Prognostic value of metabolic tumor volume and total lesion glycolysis from $^{18}$F-FDG PET/CT in lymph node metastases and risk stratification of endometrial carcinoma

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**ABSTRACT**

**Objective:** To investigate the prognostic value of metabolic tumor volume (MTV) and total lesion glycolysis (TLG), measured by preoperative $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), in risk stratification of patients with endometrial carcinoma (EC).

**Methods:** The patients with pathological diagnosis of EC who underwent preoperative $^{18}$F-FDG PET/CT imaging were retrospectively selected for analysis of the prognostic values of PET parameters in risk classification and lymph node metastases (LNMs). Receiver-operating-characteristic analysis was used to analyze the correlation of PET parameters cutoff values with deep myometrial invasion (MI), lymphovascular space involvement and LNM for prognostic values in risk stratification.

**Results:** The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for detection of LNM are 83.3%, 99.7%, 90.9%, 99.5% and 99.2%, respectively. The MTV and TLG of primary lesion of EC in the patients with LNM are notably higher than those in patients without LNM, $p<0.010$. The MTV and TLG of the EC primary lesions in high-risk patients are significantly higher than those in low-risk patients ($p<0.010$), but the maximum standardized uptake value (SUVmax) is not. The MTV and TLG of primary lesions were superior to SUVmax for predicting of deep MI, LNM and high-risk of EC ($p<0.005$).

**Conclusion:** MTV and TLG of primary lesions are more valuable in predicting risk stratification of EC patients. Preoperative $^{18}$F-FDG PET/CT imaging is useful in predicting the LNM of EC and may help guide pelvic lymphadenectomy to avoid unnecessary pelvic lymphadenectomy in EC patients with low-risk stratification.

**Keywords:** Endometrial Carcinoma; Lymphatic Metastases; Tumor Volume; Metabolism; Risk Assessment
INTRODUCTION

The endometrial carcinoma (EC) is the most common gynecological malignant tumors and 20%–30% of gynecologic tumors are EC [1,2]. The number of patients with EC is rapidly increasing in China [1,3]. The 20%–25% of EC recurred within three years after hysterectomy, although the 75% of EC were diagnosed at early stage [1,4,5]. The survival rate would be lower if the EC patients had pelvic or para-aortic lymph node metastases (LNMs) [4,6-8]. The LNM of EC is one of key elements for EC classified as high-risk group, according to the International Federation of Gynecology and Obstetrics (FIGO) stage and standard of EC stratification [4,6,9]. The patients of high-risk group have a higher rate of recurrence and LNM [4,8].

Pelvic LNM of EC is considered as one of most important prognostic factors for EC patients [10-12]. But it is debatable whether it is necessary to perform pelvic lymphadenectomy in each of EC patients [6]. There are different opinions regarding whether performance of lymphadenectomy is necessary for EC patients in low-risk group [11,13-15]. Some of clinicians proposed that the lymphadenectomy would be benefit for staging, prognosis, and selection of neoadjuvant chemotherapy for EC patients [10,11], while some of clinicians did not support lymphadenectomy for low-risk group EC patients based on extremely low probability of LNMs in low-risk group of patients [13,16].

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is an advanced imaging modality that has combined morphological and functional imaging capabilities and is widely used for diagnosis, staging, prognosis and restaging of cancer [8,17]. The maximum standardized uptake value (SUVmax) is often measured for semi-quantitative analysis of glucose metabolic activity of EC by 18F-FDG PET/CT examination [18,19]. However, the SUVmax has some limitations, which only represents the measurement from a single spot of most hypermetabolic area of a tumor mass [12,19]. It cannot be used to assess the overall glucose metabolic activity of a tumor mass and is limited for assessment of the overall metabolic change of total tumor volume [20,21]. SUVmax has limited use for accurate assessment of overall metabolic activity of tumor lesion due to heterogeneous glycometabolism [20,21].

Metabolic tumor volume (MTV) is an useful PET parameter that can be used to measure overall glucose metabolic activity of a cancer lesion [20,21]. Total lesion glycolysis (TLG) is another useful PET parameter that reflects the metabolic activity and volume of the tumor [8]. A number of studies have shown that MTV and TLG have prognostic significance in malignant tumors [5,6]. MTV and TLG have been used for risk stratification in esophageal cancer [22], non-small cell lung cancer [23] and other tumors [24], but there were few studies of prognostic values of MTV and TLG in preoperative risk stratification of EC [21,25].

Although previous studies suggested that 18F-FDG PET/CT can be beneficial as a preoperative diagnostic test in endometrial cancer patients [8,17], the MTV and TLG are expected to reflect the hypermetabolic tumor burden more accurately than SUVmax, but its clinical role in risk stratification of EC patients has not been well defined [20,24]. The value of various quantitative tumor parameters and the corresponding optimal cutoffs of MTV and TLG in correlation with LNM for risk stratification remain to be determined in EC [17,20]. We hypothesize that the MTV and TLG from preoperative 18F FDG PET/CT examination might correlate with LNM and have better prognostic value than SUVmax in risk stratification.
of EC. To investigate our hypothesis, we have conducted a retrospective clinical study to analyze correlation of MTV and TLG with LNM and determine cutoff values of MTV and TLG in predicting the LNM for risk stratification and surgical planning of lymphadenectomy in clinical management of EC patients.

MATERIALS AND METHODS

1. Study populations
The inclusion criteria for this study are to enroll the patients with EC who had received hysterectomy and pelvic lymphadenectomy, and had preoperative ¹⁸F-FDG PET/CT. The EC patients with the pathological data of primary lesion and pelvic lymph nodes were enrolled for this research, using a clinical data base in a period of 4 years (between January 2015 and December 2018) in our Hospital. According to the risk stratification standards proposed by European Society for Medical Oncology, the patients with EC of histological grade 1 (G1), superficial myometrial invasion (MI; i.e. invasion of less than half of the myometrium, MI<1/2) and FIGO stage Ia were classified as the low-risk group, while the patients with EC of histological grade 2/3 (G2/3), positive lymphovascular space involvement (LVSI) or deep MI (invasion of more than half of the myometrium, MI≥1/2) were classified as high-risk group.

This retrospective study was approved by Institutional Review Board at Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China ([2019]02-338-01).

2. ¹⁸F-FDG PET/CT imaging protocol
¹⁸F-FDG PET/CT examination were completed within one month before EC radical surgery in this retrospective study. To prepare for the examination, all of the patients fasted for more than 6 hours. The patient’s blood glucose level was measured to ensure the patient’s blood glucose level was within 3.9–7.0 mmol/L prior to intravenous injection of ¹⁸F-FDG (0.1–0.12 MBq/kg body weight, about 185–370 MBq). Following intravenous injection of ¹⁸F-FDG, the patient stayed in a quiet environment for about 50 minutes to allow biodistribution of the radiotracer. PET acquisition was performed from top of the head to mid-thigh, using a PET/CT scanner (Discovery Elite; GE healthcare, Chicago, IL, USA). The patients took a supine position with head slightly reclined for PET acquisition. According to the height of the patient, the patients were scanned at 7–9 beds, for 2 minutes per bed position. PET Images were reconstructed and stored in axial, coronal, and sagittal slices 3.75 mm thick using a GE workstation (advantage workstation 4.6 releases).

3. Interpretation of ¹⁸F-FDG PET/CT imaging
In this study, all PET/CT images were reviewed by two experienced nuclear medicine physicians who had no knowledge of the patient’s clinical information, and a standard PET/CT imaging report was generated. The artifactual and physiological soft tissue accumulation of ¹⁸F-FDG was taken into consideration for accurate interpretation. The diagnosis of primary tumor lesions was based on abnormal increased FDG uptake of a nodular, lumpy or irregular appearance on the PET images, the SUVmax is over 2.5.

Using GE workstation, volume of interests (VOIs) were delineated on PET images and manual adjustment was performed on axial, coronal and sagittal images to obtain optimal boundary of the primary focus. The SUVmax, MTV and TLG were generated automatically using software on GE workstation.
SUV was calculated using the following formula:

\[
\text{SUV} = \left( \frac{\text{concentration of radioactivity in the VOI (MBq/mL)}}{\text{total body weight/injected radioactivity (g/MBq)}} \right)
\]

SUVmax was the highest SUV of a voxel within a specific VOI. The MTV was measured from attenuation-corrected PET/CT images using an SUV-based automated contouring program. TLG was calculated as MTV×SUVmean.

4. Statistical analysis

The statistical analysis was performed using software SPSS 22.0 (IBM Corp., Armonk, NY, USA). Quantitative data was recorded as mean±standard deviation. The t-test was used in independent samples. Rank sum test and single factor analysis of variance were used to compare the difference of metabolic parameters (SUVmax, MTV, TLG) in different pathological features. The difference was considered to be statistically significant with p<0.05 (bilateral). The receiver-operating-characteristic (ROC) curves were constructed to evaluate the optimal predictive performance among the SUVmax, MTV, and TLG of primary lesion in EC patients.

RESULTS

1. Histopathological characteristics of EC patients

Forty-one patients diagnosed with endometrial cancer, with an age range of 33 to 81 years-old, were enrolled for this study. The preoperative ¹⁸F-FDG PET/CT were done within one month prior to hysterectomy and lymphadenectomy. The histopathological characteristics of EC in these patients were presented in Table 1. As noted on Table 1, the percentage of patients with FIGO stage I, II and III were 65.9% (27/41), 7.3% (3/41) and 26.8% (11/41), respectively. The 34.1% (14/41) patients with deep MI (MI≥1/2) and 21.9% (9/41) patients with LVSI were found, and 48.8% (20/41) of the EC patients were classified in high-risk group, with histological grade 2/3 (G2/3), positive for LVSI or deep MI. One of the high-risk group patients was presented in Fig. 1.

The resected lymph nodes in 372 lymph node regions were statistically analyzed in 41 patients with EC who underwent hysterectomy and pelvic node dissection. To correlate pathological findings of nodal metastasis with SUVmax of these nodes on preoperative ¹⁸F-FDG PET, 11 foci of abnormal increased FDG uptake on ¹⁸F-FDG on PET/CT images were interpreted positive for LNM according to the 5.2 of optimal cutoff value of SUVmax optimized by ROC analysis, in which there were 10 lymph node regions interpreted as true positive compared with histopathological results. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for detection of LNM are 83.3% (10/12), 99.7% (359/360), 90.9% (10/11), 99.5% (359/361) and 99.2% (369/372), respectively. All lymph nodes in 177 lymph node regions resected in EC patients with low-risk stratification are negative LNM determined by ¹⁸F-FDG PET/CT images with optimal cutoff of SUVmax and histopathological results.

2. ROC curve analysis of metabolic parameters of EC primary lesions

SUVmax, MTV, and TLG of EC primary lesions were obtained from ¹⁸F-FDG PET/CT examination of the participants. The median values of the SUVmax, MTV and TLG of EC primary lesions were 12.18 (3.24–26.72), 18.11 (0.65–141.00) mL and 162.63 (2.07–1,880.92) g.
respectively. The median of MTV and TLG of the EC primary lesion have a positive correlation with MI, LVSI, LNM and high-risk degree (p<0.050). The MTV and TLG (39.37±44.06 and 387.17±523.56) of primary lesion of EC in the patients with deep MI (MI≥1/2) are notably higher than those (7.08±5.96 and 46.21±52.53) in patients with superficial MI (MI<1/2), \(p<0.001\). In addition, the MTV and TLG (52.90±54.43 and 543.89±695.25) of primary lesion of EC in the patients with LNM are notably higher than those (10.94±15.35 and 84.13±132.56) in patients without LNM, \(p<0.010\).

The SUVmax (17.12±3.90), MTV (55.98±47.69) and TLG (566.99±587.00) in patients with LVSI are higher than those without LVSI (SUVmax [10.79±5.48], MTV [7.45±5.75] and TLG [48.90±45.84]), \(p<0.010\). MTV and TLG (31.28±40.01 and 295.88±471.65) of the EC primary lesions in high-risk patients are significantly higher than those (6.73±6.21 and 47.54±59.42) in low-risk patients (\(p<0.010\)), but there are no significant differences of SUVmax between high-risk group (13.41±5.38) and low-risk group (11.11±6.02), \(p>0.050\). The detailed data were shown on Table 2.

Using the time-dependent ROC curve for analysis of primary lesion of EC, the ROC curves showed that the MTV and TLG of primary lesions were superior to SUVmax for predicting of deep MI, LVSI, LNM and high-risk of EC (\(p<0.005\)) (Fig. 2). The TLG had highest area under the curves (AUCs) for predicting deep MI (0.831) and LNM (0.909). The MTV (AUC=0.787; \(p<0.005\)) and TLG (AUC=0.778; \(p<0.005\)) are valuable in distinguishing of high-risk and low-risk stratification in EC patients, but the SUVmax (AUC=0.639; \(p>0.050\)) is not helpful.
The detailed optimal cutoffs and AUCs of SUVmax, MTV and TLG for predicting of deep MI, LSVI, LNM and risk stratification were showed in Table 3.

Table 2. TLG, MTV and SUVmax in MI, LNM, LSVI and risk stratification group

| Group           | Case (%) | SUVmax       | MTV           | TLG            |
|-----------------|----------|--------------|---------------|----------------|
| MI              |          |              |               |                |
| <1/2            | 27 (65.9)| 10.95±5.71   | 7.08±5.96     | 46.21±52.53    |
| ≥1/2            | 14 (34.1)| 14.55±5.33   | 39.37±44.06   | 387.17±523.56  |
| p-value         |          | >0.050       | <0.001        | <0.005         |
| LSVI            |          |              |               |                |
| Negative        | 32 (78.1)| 10.79±5.48   | 7.45±5.75     | 48.90±45.84    |
| Positive        | 9 (21.9) | 17.12±3.90   | 55.98±47.69   | 566.99±587.00  |
| p-value         |          | <0.005       | <0.001        | <0.001         |
| LNM             |          |              |               |                |
| Negative        | 34 (82.9)| 11.80±5.65   | 10.94±15.35   | 84.13±132.56   |
| Positive        | 7 (17.1) | 14.03±6.51   | 52.90±54.43   | 543.89±695.25  |
| p-value         |          | >0.050       | <0.001        | <0.001         |
| Risk stratification | |          |               |                |
| Low-risk        | 22 (53.7)| 11.11±6.02   | 6.73±6.21     | 47.54±59.42    |
| High-risk       | 19 (46.3)| 13.41±5.38   | 31.28±40.01   | 295.88±471.65  |
| p-value         |          | >0.050       | <0.010        | <0.050         |

LNM, lymph node metastasis; LSVI, lymphovascular space involvement; MI, myometrial invasion; MTV, metabolic tumor volume; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.
DISCUSSION

LNM was an important prognostic factor of EC. The prognosis of EC patients with LNM was significantly lower than that of patients without LNM [6,9]. Surgery is considered most important and effective for treatment of primary EC, but there is still a great deal of controversy about indication and necessity of pelvic lymph node dissection [6,9,26]. Clinicians did not support lymphadenectomy for low-risk group EC patients based on low probability of LNMs in low-risk group of patients [13,16], because only 5% metastases in low-risk patients with EC [27]. Another reason is that performance of iliac lymphadenectomy is not easy and often associated with post-surgical complication due to complex anatomical structure in this region [10,13]. It is important to accurately detect and predict the LNM of EC for surgical planning of pelvic lymph node dissection in clinical management of EC patients [9].

Fig. 2. ROC curves for various tumor quantifications for prediction of MI (A), LNMs (B), LVSI (C) and risk stratification (D) in patients with endometrial carcinoma. The p-values refer to test of equal areas under the curve across tumor quantifications AUCs.

AUC, area under the curve; LNM, lymph node metastasis; LVSI, lymphovascular space involvement; MI, myometrial invasion; MTV, metabolic tumor volume; ROC, receiver-operating-characteristic; SUV, standardized uptake value; TLG, total lesion glycolysis.

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The 18F-FDG PET/CT are widely used for diagnosis, staging, prognosis and restaging of cancer [8,17]. With regard to the use of preoperative 18F-FDG PET/CT for evaluation of LNM in EC, some studies showed that the specificity of 18F-FDG PET in the detection of LNM was as high as 98%, but the sensitivity was lower (about 60%) [8,28], however, our sensitivity in detection of LNM was higher (about 83.3%). In our current study, there were 359 true negative LNM in 361 lymph node regions determined by the optimal cutoff of SUVmax of lymph nodes. The negative predictive value in the detection of LNM of EC was 99.5% and was similar with previous studies (93%–100%) [20,22,29]. These results indicated that the rate of LNM would be extremely low and the lymphadenectomy might be not necessary to done if 18F-FDG PET images could be interpreted negative for lymph node in patients with EC.

Meanwhile, the LNM of patients with EC might be predicted by the metabolic feature of primary EC lesion also [8,18,20,21]. There were a statistically differences for MTV and TLG of primary lesions between the positive and negative LNM in current study, which were compatible with the findings from previous studies [7,12]. However, the SUVmax of primary lesion have no significantly differences. These results indicated that the MTV and TLG of primary lesion were superior to SUVmax in predicting LNM of patients with EC. The reasons for superior prognostic values of MTV and TLG over SUVmax are not very clear and remained to be determined. This may be partly due to the fact that MTV of lesion may reveal the overall glucose metabolic activity of a tumor lesion and the TLG may reflect the metabolic activity and volume of the tumor [21]. They combined overall functional measurement of glucose metabolism and tumor morphology [20,21]. In contrast, the SUVmax only represents the measurement from a single spot of most hypermetabolic area of a tumor mass and is limited for assessment of the overall metabolic change of total tumor volume due to heterogeneous glycometabolism of tumor lesion [19-21].

In the matter of the preoperative risk stratification of EC, it was reported that the high SUVmax of primary EC lesion was related with the worse prognosis [22]. However, we found that there was no significant difference of primary EC lesion SUVmax between high and low-risk groups of EC patients. A number of studies have shown that MTV and TLG have prognostic significance in malignant tumors [5,6]. The MTV and TLG have been used for risk stratification in esophageal cancer [22], non-small cell lung cancer [23] and other tumors [24], but there were few studies of prognostic values of MTV and TLG in preoperative

### Table 3. The ROC curve parameters of primary lesion of EC in different groups

| Group | AUCs (95% CI) | p-value | Cutoff | Sensitivity (%) | Specificity (%) |
|-------|--------------|---------|--------|----------------|-----------------|
| Deep MI | | | | | |
| SUVmax | 0.709 (0.538–0.880) | 0.030 | 12.4 | 78.6 | 66.7 |
| MTV | 0.817 (0.670–0.962) | 0.001 | 11.8 | 71.4 | 85.2 |
| TLG | 0.831 (0.682–0.979) | 0.001 | 98.3 | 71.4 | 92.6 |
| LVSI | | | | | |
| SUVmax | 0.609 (0.366–0.852) | 0.368 | 14.9 | 57.1 | 73.5 |
| MTV | 0.832 (0.679–0.985) | 0.006 | 17.2 | 71.4 | 85.3 |
| TLG | 0.782 (0.589–0.974) | 0.020 | 79.8 | 71.4 | 80.6 |
| LNM | | | | | |
| SUVmax | 0.784 (0.634–0.934) | 0.014 | 14.2 | 66.8 | 71.9 |
| MTV | 0.898 (0.774–1.000) | 0.001 | 19.8 | 77.8 | 93.7 |
| TLG | 0.909 (0.794–1.000) | 0.001 | 166.9 | 75.0 | 96.9 |
| Risk stratification | | | | | |
| SUVmax | 0.639 (0.463–0.815) | 0.129 | 11.3 | 78.9 | 63.6 |
| MTV | 0.787 (0.641–0.933) | 0.002 | 9.5 | 73.7 | 81.8 |
| TLG | 0.778 (0.627–0.928) | 0.002 | 51.7 | 84.2 | 77.3 |

AUC, area under the curve; CI, confidence interval; EC, endometrial cancer; LNM, lymph node metastasis; LVSI, lymphovascular space involvement; MI, myometrial invasion; MTV, metabolic tumor volume; ROC, receiver-operating-characteristic; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.
risk stratification of EC [21,25]. Our results indicated that MTV and TLG of the primary lesions were significantly higher in high-risk patients than those in low-risk patients, but no significant difference of SUVmax between high and low-risk groups of EC patients. Kitajima et al. [5] also found that there was no significant difference in SUVmax between high- and low-risk groups. These results suggested that the MTV and TLG of primary lesions were more valuable parameters for distinguishing high-risk EC patients from low-risk EC patients.

Besides, the deep MI in patients with EC is a high-risk factor for LNM [5,16]. The finding of Antonsen et al. [28] suggested that 18F-FDG PET/CT was useful for screening patients with deep MI. We also found that the MTV and TLG of primary EC were significantly higher in patients with deep MI (MI ≥1/2) than those with superficial MI (<1/2). Our results demonstrated that the MTV and TLG of EC primary lesion were valuable for predicting deep MI of EC when preoperative 18F-FDG PET/CT imaging was used for risk stratification, because the prognosis of EC is associated with the pathological feature, LNM and deep MI [4,8,9]. The 18F-FDG PET/CT had been previously reported the prognostic and potential value for risk stratification in patients with EC [5,7,10,22,24].

The sample size of this retrospective study is relatively small due to stringent inclusion criteria and only a small number of patients in our hospital had both pathological data of primary endometrial adenocarcinoma lesion and pelvic lymph nodes, as well as imaging data from 18F-FDG PET/CT. Additional studies with a larger sample size are necessary to verify the findings from this retrospective study and determine prognostic values of MTV and TLG in risk stratification and surgical planning in clinical management of EC patients.

In summary, the findings from this retrospective study suggested a high negative predictive value of preoperative 18F-FDG PET/CT in evaluation of LNM of endometrial carcinoma. The MTV and TLG of primary EC lesion measured by preoperative 18F-FDG PET/CT are superior to SUVmax in distinguishing high-risk patients from low-risk patients in risk stratification of EC. In view of its high negative predictive value of lymph nodes, preoperative 18F-FDG PET/CT imaging may be used to achieve more accurate the risk stratification of EC patients and avoid the unnecessary pelvic lymph node dissection in low-risk EC patients, who are determined to be low-risk based on the MTV and TLG measured with 18F-FDG PET/CT analysis.

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