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ORIGINAL ARTICLE

HYBRIDE IMAGING IN ADVANCED MELANOMA

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Summary

Aim: To evaluate the usefulness of 18F-fluorodeoxyglucose positron emission tomography with computed tomography (18F-FDG PET/CT) in patients with advanced melanoma.

Method: This study included 264 consecutive patients with melanoma who were sent for the 18F-FDG PET/CT. The inclusion criteria were as follows: histopathologically verified melanoma stage III or IV, the absence of other malignancy/infection; glycemia ≤ 11 mmol/l. The final study population consisted of 220 patients. After the first 18F-FDG PET/CT, the follow-up examination was performed after 11.81±7.99 months, for therapy response evaluation.

Results: Pathological 18F-FDG PET/CT was present in 154 patients. Sensitivity of 18F-FDG PET/CT was estimated as 99%, specificity as 47%. There was no statistically significant difference between 18F-FDG PET/CT findings and gender (p> 0.05), and MDCT examination (p = 0.678). However, 18F-FDG PET/CT upstaged 45% patients, especially these with widespread disease. SUV max and inguinal disease localization (in patients who had lower extremities as primary localization of disease) were associated with progression free survival (PFS) (p < 0.05). SUV max (HR 1.03, CI 1.00-1.12, p=0.05) and locally advanced disease (HR 12.02, CI 1.13-148.00, p=0.04) were independent predictors of PFS. A follow up 18F-FDG PET/CT revealed active disease in 22/26 patients. Therapy type (immunotherapy or target therapy) did not correlate significantly with the 18F-FDG PET/CT follow up result (p=0.760, *ρ=-0.354*).

Conclusion: 18F-FDG PET/CT has good sensitivity in the evaluation of advanced melanoma. Small lesions and brain localization reduce specificity of the examination, then MDCT, MR are advised. Predictive factors SUV max and locally advanced disease, are more important than the timing of follow-up 18F-FDG PET/CT, since they were predictors of PFS. Follow up 18F-FDG PET/CT should be done at least in 6 months, only if there is suspicion of the presence of active disease.

Keywords: advanced melanoma, 18F-FDG PET/CT

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INTRODUCTION

Melanoma is a solid tumor formed by malignant transformation of melanocytes. It is most often localized on the skin although it can also be found on the mucous membranes of the head and neck, the urogenital tract, the gastrointestinal tract, eyes (1-3).

Surgical treatment of primary melanoma, as well as local and regional metastases, is the gold standard in the treatment of melanoma patients. Chemotherapy has a limited role in patients with melanoma, and it is mainly used for the purpose of palliative care (1). Radiotherapy in patients with melanoma also becomes important in special indications (bone metastases or metastases in the central nervous system). Therapeutic strategies, such as immunotherapy and immunotherapy with checkpoint inhibitors, have significantly improved the treatment of metastatic disease.

Early diagnosis and adequate assessment of disease is crucial for the timely treatment of these patients (4,5). For these very reasons, it is necessary to define adequate criteria for monitoring and diagnosis of these patients.

Guidelines usually suggest the use of multi detector computed tomography (MDCT) or magnetic resonance (MR) imaging in patients with advanced melanoma. Nowadays, many international studies and guidelines indicate the usefulness of positron emission tomography with computed tomography with fluorodeoxyglucose (18F-FDG PET/CT) in these patients (1,6,7).

Thus, international studies indicate the usefulness of 18F-FDG PET/CT in the evaluation of patients with melanoma, given the high 18F-FDG avidity of melanoma (8-15). However, there is no universal international consensus regarding the use and frequency of 18F-FDG PET/CT in the evaluation of patients with advanced melanoma (16, 17). For that reason, the evaluation of this topic is important and ongoing.

The aim of this study was to determine the usefulness of 18F-FDG PET/CT and its timing in the evaluation of patients with advanced melanoma.

MATERIALS AND METHODS

Study population

This study included 264 consecutive patients with melanoma who were sent for the 18F-FDG PET/CT examination to the National PET Center, University Clinical Center of Serbia in the period from January 2010 to May 2020 to obtain the assessment of the prevalence of the disease. The study was designed as ambidirectional (retrospective-prospective study); in 2018 it became prospective, having obtained the Ethics committee's approval.

The criteria for inclusion in this study were as follows: (a) histolopathologically verified melanoma; (b) Stage III or IV disease; (c) the existence of clinical and /or radiological indicators of disease activity; (d) the absence of other malignancy, as well as the absence of infection; and (e) glycemia ≤ 11 mmol / l.

Out of the initial population of 264 patients, 44 patients were excluded from the study (lung cancer – 8, head cancer – 8, thyroid cancer – 7, breast cancer – 4, lymphoma –5, gastrointestinal cancer – 9, presence of infection – 3). This way, the final study population of 220 patients was obtained (mean age 57 ± 15 years, 128 men and 92 women).

This work was done in accordance with the ethical principles of the Helsinki Declaration and prospective part of the study was approved by the Ethics committee of the Faculty of Medicine, Center of Nuclear Medicine University of Belgrade, written consent was obtained from all participants (IRB 668/6; 19/4/2018).

Procedures

For all included patients, the following data were collected prior to performing the 18F-FDG PET/CT examination: (a) demographic characteristics (collected by the epidemiological questionnaire); (b) clinical data, descriptions of previous diagnostic procedures -multidetector computed tomography (MDCT) or magnetic resonance imaging (MR) (obtained from medical histories).

Twenty-six patients were invited for follow-up 18F-FDG PET/CT examination. These patients had pathological findings in the first 18F-FDG PET/CT examination and they had their therapy changed. The examination was performed 11.81±7.99 months after the first 18F-FDG PET/CT in order to evaluate the therapeutic response, collect the therapy data, disease symptoms, and diagnostic procedures.

Data Acquisition, Reconstruction, and Image Analysis

The 18F-FDG PET/CT scan was performed on a 64-slice hybrid PET/CT scanner (Siemens Biograph, Siemens Medical Solutions USA Inc., Hoffman Estates, Illinois, USA). The patients fasted for 8 hours before receiving an intravenous injection of 18F-FDG at a dose of 5.5 MBq/kg. PET/CT acquisition (imaging) began 60 minutes after the intravenous injection. A three-dimensional whole body PET scan (14-15 bed, 3 min/bed) and a low-dose CT was performed. Multidetector CT had the following characteristics: voltage 120 kV, with automatic "real-time" voltage height modulation (CareDose4D with a basal level of 45 mA); slice thickness 5 mm; pitch 1.5; rotation time 0.5 s. CT, PET (attenuation corrected) and PET/CT fusion images were processed on a SYNGO SIEMENS workstation (Syngo MMWP, Siemens AG, Berlin and Munich, 2008, Germany).

The findings of 18F-FDG PET/CT were categorized as positive or negative, based on visual and quantitative assessment. The accumulation of 18F-FDG was quantitatively analyzed as the maximum standardized value of radiopharmaceutical uptake (SUV max). SUV max was calculated as the concentration of activity at the end of the recording that was corrected for individual body weight and dose of intravenously injected 18F-FDG: SUV max = tissue activity (count / pixel / second) × calibration factor/dose of intravenously injected 18F-FDG (MBq/kilogram of body weight) (18).

SUV max equal or higher than 2.5 was considered pathological. Findings were considered positive if there was an increased accumulation of FDG compared to normal accumulation in organs (visceral organs, lungs, skin, brain parenchyma or bone ...). The follow-up 18F-FDG PET/CT examination was performed under the same conditions as the first one, in terms of administering the same amount of radiopharmaceuticals, the same time period and the method of acquisition, reconstruction and image analysis. 18F-FDG PET/CT images were interpreted by two independent physicians (nuclear medicine specialists). If there was a discrepancy between these findings, the final judgment was obtained through their consensus.

Statistical Analysis

The X2 test was performed to assess the difference between pT stage and gender. Independent sample T-test was used to assess difference between age and pT stage. The difference between 18F-FDG PET/CT result and gender was obtained with X2 test, as well as the difference between disease localization and disseminated disease. The evaluation of difference between primary melanoma site and the presence of distant metastases was also obtained with X2 test.

Independent sample T-test was used to asses differences between SUV max levels in distant metastases and positive sentinel lymph nodes, in different primary sights of disease. The difference between the MDCT and 18F-FDG PET/CT findings was assessed by the X2 test. A Cox proportional hazard model was done to determine whether age, gender, MDCT, primary localization of disease and SUV max affected the disease outcome. SUV max was used as dichotomous variable (pathological findings were above SUV max 2.5). In patients with multiple lesions, SUV max was calculated as mean of all lesions. Univariate and multivariate predictive models with confounding factor control were applied. Also, Kaplan-Meier analysis was used to determine how the localization of the disease, therapy and the pathological finding of 18F-FDG PET/CT (SUV max >2.5) could affect survival in patients with advanced melanoma. The X2 test was performed to assess the difference between genders regarding the frequency of pathological findings on 18F-FDG PET/CT examination. Sensitivity (Sn) and specificity (Sp) of 18F-FDG PET/CT in detection active disease in melanoma patients was assessed by ROC analysis. Positive predictive value, negative predictive value and diagnostic accuracy of 18F-FDG PET/CT scans were also determined. Determination of the difference between the value of SUV max during the first and follow-up examination was performed using the Paired Sample T test. The results of continuous numerical variables are presented as values of arithmetic mean ± standard deviation (SD), while P value below 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

The study population consisted of 220 patients with melanoma aged 57 ± 15 years (128 men and 92 women). All patients had advanced melanoma (stages III and IV), with high pT stage III (30.1%), IV (30.1%), II (24.1%), I (15.7%). High pT stage was frequently present in older patients (X2 test, $p<0.001$), regardless of gender (X2 test, $p=0.755$).

The majority of the study population had a previous surgical intervention. Metastasectomy was performed in the presence of solitary lesions, usually liver metastases in patients with eye melanoma. Immunotherapy with pembrolizumab/nivolumab was applied in 19 patients (pembrolizumab 14/19; nivolumab 5/19), while 4 patients received target therapy (enkorafenib+bimetinib). After initial 18F-FDG PET/CT examination, pathological findings were present in 154 patients (70%), 91 men and 63 women.

There was no statistically significant difference in the finding of 18F-FDG PET/CT in relation to gender (X2 test, $p> 0.05$). More disseminated disease was present in patients who had primary melanoma of the head region and the back, but this was not statistically significant (X2 test, $p=0.835$). Primary site of disease did not significantly affect the occurrence of distant metastases (X2 test, $p=0.893$) **(Figure 1)**.

Patients with primary melanoma localized on lower extremities had significantly higher SUV max in distant metastases than in regional lymph nodes (11.70±7.4 vs. 1.50±4.05), ($p<0.05$, CI -20.71- 1.68), which was not the case in other localizations. The most common disease localizations are shown in **Table 1**.

18F-FDG PET/CT finding and MDCT finding

18F-FDG PET / CT examination revealed an active malignancy in 154 patients (70%), with mean SUV max value 8.07 ± 8.92. MDCT examination detected active malignancy in 66% of patients. The 18F-FDG PET/CT

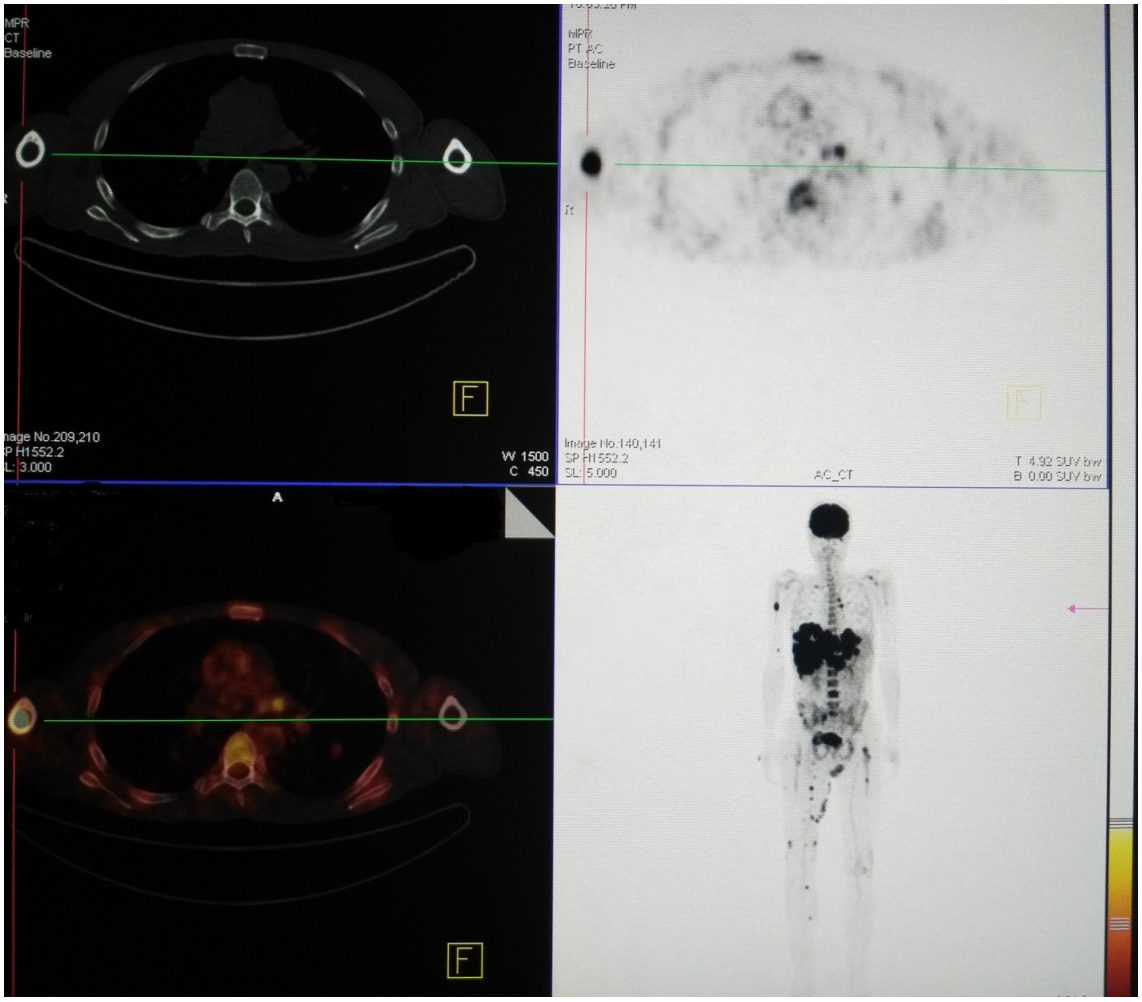

Fig 1. 18F-FDG PET / CT revealed disseminated disease and upstaged disease in this 64 years old patient. The disseminated disease on MIP (maximal intensity projection image), the active disease is present in the right humerus, mediastinal lymph nodes, liver and other bones (vertebrae, iliac bone, femur). High metastatic burden resulted in early death, 4 months after the 18F-FDG PET/CT examination.

examination found the same disease localizations as MDCT in 4% of patients. In almost half of the patients, the 18F-FDG PET/CT examination revealed a more widespread disease than it was seen on MDCT. In the majority of patients 18F-FDG PET/CT detected new sites of disease since they were out of focus in single region MDCT (e.g., only thorax/ abdomen MDCT was done, and new sites of disease were present in other regions on 18F-FDG PET/CT).

Table 1. The most common disease localizations found on 18F-FDG PET / CT examination

	Primary site of disease											
Metastasis on 18F-FDG PET/ CT	Head and face	Neck	Back	Chest	Abdomen	Gluteal region	Upper extremities	Lower extremities	Unknown primary localization	Multiple primary localization	Eye	Genital region
Sentinel lymph node metastasis	1	0	3	1	0	0	1	0	0	0	0	0
Distant metastasis												
Distant lymph nodes	30	7	50	11	4	4	15	44	16	4	5	5
Lungs	3	2	10	0	2	1	3	6	4	0	0	0
Brain	3	0	1	1	1	0	0	1	0	0	0	2
Bones	7	4	9	1	2	1	1	11	3	1	0	1
Liver	5	1	9	1	2	1	2	7	2	1	1	2
Subcutaneous tissue	6	1	11	2	1	2	3	16	3	1	0	0

* Majority of patients had multiple metastases on 18F-FDG PET/CT examination

In 7% of patients, the finding was pathological on MDCT and normal on 18F-FDG PET/CT. This was present in small lung lesions (2 %) or in lesions with FDG high background uptake (brain 5 %).

The opposite situation was present in 11% of patients where MDCT was normal and 18F-FDG PET/CT pathological. These patients had small diameter lymph nodes (smaller than 10 mm), which were classified on MDCT as normal, but they had FDG uptake higher than background and reclassified as pathological. In 33% of patients, both examinations were pathological but showed completely different localizations of the disease. 18F-FDG PET/CT usually detected disease in distant extremities, lymph nodes, even liver metastases, while MDCT was better at detecting active disease in brain, intestines and urinary tract. Based on the X2 test, there was no statistically significant difference in the finding of MDCT examination and 18F-FDG PET/CT examination (p=0.678). However, upstaging of disease was done by PET/CT in 45% of patients.

18F-FDG PET/CT finding and its sensitivity

Sensitivity of 18F-FDG PET/CT in disease detection was estimated as 99%, specificity as 47%, while negative predictive value was 87% and positive predictive value 43%. Diagnostic accuracy of the test was estimated at 69%, ROC cut off was 7.6 and ROC "area under the curve" was 0.730. **(Figure 2)**

Follow-up 18F-FDG PET/CT examination

Twenty-six patients (8 men and 18 women, mean age 54.04 ± 17.09 years) came for a follow-up 18F-FDG PET/CT examination, which was scheduled 11.81±7.99 months after the first one.

In the follow up, ten patients had a progression of disease. Partial remission was present in 2 patients, stable disease in 10 patients. There was no statistically significant decrease in the SUV max value compared to the previous examination (8.66 ± 8.84, 8.80 ± 14.94) (p>0.05). The therapy type (immunotherapy or target therapy) did not significantly correlate with 18F-FDG PET/CT follow up result (p=0.760, ρ=-0.354). However, four patients, who received immunotherapy (pembrolizumab), had complete metabolic response. **(Figure 3)**

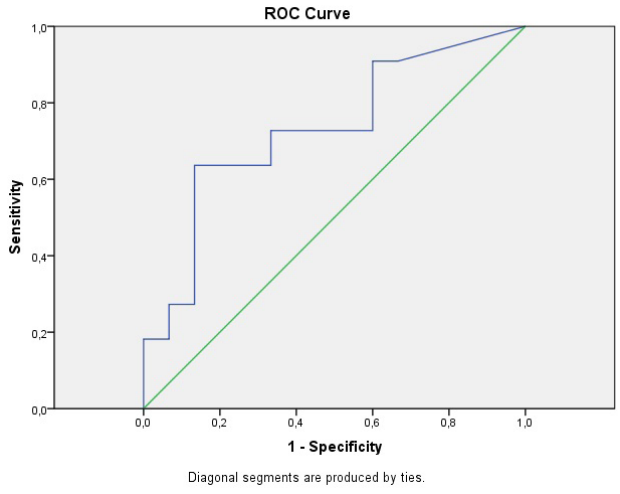

Fig 2. Statistical ROC analysis (area under the curve-0.73)

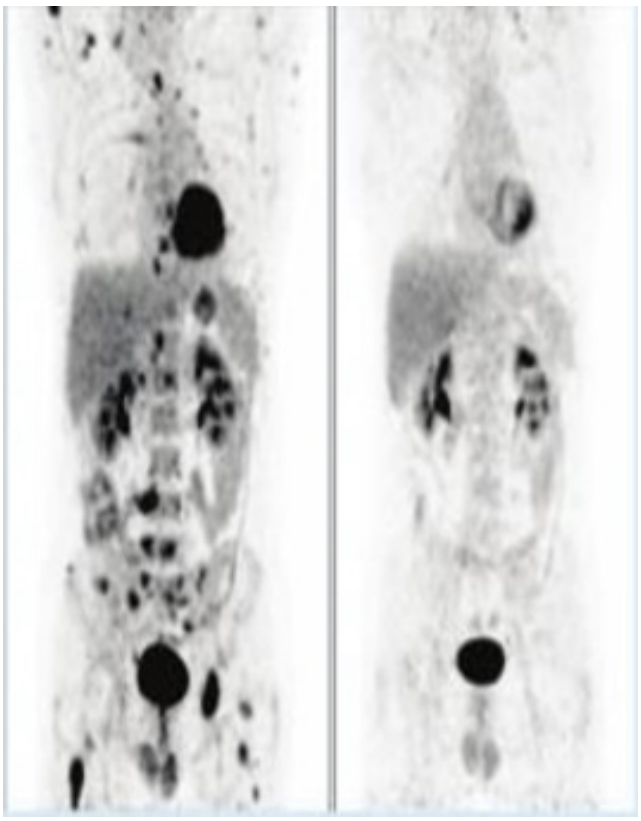

Fig 3. Complete metabolic regression of disease on control the 18F-FDG PET / CT examination. Left image-baseline 18F-FDG PET / CT revealed widely spread disease (axillary, mediastinal, retroperitoneal, para iliac and inguinal lymph nodes, right humerus, ribs, left and right femur). The right image-follow up 18F-FDG PET / CT indicates metabolic regression after immunotherapy

Influence of 18F-FDG PET/CT on disease prognosis

A univariate analysis of Cox regression analysis showed that SUV max was a predictor of a worse progression free survival (PFS), (HR 1.030 95% CI 1.00-1.06; P < 0.05). In a multivariate Cox regression analysis SUV max and locally advanced disease were independent predictors of a PFS **(Table 2)**. Other variables such as: age, gender, MDCT result, primary localization of disease had no effect on the disease outcome.

Based on the Kaplan-Meier survival analysis (Long rank test) it was observed that presence of the disease in the inguinal localization, in patients whose lower extremities were primary localization of disease, was associated with PFS (p = 0.03). **(Figure 4)** It was similar with the patients who had an increased SUV max level on 18F-FDG PET/CT examination, regardless of the primary localization of the disease (p = 0.04). **(Figure 5)**

Table 2. Univariate and multivariate Cox regression models predicting progression free survival in 220 patients with advanced melanoma

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.02	0.98-1.06	0.38	1.00	0.90-1.02	0.59
Sex (male vs. female)	0.99	0.33-2.97	0.63	1.02	0.26-6.10	0.83
SUV max	1.03	1.00-1.06	**0.04**	1.03	1.00-1.12	**0.04**
MDCT result (pathological vs. normal)	0.01	1.00-2.60	0.58	1.10	1.12-5.71	0.96
Primary localization of disease	1.10	0.94-1.29	0.23	6.68	0.05-834.99	0.44
Locally advanced disease	0.60	0.07-5.38	0.65	12.02	1.13-148.00	**0.04**

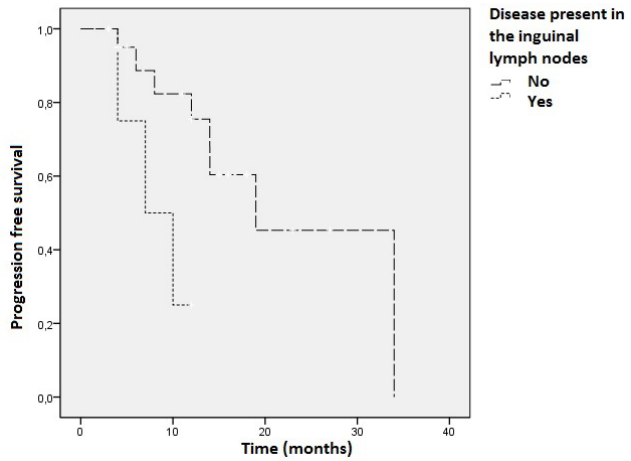

Fig 4. Kaplan-Meier curves for PFS stratified by presence of pathological inguinal lymph nodes on 18F-FDG PET/CT (Long rank test, p = 0.03

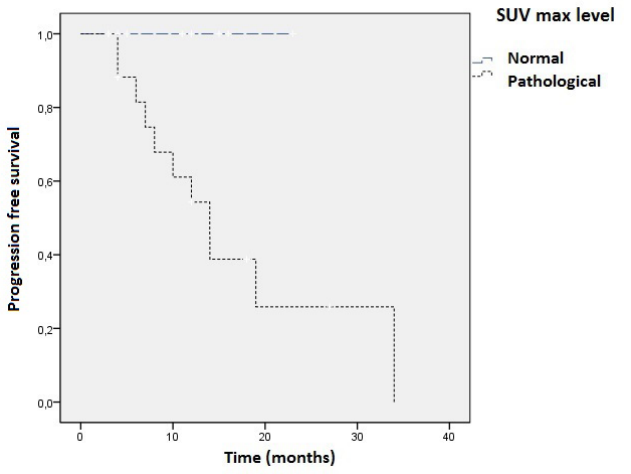

Fig 5. Kaplan-Meier curves for PFS stratified by SUV max level (cut off 2.5) on 18F-FDG PET/CT (Long rank test, p = 0.04

Therapy did not had statistically significant effect on PFS (Long rank test, p=0.34).

DISCUSSION

The frequency of newly diagnosed melanomas is gradually increasing, about 3-8% annually. More than a half of the patients with melanoma will have a relapse of the disease to local lymph nodes (20%), or to regional lymph nodes (50%), and 30% of patients will have distant metastases (1). This fact suggests the importance of adequate monitoring of the patients with melanoma, which would enable early detection of relapse, and thus, the initial treatment of the disease. Conventional monitoring of patients includes clinical examination, dermatoscopy, laboratory parameters of disease progression, ultrasound of regional lymph basins, as well as other diagnostic procedures (MDCT, MR) depending on the stage of melanoma at the time of diagnosis. The frequency and type of follow-up examinations vary depending on the national guidelines.

In addition to ultrasound analyses and MDCT/MR, the guidelines have recently suggested the use of 18F-FDG PET/CT diagnostics. The Danish National Melanoma Guide recommends 18F-FDG PET/CT examinations at 6, 12, and 24 months in patients with melanoma who have stage II B higher (19). On the other hand, American Melanoma Guides suggest 18F-FDG PET/CT or MDCT or MR heads every 3-12 months in patients with stage IIB-IV (6). Our guide to melanoma suggests the use of 18F-FDG PET/CT diagnostics only in disease stages greater than III (1). Obviously, there is no clear international consensus regarding the frequency and type of control 18F-FDG PET/CT scans (contrast CT or non-contrast CT). This can be explained by the fact that it is an expensive and insufficiently available diagnostic procedure, especially for the conditions of countries with low national income.

Therefore, the aim of this study was to discover advantages and disadvantages of 18 F-FDG PET/CT and its timing in population of advanced melanoma in our environment.

This study included 220 patients with melanoma, who met the criteria of the Serbian National Melanoma Guide when referred to 18F-FDG PET/CT examination. Hence, it was a population of patients with stage IIIa-IV disease. High pT in our population was frequently present in older patients regardless of gender.

In our study population, 18F-FDG PET/CT was positive in 70% of patients (91 men and 63 women). The disease was most often disseminated, with distant metastases, equally present in both genders. A more spread

disease was usually found in patients with primary melanoma of the head and back region.

Since most patients also had MDCT, a comparison of these two procedures was done. There was no statistically significant difference between the findings of 18F-FDG PET/CT and MDCT (p = 0.678). However, in the majority of patients 18F-FDG PET/CT found new localizations of the disease and they were upstaged.

There were 7% of patients in whom MDCT showed a more widespread disease than 18F-FDG PET/CT (usually localized in the central nervous system and in small lesions). Surely, small dimensions below 3 mm cannot be adequately assessed by 18F-FDG PET/CT diagnostics, since they are below the spatial resolution of the device. Due to a "partial volume effect", small volumes will be underestimated in terms of calculating SUV max. Thus, SUV max will be unrealistic, and, in that way, it could incorrectly suggest a benign etiology of the disease (18). On the other hand, certain localizations such as the brain parenchyma are not adequate for assessing the presence of primary and secondary tumors on the 18F-FDG PET/CT, since this organ intensively physiologically binds radioactively labeled glucose. This way, discrimination of pathological and healthy tissue will be more difficult, so the use of MR is recommended (8, 18).

The advantages of 18F-FDG PET/CT diagnostics are reflected in the fact that it involves imaging a large body area (half-body / whole-body study), and thus can detect previously unrecognized localizations of the disease. SUV max is one of the most frequently used parameters for objective quantifying the accumulation of radiopharmaceutical. It is good for evaluating the metabolic activity of the disease and for monitoring the therapeutic effect. In order to reduce the possibility of false negative results, 18F-FDG PET/CT should always be done 3-4 weeks after the completion of chemotherapy, and 3 months after radiotherapy.

Using the low dose protocol reduces the patient's irradiation by some 30%, while preserving the quality of the study (20). Thus, 18F-FDG PET/CT has increasing usefulness in clinical practice.

Based on the results of our study, the sensitivity of the 18F-FDG PET/CT was estimated at 99%, and its specificity at 47%, while the positive predictive value was calculated at 43% and the negative predictive value at 87%. The diagnostic accuracy of the test was 69%. Most studies have concordant results and also report high sensitivity values of 18F-FDG PET/CT, probably due to the inclusion of high-risk patients (Stage III and IV) (21, 22). According to some authors, the sensitivity of the procedure went up to 100%, since the inclusion criteria of the study included a positive 18F-FDG PET/CT result (23).

Although the sensitivity in our study was high, the specificity was low (47%). This can be explained by the fact that FDG uptake is not sensitive to a certain pathohistological type of tumor and it can be elevated in some benign conditions, that can be falsely classified as suspicion of metastases. Pathohistological verification is advised, since it remains the gold standard for evaluation of disease activity.

On the other hand, Vensby at al. also report in their study high negative predictive values of 18F-FDG PET/CT, which once again indicates good abilities of 18F-FDG PET/CT to rule out the presence of relapse. Low positive predictive values were mainly present in patients with a low probability of recurrence (21).

Since, 18F-FDG PET/CT upstaged half of the study population, therapy was changed in all of them. After 11.81 ± 7.99 months, the patients were invited for a follow-up 18F-FDG PET/CT examination. However, only 26 patients came for the follow-up 18F-FDG PET/CT and in 22 of them the test was positive. During the follow-up examination, the disease was most often present in distant metastases (90 %), rarely as locally advanced (10 %). There was no statistically significant correlation between the type of therapy (immunotherapy/target therapy) and 18F-FDG PET/CT result. These results must be taken with a limitation considering the small number of subjects on immuno/target therapy as well as the time of its inclusion.

Also, the comparison of both types of therapy could not be done adequately, given that almost all patients received immunotherapy since target therapy can only be received within the framework of clinical trials in our country because otherwise it has not been assigned a license for use. Additionally, this therapy can be given only to patients with verified BRAF mutation. However, our results show that in the follow up, almost two years after the first examination, all patients were alive. Stable disease was present in 10 patients, 2 had partial remission, 10 experienced a progression of disease and complete remission was present only in 4 patients. Perhaps the higher number of relapses was caused by postponed responses to immunotherapy and prompt responses to target therapy. Perhaps it would be better to perform a follow up examination after a shorter period of time, for example after 6 months. Although 18F-FDG PET/CT is an expensive procedure, especially for developing countries, its importance lies in the fact that it can assess the spread of the disease with high sensitivity, much better than other diagnostic procedures.

Some authors state that more frequent monitoring of 18F-FDG PET/CT examination in patients with melanoma could be useful for early detection and treatment of relapse. Thus, patients would have better survival (21). However, Rueth et al. showed that this approach lead to minimal improvement in survival of these patients (15). Koskivuo et al. and Danielsen et al. quote that false-positive findings were usually present in asymptomatic patients who had no clinical suspicion of disease relapse (16,17). This example demonstrates the importance of performing an 18F-FDG PET/CT examination only in

clear indications, as otherwise it may result in patient anxiety, unnecessary diagnostics, and treatment costs.

Our results suggest that 18F-FDG PET/CT, as a highly sensitive procedure, has the ability to stage disease more accurately than MDCT. Prognostic factors can be more useful than the exact timing of the follow-up 18F-FDG PET/CT examination. SUV max and locally advanced disease were independent predictors of progression free survival. Additionally, increased SUV max and the presence of the disease in the inguinal localization (in patients whose lower extremities were the primary localization of disease) were associated with worse progression free survival.

The majority of our patients in the first examination and in the follow up examination had a primary localization of the disease in the lower extremities, and the finding should be interpreted keeping this fact in mind. The presence of active disease in the inguinal lymph nodes should be considered as a locally advanced disease, which precedes further distant spread.

Other diagnostic procedures have different indications for the lymph node evaluation. Ultrasound or lymphoscintigraphy have the role in preoperative staging of regional lymph nodes and postoperative follow up, while dynamic lymphoscintigraphy is used for detection of sentinel lymph node when melanoma is localized on hull (1).

This study has certain limitations. One of them is a low response rate to the follow-up 18F-FDG PET/CT examination. Another limitation of the study is the inhomogeneity of the study population (some of them had different kind of surgery, some received immuno/target therapy before the first 18F-FDG PET/CT). The other limitation was a small number of patients who underwent immunotherapy. Immunotherapy (pembrolizumab and nivolumab) was introduced into clinical use only after 2016. Until today, other types of therapy have not received legal permission for use in our country. That's why the number of patients with target therapy is minimal, because it can be only given under cover of clinical trials. Nevertheless, this study included a significant number of patients (stage III and IV of disease) which represents one of the most numerous populations in international journals evaluating this topic, compared to other mainly retrospective studies with smaller study groups (24-27).

CONCLUSION

18F-FDG PET/CT shows high sensitivity in the detection of active disease in advanced melanoma. In patients with small diameter lesions and lesions in the central nervous system, the use of other diagnostic procedures is recommended (MR/MDCT). It seems that SUV max value and locally advanced disease are independent predictors of a worse PFS in these patients. 18F-FDG PET/CT has advantages in terms of informativeness, the existence of predictive parameters and quantitative parameters that allow early detection of disease activity and thus an early treatment. These characteristics justify the high cost of examination, which should be performed in precisely defined indications.

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HIBRIDNE DIJAGNOSTIČKE PROCEDURE U EVALUACIJI MELANOMA

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Sažetak

Cilj ovog rada je bio da utvrdi korisnost 18F-FDG PET/CT u evaluaciji pacijenata sa uznapredovalim melanomom.

Metodologija: U ovu studiju su uključena 264 uzastopna pacijenta sa uznapredovalim melanomom, koja su upućena na 18F-FDG PET/CT. Kriterijumi za uključivanje su bili: patohistološki verifikovani melanom III/IV stadijuma, odsustvo drugih maligniteta/infekcija, glikemija ≤ 11 mmol/l. Konačnu populaciju činilo je 220 pacijenata. Nakon prvog 18F-FDG PET/CT, obavljen je kontrolni pregled nakon 11.81±7.99 meseci, u cilju procene efikasnosti terapije.

Rezultati: Patološki 18F-FDG PET/CT je bio prisutan kod 154 pacijenta. Senzitivnost procedure je procenjena na 99% a specifičnost 47%. Nije bilo statistički značajne razlike između 18F-FDG PET/CT nalaza, pola i MDCT pregleda (p>0,05). 18F-FDG PET/CT je pogoršao stejdžing kod 45% pacijenata, posebno onih sa raširenom bolešću. SUV max i ingvinalna lokalizacija bolesti (kod pacijenata sa primarnim tumorom lokalizovanim na donjim ekstremitetima) su uticali na preživljavanje bez progresije bolesti (PFS), (p < 0,05). SUV max (HR 1,03, p<0,05) i lokalno uznapredovala bolest (HR 12,02, p<0,04) bili su nezavisni prediktori PFS. Kontrolni 18F-FDG PET/CT otkrio je aktivnu bolest kod 22/26 pacijenata. Tip terapije (imunoterapija ili target terapija) nije značajno korelirao sa 18F-FDG PET/CT rezultatom praćenja (p=0,760, ρ=-0,354).

Zaključak: 18F-FDG PET/CT ima dobru senzitivnost u evaluaciji uznapredovalog melanoma. Mali dijametar lezija i prisustvo bolesti u moždanom parenhimu smanjuju specifičnost pregleda. SUV max i lokalno uznapredovala bolest su prediktori PFS. Kontrolni 18F-FDG PET/CT treba raditi na 6 meseci jedino ako postoji sumnja na prisustvo aktivne bolesti.

Ključne reči: uznapredovali melanom, 18F-FDG PET/CT

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