Medicinski podmladak

Medical Youth

ORIGINAL ARTICLE

THE SIGNIFICANCE OF POSITRON EMISSION AND COMPUTERIZED TOMOGRAPHY WITH FLUORODEOXYGLUCOSE IN THE POST-THERAPEUTIC EVALUATION OF PATIENTS WITH UTERINE CARCINOMA

POZITRONSKA EMISIONA I KOMPJUTERIZOVANA TOMOGRAFIJA SA FLUORDEOKSIGLUKOZOM U POST-TERAPIJSKOJ EVALUACIJI PACIJENTINJA SA KARCINOMOM UTERUSA

Ivona Jelić[1], Vuk Isaković[1], Slađan Jovanović[1], Strahinja Odalović[1,2]

[1] Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2] Center of Nuclear Medicine, Clinical Center of Serbia, Belgrade, Serbia

Correspondence: ivonajelich@abv.bg

Abstract

Introduction: The positron emission tomography with computerized tomography is a valuable machine in identifying tumors - it can determine the exact size and position of the cancer, as well as the effect of therapy. The duality of this technique provides information on the metabolic activities of the neoplasm and a precise anatomical location.
Aim: The aim of this study was be to determine the diagnostic performance of FDG PET/CT in detection of recurrent disease and to determine the stage of the disease after the application of therapy in patients with cervical carcinoma.
Material and methods: In this study, a total of 38 patients were included, in whom FDG PET/CT was made from 2010 to 2017. The diagnostic contribution of FDG PET/CT in the detection and identification of the recurrence of cervical cancer was determined by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).
Results: The sensitivity, specificity, PPV, NPV and diagnostic accuracy of FDG PET/CT in the detection of local and distant relapses of cervical carcinoma were 90%, 75%, 93.1%, 66.7% and 86.8%, respectively. There were 27 true positive, 2 false positive, 6 true negative and 3 false negative findings.
Conclusion: The FDG PET/CT has proven to be a very sensitive method in the detection of secondary deposits of cervical cancer. Of particular importance is in the evaluation of the patient with this diagnosis. The metabolic activity of lesions (SUV max) did not have an impact on the therapeutic response.

Keywords:
FDG PET/CT,
cervical cancer,
evaluation

doi:10.5937/mp70-17690
Editorial board: podmladak.med.bg@gmail.com
e-ISSN: 2466-5525

Sažetak

Uvod: Skener za pozitronsku emisionu i kompjuterizovanu tomografiju (PET/CT) jedan je od najpreciznijih aparata za dijagnostikovanje tumora, kojom mogu da se utvrde tačna veličina i pozicija promene, kao i efekat terapije. Dualnost ove metode daje podatke o metaboličkim aktivnostima neoplazme i pruža precizne anatomske informacije.
Cilj: Cilj ovog istraživanja bio je određivanje dijagnostičkih performansi FDG PET/CT u detekciji rekurentne bolesti i određivanju stadijuma bolesti nakon primenjene terapije kod pacijentkinja sa karcinomom uterusa.
Materijal i metode: U ovu studiju je uključeno ukupno 38 pacijentkinja kod kojih je u periodu od 2010. do 2017. godine urađen FDG PET/CT. Dijagnostički doprinos FDG PET/CT u detekciji i identifikaciji recidiva karcinoma cerviksa uterusa određivan je izračunavanjem senzitivnosti, specifičnosti, pozitivne prediktivne vrednosti (PPV) i negativne prediktivne vrednosti (NPV).
Rezultati: Izračunata je vrednost senzitivnosti, specifičnosti, pozitivne prediktivne vrednosti, negativne prediktivne vrednosti i dijagnostičke tačnosti FDG PET/CT u detekciji lokalnih i udaljenih recidiva karcinoma grlića materice. Ove vrednosti su iznosile 90%, 75%, 93,1%, 66,7% i 86,8%. Pozitivnih nalaza je bilo 27, lažno pozitivnih 2, negativnih 6, a lažno negativnih 3.
Zaključak: Snimanje FDG PET/CT pokazalo se kao veoma senzitivna metoda u detekciji sekundarnih depozita karcinoma grlića materice. Poseban značaj ima u evaluaciji pacijentkinja sa ovom dijagnozom. Metabolička aktivnost lezija (*SUV max*) nije imala uticaj na terapijski odgovor.

Ključne reči:
FDG PET/CT,
karcinom grlića materice,
evaluacija

Introduction

Cervical carcinoma is the second most commonly diagnosed tumor in the female population in the whole world, and the third most common cause of death due to malignant diseases (1). Although the incidence of this disease is significantly declining in developed countries of the world, in less developed parts, cervical cancer is still one of the most significant causes of mortality (2). One of the major causes of this malignant disease is the persistent infection with *Human papillomavirus*, and oncogenic types 16 and 18 (3). Two thirds of cervical cancer are squamous cell carcinoma, adenocarcinomas constitute 15-20%, while other percentages are other histological variants (light cell carcinoma, neuroendocrine and adeno-squamous carcinoma) (4).

As a screening test for the presence of a malignant disease, a cytological examination of the cervix (Papanicolaou test) is routinely applied. However, the percentage of false-negative results is often up to 50%. Patients with a pathological finding of cytology are referred to colposcopy examination, while the definitive diagnosis of the disease is established by biopsy of the cervix (5).

After establishing a pathohistological diagnosis of the disease, visualization diagnostic methods, primarily computerized tomography (CT) and magnetic resonance imaging (MR), are used to define the status of lymph nodes and to assess the local extension of the disease, as well as the decision of therapy (6). The cervical cancer stage is clinically determined using the FIGO classification (7).

Positron emission tomography with computerized tomography and the application of radiopharmaceutical 18-F fluorodeoxyglucose as an analogue of glucose (FDG PET/CT), is an advanced imaging method that plays an important role in the detection and monitoring of oncological diseases. The application is based on the visualization of metabolically active tumor lesions, which forms the basis of this functional morphological imaging (8).

The use of FDG PET/CT in the evaluation of cervical cancer is related to the assessment of initial disease expansion, with significantly greater sensitivity and specificity in the detection of metastases in regional lymph nodes, as well as distant metastases compared to conventional imaging methods (CT and MR). Also, a significant influence of this method was recorded in the evaluation of the response to the therapy and the prognosis of this disease (9).

The aim of this paper was to examine the diagnostic ability of FDG PET/CT in the detection of local and distant cervical cancer recurrences and the role of PET/CT in evaluating response to therapy, as well as analyzing the relationship between quantitative PET parameters of detected lesions with the response to therapy.

Material and methods

Study population

In this retrospective study, patients were included in whom a FDG PET/CT examination that was performed in the National PET Center of the Clinical Center of Serbia in Belgrade after the resection of cervical cancer, due to suspicion of relapse of the disease. The criteria for the inclusion in the study were: resection of histopathologically confirmed cervical cancer, time elapsed after surgery of at least 3 months, and monitoring data after the FDG PET/CT examination for at least 12 months. After exclusion of

patients with incomplete data, a total of 38 patients (middle age 49.7 ± 13.5) were included in this study.

Procedures

The FDG PET/CT examination was performed on patients with signs and symptoms of the recurrence of cervical cancer; with negative or unclear MDCT and/or MR findings; and /or laboratory relapse indicators. For the time period of at least 12 months of follow-up, the results of pathohistological tests, visualization diagnostic methods, including FDG PET/CT examinations, as well as the results of laboratory analyzes, were collected. Findings of FDG PET/CT were compared with histopathological findings or with clinical results and follow-up by other imaging methods.

Acquisition and interpretation of findings

The FDG PET/CT recording was performed on a 64-bit PET/CT apparatus (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA) at the National PET Center in Belgrade. After a fasting period of 6-8 hours, patients were given F18-FDG at a dose of 5.5 MBq/kg bodyweight. After a low-dose CT scan (120 kV, modulated power current, with a width of up to 5mm), PET recording was done (in 7-8 "bed" positions, lasting 3 minutes per bed), from the base of the skull to half of the femur. Semi-quantitative analysis of the uptake of FDG by the pathological tissue was performed by calculating the maximum standardized uptake value of radiopharmaceuticals (SUV max), calculated using the formula: tissue activity (impulse/pixel/s) multiplied by the calibration factor divided by the applied activity FDG (MBq/kg body weight).

If any focus of abnormal FDG accumulation was observed, after exclusion of benign and physiological causes, the FDG PET/CT finding was considered positive. The final diagnosis of the disease was done by histopathological examination (after biopsy or surgical treatment) or based on the results of laboratory and other visualization methods. A truly positive finding (TP) was confirmed during the follow-up in the first 6 months after the initial FDG PET/CT test, histopathological examination or other visualization methods. In case of detection, of at least one focus of the increased FDG accumulation being considered malignant, and not confirmed by monitoring methods in the first 6 months, the finding was considered false positive (FP). A true negative finding (TN) was considered in the case of a confirmation of the absence of the disease during the first 6 months of follow-up after the initial FDG PET/CT examination, while the detection of the disease in the first 6 months of follow-up after a negative FDG PET/CT examination was considered to be a false negative finding (FN). The progression of the disease was the emergence of new lesions, an increase in the size and /or metabolic activity of existing lesions, as well as death caused by the underlying disease.

In continuation of the data analysis, the serial FDG PET/CT examination based on the change in the number, size, and metabolic activity of the lesions detected, was used to evaluate the response to therapy. Also, on the basis of SUV max, the most intense lesions were divided into two groups: group 1, consisting of patients with SUV max most active lesion below the mean SUV max of all lesions, or group 2, consisting of patients with SUV max lesions above the SUV max mean. Also, patients were divided into two groups based on the effects of therapy: group A, without response to therapy, and group B, with favorable response to therapy. The influence of the quantitatively determined metabolic activity of the most intense lesion in patients with an initially positive PET/CT finding, expressed as SUV max, on the effect of the applied therapy was examined.

Statistical analysis

Descriptive statistical analysis methods were used in statistical data processing. Diagnostic contribution of FDG PET/CT in the detection and identification of the recurrence of cervical uterine carcinoma was determined by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy based on the following formula:

Sensitivity = TP / (TP + FN)

Specificity = TN / (TN + FP)

PPV = TP / (TP + FP)

NPV = TN / (TN + FN)

Diagnostic accuracy = (TP + TN) / (TP + TN + FP + FN).

The association of SUV max of the most intense lesion and the effect of applied therapy was examined using the Chi-square test. The values of $p < 0.05$ were considered statistically significant.

Results

In our study, a total of 38 patients with the cervical cancer diagnosis were included in the post-therapeutic follow-up on FDG PET/CT testing.

A total of 99 FDG PET/CT studies were performed, out of which 25 patients had two PET/CT scans, 6 patients had three PET/CT scans, while the remaining 7 patients had four or more PET/CT scans.

Initially, the FDG PET/CT scans showed zones of increased accumulation of radiopharmacs that indicated the presence of the underlying disease in 29 cases. Out of these, 9 patients had pathological accumulation in the uterus, indicating a local recurrence. In 15 cases, pathological accumulation zones were observed in the lymph nodes. In 4 patients, PET/CT scans indicated changes in elevated glucose metabolism in the lungs, while multiple patients with disseminated pathological accumulation of radiopharmaceuticals were observed in 5 patients. Figure 1 shows FDG PET/CT image of a patient with focally elevated metabolism of glucose in the uterus, indicating a local recurrence (**figure 1**).

Subsequent testing confirmed the existence of a recurrence of cervical cancer in 30 patients. By comparing the results of the initial PET/CT test with the pathohistological examination and clinical and radiological monitoring, a positive finding of FDG PET/CT was

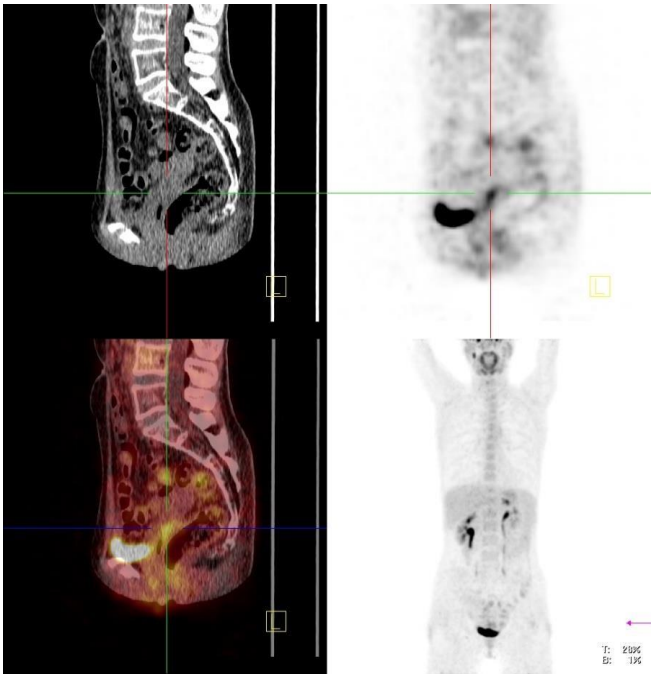

Figure 1. FDG PET/CT images (sagittal CT, PET and fusion, as well as MIP) of a patient (43 years). There is a focal enhancement of radiopharmaceuticals in the uterus, indicating a local recurrence of the cancer.

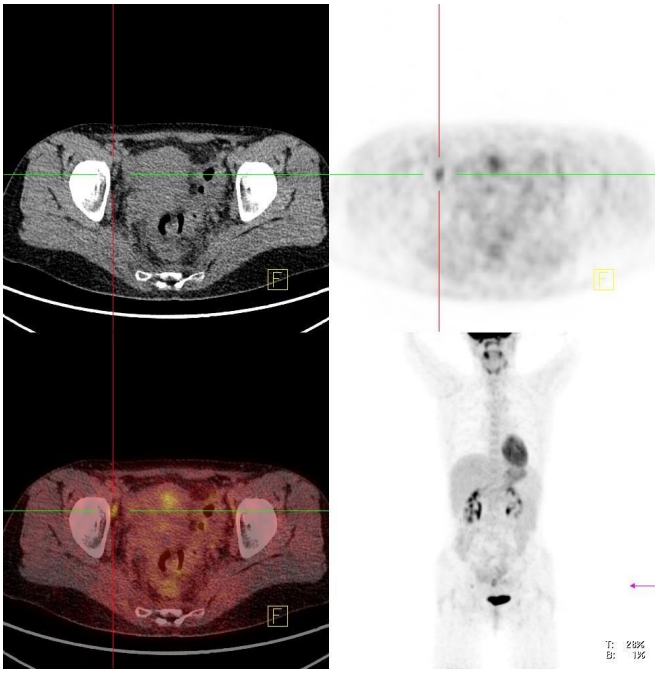

Figure 2. FDG PET/CT scan (axial CT, PET and fusion cross sections, as well as MIP) of a patient (34 years), showing an increased glucose metabolism in the uterus (pathologically confirmed recurrence of the cancer) and in obturator and parailiac lymph nodes (secondary deposits).

confirmed in 27 patients, making these findings true-positive, while in two cases, the subsequent examination did not show the presence of the underlying disease (false-positive). In 6 out of 9 negative findings, there was no recurrence of cervical cancer, which makes these findings true negative. In the remaining 3 cases, follow-up during the first 6 months after the initial PET/CT scan was detected by the underlying disease, which classifies these scans as a false-negative group. These results are shown in **table 1**. **Figure 2** shows FDG PET/CT findings of a patient with a local relapse in the uterus (later pathohistologically confirmed) and secondary deposits in the parailiatic and obturatoric lymph nodes.

Table 1. Classification of the initial FDG PET/CT scans

FDG PET/CT scan	n
True positive	27
False positive	2
True negative	6
False negative	3

Based on previous results, the calculated sensitivity, specificity, positive predictive value, negative predictive values and diagnostic accuracy of FDG PET/CT in the detection of local and distant recurrences of cervical cancer were 90%, 75%, 93.1%, 66.7% and 86.8%, respectively.

After the initial FDG PET/CT scan, 30 out of 38 patients were given a particular form of therapy (surgical treatment and/or chemo-radiotherapy). Using control FDG PET/CT scans, as well as clinical and laboratory monitoring of patients included in the study, the progression of the disease was observed in 16 patients. Complete remission of the disease was detected in 8 cases, partial remission of the disease in 5 cases, while stable disease was observed in 3 patients. In the rest 6 cases with initially negative FDG PET/CT findings, the disease was not observed during monitoring (**table 2**).

Table 2. Effects of the therapy of cervical cancer in our patients

Effects of the therapy	n
Progression of the disease (PD)	16
Stable disease (SD)	3
Partial remission (PR)	5
Complete remission (CR)	8
Without disease (WD)	6

The influence of SUV max on the most intense lesion on the effect of treatment in 29 patients with an initially positive PET/CT finding was analyzed. SUV max values in the lesions with the most intense accumulation of radiopharmaceuticals in the initial FDG PET/CT studies ranged from 2.8 to 17.0, with a mean SUV max of 9.4 ± 4.2.

In group 1, with SUV max less than 9.4, there were 15 patients, while group 2, with SUV max greater than

9.4, was made of 14 patients. Group A, with the absence of a beneficial effect of treatment, consisted of 16 patients, while in group B, with a favorable effect of treatment, 13 patients were identified. The Chi-square test did not show significant association of the metabolic activity of lesions with the effects of therapy ($p = 0.897$).

Discussion

In our study, we examined the role of FDG PET/CT in the post-therapeutic evaluation of patients with cervical cancer. The study population consisted of 38 women who were subjected to FDG PET/CT examination at least twice during the follow-up.

The results of our study have shown significant reliability of this method in the detection of local and distant secondary deposits of the cancer, with high diagnostic accuracy of this method, as well as very high values of sensitivity and positive predictive value. Our results are in line with a number of other studies that have dealt with the use of functional morphological imaging in this area (10,11). This suggests that FDG PET/CT has a significant advantage in detecting all lesions in the underlying disease compared with conventional imaging, with a particular significance in the visualization of distant metastases, since it is a "whole body" visualization method (12).

On the other hand, the specificity of FDG PET/CT in the detection of the recurrence of malignant cervical tumor in our study was somewhat lower (75%). This can be explained by a slightly higher accumulation of radiopharmaceuticals of benign etiology (inflammation) in regional and distant lymph nodes. These results agree with the results published by other authors (9), but there are also studies with other results that differ. Specifically, some authors have reported that FDG PET/CT has lower sensitivity in the detection of secondary deposits in the pelvic lymph nodes, with greater specificity, which is contrary to our results (13).

The FDG PET/CT has been proven to be a very important method, both in the preoperative, as well as in postoperative evaluation of patients with cervical cancer, with a great influence on the planning of therapy, primarily on radiotherapy planning, resulting in more effective treatment with a lower radiation dose on healthy tissues (14).

Also, the great benefit of this functional morphological imaging in the monitoring of the effects of chemo-radiotherapy has been demonstrated, both in the evaluation of the change in the number and size of lesions, as well as in the change in the intensity of the metabolic activity of the primary tumor and secondary deposits (14). The assessment of the effects of chemo-radiotherapy using FDG PET/CT testing is based on the application of the PERCIST criteria (PET Response Criteria in Solid Tumors), which, apart from the size of the changes, takes into account the intensity of the accumulation of radiopharmaceuticals (15). The FDG PET/CT has proven to be a very important method in this study, which can, with great reliability, show the effect of the applied therapy.

The quantitative parameters obtained by FDG PET/CT testing have been used in evaluating the therapeutic response of various types of malignancies. This relates primarily to SUV max of certain lesions. A positive response to therapy, demonstrated by a significant reduction of SUV max of the primary cervix tumor in preoperative circumstances, proved to be a significant predictor of a good therapeutic response, better prognosis of disease and prolonged survival (16). Also, a more predictive significance of PET quantitative parameters was observed, in relation to the quantitative parameters obtained by conventional radiological imaging, such as ADC (apparent diffusion coefficient) obtained using MR (16). In our study, we examined only the effect of SUV max of the most intense lesion on the initial FDG PET/CT test with the response to therapy. Our study did not show a significant correlation between the metabolic activity of recurrent lesions with a response to therapy. This study had certain limitations. First, the study was retrospective. Also, the limiting factor was the small number of subjects, which was encompassed by a relatively large number of total FDG PET/CT tests. Our sample was not homogeneous, with regard to the applied therapy before and after the FDG PET/CT testing.

Conclusion

The results of this study have shown that FDG PET/CT is a reliable and highly sensitive method in the detection of loco-regional and distant recurrent cervical carcinoma.

The significance of FDG PET/CT in the evaluation of patients with cervical cancer is reflected in the highlighted ability of this method in monitoring the effects of therapy. The metabolic activity of the lesions did not show any significant effect on the therapeutic response.

References

1. Mirpour S, Mhlanga JC, Logeswaran P, et al. The Role of PET/CT in the Management of Cervical Cancer. *Am J Roentgen* 2013; 201: W192-W205.
2. Vaccarella S, Lortet-Tieulent J, Plummer M, et al. Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. *Eur J Cancer.* 2013; 49:3262-3273.
3. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis.* 2010; 202:1789-1799.
4. Petignat P, Roy M. Diagnosis and management of cervical cancer. *BMJ*. 2007 Oct 13; 335(7623): 765–768.
5. Eifel PJ, Betek JS, Markman M. Cancer of cervix, vagina, and vulva. In: DeVita VT, Hellman S, Rosenberg SA; eds. *Cancer: Principles & Practice of Oncology;* 9th ed Philadelphia: Lippincott Williams & Wilkins, 2011. p. 1351-1370.
6. Hricak H, Gatsonis C, Chi DS, et al. Role of imaging in pretreatment evaluation of early invasive cervical

cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. *J Clin Oncol* 2005; 23:9329-37.

7. Creasman WT. New gynecologic cancer staging. *Gynecol Oncol* 1995; 58:157-8.
8. Kezr Czernin J, Allen-Auerbach M, Nathanson D, Herrmann K. PET/CT in Oncology: Current Status and Perspectives. *Curr Radiol Rep.* 2013 May 3; 1:177-190.
9. Herrera FG, Prior JO. The role of PET/CT in cervical cancer. *Front Oncol.* 2013; 3: 34.
10. Nogami Y, Iida M, Banno K, et al. Application of FDG-PET in Cervical Cancer and Endometrial Cancer: Utility and Future Prospects. *Anticancer Research* February 2014; 34: 585-592
11. Son H, Kositwattanarerk A, Hayes MP, et al. PET/CT evaluation of cervical cancer: spectrum of disease. *Radiographics.* 2010;30(5):1251-68.
12. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology.* 2001;218(3):776-82.
13. Jung W, Park KR, Lee KJ, et al. Value of imaging study in predicting pelvic lymph node metastases of uterine cervical cancer. *Radiat Oncol J.* 2017;35(4):340-348.
14. Khiewvan B1, Torigian DA, Emamzadehfard S, et al. Update of the role of PET/CT and PET/MRI in the management of patients with cervical cancer. *Hell J Nucl Med.* 2016;19(3):254-268.
15. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50 Suppl 1:122S-50S.
16. Ueno Y1, Lisbona R, Tamada T, et al. Comparison of FDG PET metabolic tumour volume versus ADC histogram: prognostic value of tumour treatment response and survival in patients with locally advanced uterine cervical cancer. *Br J Radiol.* 207;90(1075):20170035