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ORIGINAL ARTICLE

Diagnostic value of ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography imaging in acral melanoma–predominant Asian patients

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Abstract

Background: Tumor staging is crucial for melanoma, of which acral melanoma is the predominant subtype in Asians. ^{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) and ^{18}F-FDG-PET/computed tomography (^{18}F-FDG-PET/CT) serve as noninvasive imaging tools for tumor staging. However, the literature is scarce on the diagnostic value of PET for acral melanoma.

Methods: From January 1, 2006 to November 30, 2022, a total of 352 patients were diagnosed with melanoma at our hospital. Of them, 90 were diagnosed with cutaneous melanoma and underwent preoperative PET/CT for staging and sentinel lymph node biopsy or complete lymph node dissection. Staging of PET/CT was confirmed by histopathology or following imaging. The lymph node biopsy, distant metastasis status, and PET/CT imaging results were analyzed.

Results: Of all the 90 patients with cutaneous melanoma, 72 of them were diagnosed as acral melanoma (80.0%). Compared with the histopathologic results, the lymph nodes were true-positive, true-negative, false-positive, and false-negative in 12, 54, 7, and 17 cases, respectively. The sensitivity of PET/CT for local lymph nodes was 41.4% (95% CI, 23.5%-61.1%), whereas its specificity was 88.5% (95% CI, 77.8%-95.3%). As for the detection of distal metastasis, the PET results were true-positive, true-negative, false-positive, and false-negative in 6, 65, 15, and 4 cases, respectively. The sensitivity of PET for distal metastasis detection was 60.0% (95% CI, 26.2%-87.8%), whereas its specificity was 81.3% (95% CI, 71.0%-89.1%).

Conclusion: Although noninvasive, PET/CT has relatively low sensitivity in regional lymph node evaluations, and fair sensitivity in distal metastasis detection in Asian patients with acral melanoma. Thus, PET/CT may be more useful in patients with clinically palpable nodes or more advanced disease stages.

Keywords: Melanoma; Neoplasm Staging; Positron emission tomography; sentinel lymph node biopsy; sentinel lymph node

1. INTRODUCTION

Melanoma is among the deadliest skin cancer, and its incidence is increasing worldwide with racial differences.[1] Its incidence in Caucasians is 21.9 to 55.9 per 100 000 patient-years in Western countries vs only 0.2 to 0.5 per 100 000 patient-years in Asian countries.[1] The staging of melanoma is crucial because different stages require different treatments and feature different prognoses.[2] Surgical excision with adequate margins is the primary curative treatment for localized melanoma. If malignant cells are also present in the regional lymph nodes, nodal basin surveillance or complete lymph node dissection for local control has been recommended.[3] Although surgical removal remains an option for specific patients with more advanced disease, multiple treatment options are available and under study, including traditional chemotherapy, targeted therapy, and immunotherapy.[3,4]

The early detection of distant metastases is important for subsequent systemic therapy. Studies have revealed that nodal status is the most important and independent prognostic factor for melanoma.[5–7]

To evaluate regional nodal status, sentinel lymph node biopsy has become common in patients with melanoma without clinically palpable nodes.[2] According to American Society of Clinical Oncology and Society of Surgical Oncology, sentinel lymph node biopsy may be considered for tumor thickness between 0.8 and 1 mm or <0.8 mm with ulceration (T1b) and is often recommended when the tumor thickness exceeds 1 mm.[8] However, sentinel lymph node biopsy is invasive; thus, it features morbidities including, seroma, lymphedema, and infection. Over the last 20 years, the role of ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in the evaluation and staging of melanoma has been discussed.[9–11]

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Positron emission tomography/computed tomography (PET/CT) is a relatively expensive modern tool for oncological staging. Before examination, ^{18}FDG was injected intravenously. Because tumor cells often have a higher glucose metabolic rate than normal cells, PET/CT can identify the tumor location and possible metastatic site.[12] Therefore, PET/CT has been applied to various malignancies, such as melanoma, lung cancer, and colorectal cancers.[13] Compared with sentinel lymph node biopsy or lymph node dissection, positron emission tomography (PET) is a noninvasive imaging technology that evaluates the possible tumor status throughout the body except for the brain because normal brain cells also prefer utilizing glucose as an energy source.[12] In addition to the local nodal status, PET/CT can evaluate the primary tumor site and size, distal suspicious nodes, and distant metastasis.

Previous studies investigated the role of PET/CT in melanoma staging.[1,9,14,15] However, most were conducted in Western countries, where acral melanoma is a rare melanoma subtype. In contrast, it is the predominant subtype in non-Caucasian societies; it is also distinct because it has a different pathogenesis and genetic background and is less often related to excess ultraviolet exposure.[16–19] To the best of our knowledge, there is only one study reported the staging function of PET/CT in Japanese with acral melanoma (by Ide et al[20]). However, the study exclude any clinical signs of distal metastasis and most of them (100 over 109) did not have clinical palpable nodes. Thus, this study aimed to evaluate the role of PET/CT in the assessment of regional nodal status and distal metastasis in Asian patients, especially in the acral subtype and comparing to the studies from Caucasians.

Due to the relatively poor prognosis of acral over melanoma, diagnostic tools for its staging and early detection are even more important. However, the literature on the diagnostic value of PET in Asian patients is scarce, especially for acral melanoma.

Thus, this study aimed to evaluate the role of PET/CT in the assessment of regional nodal status and distal metastasis in Asian patients with acral melanoma.

2. METHODS

This study was conducted in accordance with the tenets of the 2013 version of the Declaration of Helsinki. Upon receiving study approval from the local research ethics board (nos. 2020-01-013BC and 2022-06-007A), a retrospective chart review was performed of all patients diagnosed with cutaneous melanoma who underwent surgical treatment at the institution between January 2006 and December 2022. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in this study.[21] Clinicopathological staging was determined according to the American Joint Committee on Cancer staging criteria. Patients with inadequate data, who had significant comorbidities, who did not undergo PET/CT scans, and/or who were diagnosed with other malignant solid tumors were excluded from the study. The patients' demographics and tumor characteristics, including age, sex, location, Breslow thickness (tumor depth classified as T1 [≤1.0 mm], T2 [1.1-2.0 mm], T3 [2.1-4.0 mm], or T4 [>4.0 mm]), primary tumor site, lymphovascular invasion, ulceration, and lymph node characteristics were collected and analyzed. The study design is illustrated in Fig. 1.

Any suspicious finding of lymphadenopathy or distal metastasis on PET/CT was considered positive. The accuracy of regional nodal status assessment for PET/CT was evaluated by histopathology of sentinel lymph node biopsy or complete lymph node dissection. The distal metastasis result was evaluated by biopsy, computed tomography (CT), magnetic resonance imaging (MRI), or a whole-body bone scan. A newly detected metastasis within 3 months after the PET/CT was viewed as a false-negative result.[20]

All analyses were performed using Windows Excel 2013 (Microsoft, Redmond, WA) and SPSS for Windows version 29.0 (IBM Inc., Armonk, NY). The results were analyzed using the chi-squared test and the two-sample t test. Statistical significance was set at $p < 0.05$. A comprehensive literature review was then conducted.

3. RESULTS

A total of 352 patients were diagnosed with melanoma, of whom 90 had cutaneous melanoma and had undergone sentinel lymph node biopsy or complete lymph node dissection with PET/CT. The patients' demographic characteristics are presented in Table 1. Of the 90 patients, 72 (80%) were diagnosed with acral melanoma, all of whom were East Asian.

The mean patient age was 67.1 ± 15.1 years; 57 (63.3%) were male and 33 (36.7%) were female. Most of the tumors were located in the acral region (80%), followed by the trunk (8.9%), extremities (7.8%), and head and neck (3.3%). The

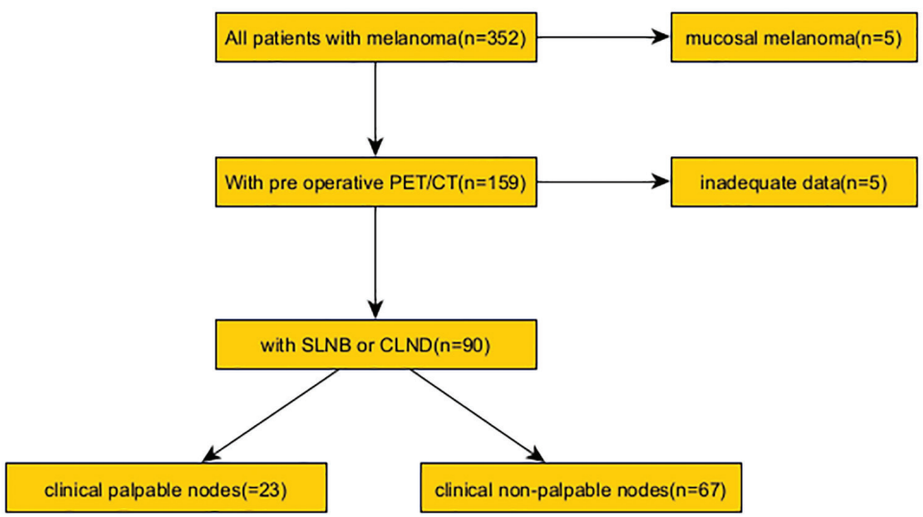

Fig. 1 Flow diagram of the retrospective study design. CLND = complete lymph node dissection; CT = computed tomography; PET = positron emission tomography; SLNB = sentinel lymph node biopsy.

Table 1

Baseline characteristics and clinical factors

Characteristics		
Gender		
Male	57 (63.3%)	
Female	33 (36.7%)	
Mean age (years old)		67.1 ± 15.1
Age	≥65 yr old	53 (58.9%)
	<65 yr old	37 (41.1%)
Race		
	East Asian	100 (100%)
Subtype		
	Acral	72 (80%)
	Nonacral	18 (20%)
Location		
	Extremity	7 (7.8%)
	Trunk	8 (8.9%)
	Head and neck	3 (3.3%)
	Acral	72 (80%)
Breslow depth		3.9 ± 3.03 mm
Breslow thickness		
	Tis	2 (2.2%)
	T1	9 (10%)
	T2	21 (23.3%)
	T3	31 (34.4%)
	T4	27 (30%)
Palpable lymph nodes before operations		
	Yes	23 (25.6%)
	No	67 (74.4%)
Other characteristics		
	Ulceration	49 (54.4%)
	Lymphovascular invasion	2 (2.2%)
	Mean LDH level (129-565 IU/L)	210 ± 65.2 IU/L
	Average mitotic rate (0-15 mitoses/mm^2)	4.6 ± 3.8 mitoses/mm^2

LDH = lactate dehydrogenase.

mean Breslow thickness was 3.9 ± 3.03 mm; for staging, two (2.2%) patients were Tis, nine (10%) at T1, 21 (23.3%) at T2, 31 (34.4%) at T3, and 27 (30%) at T4. There were 49 (54.4%) cases of ulceration and two (2.2%) cases of identified lymphovascular invasion. The mean serum lactate dehydrogenase level at the time of diagnosis was 210 ± 65.2 IU/L, with an average mitotic rate of 4.6 ± 3.8 mitoses/mm^2.

One (1.1%) patient had satellite nodules, whereas 23 (25.6%) had clinically palpable nodes before surgery.

All 90 patients, including the 23 with clinically palpable lymph nodes, underwent preoperative PET/CT and sentinel lymph node biopsy or complete lymph node dissection during surgery. The diagnostic value of PET/CT for the included patients and the sensitivity of lymph node status were 41.4% and 88.5%, respectively. In patients with clinically palpable regional lymph nodes, the sensitivity of lymph node status by PET/CT was 68.8%, whereas the specificity was 57.1%. For patients without clinically palpable lymph nodes, the sensitivity of PET/CT for regional lymph node status was 7.7%, whereas the specificity was 92.6%. Regarding distal metastasis detection, the sensitivity of lymph node status was 60.0%, whereas the specificity was 81.3%. The sensitivity of PET in patients with clinically palpable lymph nodes was 50% with 86.7% specificity, whereas those for patients without clinically palpable lymph nodes were 100% and 80%, respectively. The sensitivity and specificity of PET/CT for regional lymph node detection between patients with palpable vs nonpalpable lymph nodes were statistically significant. The results are summarized in Table 2.

Table 2

The sensitivity and specificity of PET/CT in lymph node status

	Total (n = 90)	Palpable LNs (n = 23)	Nonpalpable LNs (n = 67)	*p*
Regional lymph nodes				
Sensitivity	41.4% (12/29)	68.8% (11/16)	7.7% (1/13)	**0.001**
Specificity	88.5% (54/61)	57.1% (4/7)	92.6% (50/54)	**0.032**
Distal metastasis				
Sensitivity	60.0% (6/10)	50% (4/8)	100% (2/2)	0.47
Specificity	81.3% (65/80)	86.7% (13/15)	80% (52/65)	0.82

LN = lymph node; PET/CT = positron emission tomography/computed tomography.

p-values < 0.05 are in bold font and represent statistical significance.

4. DISCUSSION

PET/CT has become a relatively modern and noninvasive imaging tool for detecting various tumor stages, and its role in malignant melanoma has been discussed in many studies. Nodal status is the most important prognostic factor in melanoma, for which lymph node status assessment is crucial.[2] Here, we investigated the accuracy of PET/CT in evaluating the regional lymph node status and detecting distal metastases among Asians with acral melanoma. However, PET/CT showed poor sensitivity for the local lymph node status assessment, with a sensitivity of only 41.4% and specificity of 88.5%. In our literature review, most studies also showed poor sensitivity of PET/CT for local lymph node evaluations. The sensitivity and specificity of PET/CT for local nodal status across different studies are listed in Table 3.

The majority of the above studies were conducted in Western countries, and all except for the study by Aukema et al[26] showed poor sensitivity for PET/CT in regional lymph node status assessments. The unsatisfactory sensitivity of PET/CT in nodal staging may be due to the limitations of the radiation detected by the machine. Wagner et al[30] investigated the threshold of tumor volume that can be detected by PET/CT. In that study, the sensitivity for the detection of all tumors was 0.49, with an observed 90% sensitivity threshold for nodal metastases of 79 mm^3, whereas the sensitivity decreased to 0.14 with tumor volumes <78 mm^3. This may explain why most studies to date reported poor sensitivity of PET/CT for detecting the local nodal status of melanoma. In contrast, sentinel lymph node biopsy or lymph node dissection can identify nodal micrometastases through microscopy; thus, it is a more sensitive method for local nodal status evaluations.

This result may also explain why the sensitivity of the study by Aukema et al[26] was high at 86.7%. In that study, the inclusion criterion of the study group was clinically palpable nodes. With a clinically positive regional nodal status, the tumor load of the palpable nodes was much higher, making the radiation sufficient for detection. Thus, in advanced-stage disease, due to the higher tumor volume of lymph nodes, PET/CT has higher diagnostic accuracy, and its noninvasive systematic screening characteristics remain valuable for clinicians.[31] In our study, among patients with clinically palpable lymph nodes, the sensitivity was 68.8%, whereas in patients without clinically palpable lymph nodes, the sensitivity was only 7.7%, showing a statistically significant difference. This can be explained by the fact that greater tumor load in the lymph nodes was detectable by PET/CT. However, the specificity of PET/CT in patients with clinically palpable lymph nodes was also significantly lower. This might be due to some clinically palpable lymph nodes being reactive, which resulted in more false-positive results and lower specificity.

Most studies in Table 3 were conducted in Western countries, with acral melanoma being a rare subtype. However, comparing our study to the studies listed in Table 3, racial differences may not have a significant impact on the sensitivity and specificity of PET/CT. Ide et al[20] conducted a study in Japan of all patients diagnosed with acral melanoma without clinically palpable nodes, and the sensitivity and specificity of the study seemed not to differ significantly compared with those of other studies that only included patients without clinically palpable nodes compared with our study, which showed ethnic similarities and a higher sensitivity of 41.4%. However, if we included only patients with a clinically negative lymph node status, its sensitivity decreased to 7.7%, which is similar to the results of Ide et al.[20] In conclusion, ethnicity may not significantly impact PET/CT sensitivity.

For distal metastasis detection, various studies have evaluated the sensitivity and specificity of PET/CT and reported differing results (Table 4). The sensitivity of the studies varied, but generally, the sensitivity of PET for distal metastasis was higher than that for regional lymph node assessment, with acceptable specificity for both. The difference in sensitivity across studies may also have been caused by the differences in inclusion criteria of the study populations. As previously stated, the sensitivity of PET was determined by tumor volume. As shown in Table 4, the study populations with more advanced-stage disease mostly had higher sensitivity. According to Wagner et al,[29] the sensitivity of PET/CT for distal metastasis detection was only 4%. However, patients with clinically palpable nodes and clinical evidence of distal metastasis were excluded from that study, which may explain the poor sensitivity.

The sensitivity and specificity of our study were similar to those of most studies listed in Table 4. As previously stated, ethnicity or melanoma subtype may not have a significant impact on the sensitivity or specificity of PET/CT in melanoma. This result implies that the use of PET/CT is more suitable for distal metastasis assessment in advanced-stage melanoma cases.

Here, we investigated the diagnostic value of PET/CT in melanoma. Although PET/CT has been widely adopted as a systemic diagnostic tool for staging, other diagnostic tools, including ultrasound for local nodal status assessment, MRI, or CT for distal metastasis detection, have been used. Dinnes et al[38] conducted a systematic review evaluating different diagnostic tools for melanoma staging. However, this review showed a lack of evidence regarding the accuracy of imaging.

Table 3

The sensitivity and specificity of PET/CT in local nodal status across different studies and countries

Study	Design	n	Sensitivity	Specificity	Inclusion criteria	Country
Acland et al[22]	Prospective	50	0	80.6	T stage ≥2 or lymph invasion	UK
Fink et al[23]	Prospective	48	13	100	T stage ≥2 with cN negative	Austria
Singh et al[24]	Prospective	52	14.3	94.7	T stage ≥2 with cN negative	Germany
Hafner et al[25]	Prospective	100	8	100	T stage ≥2	Switzerland
Aukema et al[26]	Prospective	70	86.7	97.5	cN positive	The Netherland
Veit-Haibach et al[27]	Prospective	56	38.5	100	-	Germany
Havenga et al[28]	Prospective	45	15%	84%	T stage ≥2 with cN negative	The Netherland
Wagner et al[29]	Prospective	144	21%	97%	T stage ≥2 with cN negative	The United States
Schaarschmidt et al[10]	Retrospective	52	17.7%	95.6%	-	Germany
Ide et al[20]	Retrospective	100	14.3	82.6	Acral melanoma No clinical signs of distal metastasis cN negative	Japan
Our study	Retrospective	90	41.4%	88.5%	-	Taiwan

cN = clinically palpable nodes; PET/CT = positron emission tomography/computed tomography.

Table 4

The sensitivity and specificity of PET/CT for distal metastasis across different studies and countries

Study	Design	n	Sensitivity	Specificity	Inclusion criteria	Country
Hafner et al[25]	Prospective	100	NA (0/0)	98%	T stage ≥2	Switzerland
Reinhardt et al[32]	Prospective	250	93.8%	97.6%	-	Germany
Bastiaannet et al[33]	Prospective	251	86.1%	93.6%	cN positive	The Netherlands
Veit-Haibach et al[27]	Prospective	56	41.7%	93.2%	-	Germany
Swetter et al[34]	Retrospective	104	84%	97%	-	The United States
Wagner et al[29]	Prospective	136	4%	86%	T stage ≥2 with cN negative	The United States
Brady et al[35]	Prospective	103	68%	92%	Clinical stage IIC, III, IV	The United States
Arrangoiz et al[36]	Retrospective	100	61.5%	80.5%	T4	The United States
Tyler et al[37]	Prospective	95	87%	44%	Clinically palpable nodes	The United States
Our study	Retrospective	90	60%	81.3%	-	Taiwan

PET/CT = positron emission tomography/computed tomography.

For local nodal status assessments using ultrasound, most studies were small, whereas the CI was wide. When it comes to CT or MRI, comparative data with PET/CT are lacking. Thus, the comparative diagnostic value of other imaging tools requires investigation.

In conclusion, although with noninvasive characteristics, the role of PET/CT in local nodal status assessment may be just limited to patients with clinically palpable nodes. The sensitivity and specificity of PET/CT for local nodal status and distal metastasis assessment seemed to be dependent on the tumor volume being detected, with little racial or histological subtype difference. For patient without palpable regional lymph nodes, the role of PET/CT for staging is very limited, and invasive procedure as sentinel lymph node biopsy was still needed for staging.

This study has some limitations. First, it was a retrospective study, and all data were drawn from medical records. Second, the accuracy of PET/CT for distal metastasis was not confirmed by histopathology. Newly detected metastasis by CT scan, MRI, and whole-body bone scan within 3 months after PET/CT were considered false-negative results,[20] which may have limited the applicability of the present study's findings.

Furthermore, although noninvasive, PET/CT has relatively poor sensitivity for local nodal evaluation in melanoma. Thus, its use may be more suitable in more advanced melanoma cases, in patients with clinically palpable nodes, or for distal metastasis detection.

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