PET/CT to optimize treatment management of high-risk stage III and IV melanoma

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SECTION

Integration of [^{18}F]FDG PET/CT in Neoadjuvant and Postoperative Settings

CHAPTER 2

The Use of [^{18}F]FDG PET/CT to Detect Early Recurrence after Resection of High-Risk Stage III Melanoma

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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 fluorine-18 fluorodeoxyglucose positron emission Tomography / Computed Tomography ([^{18}F]FDG PET/CT) protocols in two cohorts.

Methods

Cohort 1 (n=35) focused on surveillance in asymptomatic patients (before approval and reimbursement of adjuvant therapy) and was assigned to 5x [^{18}F]FDG PET/CT's after surgery: one every 6 months for 2 years, with one final scan after 3 years. Cohort 2 (n=42) was assigned to one screening [^{18}F]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 [^{18}F]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

[^{18}F]FDG PET/CT is a valuable imaging tool to detect recurrence in stage III melanoma, even shortly after surgery. A surveillance [^{18}F]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 tumor tissue typically visualizes high glucose metabolism and is therefore easily detected by Fluorine-18 Fluorodeoxyglucose ([18F]FDG) Positron Emission Tomography / Computed Tomography (PET/CT). In a pilot study, Madu et al. examined the yield of a recently introduced [18F]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 [18F]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 [^{18}F]FDG PET/CT and Magnetic Resonance Imaging (MRI) of the brain after resection of disease (sentinel node for microscopic disease or lymph node dissection [LND] 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 analyze the role of [^{18}F]FDG PET/CT in detecting (early) recurrences after complete resection of advanced stage III melanoma. We aim to determine both the role of [^{18}F]FDG PET/CT as surveillance tool during follow-up, as well as before 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 **Supplemental 1**), entered follow-up and therefore the surveillance protocol between January 2015 and December 2017. All patients had already undergone an [^{18}F]FDG PET/CT and whole brain MRI, that showed no additional metastases, before 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 lactate dehydrogenase (LDH) (17). If patients stayed asymptomatic and S100B was within normal values, a surveillance [^{18}F]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 could have been made per patient, depending on when he or she entered the surveillance protocol, but patients had to undergo at least one [^{18}F]FDG PET/CT according to protocol in order to be included. Patients who received an [^{18}F]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 an [18F]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 [18F]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 [18F]FDG PET/CT scan prior to adjuvant therapy.

Subsequently, patients were followed up with contrast-enhanced CT (ceCT) or [18F]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 480mg every 4 weeks for 12 months or pembrolizumab 200mg every 3 weeks for 12 months). Patients with a BRAF mutation, could also be considered for treatment with the combination of dabrafenib (150mg trice daily) and trametinib (2mg once daily) for 12 months, which is according to Dutch guidelines.

Imaging

Whole body [18F]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 6 hours and adequate fluid intake, radioactive FDG was administered intravenously in a dosage of 180-240MBq, 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 min per bed position. Abnormal [18F]FDG accumulation was evaluated according to location, size and intensity.

The [18F]FDG PET/CT images were reviewed by an experienced nuclear medicine physician, after which the treating surgeon assessed the report, considering the clinical setting.

[18F]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 ceCT or MRI. In case of suspected recurrence on surveillance [18F]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 2 months of surveillance [18F]FDG PET/CT. When recurrence

was found by physical examination but not detected by imaging or when patients suffered recurrence within 2 months after the surveillance [^{18}F]FDG PET/CT, the scan was considered false negative (FN). Incidental findings that were not related to melanoma were reported and assessed as TN.

Statistics

Baseline characteristics were summarized using descriptive statistics. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (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

[^{18}F]FDG PET/CT in surveillance (cohort 1)

Eighty patients with 7th AJCC stage IIIB and IIIC melanoma entered the [^{18}F]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 an [^{18}F]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.

Table 1. Baseline characteristics of cohort 1 and 2.

	Cohort 1	**Cohort 2**
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	16 (46)	15 (36)
Trunk	12 (34)	15 (36)
Head/neck	1 (3)	11 (26)
Unknown primary	6 (17)	1 (2)
Type primary melanoma [n (%)]		
Superficial spreading	14 (40)	23 (55)
Nodular	7 (20)	7 (17)
Acrolentiginous	1 (3)	2 (5)
Naevoid	7 (20)	1 (2)
Unknown	6 (17)	8 (19)
Unknown primary		1 (2)

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Table 1. *[continued]*

	Cohort 1	Cohort 2
Breslow thickness, mm [n (%)]		
≤1.0	6 (17)	2 (5)
>1.0 – 2.0	10 (29)	7 (17)
>2.0 – 4.0	10 (29)	17 (41)
>4.0	3 (9)	14 (33)
Unknown	6 (17)	2 (5)
Ulceration [n (%)]		
Present	10 (29)	15 (36)
Absent	16 (44)	25 (60)
Unknown/unknown primary	9 (26)	2 (5)
Type of surgery [n (%)]		
WLE + sentinel lymph node biopsy	-	17 (41)
WLE + node dissection	-	7 (17)
Inguinal dissection	3 (9)	2 (5)
Iliacal dissection	-	1 (2)
Ilio-inguinal dissection	7 (20)	1 (2)
Axillary dissection	5 (14)	5 (12)
Neck dissection	1 (3)	4 (10)
Excision node pro diagnosi	2 (6)	-
Resection in-transit metastasis	13 (37)	4 (10)
Node dissection and resection ITM	4 (11)	1 (2)
AJCC stage, 7th edition [n (%)]		
IIIA	-	5 (12)
IIIB	16 (48)	19 (45)
IIIC	19 (54)	18 (43)
AJCC stage, 8th edition [n (%)]		
IIIB	15 (49)	13 (31)
IIIC	18 (51)	28 (67)
IIID	2 (6)	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)

Note: Percentages may not total 100 because of rounding. AJCC=American Joint Committee on Cancer; IQR=interquartile range; ITM=in-transit metastases; NA=not applicable; WLE=wide local excision.

The remaining 35 patients were included and received [18F]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, 12 patients (34.3%) developed a recurrence, seven (20.0%) of which were detected by the first scan (**Table 2**).

Table 2. Recurrences in cohort 1 and 2.

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

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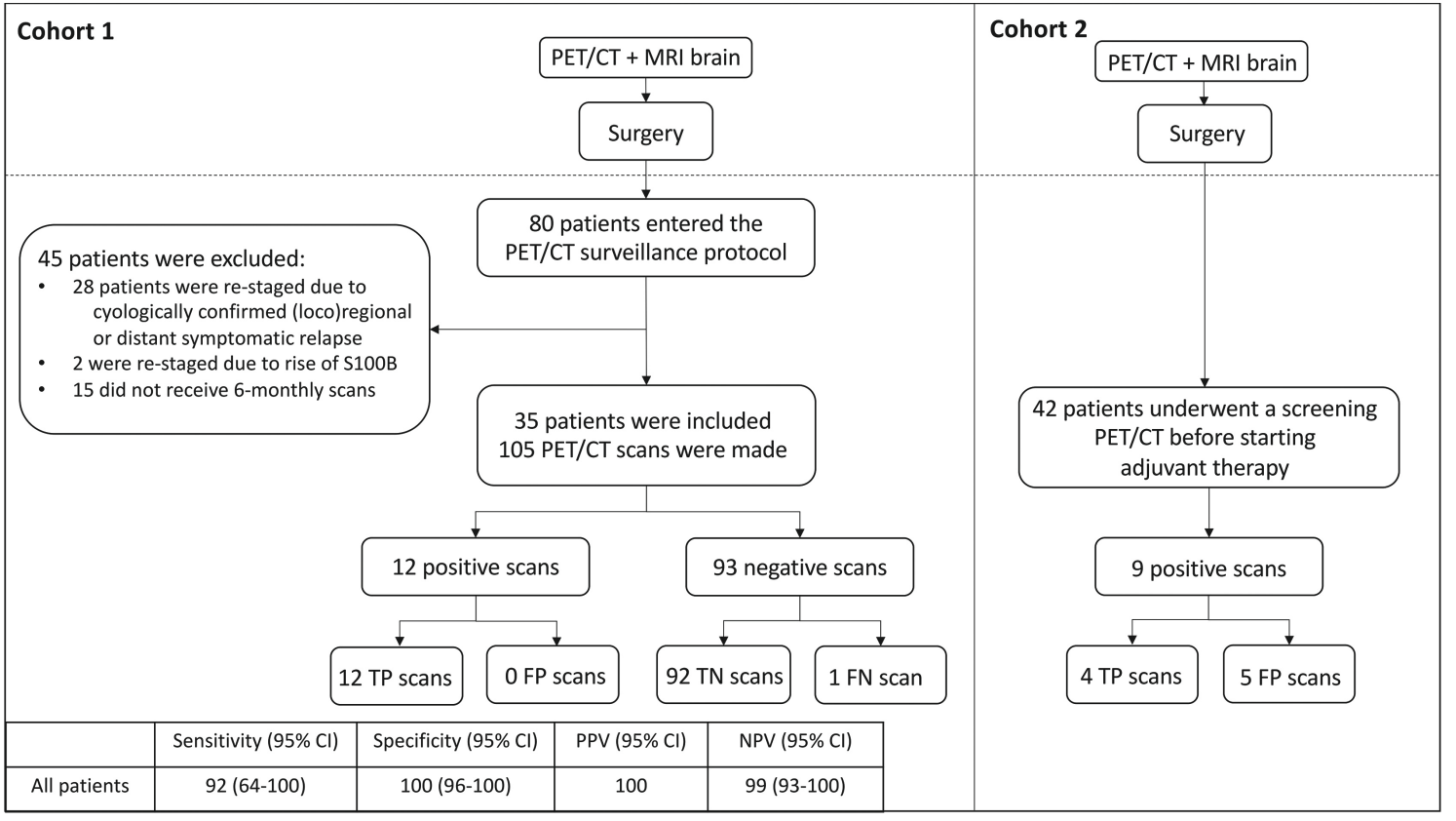
Table 2. *[continued]*

Cohort 2										
No.	M/F	Age	Stage (8th AJCC)	Surgery	Time PET/CT after surgery (days)	Type of 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 radiotherapy	63	Distant	Nivolumab	RT (spine), nivolumab, then switch to dabrafenib/ trametinib	PD
3	M	51	IIIC	Re-excision and LND followed by radiotherapy	117	Distant	Nivolumab	Nivolumab, then switch to ipilimumab	PD
4	F	64	IIIC	Re-excision and LND	120	Distant	Nivolumab	Nivolumab	CR

ITM=in-transit metastases; LND=lymph node dissection; NED=no evidence of disease; PD=progressive disease; CR=complete response; PR=partial response.



	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. *[^{18}F]FDG PET/CT imaging outcomes for cohort 1 and 2 and diagnostic test accuracy of [^{18}F]FDG PET/CT for cohort 1. CI=confidence interval; FN=false negative; FP=false positive; MRI=magnetic resonance imaging; NPV=negative predictive value; PPV=positive predictive value; TN=true negative; TP=true positive.*

Seven (58.3%) recurrences concerned stage IIIC patients and five (41.7%) stage IIIB patients. In eight [18F]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 [18F]FDG PET/CT scans were found to be FP. Ninety-two scans were TN and one scan was assessed FN because [18F]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 [18F]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) (**Supplementary Table S1** and **S2**).

[18F]FDG PET/CT for screening prior to adjuvant therapy (cohort 2)

Between December 2018 and May 2019, 42 patients underwent a screening [18F]FDG PET/CT before starting adjuvant therapy. Baseline characteristics of these patients are described in **Table 1**. Median time between surgery and [18F]FDG PET/CT was 6 weeks. Twenty patients (47.6%) were eligible for adjuvant therapy after complete 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 [18F]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.

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).

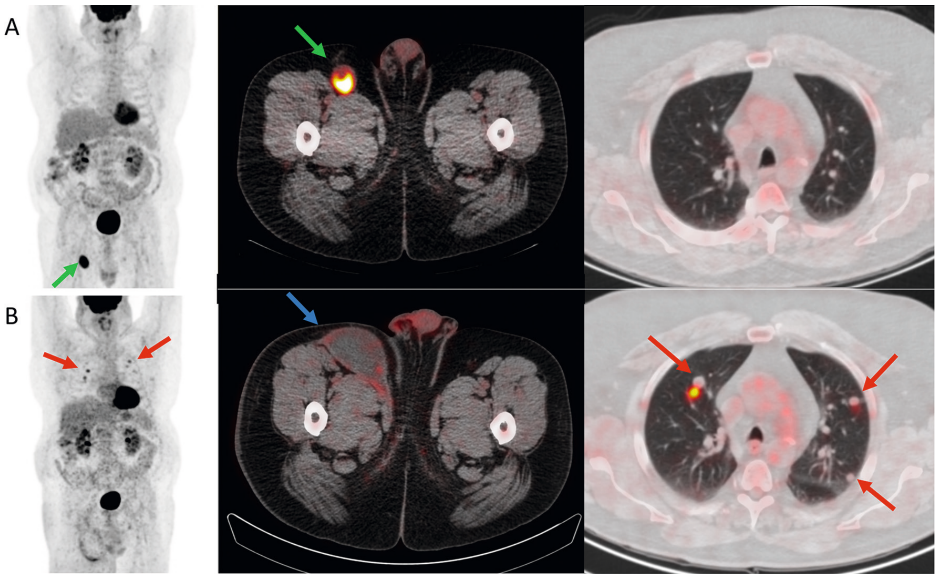


***Figure 2**. [¹⁸F]FDG PET/CT of a patient with recurrence in cohort 1: patient with previous melanoma of the right leg, presenting with stage IIIC disease. [¹⁸F]FDG PET/CT before inguinal lymph node dissection (A) shows a lymph node metastasis in the right groin (green arrow) and no evidence of disease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

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 [¹⁸F]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.

Recurrences during adjuvant therapy (cohort 2)

Eight patients (21.1%) of the remaining 38 with a negative [¹⁸F]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 [18F]FDG PET/CT and three by ceCT. In one patient S100B was rising and [18F]FDG PET/CT revealed wide spread metastases. The remaining two were found by physical examination.

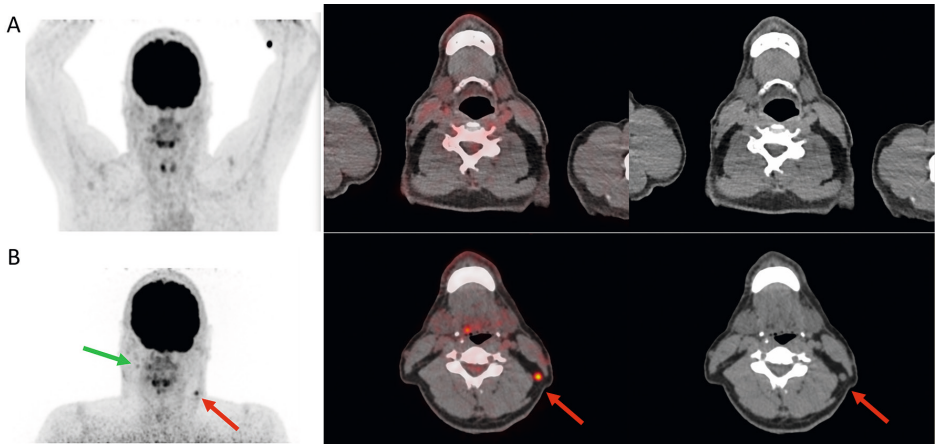


Figure 3. *[18F]FDG PET/CT of a patient with recurrence in cohort 2: stage IIIC melanoma of the scalp. [18F]FDG PET/CT before reexcision and sentinel lymph node procedure (A), with no signs of metastases in head/neck region or elsewhere in the body (not shown). [18F]FDG PET/CT before adjuvant therapy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

One patient developed a recurrence after the postoperative [18F]FDG PET/CT and before starting adjuvant therapy. The [18F]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 [18F]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 [18F]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. [18F]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 [18F]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 [^{18}F]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 [^{18}F]FDG PET/CT, we demonstrated that surveillance with 6-monthly [^{18}F]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 [^{18}F]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 (18-21). 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. (22). His group retrospectively reviewed patients with completely resected stage III/IV melanoma with at least one [^{18}F]FDG PET/CT performed within 1 year after surgery. They evaluated whether surveillance with [^{18}F]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 [^{18}F]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 (23). 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 [18F]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 more than 12 weeks. This was due to postsurgical 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 [18F]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 [18F]FDG PET/CT, which is very similar to ours (24). 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 (12). 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 (14, 16).

Although this study focused on one screening [18F]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 [18F]FDG PET/CT is useful for detecting early recurrence, especially within the first 6 months after surgery and therefore should be

considered as a tool for monitoring patients during follow-up. In addition, [^{18}F]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

Supplemental 1 - 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 metastases 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).

Table S1. Predictive factors for recurrence, estimated by univariable logistic regression analyses.

	Univariable analyses		
	OR	95% CI	P
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	5.00	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
Stage (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	2.00	0.22 – 17.89	0.535
Number of N+			
1	1		
2	0.0	0.00	0.999
3 or >3	1.00	0.12 – 8.31	1.000
Extracapsular			
No	1		
Yes	1.22	0.16 – 9.47	0.848

Number of patients with recurrence=12. Number of patients without recurrence=23.

Table S2. Predictive factors for early (versus late) recurrence, estimated by univariable logistic regression analyses.

	Univariable analyses		
	OR	95% CI	P
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		
>1.0 – 4.0	high	0.00	0.999
>4.0	high	0.00	0.999
Unknown	1.00	0.00	1.000
Ulceration			
Present	1		
Absent	0.00	0.00	0.999
Unknown	0.00	0.00	0.999
Stage (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+			
1	1		
2 or >2	2.00	0.09 – 44.35	0.661
Extracapsular			
No	1		
Yes	0.67	0.03 – 18.06	0.81

Early recurrence=at 6 months (n=7), late recurrence=at 12, 18, 24 or 36 months (n=5).