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ORIGINAL ARTICLE

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Diagnostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography over conventional imaging studies to detect malignant lesions in staging and restaging after radically treated primary and recurrent locoregional cutaneous melanoma

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ABSTRACT

Introduction. Cutaneous melanoma (CM) has a high metastasizing potential and requires many imaging tests for accurate staging and restaging. As a hybrid imaging method, 18F-FDG PET/CT has the power to diagnose clinically undetected regional and distant metastatic disease with a better detection rate than conventional imaging. The aim of our study was to assess the value of 18F-FDG PET/CT in detecting different types of malignant lesions – local recurrences, regional lymph nodes (RLN), in-transit (ITM) and distant metastases (DM) after radical excision of the primary lesion or regional recurrence.

Materials and methods. A retrospective analysis was performed of all patients with CM referred for 18F-FDG PET/CT for staging or after resection of locoregional recurrent disease. All patients had a combination of pre-PET/CT conventional imaging studies (CIS), including a whole body computed tomography (CT) and ultrasonography (US) of the RLN basin/s. The results from 18F-FDG PET/CT were compared with the CIS results.

Results. 246 consecutive patients, aged 10–87 years were included with identification of 71 malignant lymph nodes, 4 local recurrences, 28 ITM, and 65 DM in total. The detection rate of 18F-FDG PET/CT for RLN was 84.5%, and in the diagnosis of ITM and DM, it reached a sensitivity of 100.0% with 0.7% of false positive results.

Conclusions. 18F-FDG PET/CT has an invaluable role in the detection of small, clinically silent ITM and DM and has a smaller value in RLN detection. It may guide the process of selection of suspicious lesions, suitable for biopsy or further ultrasound follow-up.

Key words: 18F-FDG PET/CT, melanoma, staging, restaging

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Introduction

Cutaneous melanoma (CM) is the fifth most common cancer in men and women [1, 2], with a worldwide incidence in 2020 of 3.8% in males and 3.0% in females. It remains the predominant cause of skin cancer death. [3] CM is an aggressive malignant disease with a very high risk for recurrence and dissemination.

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Around 84% of cases present with localized disease, 9% with involvement of regional lymph nodes, and 4% with distant metastases (DM) at diagnosis [1]. Adequate staging and restaging after initial management of recurrent disease are crucial for early radical treatment or appropriate subsequent therapy of clinically silent disease, unrecognized by conventional imaging studies (CIS). Sentinel lymph node biopsy (SLNB) is the acknowledged gold standard for pathological staging of clinically negative lymph nodes. Ultrasound is the most important noninvasive method for regional lymph node staging and follow-up. The role of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) is predominantly in whole-body staging in advanced stages (III and IV) and restaging after CM progression.

Aim

To assess the diagnostic value of 18F-FDG PET/CT for detection of different types of malignant lesions in patients with CM — regional lymph nodes, *in-transit*, distant metastases, and local recurrences after radical excision of the primary lesion, or radical treatment of the local recurrent disease, in comparison with CIS. The latter included contrast-enhanced computed tomography (CECT) of the thorax, abdomen, pelvis, and ultrasonography (US) of regional lymph nodes.

Material and methods

Patients and inclusion criteria

A retrospective analysis was performed of all CM patients without DM disease, referred for staging and restaging after radical surgical treatment between January 2007 and December 2018. We identified 246 consecutive patients with those inclusion criteria: 103 (41.9%) female and 143 (58.1%) male, aged 10–87 years, mean of 59.19 years (SD 13.35). The mean Breslow thickness of the primary lesions was 4.63 mm (SD 2.85 mm), ranging from 0.75 mm to 17.0 mm. All of them underwent 18F-FDG PET/CT at the Nuclear Medicine Department of St Marina University Hospital, Varna. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristics	n (%)
Stage	
IIA	31 (12.6%)
IIB	51 (20.7%)
IIC	48 (19.5%)
IIIB	18 (7.3%)
IIIC	79 (32.1%)
IIID	19 (7.7%)
Localization	
Upper Extremity	25 (10.2%)
Lower Extremity	59 (24.0%)
Trunk	119 (48.4%)
Head & Neck	38 (15.5%)
Regressed, T0	7 (2.8%)
Indication	
Staging	141 (57.3%)
Restaging after radically treated regional recurrent disease	105 (42.7%)

Method

The examinations were held with Gemini TF PET/CT, Philips, equipped with 16-slice CT. The PET/CT scan was performed at 60–90 min intervals after 18F-FDG application. A whole-body scan was performed for all patients, including the region of excision. At the time of 18F-FDG administration, fasting plasma glucose values were lower than 150 mg/dL in all patients. If the primary CM was located in the upper extremity, the contralateral arm was used for ^{18}FDG administration.

SLNB was performed in 28 of all 141 patients, referred for staging with 18F-FDG PET/CT. SLNB was performed by a combination of radionuclide scintigraphy and gamma probe-guided surgery and injection of patent blue V.

18F-FDG PET/CT was a staging method in patients with CM in the IIA-IIID stage. In patients for restaging after radical excision of the recurrence, we assessed the first 18F-FDG PET/CT scan. Patients with initial DM at diagnosis, second primary and metachronous tumors were excluded. All the patients had a pre-18F--FDG PET/CT, diagnostic CT of the thorax, abdomen, and pelvis and ultrasonography of the regional lymph node basin/s. To avoid false positive results, staging and restaging were performed one month after tumor or lymph node excision or two weeks after a biopsy.

We explored the ability of 18F-FDG PET/CT to reveal different types of malignant lesions, including local recurrence, regional nodal involvement, *in-transit* (ITM), and distant metastases (DM), performing lesion-by-lesion analysis in patients with CM. In every patient we studied the diagnostic value of 18F-FDG PET/CT vs. a combination of CIS, identifying four categories of malignant lesions: local recurrence, regional lymph nodes, ITM, and DM. We assessed the true positive, true negative, false positive, and false nega-

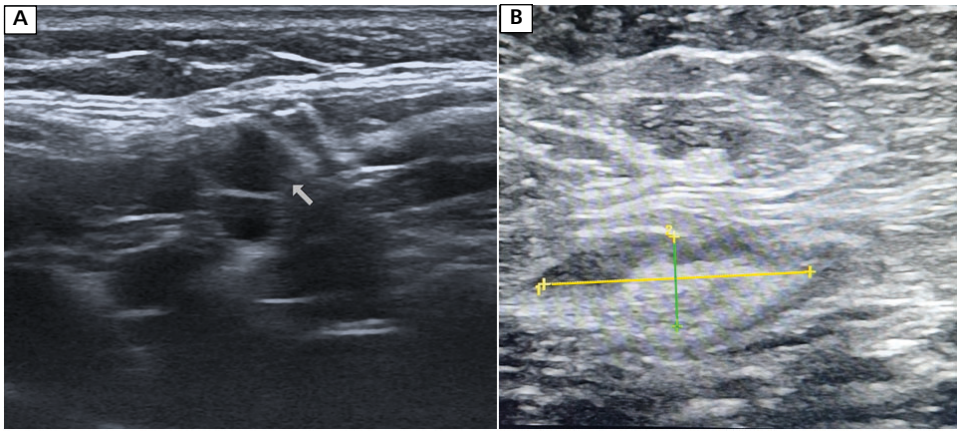

Figure 1. Suspicious sentinel lymph nodes with oval or rounded shape, local thickening of the cortex, and dislocated gate; **A.** Inguinal lymph nodes; **B.** An axillary lymph node

tive results in staging and restaging after progression. The advantages and weaknesses of the method in all of the above lesions, in comparison with CIS, were studied in detail. The role of 18F-FDG PET/CT in patients after SLNB was also studied. We also explored the additional value of 18F-FDG PET/CT in patients after SLNB.

Image interpretation

Cutaneous melanoma lesions are characterized by high 18F-FDG avidity. This is the reason why 18F-FDG PET/CT has a very good sensitivity even in subcentimeter lesions. The image interpretation always included CT and PET-image interpretation, separately and in fused images. Special attention was paid to regional lymph node interpretation, with the nodes divided into three categories – definitely malignant, non-malignant, and suspected of malignancy. Suspicious lymph nodes were those with at least two of the following characteristics: a round shape, partly or completely missing fatty hilum, and FDG uptake close to that of the liver. All of them were considered PET-negative, but a follow-up study was recommended.

Pathological confirmation of suspicious/positive lesions with FDG uptake on PET/CT was pursued. If pathological confirmation was not possible, clinical outcome and imaging after 6 months were used as gold standards. Scans were classified as true-positive if metastatic melanoma was suggested and confirmed and as false-positive if the suspected metastatic melanoma was confirmed to be something else. Scans that were considered negative were classified as true-negative if the patient did not develop a recurrence during the 6 months following the baseline imaging. Scans were considered false-negative if the baseline scan failed to reveal the initial suspected metastatic lesion that was still present or if evidence of any further metastasis was established during the 6 months of follow-up.

Ultrasonographic characteristics of malignant lymph nodes

The RLN assessment was made in oncological centers as part of the conventional staging of CM patients. We compared the 18F-FDG PET/CT study results with ultrasonographic files in patient documentation. The main features of malignant lymph nodes are round shape, loss of echogenic fatty hilum, cystic change, calcification, and abnormal peripheral vascularity (Fig. 1).

Sentinel lymph biopsy technique

Twenty-eight of the patients referred for an 18F-FDG PET/CT scan staging had previously performed a sentinel lymph node biopsy procedure. It included 1) injecting 0.28 to 10μCi of a radiopharmaceutical agent (99Tcsulphur colloid) at 4 intradermal spots around the biopsy scar of the MM, 2) examining the patients in a gamma camera to make a lymphoscintigraphic map, 3) visualizing the regional lymph drainage, location and number of sentinel lymph nodes, and 4) presence or absence of in-transit lesions in the operating room. One ml of lymphotropic dye (Patent Blue V) was intradermally applied at ten locations around the scar. After 6 to 10 minutes, the areas marked on the lymphoscintigraphic map were explored to find the sentinel lymph node. The blue node and its location corresponded to the spot as indicated on the map.

Ethical considerations

All of the patients included in the study signed informed consent allowing us to use the results of their imaging studies in scientific projects while maintaining rules of confidentiality. This retrospective study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee at the Medical University "Prof. Paraskev Stoyanov", Varna, Bulgaria.

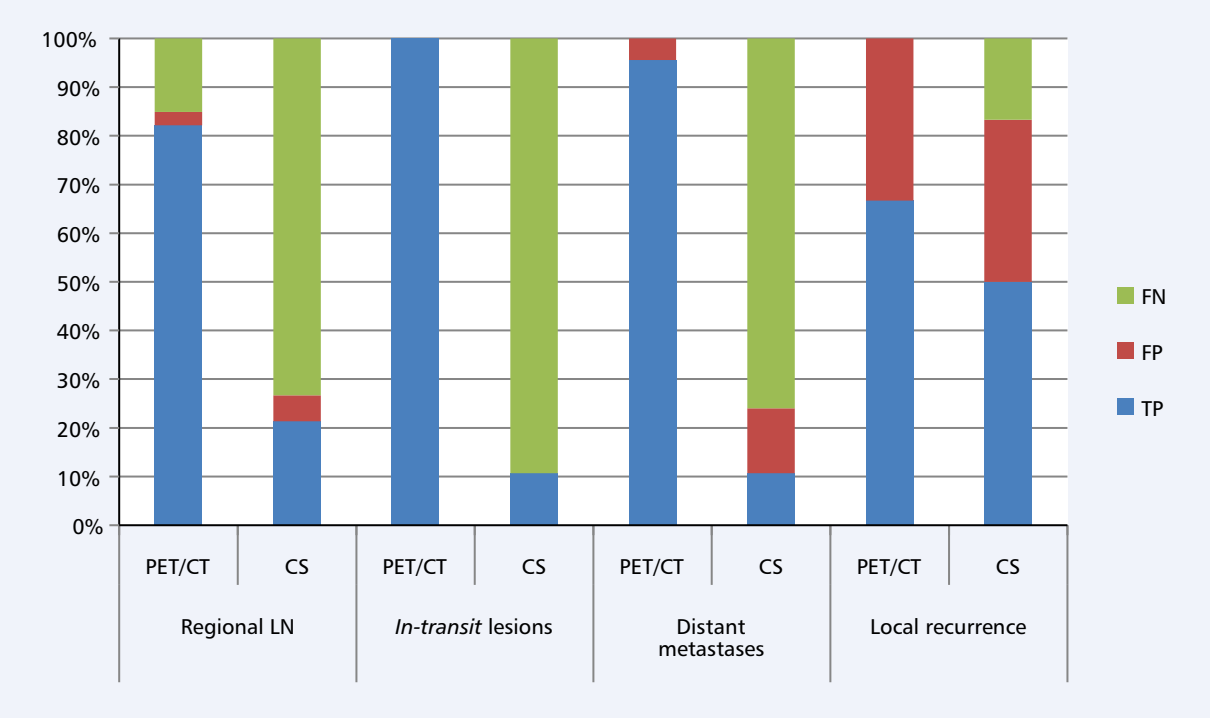

Figure 2. Diagnostic accuracy of 18F-FDG PET/CT in different malignant lesions in cutaneous melanoma patients; PET/CT — positron emission tomography/computed tomography; CS — conventional studies; LN — lymph node; FN — false negative; FP — false positive; TP — true positive

Statistics

The statistical analysis was done using IBM®SPSS®Statistics, v.19.0.0. The tables were made with Microsoft Office 2010. We processed the qualitative data of the patients using descriptive statistics. The quantitative data were presented as mean values, ranges, and standard deviations of the variables. The accuracy of 18F-FDG PET/CT was studied by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of 18F-FDG PET/CT in comparison with a combination of CIS, using lesion-based analysis.

Results

In total, in all patients, there were 71 malignant lymph nodes, 4 local recurrences, 28 cases of ITM, and 65 DM, confirmed histologically or during follow-up. 18F-FDG PET/CT identified 84.5% of all malignant lymph nodes (60/71), all local recurrences, ITM, and DM. 18F-FDG PET/CT additionally identified 12 undiagnosed DMs in patients with an initial non-metastatic result from conventional imaging (Fig. 2).

The true positivity rate of conventional studies in the detection of malignant lymph nodes was significantly lower than that of 18F-FDG PET/CT, leading to identification of only 16 (22.5%) true positive lymph nodes out of the 71 metastatic lymph nodes (Tab. 2, 3).

18F-FDG PET/CT had 100% sensitivity in the diagnosis of ITM, revealing all of them (28/28). By contrast, CIS performed worse in those lesions with a sensitivity of 10.7% (3/28) (Tab. 2, 3).

In our study, only 28 of all 141 patients, referred for staging with 18F-FDG PET/CT, had previous SLNB. In 12 (42.9%) of them, 18F-FDG PET/CT detected additional lesions, which changed the stage and further management of the patients. In 3 of the patients with positive SLN (stage III), additional regional lymph nodes were found, in 2 — ITM and in 6 — previously undetected DM. In one patient in the IIA CM stage and with negative SLNB, one ITM was detected. CIS performed significantly poorer, also in detecting ITM, as only 3/28 (10.7%) of them were detected (Tab. 4).

18F-FDG PET/CT has a 100% detection rate of DM and revealed all 65 lesions. Most DM were missed by CIS — 57/65 (87.7%), mainly because of small size but also due to hard-to-diagnose metastatic sites, such as peritoneal or bone marrow lesions.

In the small group of 4 patients with the local recurrent disease only, there was no significant difference in the detection rate between 18F-FDG PET/CT and CIS, mostly because of false positive lesions after excision (Fig. 3, 4).

Table 2. Diagnostic accuracy of 18F-FDG PET/CT in different cutaneous melanoma lesions

Metastatic localizations	Diagnostic accuracy of 18F-FDG PET/CT				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Regional LN	84.50	98.90	96.80	94.00	94.70
In-transit lesions	100.00	100.00	100.00	100.00	100.00
Distant metastases	100.00	98.30	95.60	100.00	98.80
Local recurrence	100.00	99.20	66.70	100.00	99.20

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

Table 3. Diagnostic accuracy of conventional studies in different cutaneous melanoma lesions

Metastatic localizations	Diagnostic accuracy of conventional imaging methods				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Regional LN	22.50	97.70	80.00	75.70	76.00
In-transit lesions	10.70	100.00	100.00	89.70	89.80
Distant metastases	12.30	94.50	44.40	75.00	72.80
Local recurrence	75.00	99.20	60.00	99.60	98.80

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

Table 4. 18F-FDG PET/CT findings in patients who had sentinel lymph node biopsy (SLNB) performed before imaging.

Additional 18F-FDG PET/CT findings	SLNB result	
	positive	negative
Regional lymph node	3	0
Distant metastasis	6	0
In-transit metastasis	2	1
No lesions	5	11

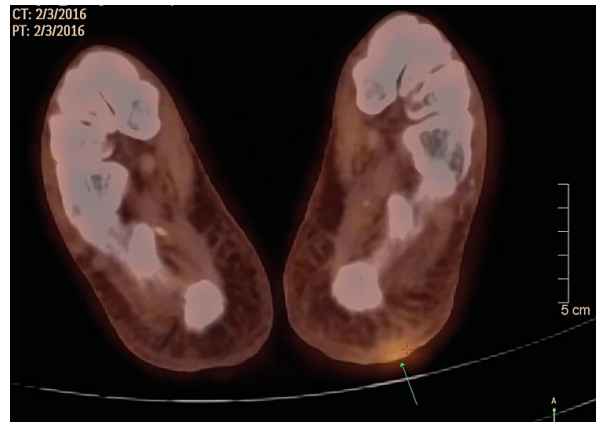

Figure 3. Staging of a cutaneous melanoma patient one month after tumor excision in the left foot, pT3b pN0 cM0. False positive skin thickening in the excision place, which was proven to be benign

Despite the high sensitivity (84.5%) of 18F-FDG PET/CT in the detection of regional lymph nodes, compared to 22.5% for CIS, 18F-FDG PET/CT failed to recognize 11 (1.1%) malignant lesions. All of them were non-significant lymph nodes, well recognized by further ultrasonography, which in those cases performed better than 18F-FDG PET/CT (Fig. 5).

Additionally, 18F-FDG PET/CT demonstrated 0.7% false positive results (FP), with 7 identified as malignant FP lesions: 3 DM, 2 metastatic regional lymph nodes, and 2 local recurrences (Fig. 3, 4), all proven FP by histology. The FP distant metastases (DM) were two cases of mediastinal lymph nodes due to sarcoidosis (Fig. 6) and one metabolically active hepatic lesion, all of them histologically proven benign.

Discussion

Cutaneous melanoma accounts for a small percentage of skin cancer cases but is responsible for the majority of skin cancer deaths. PET scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease. Most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma [4, 5]. In patients with stage III disease, 18F-FDG PET/CT may be more useful. In particular, 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) [6, 7]. No randomized controlled studies (RCTs) comparing CT and 18F-FDG PET/CT in the staging of melanoma were identified. A meta-analysis by Xing et al. found that for staging of DM, 18F-FDG PET/CT had the highest sensitivity (80%, 95% CI = 53% to 93%), specificity (87%, 95% CI = 54% to 97%), and diagnostic odds ratio

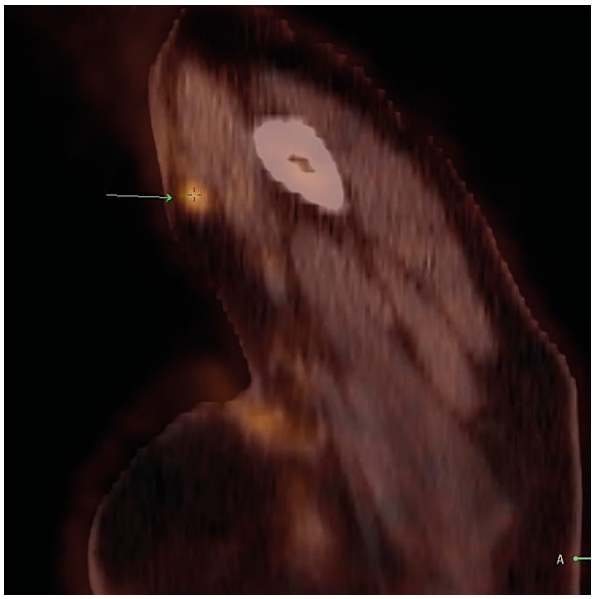

Figure 4. A patient with a right brachial cutaneous melanoma. 18F-FDG PET/CT was performed one month after axillary lymph node dissection for recurrent disease (rpN3b). A nodular lesion with high metabolic activity was found in the proximal brachium, suggesting a local recurrent disease. The latter was histologically proven benign granuloma

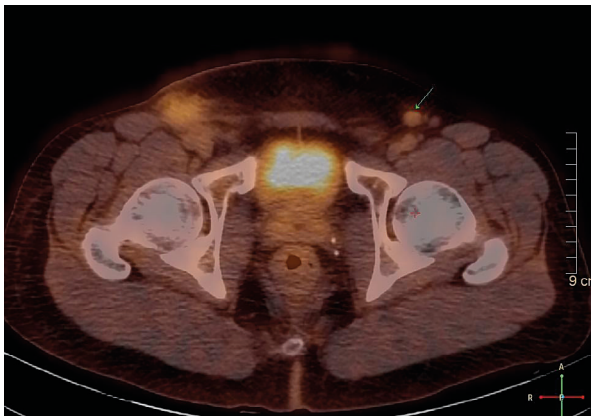

Figure 5. A patient with cutaneous melanoma of the trunk after excision of the primary tumor and right inguinal lymph node dissection, pT4b pN1b cM0. The patient was referred for an 18F-FDG PET/CT staging. There was a non-significant, but suspicious inguinal lymph node on the left, with no fatty center, with round shape, and metabolic activity slightly higher than the background. The patient was referred for an ultrasonographic exam and afterward for an excision

(25, 95% CI = 3.58 to 198.7) [8]. These results comply with our observation on 18F-FDG PET/CT sensitivity for DM, revealing 100% sensitivity compared to 12.3% for CIS. The specificity was good for both methods — 98.3% for 18F-FDG PET/CT and 94.5% for CIS.

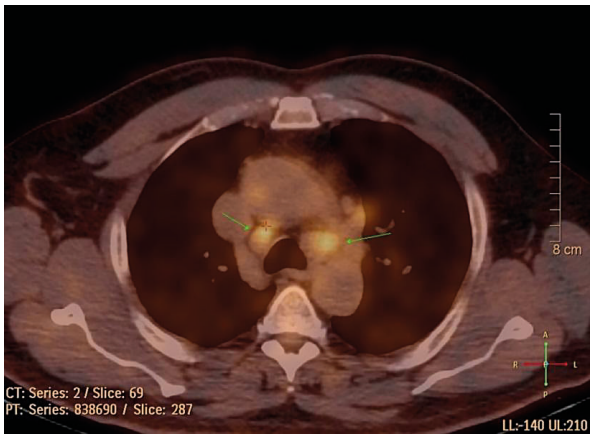

Figure 6. Patient with lower extremity cutaneous melanoma referred for restaging after recurrent disease. 18F-FDG PET/CT found mediastinal and symmetrical bilateral hilar lymphadenopathy, proven to be benign sarcoidosis

Systematic reviews on melanoma found 18F-FDG PET/CT to have a sensitivity of 68–87% and specificity of 92–98% in patients with stage III or stage IV disease [9] and specificity of 89% in patients with stage III disease [10]. According to most guidelines, 18F-FDG PET-CT should only be considered for patients with indeterminate findings on CT or for patients who are being considered for major surgical resection, after discussion with the specialist multidisciplinary team [11, 12]. NCCN recommends staging using 18F-FDG PET-CT from stage IIC whole-body examinations as an alternative to CT [13]. According to European Society for Medical Oncology (ESMO) recommendations, in IB–IIC stage CM 18F-FDG PET-CT, along with US for RLN, and/or CT, as well as brain magnetic resonance imaging (MRI), represent options for tumor extension assessment before surgical treatment and SLNB. Also, they recommend 18F-FDG PET/CT for staging only in very high-risk patients (pT3b and higher (III, C) [14]. The CM diagnosis and management recommendations from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization of Research and Treatment of Cancer (EORTC) [15] state that ultrasound is the best method to detect subclinical metastatic nodal disease, compared to palpation, CT, or 18F-FDG PET/CT, with the highest sensitivity (60%, 95% CI = 33% to 83%), specificity (97%, 95% CI = 88% to 99%), and diagnostic odds ratio (42, 95% CI = 8.08 to 249.8). The better sensitivity of 18F-FDG PET/CT in malignant lymph node recognition demonstrated an 84.5% detection rate in our study. It was possibly due to careful attention to regional lymph node basins which took into account their morphology, not only the metabolic activity, and further investigation of lymph nodes with oval or round shape, partly or fully

missing fatty hilum, and metabolic activity higher than the background. There are meta-analyses, confirming that 18F-FDG PET/CT is superior to CT for the diagnosis of DM or recurrence in restaging, but not during initial staging [16, 17].

The main role of US is in the diagnosis and follow-up of regional lymph nodes. US examinations have been shown to be superior to clinical examinations in the diagnosis of nodal metastases [15], but they may give false negative results in metastatic deposits smaller than 2 mm in size [18]. In the latest revision of the National Comprehensive Cancer Network (NCCN) 3.2022 recommendations, a new footnote states that US of lymph nodes requires specific radiologic expertise. Criteria for early nodal involvement by CM include the following features: hypoechoic island(s) in the cortex, asymmetric focal cortical thickening, and peripheral blood supply, especially when blood supply is established in areas of cortical thickening (Fig. 1). Core biopsy or aspiration biopsy of suspicious lymph nodes should be directed at the atypical areas in the cortex of the lymph node identified by US [13].

Sentinel lymph node biopsy is the gold standard for non-palpable lymph node staging in CM, which was also proven in our study, where 18F-FDG PET/CT found additional lesions only in patients with stage III disease after SLNB. Most guidelines do not recommend using 18F-FDG PET/CT in SLNB-positive patients because the yield is low in this setting (0.5–3.7%) [19]. Although American Academy of Dermatology (AAD) recommends PET-CT if the patient has nodal metastasis in SLNB (stage III). [12] In our study, 18F-FDG PET/CT detected additional malignant lesions in 12/28 patients (42.9%), which changed the stage and further management of the patients.

18F-FDG PET/CT also acted as an invaluable method for ITM recognition with 100% sensitivity, specificity, PPV, NPV, and accuracy. It was also able to reveal clinically not evident ITM in one patient in stage IIA, after negative SLNB. The superiority of SLNB over 18F-FDG PET/CT in detecting clinically not evident RLN has been previously discussed and confirmed in the literature [16]. ITMs occur in 2–10% of CM patients and are frequently associated with the development of nodal and/or systemic metastases [20], even in sentinel node-negative patients [21]. In our study, all of the ITM were identified, and all of them were smaller than 1 cm. All of them, except one, were detected in patients after surgical resection of locoregional recurrence. CM cells have high glutamine receptor activity and high levels of intracellular hexokinase. For this reason, CM has high avidity for the glucose analog ^{18}F-fluorodeoxyglucose (FDG) that is used for 18F-FDG PET/CT and is useful in detecting subcentimeter malignant lesions [22]. SLNB cannot detect in-transit metastases, which account for most locoregional recurrences [23]. High-frequency ultrasound is considered the best modality for detecting and diagnosing in-transit metastases due to its high accuracy in detecting smaller lesions [24, 25]. However, this technique has several limitations, including its dependence on operator skills, availability of an expert radiologist, and long study-performance time (at least 30–40 min for each limb or body area).

Conclusions

18F-FDG PET/CT is a key imaging method for staging and restaging patients with CM after complete resection of the recurrent locoregional disease, performing significantly better than CIS. The hybrid technique has a great advantage to detect DM disease and ITM in comparison to the conventional studies and must be used also in stage II patients as a baseline study after SLNB to exclude additional lesions. There is a high true positivity rate in the detection of malignant lymph nodes but still not enough to rely only on this method, mandating further SLNB and follow-up. This article underlines the complexity of the multimodality management of CM and also the need for further assessment of any suspicious lymph nodes detected by 18 F-FDG PET/CT in the draining LN basin with ultrasonography and/or biopsy.

Conflict of interest

Authors declare no conflict of interest.

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