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

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CHAPTER 3

[^{18}F]FDG PET/CT During Neoadjuvant Targeted Therapy in Prior Unresectable Stage III Melanoma Patients: Can (Early) Metabolic Imaging Predict Histopathologic Response or Recurrence?

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ABSTRACT

Background

To investigate whether [^{18}F]FDG PET/CT can predict histopathological response or recurrence in BRAF-mutated unresectable locally advanced stage III melanoma treated with neoadjuvant BRAF/MEK inhibition followed by resection and the value of PET in detecting early recurrence after resection.

Methods

Twenty BRAF-mutated, unresectable stage III melanoma patients received BRAF/MEK inhibitors prior to surgery. [^{18}F]FDG PET/CT was performed at baseline and 2 and 8 weeks after initiation of therapy. After resection, PET/CT was performed at specific time points during 5 years follow-up. Pathological response was assessed on the dissection specimen. Response monitoring was measured with SUVmax, SUVpeak, MATV, and TLG and according to EORTC and PERCIST criteria.

Results

Pathologic response was assessed in 18 patients. Nine patients (50%) had a pathologic complete- or near-complete response (pCR/nearCR) and nine (50%) had a pathologic partial-or no response (pPR/NR). EORTC or PERCIST response measurements did not correspond with pathologic outcome. SUVmax, SUVpeak, MATV and TLG at all time points and absolute or percentage change between the three initial time points did not differ between the groups. During follow-up, eight out of 17 patients with R0 resection developed a recurrence, six recurrences were detected with imaging only, four of which with PET/CT in less than 6 months after surgery. PET parameters prior to surgery did not predict recurrence.

Conclusions

Baseline [^{18}F]FDG PET or PET response in previous unresectable stage III melanoma patients seems not usefull to predict pathologic response after neoadjuvant BRAF/MEK inhibitors treatment. However, PET/CT seems valuable in detecting recurrence early after R0 resection.

INTRODUCTION

In stage III/IV BRAF-mutated melanoma patients, targeted therapy with BRAF inhibitors has shown to induce significant levels of tumor shrinkage in the majority of patients, even shortly after treatment initiation. When combined with MEK inhibitors, even higher objective response rates of around 65% have been reported (1-4).

These impressive therapy responses have led to an increased interest in BRAF/MEK inhibitors as neoadjuvant systemic therapy (NAST), especially in borderline resectable or unresectable stage III or oligometastatic melanoma. Several studies have demonstrated encouraging results that sufficient downsizing of the tumor enables radical resection of previous unresectable locally advanced or oligometastatic disease (5-7). Despite these encouraging data, however, recurrences after radical surgery still occur.

The ability to predict recurrence prior to surgery could help to personalize patient monitoring after surgery. Furthermore, recurrent disease is preferably detected at an early stage. Indeed, at this phase, the tumor is either still resectable or the tumor burden is still low, resulting in better efficacy of immuno- and targeted therapies which could benefit patients' survival.

In melanoma patients treated with neoadjuvant BRAF/MEK inhibition the degree of pathologic response depends on the response pattern found in the histologic specimen and varies from pathologic complete response (pCR) to pathologic partial response(pPR) or pathologic no response (pNR) (8). These histopathologic response patterns seem a predictive biomarker for relapse-free survival (RFS) in these patients, where the extent and histopathologic features of the response following neoadjuvant BRAF/MEK inhibitors correlates with RFS (9). In the recently published NeoCombi-trial, in which 35 BRAF-mutated stage IIIB or IIIC (AJCC 7th ed.) melanoma patients received neoadjuvant and adjuvant dabrafenib and trametinib, pCR was associated with an improved prognosis compared to patients without a pCR (10). Similar results were shown in the study of Eroglu et al. in which patients with a pCR had a significantly improved RFS and overall survival (OS) compared to patients with residual viable tumor (11).

Metabolic imaging with 18F-Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography ([18F]FDG PET/CT) is a non-invasive imaging technique that shows a homogeneous and rapid decrease of glucose metabolism in melanoma metastases treated with BRAF targeted therapy (12). Since these metabolic alterations occur even shortly after the initiation of therapy, [18F]FDG PET/CT imaging might be predictive for pathologic response. Furthermore, since metabolic alterations often are the first sign of recurrent disease, [18F]FDG PET/CT could be of value to detect early recurrence. With this study we aim to investigate whether [18F]FDG PET/CT prior to- and during treatment with BRAF/MEK inhibitors dabrafenib and trametinib in high-risk unresectable stage

III melanoma can predict histopathologic response or recurrence. Secondly, we aim to investigate the additive value of PET to detect early recurrence after surgery.

PATIENTS AND METHODS

Patients

This study was designed as a side study of the Reductor trial (EudraCT no. 2013-002616-28), which was a prospective, single arm, phase II study to investigate the ability to achieve R0 resection after neoadjuvant treatment with BRAF/MEK inhibitors in patients with prior inoperable BRAF-mutated stage III or oligometastatic stage IV cutaneous melanoma (7). Patients were treated with neoadjuvant dabrafenib 150mg twice daily and trametinib 2mg once daily for a period of 8 weeks. In case of sufficient downsizing of the tumor as defined by a multidisciplinary board and without occurrence of new lesions, surgical resection was planned within 2 to 3 weeks. Dabrafenib and trametinib were continued until surgery. Patients were assigned to two groups based on histopathological outcome: (1) pathologic complete- or near-complete response (pCR/nearCR) and (2) pathologic partial- or no response (pPR/NR). Patients with R0 resection and no evidence of disease elsewhere were monitored for recurrence.

[^{18}F]FDG PET/CT

All patients underwent [^{18}F]FDG PET/CT at baseline as part of the staging procedure, 2 weeks after starting neoadjuvant therapy (early), and at 8 weeks (late), the latter being within 2 to 3 weeks prior to surgical resection. [^{18}F]FDG was administered intravenously with an activity of 180-240MBq (4.9- 6.5 mCi) depending on body mass index, after fasting for 6 hours and 400mL fluid intake. Approximately 60 minutes after administration low-dose CT images (40 mAs, 140 keV, 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. Patients were scanned on a cross-calibrated Phillips Gemini TF 16 or Phillips Gemini TF big-bore PET/CT scanner (Philips, Cleveland, USA). The [^{18}F]FDG PET/CT images were reviewed by experienced nuclear medicine physicians using a commercially available software package (OsiriX MD, Pixmeo Sarl, version 12.0.1). Semi-quantitative PET/CT analysis was performed according to the EORTC and PERCIST criteria (13, 14). The total tumor burden was delineated by a threshold of 50%SUVmax, 41%SUVmax, SUVmax2.5, and SUVmax4.0. Each voxel included in at least three delineations was taken into account for further analysis (14, 15). Quantitative PET/CT analysis of the total tumor burden was performed using Accurate (v06-07-2019, developed by professor R. Boellaard et al.). Data were normalized for patient body weight and injected dose. Tumor maximum, mean, and peak Standardized Uptake Values (SUVmax, SUVmean, SUVpeak), Metabolic Activity Tumor Volume (MATV), and Total Lesion Glycolysis (TLG, defined as SUVmean x MATV) of the total tumor burden were measured. Metabolic response was calculated by measuring early and late absolute and percentage changes in relation to baseline.

Surgery and histopathologic response analysis

Surgery was performed by experienced melanoma surgeons and consisted of lymph node dissection of the involved metastatic area. Histopathologic response assessment in the resected specimen was performed by an experienced melanoma pathologist. Histopathologic response was graded according to guidelines published by Tetzlaff et al. (8): pathologic complete response (pCR) in case of complete absence of viable tumor cells, near-complete response (nearCR) if 0-≤10% of viable tumor cells were observed, pathologic partial response (pPR) when >10-≤50% is occupied by viable tumor cells and pathologic no response (pNR) when >50% viable tumor cells were observed. pCR/nearCR and pPR/NR were analyzed as two separate groups for the purpose of this current study.

Follow-up

Recurrence-free survival (RFS) after surgery was assessed every 3 months by physical examination and imaging with [18F]FDG PET/CT for 2 years, then every 6 months for 2 years, and once in year 5. PET/CT was considered true positive when patients had a recurrence which was either confirmed with pathology or sequential imaging with contrast-enhanced CT or MRI.

Statistical analysis

Baseline patient and tumor characteristics were recorded and summarized, quantitative values are expressed as mean (range). For analysis of baseline PET characteristics and quantified PET parameters, the Shapiro-Wilk test was used to test normality of distribution between pCR/nearCR and pPR/NR groups, and between the recurrence and non-recurrence groups. The independent T-test was used in case values were normally distributed, the nonparametric Mann-Whitney U test was used when values were not normally distributed. A P-value smaller than or equal to 0.05 was considered statistically significant. Quantified PET parameters were described as median and Interquartile Range [IQR]. Sensitivity, specificity, positive and negative predictive value of [18F]FDG PET/CT were calculated. Statistical analysis was performed by using SPSS (IBM,v.22.0, NY, USA). RFS was defined as the time interval between the date of surgical resection and the date that recurrence was identified by imaging or clinical examination during the follow-up period.

RESULTS

Study population

From August 2014 to March 2019, 21 patients with unresectable locally advanced stage IIIC (AJCC 7th edition) melanoma were included in the Reductor trial (7). In one patient treatment response was not monitored with PET/CT for unknown reasons, one patient did not proceed to surgery due to progressive disease and in one patient resection turned out unfeasible intraoperatively due to encasement of vital structures.

Table 1. Patient demographics and imaging characteristics.

	Total	pCR/nearCR	pPR/NR	P
Number of patients	18	9	9	
Male/female	11/7	4/5	7/2	
Age in years (mean, (range))	52 (25-76)	56 (39-76)	47 (25-73)	
Stage IIIC AJCC 7th edition	18	9	9	
Location primary				
Extremity	6	4	2	
Trunk	3	1	2	
Unknown primary	9	4	5	
Breslow thickness				
≤1.0 mm	0	0	0	
>1.0–2.0 mm	5	4	1	
>2.0–4.0 mm	1	0	1	
>4.0 mm	1	0	1	
Unknown primary	9	4	5	
Unknown	2	1	1	
Ulceration				
Yes	2	1	1	
No	7	4	3	
Unknown	9	4	5	
Site locoregional metastases				
Axillary LN	9	3	6	
Axillary with cervical LN	5	4	1	
Inguinal with iliac LN	2	1	1	
Iliac LN	2	1	1	
No. of lymph nodes resected				
0-10	2	1	1	
11-20	5	2	3	
21-30	5	3	2	
>30	5	3	2	
NA	1	0	1	
Size largest lnn metastasis				
≤6.0 mm	2	0	2	
>6.0-8.0 mm	10	7	3	
>8.0 mm	5	2	3	
Unknown	1	0	1	
Timeframe in days (mean, (range)):				
PET_{bl} to Start therapy	20.17 (2-49)	24.44 (3-49)	15.89 (2-28)	0.206*
Start therapy to PET_{2weeks}	15.24 (12-19)	15.67 (12-19)	14.75 (13-18)	0.420*
Start therapy to PET_{8weeks}	56.56 (49-67)	55.33 (49-61)	57.78 (53-67)	0.208*
PET_{8weeks} to surgery	9.44 (2-18)	9.56 (3-18)	9.33 (2-17)	0.935*
R0 resection and NED elsewhere, n=17, mo (median (range))				
Time of follow-up	36 (10-61)			
Time to recurrence (n=8)	6 (3-9)			

*Independent T-test. pCR/nearCR=pathologic complete response/near-complete response; pPR/NR=pathologic partial response/no response; NED=no evidence of disease; mo=months.

Therefore, pathology response was assessed in 18 dissection specimens. The site of the regional metastases dissected was axillary (n=9), axillary and cervical (n=5), iliac (n=2), or inguinal and iliac (n=2). In one patient the resected specimen revealed tumor positive microscopic resection margins (R1). Recurrence was evaluated in the remaining 17 patients with R0 resection and no evidence of disease elsewhere in the body. Median follow-up after surgery was 36 months (range 10-61 months). Patient demographics are listed in **Table 1**.

Metabolic response evaluation

Baseline and late [18F]FDG PET/CT at 8 weeks were performed in all patients and the early [18F]FDG PET/CT at 2 weeks was performed in 17/18 (94%) patients. Median time between baseline [18F]FDG PET/CT and start neoadjuvant therapy was 20 days (range 2-49 days), and between start neoadjuvant therapy and early [18F]FDG PET/CT and late [18F]FDG PET/CT 15 days (range 12-19 days) and 57 days (range 49-67 days), respectively. Median time between late [18F]FDG PET/CT and surgery was 9 days (range 2-18 days) (**Table 1**).

Semi-quantitative analysis according to EORTC criteria classified 4/18 (22%) patients as metabolic complete responders (CMR), 12/18 (67%) as metabolic partial responders (PMR) and one (6%) patient as progressive metabolic disease (PMD) based on the presence of new lesions. These outcomes were the same when classifying according to PERCIST, except for one patient who was classified as stable metabolic disease (SMD) with PERCIST instead of PMR with EORTC criteria.

Median SUVmax, SUVpeak, MATV, and TLG of the total group at baseline and early and late scan are displayed in the **Supplementary Table S1**. The results show a decrease of all quantitative PET parameters during treatment compared to baseline, already measurable at the early scan. Furthermore, the largest decrease for all parameters occurred between baseline and 2 weeks.

[18F]FDG PET/CT parameters in relation to histopathological response

Histopathologic evaluation of the resected specimens revealed pCR/nearCR in 9/18 (50%) specimens and pPR/NR in 9/18 (50%). EORTC or PERCIST response measurements did not correspond with pathologic outcome. Only 1/6 (17%) patients with pCR was classified as CMR on PET/CT (EORTC and PERCIST). All eight patients with pathologic nearCR or pPR were classified as PMR. Four patients with pNR were also classified as PMR on PET, three of which with only minimal residual uptake in the remaining lymph node metastases.

At baseline, median SUVmax in the pCR/nearCR group was 17.8 [IQR 12.3-21.6] and in the pPR/NR group 16.1 [IQR 11.3-23.6, P=0.931] (**Supplementary Table S1**). Median SUVpeak was 13.7 [IQR 10.0-18.8] in the pCR/nearCR group and 12.6 [IQR 8.4-18.9, P=0.863] in the pPR/NR group.

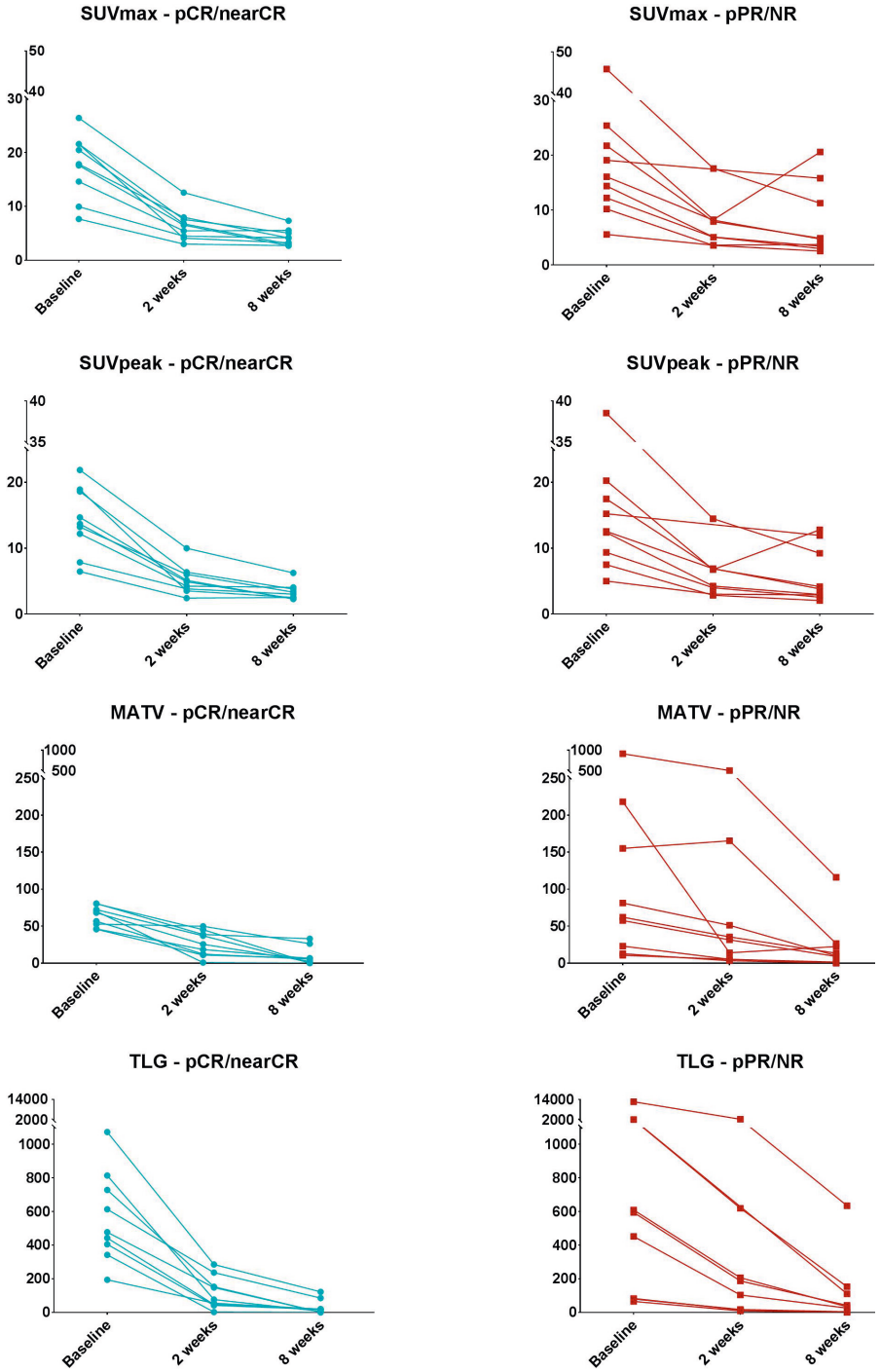

Figure 1. *Absolute changes of PET parameters per patient from baseline. SUV=standardized uptake value; MATV=metabolic activity tumor volume; TLG=total lesion glycolysis.*

Similarly to SUVmax and SUVpeak, the median MATV and TLG at baseline did not differ significantly between the pCR/nearCR group and pPR/NR group. However, with regard to MATV at baseline, three patients had an MATV between 155-914cc, compared to the other 15, who had an MATV ranged between 10-81cc. All three patients with high MATV had pPR/NR.

Absolute and percentage changes of SUVmax, SUVmean, MATV, and TLG are shown in **Figure 1 and 2**. In the pCR/nearCR group, after the first 2 weeks of treatment a decrease of SUVmax and SUVpeak was seen of 63% [IQR 55-66%] and 64% [IQR 54-66%], respectively. This was not significantly different from the pPR/NR group in which the decrease of SUVmax was 63% ([IQR 24-65%], P=0.888) and of SUVpeak 61% ([IQR 50-65], P=0.423). As with SUV, MATV also showed a large decrease (60%, [IQR 46-77]) in both the pCR/nearCR and the pPR/NR groups (45%, [IQR 40-84]), though not significantly different (P=0.436). At 8 weeks after the initiation of treatment, a smaller but further decrease of SUVmax, SUVmean, MATV, and TLG was seen in both pCR/nearCR and pPR/NR groups. Neither of the parameters were significantly different between the two groups.

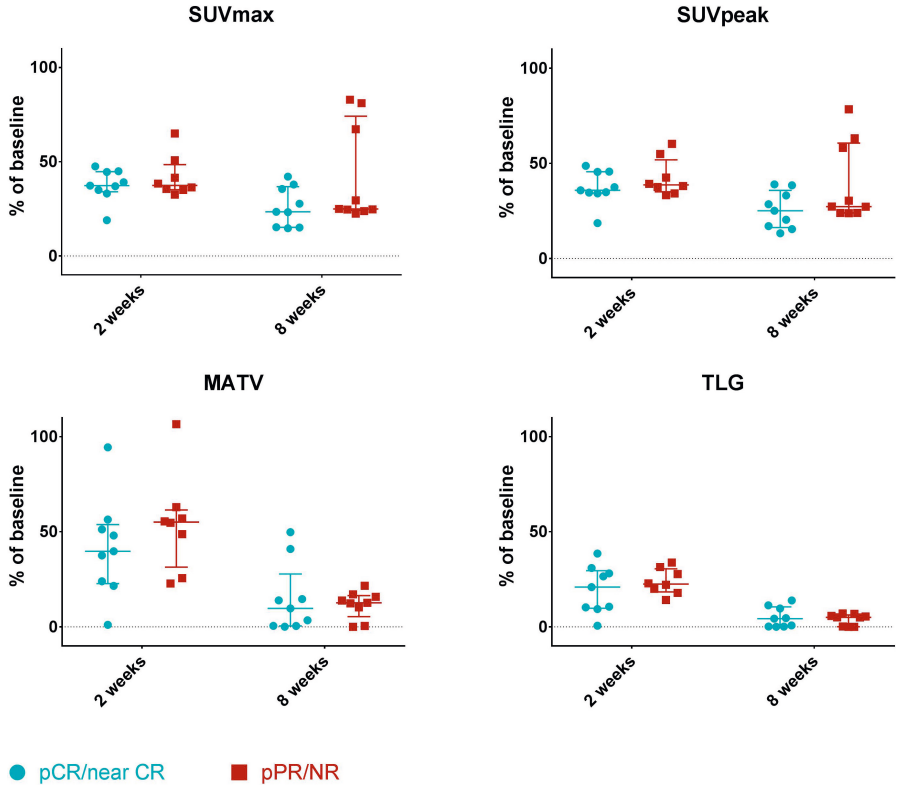

Figure 2. *Median and interquartile range percentage changes of PET parameters from baseline. SUV=standardized uptake value; MATV=metabolic activity tumor volume; TLG=total lesion glycolysis.*

Figure 3 shows the [18F]FDG PET/CT scans of a patient (A) with a pCR in the histopathologic specimen after resection with still significant uptake of [18F]FDG PET/CT at 8 weeks. The histopathologic specimen of this patient showed predominantly lymphoid hyperplasia in addition to widespread necrosis and melanosis. On the contrary, one of the patients (B) showed only faint uptake of [18F]FDG at week 8 and the histologic specimen after surgery revealed partial response (10-15% viable tumor cells).

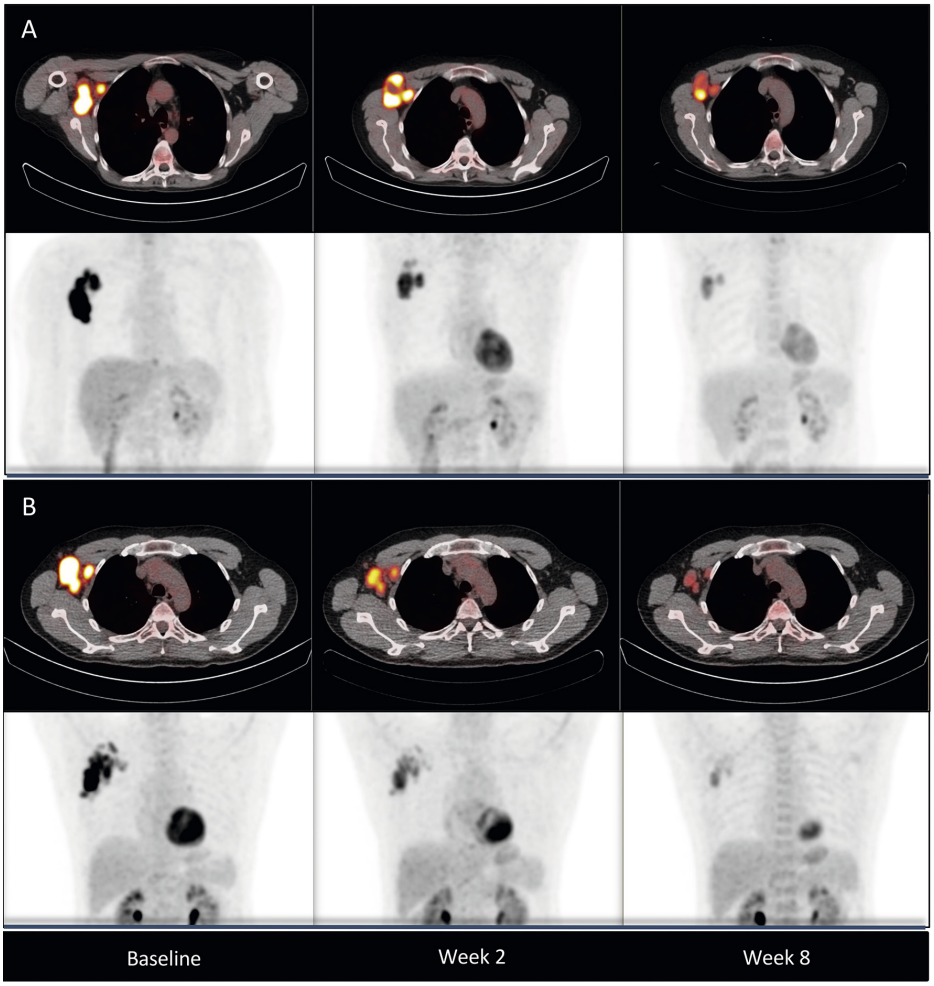

Figure 3. *[18F]FDG PET/CT transaxial fused and maximum intensity projection (MIP) images at baseline and 2 and 8 weeks after starting BRAF/MEK inhibitors. Lymph node dissection of the axilla after week 8 revealed a complete response in the histologic specimen of patient A, whereas the histologic specimen of patient B showed a partial response.*

In general, patients showed a substantial decrease of [18F]FDG uptake. However, in some patients a deviant course was seen. In three patients in the pPR/NR group SUVmax and SUVpeak was relatively high at 8 weeks as compared to baseline. Patient

#8 already had a low SUVmax and SUVpeak at baseline (5.6 and 5.0 respectively), resulting in a relatively low percentage change at 2 and 8 weeks. Patient #12 had a significant metabolic volume reduction (218cc at baseline to 22cc at 8 weeks), however the [18F]FDG avidity after 8 weeks was still quite high in the remaining tumor volume (SUVmax 15.8, SUVpeak 11.9 versus 19.1 and 15.3 at baseline respectively). Patient #13 had large bulky disease at baseline (MATV 155cc), which after 2 weeks of therapy responded with a decrease in FDG-avidity but no response in MATV. [18F]FDG uptake at 8 weeks was decreased compared to baseline with additional decrease of tumor burden on CT, which was confirmed with partial response in the histopathologic specimen. However, compared to [18F]FDG PET/CT at 2 weeks, at 8 weeks an increase of [18F]FDG avidity in several lymph nodes was seen, resulting in a high SUVmax and SUVpeak and indicating progressive disease.

In the pCR/nearCR group, patient #9 had a fast reduction of [18F]FDG avidity after 2 weeks, but no significant changes in tumour shrinkage, resulting in a relatively high MATV after 2 weeks, but a low SUVmax and SUVpeak.

Recurrence

In eight (47%) patients recurrence occurred with a median time to recurrence of 6 months (range 3-9 months). One patient suffered locoregional recurrence, being a new subcutaneous metastasis in the scar tissue. Three patients had recurrence in regional lymph nodes and four patients had distant metastases as a first presentation of relapse.

SUVmax, SUVpeak, MATV, and TLG at baseline, 2 weeks, or 8 weeks were not significantly different between the recurrence and non-recurrence group, nor were absolute or percentage decrease of PET parameters between the different time points (**Supplementary Table S1**). The histopathologic response after initial surgery prior to recurrence was as follows: CR n=1, nearCR n=2, PR n=2, and NR n=3 (**Table 2**). In five out of nine patients that did not develop recurrence during follow-up, CR after surgery was seen (CR n=5, nearCR n=1, PR n=2 and NR n=1).

In all eight patients with recurrent disease, recurrence was detected with [18F]FDG PET/CT, three of which as early as 3-4 months after surgery. In 2/8 (25%) patients, recurrence was first detected with physical examination at 4 and 9 months respectively. [18F]FDG PET/CT performed shortly thereafter confirmed local recurrence in both patients and in one of them additional wide spread metastases in lungs, liver and bone. In two patients, ceCT was performed for surveillance instead of [18F]FDG PET/CT for unknown reasons. The ceCT revealed recurrence at 9 months in both patients, being a new pulmonary metastasis and locoregional lymph node metastases respectively. In both patients, the recurrences were [18F]FDG-avid on PET/CT which was performed shortly thereafter to rule out other sites of disease.

Table 2. Recurrence in patients with R0 resection and no evidence of disease elsewhere at time of resection.

No.	M/F	Age	Surgery	PA response	Interval surgery-recurrence, mo	Type of recurrence	Diagnostic modality
1	F	53	Axillary and cervical LND	CR	3	Distant, breast	PET/CT
2	M	73	Axillary LND	NR	4	Regional, lnn	PET/CT
3	F	59	Inguinal and iliac LND	NR	4	Distant, brain, lung, liver, bone	Clinical examination, PET/CT
4	F	53	Inguinal and iliac LND	nearCR	6	Distant, intramuscular	PET/CT
5	M	51	Axillary LND	PR	7	Regional, lnn	PET/CT
6	M	76	Axillary and cervical LND	nearCR	8	Regional, lnn	ceCT, PET/CT
7	M	47	Iliac LND	NR	9	Locoregional, subcutaneous	Clinical examination, PET/CT
8	M	25	Axillary LND	PR	9	Distant, lung	ceCT, PET/CT

LND=lymph node dissection; CR=complete response; PR=partial response; NR=no response; Lnn=lymph nodes; ceCT=contrast enhanced CT.

[18F]FDG PET/CT during follow-up

During follow-up, a total of 95 [18F]FDG PET/CT scans were performed in 15 patients. Eight scans were true positive, one of which recurrence was confirmed by physical examination the same day. Four scans could not distinguish between postoperative inflammation or residual disease even up to 3 months after surgery. Five scans were false positive and revealed uptake in lymph nodes (2), the thyroid gland (1), nasopharyngeal region (1), and bone (1). All findings were negative for metastases after additional imaging with ultrasound and fine needle aspiration or MRI. Sensitivity and specificity were 100% and 94.3% respectively, with a positive predictive value of 61.5% and a negative predictive value of 100%.

Incidental findings were found in two patients, being liver steatosis, a benign thyroid nodule, and sarcoidosis in one patient and gastritis in another patient.

DISCUSSION

In patients with locally advanced stage III BRAFV600-mutated melanoma, neoadjuvant targeted therapy enables complete resection (R0) of previous borderline resectable and unresectable disease, resulting in better patient prognosis (5-7). Even so, recurrences still occur and histopathologic response of the resected specimen might be a predictor for recurrence-free survival in these patients. Since glucose uptake on [18F]FDG PET/CT changes rapidly after starting targeted therapy, non-invasive early metabolic imaging with PET/CT might be able to predict pathologic response or recurrence.

In this prospective study, we measured total tumor burden SUVmax, SUVpeak, MATV, and TLG on [18F]FDG PET/CT to investigate whether absolute uptake at baseline or (early) changes after starting neoadjuvant therapy could distinguish pathologic complete- or near-complete responders from pathologic partial- or non-responders. The same parameters were used to predict the appearance of recurrence.

In this study, nine out of 18 patients had pCR or nearCR, but neither baseline PET parameters nor absolute or percentage changes from baseline to 2 or 8 weeks could predict histopathologic response. Similarly, in the 8/17 patients with R0 resection who developed a recurrence, PET parameters could not predict recurrence. However, in the follow-up after surgery [18F]FDG PET/CT could detect all recurrences, and as early as 3 months after surgery. To our knowledge, no other studies are known in which PET is investigated as a predictive biomarker for pathologic response in melanoma patients treated with BRAF/MEK inhibition.

For pathologic response assessment we used the consensus guidelines presented by the International Neoadjuvant Melanoma Consortium (8), which classifies histopathologic response as complete, near-complete, partial or no response. In our

study, we investigated PET parameters in two groups; pCR/nearCR and pPR/NR. This has also been used by other NAST studies (16, 17).

It is questionable whether RECIST can predict pathologic response, since radiologic partial responses on BRAF-targeted therapy may actually have minimal to no viable malignant cells in residual masses seen on imaging. Therefore, it has been suggested that metabolic imaging with serial PET scanning might be a better predictor for response (18). Despite this hypothesis, in our study PET parameters could not distinguish pathologic complete- or near-complete responders from partial- or non-responders. An explanation could be that metabolic response on [^{18}F]FDG PET/CT is masked by T-cell infiltrates, which is a known phenomenon mimicking tumor metabolism, or the occurrence of cell volume reduction and increased intercellular distance rather than cell death, as presented in a study by Theodosakis et al (19).

Though we did not find a correlation between [^{18}F]FDG response and pathologic response, some other interesting findings were found. As already shown by McArthur et al, we found the biggest decline of [^{18}F]FDG uptake in the first 2 weeks after starting BRAF/MEK inhibition (12). An advantage of performing a scan early after the initiation of therapy could be the early identification of resistance as was demonstrated in one patient. In this patient, [^{18}F]FDG PET/CT at 8 weeks revealed metabolic response compared to baseline, but an increase in FDG-avidity compared to the [^{18}F]FDG PET/CT at 2 weeks, suggesting resistance to therapy. Without the [^{18}F]FDG PET/CT at 2 weeks, progressive disease could not have been discovered this early. Another potential interesting finding in our study was that in patients with a large tumor burden, an MATV higher than 150cc, no pCR/nearCR was achieved. Though the number of patients was too low to draw any significant conclusions, this might suggest the presence of a certain threshold of MATV above which pathologic CR/nearCR cannot be achieved.

In both the recurrence and non-recurrence group pathologic response varied. Even so, in the non-recurrence group more patients with pCR were seen than in the recurrence group (5/9 (56%) vs 1/8 (17%)). These results are in line with the INMC pooled analysis of Menzies et al, in which pCR after anti-PD1-based immunotherapy or BRAF/MEK targeted therapy correlated with relapse-free survival (17).

Preoperative [^{18}F]FDG PET/CT was not predictive for recurrence, which developed within 3-9 months after surgery. However, during follow-up, all recurrences were found with [^{18}F]FDG PET/CT, two (25%) of which within 3 months. This is in line with the study of Stahlie et al., in which [^{18}F]FDG PET/CT detected early recurrence in 20% of patients who were included in a surveillance protocol after R0 resection of high-risk melanoma (20). The strength of [^{18}F]FDG PET/CT in relation to recurrent disease therefore might lie in early detection after surgery rather than being predictive before surgery. Though it is known that [^{18}F]FDG PET/CT is less accurate in detecting locoregional recurrences,

the value of [18F]FDG PET/CT lies in the high sensitivity for early detection of distant metastases increasing the chance that local therapies with curative intent are still possible. In our study, [18F]FDG PET/CT revealed three early recurrences with distant metastases at 3, 4 and 6 months respectively. One of these recurrences revealed a subcutaneous metastasis by physical examination, but [18F]FDG PET/CT showed widespread disease in lungs, liver and bone. This emphasizes the value of [18F]FDG PET/CT not only as a tool for early detection of recurrence, but also for determining the extend of disease and therefore therapeutic options.

A limitation of our study is the small number of patients included. Accrual rate for the Reductor trail was slower than expected due to a combination of the specific patient population, BRAF/MEKi availability for unresectable stage III melanoma patients outside of clinical trials and the changing landscape with adjuvant systemic therapy as the new standard of care.

In conclusion, in this prospective study SUVmax, SUVpeak, MATV, and TLG on [18F]FDG PET/CT at baseline and during neoadjuvant targeted therapy could not predict pathologic response or recurrence in patients with unresectable stage IIIc BRAFV600-mutated melanoma, but a high MATV might suggest pCR/nearCR cannot be achieved. Furthermore, in the follow-up after R0 resection [18F]FDG PET/CT seems valuable in early detection of recurrence.

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SUPPLEMENTARY

Table S1. PET tumor measurements.

		Total (n=18)	pCR/nearCR (n=9)
Parameter	**Time-point**	***Median (range)***	***Median (IQR 25-75%)***
SUVmax	BL	17.7 (5.6-45.8)	17.8 (12.3-21.6)
	2 wks	6.5 (3.0-17.6)	6.5 (4.3-7.8)
	8 wks	4.2 (2.6-20.6)	4.2 (2.9-5.3)
	Δ BL – 2wks (absolute)	9.9 (2.0-28.2)	11.1 (7.3-13.9)
	Δ BL – 2wks (%)	63 (35-81)	63 (55-66)
	Δ BL – 8 wks (absolute)	11.2 (1.8-34.6)	14.9 (7.4-17.9)
	Δ BL – 8 wks (%)	75 (17-85)	77 (63-85)
	Δ 2 wks – 8 wks (absolute)	2.1 (-12.3-6.3)	2.5 (0.3-3.8)
	Δ 2 wks – 8 wks (%)	33 (-149-59)	33 (8-52)
SUVpeak	BL	13.5 (5.0-38.6)	13.7 (10.0-18.8)
	2 wks	4.9 (2.4-14.5)	4.9 (3.8-6.2)
	8 wks	3.2 (2.0-12.8)	3.0 (2.4-3.9)
	Δ BL – 2wks (absolute)	8.1 (2.0-24.1)	8.8 (5.6-12.1)
	Δ BL – 2wks (%)	62 (40-81)	64 (54-66)
	Δ BL – 8 wks (absolute)	9.1 (2.1-29.3)	11.4 (6.5-15.2)
	Δ BL – 8 wks (%)	73 (22-87)	75 (64-84)
	Δ 2 wks – 8 wks (absolute)	1.4 (-6.1-5.3)	2.6 (0.5-2.8)
	Δ 2 wks – 8 wks (%)	36 (-90-56)	38 (13-49)
MATV	BL	65.1 (10.6-913.9)	68.1 (50.0-76.2)
	2 wks	28.5 (0.8-507.1)	25.6 (11.6-42.0)
	8 wks	6.6 (0.0-116.0)	5.5 (0.4-16.5)
	Δ BL – 2wks (absolute)	32.5 (-10.2-406.78)	35.2 (31.4-43.5)
	Δ BL – 2wks (%)	52 (-7-99)	60 (46-77)
	Δ BL – 8 wks (absolute)	50.0 (9.2-798.0)	51.2 (39.5-71.0)
	Δ BL – 8 wks (%)	87 (39-100)	90 (72-99)
	Δ 2 wks – 8 wks (absolute)	17.0 (-8.4-391.1)	12.0 (5.0-30.1)
	Δ 2 wks – 8 wks (%)	74 (-60-100)	65 (43-95)
TLG	BL	535.4 (65.3-12676.1)	476.6 (373.1-770.7)
	2 wks	103.4 (2.1-2537.0)	76.2 (44.3-194.4)
	8 wks	23.1 (0.0-634.2)	17.6 (0.9-52.7)
	Δ BL – 2wks (absolute)	376.5 (56.1-10139.0)	376.5 (334.3-656.4)
	Δ BL – 2wks (%)	78 (61-99)	79 (70-90)
	Δ BL – 8 wks (absolute)	501.8 (65.2-12041.9)	475.7 (364.3-767.0)
	Δ BL – 8 wks (%)	95 (67-100)	96 (89-100)
	Δ 2 wks – 8 wks (absolute)	77.5 (1.9-1902.9)	69.7 (25.4-151.3)
	Δ 2 wks – 8 wks (%)	77 (75-100)	66 (57-95)

pCR/nearCR=pathologic complete response/near-complete response; pPR/NR=pathologic partial response/no response; SUV=standardized uptake value; MATV=metabolic activity tumor volume; TLG=total lesion glycolysis; Δ=change; BL=baseline; wks=weeks.

pPR/NR (n=9)		R0 resection and Recurrence (n=8)	R0 resection and No Recurrence (n=9)	
Median (IQR 25-75%)	P	*Median (IQR 25-75%)*	*Median (IQR 25-75%)*	P
16.1 (11.3-23.6)	0.931	16.2 (12.8-21.4)	17.6 (10.1-21.6)	0.963
6.5 (3.9-8.2)	0.743	6.1 (5.1-7.9)	5.5 (3.7-8.0)	0.505
4.7 (3.2-13.6)	0.436	4.0 (3.1-5.4)	4.2 (2.7-6.2)	0.815
8.6 (6.8-16.3)	0.743	9.6 (7.7-13.8)	9.5 (5.8-14.0)	0.959
63 (52-65)	0.888	62 (56-64)	62 (53-65)	0.959
9.2 (4.0-14.1)	0.222	12.3 (9.1-17.3)	11.4 (5.3-17.4)	0.743
75 (26-76)	0.190	76 (65-77)	72 (61-81)	0.481
1.8 (-0.1-3.3)	0.673	2.5 (0.4-3.8)	1.8 (0.4-3.7)	0.959
35 (-3-40)	0.541	37 (7-46)	31 (12-42)	0.959
12.6 (8.4-18.9)	0.863	12.8 (10.1-16.5)	14.7 (7.7-18.8)	0.743
5.5 (3.1-6.9)	0.606	4.6 (4.0-6.7)	4.5 (3.0-6.8)	0.645
3.8 (2.7-10.6)	0.258	3.1 (2.6-4.1)	3.0 (2.4-5.0)	0.673
6.9 (4.8-12.8)	0.815	8.1 (5.8-10.2)	7.6 (4.2-12.2)	1.000
61 (50-65)	0.423	62 (55-65)	62 (52-66)	0.878
7.5 (4.4-11.4)	0.258	9.7 (7.2-12.8)	8.7 (4.4-15.2)	0.888
73 (39-76)	0.222	76 (68-76)	71 (61-82)	0.673
1.4 (0.0-3.0)	1.000	2.0 (0.5-2.7)	1.8 (0.8-3.0)	1.000
33 (-1-39)	0.423	36 (11-44)	33 (23-44)	0.959
62.1 (17.9-186.5)	0.796	57.1 (28.8-79.0)	68.1 (49.6-80.4)	0.673
31.5 (5.2-108.2)	0.863	21.9 (6.6-47.6)	25.6 (8.7-42.0)	0.963
10.0 (0.8-24.5)	0.489	6.1 (0.7-9.8)	6.46 (0.22-24.4)	0.815
26.0 (7.5-117.0)	0.190	32.5 (19.9-42.2)	34.9 (18.1-55.9)	0.888
45 (40-76)	0.387	50 (45-78)	60 (43-84)	0.888
48.7 (17.9-162.0)	0.931	49.8 (27.1-71.7)	48.7 (33.2-74.9)	0.963
86 (81-89)	0.340	87 (84-90)	90 (69-100)	0.541
22.0 (3.5-89.9)	1.000	14.6 (4.5-40.0)	11.97 (2.0-23.4)	0.481
77 (76-91)	0.730	74 (59-94)	65 (31-95)	0.606
594.2 (81.2-2291.8)	1.000	446.8 (163.3-576.0)	612.9 (267.7-942.8)	0.423
145.2 (11.3-515.6)	0.743	75.2 (23.6-191.4)	114.3 (20.6-224.0)	0.878
33.3 (14.9-131.7)	0.436	18.9 (1.7-31.4)	18.8 (0.6-97.8)	0.815
375.7 (63.5-1308.0)	0.815	355.7 (133.3-401.1)	391.9 (189.3-696.9)	0.574
77 (69-84)	0.481	79 (71-88)	76 (69-89)	0.959
552.1 (79.2-2160.1)	0.863	423.8 (158.9-550.8)	552.1 (258.2-878.7)	0.481
95 (93-95)	0.258	95 (94-96)	95 (89-100)	0.815
111.2 (13.9-392.6)	0.743	52.1 (17.1-166.2)	107.3 (15.8-151.4)	0.959
77 (75-95)	0.370	76 (62-96)	84 (64-97)	0.959