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Rational use of ^{18}F-FDG PET/CT in patients with advanced cutaneous melanoma: A systematic review

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ABSTRACT

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is increasingly used in patients with advanced melanoma. Immune checkpoint inhibitors and BRAF/MEK-targeted therapy have transformed the therapeutic landscape of metastatic melanoma. Consequently, a need for markers predicting (early) response to treatment and for monitoring treatment (toxicity) has arisen. This systematic review appraises the current literature evidence for rational use of ^{18}F-FDG PET/CT scans in staging, clinical decision-making, treatment monitoring and follow-up in advanced melanoma. ^{18}F-FDG PET/CT has high overall accuracy for detection of distant metastases and is, combined with cerebral MRI, the preferred imaging strategy for staging metastatic melanoma. In contrast, strong evidence supporting the standard use of ^{18}F-FDG PET/CT for predicting and monitoring therapy response and toxicity is currently lacking. Essential for determining the position of ^{18}F-FDG PET/CT during treatment course in advanced melanoma are well-designed studies with standardized scanning protocols, incorporation of clinical parameters and comparison with contrast-enhanced CT alone.

1. Introduction

Immune checkpoint inhibitors and targeted therapy with small molecule inhibitors have markedly improved the prognosis of metastatic melanoma, with five-year overall survival (OS) rates as high as 52 % in patients treated with the combination of the immune checkpoint inhibitors ipilimumab and nivolumab (Larkin et al., 2019). Patients with metastases in more than two organs and high tumour burden have worse response to therapy and lower survival rates, emphasizing the importance of adequate and early detection of metastases for proper treatment selection (Nakamura et al., 2016; Long et al., 2016).

Positron emission tomography (PET) using the radioactively labelled glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) visualizes glucose uptake, which enables the identification of tumours based on their increased glucose metabolism compared to most normal tissues. In contrast, conventional imaging modalities used in oncology, such as contrast-enhanced computed tomography (ce-CT), magnetic resonance imaging (MRI) and ultrasound (US), are most commonly used to obtain structural information. ^{18}F-FDG PET scanning is routinely combined with low-dose CT scanning (^{18}F-FDG PET/CT) to obtain attenuation corrected PET images and improve specificity and accuracy by providing anatomical information.

For early stage melanoma patients (stage I and II), ^{18}F-FDG PET/CT has a low yield for detection of distant metastases (Veit-Haibach et al., 2009; Mena et al., 2016; Wagner et al., 2012). The evidence in advanced melanoma is more variable and melanoma guidelines provide different recommendations regarding clinical indications for ^{18}F-FDG PET/CT in this setting (Suppl. Table 1) (Australian Cancer Network Melanoma Guidelines Revision Working Party, 2008; Michielin et al., 2019; Coit et al., 2019). Moreover, novel clinical questions regarding the value of ^{18}F-FDG PET/CT have arisen following the introduction of targeted therapy and immunotherapy for advanced melanoma. It is important to determine the value of ^{18}F-FDG PET/CT in patient selection, response and toxicity monitoring and follow-up of patients with an ongoing response. Quantitative ^{18}F-FDG measurements, such as standardized uptake value (SUV) and metabolically active tumour volume (MTV), can predict prognosis and treatment response in other malignancies, including metastatic non-small cell lung cancer and lymphoma, and are increasingly under investigation in melanoma (Kahraman et al., 2011; Meignan et al., 2016; Kim et al., 2013; Liao et al., 2012). Advances in conventional imaging techniques and new techniques such as whole-body (wb) (PET/)MRI might also alter the

previously established role of ^{18}F-FDG PET/CT (Fraum et al., 2016). The aim of this systematic review is to provide a critical overview of the available evidence on the role of ^{18}F-FDG PET/CT imaging in staging, monitoring of therapy and follow-up of advanced melanoma.

2. Methods

2.1. Article selection

The EMBASE and MEDLINE databases were systematically searched for relevant articles published between January 2000 (first FDA approval of integrated PET/CT (Townsend et al., 2004)) and January 2020 using the terms "melanoma" and "fluorodeoxyglucose f 18 or fdg or fluorodeoxyglucose or 18fdg or 2 fluoro 2 deoxy", including the expanded Emtree terms "melanoma" and "fluorodeoxyglucose f 18" (see Suppl. File 1 for the full search strings). Conference abstracts were excluded. Eligibility screening of titles and abstracts and subsequent full-text assessment of the eligible articles were performed by two authors (CB, ECH). Articles were excluded in case of non-English language, inaccessibility of the full text, preclinical research, commentaries, non-cutaneous melanoma, no stage IV or advanced melanoma, non-^{18}F-FDG PET tracers and/or use of only ^{18}F-FDG PET scanning (i.e. without concurrent CT) (Suppl. Fig. 1). Disagreements on article selection were resolved through discussion until consensus was reached. Article references were additionally checked for relevant studies not identified by the database search, and current guidelines for melanoma and nuclear imaging in oncology were consulted. The international clinical trial registry ClinicalTrials.gov was searched in January 2020 for unpublished studies (updated < 5 years ago) on ^{18}F-FDG PET/CT in stage IV melanoma. Levels of Evidence (LoE) of listed studies were determined using the Oxford 2011 Levels of Evidence, v2.1 (OCEBM Levels of Evidence Working Group, 2011).

2.2. Terminology

This review appraises studies using integrated ^{18}F-FDG PET/CT scanning, i.e. studies that involve ^{18}F-FDG PET scanning with at least low-dose, non-contrast-enhanced CT (ld-/nce-CT) scanning. PET only studies were excluded. When the term ^{18}F-FDG PET is used, this indicates study results that have been described to be interpreted solely based on the ^{18}F-FDG PET part of ^{18}F-FDG PET/CT scans. ce-CT refers to CT scans obtained for diagnostic purposes using higher radiation doses and intravenously administered contrast. In sections where the term ^{18}F-FDG PET/ce-CT is explicitly used, this refers to a study unequivocally describing the use of ce-CT in its methods.

3. ^{18}F-FDG PET/CT in detection of distant melanoma metastases

Although ^{18}F-FDG PET/CT is most commonly utilized in patients with advanced stage melanoma, the majority of studies have focused on detecting melanoma metastases by ^{18}F-FDG PET(/CT) in the clinically non-metastatic setting. Twenty–two studies that investigated the detection of distant metastases by ^{18}F-FDG PET/CT were identified by our search (Suppl. Table 2) (Veit-Haibach et al., 2009; Mena et al., 2016; Wagner et al., 2012; Xing et al., 2011; Pfluger et al., 2011; Pfannenberg et al., 2007; Laurent et al., 2010; Jouvet et al., 2014; Mottaghy et al., 2007; Aukema et al., 2010; Abbott et al., 2011; Bastiaannet et al., 2012; Gellén et al., 2015; Eldon et al., 2017; Rodriguez Rivera et al., 2014; Madu et al., 2017; Lewin et al., 2018; Reinhardt et al., 2006a; Leon-Ferre et al., 2017; Koskivuo et al., 2016; Vensby et al., 2017; Lee et al., 2018). In stage III, sensitivity of ^{18}F-FDG PET/CT in detecting distant melanoma metastases during follow-up ranged between 82 % and 100 % and the specificity ranged between 45 % and 100 % (Pfluger et al., 2011; Pfannenberg et al., 2007; Mottaghy et al., 2007; Aukema et al., 2010; Abbott et al., 2011; Bastiaannet et al., 2012; Gellén et al., 2015; Eldon et al., 2017; Rodriguez Rivera et al., 2014; Madu et al., 2017;

Reinhardt et al., 2006a, a; Leon-Ferre et al., 2017; Koskivuo et al., 2016; Vensby et al., 2017). Sensitivity within stage III patients increases from stage IIIa to IIIc (American Joint Committee on Cancer 7th edition), although negative predictive value is high across all substages (80 %) (Lewin et al., 2018). The performance of ^{18}F-FDG PET/CT in detection of melanoma metastases compared to other specific imaging modalities is discussed below.

3.1. ^{18}F-FDG PET/CT versus contrast-enhanced CT

Most centres consider ce-CT of chest and abdomen (with brain MRI) as the standard imaging procedure for detection of stage IV melanoma. The performance of ^{18}F-FDG PET/CT vs CT was studied in a detailed meta-analysis on imaging modalities in melanoma, which included 13 ^{18}F-FDG PET/CT (1030 patients) and 13 CT studies (1320 patients) (Xing et al., 2011). All included studies involved > 10 patients and lesions identified by imaging were confirmed by histology or follow-up imaging studies at least six months after identification. When considering primary staging of stage IV melanoma, overall estimates for sensitivity of ^{18}F-FDG PET/CT vs CT were 80 % vs 51 % and 87 % vs 69 % for specificity. However, both studies with ce-CT and nce-CT in combination with ^{18}F-FDG PET were regarded as ^{18}F-FDG PET/CT in this meta-analysis (Veit-Haibach et al., 2009; Xing et al., 2011). Sensitivity of regular ^{18}F-FDG PET/CT might thus have been overestimated. A more recent study in 50 patients with metastatic melanoma indeed reports less false-negative results by ^{18}F-FDG PET/ce-CT than ^{18}F-FDG PET/nce-CT (Pfluger et al., 2011). Nevertheless, the superiority of ^{18}F-FDG PET/CT over ce-CT for detection of metastases was confirmed, with a sensitivity of 97 vs 85 % and specificity of 93 vs 63 %. The false-negative findings did not affect staging results (Pfluger et al., 2011). Overall, ^{18}F-FDG PET/CT outperforms ce-CT for staging stage IV melanoma when considering all possible disease locations. The lower radiation exposure of ^{18}F-FDG PET/ld-CT compared to ce-CT (approximately 5–10 mSv vs. 15–20 mSv (Boellaard et al., 2015; Li et al., 2019; Smith-Bindman et al., 2019)) provides an additional advantage.

3.2. ^{18}F-FDG PET/CT versus whole-body MRI

Brain MRI is part of the standard work-up in stage IV melanoma. Whole-body MRI (wb-MRI), in contrast, is a relatively new imaging modality in advanced melanoma, both as a standalone imaging method as well as when integrated with PET. An advantage of wb-MRI over CT is the lack of exposure to ionizing radiation. Studies comparing the performance of wb-MRI to ^{18}F-FDG PET/(ce-)CT in advanced melanoma have varying outcomes (Pfannenberg et al., 2007; Laurent et al., 2010; Jouvet et al., 2014; Ciliberto et al., 2013; Berzaczy et al., 2020). In a prospective study in 35 patients with advanced melanoma, sensitivity of wb-MRI for detection of melanoma metastases was higher than ^{18}F-FDG PET/CT (82 % vs. 72.8 %) (Laurent et al., 2010). Two other studies with a comparable design (n = 37 and 64 respectively) also reported a higher or similar sensitivity of wb-MRI compared to ^{18}F-FDG PET/CT with a similar specificity (Pfannenberg et al., 2007; Jouvet et al., 2014). The diagnostic accuracy differed between anatomical locations of metastases: wb-MRI was more accurate in detecting metastases in liver, bone and brain, whereas ^{18}F-FDG PET/CT was more accurate in detecting lymph node and (sub)cutaneous metastases (Pfannenberg et al., 2007). In contrast, two more recent studies could not find any metastatic site-specific differences in diagnostic accuracy of wb-MRI and ^{18}F-FDG PET/CT (Jouvet et al., 2014; Heusner et al., 2011). The lack of unequivocal evidence that wb-MRI leads to better patient staging than ^{18}F-FDG PET/CT, its high costs and limited availability make it unlikely that wb-MRI will replace ^{18}F-FDG PET/CT in the near future.

3.3. ^{18}F-FDG PET/CT for detection of melanoma metastases in specific locations

3.3.1. Lymph nodes

Ultrasound (US) is the preferred imaging modality for staging of locoregional lymph nodes in stage III melanoma due to its higher accuracy compared to ^{18}F-FDG PET/CT (Xing et al., 2011). A meta-analysis evaluated the performance of US and ^{18}F-FDG PET/CT in detecting melanoma lymph node metastases during respectively primary staging and surveillance (Xing et al., 2011). During primary staging, sensitivity was 60 % for US vs 11 % for ^{18}F-FDG PET/CT and during surveillance respectively 96 % vs 65 %. Both imaging modalities had an equal specificity of 97–99 % in these two settings (Xing et al., 2011). A more recent prospective study in 37 melanoma patients demonstrated that ^{18}F-FDG PET/CT has an equal sensitivity (100 %) and lower specificity than US (95 % vs 100 %) for superficial lymph node detection in stage IV patients, but this was based on only 13 melanoma-positive lymph nodes (Jouvet et al., 2014). Compared to ce-CT, ^{18}F-FDG PET/CT maximum standardized uptake value (SUV$_{max}$) above 2.4 had the highest sensitivity (91 %) and accuracy (89 %) for detection of regional lymph node metastases ≥1 cm in a retrospective study (Cha et al., 2018).

3.3.2. Lung

Ce-CT has a higher sensitivity than ^{18}F-FDG PET/CT for lung metastases (Fig. 1). Lung lesions smaller than 11 mm are frequently missed by ^{18}F-FDG PET (Pfannenberg et al., 2007; Jouvet et al., 2014; Reinhardt et al., 2006b). In a retrospective study, no lung lesions smaller than five mm on the nce-CT of an ^{18}F-FDG PET/CT scan were PET positive (Reinhardt et al., 2006b). Sensitivity increased size-dependently from 38.8 % to 87.5 % in 5–13 mm-sized lesions and reached 100 % in lesions ≥14 mm. The addition of ce-CT to the ^{18}F-FDG PET increased its sensitivity from 26.4 % to 96.2 % for lung metastases in melanoma, however the high false-positive rate of pulmonary findings on CT resulted in a low specificity (35.3 %) (Pfannenberg et al., 2007).

3.3.3. Brain

Up to 50 % of the patients with advanced melanoma develop brain metastases (Davies et al., 2011). These metastases may require (stereotactic) radiotherapy or surgery to gain local control. Brain imaging is therefore important in advanced melanoma. Detection of brain metastases by ^{18}F-FDG PET/CT is limited by the high ^{18}F-FDG uptake of normal brain tissue and low spatial resolution of ^{18}F-FDG PET, making MRI the preferred brain imaging modality (Ludwig et al., 2002) (Fig. 1). In a prospective analysis, 15 of 64 patients with advanced melanoma had cerebral metastases diagnosed by MRI that could not be detected on the ^{18}F-FDG PET/CT scan (Pfannenberg et al., 2007). MRI provides better soft tissue contrast resolution than ce-CT and can detect smaller brain metastases (Laurent et al., 2010).

3.3.4. Bowel

Melanoma commonly metastasizes to the gastro-intestinal tract, predominantly the small bowel. ^{18}F-FDG PET detection of gastro-intestinal metastases can be complicated by physiological gastro-intestinal ^{18}F-FDG uptake. In cases where confirmed diagnosis of bowel metastases would change the therapeutic strategy, (capsule) endoscopy can be considered (Goenka et al., 2014; Bender et al., 2001). This may be preceded by ^{18}F-FDG PET/CT to guide the initial endoscopic approach towards a specific bowel segment. A prospective study reported increased bowel ^{18}F-FDG uptake in 12/21 patients with stage IV melanoma (Prakoso et al., 2011). Capsule endoscopy confirmed small-bowel metastases in only five of these patients. A possible explanation is a submucosal or exo-enteric localization of bowel metastases, which impedes detection by endoscopy. Furthermore, it was not specified whether the increased bowel ^{18}F-FDG uptake in these 12 patients was diffuse, i.e. likely due to non-malignant causes, or focal, i.e. more suspicious of malignancy. Such differentiation is essential to minimize the rate of false-positive results for bowel ^{18}F-FDG uptake.

3.3.5. Bone and soft tissue

Adequate diagnosis of melanoma bone metastasis enables timely local therapy (e.g. radiotherapy) to relieve pain and to prevent fractures. ^{18}F-FDG PET/CT scanning outperforms ce-CT in the detection of bone metastases (Fig. 1) (Pfannenberg et al., 2007; Jouvet et al., 2014; Bier et al., 2016). Lesion-based sensitivity for bone metastases was only 36.8 % for ce-CT compared to ^{18}F-FDG PET/CT as a reference (Bier
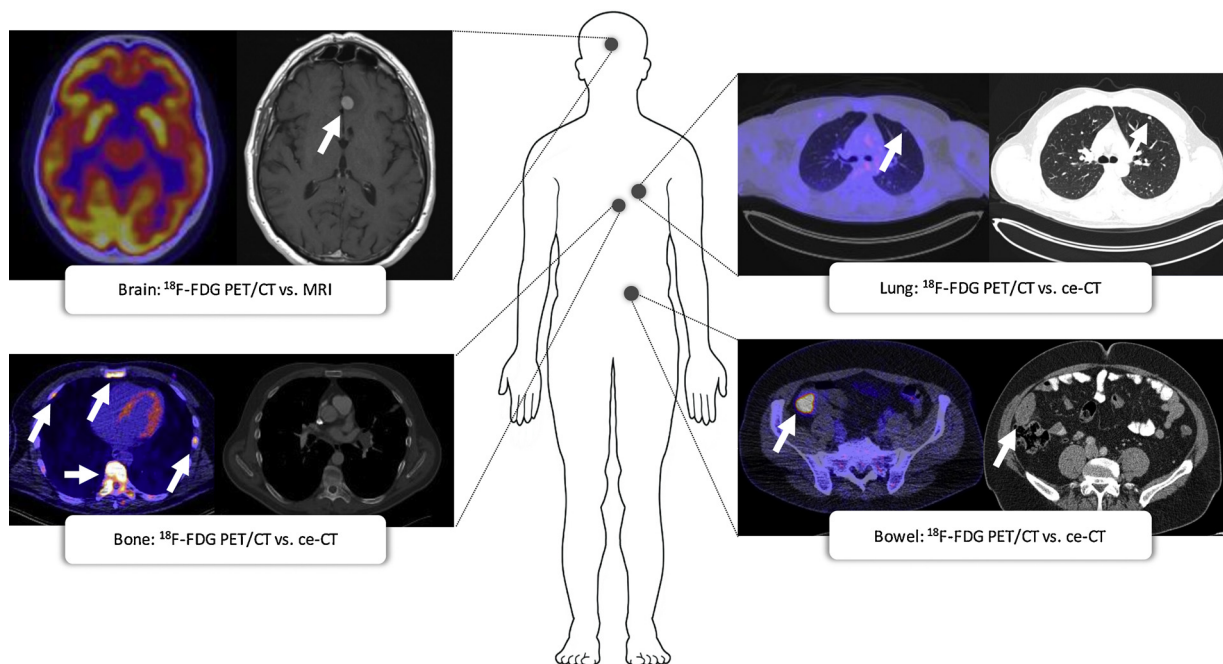

Fig. 1. Examples of detection of melanoma metastases (arrows) in specific locations by ^{18}F-FDG PET/CT compared to ce-CT or MRI (brain). (Patient drawing adjusted from Wikimedia Commons [Internet] (2020)).

et al., 2016). Nevertheless, isolated musculoskeletal ^{18}F-FDG-avid sites have a low positive predictive value for melanoma (31 %), even after excluding lesions that were unsuspicious based on additional clinical or CT information, as was shown in a retrospective study in 342 patients with stage IIb-IV melanoma (Mansour et al., 2010). The relative risk (RR) for a false-positive musculoskeletal ^{18}F-FDG-avid site was higher when no other metastases were present on the ^{18}F-FDG PET/CT scan (RR 5.33 [95 % CI 2.85–9.94]).

Bone and soft tissue metastases can be localized throughout the body and can thus be missed when the ^{18}F-FDG PET/CT field of view (FOV) only includes the torso. Torso ^{18}F-FDG PET/CT scanning diminishes scan duration, which has practical advantages, is more patient-friendly and diminishes the risk of movement artefacts. Several studies in stage III and IV melanoma have compared true whole-body imaging (i.e. from top of the head to the feet) to torso imaging (i.e. from the base of the skull to the mid-thigh), the standard-of-care in melanoma. False-positive lesions (determined by follow-up or pathology) located in the legs were found in 1–3 % of the scans. Lesions below the mid-thigh on ^{18}F-FDG PET/CT were only true-positive in patients with the primary melanoma on the lower extremities, clinical suspicion of metastatic disease below the mid-thigh upfront or additional ^{18}F-FDG PET positive lesions in the torso FOV (Niederkohr et al., 2007; Davidson and Sundram, 2011; Nguyen et al., 2007; Querellou et al., 2010; Lazaga et al., 2013; Plouznikoff and Arsenault, 2017a, b). Taking these factors into account for the individual patient, either a torso or true whole-body FOV can be chosen.

In conclusion, overall, ^{18}F-FDG PET/CT imaging is superior to ce-CT in the detection of distant metastases in high-risk melanoma, except for small pulmonary metastases. For the detection of brain metastases and their therapeutic and prognostic consequences, MRI should be additionally performed.

4. Clinical implications of ^{18}F-FDG PET/CT for advanced melanoma

Studies on the clinical impact of ^{18}F-FDG PET/CT in patients with stage III/IV disease report treatment changes in 13–74 % of the cases, depending on the investigations already performed prior to the ^{18}F-FDG PET/CT (Pfannenberg et al., 2007; Reinhardt et al., 2006a; Bronstein et al., 2012; Schüle et al., 2016; Subesinghe et al., 2013; Forschner et al., 2017; Bastiaannet et al., 2009; Singnurkar et al., 2016; Falk et al., 2007; Taghipour et al., 2017). Some studies compared treatment changes after ^{18}F-FDG PET/CT to an initial treatment plan based on clinical information only, whereas others used a treatment plan based on ce-CT with or without brain MRI or laboratory parameters as reference. In a prospective study in 64 stage III/IV patients, treatment changes (either from metastasectomy to systemic therapy or changes in surgical approach or systemic treatment) were seen in 64 % of all patients after performance of ^{18}F-FDG PET/ce-CT and wb-MRI, of which 90.2 % could be motivated by PET/ce-CT alone (Pfannenberg et al., 2007). A prospective study in 107 patients with stage III/IV melanoma evaluated treatment changes after an ^{18}F-FDG PET/ce-CT was performed to exclude new metastases (Forschner et al., 2017). All patients were scheduled for radical metastasectomy, based on results of conventional imaging and clinical and laboratory parameters. Conventional imaging involved whole-body imaging by ce-CT and/or MRI in 66 % of the patients and local imaging such as ultrasound only in the remainder. Treatment was changed after PET/ce-CT in 79 out of 107 patients (74 %), including 32 patients (30 %) in whom new and/or inoperable metastases were found and who were re-allocated to systemic therapy and/or palliative surgery. Precise changes within the subgroup of stage IV patients (n = 57) and the specific cases in which no prior imaging was done (34 % of total population) were not mentioned. More importantly, immunotherapy and BRAF inhibitors were not standard treatment when these studies were performed and might nowadays be favoured over surgery in patients with low tumour burden

(Ugurel et al., 2016).

In 2018, both immunotherapy and targeted therapy were approved for adjuvant systemic treatment of patients with resected stage III melanoma (Eggermont et al., 2018; Maio et al., 2018; Amaria et al., 2018). The value of ^{18}F-FDG PET/CT to rule out metastases before start of adjuvant therapy, i.e. immediately after resection, has not yet been evaluated. Adjuvant trials applied differing baseline imaging strategies that did not always include ^{18}F-FDG PET/CT, and most trials did not report the number of patients that were excluded based on ^{18}F-FDG PET/CT findings (Eggermont et al., 2018; Maio et al., 2018; Amaria et al., 2018; Bloemendal et al., 2019). The current best estimation of the yield of ^{18}F-FDG PET/CT in this setting is based on two recent imaging studies in respectively clinically newly diagnosed stage IIIa-c melanoma patients (n = 73) (Groen et al., 2019) and completely resected stage IIIb/c melanoma patients within 6 weeks prior to adjuvant therapy (n = 120) (Bloemendal et al., 2019). Upstaging or disease recurrence was seen in 18 % of patients in both studies, but direct implications for the use of ^{18}F-FDG PET/CT are clouded by unmentioned scan interval (Groen et al., 2019) and use of ce-CT scanning (96 % of cases) rather than the more commonly applied ^{18}F-FDG PET/nce-CT (Bloemendal et al., 2019).

Whereas previous studies have shown that ^{18}F-FDG PET/CT leads to change in initial treatment plan in a substantial proportion of advanced melanoma patients, the practical impact of ^{18}F-FDG PET/CT in advanced melanoma needs to be re-evaluated for the current therapeutic arsenal, i.e. including BRAF/MEK-inhibition, immunotherapy and adjuvant systemic treatment. A feasible first approach for the latter would be describing the proportion of patients that are excluded from adjuvant treatment based on the screening with ^{18}F-FDG PET/CT.

5. Monitoring treatment effects using ^{18}F-FDG PET/CT

Treatment response in clinical studies is assessed using ce-CT-based Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, which have been validated for cytotoxic chemotherapy and targeted therapy (Eisenhauer et al., 2009; Litière et al., 2019). For immunotherapy, ce-CT-based response criteria require confirmation of progressive or newly detected lesions on a subsequent scan before the patient is classified as progressive. This confirmation minimizes the risk of falsely classifying patients with pseudoprogression (< 10 % of patients), i.e. initial enlargement before subsequent shrinkage of a responsive lesion caused by immune cell influx (Borcoman et al., 2019). Numerous ce-CT response criteria for immunotherapy have been developed (reviewed in (Dimitrakopoulou-Strauss, 2019)). The iRECIST criteria, adapted from RECIST 1.1 criteria, are recommended for uniform ce-CT response evaluation in clinical trials on immunotherapy (Seymour et al., 2017). At this time, data collection for formal validation of the iRECIST criteria is ongoing.

For ^{18}F-FDG PET/CT, the most commonly applied criteria for standardized and objective response measurement are those by the European Organisation for Research and Treatment of Cancer (EORTC) and the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) (Suppl. Table 3) (Young et al., 1999; Wahl et al., 2009). These have not yet been validated on large uniform data sets.

^{18}F-FDG PET/CT therapy monitoring showed no additional value in chemotherapy response assessment when compared to the tumour marker S100B and ld-CT in melanoma, although neither are regarded to be the gold standard for response assessment (Hofman et al., 2007; Strobel et al., 2008, 2007). Research now focuses on the use of ^{18}F-FDG PET/CT for predicting and monitoring (early) response and toxicity in the current therapeutic landscape of immunotherapy and BRAF(/MEK) targeted therapy (Suppl. Table 4) (Ribas et al., 2010; Sachpekidis et al., 2014; Breki et al., 2016; Cho et al., 2017; Sachpekidis et al., 2018a; Anwar et al., 2018; Sachpekidis et al., 2018b; Tan et al., 2018; Ito et al., 2019a; Sachpekidis et al., 2019a; Amrane et al., 2019; McArthur et al., 2012; Kraeber-Bodéré et al., 2012; Carlino et al., 2013; Falchook et al.,

2014; Schmitt et al., 2016).

5.1. Monitoring immunotherapy using ^{18}F-FDG PET/CT

The CTLA-4 inhibitor ipilimumab was the first immune checkpoint inhibitor that received regulatory approval for treatment of advanced melanoma (Hodi et al., 2010; Robert et al., 2011). A retrospective study in 20 patients with metastatic melanoma, of which 16 were treated with ipilimumab, analysed interim ^{18}F-FDG PET/CT scans obtained 3 – 4 weeks after treatment start (Cho et al., 2017). At this early time-point, the combination of RECIST CT response and SUL$_{peak}$ (SUV$_{peak}$ normalized by lean body mass) outperformed respectively single RECIST, immune-related RECIST, PERCIST or EORTC response evaluation in predicting final best overall (RECIST) response after ≥four months (accuracy of 95 % vs. 65–75 %). However, in an undefined subset ld-CTs were used to determine response, while RECIST is only validated for ce-CT, and in a later retrospective study the RECIST/SUL$_{peak}$ combination was not able to predict PFS or OS (Amrane et al., 2019). Interestingly, in patients with RECIST stable disease at the interim scan (n = 9), an increase in maximum SUL$_{peak}$ was associated with long-term clinical benefit (Cho et al., 2017). This was hypothesized to be caused by early influx of immune cells into the tumour, which have a high ^{18}F-FDG uptake in an activated state, and reflect pseudoprogression. In a similar study (n = 22), two patients with a partial metabolic response after four cycles of ipilimumab were also initially falsely classified as progressive, based on lesion enlargement and higher SUVs on ^{18}F-FDG PET/CT after two cycles (Sachpekidis et al., 2014). In the same study, ^{18}F-FDG PET/CT after two cycles correctly predicted progressive metabolic disease (PMD) according to the EORTC criteria after completion of four cycles in 13 out of 15 patients and stable metabolic disease (SMD) in five out of five patients (Sachpekidis et al., 2014). Based on an extended cohort (n = 41) with long-term follow-up (median 21.4 months) the authors proposed new PET Response Evaluation Criteria for Immunotherapy (PERCIMT) centred around the number of new ^{18}F-FDG PET/CT-positive lesions. New lesions on the interim ^{18}F-FDG PET/CT scan after two cycles had a higher sensitivity than EORTC criteria (P = 0.004) for predicting eventual treatment relapse, while specificity did not differ (P = 0.5) (Sachpekidis et al., 2018a). In contrast to post-therapy SUV$_{mean}$ and SUV$_{max}$ changes of target lesions, emergence of four or more new lesions on the ^{18}F-FDG PET/CT scan performed immediately after finishing four cycles of ipilimumab (compared to baseline ^{18}F-FDG PET/CT) was predictive of treatment failure (Anwar et al., 2018; Sachpekidis et al., 2018b). Different immunotherapy-modified PERCIST criteria (imPERCIST5) were suggested in a retrospective study of 60 metastatic melanoma patients treated with ipilimumab. In these imPERCIST5 criteria, new lesions on the ^{18}F-FDG PET/CT scan after treatment completion were included in total SUV$_{peak}$ measurements but did not define PMD per se, as is the case in PERCIST criteria. Two-year OS was 66 % vs 29 % (P = 0.003) for patients with and without an imPERCIST5-based response and 61 % vs 33 % (P = 0.028) for PERCIST criteria (Ito et al., 2019a). Other quantitative ^{18}F-FDG PET/CT studies evaluating dynamic (continuous tracer acquisition) and longitudinal (repetitive tracer acquisition) scanning did not show additional value for prediction of ipilimumab responses (Breki et al., 2016; Sachpekidis et al., 2018b, a). The studies performed so far are based on small populations, do not take known prognostic factors including lactate dehydrogenase (LDH) into account and/or lack standardized scan timing (Sachpekidis et al., 2014; Ito et al., 2019a). More importantly, the applied ^{18}F-FDG PET/CT criteria, including the EORTC and PERCIST criteria that are used as standards, are unvalidated. Whether ^{18}F-FDG PET/CT response measurements have additional value over conventional ce-CT-based (RECIST) evaluation is yet to be determined.

The PD-1 immune checkpoint inhibitors pembrolizumab and nivolumab showed superior clinical efficacy to chemotherapy and ipilimumab in phase III trials (Ribas et al., 2015; Robert et al., 2015; Weber et al., 2015). One study in 27 melanoma patients investigated whether a prolonged response to PD-1 inhibitors after > 12 months of treatment could be characterized by the absence of metabolically active lesions on ^{18}F-FDG PET/CT (Kong et al., 2016). ^{18}F-FDG PET/CT scans were performed at a median of 15.2 months (range 12–29 months) after treatment initiation and showed metabolically active lesions in 15/27 patients (56 %). Biopsies were taken in eight patients with metabolically active lesions and revealed an immune cell infiltrate instead of melanoma in three patients as the cause of ^{18}F-FDG uptake. A trend towards higher SUV$_{max}$ values in the five patients with biopsy-proven progression compared to the three patients with immune infiltrates (median SUV$_{max}$ 18 vs. 7.1) was observed. Interestingly, all twelve patients without metabolically active lesions showed ongoing response over the following six to 15 months, including five patients who stopped treatment after the negative ^{18}F-FDG PET/CT scan and six patients who had residual lesions on the CT scan. A retrospective analysis of 104 patients with stage IIIc/IV melanoma treated with PD-1 inhibitors +/- ipilimumab supports the complementary role for ^{18}F-FDG PET/CT to ce-CT in the decision to stop treatment after prolonged response (Tan et al., 2018). Forty-seven of the 75 patients (63 %) with RECIST partial response (PR) on ce-CT after one year had a complete metabolic response (CMR) on corresponding ^{18}F-FDG PET/CT. Patients with both ce-CT PR and ^{18}F-FDG PET/CT CMR had better one-year progression-free survival than PR patients without CMR (100 % vs. 58 %, P < 0.01). Seventy-five of 78 CMR patients (96 %) remained progression-free after treatment discontinuation, with a median follow-up of 14.5 months.

The prognostic value of baseline quantitative ^{18}F-FDG PET/CT parameters for immunotherapy response was studied in 142 melanoma patients treated with ipilimumab (Ito et al., 2019b). Of the baseline parameters SUL$_{max}$, SUL$_{peak}$, whole-body MTV and total lesion glycolysis (TLG; product of MTV and SUV$_{mean}$), whole-body MTV was the best independent prognostic factor for OS (P = 0.001). This remained prognostic in a multivariate model including clinical parameters such as LDH levels and presence of brain metastases. Other retrospective studies also show correlations between response or OS and quantitative ^{18}F-FDG parameters, such as baseline intratumoural heterogeneity in ^{18}F-FDG uptake (Sanli et al., 2019), baseline tumour SUVs, whole-body MTV and TLG (de Heer et al., 2018; Seban et al., 2019), BLR (bone marrow-to-liver SUV$_{max}$ ratio) (Seban et al., 2019) or baseline physiological ^{18}F-FDG uptake of the colon (Boursi et al., 2019), although all studies were complicated by low patient numbers (14–64 patients) and/or heterogeneously treated populations.

Although the abovementioned studies have shown interesting results, such as the stronger correlation of PFS with ^{18}F-FDG PET/CT response than ce-CT response after one year, the evidence so far is limited and based on small prospective cohorts and retrospective analyses. Consequently, there is currently no evidence to support the use of ^{18}F-FDG PET/CT as a radiologic modality for response prediction and response monitoring of immunotherapy in melanoma. Future large-scale studies with standardized and well-described imaging protocols are needed to enable sound comparisons. Critical aspects to include in future studies are well-described homogeneous populations with standardized and repeated imaging (e.g. following EANM guidelines), clearly defined response definitions, comparison of ^{18}F-FDG PET/CT with the current gold standard of ce-CT based (i)RECIST, histological confirmation of metabolically active lesions to elucidate the phenomenon of pseudoprogression, and incorporation of clinical information, such as symptoms and biomarkers of progression (e.g. LDH levels).

5.2. Monitoring systemic treatment with BRAF(/MEK)-targeted therapy

As opposed to immunotherapy, initiation of BRAF(/MEK) inhibitor therapy can result in a rapid, massive reduction in tumour burden (Sullivan and Flaherty, 2013). Several phase I studies describe no or only a weak correlation between SUV reduction early after start of

targeted therapy (approx. two weeks) and RECIST v1.0 CT response after 8–12 weeks or survival (McArthur et al., 2012; Kraeber-Bodéré et al., 2012; Falchook et al., 2014; Schmitt et al., 2016). This could be partly explained by a previous observation in paired biopsies (n = 15) that metabolic response on ^{18}F-FDG PET/CT, measured as SUV_{max} decrease, reflects cell volume reduction and increased intercellular distance rather than cell death (Theodosakis et al., 2015). Interestingly, absence of an early metabolic response was highly predictive of absent RECIST response after 12 weeks, with a negative predictive value of 97 % (95 %-CI 86–100 %) (Kraeber-Bodéré et al., 2012). A heterogeneous response after 15 days of treatment (i.e. lesions with metabolic response alongside progressive or new lesions; 6/23 patients, 26 %) and < 50 % change in SUV_{max} of the least responsive tumour lesion were correlated with shorter PFS but not OS (Carlino et al., 2013; Schmitt et al., 2016). OS results may, however, be influenced by patients receiving immunotherapy after targeted therapy. LDH levels and ECOG performance status, respectively, were also response predictors in the latter two studies, but it was not studied whether PET parameters remain prognostic when incorporating these variables into multivariate analyses.

These results imply that although ^{18}F-FDG PET/CT is able to detect an early metabolic response to BRAF and MEK inhibitors, this is not predictive for subsequent RECIST response on ce-CT. The small number of patients in these drug dose-escalating phase I trials and the inherent dose differences among patients prevent making definitive conclusions. Since clinical response is often clear and rapid the need for other early response markers is limited. For future prospective studies in patients treated with standard BRAF(/MEK) inhibitors it is of more interest to determine whether ^{18}F-FDG PET is able to detect resistance to BRAF (/MEK) at an earlier time-point than CT-based RECIST progression or clinical symptoms, which could aid in clinical decision making, for instance in a timely switch to immunotherapy.

5.3. Detection of immune-related adverse events of systemic treatment on ^{18}F-FDG PET/CT

Immune checkpoint inhibition can induce severe inflammatory reactions in normal organs and tissues. Inflamed tissue and active, infiltrating immune cells have a high glucose metabolism which results in a high ^{18}F-FDG uptake (Fig. 2). Colitis, for example, is a regularly observed immune-related adverse event (irAE) of ipilimumab and clinically characterised by diarrhoea (Hodi et al., 2010; Robert et al., 2011). Radiologic manifestations of colitis on ^{18}F-FDG PET/CT are an increased focal or diffuse ^{18}F-FDG uptake of the colonic wall and associated thickening of the bowel wall on CT (Tirumani et al., 2015; Bronstein et al., 2011; Wachsmann et al., 2017; Koo et al., 2014). However, also normal bowel may show ^{18}F-FDG uptake, e.g. in patients on metformin, making the distinction with colitis challenging. In a cohort of 100 patients with stage IV melanoma treated with ipilimumab, ^{18}F-FDG PET/CT after two or four cycles showed signs of colitis in 49 out of 100 patients (Lang et al., 2019). Only 21 (43 %) of these developed symptoms (grade 1–3 diarrhoea) and in eight patients with diarrhoea the ^{18}F-FDG PET/CT was false-negative. It was not mentioned whether the ^{18}F-FDG PET/CT colitis diagnosis preceded clinical manifestations or expedited start of immunosuppressive therapy. In a retrospective analysis of 17 melanoma patients who developed thyroid dysfunction during pembrolizumab treatment, the ^{18}F-FDG PET showed diffuse thyroid ^{18}F-FDG uptake in all patients with clinically detectable thyroiditis (n = 7) (De Filette et al., 2016). Interestingly, ^{18}F-FDG uptake in the thyroid gland before treatment with nivolumab was a significant predictor of overt thyroid irAEs (adjusted odds ratio of 14.48 [95 %-CI 3.12–67.19]), but not subclinical thyroid irAEs (Yamauchi et al., 2019). Cases have been reported where ^{18}F-FDG PET/CT scans performed for treatment monitoring revealed immune-related adverse events weeks before clinical symptoms became apparent (Tirumani et al., 2015; Bronstein et al., 2011; Wachsmann et al., 2017; van der Hiel et al., 2013; Mekki et al., 2018; van Willigen et al., 2019;

Calugareanu et al., 2019). These included hypophysitis, gastro-intestinal inflammation and inflammatory reactions of soft tissues such as myositis or fasciitis and sarcoid-like lymphadenopathy.

An association between radiologically detected irAEs (by ^{18}F-FDG PET/CT or ce-CT) and response to anti-CTLA-4 therapy was shown in 119 patients with metastatic melanoma (Bronstein et al., 2011). Disease control rate (i.e. radiological response and stable disease) was 55 % in the group with (n = 20) and 10 % in the group without (n = 99) radiologic manifestations of irAEs (P < 0.0001). Additionally, sarcoid-like lymphadenopathy on ^{18}F-FDG PET/CT during ipilimumab treatment was associated with clinical response (Sachpekidis et al., 2019b). In contrast, neither signs of colitis on ^{18}F-FDG PET/CT or symptoms of diarrhoea correlated with best treatment response or OS (Lang et al., 2019).

Generally, clinical information and/or biopsies of newly detected lesions are still needed to differentiate between adverse events and melanoma progression. Moreover, it is unclear in how many cases ^{18}F-FDG PET/CT can detect adverse events (long) before they become clinically or biochemically manifest and whether this would alter clinical management. Hence, evidence so far does not justify use of ^{18}F-FDG PET/CT for mere detection or monitoring of adverse events.

6. Discussion and future perspectives

The majority of studies on ^{18}F-FDG PET/CT in melanoma have focused on detection of distant metastases in clinically stage I-III melanoma and complete staging of stage IV melanoma (Fig. 3). They indicate that torso or whole-body ^{18}F-FDG PET/CT is the most accurate imaging work-up for staging in advanced melanoma when considering non-cerebral metastases. Nevertheless, the current clinical consequences of staging by ^{18}F-FDG PET/CT + MRI brain, the current standard in many melanoma centres, has thus far not been systematically compared to other imaging strategies.

Solid evidence justifying the use of ^{18}F-FDG PET/CT for therapy choices, monitoring and clinical decision-making regarding early systemic therapy stopping or switching is lacking (Fig. 3). Limited data suggests that ^{18}F-FDG PET/CT might aid in expedited detection of non-responders to BRAF-/MEK-inhibition and could be useful in predicting in which long-term responders to anti-PD-1-therapy this response will be persistent. The correlation of long-term outcomes with early ^{18}F-FDG PET/CT response after start of BRAF-/MEK-inhibition or immunotherapy is disappointing. Several ongoing and planned ^{18}F-FDG PET/CT studies addressing these and other questions are currently registered at ClinicalTrials.gov (Table 1).

So far, RECIST response measurement by ce-CT remains the currently best available gold standard. Therefore, a baseline reference ce-CT is still required to eventually determine response according to validated criteria. It currently remains unclear whether ^{18}F-FDG PET/CT can detect disease progression earlier than conventional imaging using ce-CT, facilitating a timely switch of treatment strategy when applicable. The high number of patients that are falsely classified as responders, insufficient understanding of the significance of new or progressive metabolically active lesions and mixed responses pose the same challenges as with ce-CT response monitoring. More importantly, interpretation of the studies performed so far is clouded by small heterogeneous populations without validation cohorts, absence of studies on anti-PD-1-therapy, inconsistent scan timing, the use of various non-validated sets of response criteria and insufficient information on use of accredited systems and adherence to harmonization guidelines (e.g. EANM Research Ltd. [EARL]). Strict adherence to uniform scan protocols and detailed descriptions hereof is vital for evaluating existing and novel proposed ^{18}F-FDG PET/CT response measures and the potential complementary role of ^{18}F-FDG PET/CT to current ce-CT-based response measurement. The lack of these uniform and well-described studies so far has prevented pooled meta-analyses of large-scale study cohorts that are required for validation and implementation of ^{18}F-FDG
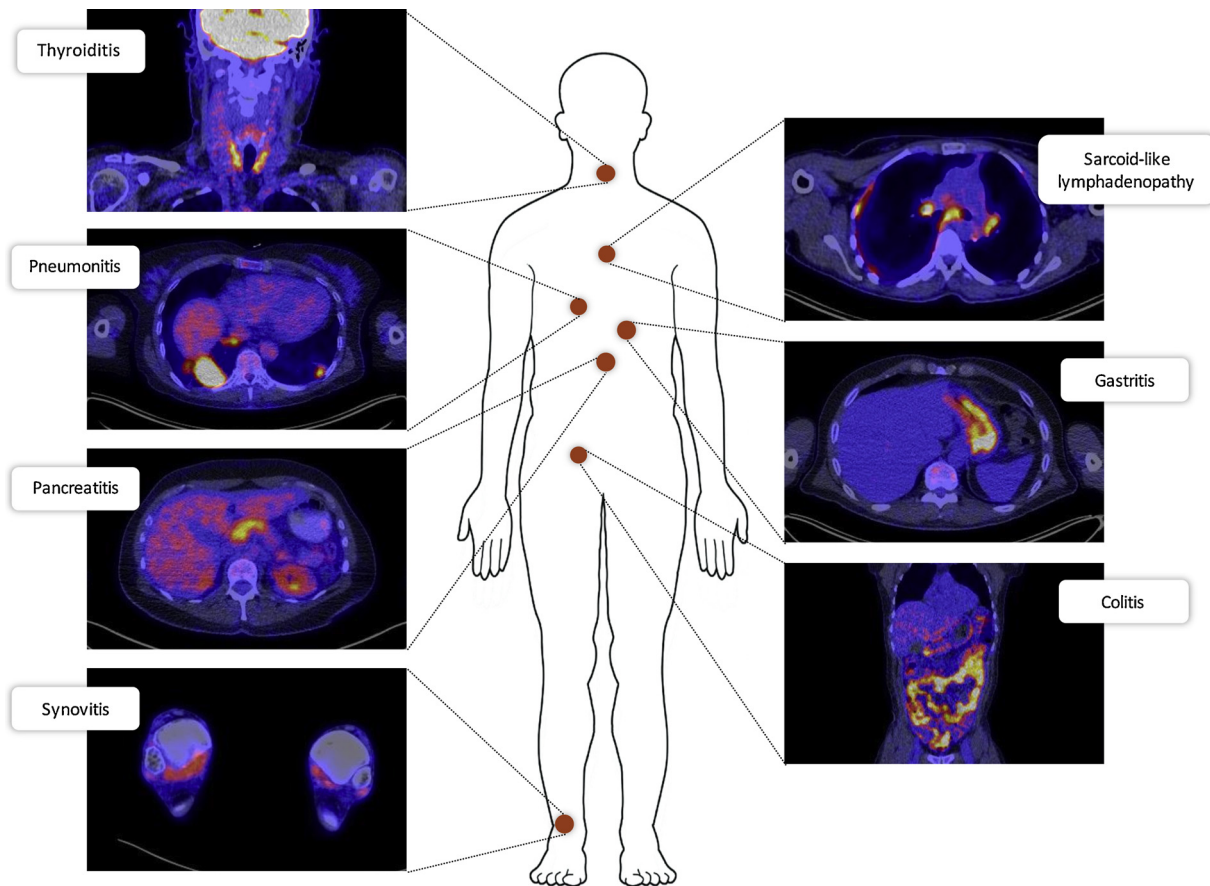
Fig. 2. Appearance of various immune-related adverse events in patients with metastatic melanoma treated with immunotherapy on ^{18}F-FDG PET/CT. (Patient drawing adjusted from Wikimedia Commons [Internet] (2020)).

PET/CT measurements in existing response criteria (Litière et al., 2017). Initiatives are ongoing to provide practical protocols and aids for performing and describing (quantitative) ^{18}F-FDG PET/CT studies to facilitate such large-scale analyses and validation in the future (RECIST Working Group, 2020; Kinahan et al., 2020). Meanwhile, novel PET tracers that are thought to be more specific than ^{18}F-FDG for evaluating immunotherapy response in melanoma are rapidly being developed. Approaches that are currently investigated in preclinical models or in early phase clinical trials include novel PET tracers that bind to melanin, immune checkpoints or CD8$^+$ T cells (Dimitrakopoulou-Strauss, 2019; Gilardi et al., 2014; Pandit-Taskar et al., 2020; Bensch et al., 2018).

Radiation burden and cost-effectiveness are important when considering incorporation of ^{18}F-FDG PET/CT scanning into clinical practice. Lifetime attributable risk estimates for cancer incidence following exposure to 10 mSv are highly age- and gender-dependent, with young

Fig. 3. Overview of relevant referenced studies (dots) and the value of ^{18}F-FDG PET/CT (squares) during the disease course of advanced melanoma. Studies are depicted according to their Level of Evidence (OCEBM Levels of Evidence Working Group, 2011) and (main) topic. Subsequent interpretation of the final value of ^{18}F-FDG PET/CT for each timeframe has been based on overall conclusions of the studies and their LoE. ^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, LoE = Level of Evidence.

Table 1
Ongoing or planned ^{18}F-FDG PET/CT studies in advanced melanoma identified on ClinicalTrials.gov.

NCT number	Study design	Population	(Planned) n	Treatment	^{18}F-FDG PET/CT timing	Outcome measure(s)
Immunotherapy						
NCT02716077	Phase I	Stage III/resectable stage IV melanoma	20	Pembrolizumab	Not mentioned	Disease-free survival
NCT02791594	Prospective cohort	Metastatic melanoma	30	Pembrolizumab	Baseline Week 3 Week 10	6-months RECIST 1.1 response
NCT03584334	Prospective cohort	Unresectable melanoma and metastatic/locally advanced non-small cell bronchopulmonary cancer	100	Anti-PD-1	Week 7 Week 13 (dual-pointPET acquisition)	Threshold of the ^{18}F-FDG retention index and other PET criteria for distinction tumour progression from pseudoprogression
NCT03888950	Prospective cohort	Advanced melanoma	20	Anti-PD-1	Baseline Week 3–4 Week 13	Correlation 7-week PET response (PERCIST) with 3-months (i)RECIST response and 12-month overall survival Change in ^{18}F-FDG uptake of resp. 1 and 5 lesions (PERCIST criteria) and number of lesions
NCT03356470	Prospective cohort	Stage IV melanoma	4	Anti-PD-1	Baseline	Correlation ^{18}F-FDG-to-^{18}F-FLT ratio with antitumor response
NCT04193956	Prospective cohort	Advanced/metastatic melanoma and non-small cell lung cancer	3500	Anti-PD-1	Week 10 – 12	Correlation ^{18}F-FDG uptake with clonally amplified T-cells 5-year RECIST 1.1 response
NCT04165967	Phase I	Unresectable/metastatic melanoma	9	Nivolumab + TIL transfer + IL-2	Not mentioned	3-months and 2-year RECIST 1.1 response
BRAF/MEK inhibition						
NCT02414750 (van der Hiel et al., 2017)	Phase II	Unresectable stage IIIc/stage IV BRAFV600E/K-mutated metastatic melanoma	90	Vemurafenib + cobimetinib	Baseline Week 2 Week 7 At progression	Progression-free and overall survival Diagnostic accuracy and cut-off values of ^{18}F-FDG uptake for response RECIST 1.1 response Correlation ^{18}F-FDG uptake with lab and pathology results

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; FLT = ^{18}F-fluorothymidine; IL = interleukin; PD-1 = programmed cell death protein 1; PERCIST = Positron Emission Tomography Response Criteria in Solid Tumors; PET = positron emission tomography; RECIST = response evaluation criteria in solid tumours; TIL = tumour-infiltrating lymphocyte.

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females being especially sensitive to radiation (Wall et al., 2011). Young melanoma patients are relatively common and the number of follow-up scans has increased with increasing numbers of long-term survivors. Although radiation exposure of an ^{18}F-FDG PET/CT scan is approximately two-fold lower than of ce-CT, as mentioned earlier, deliberate application remains indicated for this reason as well.

The three existing studies addressing economic evaluation of ^{18}F-FDG PET/CT scans do not include immunotherapy and targeted therapy as possible treatment options, are based on outdated cost information (e.g. from 1996) and/or PET-only technology or have a merely hypothetical economic model (Bastiaannet et al., 2012; Krug et al., 2010; Buck et al., 2010). It is likely that cost-effectiveness analyses will turn out differently nowadays, considering the decreasing costs of integrated ^{18}F-FDG PET/CT, the high costs of immunotherapy and targeted therapy, and the prolonged survival of responders which increases follow-up surveillance time. Key questions for novel cost-effectiveness analyses are whether ^{18}F-FDG PET/CT scanning diminishes or increases the number of additional diagnostic procedures and whether baseline ^{18}F-FDG PET/CT scanning contributes to better decision-making between different systemic therapies by identifying patients with highest response chances upfront.

In conclusion, ^{18}F-FDG PET/CT has a clear role during diagnostic work-up in advanced melanoma and well-designed studies will aid in determining whether it is rational to also include ^{18}F-FDG PET/CT during treatment and follow-up of patients with metastatic melanoma.

Declaration of Competing Interest

M. Jalving: advisory board for Merck, BMS, Novartis, Pierre Fabre, Tesaro, AstraZeneca (honoraria to the institution). Speaker fees: Sanofi. Clinical studies: BMS, AbbVie, Merck, Cristal Therapeutics. G.A.P. Hospers: consulting and advisory role for Amgen, Roche, MSD, BMS, Pfizer, Novartis, Pierre Fabre (honoraria to the institution). Research grants: BMS, Seerave (honoraria to the institution). The other authors report no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.103044.

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