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Standardized uptake value and metabolic tumor volume measured by ^{18}F FDG PET/CT are sensitive biomarkers for the presence of lymph node metastasis in patients with cervical carcinoma

G.U. Vural*, B.E. Akkas, B.B. Demirel

Department of Nuclear Medicine, Ankara Oncology Education and Research Hospital, Ankara, Turkey

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ABSTRACT

The aim of this study was to evaluate whether tumor standardized uptake value (SUVmax) and metabolic tumor volume (MTV) associate with the presence of PET-positive pelvic/para-aortic lymph nodes (LN) in cervical cancer patients.

Method: Seventy-four patients with stage IB-IVB cervical cancer (squamous [n:66], nonsquamous [n:8]), who were referred to FDG-PET/CT department for initial staging, were enrolled in this study.

Results: Patients were staged according to International Federation of Gynecology and Obstetrics [FIGO] criteria as; stage I (n:5), stage II (n:25), stage III (n:15) and stage IV (n:29). PET/CT detected 53 patients with hypermetabolic LN (average SUVmax: 7.5 ± 4.1 , range: 4.1–22.8, pelvic LN: 29 patients, para-aortic LN: 5 patients, pelvic and para-aortic LN: 19 patients). SUVmax and MTV were significantly higher in patients with PET-positive LN compared to others (18.4 and 88.8 cm^3 vs. 13.9 and 39.9 cm^3 respectively, $p=0.007$ for SUVmax, $p=0.0001$ for MTV). Cut-off values in association with PET-positive LN were 15.2 for SUVmax and 35 cm^3 for MTV on ROC curve analysis. There was no correlation between SUVmax and MTV (correlation coefficient (R^2) = 0.07). MTV differed significantly with FIGO stages (41 , 98 and 107 cm^3 , in stage II, III and IV respectively, $p=0.015$).

Conclusion: Presence of PET-positive LN correlates with tumor SUVmax and MTV of cervical tumor. These findings support the use of PET/CT in the pretreatment evaluation of cervical cancer patients in order to identify cases with high risk of lymphatic involvement.

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El valor de captación estándar y el volumen metabólico tumoral medidos mediante ^{18}F FDG PET/TC constituyen biomarcadores sensibles a la presencia de metástasis de ganglios linfáticos en pacientes con carcinoma cervical

RESUMEN

El objetivo de este estudio fue el de evaluar si el valor de captación tumoral estándar (SUVmax) y el volumen tumoral metabólico (VTM) se asocian a la presencia de ganglios linfáticos pélvicos/para-aórticos PET-positivos en los pacientes de cáncer cervical.

Método: Se incluyó en este estudio a setenta y cuatro pacientes con cáncer cervical en estadio IB-IVB (escamoso [n:66], no escamoso [n:8]), que fueron remitidos a la unidad de FDG-PET/TC para una estadificación inicial.

Resultados: Se clasificó a los pacientes de acuerdo a los criterios de la Federación Internacional de Ginecología y Obstetricia [FIGO], es decir; estadio I (n:5), estadio II (n:25), estadio III (n:15) y estadio IV (n:29). La exploración PET/CT detectó 53 pacientes con ganglios hipermetabólicos (SUVmax medio: $7,5 \pm 4,1$, rango: 4,1–22,8, ganglios pélvicos: 29 pacientes, ganglios para-aórticos: 5 pacientes, ganglios pélvicos y para-aórticos: 19 pacientes). Los valores de SUVmax y VTM fueron considerablemente superiores en pacientes con ganglios PET-positivos en comparación al resto ($18,4$ y $88,8 \text{ cm}^3$ frente a $13,9$ y $39,9 \text{ cm}^3$ respectivamente, $p=0,007$ para SUVmax, $p=0,0001$ para VTM). Los valores límite en cuanto a ganglios PET-positivos fueron de $15,2$ para SUVmax y 35 cm^3 para VTM en un análisis de curva ROC. No se produjo correlación entre SUVmax y MTV (coeficiente de correlación: (R^2) = 0.07). El VTM difirió significativamente de los estadios FIGO (41 , 98 y 107 cm^3 , en los estadios II, III y IV respectivamente, $p=0,015$).

Conclusión: La presencia de ganglios PET-positivos guarda correlación con el SUVmax tumoral y el VTM del tumor cervical. Estos hallazgos apoyan el uso de PET/TC en la evaluación previa al tratamiento de los pacientes de cáncer cervical, a fin de identificar los casos con elevado riesgo de implicación linfática.

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Palabras clave:

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* Corresponding author.

E-mail address: drgulin@yahoo.com (G.U. Vural).

Introduction

Cervical carcinoma is the second most frequently diagnosed malignancy in women worldwide and is one of the leading causes of cancer deaths.¹ The presence of lymph node metastasis is well accepted to have a negative effect on prognosis.² Besides, the status of para-aortic lymph nodes, the higher level of lymph node involvement and the higher standardized uptake value (SUVmax) in metastatic lymph nodes are now known to be significant prognostic factors in patients with cervical carcinoma.^{2–5} Additionally, the detection of para-aortic lymph nodes has significant consequences on patient management, in that it helps determine whether the para-aortic lymphatic chain should be included in the radiation therapy field.⁶

Cervical cancer staging is defined by the International Federation of Gynecology and Obstetrics [FIGO] staging system. Although lymph node assessment is not part of the FIGO staging system, it must be performed during the initial workup of patients with cervical cancer as an important component of treatment planning. Morphological imaging with Magnetic Resonance Imaging (MRI) has been the most widely used modality for assessment of nodal metastases and the extent of pelvic disease. Despite its high sensitivity to detect parametrial involvement and local invasion of the tumor to adjacent organs and structures, MRI has limited ability to detect small-volume metastatic involvement in normal-size lymph nodes.⁷

¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) appears to have higher sensitivity and specificity, higher positive likelihood ratio and lower negative likelihood ratio compared to CT and MRI in recent studies in the detection of lymph node metastasis and the extent of disease.^{7–9} Researchers have demonstrated the value of PET and PET/CT in identifying lymph node involvement, distant disease and recurrent disease in patients with cervical cancer.^{3,10} On the basis of these evidences, National Comprehensive Cancer Network (NCCN) guideline recommends the use of PET/CT in the pretreatment workup of patients with cervical carcinoma.¹¹ Moreover, the use of FDG PET and PET/CT in a large oncology practice has proved the importance of PET to provide prognostic information for patients with malignant diseases. In many cancers, high FDG uptake of the primary tumor, typically characterized as the standardized uptake value (SUV) predicts a worse clinical outcome.^{10,12} Additionally, tumor volume, defined as the three-dimensional volume of the primary tumor with increased FDG uptake, can be accurately measured from attenuation corrected PET/CT images.^{13,14} Furthermore, previous studies report that quantitative measurement of tumor volume by PET help to separate patients with a good prognosis from those with a poorer prognosis.¹³

In this study, we investigated the associations of metabolic tumor volume (MTV) and SUV max with the presence of PET-positive lymph nodes in 74 patients with cervical carcinoma. Additionally, we aimed to determine cut off values for tumor SUVmax and volume in association with the presence of PET-positive pelvic and/or para-aortic lymph nodes.

Methods

Patient population

A total of 74 patients with cervical carcinoma who were referred to our department for FDG PET/CT imaging as a part of initial staging and treatment planning were included in this retrospective study. Patients with previous diagnosis of another malignant disease were excluded from the study.

This study was approved by the ethics committee of our institution.

Patients were imaged on an integrated PET/CT scanner (Siemens Biograph 6 – True Point PET/CT systems). Patients were fasted for at least 6 h prior to injection of 5.3 MBq/kg (144 μ Ci/kg) ¹⁸F-FDG. The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. PET/CT scan was performed 60 min after FDG injection. Unenhanced CT images were acquired from the skull vertex to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. Oral contrast medium was administered to all patients. The PET and CT images were reviewed on a workstation (Leonardo, Siemens Medical Solutions) in all standard planes along with maximum-intensity-projection images and were analyzed visually and quantitatively by two reviewers experienced in interpreting PET/CT scans. Findings were recorded by consensus.

The maximum standardized uptake value (SUVmax) was used to quantify FDG uptake. SUVmax was calculated using the following formula:

$$\text{SUVmax} = \frac{\text{Cmax} \times \text{TBW}}{\text{IA}}$$

where Cmax: activity concentration in the voxel of highest tumor activity (Bq/ml), TBW: total body weight (kg), IA: injected activity (kBq).

Tumor volume was measured from attenuation-corrected FDG-PET/CT images using an SUV-based automated contouring program (Syngo MI applications, Siemens Medical Solutions). The boundaries of tumor were drawn large enough to incorporate each target lesion in the axial, coronal, and sagittal FDG PET/CT images. The contour around the target lesions inside the boundaries was automatically produced. Depending on previous data, a fixed threshold value of 40% of SUVmax was used.¹³ The voxels presenting SUV intensity greater than that of 40% of SUVmax within the contouring margin were incorporated to define the tumor volumes.

The FDG uptake in pelvic and para-aortic lymph nodes was evaluated by PET/CT. Since standard uptake values can be affected by many technical factors, and besides, SUV measurements in small lesions can be underestimated by partial volume effect,¹⁵ the presence of focally increased FDG uptake in the lymph nodes, regardless of its size was considered as “PET positive” and suggestive of nodal disease.

Statistical analysis

The differences between tumor volumes according to FIGO clinical stage were analyzed by Kruskal–Wallis test. The differences between tumor volume and SUVmax according to the presence of PET-positive lymph nodes were analyzed by Mann–Whitney *U* test. *p* values < 0.05 were considered to be statistically significant. Tumor SUVmax were compared to MTV and SUVmax of lymph nodes by using regression analysis. Receiver Operating Characteristic (ROC) curve analysis was used to mark the cut off values of tumor volume and tumor SUVmax for cervical tumor in association with the presence of PET-positive lymph nodes.

Results

Patient characteristics, including age at diagnosis, FIGO clinical stage, histology, lymph node status are listed in [Table 1](#).

All patients were staged clinically according to International Federation of Gynecology and Obstetrics [FIGO] staging criteria with the distribution as follows: stage I: 5 patients, stage IIA: 5 patients, stage IIB: 20 patients, stage IIIA: 7 patients, stage IIIB: 8 patients, stage IVA: 11 patients and stage IVB: 18 patients.

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