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Diagnostic and clinical value of [18F]FDG PET/CT in the follow-up regimen in IIA–IIID stage cutaneous malignant melanoma after first regional recurrence

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Abstract

Background: Malignant melanoma stands out as a disease with highly aggressive behavior and frequent recurrences. It is crucial to find a non-invasive method for early recurrence detection which allows early and radical treatment. Our aim was to assess the diagnostic and clinical value of [18F]FDG PET/CT in the follow-up regimen of patients after radically treated first regional recurrence and for early detection of operable disease progression.

Material and methods: We performed [18F]FDG PET/CT in 96 consecutive patients who had a histologically proven regional recurrent disease that was radically treated. In 46 patients [18F]FDG PET/CT was used in the follow-up regimen and in the other 50 it was used for clarification of suspicious lesions seen in conventional studies. We explored the diagnostic performance of [18F]FDG PET/CT. We also compared the results with conventional studies and explored the clinical impact of [18F]FDG PET/CT by its ability to find localized disease progression in those groups.

Results: [18F]FDG PET/CT had better sensitivity, specificity, PPV and NPV, and accuracy in patients with symptoms. Good results in the second group had a high price for the patients, as there was a prevalence of distant metastatic disease in the second group — 64.0% *vs.* 28.3% in the surveillance group (p = 0.001). [18F]FDG PET/CT revealed more of the distant and in-transit lesions and assisted in lymph node detection by guiding the ultrasonography. Owing to the [18F]FDG PET/CT surveillance, 64.5% of all operable lesions were found in the surveillance group *vs.* only 35.5% in the second group, where the distant metastatic disease was prevalent.

Conclusions: [18F]FDG PET/CT used as a follow-up tool in the surveillance regimen of patients after the first recurrence showed excellent performance in timely and accurate recognition of operable lesions. It had significantly better performance than conventional studies in the follow-up regimen of the patients in this high risk of progression group.

KEY words: cutaneous melanoma, [18F]FDG PET/CT, follow up

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Introduction

Cutaneous melanoma (CM) has a higher risk for recurrence and dissemination, dependent on the stage and other risk factors such as ulceration, mitotic rate, and biology. Another group of patients with a higher risk for new relapse occurrence are the patients who have already had a recurrence [1–3]. Follow-up in cutaneous tumors is performed to enhance early recurrent disease diagnosis and fast treatment of minimally progressed disease. This especially concerns CM because the chance for radical treatment is time-limited to fast and unpredictable distant metastatic disease after regional lymph node (LN) metastases. Positron emission tomography/computed tomography with ^{18}F-Fluordeoxyglucose ([18F]FDG PET/CT) has a major role, not only in the restaging of CM after the first progression, but also in follow-up of these high-risk patients. Follow-up of patients after localized disease recurrence (local recurrence, regional LNs or in-transit lesions) is crucial for the early operable progression registry. Patients with regional LN metastases can be radically cured with a therapeutic lymph node

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dissection (TLND). Patients with distant metastases and oligometastatic disease could benefit from surgery, targeted therapy, and/or immunotherapy. There is no existing consensus on the appropriateness of follow-up with [18F]FDG PET/CT after staging, even in high-risk CMs.

Our aim was to assess the diagnostic and clinical value of [18F]FDG PET/CT in the follow-up regimen of patients after the first localized recurrence of skin melanoma for early detection of operable disease progression.

Material and methods

We performed a retrospective analysis of the [18F]FDG PET/CT studies in 96 consecutive patients who had a histologically proven localized recurrent disease — local recurrence, in-transit metastasis, and/or regional LNs that were radically treated with surgery. The patients had primary CM of the skin, diagnosed between January 2007 and August 2018. They had a CM recurrence in IIA–IIID stage defined using histology results for the T and N stage and an [18F]FDG PET/CT study that excluded metastatic disease. Forty-four (45.8%) of the patients were female and 52 were male (54.2%), aged 29–85, mean of 60.8 (SD 12.38). We performed the [18F]FDG PET/CT studies in the time interval between September 2014 and March 2021, thus the follow-up period after recurrence was between 2.5 and 6.5 years. In Table 1 the TNM stage distribution of patients, according to the 8th revision TNM AJCC, after the recurrence is demonstrated.

The primary melanoma was located on the trunk in 46 (47.9%), lower extremity in 25 (26.0%), upper extremity in 9 patients (9.5%), head and neck, and in 13 (13.5%) and 3 CM without the primary lesion found (Tab. 1).

The examination was held on Gemini TF PET/CT, Philips, equipped with 16 slice CT. The [18F]FDG PET/CT scan was held 60 min after 18-fluordeoxyglucose (FDG) administration. A whole body scan was obtained from the vertex of the skull to the toe. We performed a low-dose CT. All of the patients fasted for at least 4–6 h before the examination to ensure standardized glucose metabolism. At the time of FDG administration, fasting plasma glucose values were lower than 150 mg/dL in all patients. Depending on the patient's weight, a dose of 185–555 mBq was administrated through a catheter inserted into an antecubital vein.

Table 1. Patients characteristics

Stage	IIA	7 (7.3%)
	IIB	10 (10.4%)
	IIC	7 (7.3%)
	IIIB	13 (13.5%)
	IIIC	48 (50.0%)
	IIID	11 (11.5%)
Localization	Upper extremity	9 (9.4%)
	Lower extremity	25 (26.0%)
	Trunk	46 (47.9%)
	Head & neck	13 (13.5%)
	Regressed, T0	3 (3.1%)
[18F]FDG PET/CT surveillance group	Yes	46 (47.9%)
	No	50 (52.1%)
[18F]FDG PET/CT intervals	3 months	6 (13.0%)
	6 months	30 (65.2%)
	9 months	6 (13.0%)
	12 months	4 (8.7%)

The patients were divided into two main groups — in the 1st group, [18F]FDG PET/CT was used in the follow-up regimen, and a 2nd group, in which, [18F]FDG PET/CT was not used as a surveillance method (Tab. 1). The patients in the second group were referred for an [18F]FDG PET/CT scan in case of symptomatic disease, palpable LNs, elevated tumor marker or conventional studies suspicious for progression. All the patients in the two groups were previously examined with palpation and had performed a set of conventional studies ultrasonography of the regional lymph node basins, chest X-ray, and/or contrast-enhanced computer tomography (CT) of the thorax, abdomen, and pelvis. All the recurrences occur in the period between January 2013–December 2018 and the follow-up continued until May 2021, determining a follow-up period of minimum of 2.4 years and a maximum of 8.4 years.

[18F]FDG PET/CT was used to follow up 46/95 of the patients at 3, 6, 9, or 12 months. The time interval was chosen by the referring physician and depended on the TNM stage of the recurrent melanoma. The most common time interval was 6 months, used in 50% of patients in IIIB and 75% of patients in IIIC stage. The 3 months interval was used in half of the patients in the IIID stage. The patients with an [18F]FDG PET/CT scan performed more than 12 months after progression was considered not followed up with an [18F]FDG PET/CT.

Interpretation criteria

The interpretation of [18F]FDG PET/CT was made upon the CT scan, metabolic scan, and fused scans. All the [18F]FDG PET/CT scans were interpreted by two skilled nuclear medicine physicians with great attention paid to regional lymph node basins and subcutaneous tissue in the region between the primary cutaneous melanoma and the draining basin/s. All the results were compared to those from the conventional studies and the reference method was histology or follow-up scans.

Results

Diagnostic performance of [18F]FDG PET/CT in patients included in the follow-up regimen compared to patients in which [18F]FDG PET/CT was used only in symptom appearance

There were 32/46 (69.6%) people in the follow-up group in whom a progression was documented at some point of the follow-up program and 42/50 (84.0%) in the symptomatic group ($p = 0.047$). [18F]FDG PET/CT managed to detect 28/32 (87.5 %) progressions in the first group and 41/42 (97.6%) in the second (Tab. 2).

According to the results in Table 2, the sensitivity, specificity, PPV, NPV, and accuracy of the [18F]FDG PET/CT in the follow-up group *vs.* no-PET/CT surveillance group were calculated (Tab. 3).

From these results, it is clear that [18F]FDG PET/CT had an excellent performance in all of the patients with clinical or instrumental

Table 2. Distribution of patients according to true positivity, false positivity, true negativity, and false negativity rate of [^{18}F]FDG PET/CT studies in the two groups in a patient by patient analysis

PET/CT surveillance	PET/CT result			
	TP	FP	TN	FN
Yes, n = 46	28 (60.9%)	4 (8.7%)	10 (21.7%)	4 (6.5%)
No, n = 50	41 (82.0%)	0 (0.0%)	8 (16.0%)	1 (2.0%)

TP — true positive; TN — true negative; FN — false negative; FR — false positive

Table 3. Distribution of patients according to sensitivity, specificity, PPV, NPV, and accuracy of [^{18}F]FDG PET/CT results in the two groups

Diagnostic performance of PET/CT	[^{18}F]FDG PET/CT surveillance group	No PET/CT surveillance group
Sensitivity	87.5%	97.6%
Specificity	71.4%	100.0%
PPV	87.5%	100.0%
NPV	71.4%	88.9%
Accuracy	77.5%	98.0%

PPV — positive predictive value; NPV — negative predictive value

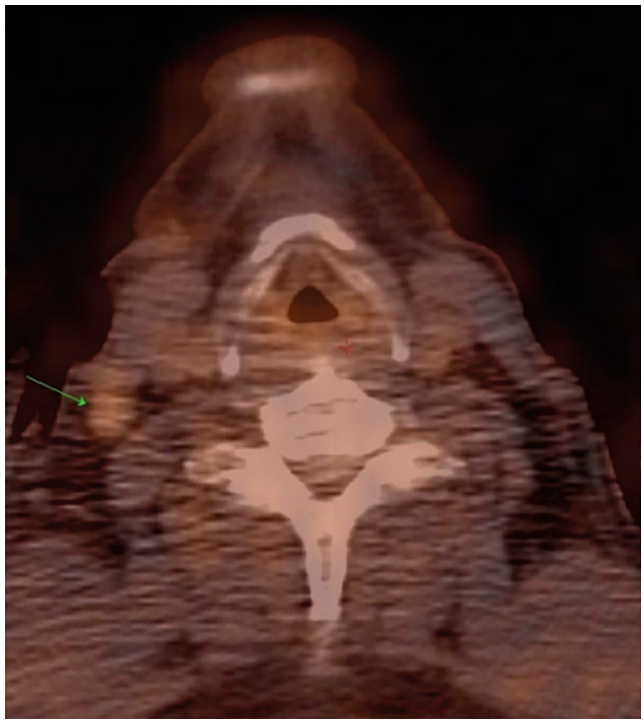

Figure 1. A patient with head & neck MM, pT3b N0 M0. The patient had regional LN recurrent disease, which was treated radically. [^{18}F]FDG PET/CT was used in the follow-up regimen of the patient. A suspicious but not significant LN was detected in the right cervical level II. It was confirmed metastatic by ultrasound and histology

suspicion of recurrent disease. Although, a closer look at those results reveals the high price of the excellent performance of the method in the second group. There were 92 documented malignant lesions, including 29 regional LNs, 16 in-transit lesions, 45 metastatic lesions, and 2 local recurrences. The patients with true malignant lesions detected in the surveillance group in the follow-up period were 60.9 %, while there were 82.0% TP patients the in symptomatic group ($p = 0.011$) (Tab. 2).

In the lesion by lesion analysis, the true positivity rate of malignant LNs was similar in the two groups — 19.5% in the surveillance group and 32.0% in the symptomatic group ($p = 0.8$). But most importantly, in 64.0% of the patients in the symptomatic group, a distant metastatic disease was detected, which was significantly more than 28.3% in patients in the [^{18}F]FDG PET/CT surveillance group ($p < 0.001$) (Tab. 4).

The four false negative results in [^{18}F]FDG PET/CT studies were because of FDG negative metastatic LNs. In our patients at a follow-up regimen, 3/12 (25.0 %) had PET negative LNs, which was confirmed by echography and subsequent histopathology results (Fig. 1). There was no such issue in the symptomatic patients' group, as the LNs were bigger and metabolically active, in which there was only one FN lymph node.

Comparison of the diagnostic performance between [^{18}F]FDG PET/CT and CIS in the two patients' groups

The values from the diagnostic performance of the [^{18}F]FDG PET/CT obtained were compared with the values from the conventional studies (Tab. 5, 6).

Conventional imaging studies (CIS) managed to detect only 7/32 (21.9%) progressions in the first group and 7/42 (16.7%) in

Table 4. Malignant [^{18}F]FDG PET/CT findings in the two groups (lesion by lesion analysis)

[^{18}F]FDG PET/CT surveillance	Recurrence type	[^{18}F]FDG PET/CT results			
		TP	TN	FN	FP
Yes, n = 46	Regional LN	9 (19.5%)	33 (71.7%)	3 (6.52%)	1 (2.2%)
	In-transit	11 (23.9%)	35 (76.1%)	0 (0.0%)	0 (0.0%)
	Metastatic disease	13 (28.3%)	31 (67.4%)	0 (0.0%)	2 (4.4%)
	Local recurrence	2 (4.4%)	43 (93.5%)	0 (0.0%)	1 (2.2%)
No, n = 50	Regional LN	16 (32.0%)	33 (66.0%)	1 (2.0%)	0 (0.0%)
	In-transit	5 (10.0%)	45 (90.0%)	0 (0.0%)	0 (0.0%)
	Metastatic disease	32 (64.0%)	18 (36.0%)	0 (0.0%)	0 (0.0%)
	Local recurrence	0 (0.0%)	0 (0.0%)	50 (100.0%)	0 (0.0%)

LN — lymph node; TP — true positive; TN — true negative; FN — false negative; FR — false positive

Table 5. Distribution of patients according to true positivity, false positivity, true negativity, and false negativity rate of the conventional studies in the two groups — with and without [18F]FDG PET/CT surveillance in a patient by patient analysis

[18F]FDG PET/CT surveillance	Conventional studies result			
	TP	FP	TN	FN
Yes, n = 46	7 (15.2%)	2 (4.3%)	12 (26.1%)	25 (54.3%)
No, n = 50	7 (14.0%)	0 (0.0%)	8 (16.0%)	35 (70.0%)

TP — true positive; TN — true negative; FN — false negative; FR — false positive

Table 6. CIS imaging characteristics — true positive/negative, and false positive/negative results in different types of recurrent lesions in the two groups

[18F]FDG PET/CT surveillance	Recurrence type	CIS result			
		TP	TN	FN	FP
Yes, n = 46	Regional LN	5 (10.9 %)	33 (71.7%)	7 (15.2%)	1 (2.2%)
	In-transit	0 (0.0%)	35 (76.1%)	11 (23.9%)	0 (0.0%)
	Metastatic disease	3 (6.5%)	31 (67.4%)	10 (21.7%)	2 (4.4%)
	Local recurrence	1 (2.2 %)	44 (95.7%)	1 (2.2%)	0 (0.0%)
No, n = 50	Regional LN	6 (12.0%)	33 (66.0%)	11 (22.0%)	0 (0.0%)
	In-transit	3 (6.0%)	45 (90.0%)	2 (4.0%)	0 (0.0%)
	Metastatic disease	4 (8.0%)	18 (36.0%)	28 (56.0%)	0 (0.0%)
	Local recurrence	0 (0.0%)	50 (100.0%)	0 (0.0%)	0 (0.0%)

LN — lymph node; TP — true positive; TN — true negative; FN — false negative; FR — false positive

the second. We used lesion by lesion analysis to explore the weaknesses of the CIS in different types of malignant lesions (Tab. 6).

CIS were able to recognize 11/29 (37.9%) regional LNs (Fig. 2), only 3/16 (18.8%) in-transit lesions (in the second group) (Fig. 3) and 7/45 (15.5%) distant metastatic lesions.

There was a significant difference in the true positivity rate for those studies *vs.* [18F]FDG PET/CT. In the first group, CT failed to recognize 10 of the distant lesions in the first group including 3 distant LNs (Fig. 4), two small but metabolically active lung lesions, and one of the listed: skin (Fig. 5), bone marrow (Fig. 6), muscle (Fig. 7), adrenal and peritoneal metastasis. All of these localizations are as a general rule difficult to diagnose with contrast-enhanced CT. In the second group, there was a bigger rate of distant metastatic disease patients [32 (64.0 %)], 11 of them with generalized metastatic disease. CIS was unsuccessful in revealing 28 of the distant metastatic lesions all of the cutaneous (7), distant LN (3), muscle (3), peritoneal (2), colon (1), and pleural (1) lesions, as well as some of the osseous (5), lung (2), hepatic (2), adrenal (1) and spleen (1), metastases.

We compared the diagnostic performance of [18F]FDG PET/CT and CIS in detecting different malignant lesions in lesion by lesion analysis (Tab. 7). There was no significant difference between the results of [18F]FDG PET/CT diagnostic performance in the surveillance and symptomatic patients group.

We compared those results with the diagnostic performance of CIS (Tab. 8). According to the results in Table 6, the sensitivity, specificity, PPV, NPV, and accuracy of the conventional studies in the follow-up group *vs.* no-PET/CT surveillance group were calculated (Tab. 8). There was a significant difference in [18F]FDG PET/CT sensitivity over CIS in regional LN detection, but it was exclusively high in in-transit and metastatic lesions.

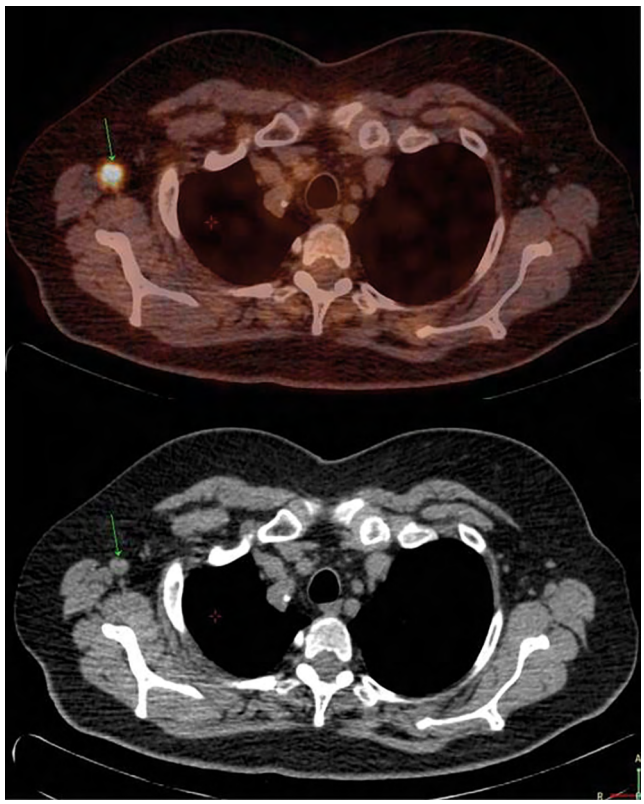

Figure 2. A patient with a right arm MM, stage at diagnosis pT4b N0M0. The patient had a recurrent in-transit lesion, treated surgically. Ten months after the recurrence, an axillar LN appeared, with a fatty hilum and diameter below 10 mm — negative in conventional studies. [18F]FDG PET/CT demonstrated a definite metastatic lesion with high FDG uptake, proven malignant after the operation

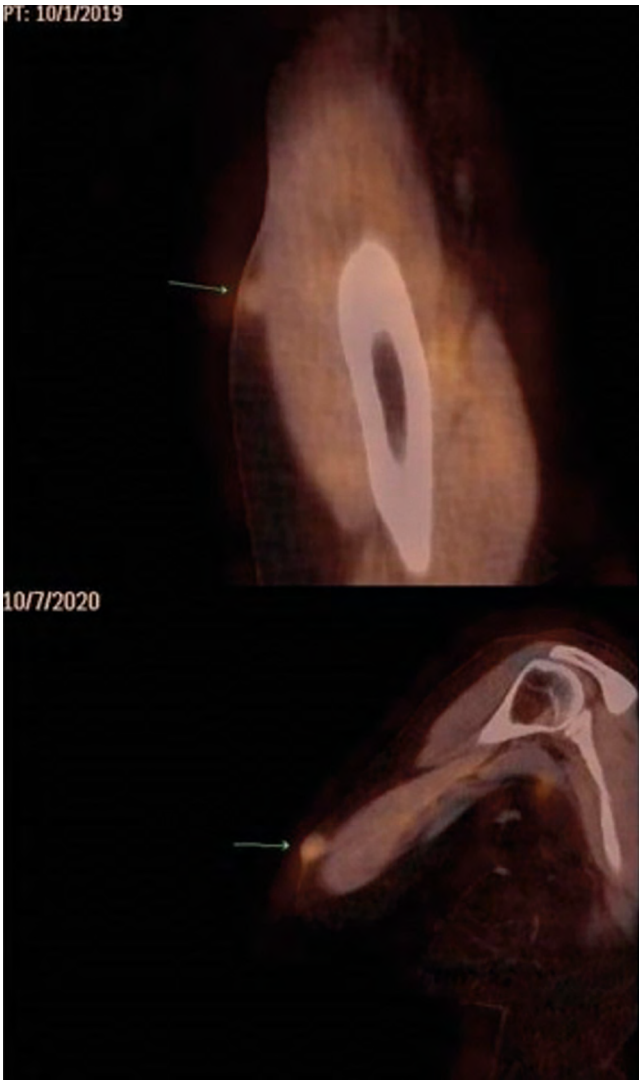

Figure 3. A patient with a non-symptomatic in-transit lesion detected as malignant on [^{18}F]FDG PET/CT (**A**). It was not found in conventional studies and the patient came for a follow-up scan 12 months later with the clinically evident in-transit lesion (**B**)

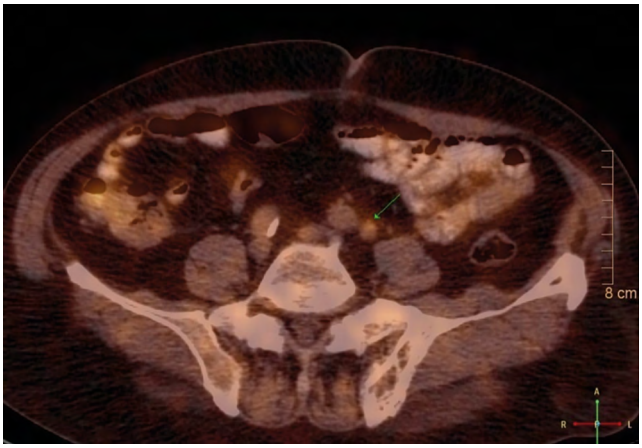

Figure 4. A follow-up [^{18}F]FDG PET/CT study of a patient with CM of the right gluteal skin region after recurrent right inguinal LNs, pT2a pN1b cM0. Seven months after regional progression a small distant left common iliac LN was detected, not recognized on follow-up CT

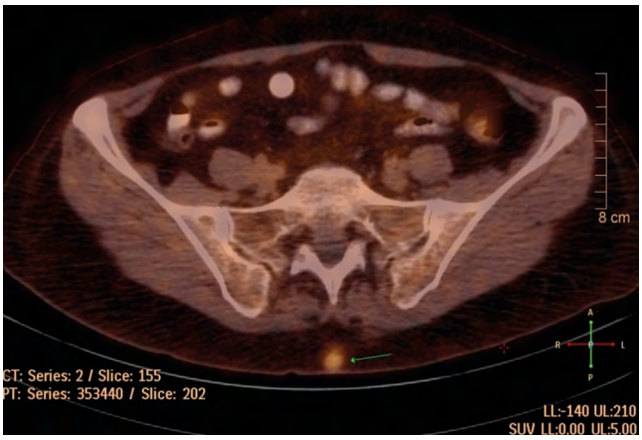

Figure 5. A patient with CM of the thorax, pT3b N0 M0. The patient had a recurrent in-transit lesion, IIIC stage after recurrence. Three months after recurrence [^{18}F]FDG PET/CT was performed as a follow-up study and a distant metastatic skin lesion was revealed

Clinical significance of [^{18}F]FDG PET/CT

The clinical significance of [^{18}F]FDG PET/CT in follow-up CM patients was explored by its ability to find a localized, operable disease progression in the patients in a follow-up regimen group, in contrast to the patients without [^{18}F]FDG PET/CT surveillance.

The distribution of patients according to the operability of the disease found in the two groups is shown in Table 9.

There was a significant difference between the two groups, as the follow-up regimen group achieved better results in localized disease recognition — 43.5%, *vs.* 22.0% in the second group. Owing to the [^{18}F]FDG PET/CT surveillance, 64.5% of all operable lesions were found in this group *vs.* only 35.5% in the group with no [^{18}F]FDG PET/CT surveillance, where the distant metastatic disease was prevalent.

Discussion

Cutaneous melanoma has a high metastasizing potential and the ability to spread fast beyond the regional nodal basin which reduces the time for surgical treatment options. A non-symptomatic relapse is easier to treat radically with smaller morbidity and shorter time to recovery [4]. Until recently there have been no effective therapies for metastatic and IIIC stage melanoma, that is why no need for regular imaging surveillance for early relapse detection of CM existed. In the new therapeutic era of evolving immunotherapies and targeted therapies, an early start of treatment is crucial in order to prolong disease-free survival because takes sometimes a number of months to take effect. On the other hand, routine imaging has resource implications and involves more

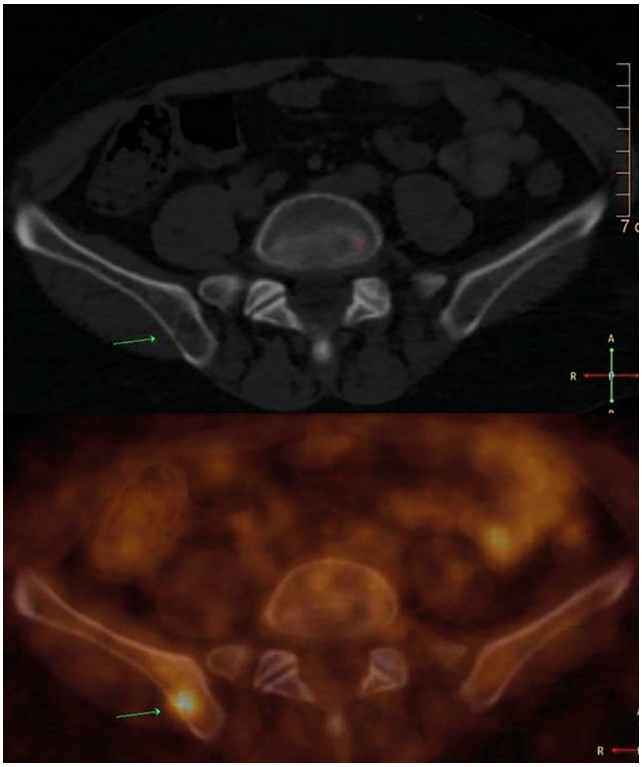

Figure 6. A patient with CM of the right thorax, pT4b cN0 cM0. The patient had right axillar LNs recurrence, staged pT4 pN2b M0 after the radical treatment. A follow-up [18F]FDG PET/CT study was performed 4 months after the first recurrence where a right iliac lesion was found, indistinguishable on CT

hospital visits, increased patient anxiety, and radiation exposure. However, research on the value of [18F]FDG PET/CT in the follow-up of melanoma patients is limited. A balance is needed to categorize different high-risk groups of patients that would benefit most from [18F]FDG PET/CT studies without negative effects.

The routine use of [18F]FDG PET/CT is recommended in an increasing number of guidelines and only for patients in stage IIC and higher. Speijers et al. [6] made a review of follow-up guidelines in 2010, revealing that only 4 of them recommend the use of [18F]FDG PET/CT in follow-up of risk groups CM patients [5]. Nowadays their number is bigger, some of them with precise follow-up schedule recommendations in high-risk groups of patients in the first three years [6]. Our aim was to study a specific high-risk group of patients, those who have already had a local recurrent disease, radically treated with surgery. Following local recurrence, patients have significantly worsened prognoses, with a subsequent probability of survival estimated to be approximately 40–60% at 5 years of follow-up [1, 3]. Long-term survival (> 10 years) was estimated to be 34.9%. Those patients have a high risk for a new local or distant metastatic disease and need an individual follow-up plan [7].

The time intervals recommended by the guidelines depend on the TNM stage and are usually at 6–12 months intervals for IIB–IIIB, every 3–6 months for stage IIIC–IIID, and every 3 months for stage IV NED (no evidence of disease) [6, 8–12]. In the US, the most recent guidelines from the National Comprehensive Cancer Network (NCCN Guidelines Version 3, 2022) suggest considering chest CT, brain MRI and/or [18F]FDG PET/CT every 3 to 12 months for stage IIB–IV for two years and every 6–12 months for the next 3 years (evidence level 2B) [5]. European Society for Medical Oncology ESMO

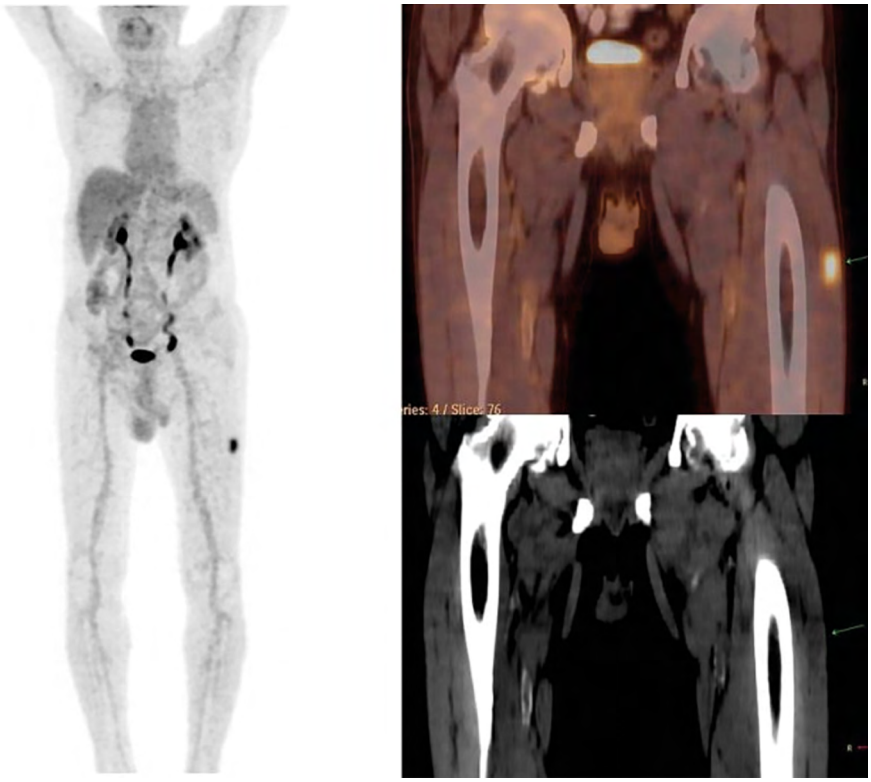

Figure 7. A patient staged pT3b N2b M0, with primary CM of the thorax. Six months after regional LN recurrence, a solitary, non-symptomatic distant muscle metastasis of the left femur was revealed

Table 7. Distribution of patients according to sensitivity, specificity, PPV, NPV, and accuracy of [^{18}F]FDG PET/CT results in the two groups

[^{18}F]FDG PET/CT surveillance	Recurrence type	[^{18}F]FDG PET/CT results				
		Sensitivity	Specificity	PPV	NPV	Accuracy
Yes, n = 46	Regional LN	75.0%	97.1%	90.0%	91.7%	85.7%
	In-transit	100.0%	100.0%	100.0%	100.0%	100.0%
	Metastatic disease	100.0%	100.0%	86.7%	100.0%	95.7%
	Local recurrence	100.0%	100.0%	66.7%	100.0%	97.8%
No, n = 50	Regional LN	84.2%	97.1%	94.1%	94.1%	98.0%
	In-transit	100.0%	100.0%	100.0%	100.0%	100.0%
	Metastatic disease	100.0%	100.0%	100.0%	100.0%	100.0%
	Local recurrence	–	–	–	–	–

Table 8. Distribution of patients according to sensitivity, specificity, PPV, NPV, and accuracy of CIS results in different malignant lesions in the two groups

[^{18}F]FDG PET/CT surveillance	Recurrence type	CIS results				
		Sensitivity	Specificity	PPV	NPV	Accuracy
Yes, n = 46	Regional LN	41.7%	97.1%	83.3%	82.5%	82.6%
	In-transit	0.0%	100.0%	0.0%	76.1%	76.1%
	Metastatic disease	23.1%	93.9%	60.0%	75.6%	73.9%
	Local recurrence	50.0%	100.0%	100.0%	97.8%	97.8%
No, n = 50	Regional LN	35.3%	100.0%	100.0%	75.0%	78.0%
	In-transit	60.0%	100.0%	100.0%	95.7%	96.0%
	Metastatic disease	12.5%	100.0%	100.0%	39.1%	44.0%
	Local recurrence	–	–	–	–	–

LN — lymph node; NPV — negative predictive value; PPV — positive predictive value

Table 9. Distribution of patients in the two groups according to the recurrence type — localized (operable) or disseminated disease

[^{18}F]FDG PET/CT surveillance regimen group	Operable lesion		
	Yes	No	No disease
Used, n = 46	20 (43.5 %)	13 (28.3 %)	13 (28.3%)
Not used, n = 50	11 (22.0%)	31 (62.0%)	8 (16.0%)

Pearson Chi-Square, p = 0.004

states that in high-risk patients (i.e., those with thick primary tumors or recent tumor resection), CT +/− PET scans are suggested for earlier detection of relapse. The 2020 edition of the guideline states that patients with in-transit lesions are at high risk for distant dissemination and recommends staging with [^{18}F]FDG PET/CT [13].

Most of the patients after recurrence are upstaged to stage III or IV. That was why a surveillance strategy to detect occult, radically treatable new progression was needed. In patients who have already had one recurrence, which usually is local, but leads to patients' upstaging to stage III, subsequent recurrences tend to occur at progressively shorter intervals [14]. This must be taken into account when planning the frequency of the follow-up [^{18}F]FDG PET/CT studies. The most common time interval we used was 6 months for 50% of patients in IIIB and 75% of patients in IIIC stage. The 3 months interval was used in half of the patients in IIID stage. These are also the recommendations in most of the guidelines.

Large retrospective studies show that between 60% and 80% of first recurrences are local and/or nodal [8, 14–19]. Local recurrences and regional local involvement is usually detected by the patient himself or by palpation and ultrasonography. Xing et al [20] conducted a large meta-analysis comparing ultrasound imaging, CT, PET, and [^{18}F]FDG PET/CT for the staging and surveillance of patients with melanoma. For both staging and surveillance purposes, ultrasound was found to be associated with the highest sensitivity and specificity for LN metastases, while [^{18}F]FDG PET/CT was superior for detecting distant metastases. The role of SLNB in nodal staging has no imaging study alternative but it is not recommended after radical excision of the primary tumors.

Before the [^{18}F]FDG PET/CT, all of our patients were examined with palpation, ultrasonography, and CT of the thorax, abdomen, and pelvis — CIS. The diagnostic value of [^{18}F]FDG PET/CT for LN detection we gained in our study exceeded but was not significantly better than CS in both groups. Regional LNs diagnosis demands knowledge about potential regional nodal basins and special attention must be paid to suspicious LNs recognition, eligible for extensive ultrasonography follow-up. Although there were 4/29 (13.8%) false negative recurrent LNs, [^{18}F]FDG PET/CT was able to point out the suspicious LNs which were further examined and surgically treated. There was no such issue in the symptomatic patients' group, as the LNs were bigger and metabolically active.

The performance of the CS in follow-up of non-symptomatic patients was significantly poorer than that of the [^{18}F]FDG PET/CT studies. That was because of the unpredictable

hematogenous dissemination of CM that metastasizes to skin, muscles, bone marrow, subcentimeter but high metabolically active lung, hepatic, spleen peritoneal and pleural lesions, generally difficult to detect by CT. Sensitivity, specificity, and accuracy of [18F]FDG PET/CT in a patient by patient analysis in the follow-up group were, respectively 87.5%, 71.4% and 77.5%, compared to 21.9%, 85.7% and 41.3% for CIS. [18F]FDG PET/CT scans can help to further characterize lesions found to be indeterminate on CT scan, and can image areas of the body not studied by the routine body CT scans (i.e., arms and legs) [21, 22]. In symptomatic patients, [18F]FDG PET/CT was often used to clarify vague metastatic lesions, in which CIS was non-diagnostic. In lesion by lesion analysis, [18F]FDG PET/CT showed a sensitivity of 75% for LN and 100% for in-transit and distant metastases, which does not differ significantly from the results in the symptomatic group ($p = 0.13$). CS showed much poorer results, especially in distant metastatic detection (with the sensitivity of 12.5% and accuracy of 44.0%) and in transit lesions, while the follow-up group CS did not find any of them.

In our study, we found a significant prevalence of recurrence patients in the symptomatic group *vs.* the follow-up group. Although the high sensitivity, specificity, and accuracy of the method in the symptomatic group, which was significantly better than the conventional studies, it revealed predominantly distant metastatic disease in 64.0% *vs.* 28.3% in the surveillance group. Metastatic CM demands an expensive systemic treatment and the patients have significantly lower life expectancy time. Also, treatment procedures in advanced MM, including surgery, radiotherapy, and systemic therapies are associated with more pronounced morbidity. A review of the role of PET-CT in the surveillance of patients with CM found a sensitivity of 96% and specificity of 92% [23].

The clinical impact of [18F]FDG PET/CT in high-risk groups of CM patients, such as patients after the first recurrence we found was very important because of the ability of [18F]FDG PET/CT to detect early a new occult progression. Earlier occult disease detection by [18F]FDG PET/CT surveillance enabled radical surgical treatment in 43.5%, *vs.* 22.0% in the second group. Owing to the [18F]FDG PET/CT surveillance, 64.5% of all operable lesions were found in the first group *vs.* only 35.5% in the group with no [18F]FDG PET/CT surveillance, where the distant metastatic disease was prevalent. This was another benefit found from [18F]FDG PET/CT surveillance in patients after the first recurrence, being a valuable modality in the follow-up of high-risk melanoma to diagnose recurrences and to select patients who are suitable for metastasectomy.

Conclusions

[18F]FDG PET/CT used as a follow-up tool in the surveillance regimen of patients after first regional recurrence showed an excellent performance in timely and accurate recognition of operable lesions. It had significantly better performance than conventional studies in the follow-up regimen of the patients in this high-risk group. The main diagnostic issue faced by the [18F]FDG PET/CT follow-up studies was the PET negative non-significant lymph nodes which demand knowledge of the specific skin lymphatic drainage and further echography or biopsy evaluation of any suspicious LN in that region.

Conflict of interest

The authors have no conflicts of interest to declare.

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