

# Thyroid incidentaloma as a “PAIN” phenomenon—does it always require surgery?

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## Abstract

A thyroid nodule discovered during imaging study performed due to unrelated thyroid disease is known as a thyroid incidentaloma, while positron emission tomography (PET) associated incidental neoplasm of thyroid is known as a “PAIN” phenomenon.

To evaluate which patients with “PAIN” phenomenon should undergo surgery in regards to cytology results.

Retrospective review of 4716 patients consecutively admitted and surgically treated in tertiary surgical center. 49 (1.04%) patients with “PAIN” phenomenon were identified. All of them had ultrasound-guided fine needle aspiration biopsy (UG-FNAB) performed and cytological results were evaluated according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Patients were divided into 2 subgroups according to histopathological diagnosis: group 1 (n=25) with benign tumor and group 2 (n=24) with thyroid cancer.

Cytology results were the significant predictors of cancer occurrence in patients with “PAIN” phenomenon ( $P < .0001$ ). Logistic regression analysis confirmed that category III or higher of TBSRTC in patients with “PAIN” phenomenon significantly increased the risk of cancer (OR = 168.7,  $P < .0001$ ).

Patients with “PAIN” phenomenon and cytology assigned to category III or higher of the Bethesda system should undergo surgery due to significant risk of thyroid malignancy.

**Abbreviations:** PAIN = positron emission tomography associated incidental neoplasm, PET = positron emission tomography, TBSRTC = The Bethesda System for Reporting Thyroid Cytopathology, UG-FNAB = ultrasound guided-fine needle aspiration biopsy.

**Keywords:** Bethesda system, PET, thyroid cancer, thyroid incidentaloma

## 1. Introduction

A thyroid nodule discovered during imaging study or surgery, performed due to unrelated thyroid gland pathology is known as a thyroid incidentaloma (TI).<sup>[1,2]</sup> Therefore, TI is defined also as an unsuspected and asymptomatic thyroid tumor.<sup>[3]</sup> TIs are the most commonly detected by neck ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), carotid duplex scanning or 2-(18)[F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET).<sup>[1]</sup> Currently, because of wide use of US in clinical practice, some authors emphasize that TIs can be detected even in up to 50% of general population.<sup>[4]</sup> Thus, others suggest thorough US examination of

all TIs diagnosed in CT, MRI or PET imaging, because of the significant shortcomings of these diagnostics.<sup>[1]</sup>

From several years, the use of FDG-PET examination has become one of the basic diagnostic tools in oncological practice.<sup>[5]</sup> Furthermore, according to some studies successfully accomplished in recent years, the incidence rate of TIs diagnosed in FDG-PET performed due to oncological indications varying from 1.0% to 4.3%.<sup>[5–7]</sup> However, some authors suggest that increasing use of FDG-PET in oncology, makes TI detection more widely observed in clinical practice.<sup>[8]</sup> The others say that TI localized by FDG-PET has the highest incidence rate of malignancy, which was estimated by some authors even up to 50% of all cases.<sup>[7,9]</sup> Because of this, in 2008 the researchers have paid attention to the specific clinical situation called “PAIN” phenomenon, what stands for PET associated incidental neoplasm of thyroid, and was described by Katz et al.<sup>[10]</sup> This acronym refers to the patients in whom thyroid tumor is diagnosed incidentally by PET imaging. They are very often under treatment or evaluation for another malignant process. In such situations clinical dilemmas appear.

The main question is, how often TI as a “PAIN” phenomenon turns out to be malignant and what is the most favorable management in such situation. Some authors state that TIs should be managed in the same way as clinically evident nodules.<sup>[1]</sup> Al-Hakami et al. estimated that significantly high maximum standardized uptake value (SUV max) of the thyroid nodule localized in FDG-PET examination strongly suggest the presence of malignancy,<sup>[11]</sup> so thyroidectomy in such situation might be recommended. Some others add that the presence of focal uptake with high SUV max level in FDG-PET examination and euthyroidism correlate with high likelihood of malignancy.<sup>[12]</sup>

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However what about the patients with “PAIN” phenomenon where SUV max level in FDG-PET examination is not significantly high. Should these patients avoid surgery or maybe undergo surgical procedure too? Next is ultrasound-guided fine needle aspiration biopsy (UG-FNAB) is a useful diagnostic tool helping to take the proper decision? There is very few data concerning the patients with “PAIN” phenomenon, in whom SUV max level is not significantly high.

In this study we tried to<sup>[1]</sup> determine the percentage of patients with “PAIN” phenomenon among all individuals undergoing thyroid surgery,<sup>[2]</sup> to evaluate the incidence of thyroid malignancy in this specific, clinical situations,<sup>[3]</sup> to estimate what exact clinical situations “PAIN” phenomenon appears in, and finally<sup>[4]</sup> to evaluate which patients with “PAIN” phenomenon and without significantly high SUV max level should undergo surgery in regards to UG-FNAB results.

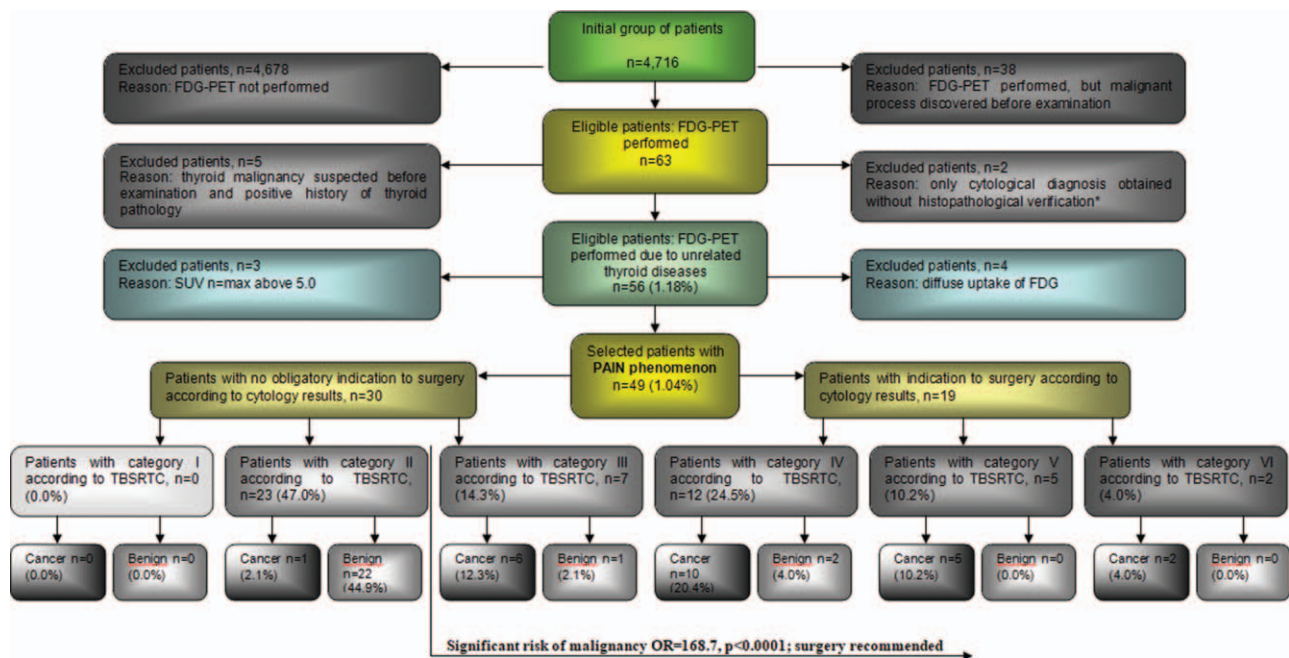
## 2. Materials and methods

The study protocol was approved by the Bioethics Committee of Wrocław Medical University (signature number: KB-296/2015). The data were analyzed anonymously and retrospectively on the basis of medical records. The authors did not have access to patient identifying information or direct access to the study participants. This approach was accepted and approved by the Bioethics Committee of Wrocław Medical University. The patients were partially represented in photographs, but without a visible face, and they signed informed consent to be disclosed for scientific purposes.

### 2.1. Patients selection

We performed a retrospective medical records review of 4716 patients consecutively admitted and surgically treated for thyroid

tumors in The First Department and Clinic of General, Gastroenterological and Endocrine Surgery from January 2008 to December 2017. Around 101 (2.14%) FDG-PET nuclear imaging studies were performed in the analyzed period, but 56 (1.18%) were performed due to of unrelated thyroid diseases. TI was defined as a focal FDG uptake on PET scans in patients without previous history of thyroid diseases, while the focal uptake was defined as an uptake within maximum one lobe of the thyroid gland. The FDG-PET examinations were retrospectively reviewed according to the patterns and the intensity of FDG uptake. Patients with diffuse uptake as a whole thyroid tissue uptake were excluded. FDG uptake was quantified in the thyroid region with increased tracer uptake and maximum SUV were calculated.<sup>[13]</sup> An arbitrary cut-off level of 5.0 for the SUV max was chosen as not significant for malignant tumors.<sup>[12,14]</sup> According to inclusion criteria finally 49 (1.04%) “PAIN” phenomenon patients were identified in analyzed cohort. The steps for patient selection are presented in Figure 1. All individuals had FDG-PET examinations performed as a part of the initial assessment of index cancer of nonthyroid organ or as a follow-up surveillance scan (Table 1). As a main presurgical diagnostic test, all patients underwent UG-FNAB. All cytological specimens were evaluated according to The Bethesda System for Reporting Thyroid Cytopathology<sup>[15]</sup> and adequate category was assigned to every TI, which manifested as a “PAIN” phenomenon. Subsequently, demographic data, diagnostic results, clinical and histopathological characteristics of included patients were evaluated (Table 2). Clinical and pathological classification was performed according to the TNM classification criteria (8th edition, 2017) by the American Joint Committee on Cancer (AJCC). All of the TI patients were operated by the same team of surgeons, and cytological and histopathological specimens were examined by 2 pathologists experienced in thyroid malignancy. Histopathology reports and immunohistochemical staining were



**Figure 1.** Selection of study group from 4716 individuals referred for surgery in one center from 2008 to 2017. All participants underwent UG-FNAB. Histopathological verification was obtained for all participants. \*: in one case we performed only surgical biopsy due to advanced malignant process, and one individual did not undergo surgery due to extremely advanced malignant process and extremely poor general condition (ASA 4)—excluded.

**Table 1****Indication for FDG-PET examination in patients with “PAIN” phenomenon.**

Indication for FDG-PET	Number of patients n (%)
Evaluation of suspected disease recurrence, relapse, and residual disease	
Breast cancer	16 (32.65%)
Lymphoma	1 (2.04%)
Clear cell renal carcinoma (CCRC)	11 (22.44%)
Nonsmall cell lung cancer	5 (10.20%)
prostate cancer	1 (2.04%)
Evaluation of suspected recurrence in equivocal conventional imaging	
x-ray picture	2 (4.08%)
Neck US	1 (2.04%)
Neck CT	1 (2.04%)
Neck MRI	2 (4.08%)
Staging of nonthyroid cancer	
Colon cancer	3 (6.12%)
Ovarian cancer	2 (4.08%)
Establish baseline staging	
Esophagus cancer	1 (2.04%)
Evaluation of an indeterminate lesion	
Solitary pulmonary lesion	1 (2.04%)
Assessing response to therapy	
lymphoma	1 (2.04%)
Occult primary lesion nonmetastatic manifestation of vertebral	
Plasmocytoma	1 (2.04%)
Total	49 (100%)

CCRC=clear cell renal carcinoma, CT=computed tomography, FDG-PET=fluorodeoxy-glucose positron emission tomography, MRI=magnetic resonance imaging, US=ultrasonography.

analyzed to determine tumor size (pT), subtype, aggressive characteristics such as extrathyroidal extension, surgical margins, surrounding organs and tissue infiltration and lymph node metastases (pN).

The patients were divided into 2 subgroups according to final histopathological diagnosis: group 1 (n=25) with benign tumor and group 2 (n=24) with thyroid malignancy.

## 2.2. Statistics

Data were analyzed by Statistica 13.1 software (StatSoft, TIBCO Software Inc., CA). Descriptive data were presented as numbers of observation and percentages or as averages and standard deviations. The Fisher exact test was used for frequency analyses, and Student *t* test was performed for the analysis of continuous variables. The logistic regression analysis was used to determine of impact of TBSRTC classification on indication to surgery and prediction of malignancy in thyroid incidentalomas. All tests were 2-sided and  $\alpha \leq 0.05$  were considered statistically significant.

## 3. Results

Around 4716 patients with thyroid tumors were analyzed and 101 (2.14%) whole-body FDG-PET examinations were performed in the analyzed period, while 56 (1.18%) were done due to of unrelated thyroid diseases. According to the inclusion criteria, finally 49 (1.04%) patients with “PAIN” phenomenon were identified (Table 1). UG-FNAB results of all TIs treated as “PAIN” phenomenon revealed 23 (47.0%) cases assigned to category II of the Bethesda system, 7 (14.3%) to category III, 12 (24.5%) to category IV, 5 (10.2%) to category V, and 2 (4.0%) to category VI (Fig. 1). In 23 patients with category II, in histopathological verification we obtained 1 (4.2%) individual

**Table 2****Relationship between demographic or clinical characteristics and final diagnosis: benign/malignancy in surgical patients with thyroid incidentaloma (n = 49).**

Parameters	Benign (n=25)	Malignancy (n=24)	P-value
Gender			
Women	22 (88.0%)	20 (83.3%)	.702
Men	3 (12.0%)	4 (16.7%)	
Age, years	53.16 ± 16.92	60.04 ± 15.57	.145
Age			
<55 years	6 (24.0%)	5 (20.8%)	1.000
≥55 years	19 (76.0%)	19 (79.2%)	
Category of TBSRTC			
II	22 (88.0%)	1 (4.2%)	<.0001*
III–VI	3 (12.0%)	23 (95.8%)	
AJCC staging			
I	—	15 (62.5%)	—
II	—	4 (16.7%)	—
III	—	3 (12.5%)	—
IV	—	2 (8.3%)	—
SUVmax			
2.1–3.0	3 (12.0%)	2 (8.4%)	
3.1–4.0	10 (40.0%)	11 (45.8%)	.809
4.1–5.0	12 (42.0%)	11 (45.8%)	
Tumor dimension, cm			
0.5–1.0	10 (40.0%)	11 (45.8%)	
1.1–2.0	8 (32.0%)	8 (33.4%)	.705
2.1–3.0	2 (8.0%)	2 (8.3%)	
3.1–4.0	3 (12.0%)	2 (8.3%)	
≥4.1	2 (8.0%)	1 (4.2%)	
TNM classification			
pT1a	—	11 (45.8%)	
pT1b	—	8 (33.3%)	
pT2	—	2 (8.3%)	
pT3	—	3 (12.5%)	
pN0	—	17 (70.8%)	—
pN1a	—	2 (8.3%)	
pN1b	—	1 (4.1%)	
pNx	—	4 (16.6%)	
pM0	—	16 (66.6%)	
pM1	—	3 (12.5%)	
pMx	—	5 (20.8%)	
Histopathology			
Adenoma	19 (76.0%)	—	
Goiter	5 (20.0%)	—	
Thyroiditis	1 (4.0%)	—	
PTC			
-Classical type	—	15 (62.4%)	
FTC	—	1 (4.2%)	
MTC	—	1 (4.2%)	
SEMP	—	1 (4.2%)	
Secondary	—	6 (25.0%)	

Descriptive data were presented as number (percent) or average ± standard deviation (± SD).

AJCC=8th Edition of American Joint Commission on Cancer, FTC=follicular thyroid cancer, MTC=medullary thyroid cancer, PTC=papillary thyroid cancer, SEMP=solitary extramedullary plasmocytoma, TBSRTC=The Bethesda System for Reporting Thyroid Cytopathology, TNM=tumor, nodules, metastases according to 8th edition AJCC.

\*Statistically significant.

with malignant tumor, and 22 (88.0%) cases with benign lesions. In 26 patients, who had indeterminate, suspected or evident malignant tumor in cytological analysis (categories III–VI of the Bethesda system) almost all individuals (23/26) had malignant tumor in histopathological verification (95.8%).

Subsequently all patients with “PAIN” phenomenon were divided into 2 subgroups according to the final diagnosis of

disease. The first subgroup consisted of patients with benign thyroid disease ( $n=25$ ) and in second subgroup were patients with thyroid malignancy ( $n=24$ ). The comparative characteristics of the subgroups of TI patients were demonstrated in Table 2. There were no significant differences in gender and age parameters between the 2 subgroups. However, cytology results (TBSRTC) were the significant predictors of the thyroid malignancy occurrence ( $P<.0001$ ). Logistic regression analysis confirmed that classification of TI in patients with “PAIN” phenomenon to stage III or higher significantly increased the risk of the thyroid malignancy ( $OR = 168.7, P<.0001$ ).

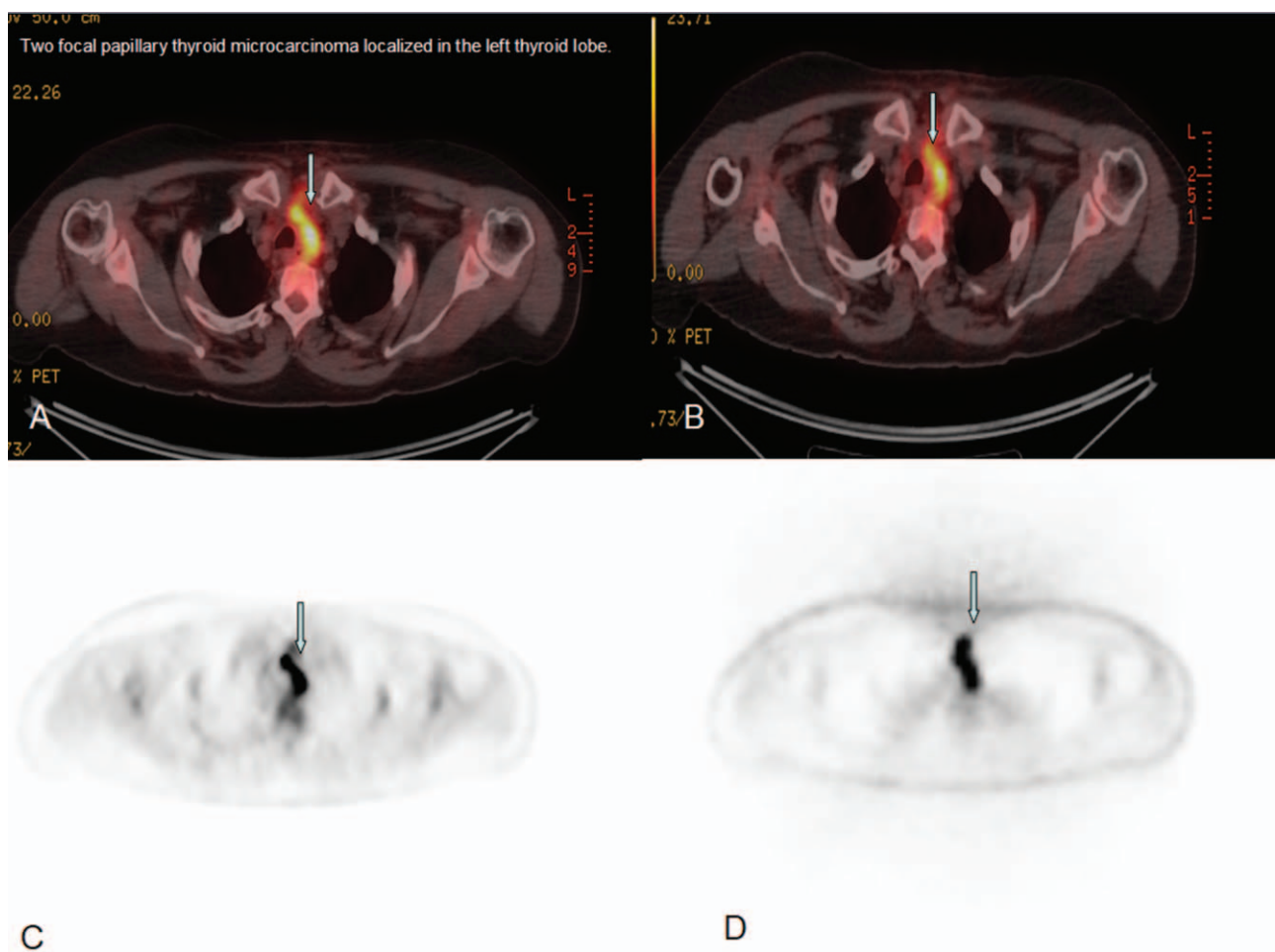
#### 4. Discussion

Nowadays, TI still remains a diagnostic and therapeutic challenge.<sup>[16]</sup> The increase of the necessity for imaging connected with rapidly advancing image resolution is leading to the rise of the new cases of incidentalomas.<sup>[17]</sup> Subsequently, these incidentally diagnosed tumors very often lead to patient anxiety.<sup>[18]</sup>

FDG-PET is one of the most common diagnostic tools, in which thyroid tumors are discovered incidentally. It might be connected with a wide availability of this imaging technique in clinical practice.<sup>[5]</sup> O’Sullivan et al<sup>[17]</sup> noticed that the rate of malignancy in incidentalomas varies and depends on specific

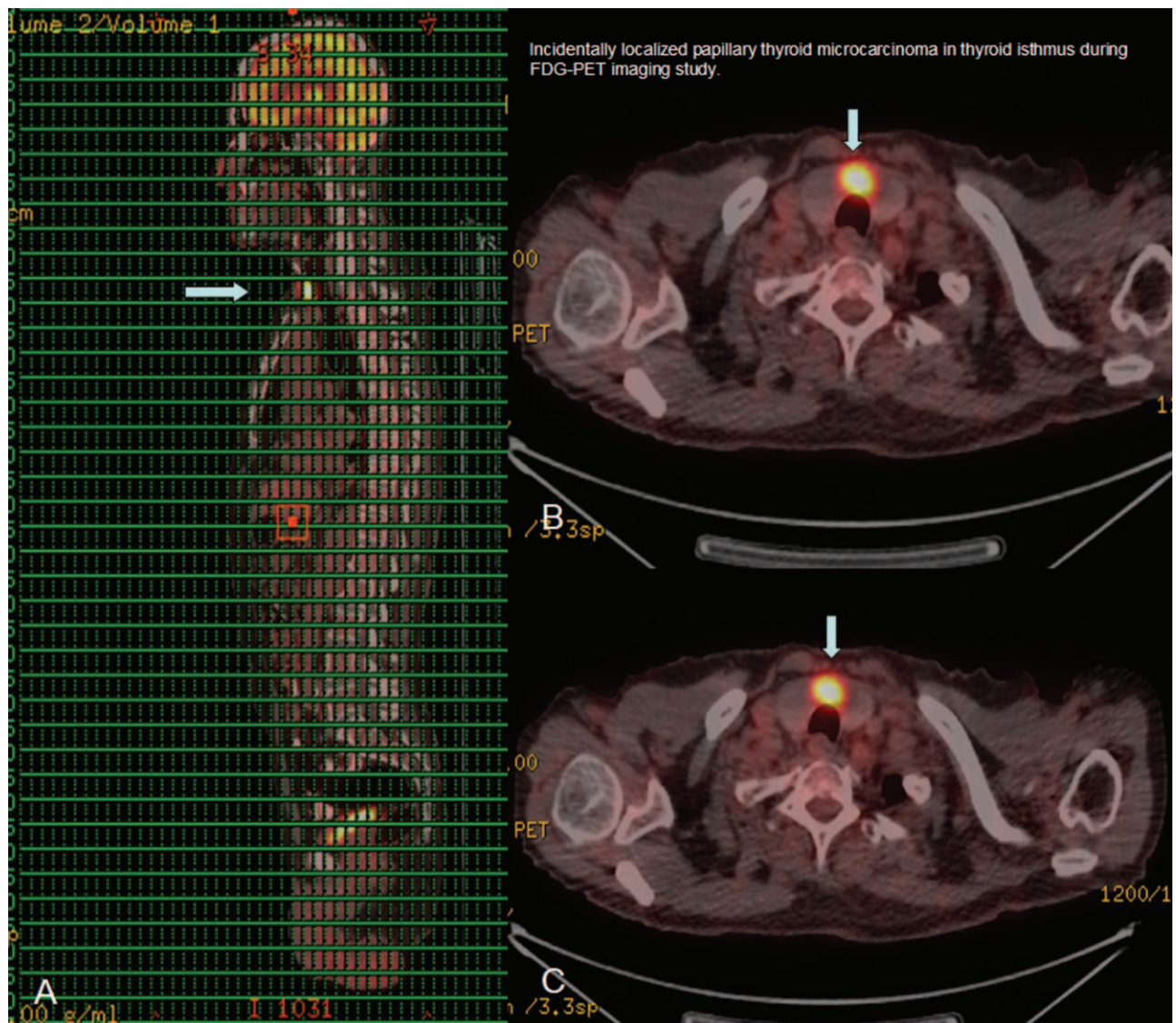
organs. He estimated that the incidence of malignancy of incidentalomas of the brain, parotid, and adrenal gland was  $<5\%$ . Prostatic and colonic incidentalomas were malignant in 10% to 20%, while the malignancy of TIs was in about the quarter of all cases. He also revealed that the breast incidentalomas had the highest percentage of malignancy (42%, 95% confidence interval 31%–54%).<sup>[17]</sup> In our study, the percentage of malignancy of TIs was 48.97%, however this number of malignant cases might be so high, because we estimated it in selected patients with “PAIN” phenomenon.

Papillary thyroid cancer (PTC) is the most common malignant TI.<sup>[19]</sup> In our study, PTC was the most common TI in “PAIN” phenomenon. We diagnosed PTC in 7 patients undergoing breast cancer staging (Fig. 2) and in 1 patient evaluated due suspicion of colon cancer metastases (Fig. 3). Well-differentiated thyroid cancers (WDTCs) are characterized by increased expression of glucose transporters, so every focal uptake of FDG should be treated as potentially malignant lesion.<sup>[20]</sup> This is why we decided to investigate the focal uptakes of FDG in the thyroid, however without significantly high SUV max levels. In our study almost 67% of patients with “PAIN” phenomenon had WDTC diagnosed, however 62.4% had PTC. Kresnik et al<sup>[21]</sup> estimated that PTC and follicular thyroid cancer (FTC) show up as focal FDG avid tumors, but distinguishing these 2 lesions can only be



**Figure 2.** Image of malignant thyroid FDG-PET incidentaloma. An FDG-PET transaxial scans (ABCD) of a 56-year-old female undergoing breast cancer screening demonstrated a 2 nodules with increased FDG uptake (arrows, SUVmax4.7) in the left thyroid lobe. Multifocal papillary thyroid microcarcinoma (pT1amN0M0) was confirmed by histopathology. FDG-PET=fluorodeoxy-glucose positron emission tomography.





**Figure 3.** Image of malignant thyroid FDG-PET incidentaloma. FDG-PET examination for metastasis evaluation of colon cancer of a 61-year-old male, sagittal (A) and transaxial (BC) scans showed increased uptake in the thyroid isthmus (arrows, SUVmax4.9). Papillary thyroid microcarcinoma was confirmed by histopathology (pT1b, N0, M0). FDG-PET = fluorodeoxy-glucose positron emission tomography.

performed in fine needle aspiration cytology or histopathology. As far as we are able to diagnose PTC in UG-FNAB, however it cannot be done in case of FTC. If the result of UG-FNAB shows category V and VI of the Bethesda system, the further clinical steps are predictable. Dilemma appears when we have “indeterminate” cytological results.<sup>[1,5]</sup> In our study group we had 19 (38.8%) patients with “indeterminate” cytological diagnosis, and only 3 of them had benign tumor in histological examination (6.1%).

The value of FDG-PET in thyroid diagnostics is high, because thyroid tissue without pathology, usually does not accumulate this radionuclide.<sup>[22]</sup> However, it might be also observed in chronic thyroiditis and Graves' disease.<sup>[23]</sup> Some authors suggest that the incidental finding of focal thyroid uptake in PET imaging has the higher risk of malignancy compared to other thyroid nodules.<sup>[3,5]</sup> They add that the risk of malignancy in TI found in FDG PET imaging may be even 10 times higher compared to the risk of malignancy in thyroid nodules.<sup>[5]</sup> Therefore they suggest

multidisciplinary approach in aspect of diagnosis, treatment and follow-up of these patients. Stangierski et al<sup>[5]</sup> confirmed that individuals with incidental focal uptake of FDG-PET in thyroid were at a high risk of malignancy. However, they suggest that small TIs with focal uptake of FDG-PET should be interpreted cautiously. In our series we had 3 cases of focal thyroid uptake of FDG being malignant lesions derived from nonthyroid tissue. Two of them were the results of the contiguous involvement from surrounding tissues like oesophagus and submandibular salivary gland. We revealed 3 cases of metastatic tumors derived from clear cell renal cancer (CCRC). All of these patients underwent nephrectomy several years ago. Generally, metastatic index cancer to the thyroid gland has been reported in the literature to occur in about 1.25% individuals in unselected autopsy study.<sup>[24]</sup> The most common areas of metastasis to the thyroid gland, what we confirmed in our study, are kidney, breast, and lung.<sup>[7]</sup> Some authors described the metastatic involvement of the thyroid from the oesophagus and breast cancer.<sup>[25]</sup>

FDG uptake in the thyroid tissue might be focal and diffuse.<sup>[7]</sup> However these 2 types of uptakes usually present different thyroid pathology. As far as diffuse uptake almost always presents inflammatory process, such autoimmune thyroiditis, the focal uptake usually presents malignancy.<sup>[7,12,14]</sup> American Thyroid Association (ATA) guidelines recommend further evaluation of the thyroid nodules with diameter equal or more than 1 cm.<sup>[26,27]</sup> However, according to ATA guidelines there are strong recommendation for evaluation of all FDG avid thyroid nodules with diameter size 1 cm or larger. Such recommendation is supported by increased incidence of malignancy in PET discovered TIs.<sup>[7]</sup> The others considering the increasing rate of malignancy of TIs diagnosed in PET, which is even up to 50%, state that also nodules below 1 cm in diameter should be further evaluated.<sup>[25,28]</sup> They recommend thorough US examination followed by UG-FNAB. In the previous study,<sup>[29]</sup> we described the clinicopathological characteristics of TIs, which may suggest malignant nature of these lesions.<sup>[29]</sup>

When the general condition of the patient with “PAIN” phenomenon is not well, the index cancer is advanced or the probability for total recovery is low, “stronger” dilemmas of further management appear. In our study all patients (100%) with FDG avid TI, even under 1 cm in diameter, underwent UG-FNAB and surgery. 48.97% (24/49) of them had malignant process confirmed. Such observations suggest that almost half of the patients with “PAIN” phenomenon, with even not significantly high SUV max level, might have malignant process. This is why some authors in specific, clinical situation suggest various approaches.<sup>[7]</sup> Because the most common TI is PTC, which has a slow rate of growth (1–2 mm/year), some authors do not recommend any further evaluation.<sup>[30]</sup> Additionally, such approach might be supported by the fact that FDG-PET is ordered in patients with disseminated or locally advanced malignant process. It was estimated that in patients with advanced malignant disease and poor prognosis further evaluation of “PAIN” phenomenon is not obligatory recommended.<sup>[7,30]</sup>

The next very interesting issue of “PAIN” phenomenon concerns the size of TI and its correlation with probability of malignancy. From this reason we evaluated only the focal uptakes of TIs. We noticed that there was no correlation between the size of TI and the risk of malignancy. In our study we demonstrated that TIs localized in FDG-PET examination had both benign and malignant nature, and even very small lesions with dimension size below 1 cm were malignant. In our study, we revealed in 11 (45.8%) patients with TIs assigned to pT1a stage (diameter 1 cm or lower) malignant process. All of our patients (100%) had low intensity of FDG uptake (SUV max  $\leq$  5.0); however, some authors suggest that there is not significant correlation between intensity of FDG uptake in small thyroid lesion, especially below 1 cm of diameter like microcarcinoma.<sup>[25]</sup> The others did not confirm these observations.<sup>[31]</sup> Some authors explain that SUV max apart from the nodule size depends on the glucose transporters expression in the tumor what influences FDG uptake.<sup>[32]</sup>

In our clinic, we warily recommend surgery for the patients with TI recognized in FDG-PET examinations, despite the increasing prevalence of thyroid cancer in general population<sup>[5,19,29,33]</sup> and the high incidence rate of malignancy in TIs localized by PET (up to 50%).<sup>[7,9]</sup> We are aware that physical status of the patients with “PAIN” phenomenon might be not well and “clinically complex.” Surgical treatment not necessary might be the optimal management in some individuals with “PAIN” phenomenon. We estimated that the most common

malignancy of all TIs was PTC, and therefore our approach is always thoughtful. PTC very often is indolent tumor without clinical manifestation. Ito et al<sup>[34]</sup> support our opinions. They suggest that majority of thyroid malignancy are PTCs, which are indolent tumors not requiring surgery. However, on the other hand we noticed that thyroidectomy conducted by the surgeons experienced in thyroid surgery is rather safe, so the risk of the malignant disease extension might be higher than the risk of the potential postsurgical complications.<sup>[33]</sup>

## 5. Conclusion

“PAIN” phenomenon in thyroid pathology occurs rare, but the incidence rate of malignancy in this specific clinical situation is high. Patients with “PAIN” phenomenon and cytology assigned to minimum III category of the Bethesda system should undergo surgery because of significantly high risk of malignancy. The most common malignant tumor in “PAIN” phenomenon is PTC. “PAIN” phenomenon is most commonly observed in oncological follow-up patients. Because of high likelihood of malignancy in patients with “PAIN” phenomenon, every patients should be further evaluated. The next step of diagnostic algorithm should be UG-FNAB. Patients with “PAIN” phenomenon who benefit from thyroidectomy and if cytology result showed minimum third category of the Bethesda system should be qualified to surgery, however there should not be one rigid standard management. Everyone should be diagnosed and treated individually in the multidisciplinary approach.

## Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

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