Defining optimal oncolytic virus treatment and diagnostics in high risk melanoma patients

Stahlie, E.H.A.

PART II

Refining treatment and diagnostics in high risk melanoma

CHAPTER 7

The use of FDG-PET/CT to detect early recurrence after resection of high-risk stage III melanoma

Emma H.A. Stahlie*
Bernies van der Hiel*
Marcel P.M. Stokkel
Yvonne M. Schrage
Winan J. van Houdt
Michel W.J.M. Wouters
Alexander C.J. van Akkooi
**Authors contributed equally to this study*

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ABSTRACT

Background
The role of surveillance imaging in high risk stage III melanoma patients after complete surgical resection remains controversial, and with the advent of adjuvant therapy, it may also be expanded. Therefore, we evaluated two FDG-PET/CT protocols in two cohorts.

Methods
Cohort 1(n=35) focused on surveillance in asymptomatic patients (prior to approval & reimbursement of adjuvant therapy) and was assigned to 5x FDG-PET/CT's after surgery: one every 6 months for two years, with one final scan after 3 years. Cohort 2(n=42) was assigned to one screening FDG-PET/CT, which took place in between surgery and the start of adjuvant treatment.

Results
In cohort 1 (median follow-up: 33 months), 12 patients(34.3%) developed recurrence detected by FDG-PET/CT, of which seven(20.0%) were detected with the first scan. Sensitivity and specificity were 92.3% and 100% respectively. In cohort 2, recurrence was suspected on nine scans(21.4%) and four(9.5%) were true positive. The number of scans needed to find one asymptomatic recurrence were 8.8 and 10.5 in cohort 1 and 2 respectively.

Conclusions
FDG-PET/CT is a valuable imaging tool to detect recurrence in stage III melanoma, even shortly after surgery. A surveillance FDG-PET/CT protocol after surgery or a screening PET/CT prior to adjuvant therapy should be considered.

INTRODUCTION

Even after appropriate surgical management, melanoma patients with American Joint Committee on Cancer (AJCC) stage IIIB-D have a high risk of recurrence and death due to melanoma. The 5-year melanoma-specific survival (MSS) rates according to the 8th AJCC are 83% and 69% for stage IIIB and IIIC respectively, diminishing to 32% for stage IIID patients [1]. Many recurrences develop within the first 2 years after surgery[2]. Until 2010, early detection of recurrence was focused on surgically removing disease to prevent progression to stage IV disease, as diagnosis of stage IV disease was usually infaust. In the absence of effective systemic therapy options in patients with metastatic melanoma, a comparative analysis in which stage-specific surveillance strategies were analyzed on a patient cohort from 1992-2007, demonstrated nearly no survival benefit for routine surveillance imaging of high-risk melanoma [3]. However, over the last 10 years the treatment landscape for these patients has changed dramatically, calling for re-evaluation of surveillance strategies.

Modern therapies for locally advanced and metastatic melanoma have shown impressive results and durable responses, increasing the survival of patients. Reponse rates and survival are even higher when the tumor is still resectable, tumor burden is relatively low and brain metastases are absent, although a lead-time bias effect could play a role [4-6]. Therefore diagnosing recurrences early might benefit outcome for patients in this modern era.

Melanoma tumour tissue typically visualizes high glucose metabolism and is therefore easily detected by Fluorine-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT). In a pilot study, Madu et al. examined the yield of a recently introduced FDG-PET/CT surveillance protocol (prior to the availability of adjuvant therapy) and concluded that this seems to be an effective strategy to detect early asymptomatic recurrence [7]. In addition, PET/CT has proven to be an invaluable imaging modality for restaging, which can lead to alterations in treatment strategy [8-10]. Bastiaannet et al. demonstrated that 27% of melanoma patients with palpable lymph node metastases were upstaged as a result of FDG-PET and CT and treatment changed in five [11].

Recent developments in the use of adjuvant systemic therapy with either checkpoint inhibitors (ICI) or the combination of a BRAF inhibitor and MEK inhibitor have led to significant improvements in terms of relapse free survival (RFS) for stage III disease [12-15]. Since December 2018, adjuvant therapy with anti PD-1 and combined BRAF/MEK inhibitors have been approved and are reimbursed by health care payers in the Netherlands.

However, approximately 10-15% of patients in the EORTC 1325/Keynote054 and Checkmate 238 trials failed screening due to progression in the 12 weeks between surgical resection and starting adjuvant therapy[12, 16]. Therefore, at our institute, accurate baseline (re-)screening with whole body FDG-PET/CT and Magnetic Resonance Imaging (MRI) of the brain after resection of disease (sentinel node for microscopic disease or lymph node dissection for macroscopic disease) but before starting adjuvant therapy is performed. The goal of this protocol, is to exclude patients with newly developed metastases or progression to stage IV disease, from adjuvant therapy. However, this practice is not yet standard of care across the world. Moreover, some patients decline adjuvant therapy because of its potential related toxicities, thereby missing out on this interim check-up within 3 months after surgery.

With this study we aim to analyse the role of FDG-PET/CT in detecting (early) recurrences after complete resection of advanced stage III melanoma. We aim to determine both the role of FDG-PET-CT as surveillance tool during follow-up, as well as prior to adjuvant after surgery.

METHODS

Study design, setting and patients

Patients included in this prospective study were treated at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL). The study was performed in accordance with the institutional ethical guidelines. Patients were included in two cohorts.

Cohort 1

Cohort 1 included melanoma patients that, after complete resection of macroscopic lymph node(s) and/or in-transit disease (stage IIIB or IIIC melanoma according to the 7th AJCC, see supplementary appendix), entered follow-up and therefore the surveillance protocol between January 2015 and December 2017. All patients had already undergone a FDG-PET/CT and whole brain MRI, that showed no additional metastases, prior to surgery. Here we describe the yield of the follow-up surveillance protocol after surgery.

After complete resection of disease, patients underwent a 3-monthly physical examination and assessment of serum S100B and LDH[16]. If patients stayed asymptomatic and S100B was within normal values, a surveillance FDG-PET/CT scan was performed 6 months after surgery and every 6 months thereafter for 2 years, with one final scan after 3 years. So a total of five scans per patients could have been made per patient, depending on when he or she entered the surveillance protocol, but patients had to undergo at least one FDG-PET/CT

according to protocol in order to be included. Patients who received a FDG-PET/CT during follow-up for another indication, like restaging due to symptomatic and histologically or cytologically confirmed recurrence or for an increased serum S100B level, were excluded. Patients who participated in (neo-)adjuvant clinical trials were also excluded.

Cohort 2
Cohort 2 included melanoma patients that, after complete resection of stage IIIB, IIIC or IIID melanoma (staged according to the 8th AJCC) were eligible for- and willing to start adjuvant therapy, between December 2018 and May 2019. Before surgery, patients with macroscopic nodal disease, underwent a FDG-PET/CT and MRI of the brain. Within 12 weeks after complete resection of disease patients underwent, besides physical examination and assessment of S100B and LDH, a screening FDG-PET/CT in order to exclude newly arised metastases. For the sentinel node positive patients, this was their first PET/CT. Here we describe the yield of this screening FDG-PET/CT scan prior to adjuvant therapy.

Subsequently, patients were followed up with ceCT or FDG-PET/CT during adjuvant treatment, however the choice of- and interval in between these scans differed as there is no national guideline yet.

Adjuvant treatment consisted of treatment with anti-PD-1 (either nivolumab 480 mg every 4 weeks for 12 months or pembrolizumab 200 mg every 3 weeks for 12 months). Patients with a BRAF-mutation, could also be considered for treatment with the combination of dabrafenib (150 mg trice daily) and trametinib (2 mg once daily) for 12 months, which is according to Dutch guidelines.

Imaging

Whole body FDG-PET/CT imaging was conducted on a cross-calibrated Phillips Gemini TF time-of-flight 16 or Phillips Gemini TF big-bore PET/CT scanner (Philips, Cleveland, USA). After fasting for six hours and adequate fluid intake, radioactive FDG was administered intravenously in a dosage of 180-240 MBq, depending on body mass index. Approximately 60 minutes after administration low-dose CT images (40 mAs, 2-5 mm slices) without intravenous contrast were obtained for attenuation correction and anatomic correlation, followed by whole body PET acquisitions with an acquisition time of 1-3 minutes per bed position. Abnormal FDG accumulation was evaluated according to location, size and intensity.

The FDG-PET/CT images were reviewed by an experienced nuclear medicine physician, after which the treating surgeon assessed the report, considering the clinical setting.

FDG-PET/CT scans were considered true positive when patients had a recurrence which was either confirmed with cytologic puncture or histologic biopsy, or sequential imaging with contrast-enhanced CT or MRI. In case of suspected recurrence on surveillance FDG-PET/CT, but no confirmation by pathology or sequential imaging, the scan was assessed as false positive (FP). In cohort 1, scans were considered true negative (TN) when patients had no recurrence within two months of surveillance FDG-PET/CT. When recurrence was found by physical examination but not detected by imaging or when patients suffered recurrence within two months after the surveillance FDG-PET/CT, the scan was considered false negative (FN). Incidental findings that were not related to melanoma were reported and assessed as true negative (TN).

Statistics

Baseline characteristics were summarized using descriptive statistics. Sensitivity, specificity, positive- and negative predictive value (PPV, NPV) were determined using standard definitions. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 25.0.

RESULTS

FDG-PET/CT in surveillance (cohort 1)

Eighty patients with 7th AJCC stage IIIB and IIIC melanoma entered the FDG-PET/CT surveillance protocol between January 2015 and December 2017 after undergoing complete surgical resection. Forty-five patients were excluded: 28 patients presented with clinically symptomatic recurrences and therefore needed to undergo a FDG-PET/CT prior to the planned surveillance scan, 15 patients did not receive 6-monthly scans because they were made outside the protocol and two patients had elevated S100B prior to the scheduled scan.

The remaining 35 patients were included and received FDG-PET/CT scans according to the surveillance follow-up schedule. Table 1 summarizes the baseline characteristics of patients in cohort 1. A total of 105 scans (with an average of three scans per person) were acquired with a median follow-up of 33 months (IQR: 27-48). Overall, twelve patients (34.3%) developed a recurrence, seven (20.0%) of which were detected by the first scan (Table 2). Seven (58.3%) recurrences concerned stage IIIC patients and five (41.7%) stage IIIB patients. In eight FDG-PET/CT positive scans, recurrence was confirmed by cytologic puncture or histologic biopsy, one scan was confirmed by MRI and one scan by ceCT. The last two recurrences were so extensive, no immediate diagnostic confirmation was considered necessary and recurrence was confirmed with sequential imaging thereafter. No FDG-PET/CT scans were found to be FP. Ninety-two scans were TN and one scan was assessed FN because FDG-PET/CT did not detect the in-

transit metastases found with physical examination. Figure 1 shows a summary of the outcomes.

The sensitivity and specificity of FDG-PET/CT to detect recurrence in asymptomatic patients were 92.3% and 100.0% respectively, with a PPV of 100.0% and a NPV of 98.9%. The number of scans needed to find one asymptomatic recurrence was 8.8.

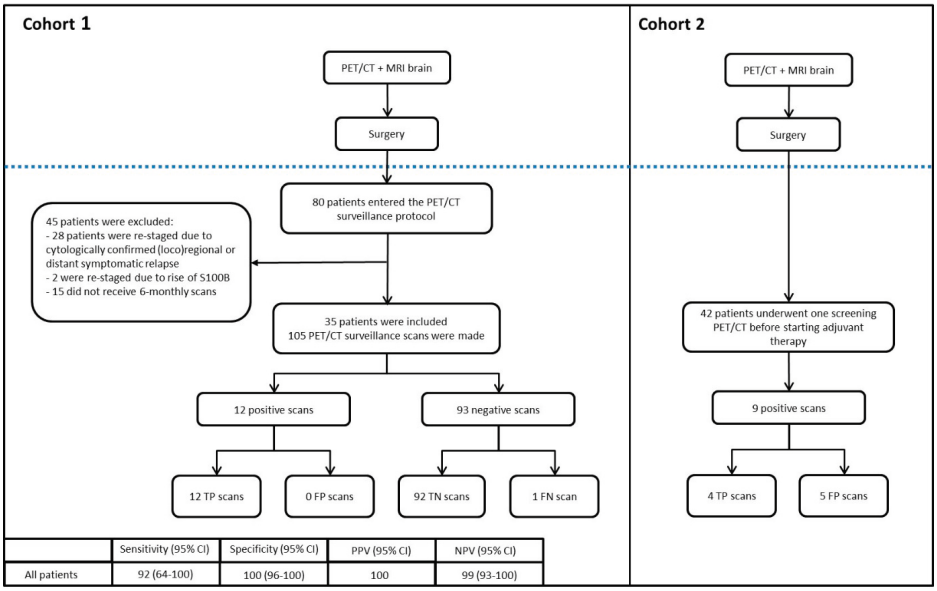
Univariable analyses showed neither predictors for developing recurrence, nor predictors when comparing early recurrence (at 6 months) versus late recurrence (at 12, 18, 24 and 36 months) (Table S1 and S2).

FDG-PET/CT for screening prior to adjuvant therapy (cohort 2)

Between December 2018 and May 2019, 42 patients underwent a screening FDG-PET/CT before starting adjuvant therapy. Baseline characteristics of these patients are described in Table 1. Median time between surgery and FDG-PET/CT was 6 weeks. Twenty patients (47.6%) were eligible for adjuvant therapy after complete lymph node dissection (LND) and 17 patients (40.5%) after sentinel node procedure (SNP). On nine of 42 scans recurrence was suspected, four of which proved TP (9.5%), of which three after LND and one after SNP. The recurrences are summarized in Table 2. Recurrence was confirmed with cytological puncture in two patients and in the two other patients FDG-PET/CT showed such widespread metastases that no further cytology or histology was considered necessary. Recurrence in these patients was confirmed by sequential imaging thereafter. Five scans turned out FP (11.9%), none of these findings were related to the preceded surgery: a hypermetabolic lymph node on the contralateral side of the prior LND, mediastinal and supraclavicular lymph nodes after an axillary LND, two suspect lesions in the liver and a rise in uptake suspect for metastasis between the tibia and fibula. The first scan was confirmed negative with cytological puncture and the other four scans were confirmed negative by subsequent imaging (two with MRI, one with ceCT and one with ultrasound). Figure 1 shows a summary of the outcomes. The number of scans needed to find one asymptomatic recurrence was 10.5.

		Cohort one	Cohort two
Number of patients included		35	42
Sex [n (%)]	Male/Female	14 (40) /21 (60)	30 (71) / 12 (29)
Age [median (IQR)]		60 (48 - 70)	62 (51 - 69)
Location primary melanoma [n (%)]	Extremity Trunk Head/neck Unknown primary	16 (46) 12 (34) 1 (3) 6 (17)	15 (36) 15 (36) 11 (26) 1 (2)
Type primary melanoma [n (%)]	Superficial spreading Nodular Acrolentiginous Naevoid Unknown Unknown primary	14 (40) 7 (20) 1 (3) 7 (20) 6 (17)	23 (55) 7 (17) 2 (5) 1 (2) 8 (19) 1 (2)
Breslow thickness, mm [n (%)]	≤1.0 >1.0 – 2.0 > 2.0 – 4.0 >4.0 Unknown	6 (17) 10 (29) 10 (29) 3 (9) 6 (17)	2 (5) 7 (17) 17 (41) 14 (33) 2 (5)
Ulceration [n (%)]	Present Absent Unknown/unknown primary	10 (29) 16 (44) 9 (26)	15 (36) 25 (60) 2 (5)
Type of surgery [n (%)]	WLE + sentinel lymph node biopsy WLE + node dissection Inguinal dissection Iliacal dissection Ilio-inguinal dissection Axillary dissection Neck dissection Excision node pro diagnosi Resection in-transit metastasis Node dissection and resection ITM	 3 (9) 7 (20) 5 (14) 1 (3) 2 (6) 13 (37) 4 (11)	17 (41) 7 (17) 2 (5) 1 (2) 1 (2) 5 (12) 4 (10) 4 (10) 1 (2)
AJCC stage, 7th edition [n (%)]	IIIA IIIB IIIC	 16 (48) 19 (54)	5 (12) 19 (45) 18 (43)
AJCC stage, 8th edition [n (%)]	IIIB IIIC IIID	15 (49) 18 (51) 2 (6)	13 (31) 28 (67) 1 (2)
Median follow-up, months (IQR)		33 (27-48)	10 (8-11)
Median time to scan after surgery, weeks (IQR)		NA	6 (3-8)
Median time to recurrence, months (IQR)		6 (6-12)	4 (3-7)

Table 1. *Baseline characteristics of cohort one and two. Abbreviations: IQR, interquartile range; WLE, wide local excision; IT, in-transit metastases; NA, not applicable. Percentages may not total 100 because of rounding*



	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All patients	92 (64-100)	100 (96-100)	100	99 (93-100)

Figure 1. *FDG-PET/CT imaging outcomes for cohort 1 and 2 and diagnostic test accuracy of FDG-PET/CT for cohort 1. Abbreviations: TP, true positive; FP, false positive; TN, true negative; FN, false negative; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.*

Management of recurrences

Cohort 1

Change in- and response to management of recurrences are summarized in Table 2. In cohort 1, a total of 12 patients suffered from recurrence, two of which had a locoregional recurrence. One was managed with surgical excision and the other patient was treated with systemic immunotherapy. Four patients had a regional recurrence, three of them were managed by LND with or without adjuvant therapy (Figure 2). The fourth regional recurrence was treated with radiotherapy. Six patients had a distant recurrence, all were treated with systemic immunotherapy. For six patients, the early detection of recurrence led to a change in management leading to a complete respone (CR) or no evidence of disease (NED).

Cohort 2

Of the four recurrences detected in cohort 2, one patient had a regional recurrence. In this patient, with previously a primary tumor with microsatellites and therefore staged as IIIC, management was changed with an additional LND after which adjuvant therapy was started (Figure 3). In three patients, distant metastases were detected by FDG-PET/CT, for which they started systemic immunotherapy. For two patients, the detection of a recurrence prior to adjuvant therapy led to a change in management leading to a CR or NED.

Cohort 1

No.	M/F	Age	Stage (7th AJCC)	Surgery	Time point PET/CT recurrence	Type or recurrence	Change in management	Response to treatment
1	M	59	IIIC	Resection of ITM	6 months	Locoregional	Excision	NED
2	F	66	IIIB	Resection of ITM	6 months	Locoregional	Nivolumab	PD
3	M	48	IIIB	Neck LND	6 months	Regional	Neck LND followed by adjuvant therapy in EORTC1325 study	PD
4	F	52	IIIC	Ilio-inguinal LND	6 months	Distant	Ipilimumab (2 cycles) followed by pembrolizumab	PD
5	F	78	IIIC	Inguinal LND and resection of ITM	6 months	Distant	Nivolumab	PD
6	F	67	IIIC	Resection of ITM	6 months	Distant	Dabrafenib/trametinib	CR
7	M	67	IIIC	Inguinal LND	12 months	Distant	Pembrolizumab	PR
8	F	48	IIIC	Axillary LND	12 months	Regional	Neck LND followed by adjuvant therapy in EORTC 1325 study	PD
9	F	59	IIIB	Resection of ITM	12 months	Regional	Radiotherapy	CR
10	F	45	IIIB	Excision node pro diagnosi	12 months	Regional	Ilio-inguinal LND	NED
11	F	57	IIIC	Resection of ITM	18 months	Distant	Nivolumab	CR
12	M	49	IIIB	Axillary LND	36 months	Distant	Pembrolizumab	CR

Cohort 2

No.	M/F	Age	Stage (8th AJCC)	Surgery	Time scan after surgery (days)	Type or recurrence	Planned adjuvant therapy	Change in management	Response to treatment
1	M	60	IIIC (N1c)	Re-excision and SLNB	59	Regional	Nivolumab	Neck LND followed by adjuvant nivolumab	NED
2	M	71	IIIB	LND followed by RT	63	Distant	Nivolumab	RT (spine), nivolumab, then switch to dabrafenib/trametinib	PD
3	M	51	IIIC	Re-excision and LND followed by RT	117	Distant	Nivolumab	Nivolumab, then switch to ipilimumab	PD
4	F	64	IIIC	Re-excision and LND	120	Distant	Nivolumab	Nivolumab	CR

Table 2. *Recurrences in cohort one and two. Abbreviations: ITM, in-transit metastases; SLNB, Sentinel lymph node biopsy; LND, Lymph node dissection; NED, No evidence of disease; RT, Radiotherapy PD, Progressive disease; CR, Complete response; PR, Partial response.*

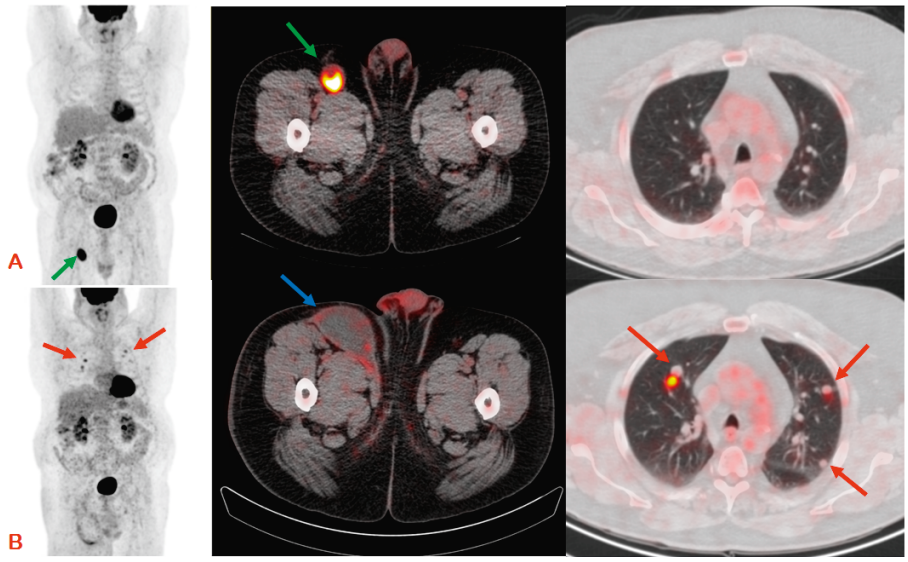


Figure 2. *FDG-PET/CT of patient with recurrence in cohort 1: patient with previous melanoma of the right leg, presenting with stage IIIC disease. A, FDG-PET/CT before inguinal lymph node dissection shows a lymph node metastasis in the right groin (green arrow) and no evidence of disease elsewhere in the body (maximum intensity projection of legs not shown). B, FDG-PET/CT 6 months after surgery shows postoperative inflammation around a seroma in the right groin (blue arrow) with newly developed FDG-avid lung metastases (red arrows). Abbreviations: FDG-PET/CT, fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography*

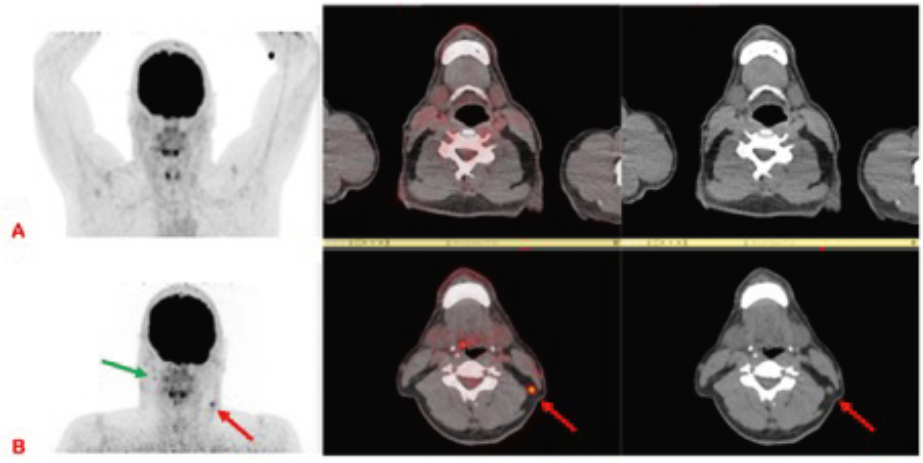


Figure 3. *FDG-PET/CT of patient with recurrence in cohort 2: patient with stage IIIC melanoma of the scalp. A, FDG-PET/CT before reexcision and sentinel lymph node procedure, with no signs of metastases in head/neck region or elsewhere in the body (not shown). B, FDG-PET/ CT before adjuvant therapy after surgery. FDG-avid lymph nodes were found in level 2b in the left neck (red arrow) and level Vb (green arrow), which after cytologic puncture appeared melanoma metastases. Abbreviations: FDG-PET/CT, fluorine-18 fluorodeoxyglucose-positron emission tomography/ computed tomography*

Recurrences during adjuvant therapy (cohort two)

Eight patients (21.1%) of the remaining 38 with a negative FDG-PET/CT developed a recurrence during adjuvant therapy (within 11 months), six of which within 6 months (15.8%). Four recurrences were locoregional, two regional and two distant.

Five recurrences were asymptomatic with normal S100B and found by imaging: two by FDG-PET/CT and three by ceCT. In one patient S100B was rising and FDG-PET/CT revealed wide spread metastases. The remaining 2 were found by physical examination.

One patient developed a recurrence after the postoperative FDG-PET/CT and before starting adjuvant therapy. The FDG-PET/CT showed lesions in the liver suspicious for metastases and an MRI was performed, which revealed cysts. Adjuvant immunotherapy was intended to start, but due to the intervening examinations this was with a delay of 58 days after FDG-PET/CT. On the day of the first treatment, a palpable nodule was found with physical examination and cytology confirmed as recurrence. Systemic therapy was nevertheless continued.

Incidental findings

In both cohorts, a total of 12 (over 147 scans; 8.2%) incidental findings not suspicious of melanoma were detected by FDG-PET/CT. These included one second primary malignancy: an indolent lymphoma of the fossa tonsillaris. One patient had hypermetabolic retroperitoneal and mesenterial lymph nodes, which were suspicious for either reactive lymph nodes or indolent lymphoma. These lymph nodes were not accessible for diagnosis, but follow-up imaging and serum blood results strengthened the suspicion for indolent lymphoma. FDG-PET/CT revealed a lung lesion without hypermetabolic activity in another patient. Follow-up with imaging was advised, but the lesion has not changed since. In three patients FDG-PET/CT revealed findings that needed further examination. These turned out to be a Warthin tumor, an adenoma of the ascending colon and cysts in the liver. Six other findings which did not need further examination were described: posttraumatic (n=3), sarcoid-like reaction, non-specific skin inflammation, degeneration of the lumbar spine.

DISCUSSION

This prospective study evaluated the role of FDG-PET/CT after complete resection of disease in stage IIIB/C/D melanoma patients, thereby determining the role of surveillance scans during follow-up (cohort 1) and the role of one screening scan prior to adjuvant therapy (cohort 2).

Cohort 1 is an expanded cohort of the previously published pilot study of Madu et al.[7] We expanded the number of patients included from 18 in the pilot study to 35, with an extended follow-up of 21 months. With 12 asymptomatic recurrences detected by FDG-PET/CT, we demonstrated that surveillance with 6-monthly FDG-PET/CT scans after complete surgical resection of stage IIIB/C melanoma has a high sensitivity and specificity, although with a broad confidence interval, for detecting asymptomatic recurrence and a high NPV and PPV. Other studies investigating FDG-PET/CT as a surveillance tool in the follow-up of melanoma patients show a sensitivity and specificity ranging from 67-100% and 90-100% respectively and reported PPV and NPV from 18-100% and 79-100% respectively [17,18-20]. The wide range of these percentages is amongst others explainable by aberrant inclusion criteria: symptomatic versus asymptomatic patients, different AJCC stages and different follow-up protocols.

A study comparable to ours regarding patient population in cohort 1 was performed by Leon-Ferre et al. [21] His group retrospectively reviewed patients with completely resected stage III/IV melanoma with at least one FDG-PET/CT performed within 1 year after surgery. They evaluated whether surveillance with FDG-PET/CT was associated with the detection of clinically-occult recurrences. They reported sensitivity and specificity rates of 88% and 90% respectively with a NPV of 99% but PPV of 37%, indicating that FDG-PET/CT is an accurate tool to rule out recurrence, but its limitation lies in proving recurrence. As a consequence, cytologic or histopathologic confirmation of recurrence remains essential. Nonetheless, in 66% of the clinically-occult recurrences surgical or ablative treatment to curative-intent was possible, which was associated with superior overall survival. It is assumed that in our surveillance cohort, the survival benefit has advantages over the created lead-time bias, however evidence to support this is lacking. Wanting to prove this with a significant survival analysis, we find ourselves limited by our sample size and follow-up duration.

To date, there is no international consensus for an appropriate schedule and duration of a surveillance protocol for high-risk melanoma patients[22]. In our study, seven of 12 (58.3%) recurrences in cohort 1 were detected by the first 6-monthly scan. Besides this, 25 of our excluded patients had a symptomatic recurrence which occurred prior to this first scan. A study by Romano et al. also reports high relapse rates shortly after surgery, they found that +/- 25% of stage IIIB and +/- 45% of stage IIIC melanoma patients had developed a recurrence at 6 months[2]. As recurrences in this group of patients apparently occur early, it might be an idea to plan the first surveillance scan even earlier than 6 months, for example after only 3 or 4 months. Subsequently, in terms of duration we would propose a 2-year protocol instead of a 3-year protocol, also because only one of the patients in cohort 1 had a recurrence later than 24 months. This finding is also consistent

with the results of Romano et al., who concluded that for stage IIIB patients most recurrences occur within 24 months and for stage IIIC patients within 12 months[2].

This study is the first evaluating the use of FDG-PET/CT as a screening tool in patients eligible for adjuvant immune- or targeted therapy. Of the four patients (9.5%) with recurrence in cohort 2, two recurrences occurred within the standard maximum of 12 weeks between surgery and starting adjuvant immunotherapy. The two other patients had a delay between surgery and starting immunotherapy of >12 weeks. This was due to post-surgical radiotherapy after irradical resection in one patient and for the other patient, adjuvant therapy became available at a later time point. Finding recurrences in these patients with an unforeseen delay before starting adjuvant therapy, emphasizes the value of performing a screening FDG-PET/CT especially in this group of patients.

A study investigating recurrence prior to adjuvant therapy in a trial using adjuvant dendritic cell therapy, demonstrated a recurrence rate of 14% detected by FDG-PET/CT, which is very similar to ours [23]. The checkmate 238 study reported that 309 patients did not participate in the randomization between nivolumab and ipilimumab, of which we only know that they did not meet the inclusion criteria [11]. One might assume that in some patients, exclusion was caused by progression on re-screening before entering the trial. Unfortunately, other studies investigating ICI's and targeted therapy in the adjuvant setting, did not describe their excluded patients [13, 15].

Although this study focused on one screening FDG-PET/CT scan prior to adjuvant therapy, we found that when this scan was assessed as negative, this did not seem to be predictive for not developing a recurrence during adjuvant therapy. Thus, also maintaining a surveillance protocol during adjuvant therapy seems wise to prevent unnecessary toxicity and costs. As 75% of these recurrences developed within 6 months after starting adjuvant therapy, a surveillance scan earlier than 6 months, similar as for cohort 1, could be considered.

In conclusion, this study has shown that FDG-PET/CT is useful for detecting early recurrence, especially within the first 6 months after surgery and therefore should be considered as tool for monitoring patients during follow-up. In addition, FDG-PET/CT prior to the start of adjuvant therapy is useful because it detects up to 9.5% of metastases post-operatively, leading to alterations in therapy.

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SUPPLEMENTARY MATERIAL

Staging

According to the 7th AJCC, stage IIIB is defined as a primary melanoma (a) with ulceration and less than four micrometastases in lymph nodes, (b) without ulceration and less than four macrometastases (clinically detectable nodal metastases) or (c) with in-transit metastases without nodal involvement. Stage IIIC is defined as a primary melanoma (a) with ulceration and with any number of macrometastases, (b) in-transit metastasis without nodal involvement or (c) with or without ulceration but with more than four nodal metastases or in-transit metastases and with any number of macroscopic involved lymph nodes.

According to the 8th AJCC, stage IIIB, IIIC and IIID are defined as all melanoma patients with micro- or macroscopic nodal involvement or in-transit metastases, except for either primary melanoma (a) with a Breslow thickness of less than 1.0 mm with or without ulceration or (b) with a Breslow thickness of less than 2.0 mm without ulceration and less than four microscopic nodal metastases (stage IIIA).

		Univariable analyses		
		OR	95 % CI	p-value
Sex	Male	1		
	Female	1.54	0.36 – 6.60	0.562
Mean age in years at surgery		0.95	0.89 – 1.03	0.228
Breslow thickness	≤1.0	1		
	>1.0 – 2.0	2.14	0.17 – 27.10	0.556
	> 2.0 – 4.0	2.14	0.17 – 27.10	0.556
	>4.0	10.0	0.40 – 250.42	0.161
	Unknown	5.0	0.34 – 72.77	0.239
Ulceration	Present	1		
	Absent	0.23	0.40 – 1.35	0.103
	Unknown	0.80	0.13 – 4.87	0.809
Substage (AJCC 7)	IIIB	1		
	IIIC	1.28	0.31 – 5.25	0.729
Surgery	Dissection (+ excision node pro diagnosi)	1		
	Resection ITM	0.89	0.19 – 4.11	0.880
	Dissection & resection ITM	2.0	0.22 – 17.89	0.535
Number of + N (in total) (n=	1	1		
	2	0.00	0.00	0.999
	3 or >3	1.00	0.12 – 8.31	1.000
Extracapsular nodes	No	1		
	Yes	1.22	0.16 – 9.47	0.848

Table S1. *Predictive factors for recurrence, estimated by univariable logistic regression analyses.*
Number of patients with recurrence = 12.
Number of patients without recurrence = 23.

		Univariable analyses		
		OR	95 % CI	p-value
Sex	Male	1		
	Female	0.33	0.02 – 4.74	0.417
Mean age in years at surgery		1.18	0.97 – 1.43	0.092
Breslow thickness	≤1.0	1.00	0.00	1.000
	>1.0 – 4.0	high	0.00	0.999
	>4.0	high	0.00	0.999
	Unknown	1		
Ulceration	Present	1		
	Absent	0.00	0.00	0.999
	Unknown	0.00	0.00	0.999
Substage (AJCC 7)	IIIB	1		
	IIIC	3.75	0.33 – 42.47	0.286
Surgery	Dissection (+ excision node pro diagnosi)	1		
	Resection ITM	3.00	0.19 – 47.96	0.437
	Dissection & resection ITM	1.00	0.04 – 24.55	1.000
Number of + N (in total)	1	1		
	2 or >2	2	0.09 – 44.35	0.661
Extracapsular nodes	No	1		
	Yes	0.67	0.03 – 18.06	0.810

Table S2. *Predictive factors for early (versus late) recurrence, estimated by univariable logistic regression analyses.*
Early recurrence = at 6months (n=7).
Late recurrence = at 12,18,24 or 36 months (n=5).