

Evaluation of the usefulness of positron emission tomography with [¹⁸F]fluorodeoxyglucose performed to detect non-radioiodine avid recurrence and/or metastasis of differentiated thyroid cancer — a preliminary study

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Abstract

Background: About 30% of patients with disseminated differentiated thyroid cancer (DTC) may experience a loss of iodine uptake. It is associated with higher aggressiveness of the tumour and a reduced 10-year survival rate. The diagnosis of non-radioiodine avid DTC metastases remains a diagnostic challenge. A helpful technique for this diagnosis is positron emission tomography with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (PET/CT with [¹⁸F]FDG). On the other hand, there are still discussions about the clinical value of using exogenous thyroid-stimulating hormone (TSH) stimulation before PET/CT with [¹⁸F]FDG.

The aim of the study was the assessment of the usefulness of PET/CT with [¹⁸F]FDG under TSH suppression and stimulation of TSH performed in the detection of non-radioiodine avid DTC metastases, as well as determination of the thyroglobulin concentration under suppression and stimulation of TSH, which influences the result of PET/CT with [¹⁸F]FDG in patients with non-radioiodine avid DTC.

Material and methods: Retrospective analysis of 37 PET/CT with [¹⁸F]FDG performed in patients with DTC diagnosed and treated at the Department of Endocrinology and Isotope Therapy of the Military Institute of Medicine from January 2018 to July 2020. Of these, PET/CT with [¹⁸F]FDG under exogenous rhTSH stimulation was performed in 22 patients and PET/CT with [¹⁸F]FDG under TSH suppression in 15 was performed. In all analyzed patients, the result of diagnostic whole-body scintigraphy (WBS) using 80 MBq ¹³¹I under rhTSH stimulation was negative, and the concentration of thyroglobulin after stimulation (sTg) was greater than 1.0 ng/mL.

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Results: In the group of patients examined under TSH suppression, non-radioiodine avid in PET/CT with [¹⁸F]FDG were found in 6 out of 15 patients (40%) and in the group of patients examined under rhTSH stimulation in 10 out of 22 patients (45%). The differences between the groups were not statistically significant. The analysis of the receiver operating characteristic (ROC) curves allowed to determine the cut-off point for the positive result of PET/CT performed under TSH suppression with sTg concentration of 11.03 ng/mL. In the group of studies performed under rhTSH stimulation, the cut-off point for sTg was 6.3 ng/mL. There was no statistically significant difference between the baseline thyroglobulin (natTg) and sTg levels and the positive PET/CT result. The administration of rhTSH before the PET/CT examination also had no statistically significant effect on the maximum standard uptake value (SUVmax) of the dominant lesion identified in the PET/CT.

Conclusions: 1) PET/CT with [¹⁸F]FDG is a useful tool for detection of non-radioiodine avid recurrence and/or metastases of DTC. 2) The concentration of natTg and sTg is highly correlated with a positive result of PET/CT with [¹⁸F]FDG. 3) The concentration of natTg is comparable with sTg in predicting a positive result of PET/CT with [¹⁸F]FDG. 4) The cut-off point for a positive result of PET/CT for natTg was 1.36 ng/mL and for sTg was 7.05 ng/mL.

KEY words: differentiated thyroid cancer; human recombinant TSH; thyroglobulin; whole-body scintigraphy; PET/CT; [¹⁸F]FDG; non-radioiodine avid thyroid cancer

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Introduction

The concentration of thyroglobulin after stimulation of TSH (sTg) combined with whole-body diagnostic scintigraphy (WBS) using radioiodine (¹³¹I) is a recognized method that allows the follow-up of patients after ablative treatment of differentiated thyroid cancer (DTC) [1]. When the concentration of sTg is increased and there is no ¹³¹I uptake foci in WBS performed under endogenous or exogenous TSH stimulation, the non-radioiodine avid disease is suspected. It is an indication for positron emission tomography (PET/CT) with 2-[¹⁸F]fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) [2]. Loss of iodine uptake may affect about 30% of patients with disseminated DTC [3, 4]. Such changes can be characterized by a poorer differentiation, usually higher aggressiveness and could show greater dynamics. The detection of non-radioiodine avid metastases is associated with a reduction in the 10-year survival rate [3, 5, 6]. The sensitivity and specificity of PET/CT with [¹⁸F]FDG for this type of lesions is assessed as 68.4%–100% and 66.7%–98.5%, respectively [4, 7–12]. Studies show a strong correlation between the concentration of sTg and the presence of foci of increased metabolism of [¹⁸F]FDG in PET/CT [4, 13, 14].

Aim

The study aimed to compare the effectiveness of PET/CT with [¹⁸F]FDG performed under TSH suppression and recombinant human TSH (rhTSH) stimulation in detecting non-radioiodine avid foci of DTC in patients with a negative result of WBS with ¹³¹I and increased concentration sTg.

The aim of the study was also a determination of the thyroglobulin concentration under suppression and stimulation of TSH, which influences the result of PET/CT with [¹⁸F]FDG in patients with non-radioiodine avid DTC.

Material and methods

The study was approved by the local Bioethics Committee at the Military Medical Chamber in Warsaw. A retrospective analysis of 37

PET/CT examinations with [¹⁸F]FDG was performed between January 2018 and July 2020 in the group of patients of the Department of Endocrinology and Isotope Therapy of the Military Institute of Medicine in Warsaw (Tab. 1) after surgery and adjuvant treatment with ¹³¹I due to DTC. PET/CT was performed in patients who, during follow-up after the adjuvant therapy, showed an increased concentration of baseline thyroglobulin (natTg) and/or sTg and a negative result of the WBS performed after administration of 80 MBq ¹³¹I. No recurrence and/or suspicious lymph nodes were found on ultrasound examination of the neck in any of the patients in the study group.

Of the analysed group, 40.5% (15/37) had PET/CT with [¹⁸F]FDG performed under TSH suppression, and 59.5% (22/37) under rhTSH stimulation (Thyrogen 0.9 mg administered twice intramuscularly with an interval of 24 hours).

PET/CT with [¹⁸F]FDG was performed at the Mazovian PET/CT Center *Affidea* in Warsaw. Post-stimulation PET/CT acquisition was performed 24 hours after the administration of the second dose of rhTSH.

PET/CT was performed 60 minutes after administration of 4 MBq/kg of [¹⁸F]FDG on a hybrid Discovery 710 64-row scanner from General Electric Medical Systems.

The following parameters were used in the tomographic part of PET/CT: voltage: 140 kV, intensity (automatically adjusted to the patient's weight): 40–100 mA, noise index: 22, the thickness of the tomographic layer in CT for absorption correction: 3.75 mm reconstructed to 1.25 mm, time lamp rotation: 0.8 s. The iterative reconstruction method was used in the PET study: the number of subsets: 18, the number of iterations: 3, the size of the matrix: 256 × 256. The Time-of-Flight technique was used to improve the image contrast concerning noise.

Assessments of TSH (reference values: 0.27–4.2 μIU/mL) and Tg (reference values: 3.5–77 ng/mL) were performed at the Department of Laboratory Diagnostics of the Military Institute of Medicine using the electrochemiluminescence method (ECLIA) on the cobas e601 device from ROCHE Diagnostics, using ROCHE Diagnostics reagents. According to the DTC treatment

Table 1. Groups characteristic

Feature	natPET/CT (n = 15)	sPET/CT (n = 22)
Mean age	46 years	53 years
Sex	F = 13, M = 2	F = 17, M = 5
Histological type:		
— papillary	13	19
— follicular	2	3
Primary lesion (TNM):		
— T1a	1	0
— T1b	5	3
— T1m	4	7
— T2	0	2
— T3 i T4	4	8
— Tx	1	2
Lymph node involvement (TNM):		
— N0	4	6
— N1	9	10
— Nx	2	6
Metastasis presence (TNM):		
— M0	12	21
— M1	3	1
Number of patients with repeated therapy	10	18
Mean number of therapies per patient	2.4	2.7
Mean activity per therapy [GBq]	3.98	4.17
Mean total activity per patient [GBq]	9.55	11.38

guidelines, sTg concentrations above 1.0 ng/mL during follow-up were considered abnormal, which was one of the qualification criteria for PET/CT.

Ultrasound examinations were performed at the Department of Endocrinology and Isotope Therapy of the Military Institute of Medicine on the Acuson X150 device from Siemens with the use of a linear probe with a frequency of 8 MHz.

The WBSs were performed at the Department of Nuclear Medicine of the Military Institute of Medicine using NM/CT 870DR or Infinia VCHWK4 gamma-cameras from General Electric Medical System. The following parameters were used during the WBS: detector configuration: H-mode, energy window: 364 keV \pm 10%, collimator: high-energy general-purpose (HEGP), body contour: on, scan mode: continuous, exposure time per pixel: 320 s, speed: 7 cm/min, matrix: 256 \times 1024, acquisition zoom: 1.

The obtained results were presented in the form of a mean with standard deviations or a median with extreme values, depending on the fulfilment of the normal distribution conditions. Nominal variables are presented in the form of numbers with a frequency of occurrence. The compliance of the distribution of variables with the normal distribution was checked using the Shapiro-Wilk test. The correlation analysis was performed using the Pearson test for variables with a distribution close to the normal, otherwise, the Spearman test was used. Differences of nominal variables between groups were tested using the Chi-square test, and quantitative variables using the Student's t-test for unrelated variables. To identify the cut-off points for the studied variables, ROC analysis was performed. The results of the performed tests were considered significant for the two-sided $p < 0.05$. All statistical analyses were performed using the Statistica v.12 package (Statsoft, Cracow, Poland).

Results

Among 37 PET/CT examinations with [^{18}F]FDG, 15 were under TSH suppression (native-PET/CT — natPET/CT), and 22 were performed under rhTSH stimulation (stimulated-PET/CT — sPET/CT). In the natPET/CT group, 6 (6/15 — 40%) positive results were obtained (natPET/CT+) (Fig. 1, 2). The remaining studies in this group (9/15 — 60%) were assessed as negative (natPET/CT-) and did not show any foci of increased metabolism of [^{18}F]FDG related to the DTC. In the group of sPET/CT, 10 (10/22 — 45%) positive results (sPET/CT+) were obtained, finding foci of pathological [^{18}F]FDG uptake, which may correspond to recurrence or

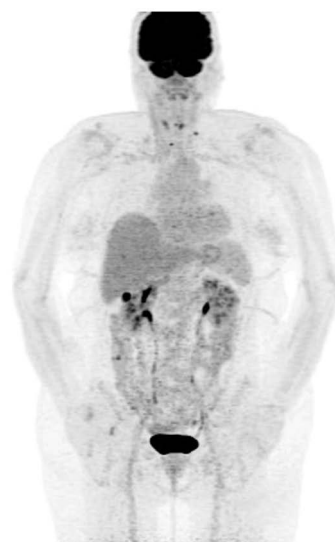


Figure 1A. PET/CT maximum intensity projection (MIP) performed under TSH suppression — accumulation of the [^{18}F]FDG in the left cervical and right mediastinal lymph nodes

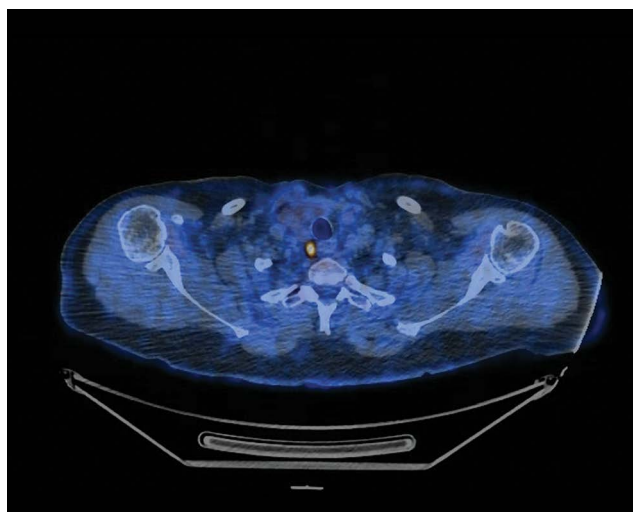


Figure 1B. PET/CT axial fusion projection performed under TSH suppression — accumulation of the [^{18}F]FDG in the right mediastinal lymph node



Figure 2A. PET/CT maximum intensity projection (MIP) performed under TSH suppression — multiple pulmonary metastasis

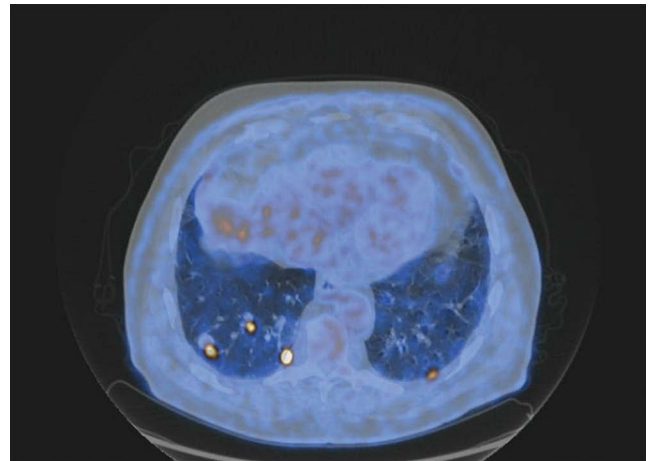


Figure 2B. PET/CT maximum intensity projection (MIP) performed under TSH suppression — multiple pulmonary metastasis



Figure 3A. PET/CT maximum intensity projection (MIP) performed under TSH stimulation — accumulation of the [18F]FDG in the right cervical lymph node

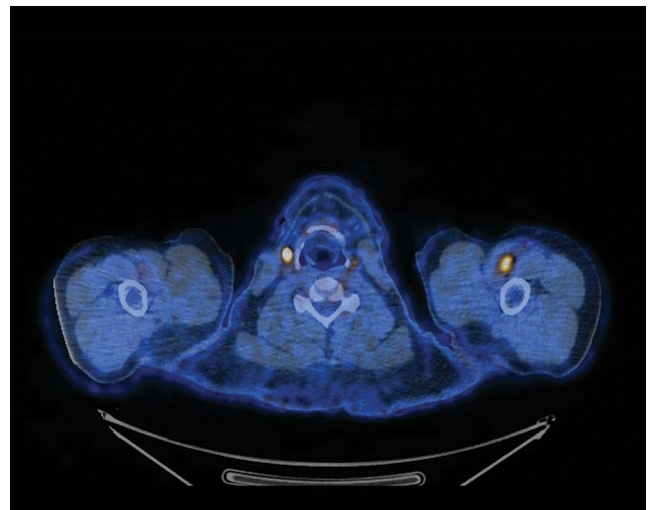


Figure 3B. PET/CT axial fusion projection performed under TSH stimulation — accumulation of the [18F]FDG in the right cervical lymph node

metastases of DTC (Fig. 3). The remaining studies in this group (12/22 — 55%) did not confirm the presence of foci of increased uptake of [18F]FDG (sPET/CT-). There were no statistically significant differences between both groups (natPET/CT and sPET/CT) to obtain a positive result of PET/CT (PET/CT+).

The mean maximum standardized uptake value (SUVmax) in the dominant lesion shown in the natPET/CT+ group was 6.08 ± 2.87 , and the tumour/background ratio for the reference point on mediastinal blood pool structures (MBPS) was 4.63 ± 2.35 . In the sPET/CT+ group, these values were respectively: 8.47 ± 5.38 and 6.36 ± 4.18 . However, these differences were not statistically significant ($p = 0.18$).

The median concentration of natTg and sTg measured during follow-up after ¹³¹I ablation treatment, which are the basis for qualification for PET/CT, in the natPET/CT group were, respectively: 1.07 ng/mL (0.04–190.3 ng/mL) and 6.87 ng/mL (1.45–882.0 ng/mL), and in the sPET/CT group: 0.54 ng/mL (0.04–3069 ng/mL) and 4.87 ng/mL (0.56–4405 ng/mL).

A statistically significant positive correlation was found both between the concentration of natTg and sTg and the number of lesions in PET/CT ($r = 0.71$; $p < 0.05$ and $r = 0.70$; $p < 0.05$, respectively). The analysis of ROC curves for the whole group (both natPET/CT and sPET/CT) showed that for obtaining a positive result of PET/CT, the optimal cut-off point for natTg and sTg

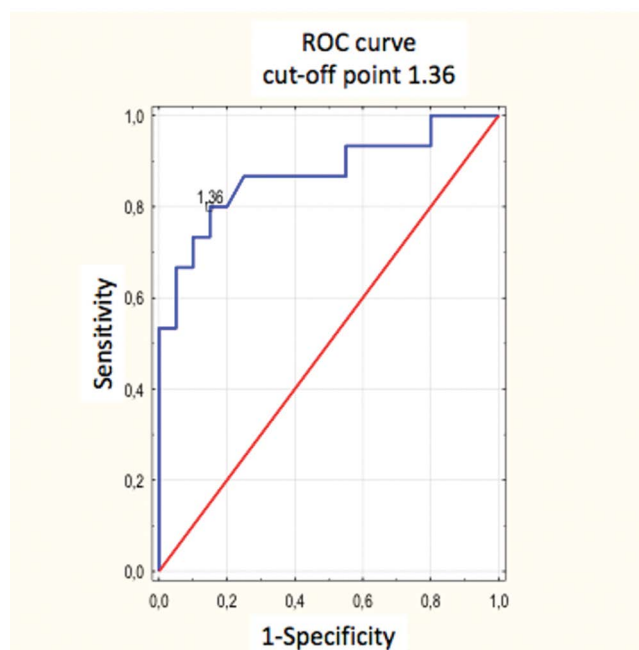


Figure 4. The ROC curve for natTg in the prediction of positive result of PET/CT

concentrations is: 1.36 ng/mL (sensitivity 80.0%, specificity 85.0%, accuracy 82.3%) and 7.05 ng/mL (sensitivity 81.3%, specificity 95.2%, accuracy 89.2%), respectively (Fig. 4, 5). However, the differences in the area under the ROC curves (AUC) between natTg and sTg were not statistically significant (0.872 vs 0.879; $p = 0.59$).

The analysis of the ROC curves for the natPET/CT group showed that to obtain a positive result of PET/CT, the optimal cut-off point for natTg and sTg concentrations is 2.7 ng/mL (sensitivity 100.0%, specificity 87.5%, accuracy 92.3%) and 11.03 ng/mL (sensitivity 100.0%, specificity 100.0%, accuracy 100.0%), respectively. For the sPET/CT group, the optimal cut-off point for natTg and sTg concentrations is 0.6ng/mL (sensitivity 80.0%, specificity 83.3%, accuracy 81.8%) and 6.3 ng/mL (sensitivity 80.0%, specificity 100.0%, accuracy 90.9%), respectively. Nevertheless, the differences in AUC for natTg and sTg between the groups (natPET/CT vs sPET/CT) were not statistically significant (0.925 vs 0.817; $p = 0.403$ vs 1.000 vs 0.833; $p = 0.124$).

Discussion

According to both the Polish recommendations and the American Thyroid Association (ATA) guidelines for the diagnosis and treatment of thyroid cancer, PET/CT with [18 F]FDG is recommended in patients with increased thyroglobulin concentration and no pathological lesions in 131 I WBS and/or ultrasound examination [1, 15]. The authors of these recommendations do not specify the thyroglobulin cut-off point above which PET/CT should be considered. Nevertheless, in the same guidelines, sTg concentration above 10 ng/mL indicates an incomplete biochemical response to the ablation treatment [1, 15].

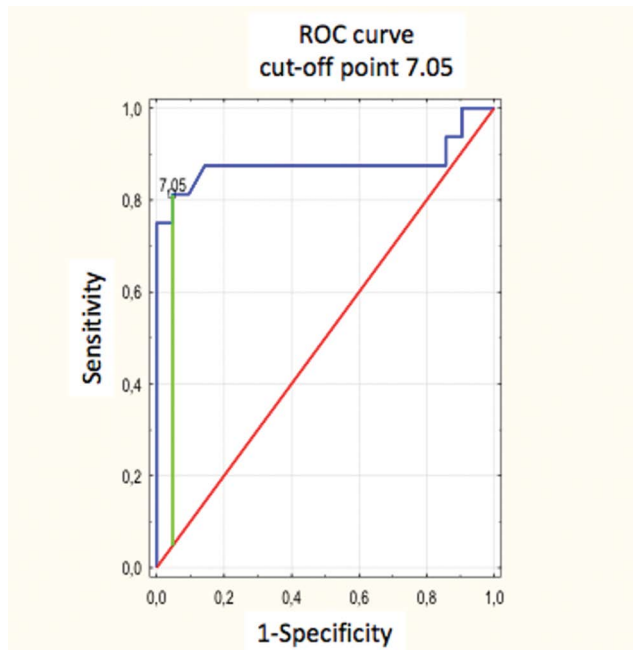


Figure 5. The ROC curve for sTg in the prediction of positive result of PET/CT

The present study found a positive correlation between both natTg and sTg concentration and the positive PET/CT result. Other authors confirmed the existence of such a correlation, but mainly concerning sTg. Trybek et al. [14] in 2014 showed that sTg has a strong and statistically significant accuracy in the diagnosis of recurrence and/or metastasis of differentiated thyroid cancer. Vural et al. [9] confirmed the relationship between the concentration of thyroglobulin under both suppression and stimulation of TSH, and the positive result of PET/CT. On the other hand, Shammam et al. [8] in a study from 2007 found that the sensitivity of PET/CT increases with the concentration of natTg. Similar conclusions, but regarding sTg, were reached by Stangierski et al. [16] in 2016, confirming that the probability of obtaining a positive PET/CT result, i.e. showing foci of pathological metabolism [18 F]FDG that may correspond to recurrence or metastasis of DTC, increases with sTg concentration. In previous years, many authors have tried to establish a cut-off point for the sTg concentration above which it is reasonable to perform PET/CT with [18 F]FDG. In a 2012 South Korean study, Na et al. [12] estimated it at 20 ng/mL. In the same year, in a study conducted on 105 patients, Vural et al. [9] found that the cut-off point for natTg is 1.9 ng/mL, while for sTg it is 38.2 ng/mL with a sensitivity of 94% and a specificity of 100%. In the Polish study by Trybek et al. [14], the concentration of sTg with a sensitivity and specificity equal to 100% was 28.5 ng/mL, while in a Chinese study from 2017, Chai et al. [17] with a sensitivity of 89.5% assessed was 49 ng/mL.

In the already cited Polish study by Stangierski et al. [16] the cut-off point for sTg was 32.9 ng/mL. This study found such correlation and established cut-off points for obtaining the positive result of PET/CT for both natTg and sTg at 1.36 ng/mL and

7.05 ng/mL, respectively. The threshold for natTg was lower, but similar to that obtained by Vural et al. [9], while the concentration of sTg determined by the authors was clearly lower than those mentioned in the above-cited studies, with a slightly lower, although still high, sensitivity. It was also lower than the values mentioned in the Polish and American recommendations for the diagnosis and treatment of DTC.

At the same time, the authors did not find statistically significant differences in the ROC curves for natTg with a cut-off point of 1.36 ng/mL and for sTg with a cut-off point of 7.05 ng/mL. Thus, the values of natTg and sTg in this study were comparable in predicting positive PET/CT in patients with non-radioiodine avid DTC. Therefore, it may be information that allows referring patients to PET/CT without prior assessment of sTg concentration. Due to the high costs of the rhTSH, basing the qualification of patients for PET/CT on the natTg concentrations performed in an outpatient setting should result in a lower burden for the health care system. Such an assumption was already made by the British group a few years ago, but then no useful cut-off point was found for natTg concentration [18].

The presented study did not find a statistically significant improvement in the detection of non-radioiodine avid recurrences and/or metastases of DTC using rhTSH stimulation before PET/CT, which is coherent with the observations of other authors [19, 20]. However, there are also data in the literature suggesting that the use of rhTSH stimulation before PET/CT may increase its sensitivity from 28% to 50% [21]. Dionigi et al. [4] found that administration of rhTSH before PET/CT increases its sensitivity in detecting recurrence of differentiated thyroid cancer from 81% to 95%. Furthermore, the Chinese meta-analysis of Ma et al. [22] covering 7 prospective studies with a total of 168 patients showed that the use of exogenous or endogenous TSH stimulation before PET/CT statistically significantly increases the chance of obtaining a positive result (OR = 2.45; 95% CI 1.23–4.9) and statistically influences the number of foci of radiotracer accumulation visible in PET/CT (OR = 4.92; 95% CI 2.7–8.95).

The present analysis of ROC curves in subgroups, separately for positive PET/CT results in the non-stimulated group (natPET/CT+) and after rhTSH stimulation (sPET/CT+), showed that the optimal cut-off point for sTg concentration to obtain a positive result of PET/CT is 11.03 ng/mL in the natPET/CT group and 6.3 ng/mL in the sPET/CT group, respectively. However, this difference was not statistically significant, perhaps due to the too-small size of both groups. Still, this may be indirect proof of the validity of using rhTSH before PET/CT in patients with slightly elevated sTg concentration (above 6.3 ng/mL). For the sTg concentration almost twice as high (11.03 ng/mL), it may be sufficient to perform a PET/CT under TSH suppression. There are no studies in the available literature that would deal with this issue in this aspect in a larger group of patients. Saab et al. [23] in a study involving a group of 15 sPET/CT stated that the use of TSH stimulation (exogenous or endogenous) allows for the identification of non-radioiodine avid metastases of DTC in PET/CT with relatively low sTg concentration, for which it was found to be 15 ng/mL. At the same time, these authors emphasize that PET/CT was useful regardless of the type of TSH stimulation. In the present study, all sPET/CT were performed with rhTSH, due to the proven equal, compared to endogenous, effectiveness of

this type of TSH stimulation in the treatment and diagnosis of DTC, with a simultaneously reduced risk of side effects of the withdrawal of levothyroxine treatment [24–26].

The work of Vera et al. [19], on the other hand, indicated low effectiveness of the sPET/CT at a natTg concentration below 10 ng/mL but did not take into the sTg concentration. The Brazilian study by Almeida et al. [27] compares the results of PET/CT before and after endogenous TSH stimulation (withdrawal of levothyroxine for 30 days). Due to the endogenous method of stimulation, the sTg concentration was measured only for the sPET/CT. In a German study, Petrich et al. [28] performed a head-to-head comparison of PET/CT before and after rhTSH stimulation in a group of 30 patients, but this work does not provide information on the analysis of ROC curves of sTg concentration for the natPET/CT and sPET/CT groups. On the other hand, these authors noticed that the use of rhTSH stimulation before PET/CT improved the tumour/background ratio of the identified lesions [28]. Other publications also indicate an improvement in the tumour/background ratio and an increase in SUVmax in PET/CT, which indicates better [¹⁸F]FDG uptake in metastatic lesions and leads to better PET/CT image quality [17, 20, 27]. The authors obtained similar results in their work, but they were not statistically significant. This may be due to the insufficient size of the analysed group, but their observations are preliminary and will be continued in the future.

The advantage and innovative approach to the presented work is not only to show a positive, statistically significant correlation between natTg and sTg and positive result of PET/CT but also to show a comparable value of natTg and sTg in predicting a positive PET/CT result, as well as determining the cut-off point for natTg and sTg separately for natPET/CT+ and sPET/CT+.

The main limitation of the present work is the small size of the analysed group, but it is a preliminary study. The analyses will be continued on a wider group of patients in the future.

Conclusions

1. PET/CT with [¹⁸F]FDG is a useful tool for detection of non-radioiodine avid recurrence and/or metastases of DTC.
2. The concentration of natTg and sTg is highly correlated with a positive result of PET/CT with [¹⁸F]FDG.
3. The concentration of natTg is comparable with sTg in predicting a positive result of PET/CT with [¹⁸F]FDG.
4. The cut-off point for a positive result of PET/CT for natTg was 1.36 ng/mL and for sTg was 7.05 ng/mL.

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