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# Comparative accuracy of qualitative and quantitative 18F-FDG PET/CT analysis in detection of lymph node metastasis from anal cancer

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## Abstract

**Purpose** To compare the diagnostic performance of qualitative and quantitative 18F-FDG PET/CT in detection of regional and distant lymph node metastasis in patients with anal cancer.

**Methods** Between 2004 and 2017, 28 patients with anal cancer who had staging PET/CT and pathological assessment of suspicious lymph nodes were included. For qualitative analysis, positive lymph nodes were defined as uptake visually higher than the liver reference uptake. For quantitative study, lymph nodes were contoured to determine maximum standard uptake value ($SUV_{max}$) and metabolic tumor volume (MTV). Receiver operating characteristic (ROC) curves were plotted to extract the optimal cut-offs and area under the curve (AUC) of $SUV_{max}$, lesion to background (L/B) ratio, short axis diameter (SAD), and MTV of lymph nodes. Histopathologic analysis was a reference standard.

**Results** A total of 28 lymph nodes (24 inguinal, 2 external iliac, 1 internal iliac, and 1 paraaortic nodes) in 28 patients on PET/CT were included. With the qualitative visual analysis, 19 patients were categorized as positive for nodal metastasis with sensitivity, specificity, and accuracy of 85%, 75%, and 82%. The optimal $SUV_{max}$ and L/B ratio cut-offs were 2.6 and 1.0 with both sensitivity and specificity of 95% and 75% (AUC of $SUV_{max} = 0.893$, AUC of L/B ratio = 0.912). Using the best cut-off of 1.6 cm for SAD and 3.65 $cm^3$ for MTV, both sensitivity and specificity were 80% and 100% (AUC of SAD = 0.950, AUC of MTV = 0.931).

**Conclusions** $SUV_{max}$ optimization may be helpful in enhancing the diagnostic accuracy of 18F-FDG PET/CT in nodal staging patients with anal cancer.

**Keywords** Anal cancer · Squamous cell carcinoma · PET/CT · Lymph node metastasis · $SUV_{max}$

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## Introduction

Anal cancer is a relatively uncommon type of cancer, accounting for 0.3% of all cancers and 1.5% of all gastrointestinal tract cancer [1]. The National Cancer Institute (NCI) estimates that there were approximately 8200 new cases (2950 men and 5250 women) of anal cancer in the United States in 2017 and 1100 deaths (450 men and 650 women) from this disease, about 0.2% of all cancer deaths [2]. The 5-year survival rate for the early stage, tumor with regional spread, and distant spread are 81%, 61%, and 30%, respectively [3]. The prognosis depends on gender, tumor cell type, staging, regional nodal involvement, and tumor site of anal cancer in anal canal or anal margin [4, 5].

The presence of nodal metastases particularly inguinal lymph nodes will affect the radiation treatment planning and prognosis [6]. The probability of nodal involvement is directly related to the tumor size [7]. Lymph node involvement at diagnosis is seen in 30%-40% of cases while systemic spread with distant extrapelvic metastasis occurs about 5%-8% of cases at onset [8]. The average incidence rate of synchronous inguinal node metastasis is 13% but the overall rate of inguinal involvement is 24% if including metachronous lesion. The 5-year overall survival rates for patients with synchronous and metachronus inguinal metastases were 54.4% and 41.4% compared with 72.8% for patients without inguinal metastases [9]. Accurate initial nodal staging of the anal cancer is of great importance and can vastly improve survival. From Mohammadkhani Shali et al. study [10], they concluded that the extent of disease (local tumor only, lymph node, or distant metastases) on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography and computed tomography (PET/CT) before combined chemoradiotherapy is strongly predictive of prognosis in anal cancer.

The standard staging of anal cancer according to National Comprehensive Cancer Network (NCCN) guideline version 1.2018 includes digital rectal examination, anoscopy, inguinal lymph node evaluation, chest and abdominal computed tomography (CT) with pelvic CT or magnetic resonance imaging (MRI) [11]. Despite PET/CT not being a standard investigation of anal cancer, the European Society for Medical Oncology (ESMO) published clinical practice guidelines for anal cancer in 2014 including PET/CT as an "optional but often recommended" modality in the workup of patients [8]. The current NCCN clinical practice guideline also recommends PET/CT for workup. The main advantage of PET/CT comes from its high sensitivity in detecting primary tumor, involved lymph nodes and distant metastasis for radiation therapeutic planning by depicting sites of increased metabolic activity [12].

Several previous studies have investigated the use of FDG-PET/CT in qualitative and semiquantitative methods in detecting nodal involvement in patients with anal cancer with many variations in the results. However, no prior study determines quantitative analysis of PET/CT or evaluates the cut-offs for lymph node metastasis in anal cancer [13–18]. Therefore, our study aimed to compare the diagnostic performance of qualitative and quantitative 18F-FDG PET/CT in detection of regional and distant lymph node metastasis in patients with anal cancer and evaluate the cut-offs to determine lymph node metastasis.

## Materials and methods

### Patients

Institutional Review Board (IRB) and Health Insurance Portability and Accountability Act (HIPAA) approvals were obtained; the requirement for informed consent was waived by our hospital IRB. In this retrospective study, we included all patients with primary anal carcinoma who underwent PET/CT for initial diagnosis and follow-up of anal cancer at our institution between January 2004 and December 2017. The patient cohort for this study was identified by searching our radiologic department database using Render software, which acquired radiologic image data from the diagnostic Picture Archiving and Communication System (PACS) workstations (AGFA Impax; AGFA Technical Imaging Systems, Ridgefield Park, NJ). A total of 528 patients diagnosed with anal cancer were identified by keywords "anal cancer; anorectal cancer; anal carcinoma; carcinoma of the anus; squamous cell carcinoma of the anus; anal malignancy" from our database. The inclusion criteria were patients with prior histopathological results confirming primary carcinoma of anal canal or anal margin and the patients performed PET/CT imaging before or after treatment. In addition, these patients having had available pathological reports of suspicious regional and metastatic lymph node biopsy, which resulted from abnormal lymph node uptake on PET/CT study, palpable lymph node on physical examination and clinician concerned this lymph node for metastasis. The exclusion criteria were (a) no PET/CT imaging ($n=373$), (b) no histopathological result of suspicious lymph node ($n=125$), (c) lack of available images in PACS ($n=1$), and (d) patient with pathological result of adenocarcinoma ($n=1$). We excluded one patient with anal adenocarcinoma in this study by the reason of the different histopathology will affect the maximum standardized uptake ($SUV_{max}$) on PET/CT and anal adenocarcinoma had different treatment from anal squamous cell carcinoma (SCCA).

Of the 28 patients [mean age of $59.7 \pm 13.7$ years (range: 15-95 years)], 17 (60.7%) were female and 11 (39.2%) were male. Twenty-five patients underwent 18F-FDG PET/CT for pre-treatment staging of the disease and 3 patients performed PET/CT to follow-up after chemoradiation with demonstrated uptake suspicious for metastatic nodes. Additional patient and tumor characteristics are shown in Table 1.

## PET/CT imaging

All patients underwent 18F-FDG PET/CT either pre-treatment staging or post-neoadjuvant chemoradiation for restaging of the disease. PET/CT studies were obtained according to our standard institutional protocol using Siemens Biograph 64 PET/CT scanners (Siemens Healthcare, Erlangen, Germany) with a multi-detector-row CT component (64 detectors). Patients were fasted for at least 6 h prior to scanning. Blood glucose value was less than 200 mg/dL in non-diabetic patients and less than 250 mg/dL in patients with diabetes (mean ± standard deviation (SD); 108 ± 2.7 mg/dL). PET/CT images were acquired 80.8 ± 5.5 min after an intravenous injection of 18F-FDG. The 18F-FDG injected dose varied base on the patient's body mass index (BMI), between 555 and 925 MBq (mean ± SD; 15.9 ± 0.4 mCi). The whole-body emission PET scan was performed in 6-8 bed positions (3–5 min acquisition time per bed position based on the BMI), covered from the base of skull to the upper thigh. Non-contrast low dose CT scan with 120 keV, 11–100 mAs (based on BMI), 5-mm collimation and pitch of 0.75 was performed for attenuation correction. Reconstruction was performed using OSEM algorithm with 2 iterations (BMI < 31) or 3 iterations (BMI ≥ 31), 8 subsets, and 5 mm Gaussian filter.

## Image interpretation

Two board-certified radiologists (one with over 8 years of experience and other with over 4 years of experience) reviewed all PET/CT images in consensus at a commercially available workstation (Syngo TrueD; Siemens Medical Solutions, Erlangen, Germany) while they were blinded to the pathological result. Prior to PET interpretation, one suspicious lymph node in each patient was marked by a radiology fellow not involved in PET interpretation for the radiologists based on the location reported on the pathology report, CT-guided biopsy images or post-procedure changes seen as needle tracks and perilesional fat stranding on the follow-up CT.

## Qualitative visual analysis

All 28 cases were included for qualitative and quantitative analysis. Initially, one suspicious lymph node in each patient was visually categorized on PET images to have mild, moderate, or intense uptake relative to liver reference (less than, similar to, or clearly above the liver background uptake, respectively) [19]. Lymph node with intense uptake, regardless of dimension, was considered suspicious for metastasis (Fig. 1a and 2a) while that with mild or moderate uptake was considered to be benign (Fig. 1b and 2b).

**Table 1** Clinical characteristic of 28 patients with anal cancer

| Characteristics | No. of patients (%) |
|---|---|
| Sex | |
| Male | 11 (39.2) |
| Female | 17 (60.7) |
| Race and ethnics | |
| White | 25 (89.3) |
| Hispanic | 2 (7.1) |
| Asian | 1 (3.6) |
| Age (years) | |
| Mean ± SD (range) | 59.7 ± 13.7 (15-95) |
| HIV | |
| Positive | 2 (7.1) |
| Negative | 18 (64.3) |
| Unknown | 8 (28.6) |
| Histological subtype | |
| Squamous cell carcinoma | 26 (92.9) |
| Basaloid squamous cell carcinoma | 2 (7.1) |
| Location | |
| Anal canal | 24 (85.7) |
| Anal margin | 4 (14.3) |
| T stage | |
| T1 | 3 (10.7) |
| T2 | 10 (35.7) |
| T3 | 6 (21.5) |
| T4 | 9 (32.1) |
| N stage | |
| N0 | 6 (21.5) |
| N1 | 2 (7.1) |
| N2 | 9 (32.1) |
| N3 | 11 (39.3) |
| TNM staging | |
| I | 0 (0) |
| II | 3 (10.7) |
| IIIA | 3 (10.7) |
| IIIB | 11 (39.3) |
| IV | 11 (39.3) |
| Pathological result | |
| Malignant lymph node | 20 (71.4) |
| Squamous cell carcinoma | 18 (64.3) |
| Basaloid squamous cell carcinoma | 2 (7.1) |
| Non-malignant lymph node | 8 (28.6) |
| Reactive lymphoid hyperplasia | 2 (7.1) |
| No malignant cell | 3 (10.8) |
| Benign lymph node | 2 (7.1) |
| Spirochetal lymphadenitis (Syphilis) | 1 (3.6) |

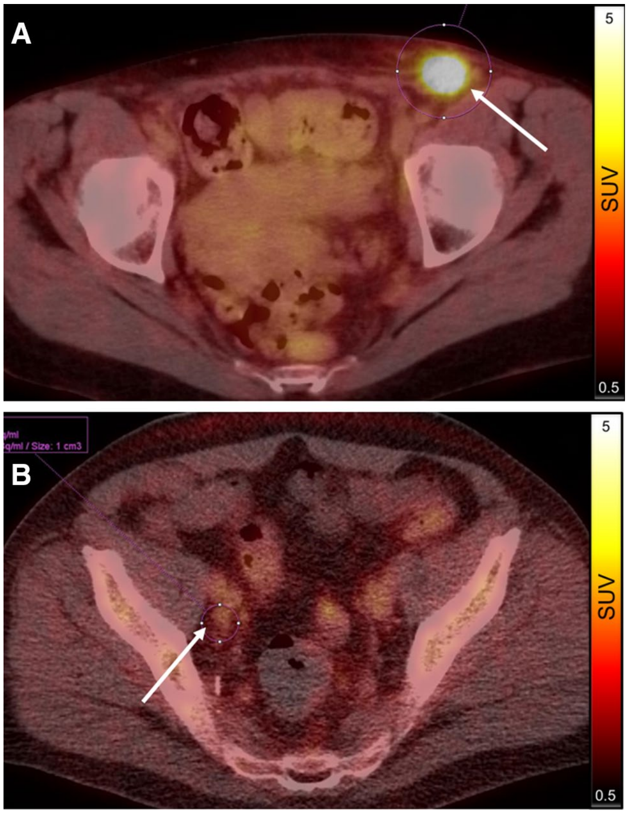


**Fig. 1** **a** A true positive case in both qualitative and quantitative analysis in a 67-year-old female who began to appreciate a mass in her left groin. On exam, her physician found a mass at anal verge. After CNB of left groin node, the pathologic result showed moderately differentiated SCCA with keratinization and necrosis, compatible with metastasis. Qualitative visual analysis definitely showed intense FDG uptake of left inguinal lymph node with $SUV_{max}$ of 11.75 on quantitative measurement. The SUVmean of liver background was 2.61 and L/B ratio was 4.5. **b** A true negative case on both qualitative and quantitative analysis. A 63-year-old male with advanced SCCA at anorectal junction. PET/CT showed intense FDG uptake of anorectal mass and low FDG uptake ($SUV_{max}=1.57$) in right external iliac lymph node (EIN). CT-guided right EIN biopsy was done and the pathologic result was benign lymph node. The SUVmean of liver background and L/B ratio were 2.2 and 0.71, respectively

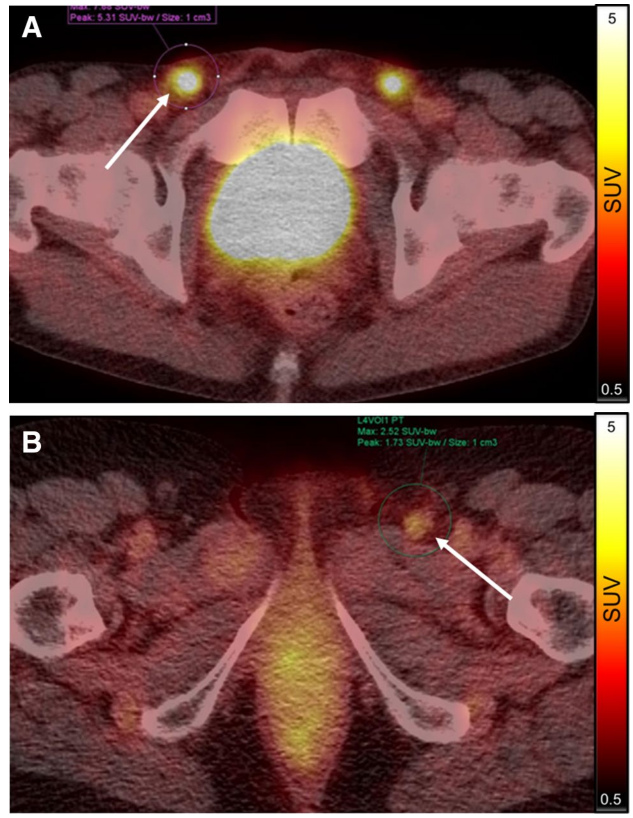


**Fig. 2** **a** One of our 2 false positive cases when we used cut-off value of $SUV_{max}$ more than 2.6. A 45-year-old male who has HIV and Hodgkin's disease with moderately to poorly differentiated invasive SCCA of perianal region post-surgical excision and chemoradiation, presented with new FDG-avid bilateral inguinal lymphadenopathy concerning for metastasis. The $SUV_{max}$ of right inguinal lymph node was 7.68 and SUVmean of liver background was 2.9 (L/B ratio = 2.65). Excisional biopsy of right inguinal lymph node was performed. The histopathological result was spirochetal lymphadenitis from syphilis. **b** A false negative case in both qualitative and quantitative methods. The $SUV_{max}$ of this left inguinal lymph node was 2.49 and the SUVmean of liver background was 2.95 (L/B ratio = 0.84). The pathology result was metastatic basaloid SCCA with necrosis

## Quantitative analysis

The $SUV_{max}$ and the metabolic tumor volume (MTV) of the suspicious lymph node where measured using the 3D region of interest (ROI) manually drawn around the contour of the lymph node on the co-registered CT. $SUV_{max}$ of the lymph node was calculated by the following formula;

$$SUV_{max} \frac{\text{maximum tissue activity concentration(Bq/mL)injected dose(Bq)}}{\text{body weight(g)}}.$$

The reference hepatic mean standardized uptake (SUVmean) was obtained the average of three 1 $cm^3$ spherical 3D ROI positioned over the right hepatic lobe. The lesion to background (L/B) ratio was calculated from the $SUV_{max}$ of the lymph node divided by SUVmean of hepatic background uptake. The longest size of lymph node was measured manually in short axis diameter (SAD) on the CT image. The MTV of lymph node was automatically drawn when $SUV_{max}$ was measured with some manual adjustment for accurate boundary contour. Histopathologic analysis was considered as the ground truth.

### Statistical analysis

Demographic data are shown as mean ± SD. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio (LR), and accuracy of PET/CT were calculated with lymph node pathology as the reference standard, shown as percentages. The receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-offs of $SUV_{max}$, L/B ratio, lymph node size and MTV. The area under the ROC curve (AUC) with 95% confidence interval (CI) was reported. A type I error rate of 5% was used for testing all hypotheses. Statistical analysis was performed using the standard software package (Stata/IC 15.0; Stata Statistical Software, College Station, TX, USA and MedCalc version 18.2.1, Medcalc Software, Ostend, Belgium).

## Results

All patients underwent lymph node biopsy or excision consisted of 14 core needle biopsies (CNB), 5 fine needle aspiration biopsies (FNAB) and 9 excisional biopsies. Of these 28 lymph nodes, 24 were inguinal nodes, 2 were external iliac nodes and the remaining two were internal iliac and paraaortic nodes. The median interval between PET/CT examination and biopsy of 28 lymph nodes was 14.5 days (range 0–160 days; interquartile range [IQR] 17 days). In three patients who performed PET/CT to follow-up after chemoradiation, the intervals between chemotherapy and PET/CT in these cases were 3 months, 6 months, and 12 months.

### Qualitative visual analysis

With visual qualitative analysis 19 patients were considered positive for the presence of nodal metastases with sensitivity, specificity, and accuracy of 85%, 75%, and 82%, respectively. The diagnostic performances for qualitative visual analysis of PET/CT are detailed in Table 2. Histopathology confirmed metastasis in 20 lymph nodes and 8 were negative for malignancy with 17 true positive, 6 true negative, 2 false positive, and 3 false negative nodes. The examples of true positive and true negative cases from qualitative analysis are shown in Fig. 1a and b. From 17 patients with malignant lymph nodes that correctly diagnosed by qualitative visual analysis from PET/CT were 14 inguinal, 1 external iliac, 1 internal iliac, and 1 paraaortic nodes. The histological type of these lymph nodes was SCCA in all cases. Of the 8 patients with confirmed negative for malignancy from biopsy (3 cases of FNAB, 3 cases of CNB, and 2 cases of excisional biopsy), the histopathologic results of them were reactive lymphoid hyperplasia, negative for malignancy and benign lymph nodes and one patient had spirochetal lymphadenitis from syphilis. All pathological diagnosis of suspicious lymph nodes is shown in Table 1.

### Quantitative analysis

The SUV max of all 28 lymph nodes ranged from 1.15 to 24.41 (mean ± SD; 6.59 ± 5.13) and the $SUV_{max}$ of 19 true positive lymph nodes ranged from 2.6 to 24.41 (mean ± SD; 9.37 ± 6.35). The cut-offs of $SUV_{max}$, L/B ratio, lymph node size (SAD) and MTV from ROC curve analysis are shown in Table 3 and Fig. 3. The optimal cut-offs of $SUV_{max}$ and L/B ratio to determine malignancy were 2.6 and 1.0 with sensitivity and specificity of 95% and 75%, respectively. The sensitivity was 100% if we used the $SUV_{max}$ of 2.49 as a cut-off and the specificity was 100% if $SUV_{max}$ of 7.69 was considered as the cut-off. When we used these cut-offs ($SUV_{max} \geq 2.6$ or L/B ratio ≥ 1.0) instead of qualitative visual analysis, the true positive cases increased from 17 to 19 cases and the false negative decreased from 3 to 1 case. The false positive cases from qualitative to quantitative analysis using $SUV_{max}$ and L/B ratio cut-offs remained unchanged. The pathologic results of these 2 false positive

**Table 2** Comparison between diagnostic performance of 18F-FDG PET/CT by qualitative visual analysis and two cut-offs from quantitative analysis ($SUV_{max} \geq 2.6$, SAD ≥ 1.6 cm) for determining lymph node metastasis

| | Qualitative visual analysis | Positive LN by $SUV_{max} \geq 2.6$ | Positive LN by SAD ≥ 1.6 cm |
|---|---|---|---|
| Sensitivity, % | 85 (62.1–96.8) | 95 (75.1–99.8) | 80 (56.3–94.3) |
| Specificity, % | 75 (34.9–96.8) | 75 (34.9–96.8) | 100 (63.1–100) |
| Accuracy, % | 82.1 (63.1–93.9) | 89.3 (71.7–97.7) | 85.7 (67.3–95.9) |
| PPV, % | 89.5 (71.5–96.6) | 90.5 (74–96.9) | 100 |
| NPV, % | 66.7 (39.6–85.9) | 85.7 (46–97.7) | 66.7 (45.4–82.8) |
| Positive LR | 3.4 (1.01–11.45) | 3.8 (1.14–12.67) | – |
| Negative LR | 0.2 (0.07–0.61) | 0.07 (0.01–0.47) | 0.2 (0.08–0.48) |

*18F-FDG PET/CT* 18F-fluorodeoxyglucose Positron emission tomography/computed tomography, $SUV_{max}$ maximal standard uptake value, *SAD* short axis diameter, *PPV* positive predictive value, *NPV* negative predictive value, *LR* likelihood ratio

Dash (–) indicates the value cannot be calculated

**Table 3** Diagnostic performance of 18F-FDG PET/CT using best cut-offs for $SUV_{max}$, L/B ratio, SAD and MTV of the lymph nodes

| | Cut-off | Sensitivity, % | Specificity, % | AUC (95% CI) |
|---|---|---|---|---|
| $SUV_{max}$ | ≥ 2.6 | 95 (75.1–99.8) | 75 (34.9–96.8) | 0.893 (0.746–1) |
| L/B ratio | ≥ 1.0 | 95 (75.1–99.8) | 75 (34.9–96.8) | 0.912 (0.796–1) |
| SAD (cm) | ≥ 1.6 | 80 (56.3–94.3) | 100 (63.1–100) | 0.950 (0.875–1) |
| MTV ($cm^3$) | ≥ 3.65 | 80 (56.3–94.3) | 100 (63.1–100) | 0.931 (0.840–1) |

*18F-FDG PET/CT* 18F-fluorodeoxyglucose Positron emission tomography/computed tomography, *$SUV_{max}$* maximal standard uptake value, *L/B ratio* lesion to background ratio, *SAD* short axis diameter, *MTV* metabolic tumor volume, *AUC* area under the ROC curve

cases were reactive lymphoid hyperplasia and spirochetal lymphadenitis with $SUV_{max}$ of 4.49 and 7.68 and SAD of 1.5 cm and 1.2 cm, respectively (Fig. 2a). For one false negative case, the lymph node located at left inguinal area showing internal necrosis. The lymph node pathology was metastatic basaloid SCCA with necrosis ($SUV_{max}$ 2.49 and SAD 1.5 cm) (Fig. 2b). The sensitivity and accuracy were improved using quantitative analysis with $SUV_{max}$ and L/B ratio compared to only visual analysis and the specificity was unchanged.

The optimal cut-offs of nodal size and MTV were 1.6 cm and 3.65 $cm^3$ with sensitivity and specificity of 80% and 100%, respectively. The sensitivity was 100% if we used the SAD of 1.0 cm as a cut-off and the specificity was 100% if SAD of 1.6 cm was considered as the cut-off. The AUC of the lymph node size (0.950) was higher than that of MTV (0.931), L/B ratio (0.912) and $SUV_{max}$ (0.893), respectively (Fig. 3).

## Discussion

18F-PET/CT is widely used for staging in many oncologic diseases. For anal carcinoma, it is used for the tumor and lymph node staging and may influence treatment planning. Currently, the standard initial treatment of anal cancer is

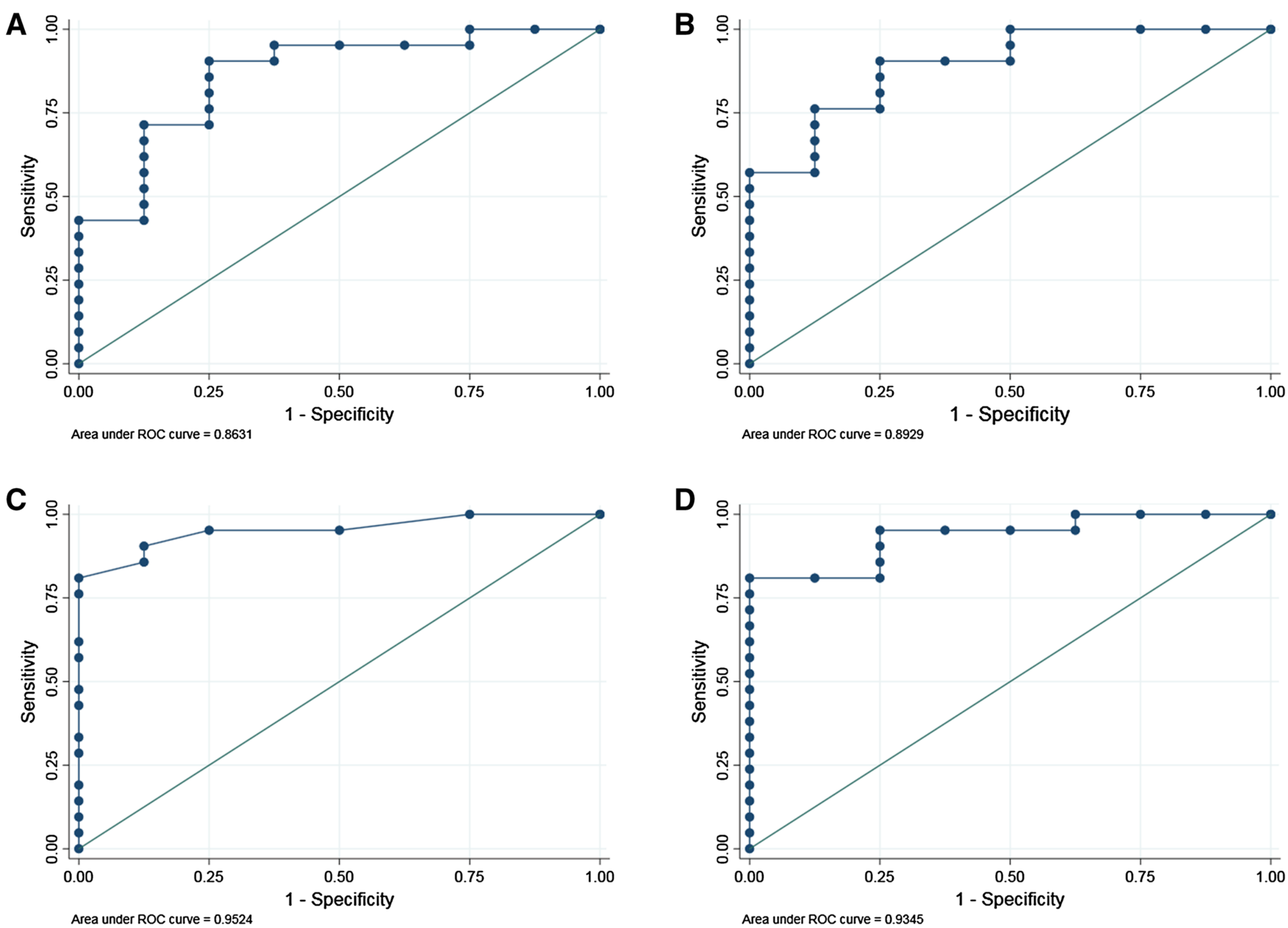


**Fig. 3** ROC curves to determine the optimal cut-off values of **a** $SUV_{max}$ **b** L/B ratio **c** SAD **d** MTV

combined external beam radiation and chemotherapy with 5-Fluorouracil and mitomycin C [20]. The presence of nodal metastasis and their sizes will determine radiation dose for each lymph node [6].

Mistrangelo et al. [13] demonstrated that PET/CT was better than CT in detection and staging of perirectal/pelvic or inguinal nodes, resulting in change of radiation fields in 12.6% of patients. But sentinel node biopsy was superior to PET/CT in detecting inguinal lymph nodes. Nonetheless, biopsy is usually performed in clinically palpable inguinal nodes or if the lymph nodes are larger than 10 mm in short axis on CT or MRI [8] and complications related procedure may occur. Noorani et al. [21] systematically reviewed from 17 studies and summarized that sentinel lymph node biopsy detection rate varied from 47 to 100% but the complication rate varied from 0 to 59%, including inguinal lymphorrhea, wound infection, hematoma, and cutaneous lymphatic fistula.

Several previous studies have investigated the use of FDG-PET/CT in qualitative and semiquantitative analysis in detecting nodal involvement in patients with anal cancer showing many variations in the results. Caldarella et al. [15] systemically reviewed and meta-analyzed published data from 7 retrospective and 5 prospective studies, summarized that FDG-PET is a high specific but less sensitive diagnostic tool in detecting locoregional lymph node involvement in patients with anal cancer. They demonstrated that the sensitivity and specificity values of FDG-PET/CT on a lesion-based analysis ranged from 31% to 100% and from 53 to 98%, with pooled estimates of 56% (95% CI 45–67%) and 90% (95% CI 86–93%), respectively. In contrast to our study, the sensitivity is good for qualitative analysis but lower specificity which is similar to the prior study by Mistrangelo et al. [14]. However, for quantitative analysis in this study, if we use the cut-off when either $SUV_{max} \geq 2.6$ or L/B ratio $\geq 1.0$ cm, the sensitivity for malignant node detection was great (95%) which is important in our cohorts because we do not want to miss any metastatic lymph nodes.

In this study, we calculated the cut-offs of $SUV_{max}$, L/B ratio, lymph node size, and MTV to determine malignant lymph node status of anal cancer. The cut-offs in our study were 2.6 cm for the $SUV_{max}$ and 1.6 cm for SAD which are close to a generally used cut-off $SUV_{max}$ of 2.5 [22] and cut-off of 1.5 cm for enlarged inguinal lymph node on CT and MRI [23]. To our knowledge, this was the first study comparing qualitative and quantitative methods of PET/CT and evaluating these particular cut-offs for lymph node metastasis in anal cancer. Several studies demonstrated the optimal $SUV_{max}$ cut-offs to distinguish benign from malignant lymph nodes in SCCA of various organs but not anal cancer, for example; a study by Kitajima et al. [24] identified an optimum $SUV_{max}$ cut-off of 3.5 by ROC curve analysis for preoperative evaluation of cervical neck lymph node metastases in patients with oral SCCA and Dequanter et al. [25] showed that the $SUV_{max}$ of 4.05 excellently predicts cervical lymph node metastasis in head and neck SCCA. From Bella et al. study [26], they suggested $SUV_{max}$ of 4.1 instead of 2.5 to distinguish benign from malignant lymph nodes in squamous esophageal carcinoma.

The factor that associated with false negative detection of lymph node metastasis when using the cut-off $SUV_{max} \geq 2.6$ in our study was possible necrotic lymph node. As we know that benign lesions such as infection and inflammation can show increased uptake on PET/CT, causing diagnostic problems. The causes of false positive PET/CT of $SUV_{max} \geq 2.6$ in this study were reactive lymphoid hyperplasia and spirochetal lymphadenitis from syphilis which had $SUV_{max}$ of 4.49 and 7.68, respectively. In a study from Kumar et al., they suggested the optimal $SUV_{max}$ of 6.2 as the cut-off used for discrimination between infected/inflammatory and malignant mediastinal lymph nodes [27], however, in our study we did not calculate the cut-off point to differentiate between these conditions. Another limitation of our study is a retrospective design with a relatively small number of patients in our cohort and the single-center experience. Therefore, for the best result of quantitative analysis, prospective study with multi-center and inclusion of a larger number of patients would be necessary for future study. The last limitation is that we just looked at the patient who performed PET/CT with available biopsy histopathologic data, could be resulting in selective bias.

In conclusion, quantitative analysis using $SUV_{max}$ of 2.6 showed higher sensitivity in detection of lymph node metastasis in anal cancer compared to qualitative analysis. Our results showed that optimizing the $SUV_{max}$ cut-off can increase the diagnostic accuracy in determining lymph node metastasis from anal cancer in clinical practice. The SAD of 1.6 cm has 100% specificity to diagnosis of metastatic lymph nodes. Therefore, when interpreting qualitative visual PET/CT analysis that is considered doubtful, using $SUV_{max}$ and SAD cut-offs will help clinician to determine malignant lymph nodes.

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors. IRB statement: Institutional Review Board (IRB) and Health Insurance Portability and Accountability Act (HIPPA) approval were obtained and requirement for informed consent was waived by our hospital IRB.

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