

ORIGINAL ARTICLE

THE SIGNIFICANCE OF 18-FLUORO-DEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY WITH COMPUTED TOMOGRAPHY IN COMPARISON WITH MULTI-SLICE COMPUTED TOMOGRAPHY IN RECURRENT BLADDER CANCER

Slobodanka Beatović^{1,2}, ✉ Miloš Veljković^{ID 2}, Isidora Grozdić–Milojević^{ID 1,2}, Jelena Petrović^{ID 1,2}, Strahinja Odalović^{1,2}, Milica Stojiljković^{ID 1,2}, Vera M. Artiko^{ID 1,2}, Dragana Šobić–Šaranović^{ID 1,2}

¹ University of Belgrade, Faculty of Medicine, University Clinical Center of Serbia, Belgrade, Serbia

² Center for Nuclear Medicine with PET, University Clinical Center of Serbia, Belgrade, Serbia

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✉ Correspondence to:

Miloš Veljković

Center for Nuclear Medicine with PET, University Clinical Center of Serbia

26, Višegradska Street, 11000 Belgrade, Serbia

Tel: +381694302475

Email: milos.veljkovic1119@gmail.com

Summary

Introduction: Positron emission tomography with computed tomography using 18-fluoro-deoxyglucose (¹⁸FDG-PET/CT) is still not applied routinely in clinical practice for the evaluation of recurrent bladder cancer. Recent guidelines recognize the importance of ¹⁸FDG-PET/CT, but multi-slice computed tomography (MSCT) is still recommended for monitoring these patients. **Aim:** To determine the agreement between ¹⁸FDG-PET/CT and MSCT findings in the categorization of patients into N and M stages of the disease and the agreement of two diagnostic modalities regarding the number of detected lesions.

Material and methods: 31 patients (22 men and 9 women), mean age 61.2 ± 9.2 years, were included in our study after surgical treatment and histopathological confirmation of bladder cancer. Zones of pathological uptake of ¹⁸FDG were interpreted visually and semi-quantitatively using the maximum standardized uptake value (SUVmax). The agreement of ¹⁸FDG-PET/CT findings was compared to previous MSCT using Cohen's kappa test for interobserver agreement, interpreted based on the Altman's criteria.

Results: The overall agreement between ¹⁸FDG-PET/CT and MSCT in N stage of the disease was 77% ($\kappa = 0.54$; moderate agreement); in stage N0 68%, N2 77%, N3 29%. In M stage, total agreement was 53% ($\kappa = 0.10$; poor agreement); in stage M0 39%, M1a 22%, M1b 44%. ¹⁸FDG-PET/CT detected a total of 29 lesions in N stage of the disease, while MSCT detected 16 lesions, with the agreement of 71% ($\kappa = 0.41$; moderate agreement). In the M stage of the disease, ¹⁸FDG-PET/CT detected 42 lesions and MSCT detected 30 lesions, with overall agreement of 52% ($\kappa = 0.07$; poor agreement).

Conclusion: Our results show that there is a moderate agreement between ¹⁸FDG-PET/CT and MSCT findings in the categorization of patients and the number of detected lesions in N stage of disease, but that ¹⁸FDG-PET/CT detects more lesions. ¹⁸FDG-PET/CT also detects a higher number of lesions in M stage, but the agreement with MSCT findings is poor.

Keywords: recurrent bladder cancer, PET/CT, MSCT

INTRODUCTION

According to the International Agency for Research on Cancer, bladder cancer is the eleventh most common malignant tumor [1]. The incidence increases with age and is more common in males, so that in men over sixty years of age, bladder cancer is in sixth place in frequency [1]. The current age-standardized incidence is higher in men (9.5) than in women (2.4) per 100,000 respondents [1].

Tobacco smoking is one of the most important risk factors for bladder cancer and is the cause of about 43% of all cases in male population, and 26% in female population [2]. The mortality rate is about 2% higher in smokers than in non-smokers, especially in those who start consuming tobacco in adolescence [3]. Other significant risk factors are exposure to certain industrial chemicals, chronic urinary tract infections and urinary tract calculosis [4,5,6].

Bladder cancer belongs to a very heterogeneous group of tumors, but in over 90% of cases the histopathological type is transitional cell (urothelial) cancer, while the remaining $\approx 10\%$ include urothelial cancers with partial squamous or glandular differentiation, micropapillary cancers, sarcomatoid carcinoma, neuroendocrine tumors, and others [7]. Transitional cell carcinomas are classified into low- and high-grade carcinomas based on the degree of nuclear anaplasia and architectural abnormalities, of which the latter are associated with a poor prognosis [8].

Involvement of the muscle wall of the bladder is a crucial factor in choosing an adequate method of treatment. Over 75% of bladder cancers are not muscle-invasive [9] and are treated surgically with transurethral resection of bladder tumors (TUR). Surgical treatment is usually accompanied by a single intravesical instillation of chemotherapy, which significantly reduces the five-year recurrence rate of the tumor [10], or immunotherapy. Muscle-invasive bladder cancers are initially treated with radical cystectomy, followed by neoadjuvant cisplatin-based chemotherapy, which significantly improves survival rates [11]. The most common sites of bladder cancer metastases are lymph nodes, followed by the liver, bones, and lung parenchyma [12].

Clinical monitoring of patients with bladder cancer without invasion of the muscle wall is most often done by cystoscopy. Recent guidelines of the European Association of Urology for invasive bladder cancer recommend multi-slice computed tomography (MSCT) check-ups every six months for the first three years, and then once a year [13]. Shorter diameter of lymph nodes on MSCT over 8mm and morphological changes in the form of irregular contours are considered significant for suspicion of disease spread [12]. The sensitivity of MSCT in the detection of bladder cancer metastases in lymph nodes is subject to large variations and amounts to 30-75% [14]. The reason for this is that metastases can be present in

lymph nodes that are not enlarged, and such, occult metastases, still cannot be reliably detected by available diagnostic modalities.

Positron emission tomography with computed tomography using 18-fluoro-deoxyglucose (^{18}F FDG-PET/CT) is based on the fact that malignant tumors show a higher degree of glycolysis than normal cells (Warburg effect), which allows the detection of metastases in lymph nodes and other parts of the body based on increased glucose metabolism. The European Association of Urology recognizes the importance of ^{18}F FDG-PET/CT for muscle-invasive bladder cancer, and the fact that its role is still being assessed, but has not yet been recommended as a diagnostic modality of choice in monitoring these patients [13]. The number of studies comparing ^{18}F FDG-PET/CT and MSCT findings in patients with bladder cancer is relatively small. With this in mind, the aim of our study was to evaluate the agreement of ^{18}F FDG-PET/CT and MSCT findings in categorization of patients in N and M stages of the disease, as well as the agreement between the number of detected lesions in each category.

MATERIAL AND METHODS

Study population. In the period between January 2016 and December 2021, 46 patients with the diagnosis of bladder cancer were referred to our center due to suspicion of disease recurrence. Criteria for inclusion in the study were histopathologically confirmed bladder cancer during surgery, the time between surgery and ^{18}F FDG-PET/CT longer than three months, MSCT examination not older than three months before ^{18}F FDG-PET/CT examination, the absence of other malignancies and serum glucose level below 11mmol/L on the day of ^{18}F FDG-PET/CT examination. According to the aforementioned criteria, 15 patients were excluded from the study. The remaining 31 patients (22 men and 9 women), mean age 61.2 ± 9.2 years, were included in the study. All included patients gave informed consent for the research and the study was approved by the Ethics Committee of the University Clinical Center of Serbia (number 668/6).

Acquisition and interpretation of ^{18}F FDG-PET/CT findings. Whole body ^{18}F FDG-PET/CT imaging was performed on all patients using 64-slice hybrid PET/CT (Biograph, TruePoint64, Siemens Medical Solutions, Inc. USA) in our center. Patients did not consume food or sweetened drinks at least 6 to 8 hours prior to the examination. 5.5MBq of ^{18}F FDG per kilogram of body weight was administered intravenously, after which patients lay down to rest in quiet and darkened room for at least 60 minutes before acquisition. Patients were instructed to void before imaging. Low dose CT (120kV, slice thickness 5mm) and three-dimensional PET/CT images were acquired from mid-thigh to skull base. Corrected and uncorrected ^{18}F FDG-PET/CT and CT images were in-

Table 1. Patient characteristic

Characteristics	Number
Total number of patients (n)	31
Age (years)	
Mean ± standard deviation	61.2 ± 9.2
Surgical treatment, n (%)	
Radical cystectomy	15 (48.4%)
Transurethral resection of the tumor	16 (51.6%)
Histopathological type of tumor, n (%)	
Transitional cell cancer	28 (90.3%)
a) Low grade	4 (12.9%)
b) High grade	24 (77.4%)
Adenocarcinoma	3 (9.7%)
Chemotherapy / radiation therapy, n (%)	
Chemotherapy	12 (38.7%)
Radiation therapy	3 (9.6%)

terpreted on *Syngo Multimodality* workstations (Siemens AG) by two nuclear medicine specialists. After excluding physiological accumulation of ¹⁸FDG and those attributed to benign lesions, the zones of increased ¹⁸FDG uptake were assessed visually and semi-quantitatively by using maximum standardized uptake value (SUV_{max}). The obtained results of ¹⁸FDG-PET/CT findings were compared to previous MSCT findings.

Statistical analysis. Patient demographics are presented as mean ± standard deviation and as percentage values. To compare the agreement between the results of ¹⁸FDG-PET/CT and MSCT, Cohen's kappa coefficient (κ) was used for N0, N2, N3, M1a and M1b stages of bladder cancer as well as for the number of detected lesions via the mentioned diagnostic modalities. Interpretation of the Cohen's kappa coefficient for interobserver agree-

Table 2. Frequency distribution of patients in nodal (N) stage of the disease based on ¹⁸FDG-PET/CT and MSCT findings (category agreement marked in bold and underlined).

	MSCT				Total
	N0	N2	N3		
¹⁸ FDG-PET/CT	N0	<u>15</u>	1	0	16
	N2	1	<u>7</u>	0	8
	N3	5	0	<u>2</u>	7
	Total	21	8	2	31

ment between two diagnostic modalities was performed based on Altman's criteria (κ value < 0.20 poor; 0.21-0.40 poor; 0.41-0.60 moderate; 0.61-0.80 good; 0.80-1.0 very good agreement). Results are presented in cross-distribution tables that show agreement and disagreement between ¹⁸FDG-PET/CT and MSCT.

RESULTS

Patient characteristics. Patients' characteristics included in our study are presented in Table 1. All patients were treated surgically, and the most common histopathological type of tumor (over 90%) was transitional cell carcinoma, while the remaining 9.7% of cases were attributed to adenocarcinoma. 12/31 patients (38.7%) received chemotherapy and 3/31 patients (9.6%) received radiation therapy.

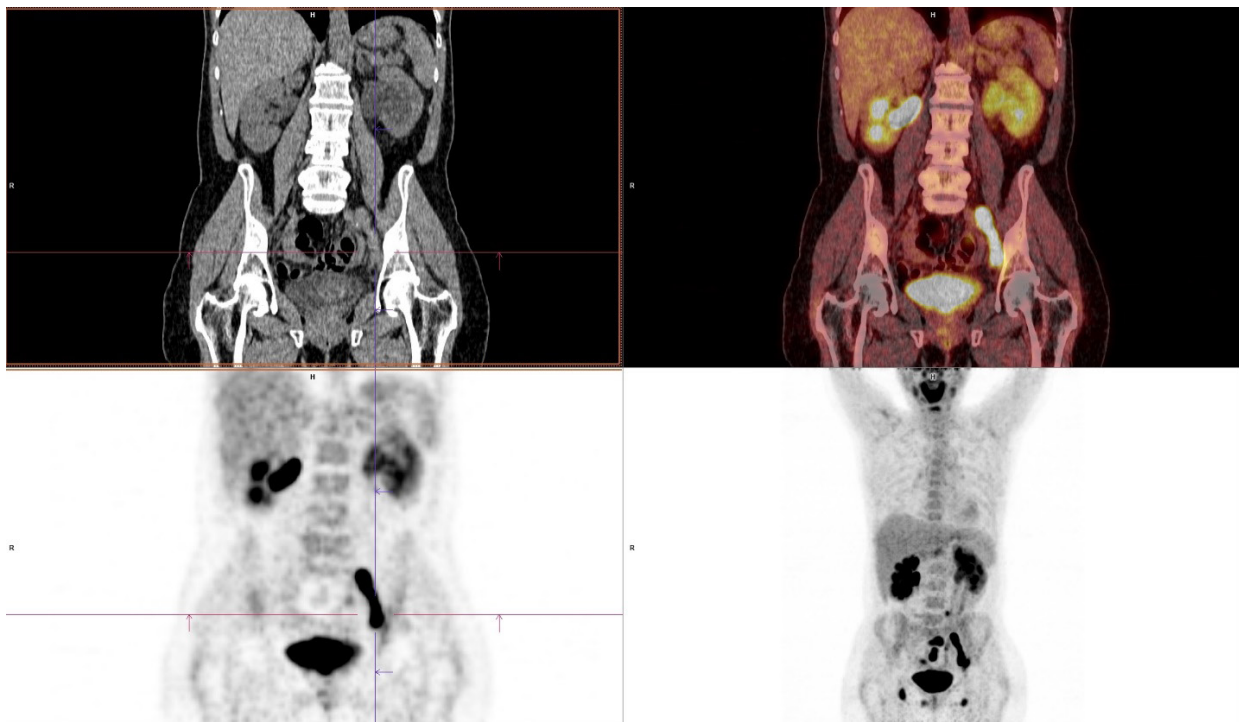
**Figure 1.** Coronal plane of unenhanced low dose CT, PET, fused PET/CT and MIP (maximal intensity projection). Increased uptake in left iliac lymph nodes and in regional bones.

Table 3. Frequency distribution of patients in metastatic (M) stage of the disease based on ¹⁸FDG-PET/CT and MSCT findings (category agreement marked in bold and underlined).

	MSCT			Total
	M0	M1a	M1b	
M0	<u>7</u>	1	4	12
¹⁸ FDG-PET/CT M1a	3	<u>2</u>	0	5
M1b	3	3	<u>8</u>	14
Total	13	6	12	31

¹⁸FDG-PET/CT and MSCT results. The distribution of patients in N stage of the disease is shown in Table 2. No patient showed N1 stage of the disease (metastases in a single pelvic lymph node) detected by analyzed diagnostic modalities, so it was excluded from further statistical evaluation. Total agreement between ¹⁸FDG-PET/CT and MSCT for N stage of the disease was 77% (observed $\kappa = 0.54$; moderate agreement). The agreement for N0 stage was 68%, 77% for N2 stage (metastases in two or more pelvic lymph nodes), while for N3 stage of the disease (metastases along the common iliac blood vessels) the calculated agreement was 29%.

Observed $\kappa = 0.54$, which shows moderate agreement of 77% in N stage of the disease between the analyzed diagnostic modalities.

Distribution of patients in metastatic (M) stage of the disease is shown in **Table 3**. Total agreement between

¹⁸FDG-PET/CT and MSCT for M stage of the disease was 53% (observed $\kappa = 0.10$; poor agreement). The agreement for M0 stage was 39%, 22% for M1a stage (metastases in distant lymph nodes), and 44% for M1b stage (distant metastases in other parts of the body).

Observed $\kappa = 0.10$, which shows poor agreement of 53% in M stage of the disease between the analyzed diagnostic modalities.

Apart from ¹⁸FDG-PET/CT and MSCT agreement in N and M stages of the disease, we also compared agreement on the number of detected lesions in N and M categories. In N category ¹⁸FDG-PET/CT detected 29 lesions, while MSCT detected 16 lesions. Total agreement in the number of detected lesions in N category was 71% ($\kappa = 0.41$; moderate agreement), as shown in **Table 4**.

Observed $\kappa = 0.41$, which shows moderate agreement of 71% in the number of detected lesions in N stage of the disease between the analyzed diagnostic modalities.

In M category, ¹⁸FDG-PET/CT detected 42 lesions, while 30 lesions were detected by MSCT. Total agreement in the number of detected lesions in M category was 52% ($\kappa = 0.07$; poor agreement). The distribution of detected lesions in M stage is shown in **Table 5**.

Observed $\kappa = 0.07$, which shows poor agreement of 52% in the number of detected lesions in M stage of the disease between the analyzed diagnostic modalities.

DISCUSSION

In our study we analyzed the agreement between ¹⁸FDG-PET/CT and MSCT in N and M stages of the disease, as well as the agreement in the number of detected lesions

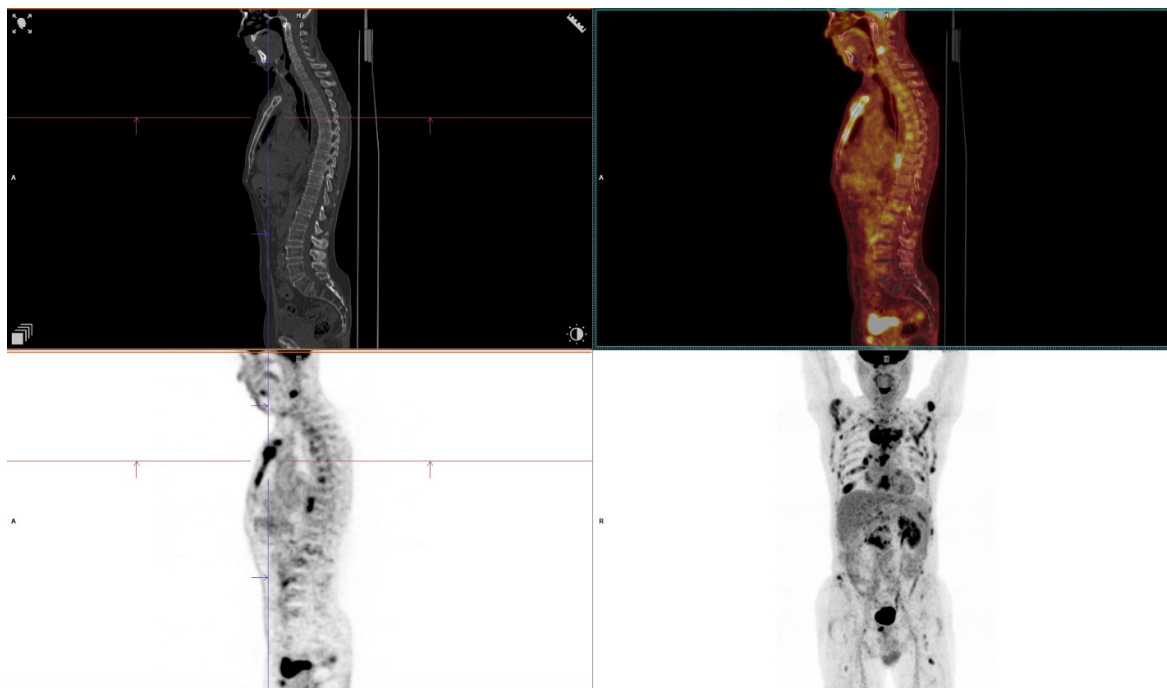


Figure 2. Sagittal plane of unenhanced low dose CT, PET, fused PET/CT and MIP (maximal intensity projection). Multiple zones of increased uptake in bones and lymph nodes.

Table 4. Frequency distribution of the number of detected lesions in nodal (N) stage of the disease based on ¹⁸FDG-PET/CT and MSCT findings (category agreement marked in bold and underlined).

	MSCT					Total
	0	1	2	3	>3	
0	<u>15</u>	1	0	0	0	16
1	3	<u>2</u>	0	0	0	5
¹⁸ FDG-PET/ CT	2	1	1	<u>4</u>	0	6
3	2	1	0	<u>1</u>	0	4
>3	0	0	0	0	<u>0</u>	0
Total	21	5	4	1	0	31

in patients with recurrent bladder cancer. Our results show that ¹⁸FDG-PET/CT classifies a higher number of patients in both N and M stages of the disease and detects a higher number of lesions compared to MSCT.

There are few studies in literature that evaluate comparison of ¹⁸FDG-PET/CT and MSCT for patients with recurrent bladder cancer, which is confirmed by the fact that ¹⁸FDG-PET/CT has not been recommended yet for follow-up of these patients following the guidelines of the European Association of Urology [13]. While searching literature, we only found one paper that compared ¹⁸FDG-PET/CT with other conventional diagnostic modalities. In this paper, by Zattoni et al. (2018), a comparison was made regarding urothelial cancers, but unlike our research, it was not limited to bladder cancers, but it also included upper urinary tract cancers [15]. In addition, the comparison of ¹⁸FDG-PET/CT was done not only with MSCT, but also with MRI, so it is expected that the results obtained between our and the above mentioned study will differ. However, the calculated Cohen's kappa coefficient in Zattoni et al.'s (2018) research was 0.43, which based on Altman's criteria indicates moderate agreement between the compared diagnostic modalities. Our study also showed a moderate agreement between ¹⁸FDG-PET/

CT and MSCT in the N stage of the disease ($\kappa = 0.54$, 77% agreement) and a moderate agreement of 71% ($\kappa = 0.41$) in the number of detected lesions in N stage. On the other hand, our results show poor agreement between ¹⁸FDG-PET/CT and MSCT in M stage of the disease ($\kappa = 0.10$, 53% agreement), especially in M1a stage where the agreement was only 22%. This can be explained by the fact that as the disease spreads in lymph nodes outside of the pelvis (retroperitoneal, mesenteric, mediastinal, as well as in other lymph node groups), the chance of metastases that have not yet caused morphological changes in lymph nodes used as a criteria for MSCT assessment increases. In our study, this was especially true for the mediastinal group of lymph nodes where ¹⁸FDG-PET/CT successfully detected bladder cancer metastases in lymph nodes whose short axis was as low as 7mm.

Aljabery et al. (2015) obtained data showing that ¹⁸FDG-PET/CT did not contribute significantly to the detection of regional lymph node metastases [16]. Our results partially agree with Aljabery et al.'s data (2015); although the agreement between ¹⁸FDG-PET/CT and MSCT in N stage of the disease is over 70%, ¹⁸FDG-PET/CT upstaged N disease from N0 to N2 in one patient, and from N0 to N3 stage in 5 patients, which effectively rep-

Table 5. Frequency distribution of the number of detected lesions in metastatic (M) stage of the disease based on ¹⁸FDG-PET/CT and MSCT findings (category agreement marked in bold and underlined).

	MSCT					Total
	0	1	2	3	>3	
0	<u>9</u>	2	1	0	1	13
1	4	<u>5</u>	0	0	0	9
¹⁸ FDG-PET/ CT	2	1	0	<u>1</u>	0	2
3	1	1	1	<u>1</u>	0	4
>3	0	1	1	1	<u>0</u>	3
Total	15	9	4	2	1	31

resents 19% change in the choice of adequate treatment, while MSCT upstaged one patient from N0 to N2 stage.

In the meta-analysis conducted by Xue et al. (2020), the overall sensitivity and specificity of ¹⁸FDG-PET/CT in detection of recurrent or residual bladder cancer were 94% and 92% respectively [17]. However, the data in literature are still heterogeneous. A review of literature by Einerhand et al. (2020), indicates that there is a larger number of studies showing that ¹⁸FDG-PET/CT is more sensitive than MSCT for the detection of lymph node metastases, with similar specificities [18]. For the detection of metastatic disease in the above mentioned literature review by Einerhand et al. (2020), it was found that while ¹⁸FDG-PET/CT was diagnostically accurate, there were still not enough papers comparing it with MSCT [18]. These data show that more research is needed on the role of ¹⁸FDG-PET/CT in relation to conventional diagnostic modalities in order to obtain the accurate data on the possible contribution of ¹⁸FDG-PET/CT in the management of bladder cancer patients.

Our study has certain limitations. The number of pa-

tients included in the study is relatively small, given the number of categories analyzed by ¹⁸FDG-PET/CT and MSCT, with the evaluation of the number of lesions by category. Furthermore, the data would probably be more accurate if the time between ¹⁸FDG-PET/CT and MSCT imaging was as short as possible, and in our study it is 46±9.2 days, but this is difficult to achieve in our country given the number of available PET scanners.

CONCLUSION

Our results show that there is a moderate agreement between ¹⁸FDG-PET/CT and MSCT findings for N stage of the disease, but that ¹⁸FDG-PET/CT detects a higher number of lesions. ¹⁸FDG-PET/CT also detects a greater number of lesions in the M stage of the disease, but the agreement with MSCT is poor, especially in M0 group. Further research is necessary on a larger number of patients in order to obtain more precise data on the agreement between the two diagnostic methods.

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ZNAČAJ POZITRONSKE EMISIONE TOMOGRAFIJE SA KOMPJUTERIZOVANOM TOMOGRAFIJOM 18-FLUORO-DEOKSIGLUKOZOM U ODNOSU NA MULTI-SLAJSNU KOMPJUTERIZOVANU TOMOGRAFIJU U REKURENTNOM KARCINOMU MOKRAĆNE BEŠIKE

Slobodanka Beatović^{1,2}, Miloš Veljković², Isidora Grozdić-Milojević^{1,2}, Jelena Petrović^{1,2}, Strahinja Odalović^{1,2}, Milica Stojiljković^{1,2}, Vera M. Artiko^{1,2}, Dragana P. Šobić-Šaranović^{1,2}

Sažetak

Uvod: Pozitronska emisiona tomografija sa kompjuterizovanom tomografijom 18-fluoro-deoksiglukozom (¹⁸F-DG-PET/CT) još uvek se ne koristi u svakodnevnoj kliničkoj praksi za evaluaciju rekurentnog karcinoma mokraćne bešike. Savremeni vodiči prepoznaju značaj ¹⁸F-DG-PET/CT, ali se još uvek preporučuje kompjuterizovana tomografija (MSCT) za praćenje ovih pacijenata.

Cilj: Određivanje slaganja između ¹⁸F-DG-PET/CT i MSCT nalaza u kategorizaciji pacijenata u N i M stadijume bolesti, kao i slaganje navedenih dijagnostičkih metoda u broju detektovanih lezija.

Materijal i metode: 31 pacijent (22 muškaraca i 9 žena) sa dijagnozom karcinoma mokraćne bešike, prosečne starosti 61.2 ± 9.2 godine, uključen je u našu studiju. Zone patološkog nakupljanja ¹⁸F-DG su interpretirane vizuelno i semi-kvantitativno koristeći maksimalnu standardizovanu vrednost preuzimanja radiofarmaka (SUVmax). Proučavano je slaganje dobijenih nalaza sa prethodnim nalazima MSCT koristeći Kohenov kappa

Ključne reči: rekurentni karcinom mokraćne bešike, PET/CT, MSCT

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test slaganja, interpretiranog na osnovu Altmanovog kriterijuma.

Rezultati: Ukupno slaganje između ¹⁸F-DG-PET/CT i MSCT za N stadijum bolesti je iznosilo 77% ($\kappa = 0.54$; umereno slaganje), za N0 stadijum 68%, N2 77%, N3 29%. Za M stadijum, ukupno slaganje je iznosilo 53% ($\kappa = 0.10$; minimalno slaganje), za M0 39%, M1a 22%, M1b 44%. ¹⁸F-DG-PET/CT je u N stadijumu bolesti detektovao ukupno 29 lezija, a MSCT 16 lezija, sa slaganjem od 71%, ($\kappa = 0.41$; umereno slaganje). U M stadijumu bolesti, ¹⁸F-DG-PET/CT je detektovao 42 lezije, a MSCT 30 lezija, ali slaganje iznosi 52% ($\kappa = 0.07$; minimalno slaganje).

Zaključak: Naši rezultati pokazuju da postoji umereno slaganje između ¹⁸F-DG-PET/CT i MSCT nalaza u kategorizaciji pacijenata i broju detektovanih lezija u N stadijum bolesti, ali da ¹⁸F-DG-PET/CT detektuje veći broj lezija. ¹⁸F-DG-PET/CT takođe detektuje veći broj lezija u M stadijumu bolesti, ali je slaganje sa nalazima MSCT minimalno.