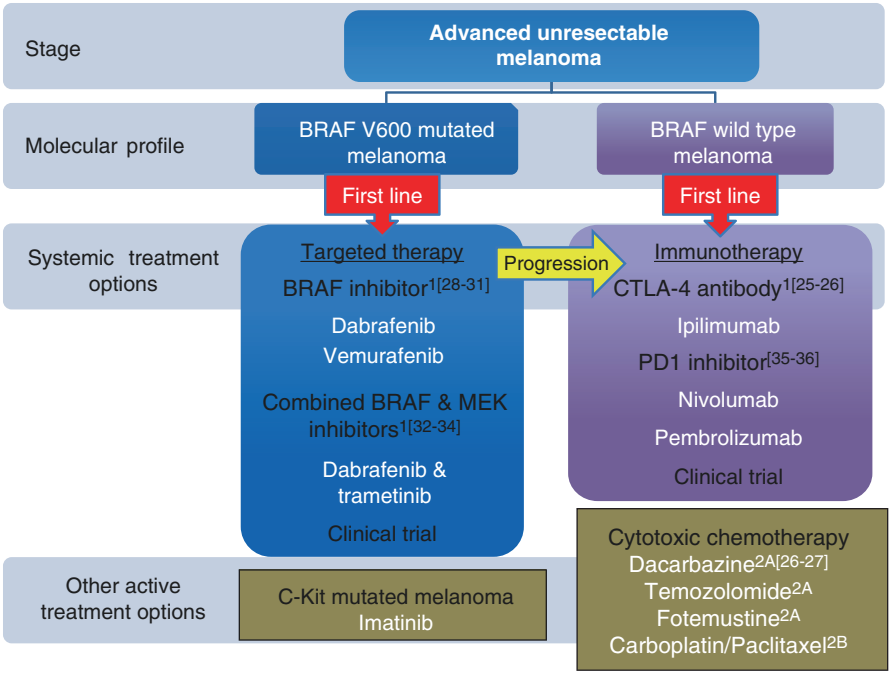

Fig. 3.1 Systemic treatment pathway for advanced melanoma

Table 3.2 Common side effects with systemic therapy

Drug	Common associated toxicities
Vemurafenib	Skin-related toxicity, keratoacanthomas, low-grade squamous cell carcinomas, photosensitivity, elevated liver enzyme, arthralgia
Dabrafenib	Skin-related toxicity, keratoacanthomas, low-grade squamous cell carcinomas, fever, fatigue, arthralgia, headaches
Combined dabrafenib and trametinib	Fever, chills, fatigue, headaches
Ipilimumab	Immune-related toxicities including skin toxicity, colitis, endocrinopathies, hepatitis, neuropathy
Trametinib	Rash, diarrhoea, peripheral oedema
Dacarbazine	Modest immunosuppression, mild fatigue and nausea
Temozolomide	Modest immunosuppression, mild fatigue and nausea
Carboplatin/paclitaxel	Immunosuppression, peripheral neuropathy, alopecia, fatigue and nausea

time to relapse on monotherapy is around 6 months [28–30]. Combination with a downstream MEK inhibitor improves response, delays resistance and reduces skin-related toxicities but increases the frequency of pyrexia [31–33].

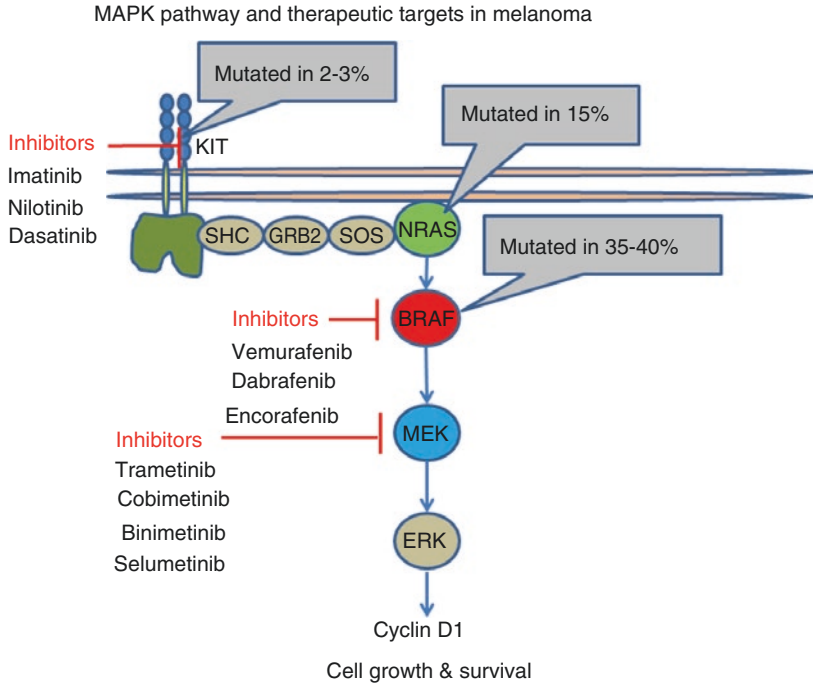

Fig. 3.2 MAPK pathway

3.6.2 Immunotherapy

Immunotherapy should be considered in patients whose melanoma is BRAF wild type. Ipilimumab, an anti-CTLA-4 antibody, potentiates T cell function. It has demonstrated improved overall survival in metastatic melanoma with a median survival of 10–11 months and long-term durable responses in 19% at 4-year follow-up [24, 25]. The programmed death-1 (PD-1) protein is another key immune checkpoint inhibitor expressed by activated T cells that mediate immunosuppression. PD-1 functions primarily in the peripheral tissues where T cells may encounter ligands (PD-L1 and PD-L2) expressed by tumour cells and/or stromal cells (see Figs. 3.3 and 3.4). There are three anti-PD1 monoclonal antibodies that have demonstrated activity in advanced melanoma in clinical trials, pembrolizumab, nivolumab and atezolizumab. Anti-PD1 therapy has reported objective response rates in the range of 26–31% [35, 36]. Anti-PD1 monoclonal antibodies are now approved for the treatment of advanced melanoma, both as single agents and in combination with ipilimumab. Responses to immunotherapy are typically slower than with targeted therapies and transient apparent worsening of disease on imaging before disease stabilisation or tumour regression may be seen. A new immune-related criterion has been defined to evaluate immunotherapy responses [37].

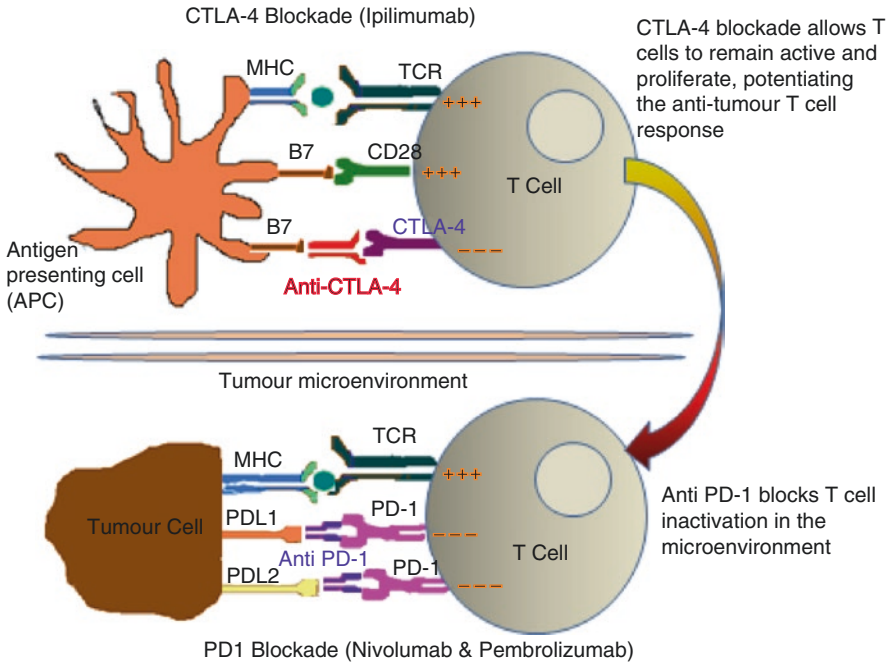

Fig. 3.3 Immunotherapy mechanisms of action for CTLA-4 and PD1 blockade

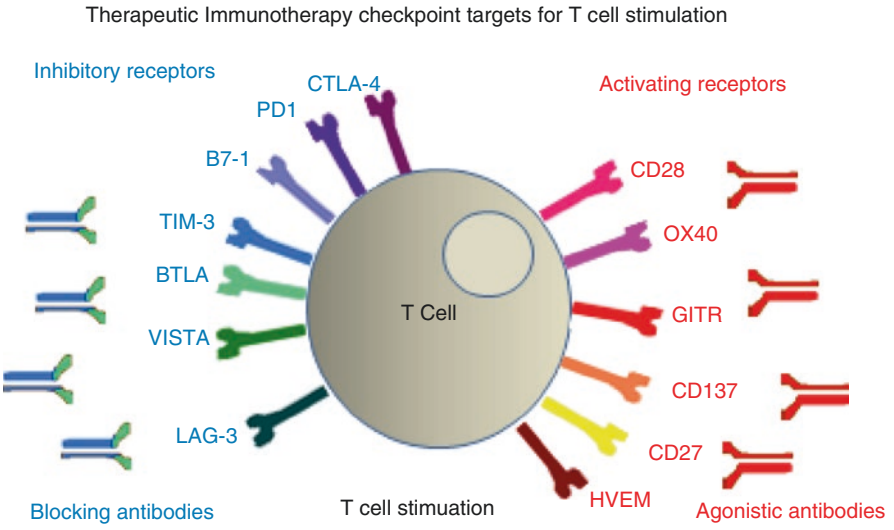

Fig. 3.4 Therapeutic immunotherapy checkpoint targets for T cell stimulation. Adapted from Mellman et al. (2011) [34]

3.6.3 Cytotoxic Chemotherapy

Dacarbazine and temozolomide have response rates in the range of 8–20%, with partial response durations typically of 4–6 months. Both drugs are well tolerated and only cause modest immunosuppression. Temozolomide crosses the blood-brain barrier and has some activity against cerebral metastases [26].

Key Points

- **Surgical management of primary melanoma:** Lesions should be excised with adequate margins, with recommended radial excision margins.
- **Sentinel lymph node biopsy:** Sentinel lymph node biopsy (SLNB) should be considered in primary melanomas greater than 1.0 mm thick as it provides staging and prognostic information.
- **Management of locoregional recurrent melanoma:** Surgery is the treatment of choice for single local or regional metastases. In-transit and local metastases can be managed with localised treatment modalities.
- Suspected local regional nodal recurrence should be confirmed by fine needle biopsy.
- **Radiotherapy:** Adjuvant radiotherapy can be considered in carefully selected cases with narrow or positive margins, or where re-excision of the primary disease is unsuitable. Palliative radiotherapy to symptomatic metastatic or unresectable nodal, satellite or in-transit disease may offer some benefit.
- **Adjuvant systemic therapy of melanoma:** Patients with resected stage 1–3 melanoma should be followed up by clinical surveillance. Adjuvant therapy with high-dose interferon alpha can be discussed with patients with stage III, high-risk disease, carefully outlining the risks and benefits associated with this therapy.
- **Management of metastatic melanoma:** Advanced melanoma should be profiled for the presence of a driving mutation. BRAF V600 mutation is detected in approximately 40% of melanomas. Treatment with either a targeted therapy or immunotherapy should be considered as first-line therapy depending on the mutational status of the tumour.
- **Targeted systemic therapy with MAPK pathway inhibition:** Treatment with a BRAF inhibitor can produce rapid tumour regression with significantly improved progression-free survival, overall survival and intracranial activity in BRAF-mutated disease.

- **Immunotherapy:** Immunotherapy should be considered in patients whose melanoma is BRAF wild type.
- **Cytotoxic chemotherapy:** Dacarbazine and temozolomide have response rates in the range of 8–20%, with partial response durations typically of 4–6 months.

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Radiological Imaging in Melanoma

4

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Contents

4.1 Introduction

Current NCCN guidelines only recommend imaging at the time of presentation in stage 1 and 2 melanoma in cases with specific signs and symptoms due to low yield and frequent false positives. In stages 3 and 4, imaging is performed at baseline and in follow-up for assessment of response, detection of recurrence and complications of treatment [1]. Image-guided biopsy is also often needed to confirm metastases or recurrence and, depending on the location of the lesion, may be performed under CT or ultrasound guidance. The imaging manifestations of melanoma and the relative merits and weakness of different conventional imaging modalities are discussed below.

4.2 Plain Radiographs

Plain radiographs have practically no role in the primary assessment or staging of melanoma [2]. Chest radiographs are, however, performed as part of preoperative workup or in the assessment of complications like fever during treatment. Similarly,

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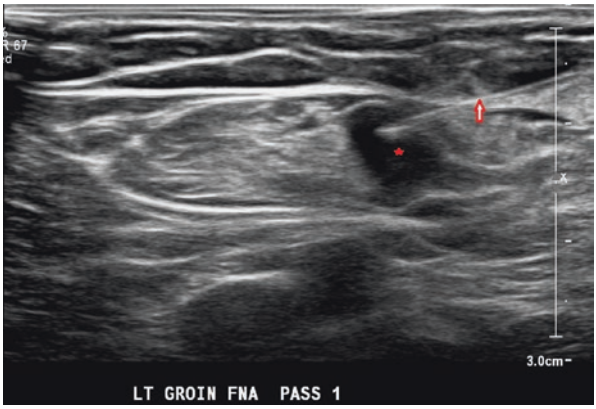

Fig. 4.1 Cytology proven 8 mm hypoechoic melanoma deposit (*asterisk*) in a 3 cm long groin node which shows otherwise normal sonographic characteristics. *Arrow* indicates aspiration needle in situ

skeletal radiographs may be done as the initial step in evaluation of bone or joint pain in patients with melanoma and may reveal melanoma metastases, most often as lytic lesions [3].

4.3 Ultrasound

High-frequency ultrasound has been used in the assessment of depth of invasion of primary cutaneous melanoma lesions [4] but is not routinely used. In the evaluation of nodal metastases, ultrasound has been shown to be better than clinical examination [5] but may be falsely negative when metastatic deposits are smaller than 2 mm (Fig. 4.1) [6]. Operator dependence and technical issues like large body habitus and obscuration of organs by bowel gas render ultrasound less useful than CT in the detection of intra-abdominal metastases. Sonographic features of hepatic metastases are non-specific, with most lesions being hypoechoic [7]. Metastases to the pancreas and adrenals may be difficult to detect, and bowel metastases are almost never detected with ultrasound.

4.4 Computerised Tomography (CT)

CT is the preferred modality for assessment of melanoma metastases to lungs and abdominal organs. Pulmonary metastases from melanoma are usually multiple and may vary in size from miliary to large (Fig. 4.2) [8] and are a relatively common site of metastasis. Isolated pleural effusion is, however, uncommon [9]. Hepatic metastases are often hypervascular (Fig. 4.3) enhancing in the arterial phase and hypo- or isodense in portal venous phase, a pattern which helps distinguish them from other metastases. Metastases to the spleen, pancreas and kidneys are rare and may be solid or cystic [7] but are otherwise non-specific in appearance. Adrenal metastases may be bilateral, and metastases to the gall bladder may be small flat nodules or polypoid and pedunculate (Fig. 4.4). Metastatic

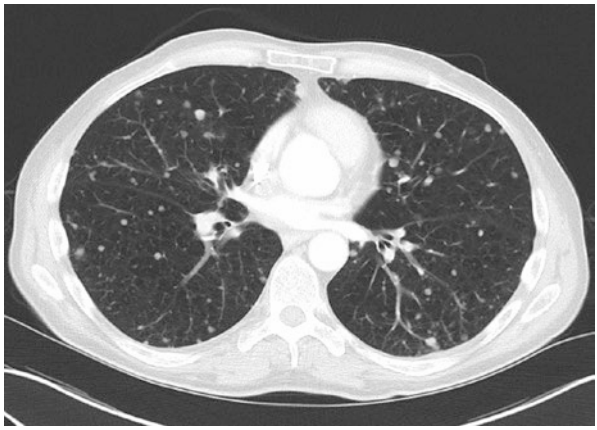

Fig. 4.2 Lung window image of CT chest demonstrating bilateral, multiple, pulmonary metastases from melanoma

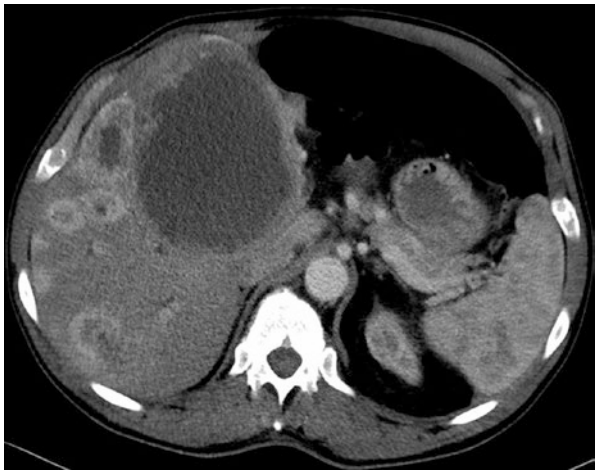

Fig. 4.3 Hypervascular liver metastases. Arterial phase CT demonstrates several hypervascular hepatic metastases with varying degree of intralesional necrosis

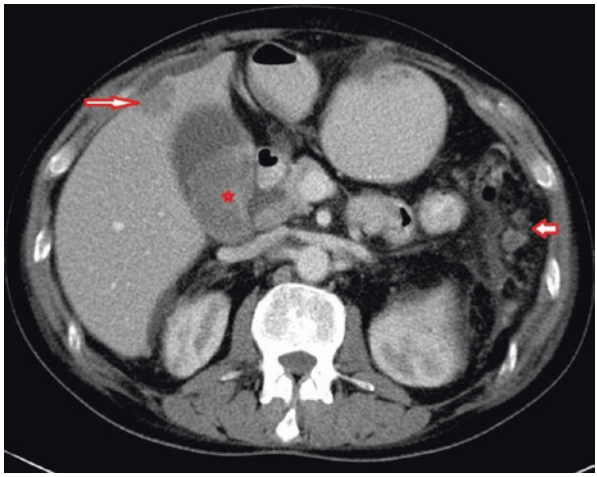

Fig. 4.4 Portal venous phase CT demonstrates hypodense metastasis in the liver (*long arrow*). A metastasis in the gall bladder is identified as a polypoid mass (*asterisk*), and there are multiple peritoneal metastases (e.g. *short arrow*) in a patient with advanced melanoma

lesions to the small bowel may cause wall thickening or manifest as small nodules, which may be missed without use of oral contrast but may sometimes be detected due to resultant intussusception (Fig. 4.5) or small bowel obstruction. Masses resulting from metastases to ovaries are usually difficult to distinguish from other ovarian masses on CT, and the uncommon occurrence of melanoma metastases to the vagina and uterus may be occult on CT, especially when small.

Metastases to the muscles may be difficult to detect especially when poorly enhancing unless they distort the contour noticeably (Fig. 4.6). Subcutaneous

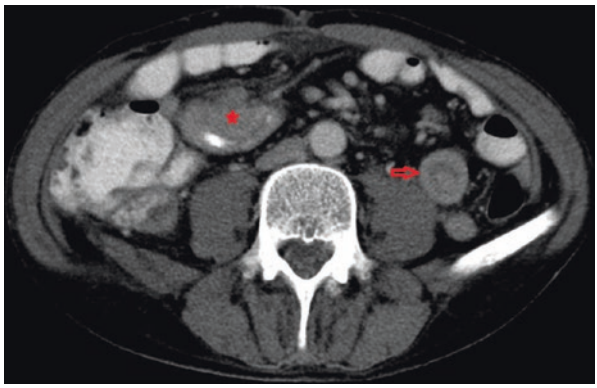

Fig. 4.5 Melanoma metastases to small bowel causing wall thickening (*asterisk*) and intussusception (*arrow*)

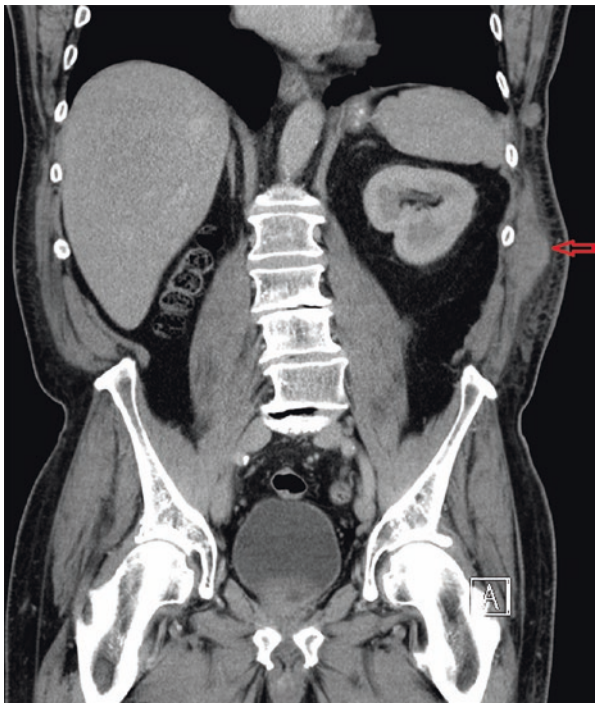

Fig. 4.6 Portal venous phase CT of abdomen demonstrates an intramuscular metastasis from melanoma in left external oblique muscle (*arrow*)

metastases are, however, well demonstrated even when small (Fig. 4.7). Nodal metastases especially in deep stations are better assessed with CT than ultrasound. Lesions in the breast may be difficult to detect prospectively, but can be identified as non-specific soft tissue nodule. Bony metastases and their associated soft tissue extension are well demonstrated by CT, though small lytic lesions may be occult and better detected on MRI or PET/CT (Fig. 4.8).

Metastases to the brain and its acute presentation with haemorrhage are well assessed by CT, though MR is better for assessing small lesions and meningeal involvement [10]. Cerebral metastases of melanoma are usually multiple and hyperdense in pre-contrast CT and enhance following intravenous contrast (Fig. 4.9), with ring pattern of enhancement seen in 15% [11].

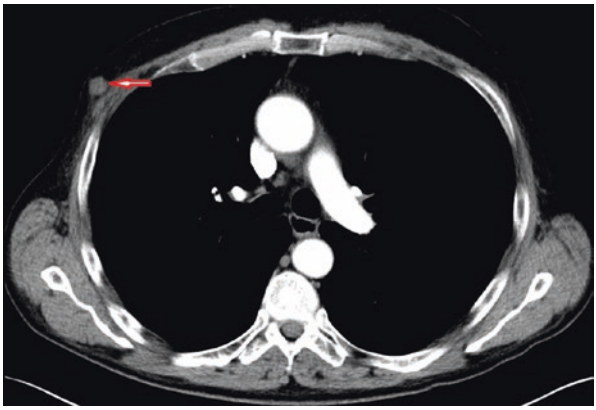

Fig. 4.7 CT chest demonstrates 8 mm subcutaneous metastases in the right anterior chest wall

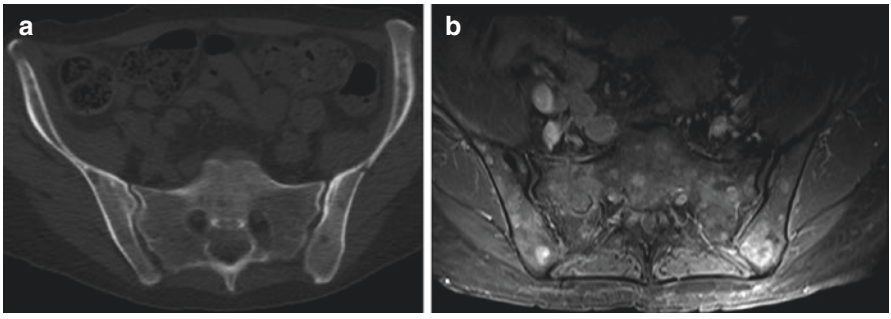

Fig. 4.8 Bone window image of CT pelvis (**a**) in a patient with melanoma demonstrating multiple small lytic bony metastases. T1-weighted post-contrast MRI (**b**) done 2 days later for assessment of neuropathy shows metastases more clearly

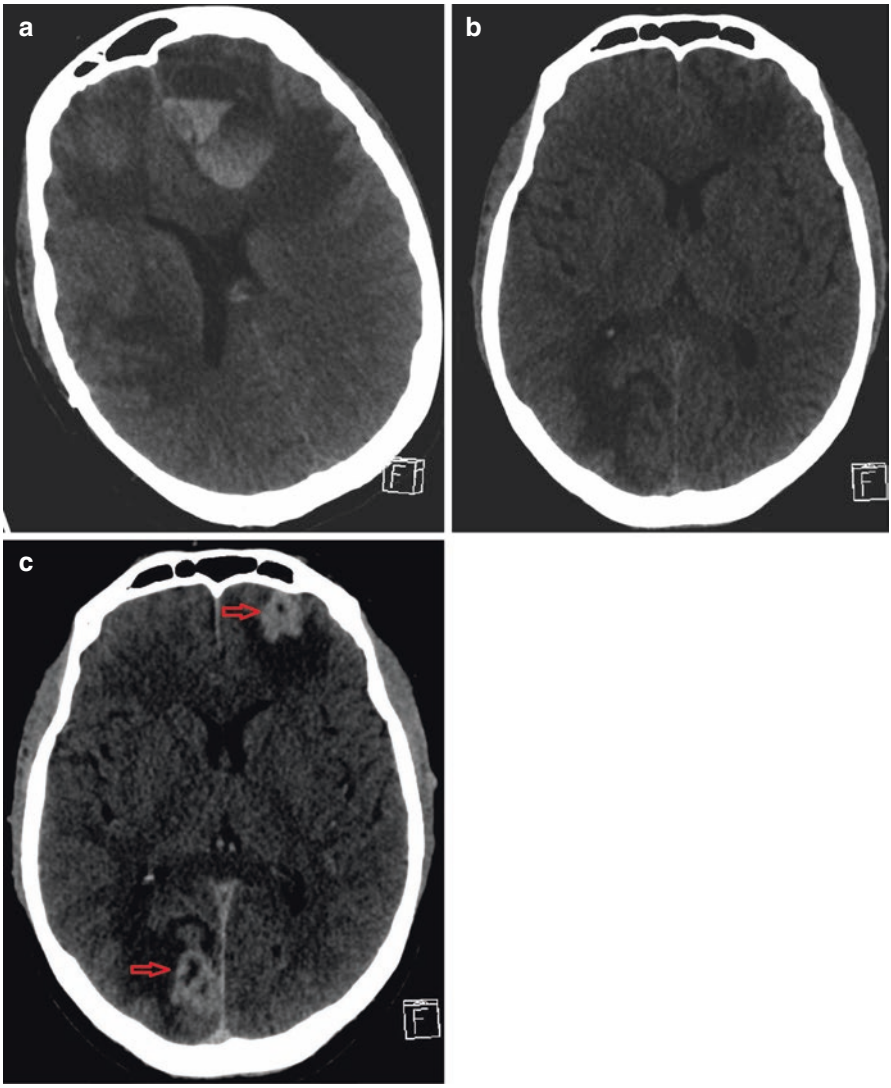

Fig. 4.9 Cerebral metastases from melanoma: non-contrast CT (**a**) shows multiple hyperdense lesions with surrounding oedema, largest in left frontal lobe with fluid level. (**b** and **c**) Right occipital and left frontal enhancing metastases (*arrows* in (**c**)), which are isodense to cortex pre-contrast (**b**)

4.5 MRI

MR is the imaging modality of choice for assessment of intracranial metastases from melanoma and can demonstrate even tiny metastases. Melanotic cerebral lesions are hyperintense on T1-weighted images and hypointense on T2-weighted images, whilst amelanotic lesions are hypo- or isointense to the cortex on T1 and

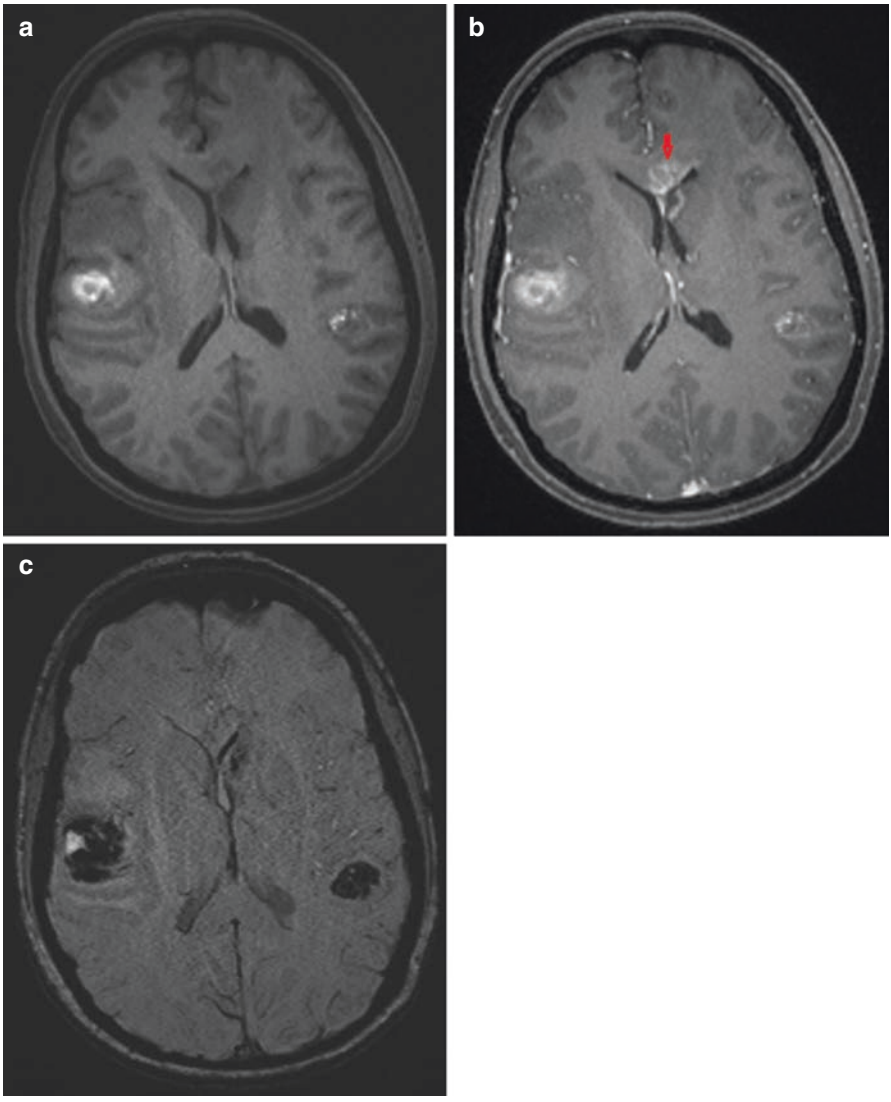

Fig. 4.10 MR appearance of melanoma metastases to the brain: melanotic metastases in each frontal lobe are hyperintense in T1 (**a**), whilst an amelanotic lesion is enhancing post-contrast (*arrow*, **b**) but hypointense pre-contrast. The three lesions show varying hypointensity in SWI (**c**) depending on the degree of haemorrhage

hyper- or isointense on T2 [12]. Innate T1 hyperintensity of melanoma metastases may be from melanin or haemorrhage [10]. Micro-haemorrhage in these lesions is well depicted with gradient echo sequences or the relatively new susceptibility-weighted imaging [SWI] (Fig. 4.10). In meningeal melanoma, the leptomeninges are involved more commonly than the dura (7) leptomeningeal metastases; both

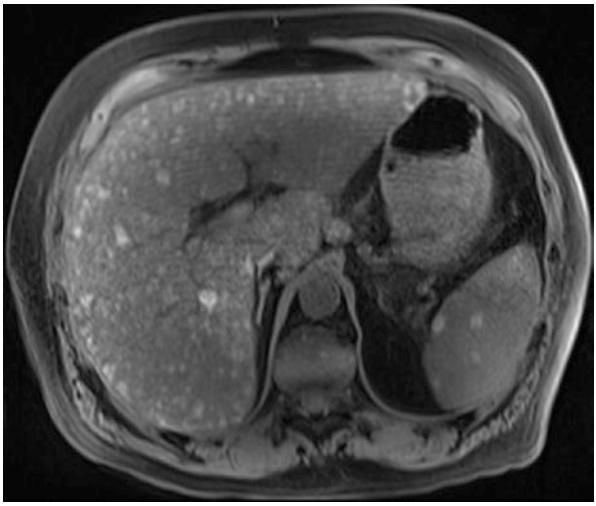

Fig. 4.11 T1 fat-suppressed MRI of upper abdomen demonstrating multiple hyperintense small metastases from melanoma in the liver and spleen

intracranial and spinal are best assessed with MRI and are demonstrated as abnormal enhancement. The innate T1 hyperintensity of melanoma lesions in visceral metastasis in MRI (Fig. 4.11) can suggest the correct diagnosis but has been reported in only 10% [13].

4.6 Restaging Imaging

Restaging of melanoma is usually done with CT, although increasingly PET/CT is used as discussed in Chap. 5. Evaluation of intracranial lesions or cord compression, however, is best performed with MRI. Response evaluation criteria in solid tumours (RECIST) criteria are widely employed for the evaluation of treatment response [14], but it should be remembered that necrotic change may lead to enlargement of lesions (pseudo-progression). Intralesional macroscopic haemorrhage may also render discrimination of margins of the lesions difficult, hampering accurate measurement for clinical trials.

Immunotherapeutic agents may result in different response patterns compared to cytotoxic agents. Whilst conventional RECIST response requires shrinkage of baseline lesions without new lesions, with immune therapy responses three additional patterns may be seen: (1) durable stable disease (in some patients followed by a slow, steady decline in tumour), (2) response after an apparent increase in total tumour burden and (3) response in the presence of new lesions. To capture these patterns of response, an immune-related response criteria (irRC) has been developed (see Table 4.1) [15]. Using irRC, a portion of patients previously classified as progressive disease by RECIST are reclassified as partial responses or stable disease.

Table 4.1 Outline of immune-related response criteria following immunotherapy

Immunotherapy can result in four distinct patterns of response, which are all associated with favourable survival:
(a) Shrinkage in baseline lesions, without new lesions
(b) Durable stable disease (in some patients followed by a slow, steady decline in tumour burden
(c) Response after an increase in total tumour burden
(d) Response in the presence of new lesions
A comparison with the response evaluation criteria in solid tumours (RECIST) is set out below:

Response evaluation	**WHO criteria**	**Immune-related response criteria**
New measurable lesions ≥5 × 5 mm	Always represent PD	Incorporated into tumour burden
New nonmeasurable lesions <5 × 5 mm	Always represent PD	Do not define progression (but preclude irCR)
Nonindex lesions	Changes contribute to defining best overall response of CR, PR, SD and PD	Contribute to defining irCR (complete disappearance required)
Complete response (CR)	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
Partial response (PR)	≥50% decrease in sum of perpendicular diameters (SPD) of all index lesions compared with baseline in two observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of nonindex lesions	≥50% decrease in tumour burden compared with baseline in two observations at least 4 weeks apart
Stable disease (SD)	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of nonindex lesions	50% decrease in tumour burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive disease (PD)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of nonindex lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumour burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

Adapted from Wolchok et al. [15]

Key Points

- Current NCCN guidelines only recommend imaging at the time of presentation in stage 1 and 2 melanoma in cases with specific signs and symptoms due to low yield and frequent false positives.

- In stages 3 and 4, imaging is performed at baseline and in follow-up for assessment of response, detection of recurrence and complications of treatment.
- Plain radiographs have practically no role in the primary assessment or staging of melanoma.
- High-frequency ultrasound has been used in the assessment of depth of invasion of primary cutaneous melanoma lesions but is not routinely used.
- CT is the preferred modality for assessment of melanoma metastases to lungs and abdominal organs.
- Metastatic lesions to the small bowel may cause wall thickening or manifest as small nodules, which may be missed without the use of oral contrast but may sometimes be detected due to resultant intussusception or small bowel obstruction.
- Metastases to the muscles may be difficult to detect especially when poorly enhancing unless they distort the contour noticeably.
- Nodal metastases especially in deep stations are better assessed with CT than ultrasound. Small lytic lesions may be occult and better detected on MRI or PET/CT.
- Metastases to the brain and its acute presentation with haemorrhage are well assessed by CT, though MR is better for assessing small lesions and meningeal involvement.
- MR is the imaging modality of choice for assessment of intracranial metastases from melanoma and can demonstrate even tiny metastases.
- Restaging of melanoma is usually done with CT, although increasingly PET/CT is used.

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Role of PET/CT in Melanoma

5

Michael S. Hofman and Rodney J. Hicks

Contents

5.1 Introduction

In line with major advances in therapy for metastatic melanoma in the last decade, there have also been significant improvements in imaging. ^{18}F-fluorodeoxyglucose (FDG) PET/CT has emerged as the imaging modality of choice for identifying locoregional nodal or distant metastatic disease and also for restaging following therapy. The spatial and contrast resolution of PET has improved owing to advances in

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both hardware and software reconstruction. The ultimate size of disease that PET can detect depends on how metabolically active the tumour cells are within an individual lesion. On a current generation PET/CT device, disease of 8 mm or greater in size is readily detected. In some patients, however, disease as small as 2–3 mm can be detected with confidence owing to the high metabolic activity of melanoma.

5.2 Primary Diagnosis/Staging

There is a very limited role for imaging, including PET/CT, in stage I or II disease due to low yield and a higher proportion of false-positive relative to true-positive results than occurs in more advanced disease. Sentinel lymph node biopsy has emerged as the standard of care for initial staging of clinical stage I and II melanoma in many institutions.

5.2.1 Sentinel Lymph Node Scintigraphy with SPECT/CT

In the absence of palpable lymphadenopathy, the pretest likelihood of macroscopic nodal disease is low, and there is a limited role of PET/CT imaging in this setting, with sentinel lymph node biopsy to detect microscopic nodal involvement being the staging technique of choice [1, 2].

When performing SLNB, SPECT/CT provides additional benefit compared to planar imaging [3]. SPECT/CT enables precise anatomic localisation and has been shown to provide a clear benefit with significant change in management. Some centres perform SPECT/CT selectively when planar imaging is difficult to interpret and demonstrates unusual drainage pathways or a draining node is non-visualised [4]. More recent data demonstrates additional value of routine SPECT/CT with a significant management impact in 46% of patients [5]. 3D volume-rendered PET/CT can be helpful for guiding surgical approach (Fig. 5.1). The use of SPECT/CT enables the surgeon to more precisely target the area of interest potentially resulting in better post-operative aesthetic results [6]. Furthermore, the local relapse rate has been shown to be significant superior when using SPECT/CT resulting in prolonged 4-year disease-free survival (94% vs 79%) [7]. Close collaboration between the nuclear medicine specialist, surgeon and pathologist is required to optimise utility of SLNB and decrease false-negative results [8].

5.2.2 Sentinel Lymph Node Positive

Although tempting to image patients with microscopic disease detected on SLNB, the a priori likelihood of nodal involvement is low, and there is a very low yield from imaging in this setting, whether this be by CT or MRI [9] or using FDG PET/CT [10]. With all modalities, there is higher number of false-positive than true-positive results in this clinical setting.

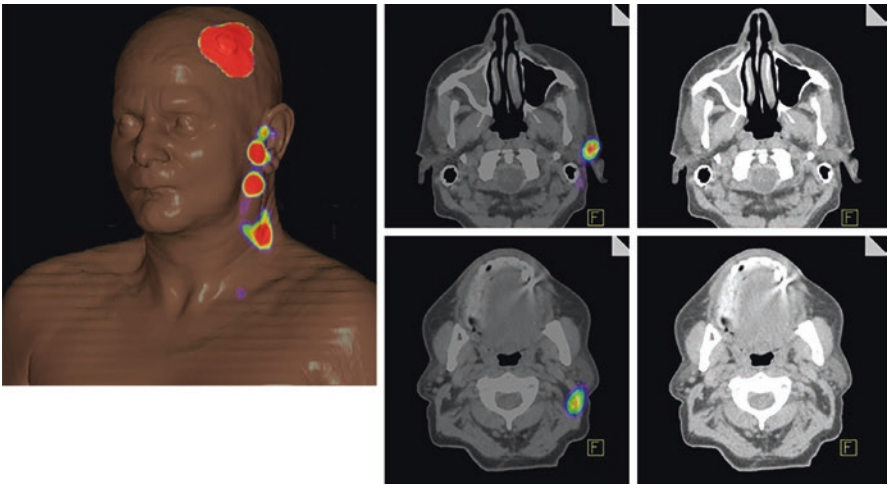

Fig. 5.1 Surface-rendered SPECT/CT showing high uptake at the injection site in the forehead and a chain of left cervical nodes. Axial SPECT/CT images demonstrate the position of the left preauricular sentinel node and secondary tier level II cervical nodes

5.2.3 High-Risk Patients with Stage I or II Disease

There may be a role for staging FDG PET/CT in patients with stage I/II disease and high-risk features, such as T4 disease or ulceration. In a study of 52 patients with T4 disease, the melanoma-related treatment plan was altered in 11% of patients. The main benefit of PET in this setting is identification of macroscopic locoregional nodal disease enabling the patient to proceed to lymphadenectomy and obviating the need for sentinel node biopsy.

5.2.4 Stage III and IV Melanoma

FDG PET/CT is the imaging modality of choice when there is clinical suspicion of locoregional or systemic metastases. Indications include:

- Staging in patients with stage III or IV disease [11–13]
- Clinical suspicion of recurrent or metastatic disease
- Prior to planned intervention (e.g. surgery or radiotherapy, with curative intent) in patients with locoregional or oligo-metastatic disease
- Response assessment of patients undergoing chemotherapy and targeted or immune-activating therapy

Substantially higher sensitivity and specificity of PET (92 and 94%, respectively) has been demonstrated compared to CT (58 and 45%, respectively) for detection of distant metastatic disease [14] (Fig. 5.2). The patterns of spread of melanoma are unpredictable

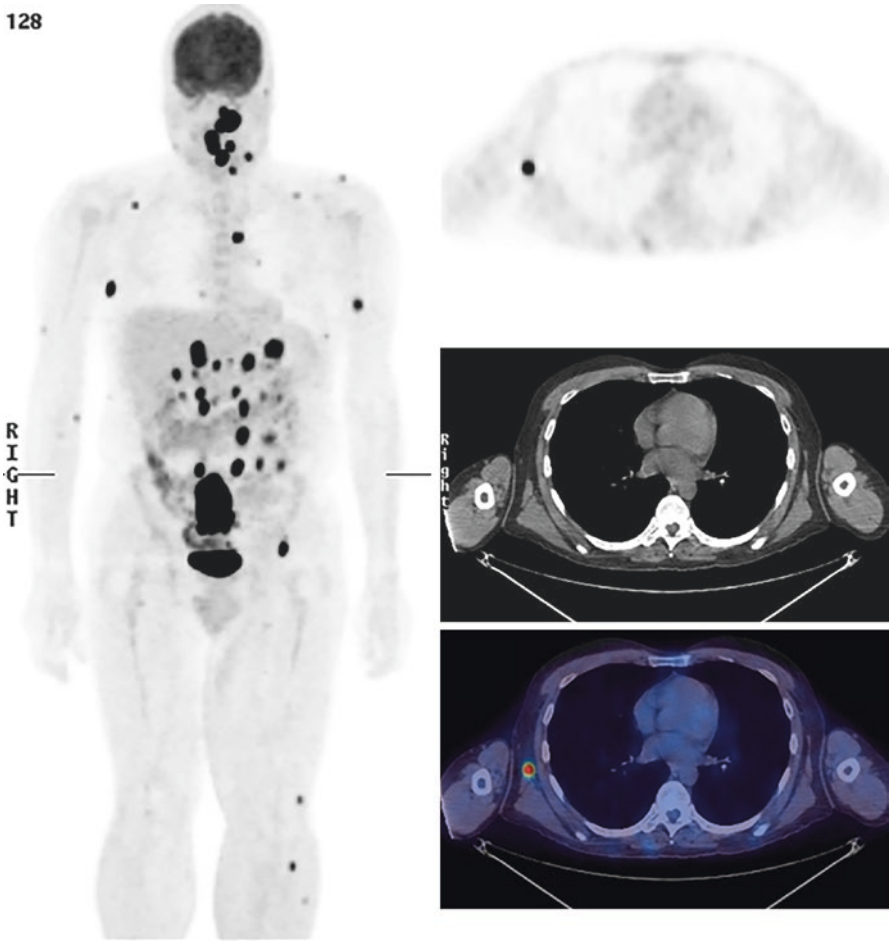

Fig. 5.2 Patient with suspected right adrenal solitary metastasis on CT staging. Despite presence of limited disease on CT, PET/CT clearly demonstrates extensive metastatic disease. The maximum intensity projection (MIP) image (*left*) provides a whole body overview with high tumour-to-background contrast. A right serratus anterior muscle metastasis is shown (PET, CT and PET-CT images). On the PET-only images, the abnormality cannot be localised. Even with the PET and CT side-by-side interpretation, localisation is difficult. The fused PET-CT images provide confident localisation of a sub-cm metastasis

with metastases seen in virtually any organ including the skin, subcutaneous tissue, lung, liver, brain, bone, gastrointestinal tract (small bowel > large bowel > stomach), muscle, adrenal cardiac, adrenal, gallbladder, breast, pancreas, thyroid and kidneys (Fig. 5.3).

The superior accuracy of PET/CT has been shown to confer a high management impact ranging from 22 to 62% [15–17]. In a study of 134 patients, PET detected 55% additional lesions compared to conventional modalities conferring a 62% management change [18]. In a prospective study of 103 patients with PET performed in high-risk patients prior to planned surgery, addition of PET changed management in 35% of patients, with most of these being cancellation of surgery [19]. In a study of

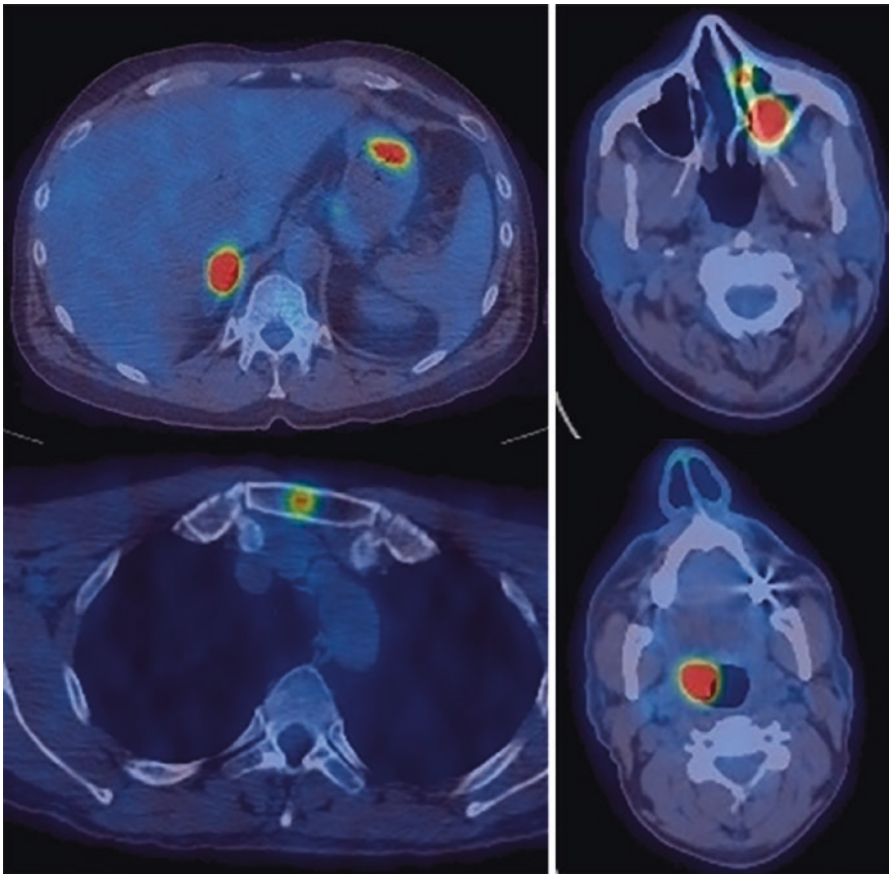

Fig. 5.3 Other occult sites of metastases seen in Fig. 5.2 including the left sinus and right tonsillar, gastric and osseous metastasis in the sternum. Also note the index right adrenal metastasis

PET/CT in patients with stage III/IV melanoma referred after review by a multidisciplinary team, major clinical impact was seen in 41% [20]. High management impact was predominantly alternation of plan from surgery to systemic therapy after identification of more extensive disease than seen on conventional workup. Although using out-dated, stand-alone PET technology and SPECT rather than SPECT/CT, an early study from our centre indicated that PET is also substantially more sensitive than Ga-67 citrate SPECT, a molecular imaging approach that was previously used for staging advanced melanoma [21]. High management impact was also demonstrated.

5.2.5 Limitations of FDG PET/CT

Stand-alone PET has lower sensitivity for pulmonary metastases, but in the PET/CT era, these are generally detected on the CT component. In a study of 50 patients, no additional benefit was demonstrated with contrast-enhanced CT compared to PET with non-enhanced non-low-dose CT [22]. Dedicated CT of the thorax can

detect smaller nodules than low-dose CT, but these are invariably too small to characterise and, in our experience, frequently represent false-positive findings. Even faint FDG uptake in lesions smaller than 8 mm is highly suggestive of malignancy, but lesions of 1–4 mm may generally require surveillance or comparison with prior imaging to differentiate between benign granulomas and small metastases. In our centre, we no longer routinely perform contrast-enhanced CT but use it selectively to further interrogate equivocal findings on PET/CT. Owing to high physiologic brain activity, FDG PET/CT has very limited utility in assessing cerebral metastases, which is better assessed with MRI or by other PET radiotracers discussed later.

Ocular/uveal melanoma. These have a distinctive propensity to metastasise to the liver. A proportion of these also have low metabolic activity [23] despite aggressive behaviour, and correlation with contrast enhanced CT or MRI of the liver is therefore advised.

5.3 Response Assessment

Data has demonstrated that assessing metabolic response on PET/CT after 2–3 cycles of conventional chemotherapy (e.g. dacarbazine) with visual dichotomisation of response as a complete or partial metabolic response versus progressive metabolic disease [24, 25] is a powerful biomarker that has the potential to replace conventional imaging endpoints such as RECIST anatomic criteria.

Management paradigms in metastatic melanoma have rapidly changed with both targeted therapies against BRAF and MEK and immunotherapy including anti-programmed death 1 (anti-PD1) monoclonal antibodies (nivolumab and pembrolizumab) and anti-CTLA4 monoclonal antibody (ipilimumab) now the treatments of choice for metastatic disease. Given the availability of several systemic therapeutic options, accurate response assessment is pivotal to guide management. Early response assessment enables an appropriate change in management thereby avoiding the morbidity and cost associated with ineffective therapy.

FDG PET/CT has been shown to be a useful marker of early biologic response to BRAF inhibition with complete or substantial reduction in metabolic activity observed as early as 15 days after commencement of therapy [26] (see Fig. 5.4). The reduction in glucose utilisation early during BRAF therapy is likely a pharmacodynamic indicator of reduced signalling through the MAP kinase pathway and is a necessary but sometimes insufficient requirement for subsequent clinical response and survival benefit. Reactivation of glucose use by previously responding tumours is a biomarker of reactivation of signalling through this pathway [27].

5.3.1 Pitfalls

Targeted and immune-modulating therapies can result in immune-related inflammatory changes on FDG PET/CT. In our experience, the following features are typical of an inflammatory immune-related response and should not be misinterpreted as disease progression:

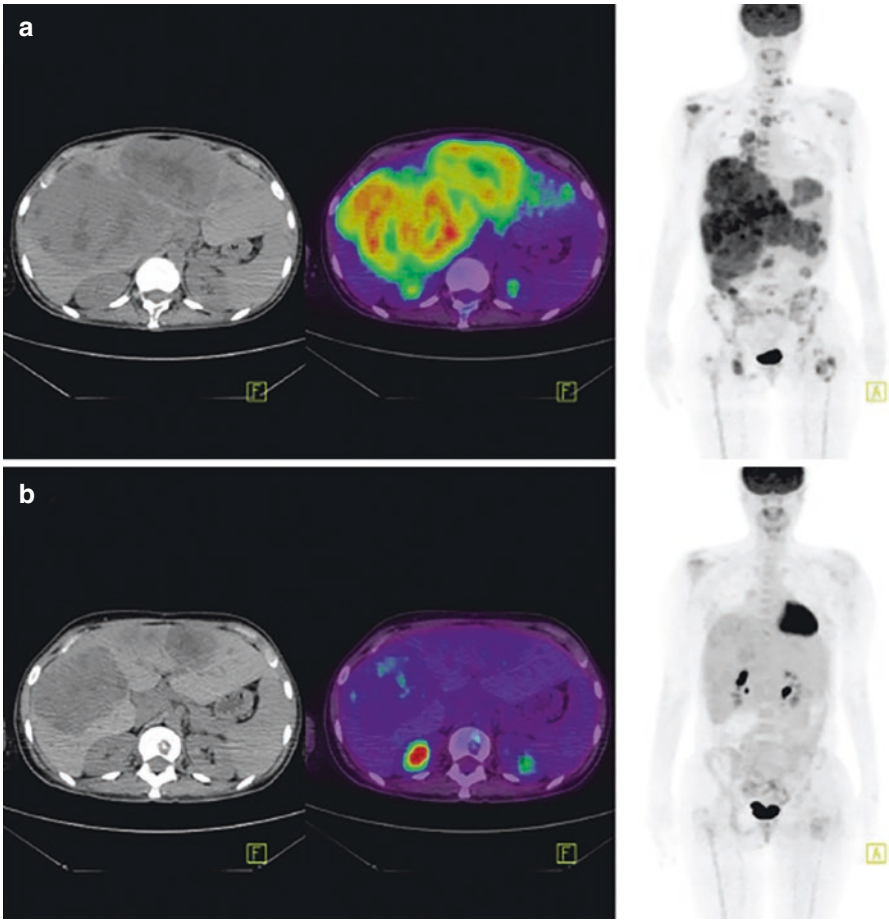

Fig. 5.4 Patient with extensive metastatic melanoma involving the liver and bone (metabolic volume of 3.1 L) (**a**). After 14 days of vemurafenib therapy (**b**), there is a complete metabolic response and partial anatomic response. Reproduced with permission [26]

- Symmetrical mediastinal and hilar nodal activity developing in the context of lung metastases (Fig. 5.5)
- New nodal uptake in a drainage basin of prior metastases (Fig. 5.6)
- Diffuse increased splenic activity
- High symmetric tonsillar activity

5.3.2 Treatment Related Adverse Effects Mimicking Malignancy

Several new drugs have specific adverse effects, which have correlates on FDG PET/CT and that can be mistaken for disease progression. In general, when a "mixed response" is visualised, that is, regression of disease with an apparent new

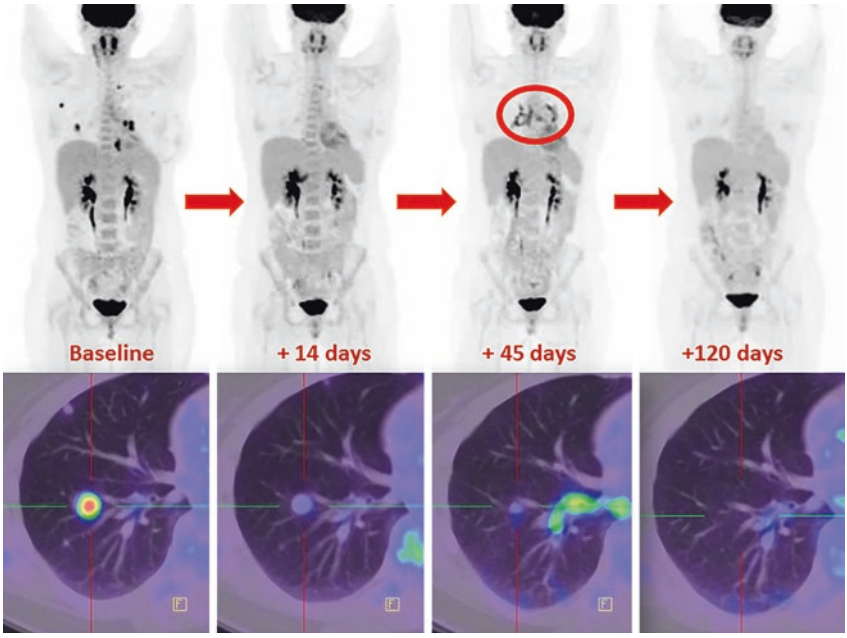

Fig. 5.5 Patient with biopsy proven pulmonary metastases from metastatic melanoma. There is a complete metabolic response 14 days after commencement of combined BRAF and MEK inhibitors. Anatomic regression is visualised at 45 days, but there are new hilar and mediastinal nodal uptake. These changes are consistent with an immune-related inflammatory response. Although BRAF/MEKi is not a form of immunotherapy there is emerging evidence that therapy directed against the MAPK pathway exerts immune modulatory effects explaining the PET findings. These changes resolve by 120 days with complete anatomic response evident in the metastases

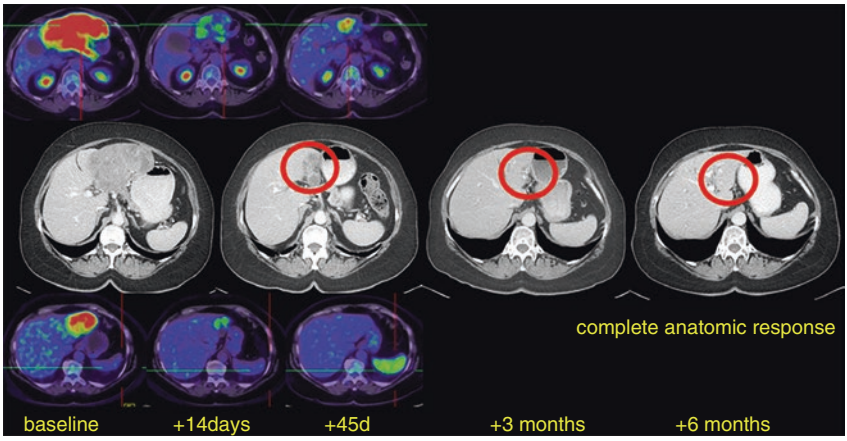

Fig. 5.6 Patient with metastatic melanoma in the left lobe of the liver. Following commencement of combined BRAF and MEK inhibitors, there is an early partial metabolic response at 14 days. FDG PET/CT at 45 days shows further reduction in size of the metastasis but more intense metabolic abnormality. This could be attributed to early progression, but the presence of diffuse splenic uptake is a clue to underlying immune-related response. In this setting, the increase in uptake is not attributed to progression. Subsequently, there was a complete anatomic and metabolic response

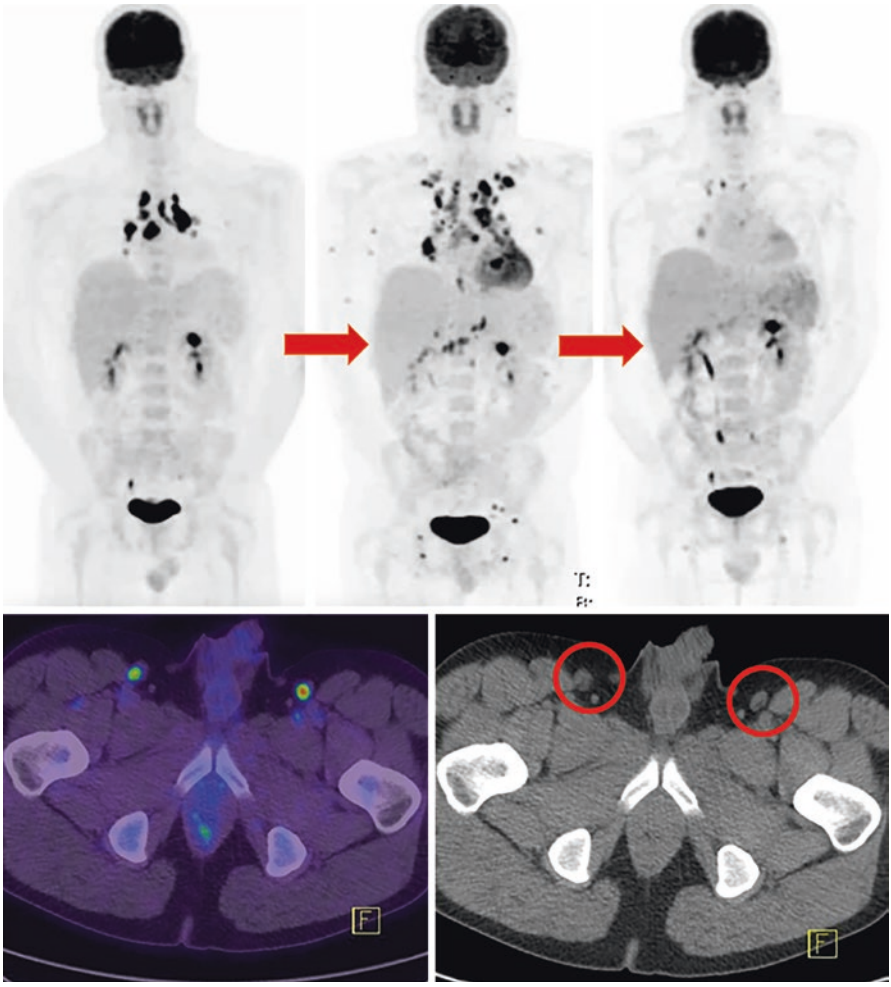

Fig. 5.7 This patient with stage III melanoma had intense but symmetric hilar and mediastinal nodal activity (*left*) most consistent with sarcoidosis or granulomatosis disease. Following adjuvant interferon therapy, pulmonary and nodal abnormalities progressed but were mostly sub-cm in size with preserved fatty hilum (*bottom left* and *right*). As interferon is known to cause exacerbation of underlying sarcoidosis, biopsy was recommended which confirmed non-necrotising granulomatous inflammation. Following cessation of interferon, abnormalities regressed (*top right*). The case highlights how knowledge of drug effects can minimise false-positive results

site of disease, consideration should be given to alternative non-malignant explanation.

Interferon is known to cause reactivation of sarcoidosis, a pattern which can mimic malignancy (see Fig. 5.7).

BRAFi can promote formation of keratoacanthomas or SCC through paradoxical activation of ERK signalling. These can be FDG-avid and confused with new dermal or subcutaneous metastases (see Fig. 5.8).

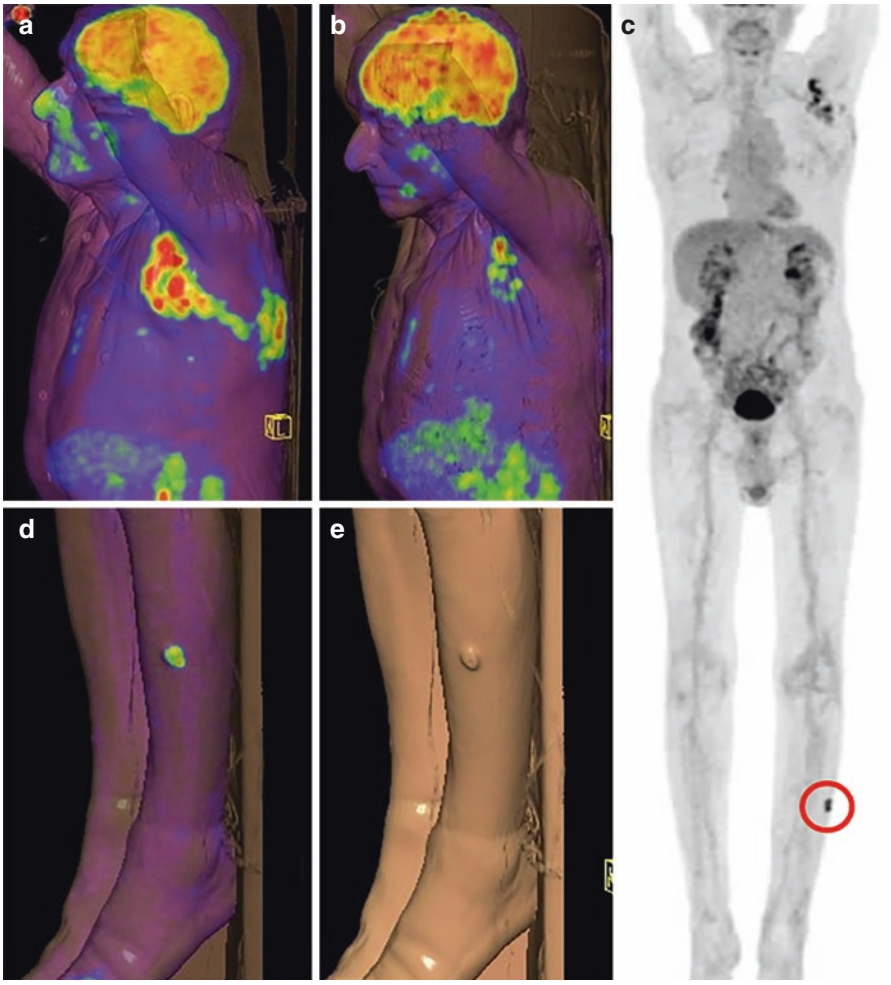

Fig. 5.8 This patient which has extensive axillary nodal disease (**a**: surface-rendered PET/CT) was treated with a BRAF inhibitor with marked reduction in extent and intensity of abnormality at 3 months (**b**). Despite this, a new intensely FDG-avid dermal/subdermal nodule was seen in the left leg (**c**, **d**, **e**). This was thought likely to be due to development of a keratoacanthoma/squamous cell carcinoma as an adverse effect of BRAF inhibition, which was confirmed following excision

Immune-modulating therapies including anti-PD1 or anti-CTLA4 antibody therapy can cause a variety of autoimmune conditions. As these processes are inflammatory, they can masquerade as new sites of malignancy on FDG PET/CT. These entities should be considered, especially when there is an apparent new site of disease in the context of a metabolic response elsewhere. These include autoimmune hypophysitis, thyroiditis, colitis or adrenalitis (see Fig. 5.9) or colitis [28].

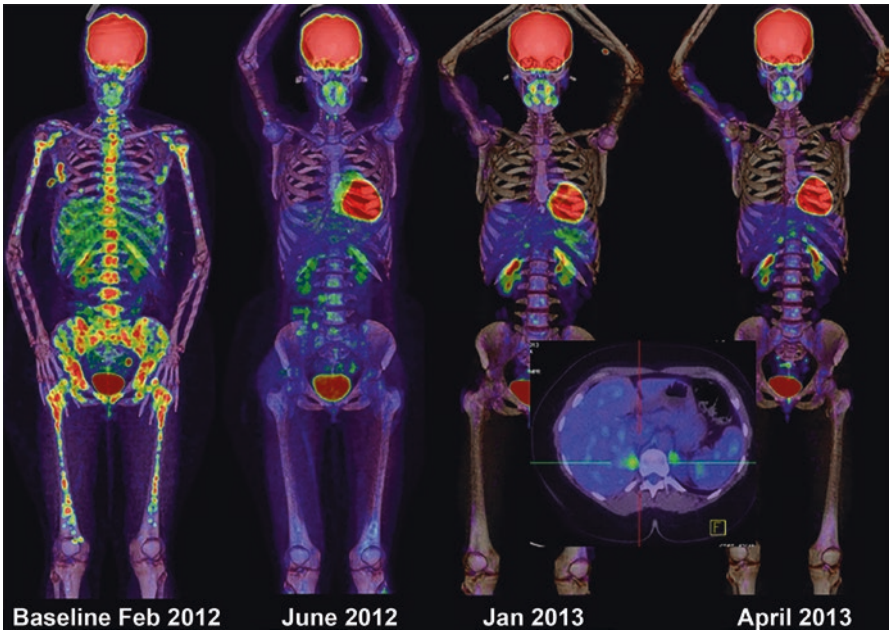

Fig. 5.9 This patient has extensive osseous metastatic disease and was treated with ipilimumab with a complete metabolic response, highlighting the ability of FDG PET/CT to assess response in sites of disease difficult to measure on anatomic modalities. Surveillance PET 1 year later demonstrated new bilateral adrenal uptake initially interpreted as metastatic disease. On review at the multidisciplinary meeting, the absence of osseous recurrence and symmetry of uptake suggested this was an immune-related adrenalitis secondary to ipilimumab therapy

5.4 Surveillance

Until recently, the absence of effective therapies for metastatic melanoma has made detection of early asymptomatic metastatic disease somewhat futile. With a range of new treatment options that may be benefit from early initiation, there is renewed interest in imaging surveillance. Ongoing research will define optimal surveillance strategies. A study from using CT surveillance of resected stage III melanoma revealed a relatively high detection rate following a Bayesian distribution with more and earlier-detected lesions in stage IIIC than in stage IIIA. It is anticipated that the higher sensitivity and specificity of FDG PET/CT would further increase the yield and timeliness of detection of systemic metastasis.

5.5 Beyond FDG PET/CT

Whilst MRI is highly sensitive for imaging cerebral metastases, its utility is diminished for differentiation of active disease from post-treatment changes after surgery or radiotherapy. Several radiotracers are very useful for both staging and restaging owing

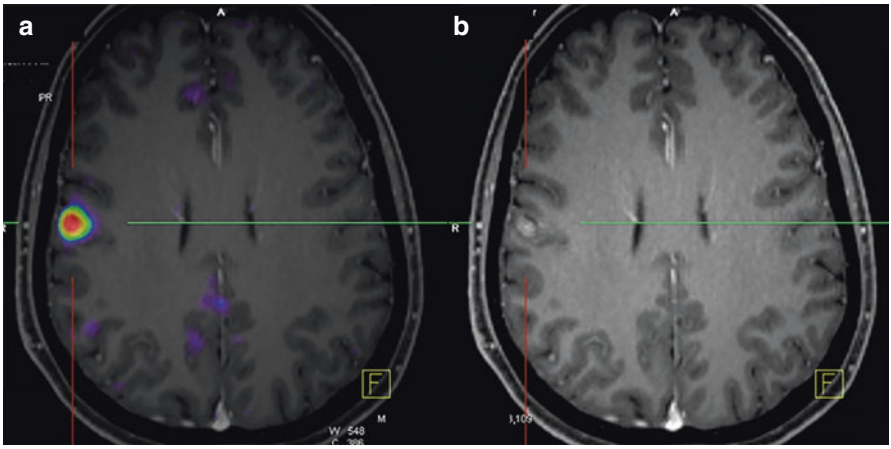

Fig. 5.10 This patient had regression of systemic metastatic disease following BRAFi therapy. On MRI, there was uncertainty whether a known lesion in the frontoparietal cortex had progressed. This lesion was not assessable on ^{18}F-FDG PET/CT owing to high physiologic cerebral activity. ^{18}F-fluorothymidine (FLT) PET demonstrated high proliferative activity indicating an active metastasis, whilst non-CNS disease was not active (**a**: PET/MRI, **b**: MRI)

to their low background activity within the brain. These include ^{18}F-fluorothimidine (FLT), ^{18}F-fluoroethyltyrosine (FET) or ^{18}F-fluorocholine (FCH), which interrogate proliferation, amino acid transport and sterol metabolism, respectively (see Fig. 5.10). All have utility in differentiating post-treatment changes from recurrent disease. It is valuable to obtain a baseline study prior to intervention as interpretation for restaging is more difficult when a comparative study is not available to define baseline PET characteristics. There is also evolving interest in melanin-specific tracers which have the potential to provide specific diagnosis [29, 30]. How these tracers might be incorporated into imaging paradigms remains to be defined.

Key Points

- ^{18}F-fluorodeoxyglucose (FDG) PET/CT has emerged as the imaging modality of choice for identifying locoregional nodal or distant metastatic disease and also for restaging following therapy.
- There is a very limited role for imaging, including PET/CT, in stage I or II disease.
- FDG PET/CT may have a role for staging in patients with stage I/II disease and high-risk features, such as T4 disease or ulceration. Node biopsy.
- FDG PET/CT is the imaging modality of choice when there is clinical suspicion of locoregional or systemic metastases: (a) staging in patients

with stage III or IV disease, (b) clinical suspicion of recurrent or metastatic disease, (c) prior to planned intervention (e.g. surgery or radiotherapy, with curative intent) in patients with locoregional or oligo-metastatic disease and (d) response assessment of patients undergoing chemotherapy and targeted or immune-activating therapy

- PET demonstrates higher sensitivity and specificity of (92 and 94%, respectively) compared to CT (58 and 45%, respectively) for detection of distant metastatic disease.
- The superior accuracy of PET/CT has been shown to confer a high management impact ranging from 22 to 62%.
- FDG PET/CT has been shown to be a useful marker of early biologic response to BRAF inhibition with complete or substantial reduction in metabolic activity observed as early as 15 days after commencement of therapy.
- Targeted and immune-modulating therapies can result in immune-related inflammatory changes on FDG PET/CT and should not be misinterpreted as disease progression.
- Several new drugs have specific adverse effects, which have correlates on FDG PET/CT and that can be mistaken for disease progression.
- Interferon is known to cause reactivation of sarcoidosis, a pattern which can mimic malignancy.
- BRAFi can promote formation of keratoacanthomas or SCC through paradoxical activation of ERK signalling. These can be FDG-avid and confused with new dermal or subcutaneous metastases.
- Immune-modulating therapies including anti-PD1 and anti-CTLA4 antibody therapy can cause a variety of autoimmune conditions.

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PET/CT in Melanoma (Additional Teaching Cases)

6

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Contents

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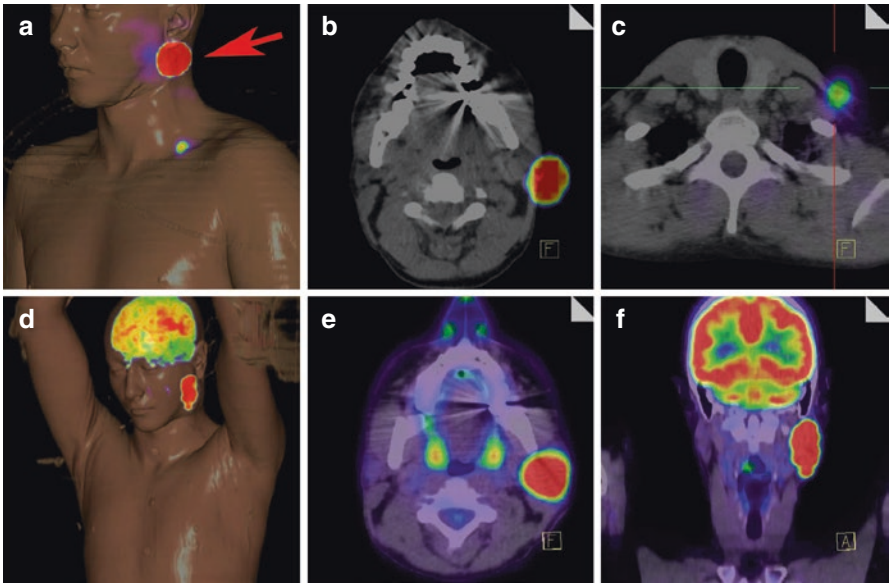

Fig. 6.1 Patient with newly diagnosed neck left melanoma. Lymphoscintigraphy following subdermal injection of ^{99m}Tc-antimony colloid was performed. Surface-rendered SPECT/CT (**a**) demonstrates high uptake at the injection site (*red arrow*) with activity flare evident on axial SPECT/CT (**b**) owing to the high number of counts. A left lower cervical sentinel node was identified (**c**). Wide local excision and sentinel node biopsy was performed, which was negative. Twelve months later, the patient presented with a left neck lump. FDG PET/CT demonstrated recurrence in a level II node deep the site of prior WLE (**d**, **e**, **f**). The location of recurrence was deep in the site of injection on the SLN SPECT/CT study and likely masked by high intensity of activity from the overlying site of injection

Teaching points:

- SPECT/CT enables precise localisation of sentinel nodes, but there is reduced sensitivity near the site of injection owing to flare of activity which may result in false-negative findings.

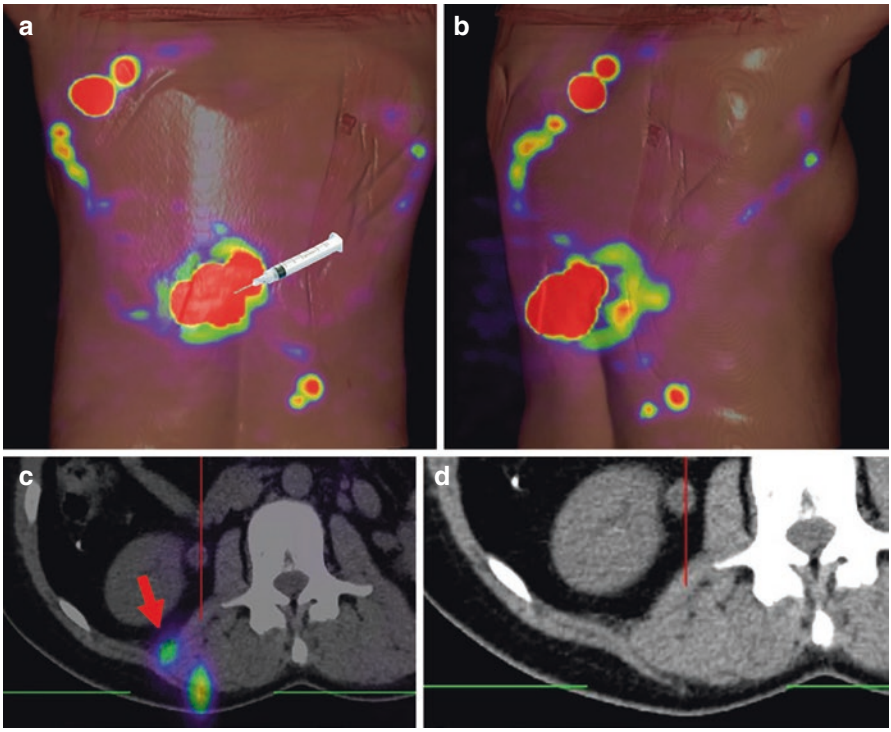

Fig. 6.2 Patient with mid-back thick melanoma scheduled for sentinel node biopsy. Four injections of ^{99m}Tc-antimony colloid were administered by subdermal injection on either side of the scar. Surface-rendered SPECT/CT images (**a**) and (**b**) demonstrate high uptake at the injection site and three separate pathways of drainage, to the left prescapular region (**a**), right axillary region (**b**) and an atypical location in the left lower back. Posterior to the left paraspinal muscles (**c**), corresponding to a tiny lymph node on CT (**d**). Further interrogation of SPECT/CT images demonstrates extension of activity from this location to the retroperitoneum (*red arrow*)

Teaching points:

- SPECT/CT is able to demonstrate atypical drainage pathways that are difficult to identify on conventional planar imaging.
- Drainage from the skin of the back to retroperitoneal and paravertebral lymph nodes is uncommon but described in 2.5% of patients with primary back melanomas [1].
- Identification of multiple sentinel nodes may present challenges for the surgical team as targeting all sites may not be feasible or result in additional morbidity. Close communication is needed between the nuclear medicine specialists and surgical team in how to deal with such scenarios.

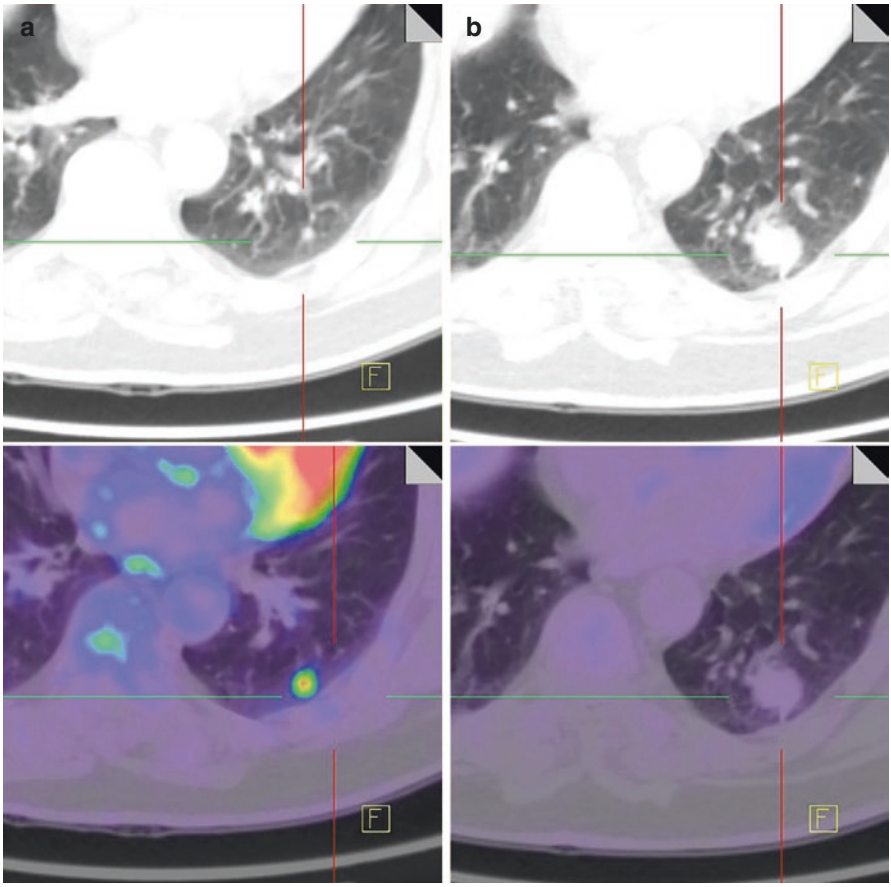

Fig. 6.3 A patient with metastatic melanoma had a 6 mm pulmonary nodule identified on surveillance CT (**a**). FDG PET/CT demonstrated focal intense uptake in this nodule suggesting metastatic disease, low dose CT (*top*) and fused PET/CT (*bottom*). The patient underwent excision via video-assisted thoracoscopic surgery (VATS) with histopathology confirming the diagnosis of metastatic melanoma. Follow-up CT performed 6 months (**b**) later demonstrated a new soft tissue abnormality within the surgical bed suggesting local recurrence. FDG PET/CT, however, demonstrated no metabolic activity in the area of concern and the finding was interpreted as benign postsurgical change. Subsequent follow-up demonstrated stable findings confirming benign aetiology

Teaching points:

- Although sensitivity of PET diminishes with sub-cm lesions, especially in the lung which is subject to respiratory motion, metastatic melanoma is usually highly metabolically active facilitating characterisation of small abnormalities.
- The sensitivity of PET has also improved significantly with modern generation devices incorporating improvements including time-of-flight, point-spread-function modelling, improved attenuation correction, reconstruction algorithms and respiratory gating.
- PET is able to differentiate postsurgical changes from recurrent disease.

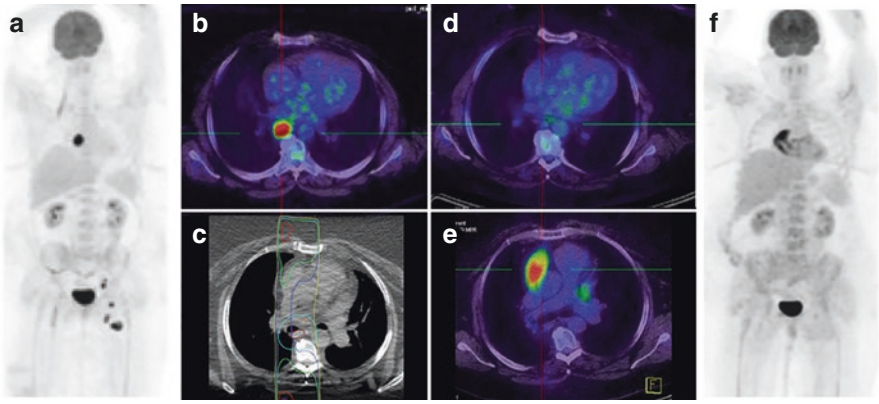

Fig. 6.4 A middle-aged lady presented with left groin nodal recurrence on the background of prior left leg primary. FDG PET/CT (**a**) prior to planned lymphadenectomy demonstrated additional sub-cm external iliac nodal metastases and a posterior mediastinal nodal metastasis (**b**). The patient proceeded to extended lymphadenectomy followed by radiotherapy to mediastinal nodal disease; radiotherapy treatment plan shown in (**c**). Restaging FDG PET/CT 4 months after completion of radiotherapy demonstrated a complete metabolic response in the posterior mediastinum (**d**) but new focal intense uptake in the right atrium (**e**). In correlation with the radiation treatment plan and annular morphology which is best appreciated on the maximum intensity projection (MIP) image (**f**), this was interpreted as post-radiotherapy change within the segment of irradiated myocardium. Follow-up PET (not shown) demonstrated partial resolution of this finding with this time

Teaching points:

- FDG PET/CT is essential prior to surgical intervention to accurately stage the patient.
- Post-radiotherapy change can be confused with recurrent disease. Incorrect interpretation can be avoided by knowledge of patterns of post-radiotherapy change in addition to correlating of PET/CT images with the radiotherapy treatment plan.
- Annular or focal increased FDG uptake in irradiated myocardium is well described after thoracic radiotherapy [2].

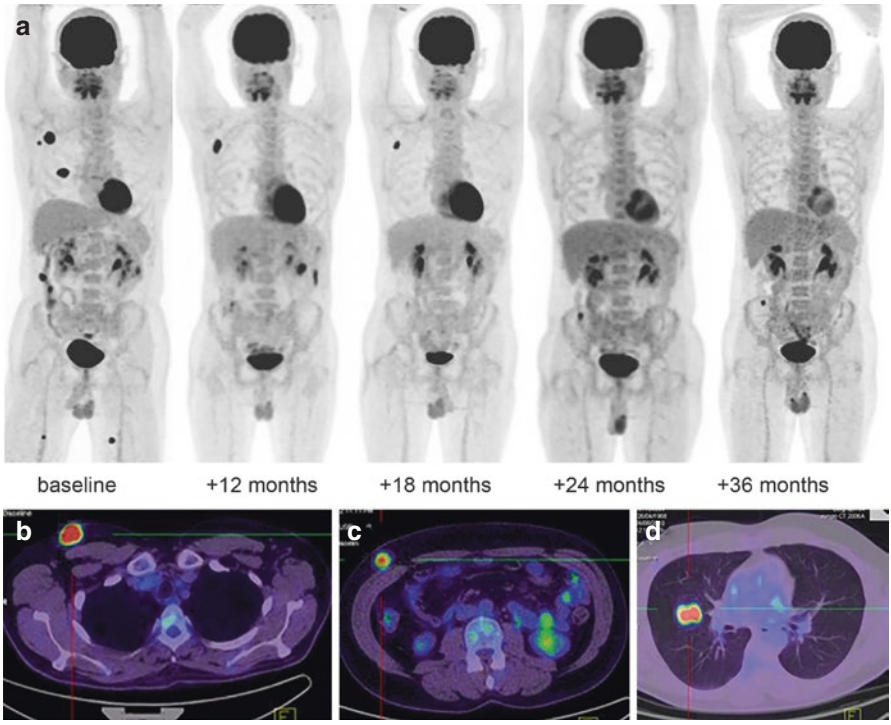

Fig. 6.5 Middle-aged man with primary back melanoma presented 10 years later with multiple subcutaneous metastases. Biopsy confirmed metastatic melanoma. FDG PET/CT (**a**, *left*) demonstrated additional subcutaneous (**b**, **c**), lung (**d**) and small bowel metastases (**c**). MRI (not shown) demonstrated multiple small cerebral metastases. The patient received 20Gy whole brain radiotherapy but subsequently declined systemic therapy. Surveillance PET studies demonstrated partial regression of disease at 12 and 18 months and a complete response at 24 and 36 months. MRI demonstrated disappearance of cerebral metastases. Note the small but prominent caecal uptake throughout the series which was interpreted as a physiologic in aetiology

Teaching point:

- Spontaneous regression can be a feature of metastatic melanoma, in this case attributable to either an innate immune response or, possibly, abscopal effects of brain radiotherapy. The abscopal effect refers to regression of nonirradiated metastatic lesions distant from the sites subject to irradiation, likely an immune-mediated phenomenon.

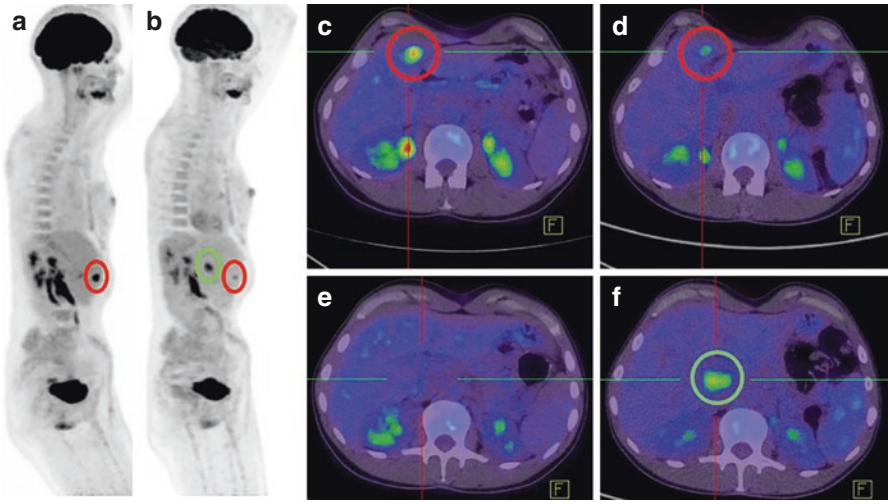

Fig. 6.6 Middle-aged female with metastatic melanoma and biopsy-proven hepatic metastatic disease harbouring the V600E mutation. The patient was treated with vemurafenib, a BRAF inhibitor. Oblique MIP images at baseline (**a**) and after 6 weeks of therapy (**b**) are shown. The hepatic metastasis (*red circle*) demonstrated a partial response (**c** to **d**). Following treatment, however, there was a new metabolically active and mildly enlarged porta hepatis lymph node (**e**, **f**). This could be interpreted as a mixed response with a partial response in the liver but nodal progression. In the context of response in the liver, however, the new nodal finding was interpreted as an immune-related inflammatory response, and the overall study reported as a partial metabolic response. Also note the subtle diffuse increase in splenic uptake on the restaging study, a feature seen in the setting of an immune-related inflammatory response. Follow-up PET (not shown) demonstrated resolution of both findings

Teaching points:

- Activating mutations in BRAF are present in 40–60% of metastatic melanoma. In the majority, this is due the V600E mutation which predicts response to BRAF inhibitors such as vemurafenib and dabrafenib.
- Although not directly an immunotherapy like CTLA-4 or PD-1 pathway blockade, features of an immune-related inflammatory response such as reactive nodal activity or diffuse splenic activity are also seen with this form of therapy. Caution not to over-report new reactive or inflammatory findings as progression is important.

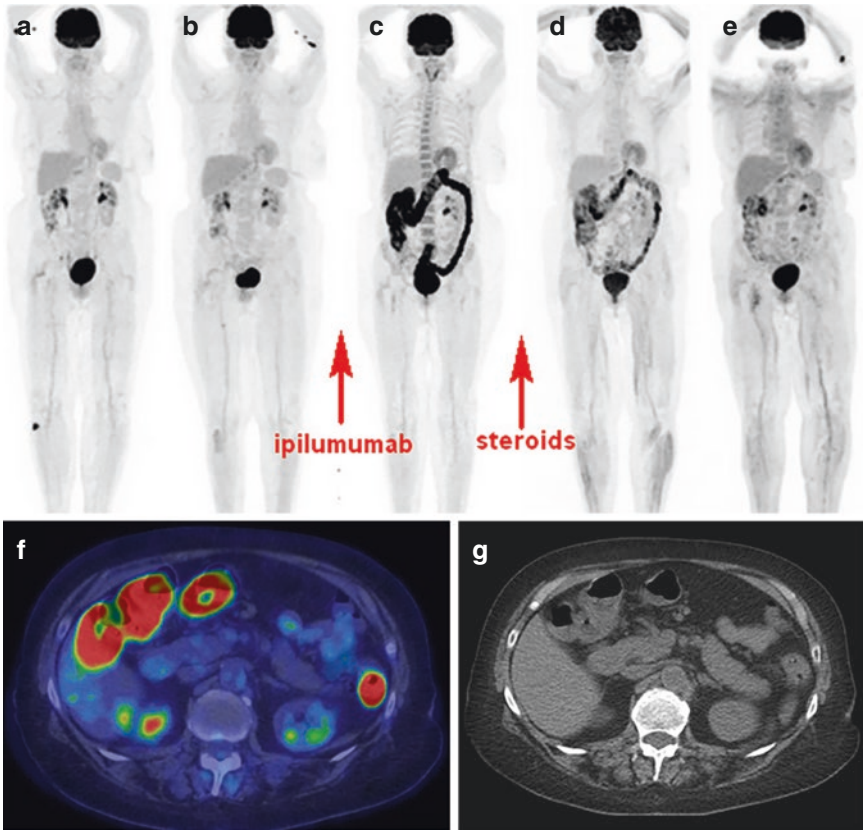

Fig. 6.7 A 70-year-old woman with primary melanoma with subcutaneous melanoma metastasis in the setting of unknown primary (**a**). The lesion was excised but there was recurrence in the right upper thigh (**b**). The patient was commenced on ipilimumab but developed severe diarrhoea. Restaging demonstrated a complete metabolic response at the site of metastases but intense pancolonic uptake (**c**, **f**) association with bowel wall thickening and stranding of adjacent mesenteric fat (**g**) consistent with an ipilimumab-associated colitis. The patient was treated with steroids which resulted in resolution of colitis (**d**, **e**). Steroid therapy was complication by a steroid-induced myopathy which was visualised on FDG PET (**d**)

Teaching points:

- Ipilimumab can have a range of autoimmune side effects including colitis, hepatitis and endocrinopathies such as thyroiditis, hypophysitis or adrenalitis. Less common sites of inflammation include the orbit, pancreas and lung. These may be visualised on FDG PET/CT and should not be misinterpreted as malignant in aetiology.
- The incidence of autoimmune side effects is greater with CTLA-4 blocking antibodies compared to inhibition of the programmed cell death-1 (PD-1) receptor.

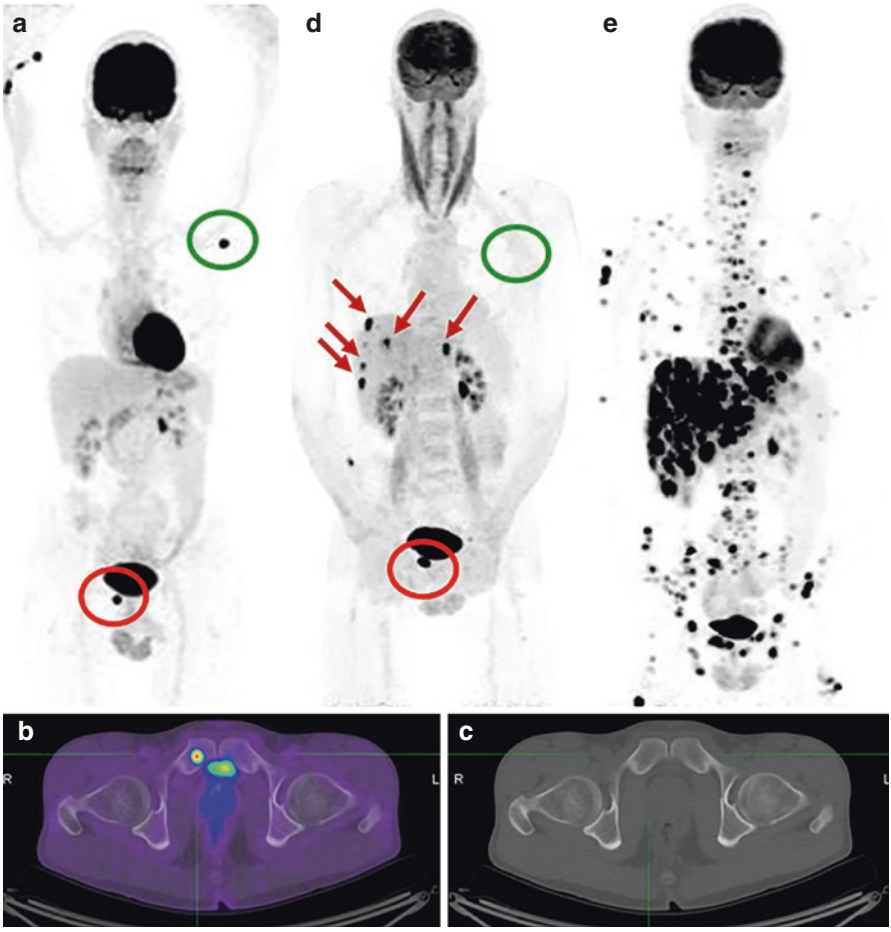

Fig. 6.8 Patient with prior history of left arm melanoma and positive sentinel node biopsy was undergoing surveillance ultrasound in outpatient clinic. A 11 mm node of abnormal morphology was identified with biopsy confirming metastatic melanoma. Prior to planned lymphadenectomy, a FDG PET/CT is performed which confirms the axillary nodal abnormality (**a**, *green circle*) but identifies an additional solitary abnormality in the right pubic symphysis (**b**, *red circle*) without any corresponding abnormality on CT (**c**). Concern was raised at the multidisciplinary meeting that the solitary bone lesion could represent an alternative aetiology potentially denying the patient curative lymphadenectomy. Both lesions, however, had similar "metabolic signatures" by virtue of nearly identical SUVs (35 compared to 32) strongly suggesting the bone lesion was metastatic. A bone biopsy organised by the treating team confirmed melanoma, and after discussion, the patient was planned for lymphadenectomy followed by stereotactic radiotherapy (SABR) to the bone lesion. A repeat FDG PET/CT was performed after lymphadenectomy prior to SABR (**d**); note the study is performed with arms down owing to pain following surgery. The study demonstrated multiple new hepatic metastases (*red arrows*), and the patient was commenced on DTIC chemotherapy but had a rapidly progressive course (**e**) and died shortly after

Teaching points:

- Oligometastases can pose a diagnose challenge because the implications of false-positive results are significant. The SUV can be useful for disease characterisation as lesions of similar "metabolic signature" are likely to have the same aetiology [3].
- Early identification of metastatic melanoma with imaging may not change survival but cause morbidity from consequences of additional interventions. In the setting of oligometastatic disease, a short period of observation with repeat imaging to ascertain rate of temporal change and metastatic progression can be a useful approach to reduce futile interventions. With availability of newer therapies, however, the treatment landscape continues to evolve.

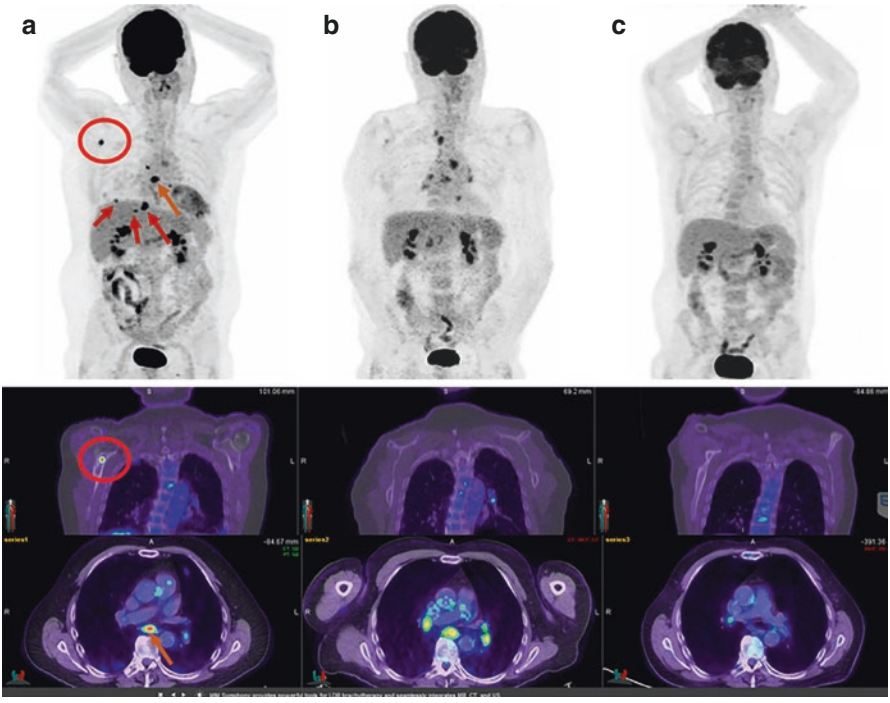

Fig. 6.9 Patient with metastatic melanoma to right scapular (**a**, *red circle*), mediastinal nodes including a subcarinal node (*orange arrow*) and multiple pleural metastases (*red arrows*). The patient was treated with three cycles of pembrolizumab, a PD1 inhibitor. Restaging FDG PET/CT (**b**) demonstrated a complete metabolic response in pleural metastases and a near-complete metabolic response in the bone metastasis. There was, however, a partial response in the subcarinal node and new, lower intensity uptake in mediastinal and bilateral hilar nodes. The symmetrical pattern of this new activity combined with favourable response at other sites and subtle increase of splenic leads to the interpretation of a favourable response to therapy with new nodal abnormalities likely representative of an immune-related inflammatory response. A follow-up PET 3 months later (**c**) demonstrated resolution of findings confirming this

Teaching points:

- Immune-related inflammatory responses can be visualised following inhibition of the programmed cell death-1 (PD-1) receptor therapy [4]. A thorough knowledge of these are required to avoid misrepresenting inflammation findings as progressive disease. Symmetrical nodal activity in the mediastinum, new nodal uptake in a drainage basin of prior metastases and diffuse increased splenic uptake are findings that may be seen.

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