

REVIEWS

Comparison between ^{18}F -FDG PET (PET/CT) and sentinel lymph node biopsy in the detection of regional lymph node metastasis of various malignancies: review of the literature

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Abstract

This article reviewed comparative studies of the use of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) and sentinel lymph node biopsy (SLNB) for the detection of regional lymph node metastasis in patients with various malignancies. We sought to evaluate the diagnostic accuracy of ^{18}F -FDG PET (PET/CT) compared with SLNB to determine the presence or absence of regional lymph node metastasis. In this paper, we review 15 comparative studies of breast tumors and 17 comparative studies of melanomas that used these methods to detect regional lymph node metastasis. Original articles for other malignancies, including oral and oropharyngeal carcinoma, penile carcinoma, anal cancer, and cervical cancer, are relatively scarce. A consensus has been reached in the literature that SLNB is much more sensitive than ^{18}F -FDG PET and PET/CT for detecting small lymph node metastasis. ^{18}F -FDG PET and PET/CT cannot replace SLNB for the evaluation of early-stage regional lymphatic tumor dissemination in this patient population.

Key words

Sentinel lymph node biopsy, ^{18}F -fluorodeoxyglucose positron emission tomography, Positron emission tomography/Computed tomography, Malignancy, Regional lymph node metastasis

1 Introduction

The term “sentinel lymph node” (SLN), designated as the first node(s) to receive metastasis from the primary tumor, was coined by Gould and his colleagues in 1960 to describe the spread of parotid cancer^[1]. The same concept was applied to penile carcinoma by Cabanas. He concluded that SLNs can predict metastatic spread to respective regional lymphatic basins in the study of the lymphatic drainage pattern of the penis^[2]. The current use of the term should be attributed to Morton, who defined an SLN as the first regional step of lymphatic drainage that receives lymph flow from a primary tumor and thus the first lymph node encountered by tumor cells that metastasize through lymphatics in a regional lymphatic basin^[3]. The histological status of SLNs, therefore, can predict the status of at-risk regional lymphatic basins. If the SLN is negative, then other lymph nodes in the same basin unlikely contain micrometastases. If the SLN is positive,

then the metastasis of additional lymph nodes in the basin is significant^[4,5]. Recently, the SLN concept was applied in the management of various malignancies. Many types of cancers spread through both the lymph and blood circulatory systems. The spread to regional lymph nodes is the most common initial site of metastasis, and the importance of the regional lymphatic basin as an initial site of metastasis has been widely accepted. In fact, the presence of regional lymph node metastasis was considered the most important prognostic factor in melanoma survival^[6] and other types of malignancies. The number of lymph nodes involved has been further shown to impact survival. Thus, ascertaining regional lymph node metastasis is important in the management of malignancies.

The sentinel lymph node biopsy (SLNB) technique was developed by Morton *et al.*, who demonstrated a false-negative rate of less than 1%^[7]. During the past 10 years, the procedure has been progressively introduced to avoid unnecessary regional lymph node dissection when the SLN is not pathologically involved. SLNB is becoming the standard of care for regional lymph node metastasis and the staging of many solid tumors in medical practice^[7]. However, SLNB is a moderately invasive surgical procedure that may require general anesthesia and additional preoperative investigations to determine regional draining basins, with potential morbidity to patients. Performing SLNB requires extra time by a team of pathologists for extensive histological examination to determine the regional draining basins, thus prolonging the surgical session. Additionally, in a limited number of cases, the SLN is not identified, and SLNB does not provide evidence of whether distant disease is present.

Positron emission tomography (PET) with fluorine-18 2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG) labeling is a noninvasive imaging procedure that can diagnose regional lymph node involvement. ¹⁸F-FDG injected intravenously accumulates not only in malignant tissues but also at sites of lymph node metastasis. One study reported that melanoma metastases as small as 3 mm were detected by ¹⁸F-FDG PET^[8]. Therefore, ¹⁸F-FDG PET may be one of the most sensitive imaging techniques available. Smith *et al.*^[9] and Greco *et al.*^[10] demonstrated that ¹⁸F-FDG PET is able to identify occult axillary lymph node metastasis in patients with breast tumors and found excellent results. However, other authors found less satisfactory results^[11,12]. Additionally, with the development of computer technology, PET imaging has been fused with computed tomography (CT) to produce PET/CT images that permit more accurate localization of areas of elevated metabolism. As a result, PET/CT has recently received attention as one of the most advanced multi-mode radiological techniques available that contributes to the detection of regional lymph node metastasis in various malignancies.

Comparing the merits and demerits of using either ¹⁸F-FDG PET (PET/CT) or SLNB for patients with malignancies is difficult. The present article reviewed comparative studies of both tests for detecting regional lymph node metastasis in patients with malignancies, including breast tumors, melanoma, oral and oropharyngeal carcinoma, penile carcinoma, anal cancer, and cervical cancer. We sought to evaluate the diagnostic accuracy of ¹⁸F-FDG PET (PET/CT) compared with SLNB in determining the presence or absence of regional lymph node metastasis.

2 Comparison of ¹⁸F-FDG PET (PET/CT) and SLNB for detecting regional lymph node metastasis in patients with breast tumors: data from the literature

To investigate the determinants of the accuracy of ¹⁸F-FDG PET for axillary lymph node staging in breast cancer, the axillary lymph node specimens and ¹⁸F-FDG PET findings from 70 patients were evaluated by van der Hoeven *et al.*^[13]. All 70 patients with primary operable breast cancer underwent ¹⁸F-FDG PET of the chest. The images were independently interpreted by three observers in a blinded fashion with regard to ¹⁸F-FDG accumulation of the primary tumor and the axillary lymph nodes. The results were compared with histopathological SLNB analyses ($n=47$) and axillary lymph node dissection (ALND; $n=23$). Overall, 32 patients (46%) had axillary lymph node metastasis as established by SLNB (18/47) and ALND (14/23). The sensitivity and specificity of ¹⁸F-FDG PET were 25% and 97%, respectively. The ¹⁸F-FDG PET

results were false-negative in all 18 positive SLNB cases and true-positive in 8/14 ALND cases. The authors concluded that the sensitivity of ^{18}F -FDG PET in detecting occult axillary metastasis in operable breast cancer was low.

In 2002, Kelemen *et al.* [14] studied 15 invasive breast cancer patients who underwent a preoperative ^{18}F -FDG PET scan before sentinel lymphadenectomy. The ^{18}F -FDG PET and SLNB results were compared. SLNB was successful in 10 patients who underwent complete axillary dissections, with no false-negative results. ^{18}F -FDG PET identified only one of five patients who had positive pathological SLNB results, resulting in four false-negative ^{18}F -FDG PET scans. The missed sizes of lymphatic metastasis ranged from a micrometastasis identified only by immunohistochemistry to a nodal tumor that measured 11 mm in diameter. Additionally, ^{18}F -FDG PET had three false-positives. One woman with intense axillary ^{18}F -FDG uptake was determined to be tumor-free by SLNB and remained free of axillary recurrence for 29 months postoperatively. Two other cases with increased mediastinal ^{18}F -FDG accumulation were determined to be tumor-free by CT. The results of this preliminary study suggested that ^{18}F -FDG PET can be used as an adjunct to SLNB rather than as an alternative staging technique.

In an investigation performed by Guller *et al.* [15], preoperative ^{18}F -FDG PET for the detection of axillary lymph node metastasis in 31 patients with invasive breast cancer was compared with the histopathologic status revealed by SLNB. SLNB revealed nine macrometastases, four micrometastases, and one SLN with disseminated single cancer cells. The remaining 17 patients were free of metastasis in the SLN. Compared with the histopathological SLNB findings, the results of preoperative ^{18}F -FDG PET were true-positive in six patients, true-negative in 16 patients, false-positive in one patient, and false-negative in eight patients. All of the micrometastases and several macrometastases up to a diameter of 13 mm were not identified by ^{18}F -FDG PET. The overall sensitivity, specificity, and negative predictive value (NPV) of ^{18}F -FDG PET for the detection of axillary lymph node metastasis were 43%, 94%, and 67%, respectively. The data from this study indicated that ^{18}F -FDG PET cannot provide the spatial resolution necessary to accurately assess axillary lymph node metastasis in this population. Selective axillary surgery in breast cancer patients based on ^{18}F -FDG PET is not yet possible.

To assess the ability of ^{18}F -FDG PET to determine axillary lymph node metastasis in patients with breast cancer who undergo SLNB, Barranger *et al.* [16] recruited 32 breast cancer patients with clinically negative axillary nodes. All of the patients underwent ^{18}F -FDG PET, SLNB, and complete ordinal ALND. Sentinel lymph nodes were identified in all of the patients. Fourteen patients (43.8%) had metastatic SLNs. The false-negative rate of SLNB was 6.6% (1/15). In contrast, ^{18}F -FDG PET identified only three lymph node metastases in the 14 patients with positive SLNs. The overall sensitivity, specificity, positive predictive value (PPV), and NPV of ^{18}F -FDG PET for the detection of axillary metastasis were 20%, 100%, 100%, and 58.6%, respectively. ^{18}F -FDG PET demonstrated no false-positive findings. In a similar study that included a total of 98 patients with clinical Stage I or II breast cancer, Lovrics *et al.* [17] reported that the sensitivity, specificity, PPV, and false-negative rate of ^{18}F -FDG PET were 40%, 97%, 75%, and 60%, respectively. A few false-positive scans were seen in the study. The ability of ^{18}F -FDG PET to detect axillary node metastasis in patients with early breast cancer appears to be limited, and this modality cannot replace the histological evaluation of axillary node status because of its high false-negative rate. However, SLNB should be foregone, and complete ALND should be the primary procedure if ^{18}F -FDG PET reveals high metabolic activity in the metastatic axillary lymphatic region because of its low rate of false-positive findings.

To evaluate the clinical usefulness of ^{18}F -FDG PET for axillary lymph node (ALN) staging in breast cancer patients who qualify for SLNB, Fehr *et al.* [18] analyzed 24 clinically node-negative breast cancer patients with tumors that were smaller than 3 cm. ^{18}F -FDG PET detected all primary breast cancer patients. The PET staging of ALNs was accurate in 15 of 24 patients (62.5%) compared with SLNB and ALND, whereas PET staging had eight false-negative results in the 10 node-positive patients and one false-positive result. The sensitivity, specificity, PPV, and NPV of ^{18}F -FDG PET for nodal status were 20%, 93%, 67%, and 62%, respectively. The mean diameter of false-negative ALN metastases was 7.5 mm. Considering these results, the authors suggested that ^{18}F -FDG PET is not recommended for reliable staging in clinically node-negative patients with breast cancer who qualify for SLNB.

To investigate whether positive ^{18}F -FDG PET can obviate the necessity for SLNB and complete ALND in patients with breast cancer, Kumar *et al.* [19] studied 80 female breast cancer patients with clinically negative axillary nodes. All of the patients underwent ^{18}F -FDG PET. Seventy-two patients underwent both SLNB and ALND; the remaining eight patients had total axillary dissection without SLNB. Of the 80 patients, SLNB was positive for metastasis in 35 of 36 patients (sensitivity, 97%) with histopathological lymph node metastasis. SLNB had one false-negative result. ^{18}F -FDG PET was true-positive in 16 of 36 patients (sensitivity, 44%). The specificity, PPV, and accuracy of ^{18}F -FDG PET for the detection of axillary lymph node metastasis were 95%, 89%, and 72%, respectively. Univariate analysis revealed that higher tumor grade and an increased size and number of axillary lymphatic metastases were significantly associated with positive ^{18}F -FDG PET results for axillary staging. ^{18}F -FDG PET cannot replace histological staging using SLNB in patients with breast cancer. However, ^{18}F -FDG PET may be used for axillary staging in patients with high-grade tumors or a greater size and number of axillary lymph nodes because of its high specificity and PPV.

Chung *et al.* [20] performed ^{18}F -FDG PET in 51 women with 54 biopsy-proven invasive breast cancers, in which the bilateral breast was involved in some cases, before axillary surgery. The imaging results were interpreted in a blinded manner. Increased ^{18}F -FDG activity was found in 32 axillae (59%). The SUVs ranged from 0.7 to 11.0. Twenty tumors had an SUV of ≥ 2.3 , and the other 34 tumors had an SUV < 2.3 . No significant differences were found in mean age, the presence of lymphovascular invasion, mean Ki-67 level, mean tumor size, or axillary metastasis size between these two groups (SUV < 2.3 vs. SUV ≥ 2.3). The only significant difference was in axillary metastasis size (mean, 0.9 cm vs. 1.7 cm). By adopting an SUV threshold of 2.3, ^{18}F -FDG PET had 60% sensitivity, 100% specificity, and 100% PPV for predicting axillary node metastasis. The authors concluded that patients with an SUV > 2.3 had axillary metastasis, and this finding obviated the need for SLNB to diagnose axillary involvement.

To compare SLNB and ^{18}F -FDG PET for the detection of occult axillary metastasis, Veronesi *et al.* [21] studied 236 breast cancer patients with clinically negative axillary lymph nodes. In all of the patients, ^{18}F -FDG PET was performed before surgery, and SLNB was performed after identification using lymphoscintigraphy (LS). ALND was performed in patients with positive FDG-PET or positive SLNB results. The PET scan results were compared with histopathological SLNB and ALND samples. A total of 103 of the 236 patients (44%) had metastasis in axillary nodes. The sensitivity, specificity, PPV, NPV, and overall accuracy of ^{18}F -FDG PET for the detection of axillary lymph node metastasis were 37%, 96%, 88%, 66%, and 70%, respectively. The corresponding SLNB values were 96%, 100%, 100%, 97%, and 98%, respectively. The sensitivity of ^{18}F -FDG PET for the detection of occult axillary metastasis was low (37%), confirming the need for SLNB in cases in which ^{18}F -FDG PET is negative in the axillae. In contrast, the acceptable specificity (96%) of ^{18}F -FDG PET indicates that patients with PET-positive axillae should undergo ALND rather than SLNB for axillary lymph node staging.

Taira *et al.* [22] retrospectively analyzed 92 breasts/axillae in 90 patients. ^{18}F -FDG PET/CT was used to indicate SLNB in axillary lymph node metastasis-negative (N0) cases. ALND was performed in cases that were axillary lymph node metastasis-positive (Nt) on ^{18}F -FDG PET/CT. Seventy-four (80.4%) and 18 (19.6%) of the 92 axillae were diagnosed by ^{18}F -FDG PET/CT as N0 and Nt, respectively. SLNB was performed in 51 of the 74 cases that were N0 on PET/CT. ALND was performed in the remaining 23 N0 cases (at the patients' request) and all 18 of the Nt cases. Fourteen pathological Nt and 60 pathological N0 cases of the 74 N0 axillae were identified by ^{18}F -FDG PET/CT, and 13 pathological Nt cases and 5 pathological N0 cases of the 18 Nt axillae were identified by ^{18}F -FDG PET/CT. The sensitivity and specificity of ^{18}F -FDG PET/CT for diagnosing axillary metastasis were 48.1% and 92.3%, respectively. The PPV and NPV were 72.2% and 81.1%, respectively. The authors suggested that the positive detection rate of ^{18}F -FDG PET/CT was insufficient for indicating SLNB. However, the use of an appropriate SUV_{max} threshold (*i.e.*, the positive rate was 90.9% with an SUV_{max} threshold of 2.0) and exclusion of surgically biopsied cases might achieve a clinically applicable positive detection rate.

In 2009, Heusner *et al.* [23] evaluated the possible role of ^{18}F -FDG PET/CT as a triage tool for SLNB vs. ALND for axillary lymph node staging in breast cancer patients. The sensitivity, specificity, PPV, NPV, and accuracy of ^{18}F -FDG PET/CT for axillary lymph node metastasis were determined in 61 patients, with histopathology as the gold standard. The

corresponding values were 58%, 92%, 82%, 77%, and 79%, respectively. ^{18}F -FDG PET/CT was evaluated as a pretest for triage to SLNB vs. ALND according to the following equation: $NPV = \text{specificity} \times (1 - \text{prevalence}) / [\text{specificity} \times (1 - \text{prevalence}) + (1 - \text{sensitivity}) \times \text{prevalence}]$. Patients with up to ~60% risk for axillary lymph node metastasis appeared to be candidates for SLNB if the axilla was unremarkable on ^{18}F -FDG PET/CT. The authors concluded that ^{18}F -FDG PET/CT isn't able to replace SLNB or ALND for axillary lymph node staging in breast cancer patients, but the indication may be extended for SLNB.

Chae *et al.* [24] evaluated the clinical usefulness of axillary lymph node involvement using ^{18}F -FDG PET/CT compared with two other imaging methods in 108 breast tumor patients with non-palpable axillary lymph nodes. ^{18}F -FDG PET/CT, SLNB, and ALND were ordinarily performed in all of the patients enrolled in the study. The ^{18}F -FDG PET/CT findings were compared with pathological findings after surgery. The sensitivity, specificity, and accuracy of ^{18}F -FDG PET/CT were 48.5%, 84%, and 73.2%, respectively. ^{18}F -FDG PET/CT was insufficiently sensitive and accurate for detecting axillary lymph node metastasis. For this reason, ^{18}F -FDG PET/CT is not a reliable non-invasive modality for assessing axillary lymph node involvement and cannot replace SLNB or ALND before decisions are made about appropriate systemic interventions.

To determine whether preoperative ^{18}F -FDG PET/CT can be used as a guide for ALND (PET/CT N+) or SLNB (PET/CT N0) in breast cancer patients, Kim *et al.* [25] performed ^{18}F -FDG PET/CT in 137 biopsy-proven breast cancer patients. Twenty-seven patients with positive ^{18}F -FDG PET/CT scans underwent complete ALND as a primary procedure, and 110 patients with negative ^{18}F -FDG PET/CT scans underwent SLNB. The overall sensitivity, specificity, PPV, and accuracy of ^{18}F -FDG PET/CT for predicting axillary metastasis were 77.1%, 100%, 100%, and 94.2%, respectively. In the subgroup of 110 patients who underwent SLNB, 104 patients had histologically negative SLN, and six patients had positive SLN in frozen sections. SLNB based on prior ^{18}F -FDG PET/CT indicated that 27 SLNB cases (true-positive scans) were unnecessary. The authors suggested that ^{18}F -FDG PET/CT was a specific imaging modality for predicting axillary lymph node metastasis. Selective SLNB based on prior ^{18}F -FDG PET/CT reduced unnecessary SLNB, enhancing the identification rates of SLN and accuracy of SLNB.

Gilardi *et al.* [26] performed a study to determine the role of ^{18}F -FDG PET in the selection of breast cancer patients as candidates for SLNB after neoadjuvant therapy. The 44 primary breast cancer patients who enrolled in the study had a positive baseline ^{18}F -FDG PET scan of both primary tumors and axillary lymph nodes. All of the patients underwent neoadjuvant therapy and then a second ^{18}F -FDG PET scan. If the axillary nodes demonstrated high ^{18}F -FDG uptake, then the patients underwent ALND. If the second ^{18}F -FDG PET scan was negative for axillary involvement, then SLNB was performed to evaluate axillary lymph node status. Total ALND was performed in the case of positive SLNs. The specificity and PPV of ^{18}F -FDG PET for the detection of axillary lymph node metastasis after neoadjuvant therapy were as high as 83% and 85%, respectively. But the sensitivity, NPV, and diagnostic accuracy were 34%, 32%, and 48%, respectively. The latter values were inadequate for correct staging. SLNB was mandatory in cases of a negative scan because of the poor sensitivity of ^{18}F -FDG PET for detecting axillary lymph node metastasis. However, the relatively high PPV suggested that ^{18}F -FDG PET may be useful for selecting patients who are candidates for ALND rather than SLNB after neoadjuvant therapy.

To determine whether ^{18}F -FDG PET is useful for evaluating axillary lymph node involvement and detecting distant metastasis in women with primary breast cancer, 325 women diagnosed with operable breast cancer were screened by Pritchard *et al.* [27]. SLNs were found in 312 (96%) of the 325 women. Ninety (29%) of these 312 cases were positive for tumors. ALND was positive in seven additional women. The sensitivity, specificity, PPV, NPV, and prevalence of ^{18}F -FDG PET were 23.7%, 99.6%, 95.8%, 75.4%, and 29.8%, respectively. Three patients were confirmed by ^{18}F -FDG PET to have distant metastatic disease. Thirteen patients had suspicious results, and 10 patients had false-positive results for distant metastasis. ^{18}F -FDG PET was insufficiently sensitive to detect axillary lymph node involvement, and it was

insufficiently specific to appropriately identify distant metastasis. However, a positive ^{18}F -FDG PET scan was indicative of disease in the axillary nodes, owing to a very high PPV, which may influence surgical care.

3 Comparison of ^{18}F -FDG PET (PET/CT) and SLNB for detecting regional lymph node metastasis in patients with melanoma: data from the literature

Wagner *et al.* [28] conducted the first study on this topic in 1999. They prospectively compared ^{18}F -FDG PET imaging of regional lymph node basins with SLNB in patients with American Joint Committee on Cancer (AJCC) Stage I, II, and III melanoma localized to the skin. These patients with cutaneous melanoma with a Breslow depth >1 mm (AJCC T2-4N0M0) or localized regional cutaneous recurrence (TxN2bM0) underwent ^{18}F -FDG PET followed by SLNB. ^{18}F -FDG PET scans were interpreted in a blind manner and compared with histological results from the SLNB specimens. Eighty-nine lymph node basins were evaluated by ^{18}F -FDG PET, and 70 assessable patients were evaluated by SLNB. Eighteen patients (25.7%) had lymph node metastasis at the time of ^{18}F -FDG PET imaging. The median tumor volume in positive SLN was 4.3 mm^3 (range, 0.07 mm^3 - 523 mm^3). The sensitivity, specificity, PPV, and NPV of SLNB for the detection of occult regional lymph node metastasis were 94.4%, 100%, 100%, and 98.6%, respectively. The corresponding values of ^{18}F -FDG PET were 16.7%, 95.8%, 50%, and 81.9%, respectively. The authors concluded that ^{18}F -FDG PET is not a sensitive indicator of occult regional lymph node metastasis in patients with minute melanoma volumes, and ^{18}F -FDG PET does not play a primary role in staging regional lymph nodes in patients with clinically localized melanoma.

In a prospective study of 50 patients with primary melanomas (thickness >1 mm or lymphatic invasion), Acland *et al.* [29] compared the sensitivity of ^{18}F -FDG PET with SLNB for the detection of micrometastatic malignant melanoma. All of the patients underwent ^{18}F -FDG PET and subsequent SLNB. The SLN was identified in all of the patients. Fourteen patients (28%) had positive SLNB results, but none of the patients who underwent ^{18}F -FDG PET demonstrated high ^{18}F -FDG metabolism in regional lymph node basins. In seven patients, ^{18}F -FDG accumulated abnormally in other locations, and four cases were suspicious of metastatic disease. However, no patients developed recurrent melanoma after a mean follow-up period of 15 months. The authors concluded that ^{18}F -FDG PET has limitations in staging patients with primary melanoma. Although SLNB is an invasive surgical procedure, it is the only reliable method for evaluating micrometastatic malignant melanoma in the regional draining node with high sensitivity.

Belhocine *et al.* [30] prospectively assessed the value of ^{18}F -FDG PET vs. SLNB for the detection of SLN metastasis in 21 consecutive patients who presented with early-stage melanoma (AJCC Stage I or II). ^{18}F -FDG PET was positive in only one (SLN >1 cm) of six cases (28.5%) that had SLN involvement, indicated by lymphatic mapping and SLNB. In the five other cases, the SLNs that were missed by ^{18}F -FDG PET were <1 cm with focal or partial involvement. In one case, ^{18}F -FDG PET and SLNB both had false-negative results without regional nodal metastasis. However, the patient had same-basin recurrence three months later. Additionally, ^{18}F -FDG PET also had one false-positive result. In another study of 55 patients with primary cutaneous melanoma by Havenga *et al.* [31], the results were similar. ^{18}F -FDG PET was positive in only two of 13 cases (13/55) that had SLN involvement, indicated by SLNB, and ^{18}F -FDG PET had five false-positive results. In 2004, Fink *et al.* [32] studied 48 patients with primary Stage I and II melanoma who underwent ^{18}F -FDG PET and SLNB. ^{18}F -FDG PET was positive in only one of eight (8/48) patients with a positive SLNB. ^{18}F -FDG PET appeared to be an insufficiently sensitive indicator of melanoma micrometastasis because of its limited spatial resolution. Thus, ^{18}F -FDG PET is not recommended as a first-line imaging modality for staging regional lymph nodes in patients with Stage I or II melanoma. SLNB remains the procedure of choice for detecting subclinical regional lymph node metastasis from primary cutaneous melanoma because it can reveal regional metastasis that is too small to be detected by ^{18}F -FDG PET.

Longo *et al.* [33] compared the sensitivity of ^{18}F -FDG PET with SLNB for the primary identification of lymph node metastasis in 25 patients with clinical Stage I and II cutaneous melanoma. The SLNB technique had sensitivity of 100%

compared with 22% sensitivity for ^{18}F -FDG PET. In summary, ^{18}F -FDG PET is not a sensitive technique for the primary staging of patients with melanoma localized to the skin. However, metabolic imaging may have a secondary role for patients at high surgical risk or with prior wide local excisions that disrupt lymphatic drainage that renders SLNB less reliable.

To compare the roles of SLNB and ^{18}F -FDG PET in the staging of melanoma patients, Schafer *et al.* [34] studied 51 Stage I and II melanoma patients according to the guidelines of the German Dermatological Society. Tumor thickness ranged from 1.0 mm to 6.0 mm (median, 1.5 mm; mean, 2.07 mm). Eighty SLNs were excised from 69 lymphatic drainage areas, with more than one SLN excised in some patients. Positive SLNs were detected in six patients (11.8%). Preoperative ^{18}F -FDG PET was performed in 40 patients and did not demonstrate any abnormal micrometastatic accumulation foci, but the subsequent SLNB results were positive. SLNB is recommended for melanoma patients if the thickness of the primary tumor is greater than 1 mm. ^{18}F -FDG PET cannot be expected to provide additional staging information for Stage I and II melanoma patients.

Hafner *et al.* [35] studied 100 consecutive patients with malignant melanoma with a Breslow tumor thickness > 1.0 mm. The sensitivity and specificity of SLNB and ^{18}F -FDG PET were evaluated with regard to the early detection of regional lymph node metastasis. ^{18}F -FDG PET detected only two of 26 histologically tumor-positive SLNs (sensitivity, 8%; specificity, 100%) that were detected by SLNB. Three other lymph node metastases had a diameter > 4 mm in the 26 histologically tumor-positive SLNs. ^{18}F -FDG PET images revealed that nine patients had enhanced uptake at distant sites, which were all false-positive upon further investigation. At 18-month follow-up, five of 26 (19%) patients with a positive SLN and four of 74 (5%) patients without a positive SLN had recurrent or progressive disease. Therefore, ^{18}F -FDG PET did not have high sensitivity during baseline staging in patients with malignant melanoma.

In a study of 43 intermediate/high-risk melanoma patients, Vereecken *et al.* [36] evaluated the pertinence of extensive preoperative staging procedures, including ^{18}F -FDG PET and SLNB. The SLNB procedure demonstrated the presence of regional lymph node metastasis in 10 patients, whereas ^{18}F -FDG PET demonstrated the presence of regional lymph node metastasis in four of the 10 patients (sensitivity of ^{18}F -FDG PET, 40%). The authors concluded that ^{18}F -FDG PET cannot replace SLNB for the initial regional staging of patients with melanoma because ^{18}F -FDG PET is not sufficiently sensitive to detect lymph nodal micrometastasis.

To determine the sensitivity and specificity of initial ^{18}F -FDG PET for the detection for occult lymph node metastasis in patients with early-stage cutaneous melanoma, Wagner *et al.* [37] performed a prospective study. ^{18}F -FDG PET findings were interpreted in a blinded manner and compared with the histological results from SLNB specimens. In 144 assessable patients with a mean tumor depth of 2.8 mm, ^{18}F -FDG PET showed that 31 patients had signs of metastatic disease. The sensitivity of ^{18}F -FDG PET for the detection of regional lymph node metastasis was 21%, and the specificity was 97%. SLNB or follow-up demonstrated regional lymph node metastasis in 43 of 184 lymph node basins in 40 patients (27.8%). The authors concluded that routine ^{18}F -FDG PET was not a sensitive indicator of occult regional lymph node metastasis in patients with early-stage melanoma. SLNB rather than ^{18}F -FDG PET was recommended for initial staging in this population with Stage I and II melanoma.

Clark *et al.* [38] retrospectively reviewed 64 patients with T2-T4 melanoma who underwent ^{18}F -FDG PET for the detection of occult metastasis compared with SLNB. ^{18}F -FDG PET did not reveal occult distant metastasis in any of the patients and showed that 94% of these patients did not have abnormally increased ^{18}F -FDG accumulation. ^{18}F -FDG PET had false-positive findings in two patients (3%). Nineteen of 64 patients had positive SLNs, and only two (11%) patients showed abnormally increased ^{18}F -FDG activity on the ^{18}F -FDG PET images. Thus, ^{18}F -FDG PET was not useful for detecting regional lymph node metastasis. This study suggested no utility of ^{18}F -FDG PET for the detection of occult metastasis in patients at the initial diagnosis of melanoma. The authors concluded that ^{18}F -FDG PET is not recommended for preoperative evaluations in patients with melanoma.

In 2007, a study conducted by Kell *et al.* [39] examined the preoperative value of ^{18}F -FDG PET/CT in patients who underwent SLNB for malignant melanoma. During a 1-year period, 83 primary melanoma patients without clinical evidence of either locoregional or systemic metastasis underwent SLNB for melanoma, of which 37 (45%) patients were selected to undergo a preoperative ^{18}F -FDG PET/CT scan. SLNB revealed that 13 (15.6%) patients had lymph node metastasis. Nine of these patients were selected to undergo ^{18}F -FDG PET/CT, which indicated that only two patients had lymph node metastasis (PPV, 24%; NPV, 76%). Although ^{18}F -FDG PET/CT revealed no previously undetected metastatic disease, it identified a second occult malignancy in four (10.8%) patients who underwent therapy for melanoma. The results of this study did not support the use of ^{18}F -FDG PET/CT in primary melanoma patients without clinical signs of lymph node metastasis. SLNB appears to be a more sensitive staging modality for the detection of lymph node metastasis, but ^{18}F -FDG PET/CT may play a role in the future as a screening tool for previously undetected occult primary malignancy.

Maubec *et al.* [40] designed a prospective study to determine the value of ^{18}F -FDG PET for the detection of regional or distant metastasis in 25 patients with primary melanomas with a thickness > 4 mm. All of the patients without a palpable regional lymph node underwent SLNB. The ^{18}F -FDG PET results indicated 0/2 primary melanomas, 1/4 residual primary melanomas after limited excision, 0/6 lymphatic basins with micrometastasis, 4/4 lymphatic basins with enlarged palpable lymph nodes, and 0 distant metastasis. The sensitivity and specificity of ^{18}F -FDG PET for microscopic lymph node metastasis in the basins were 0 and 92%, respectively. The authors concluded that ^{18}F -FDG PET was not useful for the initial work-up of patients with primary melanoma, even with primary melanoma thicknesses > 4 mm. SLNB remains the procedure of choice for the most accurate initial staging.

Singh *et al.* [41] evaluated the role of preoperative ^{18}F -FDG PET/CT, LS, and SLNB for the detection of regional lymph node metastasis in malignant melanoma. Fifty-two patients with AJCC Stage I or II melanoma were selected for the study. These patients did not have clinical or radiological evidence of regional lymph node metastasis. Fourteen of the 52 patients (27%) had at least one involved SLN. Two patients with a SLN > 1 cm had true-positive results, and two other patients had false-positive results on the ^{18}F -FDG PET/CT images. ^{18}F -FDG PET/CT demonstrated very low sensitivity of 14.3% and a PPV of 50% for localizing the subclinical nodal metastases. The specificity, NPV, and diagnostic accuracy were 94.7%, 75%, and 73%, respectively. Preoperative ^{18}F -FDG PET/CT cannot replace SLNB in patients with Stage I or II malignant melanoma.

Constantinidou *et al.* [42] reviewed 30 patients with melanomas with a Breslow thickness > 1 mm who had ^{18}F -FDG PET or PET/CT scans performed within 100 days after a positive SLNB. SLNB was positive in five cases (16%). ^{18}F -FDG PET demonstrated that two patients (6%) had focal hypermetabolic activity. The first patient had a synchronous neuroendocrine thyroid tumor, and the other patient had increased ^{18}F -FDG accumulation in the chest wall that proved to be old trauma. These results indicated that the two positive ^{18}F -FDG PET scans were false-positive. Early ^{18}F -FDG PET or PET/CT after a positive SNB did not alter subsequent melanoma management for the 30 cases. ^{18}F -FDG PET or PET/CT soon after a positive SLNB appears to have limited benefit. These results suggest that metabolic imaging might not be indicated for this group of patients.

A study by Klode *et al.* [43] directly compared SLNE and ^{18}F -FDG PET/CT in the evaluation of early-stage melanoma metastasis by analyzing data from 61 patients with primary malignant melanoma with a Breslow index > 1.0 mm. SLN involvement was found in 14 patients (23%). Seventeen involved lymph nodes were detected overall, only one of which was identified preoperatively using ^{18}F -FDG PET/CT. Thus, the sensitivity and NPV of ^{18}F -FDG PET/CT were 5.9% and 78%, respectively. Compared with ^{18}F -FDG PET/CT, SLNB is much more sensitive for discovering small lymph node metastases. The authors considered ^{18}F -FDG PET/CT unsuitable for the evaluation of early regional lymphatic tumor dissemination in patients with Stage I or II melanoma.

To assess the rate of distant metastasis detected by ^{18}F -FDG PET or PET/CT in melanoma patients with a positive SLNB, Wagner *et al.* [44] studied 46 consecutive patients who did not present any clinical signs of nodal involvement or distant metastasis. All of the patients underwent ^{18}F -FDG PET or PET/CT within six weeks of the SLNB procedure. The ^{18}F -FDG PET and PET/CT findings were divided into positive, negative, and inconclusive classifications. ^{18}F -FDG PET and PET/CT showed that no patient had a positive manifestation of distant metastasis. Six patients (13%) had inconclusive results. None of the patients presented distant metastasis within 12 months. Forty patients (87%) had a negative scan; among these, five (12%) presented with distant metastasis within 12 months. The investigation showed that ^{18}F -FDG PET and PET/CT did not detect distant metastasis at initial staging in patients with a positive SLNB and led to false-positive and false-negative results. Therefore, ^{18}F -FDG PET and PET/CT do not appear to be indicated for the initial staging of patients with lymph node metastasis detected by SLNB.

4 Comparison of ^{18}F -FDG PET (PET/CT) and SLNB for detecting regional lymph node metastasis in patients with other tumors: data from the literature

a. Oral and oropharyngeal carcinoma

To assess the value of ^{18}F -FDG PET for the staging of clinically node-negative necks in oral and oropharyngeal squamous cell carcinoma (OOSCC) using SLNB, with elective neck dissection as a “gold standard” for comparison, Stoeckli *et al.* [45] studied 12 OOSCC patients without evidence of lymph node metastasis upon physical and radiological examination. ^{18}F -FDG PET was performed in all of the patients before SLNB, and the results of both procedures were compared. The gold standard revealed occult metastasis in five of 12 cases. SLNB was successful in all 12 patients and diagnosed all five cases of occult metastasis, resulting in sensitivity and specificity of 100% and 100%, respectively. ^{18}F -FDG PET demonstrated that two patients had local ^{18}F -FDG accumulation, one of which turned out to be false-positive, resulting in a sensitivity of 25% and specificity of 88%. The size of the micrometastases ranged from 1.2 mm to 1.5 mm. ^{18}F -FDG PET had poor sensitivity and specificity in revealing occult metastasis and played no role in the evaluation of otherwise clinically node-negative necks because of resolution limitations (4 mm-5 mm). SLNB, however, provided highly accurate staging of clinically node-negative necks in OOSCC patients.

In 2002, Civantos *et al.* [46] evaluated LS/SLNB compared with ^{18}F -FDG PET of the neck in 18 oral cavity cancer patients. The LS/SLNB results suggested good prediction of lymphatic involvement. Ten true-positive sentinel nodes and one false-negative sentinel node were found out of 11 true-positive necks, providing sensitivity of 80.9%. Six of 10 true-positive cases revealed by LS/SLNB had only a positive node for that patient. Seven correctly predicted true-negative findings were also reported. ^{18}F -FDG PET scans that inaccurately indicated positive disease were correctly evaluated by LS/SLNB in only three of 10 true-positive patients, resulting in seven false-negative results. ^{18}F -FDG PET was not helpful for detecting subclinical cervical metastasis. The authors concluded that the LS/SLNB technique is promising for oral cancer.

To evaluate the utility of ^{18}F -FDG PET and SLN imaging and biopsy (SLNIB) for determining the true disease status of regional lymphatics in patients with oral squamous cell carcinoma, Hyde *et al.* [47] performed preoperative ^{18}F -FDG PET and SLNIB in 19 patients with biopsy-proven disease. None of the patients had palpable or radiological evidence of neck metastasis. SLN harvesting was successful in all of the patients. Of the 19 patients, 15 had SLNs that were negative for tumors, and three had SLNs that were positive for tumors. In one of 19 patients, the SLN was negative, but another single tumor-positive node was identified in the neck. This represented a false-negative rate of 25% for SLNIB (1/4 of the 4/19 patients with histologically proven cervical nodal metastases). However, ^{18}F -FDG PET failed to identify nodal disease in all four patients with histologically proven lymph node metastasis. The authors suggested that SLNIB was feasible for

patients with oral squamous cell carcinoma and could predict cervical nodal status. In contrast, ^{18}F -FDG PET might be less useful.

In a study by Chikamatsu *et al.* [48], SLNB was used to detect lymphatic metastasis in oral cavity cancer compared with physical examination, CT, magnetic resonance imaging (MRI), and ^{18}F -FDG PET. Eleven patients with histologically proven oral squamous cell carcinoma were enrolled in the study. Using both LS and a handheld gamma probe, the SLN was identified in all of the patients. All 11 histopathological SLNB results were consistent with the pathological N classification. Specifically, SLNB correctly predicted positivity and negativity in all 11 patients. Seven of the 11 patients in the study underwent a ^{18}F -FDG PET scan. Interestingly, only one pathologically positive node was detected by ^{18}F -FDG PET. Additionally, ^{18}F -FDG PET had one false-positive result. These results indicate that ^{18}F -FDG PET inaccurately identified neck lymphatic metastasis for staging lymph node dissection in oral cavity cancer patients. In contrast, SLNB was technically feasible and a useful diagnostic technique for this population.

b. Penile carcinoma

To evaluate the performance of ^{18}F -FDG PET/CT for the detection of occult metastasis in patients with clinically node-negative (cN0) penile carcinoma, Leijte *et al.* [49] studied 24 patients who were scheduled to undergo dynamic SLNB and hybrid ^{18}F -FDG PET/CT to assess the nodal status of cN0 groins. Eighteen of the 24 patients were bilaterally cN0, and six were unilaterally cN0. Thus, 42 cN0 groins were evaluated for occult metastasis using ^{18}F -FDG PET/CT. The ^{18}F -FDG PET/CT results were compared with histopathological tumor status revealed by SLNB as the standard of care. SLNB was tumor-positive in five (12%) of the 42 cN0 groins, two of which contained only micrometastases (< 2 mm). ^{18}F -FDG PET/CT, however, predicted only one of the five tumor-positive cN0 groins. All false-negative ^{18}F -FDG PET/CT scans contained metastases ≤ 10 mm. ^{18}F -FDG PET/CT correctly identified 34 of the remaining 37 tumor-negative groins, providing specificity of 92%. The PPV and NPV were 25% and 89%, respectively. In the authors' opinion, the value of ^{18}F -FDG PET/CT appeared to be limited in the evaluation of groins in patients with cN0 penile cancer because of its low sensitivity. SLNB and surgical staging remained the methods of choice in the management of patients with cN0 penile cancer.

c. Anal cancer

Mistrangelo *et al.* [50] compared SLNB and ^{18}F -FDG PET/CT to determine which method was better for staging inguinal lymph nodes in patients with anal cancer. Twenty-seven anal cancer patients underwent both inguinal SLNB and ^{18}F -FDG PET/CT. ^{18}F -FDG PET/CT was performed before treatment and then 1 month and 3 months after treatment. The ^{18}F -FDG PET/CT scans demonstrated abnormal inguinal ^{18}F -FDG uptake in seven of 27 patients and detected no metastasis in the remaining 20 patients. Among the seven cases, histological SLNB analysis proved that four ^{18}F -FDG PET/CT scans were false-positive. SLNB in the three other patients detected metastasis in the inguinal lymph nodes. Additionally, none of the patients who had a negative SLNB developed metastasis during the follow-up period. Both of the sensitivity and NPV of ^{18}F -FDG PET/CT were 100%. However, the specificity of ^{18}F -FDG PET/CT was 83%, and PPV was 43%, owing to the high number of false-positives. The authors concluded that inguinal SLNB was superior to ^{18}F -FDG PET/CT for staging inguinal lymph nodes in this series of patients with anal cancer.

Two years later, the same authors [51] conducted another study that included 53 consecutive patients diagnosed with anal cancer to compare ^{18}F -FDG PET/CT and SLNB results of inguinal lymph nodes and anal biopsy results for the staging and follow-up of anal cancer. All of the patients underwent ^{18}F -FDG PET/CT. The results were compared with SLNB performed in 41 patients during the pretreatment workup. At the pretreatment assessment, ^{18}F -FDG PET/CT revealed that perirectal or pelvic nodes had abnormal ^{18}F -FDG accumulation in 14 of 53 patients (26.4%). ^{18}F -FDG PET/CT upstaged 37.5% of the patients and downstaged 25% of the patients. The comparison of the SLNB and ^{18}F -FDG PET/CT findings showed that SLNB confirmed the presence of inguinal lymphatic metastasis in only eight cases, with four (9.7%) false-positive results and two (4.9%) false-negative results in the 41 patients. The authors concluded that SLNB was more accurate in the staging of inguinal lymph nodes in patients with anal cancer.

d. Cervical cancer

Patients diagnosed with Stage IA2 to IIA adenocarcinoma, adenosquamous carcinoma, or nonbulky squamous cell carcinoma cervical cancer without evidence of nodal metastasis by MRI were enrolled in a prospective study conducted by Chou *et al* [52]. All of the patients underwent preoperative ^{18}F -FDG PET, $^{99\text{m}}\text{Tc}$ -sulfur colloid LS, and intraoperative SLNB during radical hysterectomy and pelvic lymphadenectomy. When 60 patients were accrued, an interim analysis was performed to study the diagnostic efficacy of PET and SLN sampling. Of the 60 patients, 10 (16.7%) had pelvic lymph node metastasis, and one (1.7%) had histological evidence of para-aortic lymph node (PALN) metastasis. The single PALN metastasis (one of one patient) was detected by ^{18}F -FDG PET but only one (10%) of the 10 pelvic lymph node metastases was detected. On a patient basis, the sensitivity, specificity, PPV, NPV, and accuracy of ^{18}F -FDG PET for detecting metastatic pelvic lymph nodes were 10%, 94%, 25%, 84%, and 80%, respectively. The authors concluded that dual-phase ^{18}F -FDG PET had little value in the primary staging of nonbulky Stage IA2 to IIA disease and MRI-defined lymph node-negative cervical cancer.

5 Remarks and conclusions

In recent years, numerous studies have been published that compared the utility of ^{18}F -FDG PET (PET/CT) and SLNB for detecting regional lymph node metastasis in patients with breast tumors or melanoma. In the present article, 15 and 17 original articles were reviewed for each disease, respectively. However, comparative studies of both methods with regard to the detection of regional lymph node metastasis for other malignancies, including oral and oropharyngeal carcinoma, penile carcinoma, anal cancer, and cervical cancer, are relatively scarce, and only one relevant report can be found for some tumors. Almost without exception, all of these original articles were remarkably consistent in indicating the limitations of ^{18}F -FDG PET or PET/CT for detecting regional lymph node metastasis in patients with various malignancies, especially in early-stage disease with no regional lymphatic or distant metastasis. The sensitivity of PET or PET/CT for regional lymph node metastasis in patients with early-stage tumors is unacceptably low compared with SLNB because normal-size lymph nodes may contain micrometastases that are below the sensitivity threshold of the imaging method. Most reported sensitivity values of ^{18}F -FDG PET or PET/CT in the evaluation of lymphatic metastasis for breast tumors ranged from 20% to 60%, with only one value greater than 60% (*i.e.*, 77.1% sensitivity reported by Kim [25]). The sensitivity for melanoma is even lower, with most reported values ranging from 0% to 22%. A slightly higher sensitivity value of 40% (yet also too low) reported by Vereecken [36] was found only for intermediate/high-risk melanoma patients. For the other malignancies reviewed in this paper, including oral and oropharyngeal carcinoma, penile carcinoma, anal cancer, and cervical cancer, ^{18}F -FDG PET or PET/CT was insufficiently accurate to identify regional lymphatic metastasis, and SLNB was superior to ^{18}F -FDG PET or PET/CT for staging regional lymph nodes. However, limited data are available to compare ^{18}F -FDG PET (PET/CT) and SLNB in the evaluation of regional lymph node involvement for these tumors. More data are needed to make definitive conclusions.

Notably, for all of the malignancies discussed in this paper, the specificity values of ^{18}F -FDG PET or PET/CT in the detection of regional lymphatic metastasis are high. The reported values ranged from 83% to 100% in all of these original articles. The acceptable specificity of ^{18}F -FDG PET or PET/CT indicates that primary tumor patients with positive ^{18}F -FDG PET or PET/CT regional lymph nodes should undergo local lymph node resection rather than SLNB for lymph node staging.

The reported sensitivity values of SLNB in the evaluation of regional lymph node metastasis are greater than 90%, and specificity is nearly 100%. Most other indices of SLNB, such as NPV, PPV, and accuracy, are better than the ^{18}F -FDG PET or PET/CT indices. Therefore, SLNB is now the gold standard for regional lymph node staging when no clinical evidence of regional lymphatic metastasis is available. The procedure is highly accurate, with a very low false-negative rate when performed by experienced personnel.

Comparisons of the two methods indicated that ^{18}F -FDG PET (PET/CT) does not need to be indicated if the SLNB results are negative. In fact, in addition to ^{18}F -FDG PET (PET/CT), all other imaging methods, including ultrasound, CT, and MRI, have very low diagnostic value and the burden of false-positive results that lead to unnecessary workups in the detection of regional lymphatic metastasis for early-stage malignancies. When clinically palpable or imaging-positive lymph nodes are detected, fine-needle aspiration or biopsy under ultrasound guidance may otherwise be performed. If the pathological results are positive for lymphatic involvement, then the patient is sent directly for lymph node dissection, and SLNB is thus not necessary.

In conclusion, ^{18}F -FDG PET (PET/CT) appears to have limited benefit in the evaluation of regional lymphatic metastasis for early-stage malignant diseases. SLNB is much more sensitive than ^{18}F -FDG PET (PET/CT) in discovering lymphatic micrometastasis. ^{18}F -FDG PET (PET/CT) cannot replace SLNB for the evaluation of early regional lymphatic tumor dissemination in this patient population.

Conflict of interest

There is no conflict of interest.

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