research article

Clinical relevance of ^{18}F-FDG PET/CT in the postoperative follow-up of patients with history of medullary thyroid cancer

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Background. The aim of the study was evaluation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET/CT) in the detection of active disease in the patients with suspected recurrence of the medullary thyroid carcinoma (MTC).

Patients and methods. ^{18}F-FDG PET/CT investigation was performed in 67 patients, investigated from 2010 to 2019. Follow up was performed from 6 to 116 months after surgery (median 16.5 months, $\bar{x} \pm SD$ = 29±28.9 months). Twenty five of 67 patients underwent ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy, 11 underwent somatostatin receptor scintigraphy (SRS) with ^{99m}Tc-HYNIC TOC while 11 ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy.

Results. From 67 patients, 35 (52.2%) had true positive ^{18}F-FDG PET/CT findings (TP). Average maximal standardized uptake value (SUVmax) for all TP lesions was 5.01+3.6. In 25 (37.3%) patients findings were true negative (TN). Four (6%) patients had false positive (FP) findings while three (4.5%) were false negative (FN). Thus, sensitivity of the ^{18}F-FDG PET/CT was 92.11%, specificity 86.21%, positive predictive value 89.74%, negative predictive value 89.29% and accuracy 89.55%. In 27 patients (40%) ^{18}F-FDG PET/CT finding influenced further management of the patient.

Conclusions. ^{18}F-FDG PET/CT has high accuracy in the detection of metastases/recurrences of MTC in patients after thyroidectomy as well as in evaluation and the appropriate choice of the therapy.

Key words: ^{18}F-FDG PET/CT; medullary thyroid carcinoma; follow up; postoperative

Introduction

Medullary carcinoma of thyroid gland (MTC) is a malignant neuroendocrine tumor originated from the para-follicular C cells. The incidence is 1 to 2% of thyroid malignancies. It may occur as sporadic or hereditary form as a part of type 2 multiple endocrine neoplasia (MEN2) syndromes with surgery representing the primary therapeutic modality.[1,2] C cells secrete specifically calcitonin and procalcitonin which are considered as specific tumor markers.[3] Carcinoembryonic antigen (CEA) is not specific marker for this tumor but is useful in follow up of the treatment. Both calcitonin and CEA doubling times are considered as prognostic predictors in patients with persistent disease after surgery.[4]

Diagnosis of MTC during management of thyroid nodular disease could be established by fine needle aspiration cytology, immunocytochemical staining against calcitonin and/or its measurement in the needle washouts or additional immunostaining against specific biomarkers such as calcitonin, CEA, chromogranin A. Elevated basal values of serum calcitonin especially when greater than 100 pg/ml, or calcitonin levels obtained during calcium stimulation test are used for diagnosis of MTC.[5]

Total thyroidectomy and neck dissection is considered as the first line and curative treatment. In the treatment of progressive MTC, surgery, imaging-guided local treatments and tyrosine kinase inhibitors can be used and combined.[1] In the diagnosis of MTC, different anatomical and functional imaging procedures may be used. Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are used in staging of the disease before primary surgery. The role of nuclear medicine methods is reserved for detection and localization of recurrent disease when serum tumor marker levels are elevated and when the findings of morphologic imaging methods are inconclusive.[6,7]

The most frequently used radiopharmaceuticals for the diagnosis and follow up of MTC, labelled with γ emitting radionuclides, are metaiodobenzylguanidine (MIBG) labelled either with ^{131}I or ^{123}I, ^{99m}Tc-pentavalent dimercaptosuccinic acid (^{99m}Tc(V)-DMSA), ^{111}In-pentetreotide (Octreoscan) and ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (Tektrotyd).[8-13] The radiopharmaceuticals labelled with a positron-emitting radionuclides suitable for positron emission tomography with computed tomography (PET/CT) are ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA), and ^{68}Ga-labelled somatostatin analogues (^{68}Ga- DOTATATE or DOTATOC). According to the literature, overall sensitivity of conventional nuclear medicine methods γ emitting radionuclides is lower in comparison to conventional anatomic imaging (*i.e.* US, CT, MRI) and positron emission tomography/computed tomography.[7,8] However, still, application of PET/CT in the nuclear medicine worldwide is limited. Radiopharmaceuticals track different metabolic pathways or receptor expression/functioning, and proved to be useful in detecting MTC recurrences/metastasis. Nuclear medicine methods may help guiding the appropriate choice of the therapy but also offer possibility of radionuclide therapy with radiolabeled somatostatin analogues or metaiodobenzylguanidine.

The aim of our study was to examine specificity and sensitivity of ^{18}F-FDG PET/CT in comparison to other available nuclear imaging methods used for the follow-up of MTC patients treated with the first-line radical thyroidectomy.

Patients and methods

In this cohort retrospective study, ^{18}F-FDG PET/CT investigation was performed in 67 consecutive patients (32 males and 35 females, 52.2±16.2 years of age) in a period from 2010 to 2019. Follow up was performed from 6 to 116 months after surgery (median 16.5 months, $\bar{x} \pm SD$ = 29±28.9 months), in order to detect active disease after total thyroidectomy and estimate the effect of adjuvant medical or radiotherapy. The majority of patients (56) had increased serum concentration of calcitonin (45-8526 pg/ml) while 16/67 had increased concentration of CEA. All the patients underwent radiological imaging methods (CT, NMR, US). In addition to ^{18}F-FDG PET/CT investigation, 25 patients underwent ^{99m}Tc-DMSA scintigraphy, 11 somatostatin receptor scintigraphy (SRS) with ^{99m}Tc- HYNIC TOC and 11 ^{99m}Tc-MIBG scintigraphy.

The patients underwent ^{18}F-FDG PET/CT examination on a 64-slice PET/CT scanner (Biograph, TruePoint64, Siemens Medical Solutions Inc. USA). Radiopharmaceutical (5.5MBq/kg) was injected to the patient after fasting for at least 6 hours. Afterwards, patients rested in a quiet and darkened room for 60 min, after which images of PET/CT were obtained. Low-dose non-enhanced CT scans (120 kV with automatic, real-time dose modulation amperage, slice thickness of 5 mm, pitch of 1.5 and a rotation time of 0.5 s) and 3-dimensional PET scans (6-7 fields of view, 3 min/field) were acquired from the base of the skull to the mid-thigh. Non-corrected and attenuation-corrected CT, PET and fused PET/CT images were displayed for analysis on a Syngo Multimodality workplace (Siemens AG). The FDG uptake was analyzed visually and quantitatively using SUVmax index. FDG PET/CT findings were considered positive in the case of higher accumulation FDG in comparison to surrounding parenchyma, mediastinal blood vessels and the liver. For assessment of glucose metabolism level in metastasis, SUVmax was used. Tumor lesions were defined by volume of interest placed around every suspected focus of intense FDG uptake, with 50% threshold. The measurements of SUVmax, were done on reconstructed images, after using ordered subsets expectation maximization as statistical reconstruction method, but no absolute cut-off value of SUVmax was used for the diagnosis. Images were interpreted separately by two nuclear medicine physicians, unaware of results of other imaging modalities. In cases of discrepancy, images were presented to multidisciplinary team and experts' opinion was adopted.

In addition to ^{18}F-FDG PET/CT investigation, when required, whole body scintigraphy, single photon emission computed tomography (SPECT) imaging and, if necessary spot views were per-

TABLE 1. ^{18}F-FDG PET/CT findings in medullary thyroid carcinoma patients with calcitonin levels

Findings	Number	%	Increased calcitonin levels	Calcitonin levels above 1000 pg/ml
TP	35/67	52.2	35/35 (100%)	18/35 (51%)
TN	25/67	37.3	18/25 (72%)	0
FP	4/67	6	2/4 (50%)	0
FN	3/67	4.5	2/3 (66%)	2/3 (66%)
Sensitivity	92.11% (95% CI 78.62% to 98.34%)			
Specificity	86.21% (95% CI 68.34% to 96.11%)			
Positive predictive value	89.74% (95% CI 77.81% to 95.62%			
Negative predictive value	89.29% (95% CI 73.59% to 96.14%)			
Accuracy	89.55% (95% CI 79.65% to 95.70%)			

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

formed with ^{99m}Tc(V)-DMSA, ^{99m}Tc-HYNIC-TOC), and ^{123}I-MIBG using ECAM gamma camera and computer (ESOFT).

The patient underwent an intravenous injection of 740 MBq ^{99m}Tc(V)--DMSA and after 2 h 30 min, a whole body scintigraphy was performed (scanning speed 10 cm/min).

Somatostatin receptor scintigraphy (SRS) of the whole body was performed 2 h and 24 h after i.v. administration of 740 MBq ^{99m}Tc-HYNIC-TOC. Before study therapy with somatostatin analogs was withdrawn, mild laxatives were introduced, patients were fasting and were well hydrated. Scintigraphy with ^{123}I-MIBG was performed 24 h after slow intravenous injection of no less than 80 MBq. Whole-body planar images were acquired at scanning speeds of 5cm/min. Each spot view was acquired for a maximum of 10 min (about 500 kcounts).

Investigation was followed by SPECT of particular region. It was performed using 360º orbit, step and shoot mode, at 30 sec per view. The acquired data were collected in a 128 x 128 computer matrix and reconstructed using filtered back-projections with a Butterworth filter (cut-off 0.6 cycles/pixel, order 5) and iterative reconstruction.

Whole body and SPECT images were first evaluated visually by two experienced nuclear medicine physicians. Visual appearance of an increased focal uptake of tracer in the suspected tumor site was considered a positive finding.

Reference standards for active disease were surgery, biopsy and follow up of 5 years.

Descriptive statistical methods were used such as mean value, standard deviation, sensitivity, specificity, positive predictive value, negative predictive value and accuracy, as well as the percentage. Progression- free survival was assessed by Kaplan Meier survival analyses.

Ethical consideration

All the patients gave the informed consent for the investigation and the study was approved by Ethical Committee of Clinical Center of Serbia (668/6/2018) and Ethical Committee of Faculty of Medicine University of Belgrade (1550/V-9/2019).

Results

The results of PET/CT findings are shown in the Table 1. From 67 patients 35 (52.2%) had positive ^{18}F-FDG PET/CT findings (TP): 15 in the neck lymph nodes (42.9%), 13 in mediastinal lymph nodes (37.1%), 2 (5.7%) in mediastinal and abdominal lymph nodes and lungs, 2 (5.7%) in thyroid neck region and 3 on multiple localizations in bones, lungs and mediastinum (8.6%), with SUVmax 5.01+3.6. In 25 (37.3%) patients accumulation of FDG was physiological (TN). Four (6%) patients were false positive (FP), 3 with enlarged jugular lymph nodes and negative pathohistological finding and one with hilar lymphadenopathy which has not been visualized on control PET/CT scans. Three (4.5%) were false negative (FN), two of which with increased calcitonin levels (above 1000 pg/ml) and one because of the recently finished chemotherapy and slight accumulation in the neck lymph node which was considered as reactive (4.7%). In 27 patients (40%) FDG PET/CT finding influenced further therapeutic management of the patient.

The results of ^{99m}Tc(V)-DMSA scintigraphy are shown in the Table 2. In the patients who underwent ^{99m}Tc-DMSA scintigraphy, there were 4 TP, 13 TN, 3 FP (after surgery) and 5 FN (small lesions). In 11/14 (78.6%) TN patients ^{18}F-FDG PET/CT and ^{99m}Tc-DMSA findings were concordant.

Concordance of the ^{18}F-FDG PET/CT findings with the results of other radionuclide methods in selected number of MTC patients are shown in Table 3 and Figures 1–3. When patients were FDG PET true negative, they were also negative (TN) or FP with other modalities which emphasized the value of FDG PET in comparison to other methods. However, sometimes, additional information was obtained by other methods. Thus, in one TP patient with FDG PET/CT, because of lymph node metastases and suspicious but not obvious liver metastases, scintigraphy with ^{123}I-MIBG showed obvious liver metastases, *i.e.* accomplished the PET/CT finding, while scintigraphy with two other methods (DMSA, Tektrotyd) was FN. In another two TP patients on FDG PET/CT, expression of somatostatin receptors was very high, so the corresponding therapy was ordered.

Kaplan Meier progression-free survival analysis in FDG TP patients showed median survival of 15 months (95% CI 11.14+18.85 months), while median survival in TN (disease free patients) at the moment of investigation was 30 months (95% CI 1.08+58.92 months) (Figure 4).

TABLE 2. ^{99m}Tc-DMSA scintigraphy findings in medullary thyroid carcinoma patients

Findings	Number	%
TP	4	
TN	13	
FP	3	
FN	5	
Sensitivity		44.44% (95% CI 13.70% to 78.80%)
Specificity		81.25% (95% CI 54.35% to 95.95%)
Positive predictive value		57.14% (95% CI 27.55% to 82.38%)
Negative predictive value		72.22% (95% CI 58.07% to 83.00%)
Accuracy		68.00% (95% CI 46.50% to 85.05%)

^{99m}Tc(V)-DMSA = ^{99m}Tc-pentavalent dimercaptosuccinic acid; CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

TABLE 3. Concordance of the ^{18}F-FDG PET/CT findings with the results of other radionuclide methods in selected number of medullary thyroid carcinoma patients

^{18}F-FDG PET/CT	^{99m}Tc(V)-DMSA	^{99m}Tc-HYNIC-TOC	^{123}I-MIBG
14 TP (100%)	4 TP (28.6%) 4 FN (28.6%)	5 TP (35.7%) 3 FN (21.4%)	3 TP (21.4%) 2 FN (14.3%)
14 TN (100%)	**11 TN (78.6%)** 2 FP (14.3%)	1 FP (7%) 1 TN (7%)	3 TN (21.4%) 2 FP (14.3%)
4 FP (100%)	1 FP (25%) 2 TN (50%)	1 FP (7%)	
1 FN (100%)	**1 FN (100%)**		**1 FN (100%)**

^{123}I-MIBG = metaiodobenzylguanidine; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; ^{99m}Tc(V)-DMSA = ^{99m}Tc-pentavalent dimercaptosuccinic acid; FN = false negative; FP = false positive; PET/CT = positron emission tomography with computed tomography; Tektrotyd = ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide; TN = true negative; TP = true positive

Discussion

Our results point out very high sensitivity (92. 11%) of ^{18}F-FDG PET/CT in the detection of recurrence or metastases of MTC, relatively high positive (89.74%) and negative predictive value (89.29%) as well as accuracy (89.55%). Specificity was 86.21%. The main reason for FP and FN results was subjective assessment of the size and the uptake in the lymph nodes after the therapy, which emphasized the importance of follow up in order to avoid FP and FN results. According to our results, ^{18}F-FDG PET/CT can be used in the follow-up period of patients with elevated plasma calcitonin in order to detect recurrence and residual disease after the primary operation.

The results of other investigators for sensitivity vary from 47 to 93% while specificity ranged from 67-92%.[14-18] Like in our study, where ^{18}F-FDG PET/CT contributed significantly in 40% of the cases, other authors revealed that ^{18}F-FDG PET/CT provides additional information important for the further management of the patients in a significant number of cases (up to 54%).[19-21] Other studies also showed that ^{18}F-FDG PET/CT positive finding may influence the management of recurrent MTC when hypermetabolic lesions are detected. [22-24] In all our TP patients serum calcitonin levels were increased, and in 51% of them were higher than 1000 pg/ml, while 72% of TN had increased calcitonin levels but none of them higher than 1000 pg/ml. However, in 2/3 FN findings calcitonin level was increased above 1000 pg/ml. This is in accordance with the data of other investigators who proved that there is a positive relationship between serum levels of calcitonin and CEA and the sensitivity of ^{18}F-FDG PET/CT. Moreover, it was shown that sensitivity of ^{18}F-FDG PET/CT improves in patients with shorter serum calcitonin and CEA doubling times. This is confirming the usefulness of ^{18}F-FDG PET/CT method in patients with more aggressive forms

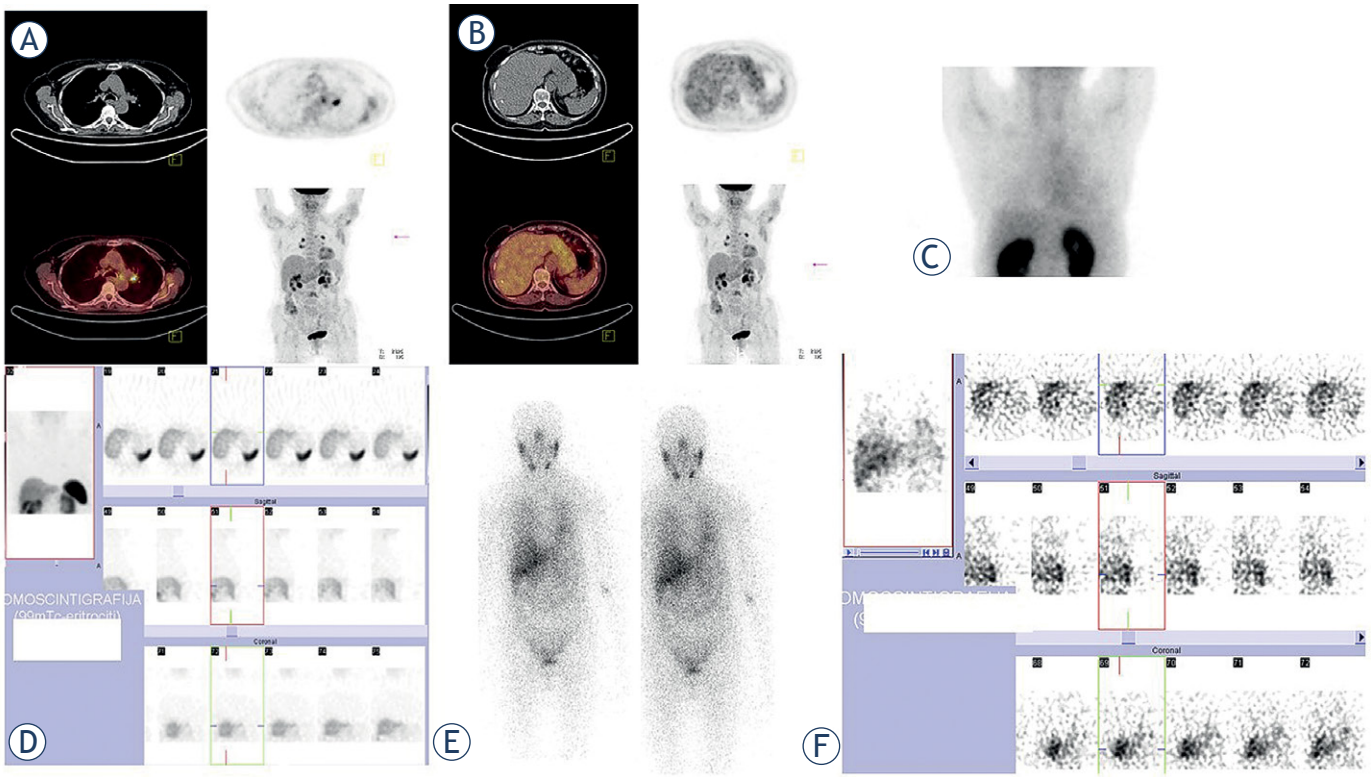

FIGURE 1. Patient with diagnosis of MTC after total thyroidectomy. **(A, B)** FDG PET/CT confirmed high uptake metastases in the mediastinal lymph nodes and uneven distribution of FDG in the liver. **(C)** ^{99m}Tc-DMSA spot view scintigraphy finding is negative. **(D)** ^{99m}Tc - tektrotyd SPECT finding is negative. **(E)** ^{123}I – MIBG WB finding showed high uptake in multiple liver metastases. **(F)** ^{123}I – MIBG SPECT finding showed high uptake in multiple liver metastases.

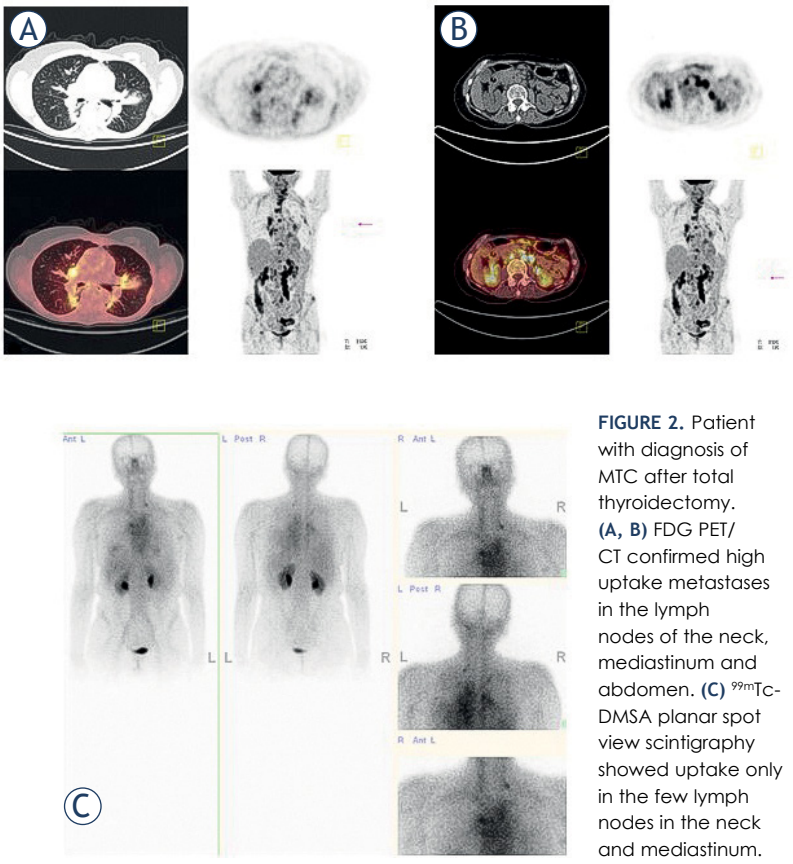

FIGURE 2. Patient with diagnosis of MTC after total thyroidectomy. **(A, B)** FDG PET/CT confirmed high uptake metastases in the lymph nodes of the neck, mediastinum and abdomen. **(C)** ^{99m}Tc-DMSA planar spot view scintigraphy showed uptake only in the few lymph nodes in the neck and mediastinum.

of disease in comparison to those with slowly progressive disease.[4,25-26] Furthermore, ^{18}F-FDG PET/CT is able to accurately identify MTC patients with poor prognosis and life expectancy, and to evaluate response to targeted therapies in patients with advanced metastatic disease.[27]

Our investigation showed that progression-free survival in FDG TP patients showed median survival of 15 months in the patients with recurrences and metastases, while median progression-free survival in disease free patients at the moment of investigation was 30 months. This is in accordance with the results of other authors. Thus, Fox *et al.* obtained that progression free survival was 19.2 months, while Elisei *et al.* obtained that progression free survival was, in dependence of the therapy 11.2 vs 4.0 months.[28,29]

Our results obtained with ^{99m}Tc(V)-DMSA showed in general slightly lower sensitivity in the detection of metastatic or recurrent disease (44.4%) in comparison to majority of other others authors. Thus Verga *et al.* reported a sensitivity rate of 50%, Ugur *et al.* even 95%, while the study of Adams *et al.*, revealed 65% and Howe *et al.* 71.4%.[30-33] However, relatively large number of TN patients in

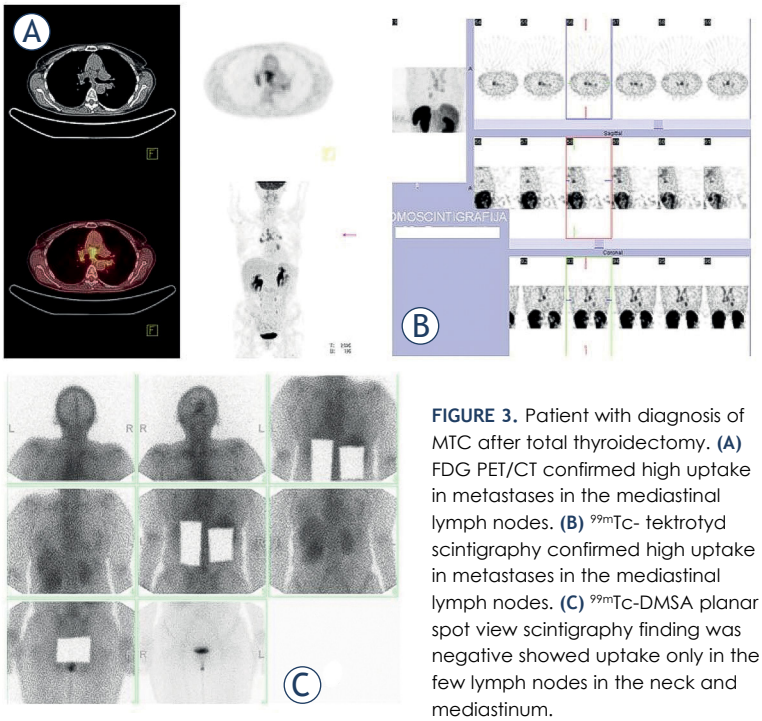

FIGURE 3. Patient with diagnosis of MTC after total thyroidectomy. **(A)** FDG PET/CT confirmed high uptake in metastases in the mediastinal lymph nodes. **(B)** ^{99m}Tc- tektrotyd scintigraphy confirmed high uptake in metastases in the mediastinal lymph nodes. **(C)** ^{99m}Tc-DMSA planar spot view scintigraphy finding was negative showed uptake only in the few lymph nodes in the neck and mediastinum.

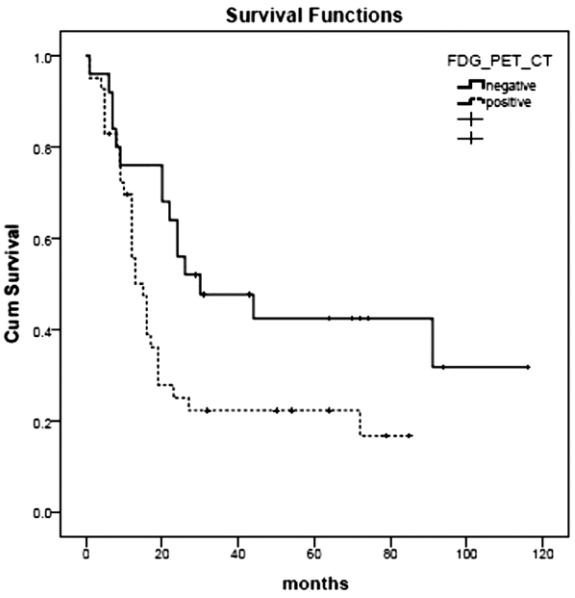

FIGURE 4. Kaplan Meier progression-free survival curve in positive FDG patients with median survival of 15 months (95% CI 11.14 ± 18.85 months), while median survival in disease free patients was 30 months (95% CI 1.08+58.92 months).

our study leads us to conclusion that DMSA scintigraphy could be used together with ^{18}F-FDG PET/CT to rule out residual or metastatic disease. A wide range of sensitivity could be explained by different commercial kits used, with different stability of the isomeric composition.[34] Taking this into consideration, DMSA scintigraphy should not be the best option in preoperative setting in comparison to postoperative detection of residual disease presumably when calcitonin level starts to increase.[7,34]

Taking into consideration our results and those of other investigators, ^{18}F-FDG PET/CT showed higher sensitivity in patients with MTC when compared to single photon emission tracers.[18-20] In our group of MTC patients who had both ^{18}F-FDG PET/CT and DMSA just a small number underwent MIBG and SRS scintigraphy, and statistical analysis could not be made. However, a small number of cases on the management of recurrent and metastatic MTC implicated that the sensitivity of ^{123}I/^{131}I-MIBG and Octreoscan used for this indication is low and ranged between 30% and 71%.[7] However, the advantage of MIBG and SRS scintigraphy is the possibility of radionuclide therapy in the cases with high uptake. Similar to our findings, Rubello *et al.* concluded that ^{18}F-FDG PET had the highest sensitivity in localizing metastatic disease in comparison to ^{99m}Tc(V)-DMSA scintigraphy, ^{111}In-DTPA-octreotide, US, CT and MRI.[21] Szakall *et al.* showed that ^{18}F-FDG PET was superior with better sensitivity than CT, MRI, and ^{131}I-MIBG in localizing lymph node involvement in patients with known MTC and postoperatively elevated calcitonin levels.[34] These authors also found that while FDG PET was superior in comparison to anatomic modalities in the lesions in neck, supraclavicular and mediastinal, CT had advantage in detection of liver and lung metastases, while FDG PET and MR were similar.[34]

Although there is no single imaging method sensitive enough to reveal all MTC recurrences, our results confirmed an advantage of ^{18}F-FDG PET/CT in comparison to gamma emitting radiopharmaceuticals. Positron emitting radiopharmaceuticals beyond FDG, such as fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) and somatostatin analogues labelled with gallium-68 (^{68}Ga-SSA) tracks different metabolic pathways or receptor expression/functioning, and proved to be useful in detecting MTC recurrences/metastasis. According to the literature data, PET/CT imaging with available radiopharmaceuticals is suggested when serum calcitonin exceed 150 pg/mL or calcitonin doubling time is shortened (*i.e.* < 24 months).[36-38] If available, ^{18}F-FDOPA PET/CT is preferred, but if the finding is negative or this radiopharmaceutical unavailable, ^{18}F-FDG PET/CT should be performed, in particular if calcitonin and CEA levels are rapidly rising (*i.e.* doubling time <

1 year) or an aggressive behavior of the disease is expected (*e.g.* CEA levels disproportionately high compared with calcitonin levels).[27,39] According to Kushchayev *et al.*, functional imaging, primarily PET/CT with ^{18}F-FDOPA and ^{18}F-FDG, plays a crucial role in the evaluation and management of MTC and has proven to be an efficient tool for the detection of metastases in patients with elevated calcitonin levels.[40] Furthermore, ^{68}Ga-SSA PET/CT could be considered in the cases with inconclusive anatomic imaging, ^{18}F-FDOPA and ^{18}F-FDG PET/CT results as well to assess the feasibility of peptide receptor radionuclide therapy.[27]

^{18}F-FDG PET/CT is a useful method with high diagnostic accuracy in the detection of secondary deposits of MTC in patients after radical thyroid surgery. It can be used alone or in line with other nuclear medicine methods as it is ^{99m}Tc(V)-DMSA especially in the cases when other position emitting radiopharmaceuticals are not available (^{18}F-FDOPA and ^{68}Ga-SSA).

Conclusions

^{18}F-FDG PET/CT has high accuracy in the detection of metastases/recurrences of MTC in patients with elevated calcitonin level after thyroidectomy and is superior to radionuclide single photon imaging modalities for identifying true positive disease.

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