Original article

Positron emission tomography-computed tomography for inguinal nodes in vulvar cancer

ABSTRACT

We aimed to determine the sensitivity and specificity of fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) for the spread of disease to inguinal lymph nodes in vulvar cancer. A retrospective review of vulvar cancer patients who underwent both inguinal nodal sampling and dissection as well as FDG PET-CT was performed, with 21 patients meeting criteria. The sensitivity and specificity of the FDG PET-CT imaging was performed using a combination of maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Using an SUV_{max} cutoff of 4.5 or of two times the average liver uptake, we had a 100% sensitivity and 89% specificity for positive inguinal nodes. MTV and TLG did not add to sensitivity or specificity. We conclude that FDG PET-CT has good sensitivity for inguinal nodal spread in vulvar cancer, and either a quantitative or semiquantitative approach is effective.

Keywords: Fluorodeoxyglucose positron emission tomography-computed tomography, maximum standardized uptake value, metabolic tumor volume, quantitative imaging, total lesion glycolysis, vulvar cancer

INTRODUCTION

Vulvar cancer is the fourth most common gynecologic cancer, with 6020 new cases and 1150 new deaths in 2017.[1] Compared to many other cancers, survival rate is favorable, with 72.1% overall 5-year survival which is broken down as 86% for localized, 57% for regional, and 17% for distant metastases.[1] These encouraging survival rates are largely due to early diagnosis, with 59% of cancers diagnosed at the localized stage, 30% at the regional, and only 6% with distant metastases.[1]

Vulvar cancer is staged using both clinical and surgical information through vulvectomy and inguinofemoral lymph node dissection. Clinical staging alone may miss a large number of microscopic nodal metastasis, and inguinal lymph node dissection is associated with significant morbidity such as lymphedema, wound breakdown, and infection.[2] There is increasing use of the sentinel lymph node (SLN) biopsy, which may reduce this morbidity. Patients with vulvar malignancies are primarily cared for by gynecologic oncology physicians, for whom, this technique is new and uptake is not yet universal. Other methods of investigating spread to inguinal lymph nodes are necessary.

Positron emission tomography (PET) with computed tomography (CT) is a functional imaging modality that uses a radiotracer, most commonly a radioactive glucose analog, F-18 fluorodeoxyglucose (FDG), to detect malignant tumors in the body. This technology capitalizes on the principle that malignant tumors take up more glucose than benign tissue, known as the Warburg effect. It is typically registered with CT, both for purposes of localizing "hot spots" indicating cancer and for attenuation correction necessary to properly generate the images. Intensity is sometimes quantified using the standardized uptake value (SUV), a measure of the concentration

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How to cite this article: Oldan JD, Sullivan SA. Positron emission tomography-computed tomography for inguinal nodes in vulvar cancer. World J Nucl Med 2018;17:139-44.

Access this article online	
Website: www.wjnm.org	**Quick Response Code**
DOI: 10.4103/wjnm.WJNM_32_17	

of radioactivity in one location divided by that averaged over the whole body. The pixel with maximum SUV (SUV_{max}) is also used to quantify the intensity of glucose uptake.

Prior work has shown that FDG PET-CT may be useful in detecting metastatic disease in vulvar cancer although studies have been small and inconsistent. Early studies using FDG PET only (not PET-CT) found an 80% sensitivity and 90% specificity on a per-patient basis, out of 15 patients offered groin exploration.[3] More recent investigations found 100% sensitivity for detecting inguinal disease in squamous cell cancers in ten patients (nonsquamous cell cancers were lower at 60%) and 100% sensitivity and specificity in eight patients.[4,5] Conversely, the work of Kamran et al. on 20 patients over 3 years showed 50% sensitivity.[6]

This literature also demonstrates heterogeneity of the metrics for assessing nodal disease, which may account for differences in detection. The earliest investigation, by Cohn et al., reported using a five-point scale to determine a positive lymph node but did not describe the criteria used in the scale.[3] Another investigation, by Peiró et al., also did not state which criteria were used to differentiate benign from malignant lymph nodes.[4] An investigation by Dolanbay et al. stated that the nodes were assessed "qualitatively and quantitatively," with good separation between reactive and metastatic nodes with the lowest SUV_{max} for a node deemed metastatic being 3.5 whereas the highest SUV_{max} for a reactive node was 3.1.[5] Thus, further investigation into the optimal evaluation is urgently needed as the use of PET-CT scan to assess nodal disease in vulvar cancer is commonly being used without uniformity.

Given the variability in the metric used for assessment as well as reported sensitivity, we sought to determine if a systematic approach to the analysis of FDG PET-CT, using both PET and CT information, could be of utility in a slightly larger dataset.

MATERIALS AND METHODS

Ethics
The study was approved by the Institutional Review Board under a waiver of consent for minimal risk studies.

Selection and description of participants
A single institution retrospective review of women with vulvar cancer who underwent a FDG PET-CT for either initial staging or diagnosis of recurrence was performed from January 1, 2000, to December 1, 2016. Patients were included if they either had newly diagnosed squamous cell cancer of the vulva or a recent recurrence followed by FDG PET-CT scan within 50 days of inguinal lymph node surgery.

Technical information
FDG PET-CT was performed using either a Siemens TruePoint or Siemens mCT scanner. Scans before 2007 were performed using a Siemens Classic single-slice PET-CT. Examination was done using 259-740 MBq of F-18 FDG using a weight-based formula and 2 min per bed position (1.5 for the mCT). CT parameters were 120 kVp and 100 mAs. Reconstruction was done using the Ordered subset expectation–maximization algorithm with two iterations and eight subsets with a Gaussian 5 mm filter and a matrix of 168 × 168 for the TruePoint and 200 × 200 for the mCT. These specifications are typical among academic medical centers in the United States.

The systematic approach for evaluation of inguinal lymph node metastasis involved two specific metrics. Given the methodological problems with acquisition of SUV_{max},[7] we examined the size of the lesions as well. The intensity of inguinal nodes on PET-CT was analyzed using both a semiquantitative score similar to the Deauville scale for lymphoma ([1] = no uptake,[2] = uptake less than mediastinal blood pool,[3] = uptake greater than mediastinal blood pool but less than liver,[4] = uptake moderately greater than liver,[5] = uptake significantly greater than liver) and in the quantitative fashion with measurement of SUV_{max}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) with a cutoff of 50% SUV_{max}. Many negative nodes did not display sufficient activity above surrounding tissue to segment (in general, this would be the case if the node had less than twice the activity of surrounding tissue), and these were listed as too small to characterize. In addition, lymph node morphology on CT was evaluated; dimensions were measured and the node was judged as having a fatty hilum or not.

Patients with vulvar cancer were included if they had a FDG PET-CT scan with a pathologic evaluation of inguinal lymph nodes either with unilateral or bilateral complete inguinal lymph node dissection or stereotactic biopsy which was up to the discretion of the provider. The staging was performed in the standard fashion with a three-incision technique. Unilateral or bilateral dissection was performed based on the discretion of the surgeon and patient factors. Pathologic evaluation of lymph nodes was performed in the standard fashion without the use of ultrastaging.

Statistics
Sensitivity and specificity were calculated for the detection rate of lymph node metastasis by FDG PET-CT, using cutoffs derived from SUVmax (both quantitative and semiquantitative), MTV, and TLG. Surgical pathology was used as the gold standard. Numbers were calculated using MATLAB.

RESULTS

Ninety-six patients with FDG PET-CT scans for vulvar cancer were identified, of whom, 69 had scans for staging initial or recurrent cancer. Of these, 21 had inguinal lymph node evaluation [Figure 1]. The mean age of the entire population is 55 with standard deviation 11 (range 41–74), and the mean body mass index is 30 with standard deviation 10 (range 19–55). The demographic characteristics of the study population are shown in Table 1. Two patient records were unable to be completely accessed due to a lack of record transfer from an older Electronic Medical Record (EMR) to the newer EMR system; therefore, their demographic data are not represented. There was a tendency for node-positive patients to be more likely to have a tobacco history, but this was not statistically significant ($P = 0.07$).

Of the 21 patients who had an inguinal lymph node evaluation, six patients had a positive biopsy before FDG PET-CT, while 15 had inguinal lymph node dissection (either complete or sentinel). Median tumor size was 1.95 cm (range 0.3–8.6 cm), and median depth of invasion was 1.5 mm (range 0.5–25 mm). In three cases, surgery was not performed to remove the tumor as systemic or palliative therapy was elected. Patients who had positive lymph node spread were more likely to have larger tumors, a deeper depth of invasion, and more perineural spread; however, none of these were statistically significant. Pathologic characteristics of the study population are shown in Table 2.

Regarding FDG PET evaluation of lymph nodes, both the semiquantitative and quantitative approaches were evaluated. With a semiquantitative cutoff of five (significantly more avid than liver), there is a 100% sensitivity and 89% specificity for the detection of metastatic lymph nodes (on a per-patient basis). An SUV_{max} cutoff of 4.5 would have the same effect.
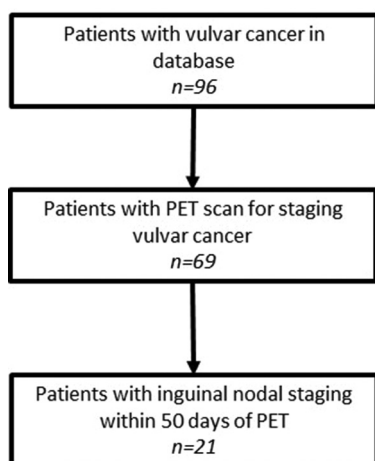
Fifteen of 21 patients had local metastases to inguinal nodes. Three of 25 patients had distant metastases, one to lung and bone, one to a right paratracheal node, and one with diffuse liver uptake. Comparing to surgical findings and using the previously stated SUV_{max} cut-off, on a per-patient basis, there were one false positive, eight true negatives, and 12 true positives. Nodes varied significantly in size, with long axis ranging from 0.7 cm to 4.0 cm and short axis from 0.4 cm to 3.4 cm. Malignant nodes measured at least 1.0 cm in short axis, and no benign node measured more than 1.1 cm. SUVmax, MTV, and TLG are shown in Figures 2-4 (one patient's MTV and TLG were not available). Full positron emission tomography characteristics of nodes are given in Supplemental Table 1.

Our sample size is too small to determine a universal SUV_{max} cutoff that can be used to discriminate benign from malignant lymph nodes although nodes with an SUV_{max} over 4.5 are likely to be malignant and over 9 certain to be so. The most avid benign nodes had SUV_{max} 8.8 and 9.0 [Figure 5], and the least avid biopsy-proven malignant node had SUV_{max} 4.8 [Figure 6], so a perfect separation is not possible.

MTV and TLG were of less sensitivity and specificity, with multiple cases of benign lesions having greater MTV and TLG than malignant lesions, rather than just one. Keeping the cutoff low enough to include all malignant nodes and maintain sensitivity at 100%, using MTV resulted in a specificity of 25% and using TLG resulted in a specificity of 75%. SUV_{max} thus appears better than these two measurements for cutoff purposes at this point in time.

Two cases of pelvic nodal metastases were detected; one was worked up and indeed proved positive, whereas the other case of pelvic nodal metastasis was not further worked up and so the sensitivity here cannot be determined. FDG PET-CT
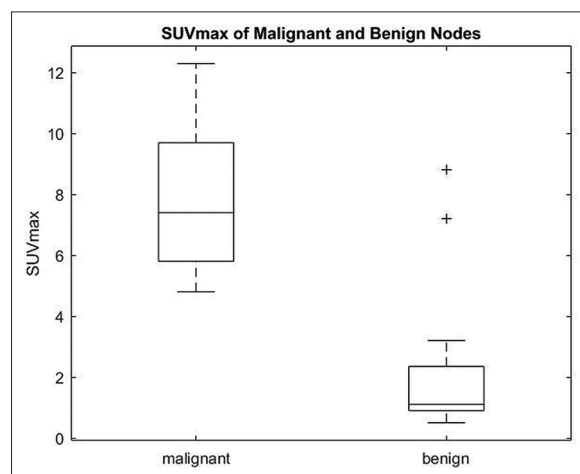

Figure 1: STARD diagram of patient flow

Figure 2: Boxplot of maximum standardized uptake value for benign and malignant nodes
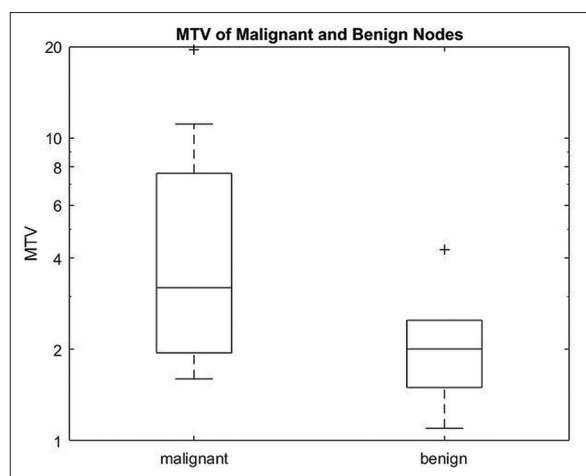
Figure 3: Boxplot of metabolic tumor volume for benign and malignant nodes
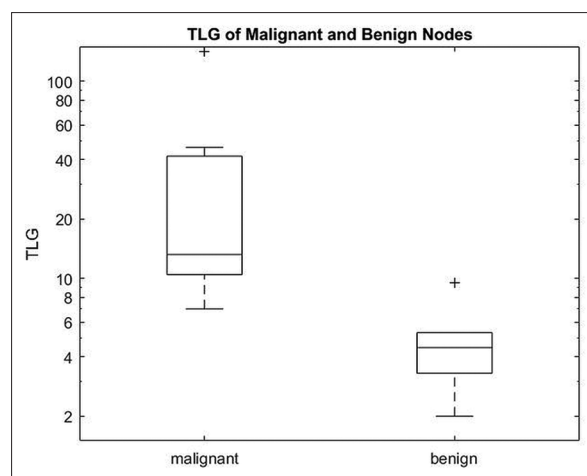

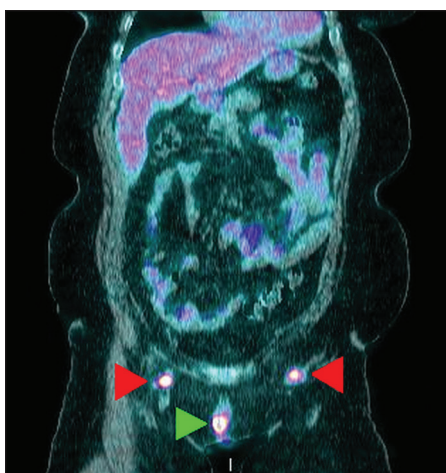Figure 4: Boxplot of total lesion glycolysis for benign and malignant nodes

Figure 5: Coronal fused fluorodeoxyglucose positron emission tomography-computed tomography image of the patient with the most avid benign nodes (red arrowheads), substantially more avid than the liver. These should not be confused with the primary malignancy below (green arrowhead)
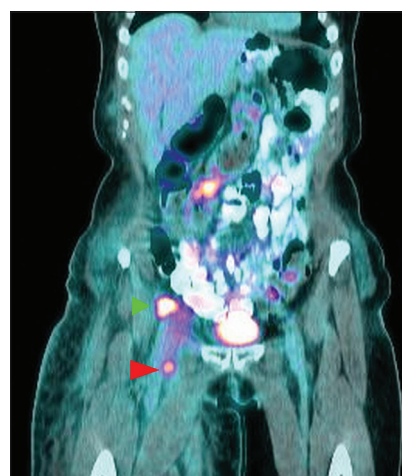

Figure 6: Coronal fused fluorodeoxyglucose positron emission tomography-computed tomography image of the patient with the least avid malignant inguinal node (red arrowhead). The node is substantially more avid than liver. Above it is an external iliac node (green arrowhead), above the inguinal ligament

did discover four cases of suggested distant metastases (one in lung and bone, one in a paratracheal node, one in bone only, and one with diffuse metastases throughout the liver). However, only the diffuse liver lesions actually were felt to be metastatic on subsequent follow-up. The bone lesion in the first case was felt to be degenerative on subsequent bone scan; the lung lesions were not specifically followed up, but the patient survived another 4 years, and thus were likely benign. The paratracheal node was later biopsied and proved benign. The bone lesion in the other case was equivocal, did not show up on future FDG PET scans, and was finally concluded by the clinical team to be degenerative.

DISCUSSION

Overall, FDG PET-CT was sensitive and specific for inguinal staging of locally advanced vulvar cancer, particularly when

FDG PET is combined with CT information to evaluate for nodal involvement. The relative lack of specificity outside of the pelvis may reflect the low rate of distant metastasis for vulvar cancer in general such that distant metastases detected are likely to be benign (i.e. low prevalence renders the modality nonspecific). As such, FDG PET-CT may be most useful for local staging rather than for detection of distant metastases.

These numbers are identical to those obtained using a cutoff of $SUV_{max} > 2$ (mean standardized uptake value of liver), which could be used as a criterion for semiquantitative interpretation if that is desired. Both the semiquantitative and quantitative methods for lymph node evaluation were found to be similar in effectiveness. This is the only study to our knowledge that utilizes FDG PET-CT with both quantitative and nonquantitative approaches for evaluation of lymph

Table 1: Characteristics of positive and negative lymph node patients

	Positive lymph node (n=11)[a]	Negative lymph node (n=8)[a]	P
Age (years)	56±11 (range 41-74)	55±10 (range 44-68)	0.72
BMI (kg/m²)	31±11 (range 19-55)	27±8 (range 18-38)	0.41
Race			
White	8 (73)	7 (88)	0.48
Black/African American	2 (18)	0	
Other	1 (09)	1 (12)	
Tobacco use	9 (82)	3 (37)	0.07
Prior dysplasia	6 (54)	4 (50)	1

Note that data for two patients were not available. [a]Clinical data on one patient each in node-positive and node-negative groups were not available due to EMR incompatibility over time. BMI: Body mass index; EMR: Electronic Medical Record

Table 2: Pathologic characteristics of nodes, where available

	Positive lymph node (n=11)[a]	Negative lymph node (n=8)[a]	P
Location of spread			
Perineural	3 (43)	1 (12)	0.24
Lymphovascular	1 (14)	1 (12)	1
Not assessed	3 (27)	0	
Tumor size	3.3 (range 0.7-8.6)	1.4 (range 0.3-6.5)	0.23
Grade			
Well differentiated	3 (27)	3 (37)	0.68
Well to moderately differentiated	0	1 (12)	
Moderately differentiated	4 (36)	3 (37)	
Poorly differentiated	2 (18)	1 (12)	
Not described	1 (9)	0	
Depth of invasion (mm)	3.3 (range 0.8-25)	1.2 (range 0.5-4.2)	0.27

[a]Clinical data on one patient each in node-positive and node-negative groups were not available due to EMR incompatibility over time. EMR: Electronic Medical Record

nodes in vulvar cancer. Indeed, given the uncertainties associated with evaluation of SUV_{max},[7] a semiquantitative approach comparing to the liver may be more robust across centers; still, it is clear that low-grade activity in the inguinal nodes is not necessary malignant.

CT alone has generally not been found to be useful for preoperative vulvar cancer staging.[8] The use of FDG PET-CT in combination, however, may provide additional diagnostic information that improves sensitivity and specificity although further investigation is needed in larger cohorts. This combined modality (FDG PET-CT) is recommended by the National Comprehensive Cancer Network for cervical cancer to detect extrapelvic disease, determine volume of coverage for radiotherapy, and for surveillance after combined chemosensitizing radiotherapy. Given the similarity of cervical cancer and vulvar cancer histologically and biologically, FDG PET-CT is a reasonable modality to evaluate vulvar malignancies, which this investigation supports.

The use of SLN biopsy for vulvar cancer has become an attractive option for providers to evaluate lymph nodes in vulvar cancer patients. Many institutions have a policy of performing SLN biopsy in patients with no evidence of abnormal lymph nodes on imaging. However, the modality and interpretation of this imaging have not been standard across investigations. FDG PET-CT may be useful in those patients in whom SLN biopsy is being considered. Positive lymph nodes detected on FDG PET-CT may allow for patients to forgo SLN biopsy for complete lymphadenectomy.

While we show similar sensitivity to prior work by Cohn et al.,[3] Peiró et al.,[4] and Dolanbay et al.,[5] our results show better sensitivity (if worse specificity) than Kamran et al.[6] This discrepancy may have been due to Kamran's taking all patients showing at least 1 mm of invasion, thus having more patients with microscopic metastases too small to detect, whereas many of our cases were referrals from other institutions and hence much more likely to have advanced disease.

Strengths of this study include the use of both FDG PET and CT and the systematic approach to evaluation. Limitations include the small sample size with only 21 patients. This may select for patients with positive nodes or for a high-risk population, producing a higher prevalence which may bias the results. The low rate of inguinofemoral lymph node dissection among the entire cohort of patients who underwent a FDG PET scan likely reflects the morbidity of this procedure and highlights the need for additional detection techniques. In addition, tumor biology was unable to be controlled for as more aggressive tumors may have higher SUVs.

Future directions for study would include performing it on a larger sample size of patients, hopefully with pathologic correlation. Long-term follow-up might also allow for other applications such as prognostication and assessment of recurrence, for which FDG PET-CT has been used for other tumors.

Overall, our data support the proposition that FDG PET-CT is sensitive for the inguinal nodal staging of locally advanced vulvar cancer although larger investigations are urgently needed.

CONCLUSION

PET-CT has good sensitivity for inguinal nodal spread in vulvar cancer, using either quantitative or semiquantitative approaches.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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