

# Incidental and non-incidental thyroid microcarcinoma

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**Abstract.** There is no clear therapeutic approach for thyroid microcarcinoma (TMC). This may be as a consequence of recent observations that have reported biologically different types of TMC, which should be treated differently. The objective of the present study was to compare incidental TMC (ITMC) and non-incidental TMC (NITMC) in order to assess the differences in the incidence, diagnostic results, clinicopathological characteristics and surgical treatment. The study consisted of a retrospective chart review of 3,218 patients consecutively admitted and surgically treated in a single institution due to thyroid pathology. A total of 246 (7.64%) patients presented with a thyroid malignancy, and 97 (39.43%) of these individuals were diagnosed with TMC; 37 (38.14%) patients exhibited ITMC and 60 (61.86%) exhibited NITMC. All 37 (100.00%) patients with ITMC exhibited a papillary type of cancer. In the NITMC group, 1 (1.67%) patient presented with follicular microcarcinoma, 1 (1.67%) individual with papillary- and follicular-type microcarcinoma, 1 (1.67%) individual with medullary microcarcinoma, and the remaining 57 (95.00%) patients presented with papillary microcarcinoma. The number of younger patients (<45 years old) was higher in the NITMC group, but this difference was not significant ( $P=0.205$ ). In all patients with ITMC, ultrasound-guided fine-needle aspiration biopsy did not reveal malignant processes. In the NITMC group, the number of larger tumors (>5 mm) was significantly higher compared with that in the ITMC group ( $P<0.001$ ). ITMC was significantly associated with multinodular goiter (MNG) ( $P<0.001$ ). Amongst the NITMC group, 18.33% of patients presented with cervical lymph node involvement ( $P<0.001$ ). Overall, the incidence of TMC is high, and consists of ITMC and NITMC, although the prevalence of NITMC is higher than that of ITMC. The majority of ITMCs and NITMCs are composed of a papillary

type of cancer. The majority of ITMCs have dimensions  $\leq 5$  mm in diameter and are significantly associated with MNG. In comparison with ITMC, NITMC more often presents with aggressive features such as cervical lymph node metastases, so the surgical approach to this tumor should be more radical.

## Introduction

The prevalence of thyroid cancer (TC) is rising (1). In Poland in 2000, the number of new cases of this malignancy amounted to 1,457 individuals, while in 2010, this number was 2,192 individuals (1,808 women and 384 men). TC accounts for 2.6 and 0.5% of all oncological diseases in women and men, respectively (2). In other countries, its prevalence varies from 2-36%, which supports the hypothesis that the incidence of TC depends on the geographical region (3). During the last two decades, the morbidity rate of TC in Poland has markedly increased (2).

One specific type of this malignancy is thyroid microcarcinoma (TMC). According to the World Health Organization, TMC is defined as TC measuring  $\leq 10$  mm at its greatest dimension (1). The clinical and pathological significance of TMC is widely debated. It is common for TMC to be diagnosed upon histopathological examination after surgery that has been performed for presumed benign thyroid disease (4).

The prevalence of incidental TMC (ITMC) is variable, ranging from 4.6-100% of TMCs in the general population (5,6). In multinodular goiter (MNG), ITMC has been observed in 2-15.2% of cases (7). The different results of the prevalence of ITMC are likely observed due to the various geographical regions, but also due to variable use of ultrasonography and ultrasound-guided fine needle aspiration biopsy (UG-FNAB), and the different experience levels of researchers (8). Regardless of diagnostic method, it has been suggested that a constantly increasing incidence of TMC is present in the general population (9). Cappelli *et al* (10) noted that the prevalence of ITMC in patients who underwent UG-FNAB with negative results for the detection of TC was 1.24%.

A number of studies have shown that an increasing number of patients surgically treated for presurgically diagnosed TC had a tumor size <5 mm (4-7,9); this may therefore be the reason for the constant increase in the prevalence of TMC. With regard to this malignancy, another specific type of thyroid tumor has been distinguished; these tumors are not

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evident clinically, are <1 cm in diameter and are found after lymph node biopsy or as an incidental finding upon autopsy examinations (11). The tumors are described as occult TMC. The high incidence of TMC found upon autopsy studies (up to 35%) may suggest that the majority of these tumors exhibit benign behavior (12).

Generally, it is known that the papillary type of TMC follows a benign clinical course, however, the proper therapeutic management in these tumors is a subject of debate. It has been suggested that there are three biologically different types of papillary TMC (PTMC) and that they should be treated differently (13). The first type consists of an incidentally detected PTMC without any symptoms, and whose clinical course is excellent (12,13). Conservative follow-up is indicated in these carcinomas (13). The second type involves the early stage of the usual low-risk PTMC, and the third type comprises high-risk cancer and is clinically symptomatic (11,13). The treatment of the aforementioned carcinomas varies from a lobectomy to a total thyroidectomy with or without radioiodine therapy (12-14). Küçük *et al* (12) suggested that the non-incidental papillary type of TMC should be treated as a conventional carcinoma with a total thyroidectomy, followed by radioiodine therapy in certain cases. Therefore, the widely debated clinical scenario concerns the proper surgical treatment of TMC recognized after surgery. When a primary surgical procedure is radical, further management may be required. Similarly, if the initial surgery is non-radical a radicalization may be required later on, which is resection of the remnant thyroid tissue after primary surgery. Occasionally, however, a 'borderline' situation occurs and a dilemma is raised. Therefore, therapeutic protocols and follow-up algorithms require modification (14). The present study aimed to compare ITMC and NITMC in order to assess the differences in the incidence, diagnostic results, clinicopathological characteristics and surgical treatments.

## Patients and methods

**Patients and approval.** The present study was a retrospective chart review of 3,218 patients consecutively admitted and surgically treated in the 1st Department and Clinic of General, Gastroenterological and Endocrine Surgery (Wrocław Medical University) between January 1, 2008, and November 30, 2014, due to the presence of thyroid tumors. For histopathological examination and immunohistochemical analysis (IHC), hematoxylin and eosin stained sections were evaluated by two independent pathologists to confirm the diagnosis of TMC (according to the World Health Organization Classification system) (1) and the AJCC/UICC 2010 staging system (6). For IHC, 4- $\mu$ m-thick sections were cut from the specimens. Each slide was immunostained with monoclonal antibodies against cytokeratin-19 (Dako, Glostrup, Denmark). IHC was performed using the EnVision™ FLEX kit (Dako) and the chromogen 3,3'-diaminobenzidine as a substrate. Finally, all slides were counterstained with Mayer's hematoxylin according to the manufacturer's protocol. All immunostaining was evaluated by two pathologists using a BX-41 light microscope (Olympus Corporation, Tokyo, Japan). The study was approved by the Bioethics Committee of Wrocław Medical University (Wrocław, Poland). Demographic data, diagnostic

results, clinical and histopathological characteristics, surgical treatment and necessity of reoperation were evaluated. As a main presurgical diagnostic test, all patients in the ITMC and NITMC groups underwent UG-FNAB.

**Statistical analysis.** The statistical significance of the differences in patient age between the ITMC and NITMC groups was verified with the aid of a t-test, and the statistical significance of the differences in the proportions of studied subclasses between the ITMC and NITMC groups was defined with the aid of the  $\chi^2$  test or Fisher's exact test (when the subclass size was <5). The statistical analysis was performed with the use of Statistica 7.1 (Dell Software, Tulsa, OK, USA) and PAST version 1.86b software (folk.uio.no/ohammer/past/terms.html).

## Results

**Patient cohort and demographic characteristics.** A total of 246 (7.64%) patients with thyroid malignancy were evaluated (out of 3,218 patients with benign and malignant thyroid tumors), and 97 (3.01% of total thyroid pathology; 39.43% of TC patients) of these were diagnosed with TMC. In this homogenous group were 37 (38.14%) patients with ITMC and 60 (61.86%) with NITMC. There were 33 (89.19%) females and 4 (10.81%) males in the ITMC group, and 57 (95.00%) females and 3 (5.00%) males in the NITMC group. The mean ages ( $\pm$ standard deviation) of the patients in the ITMC and NITMC groups were 51.45 ( $\pm$ 13.026) and 46.93 ( $\pm$ 15.317), respectively; this difference was not statistically significant.

**Pathological characteristics.** All 37 (100.00%) patients in the ITMC group exhibited a papillary type of cancer. In the NITMC group, 1 (1.67%) patient presented with a follicular type of TMC, 1 (1.67%) with a tumor composed of a papillary and follicular type of cancer, and 1 (1.61%) with a medullary type of TMC. The remaining 57 (95.00%) patients presented with a papillary type of TMC.

**Clinical characteristics.** In all 60 (100.00%) patients with NITMC, the diagnosis of suspected malignancy was estimated on the basis of UG-FNAB. In all 37 (100.00%) individuals with ITMC, UG-FNAB procedures did not reveal malignant processes. The number of younger patients (<45 years old) was higher in the NITMC group than in the ITMC group, but this difference was not statistically significant ( $P=0.20$ ). In the NITMC group, the proportion of patients with larger tumors (>5 mm) was significantly higher compared with that in the ITMC group ( $P<0.001$ ). The tumors size of the patients with ITMC and NITMC estimated upon histopathological examination (pT) are presented in Table I. ITMC was significantly associated with MNG ( $P<0.001$ ). Amongst the NITMC group, 11 (18.33%) patients presented with cervical lymph node involvement (pN1a) ( $P<0.001$ ).

All analyzed data, together with detailed results of the statistical analysis, are presented in Table II.

## Discussion

The prevalence of ITMC is rising and ranges from 4.6-100% of TMCs in the general population (5,6). The American

Table I. Size of the tumors (ITMC vs. NITMC) estimated upon histopathological examination (pT).

Type of cancer	Tumor size, mm										Total
	≤5 mm					>5 mm					
	≤1	1.1-2	2.1-3	3.1-4	4.1-5	5.1-6	6.1-7	7.1-8	8.1-9	9.1-10	
ITMC, n											
Papillary	2	3	3	6	8	4	1	4	2	4	37
NITMC, n											
Papillary	0	0	1	3	5	8	6	8	9	17	57
Follicular	0	0	0	0	0	0	0	0	0	1	1
Papillary/follicular	0	0	0	0	0	0	0	0	0	1	1
Medullary	0	0	0	0	0	1	0	0	0	0	1
Total, n (%)	31 (31.96)					66 (68.04)					
ITMC, incidental thyroid microcarcinoma; NITMC, non-incidental thyroid microcarcinoma.											

Thyroid Association (ATA) (15) and the American Association of Clinical Endocrinologists suggest that small nodules (≤10 mm in diameter) should be biopsied only when clinical and ultrasound characteristics such as microcalcifications, irregular margins, a history of neck and head irradiation, or a positive history for family cancer are present (15-17). This recommendation should decrease the number of ITMC cases and increase the diagnosis of NITMC cases. The 2015 ATA TC management guidelines accept an active surveillance management approach as an alternative to immediate UG-FNAB and surgery in such nodules and also in the cytologically confirmed very low risk papillary type of TMC (18). However, the ATA guidelines provide no specific recommendation regarding the selection of the patients who can be qualified to an active surveillance management approach. One previous study suggested that solitary nodules of <10 mm in diameter should be treated as potentially malignant tumors (19). The study also suggested that nodules ≤2 mm in diameter may be biopsied too, as often sufficient cytological material can be obtained. In the present study, in the NITMC group, the smallest nodule in which UG-FNAB was successfully performed, sufficient diagnostic material was obtained and a malignant process was revealed, measured 3 mm in diameter (Table I). Generally, the median size of TMC in each patient varies from 4.1-8.0 mm in diameter, but cases of microcarcinoma that have a size <1 mm have also been described (20). In the present study, in the ITMC group, 3 cases with a tumor size of 1.5 mm and 2 patients with a TMC measuring 1 mm in diameter were evaluated. All these tumors were of papillary type. Noguchi *et al* (19) presented an autopsy study of the thyroid gland of patients from different geographical areas, and revealed the higher prevalence of TMCs 1-3 mm in diameter versus those 4-9 mm in diameter, accounting for 50.4 and 27.3% of cases, respectively. The study suggested that this could be the result of the 'arrest of the growth' of the papillary type of TMC. Notably, Fukunaga and Yatani (20) described the sclerosing process within PTMCs. This study suggested that the process was a defensive mechanism of tumor growth. This may be the reason that this variant of PTMC is rarely

observed in the group of larger PTMCs. In the present study, it was estimated that smaller tumors (≤5 mm) were significantly associated with ITMC. In the ITMC group of patients, tumors ≤5 mm in size were diagnosed in 22 (59.46%) individuals. In the NITMC group of patients, tumors ≤5 mm in diameter were only diagnosed in 9 (15.00%) individuals (P<0.001).

The mean age at diagnosis of patients with ITMC and NITMC has been widely reported (21). The younger age of <45 years is often associated with NITMC. In the present study, in the group of patients with NITMC, there was a higher number of patients aged <45 years compared with the number in the ITMC group, but this difference was not statistically significant (36.67 vs. 24.32%, respectively; P=0.205).

The majority of TMC is PTMC, which accounts for 65-99% of all cases. The follicular type has been found in 0.3-23.6% of all cases (21). In the present study, PTMC accounted for 96.91% of all TMCs. In the group of ITMC all 37 (100%) tumors were of the papillary type. Non-papillary TMC types were observed in all NITMC cases; this group consisted of 1 (1.67%) patient with the follicular type, 1 (1.67%) individual with a tumor composed of the follicular and papillary type, and 1 (1.67%) patient with the medullary type of TMC. This last tumor measured 6 mm in diameter and was recorded in a 49-year-old female with TMC diagnosed prior to surgery (NITMC group).

In two different studies performed at different times, Pellegriti *et al* (11) and Lupoli *et al* (22) each described familial cases of TMC. Each study noted that PTMC may be observed in members of the same family, reporting 7 and 10 familial cases, respectively. Lupoli *et al* (22) suggested that familial cases of TMC are more aggressive than non-hereditary cases, but this was not confirmed by other studies. Certain studies confirmed that the outcomes of the familial type of papillary TC, compared with PTMC, differed from that of sporadic tumors, so more invasive surgery was recommended in this type of malignancy (23,24). With regard to familial and sporadic TMC, the complete opposite was observed; familial PTMC was revealed to be less aggressive, and less invasive surgical treatment was indicated for consideration. In the present study,

Table II. Demographic and clinicopathological characteristics of patients with ITMC (n=37) vs. NITMC (n=60).

Parameter	ITMC	NITMC	Statistics and significance
Age in years, mean $\pm$ SD	51.46 $\pm$ 13.03	46.93 $\pm$ 15.32	t-test: t=-1.49; df=59; P=0.138
Younger/older, n (%)			$\chi^2$ test: $\chi^2=1.60$ ; df=1; P=0.205
<45 years	9 (24.32)	22 (36.67)	
$\geq$ 45 years	28 (75.68)	38 (63.33)	
Gender, n (%)			Fisher's exact test: P=0.422
Female	33 (89.19)	57 (95.00)	
Male	4 (10.81)	3 (5.00)	
UG-FNAB, n (%)			
Suspicion	0 (0.00)	60 (100.00)	
No suspicion	37 (100.00)	0 (0.00)	
Tumor size, n (%)			$\chi^2$ test: $\chi^2=20.80$ ; df=1; P<0.001
$\leq$ 5 mm	22 (59.46)	9 (15.00)	
>5 mm	15 (40.54)	51 (85.00)	
Type of lesion, n (%)			Fisher's exact test: P<0.001
MNG	36 (97.30)	35 (58.33)	
Solitary tumor	1 (2.70)	25 (41.67)	
Histopathology, n (%)			Fisher's exact test: P=0.704
Papillary	37 (100.00)	57 (95.00)	
Papillary/follicular	0 (0.00)	1 (1.67)	
Follicular	0 (0.00)	1 (1.67)	
Medullary	0 (0.00)	1 (1.67)	
Multifocality, n (%)			Fisher's exact test: P=0.122
Solitary	35 (94.59)	49 (81.67)	
Multifocal	2 (5.41)	11 (18.33)	
Familial cases, n (%)			
Yes	0 (0.00)	0 (0.00)	
No	37 (100.00)	60 (100.00)	
Type of surgery, n (%)			$\chi^2$ test: $\chi^2=40.66$ ; df=1; P<0.001
Radical	9 (24.32)	53 (88.33)	
Non-radical	28 (75.68)	7 (11.67)	
Reoperation required, n (%)			Fisher's exact test: P=0.080
No	31 (83.78)	57 (95.00)	
Yes	6 (16.22)	3 (5.00)	
Cervical lymph node involvement, n (%)			Fisher's exact test: P<0.001 (pN0 vs. pN1a-pNx)
pN0	2 (5.41)	49 (81.67)	
pN1a	0 (0.00)	11 (18.33)	
pN1b	1 (2.70)	0 (0.00)	
pNx	34 (91.89)	0 (0.00)	
Total	37 (38.14)	60 (61.86)	

Data is presented as the mean  $\pm$  standard deviation. ITMC, incidental thyroid microcarcinoma; NITMC, non-incidental thyroid microcarcinoma; UG-FNAB, ultrasound-guided fine-needle aspiration biopsy; MNG, multinodular goiter; df, degrees of freedom.

in the two groups of patients (ITMC and NITMC), no familial cases were observed. All TMCs were sporadic types.

Sakorafas *et al* (25) suggested that amongst all the clinical and histopathological characteristics of ITMC and NITMC, for further evaluation, the most important characteristics are multifocality and bilaterality. These histopathological features

are observed in 7.1-56.8 and 2.9-48% of ITMC and NITMC cases, respectively. In the present study, multifocality was observed in 5.4% of ITMC cases and in 18.3% of NITMC cases. This difference was statistically significant (P<0.001). The next significant characteristic is lymph nodes metastases, which have been observed in 2-62.1 and 0-64% of ITMC and



NITMC cases, respectively (26). In the present study, cervical lymph node involvement was observed in 2.70 and 18.33% of ITMC and NITMC cases, respectively. Ito *et al* (27) stated that ~40% of patients with the papillary type of NITMC possessed lymph node metastases, as diagnosed after surgery, even though all patients had been classified as cN0 prior to surgery. Distant metastases are observed extremely rarely and account for ~0.37% of cases (8). In the present patient groups, this characteristic was not observed. Certain studies reported that cervical and distant metastases occurred more often in patients with NITMC than in patients with ITMC (28). Ito *et al* confirmed that the incidence of lymph node metastases is higher in patients with NITMC compared with in those with ITMC (27), which was also confirmed in the present study. Another study added that patients with larger ITMC and NITMC tumors had a higher probability of the presence of lymph node metastases at the time of diagnosis than patients with smaller tumors (29). Fu *et al* (30) suggested that the tumor size had a prognostic value in the papillary type of ITMC and NITMC, and that a larger size was associated with a higher risk of central neck lymph node metastases. In the present patients with NITMC, of the 11 (18.33%) individuals with cervical lymph node involvement, 6 (10%) patients presented with tumors >5 mm in diameter. All of these patients had metastases to the central lymph node compartment. Kim *et al* (31) revealed that the factors predictive of central lymph node metastases in patients with this type of malignancy differed by age. The study suggested that the size of such a tumor was an independent predictor of subclinical central lymph node involvement only in patients aged ≥45 years. In the present study, in the group of patients with central lymph node metastases, 6 (54.55%) patients were <45 years and all of these patients were in the NITMC group. In total, 5 (8.33%) patients in the NITMC group and 1 (2.70%) individual in the ITMC group were ≥45 years old. Zhang *et al* (32) revealed that male gender and tumor size (≥6 mm) were risk factors of central compartment lymph node metastases, and therefore recommended a prophylactic central lymph node dissection in patients with this type of TMC and the aforementioned risk factors. Another study (33) suggested that a central compartment lymph node dissection should be considered in all patients with NITMC, as even in patients without these risk factors, the incidence of central lymph node metastases is higher than expected. The study also stated that the complication rate of radical surgery with central lymph node dissection should be at an acceptable level.

One previous study indicated that the higher prevalence of lymph node metastases is connected with the follicular variant of PTMC (28). It was suggested that the coexistence of Hashimoto's thyroiditis is protective for lymph node metastases. In the present study, 1 (1.67%) patient with the follicular type of NITMC and 1 (1.67%) patient with NITMC composed of the papillary and follicular types were observed. These 2 patients presented with cervical lymph node involvement. No inflammatory processes were observed within the thyroid tissues in either group.

A meta-analysis by Mehanna *et al* (34) revealed the existence of a minimum of two different entities with regard to the papillary types of ITMC and NITMC. It was suggested that incidental tumors had distinct clinical characteristics and a much lower recurrence rate than non-incidental lesions.

Furthermore, it was suggested that management protocols for these two different groups of cancers should be reconsidered. ITMCs have significantly fewer aggressive characteristics than conventional TC. NITMC, which presents with aggressive features like conventional TC, should be treated in a similar manner and a routine total thyroidectomy with central lymph node compartment dissection should be performed (35). Similar observations were noted in a study by Vasileiadis *et al* (36), which recorded 339 individuals with the papillary type of TMC, accounting for 12% of all patients who underwent surgery for thyroid disease. It was noted that bilaterality, autoimmune thyroid disease, a tumor size of >5 mm in diameter, multifocality and lymph node metastasis were significantly associated with non-incidental tumors. It was concluded that the majority of NITMCs (papillary type) present at the time of diagnosis possessed one or more risk factors, including multifocality, bilaterality or greater tumor size; therefore, a total thyroidectomy is recommended, followed by adequate exploration of the central lymph node compartment to provide a safe therapeutic approach. Another study suggested that tumor size, a non-incidental diagnosis and neck node metastasis at the time of diagnosis were independent risk factors for aggressive NITMC (6). A further study revealed that NITMC tumors are associated with a higher cancer stage at the time of diagnosis, and therefore more invasive behavior and a higher tendency for recurrence. As a result, aggressive surgical treatment was recommended in cases of such tumors (37). In the present study, 60 (100.00%) patients with NITMC qualified to undergo radical surgery with central lymph node dissection. Of these, 53 (88.33%) patients underwent a radical procedure and 7 (11.67%) of underwent a non-radical procedure. In the group of patients with ITMC, only 9 (24.32%) patients underwent a total thyroidectomy. In total, 3 (5.00%) patients with NITMC and 6 (16.22%) patients with ITMC required radicalization, which is resection of the remnant thyroid tissue after primary surgery.

In the literature, ITMC is significantly associated with MNG, while NITMC is often found within normal or Hashimoto's thyroiditis (38,39). In the present study, ITMCs were significantly associated with MNG ( $P<0.001$ ) and only 1 (2.70%) patient in this group underwent surgery due to a solitary tumor. No coexisting autoimmune process was observed within the thyroid gland in either the ITMC or NITMC group.

Notable observations concerning the surgical treatment of ITMC and NITMC were presented by Gschwandtner *et al* (40). To evaluate a less-radical approach, the study revealed that a non-incidental finding, nodal metastases at presentation, a young age, aggregate tumor size and subcapsular tumor localization were risk factors for lymph node metastases, and therefore did not recommend surgical treatment. Multifocality, gender, maximum tumor size and the extent of surgery were not noted to be relevant factors. In the majority of PTMC cases, even with multifocality, a limited surgical approach without completion thyroidectomy, lymphadenectomy or radioiodine treatment was recommended as sufficient management. However, it was stated that in cases of intra- or pre-operative clinically suspected lymph node metastases, or in cases with post-operatively diagnosed risk factors, a standard radical procedure should be performed (40). In the present study,

in the group of patients with NITMC, 57 (95.00%) radical surgeries were performed without the necessity of a second surgery. In the group of patients with ITMC, radical procedures were performed in 31 (83.78%) cases, and 6 (16.22%) individuals required radicalization, due to coexisting risk factors, including multifocality or bilaterality. Only 3 (5.00%) patients in the NITMC group required a reoperation.

The present study concluded that: i) The incidence of TMC is high and consists of ITMC and NITMC cases; ii) the prevalence of NITMC is higher than that of ITMC; iii) the majority of ITMCs and NITMCs are of papillary type; iv) the majority of ITMCs have a diameter  $\leq 5$  mm; v) ITMC is significantly associated with MNG; and vi) NITMC compared with ITMC often presents with aggressive features such as cervical lymph node metastases, therefore a surgical approach in this tumor should be more radical.

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