Clinical and histopathological characteristics of patients with incidental and nonincidental thyroid cancer

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Abstract

Introduction: Thyroid nodules (TNs) are a common pathology. Their prevalence increases with age. Some of them are suspected of malignancy and qualified for surgery. Sometimes their malignant nature is detected incidentally after a surgical procedure. The aim of the study is to analyze clinical and histopathological characteristics of patients with incidental and nonincidental thyroid carcinoma (ITC vs. NITC).

Material and methods: The case records of 3,241 patients with solitary and multiple TNs who were treated consecutively between 2008 and 2014 were analyzed retrospectively. After the final selection 235 (7.25%) patients were included in the study (202 females and 33 males, mean age: 52.9 $\pm$16.5 years). Seventy-five (31.91%) cases were incidentally diagnosed and 160 (68.09%) were diagnosed before surgery.

Results: We did not observe any differences in age, gender or stage of disease at the time of diagnosis between the patients with ITC and NITC (p = 0.366, p = 0.850, p = 0.226 respectively). The occurrence of solitary nodules in patients with NITC was significantly higher compared to patients with ITC (p < 0.0001). There were no differences in histopathological types of thyroid cancer (TC). The logistic regression analysis showed that solitary TC was an independent predictor of NITC (p < 0.0001).

Conclusions: There are no differences in gender, age or histopathological type of cancer in patients with ITC and NITC. Papillary TC is the predominant type in both groups. Incidence of TC in a solitary nodule is significantly higher in NITC than ITC. Solitary type of TC is an independent predictor of NITC. The prevalence of ITC is associated with multifocal type of TC.

Key words: thyroid nodules, incidental, non-incidental thyroid carcinoma.

Introduction

Thyroid nodules (TNs) are a very common pathology in the general population. They are found in 19–67% by means of ultrasonography examination [1]. Their detection is increasing with the widespread use of this diagnostic method [2]. Although there is not a recommendation for or against thyroid ultrasound screening for clinically silent thyroid lesions in individuals without any risk of malignancy, it can be observed that ultrasonography examination is widespread and accessible, so in the

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majority of asymptomatic individuals TNs are diagnosed [3, 4]. Anil *et al.* [5] noticed the phenomenon that replacing palpating examination with an ultrasonography probe in elderly patients would result in "an epidemic" of TNs.

No imaging modality can accurately predict the nature of every nodule, and none of the ultrasonography characteristics have 100% accuracy in detecting or excluding thyroid cancer (TC) [6]. The discovery of the nodule leads to the next step of tumor evaluation and thyroid stimulating hormone (TSH) measurement is recommended. If TSH levels are not suppressed, then fine needle aspiration biopsy (FNAB) is performed. It has been claimed that the increasing use of FNAB with high-resolution ultrasonography makes thyroid malignancy diagnosis more frequent and at an earlier stage of disease [7]. Papini *et al.* suggest [8] that this is one reason why in the last decade we can observe smaller sizes of newly diagnosed TCs [8]. Some authors suggest that the risk of malignancy in patients with multinodular goiter is very high and unsuccessful, inconclusive or suspicious results of FNAB mandate further investigation [9]. For example, Campbell *et al.* [10] state that the incidence of TC in patients with multinodular goiter and the "negative" result of FNAB (without suspicion of malignancy) is significant [10]. The same authors suggest that all "negative" specimens obtained from the FNAB procedure in patients with multinodular goiter should be reviewed by an experienced cytopathologist to reduce the risk of undetected TC.

During the last 20 years in Poland a significant increase in the number of new cases of TC has been observed. In 2010 we recorded 2192 new cases of TC [11]. Especially, a lot of small TCs, known as microcarcinomas, are diagnosed after surgery performed for benign thyroid pathology. Such tumors are called incidental thyroid cancers (ITCs), and if they are smaller than or equal to 1 cm they are called incidental microcarcinomas [12]. Many authors agree that smaller TCs have a better prognosis than larger ones [13], but it must be remembered that some very small TCs, even less than 1 cm in diameter, have an unfavorable prognosis [14]. Some authors call these very aggressive tumors "real thyroid carcinoma" [15, 16].

Many patients are qualified for surgery due to solitary or multiple thyroid nodules with or without suspicion of malignancy. The incidence of carcinoma in TNs is approximately estimated as 9.2–13% [8, 17, 18]. Some authors suggest that the presence of multifocal nodules decreases the possibility of incidence of TC [19]. In multinodular goiter the most suspicious nodules for TC are those with high-risk sonographic features, and for that reason they should be aspirated [1]. Others say that the prevalence of TC in patients with non-palpable or incidentally diagnosed as TNs is the same as in those with palpable tumors [8, 18, 20]. On the other hand, when we compare the prevalence of TNs and the prevalence of ITC, we can describe this malignancy as a rare occurrence [5].

The most common type of this malignancy is papillary carcinoma, which accounts for about 85–90% of all TCs [21]. Papillary TC has a good prognosis and its mortality rate is less than 10% [22]. Other types include follicular, medullary and anaplastic cancers. The mortality and morbidity rates of papillary TC are low compared to other cancers, but they increase with age and stage of the disease at the time of the diagnosis [23]. There is a debate regarding the clinical significance of small thyroid carcinomas, and most authors suggest that they represent a subclinical disease with no mortality or morbidity and propose a conservative approach such as follow-up and not surgery [24].

Because of the fact that in the very near future we may observe high prevalence of ITC, it seems very important and useful to establish whether there are any clinical and histopathological differences in patients with ITC and nonincidental thyroid carcinoma (NITC).

To evaluate this issue we analyzed retrospectively the medical documentation of patients with ITC and NITC.

Material and methods

The case records of 3,241 patients with solitary and multiple TNs, who were treated consecutively between January 2008 and December 2014 at the Department and Clinic of General, Gastroenterological and Endocrine Surgery of Wroclaw Medical University, were analyzed retrospectively. After the final selection, 235 (7.25%) patients were included in the study. There were 202 females and 33 males, with a mean age of 52.9 ±16.5 years. In this TC group 75 (31.91%) patients had ITC and 160 (68.09%) had NITC. We analyzed and compared the clinical and histopathological characteristics of patients with ITC and NITC. All patients lived before the operation in geographical areas that were iodine sufficient. All patients included in the study had FNAB performed before surgery. All cytological and next histopathological specimens were reviewed by an experienced pathologist, and final diagnoses were graded according to the World Health Organization thyroid malignancy classification.

Statistical analysis

The numbers and percentages were calculated for qualitative variables, and the means and standard deviations were calculated for quantitative

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variables. Where appropriate, groups comparisons were analyzed using the χ^2 test and Student's *t*-test.

The logistic regression analysis was used for the determination of independent predictors of NITC for solitary TNs, multifocal TNs, female gender and age below 45 years. Odds ratios and 95% coefficient intervals (95% CIs) were calculated.

All values of $p < 0.05$ were considered statistically significant. The statistical analyses were performed using Statistica 10.0 software (StatSoft Inc., Tulsa, OK, USA).

Results

Among 3,241 patients operated on for thyroid nodules, 160 (4.94%) had TC diagnosed before surgery (NITC group) and 75 (2.31%) had TC diagnosed by postoperative histopathological examination (ITC group). Among 235 TC subjects, the rate of NITC patients (68.1%) was twice as high as the number of patients with ITC (31.9%).

Demographic and clinicopathological characteristics of patients with ITC and NITC are demonstrated in Table I. Incidental thyroid cancers and NITC groups were similar in terms of gender, age and histological type of cancer. Papillary TC was predominant, and it was diagnosed in 84.8% of patients with NITC and in 82.7% of patients with ITC. Incidence of solitary nodules in patients with NITC was significantly higher in comparison to ITC patients ($p < 0.0001$). The number of radical procedures (total thyroidectomy) performed in the group of patients with NITC was significantly higher than in the ITC group ($p < 0.0001$), so the number of required reoperations in the ITC group was significantly higher than in the NITC group ($p < 0.0001$).

There were no differences between study groups in terms of stage of disease and primary tumor progression ($p > 0.05$). Exclusion of metastases to lymph nodes and other organs was mainly demonstrated in patients with NITC ($p < 0.0001$). The pathological N parameter has not been determined in over 90% of patients with ITC. Therefore, the interpretation of results presented in Table I is uncertain.

Logistic regression analysis was used to determine which demographic and clinical parameters may be associated with TC diagnosis before surgical treatment. The results confirmed that solitary type of TC was an independent predictor of NITC, and that prevalence of ITC is connected with type of multifocal TC ($p < 0.0001$ for both, Table II).

Discussion

Since 1980, when ultrasonography examination and ultrasound guided FNAB (UG-FNAB) were widely introduced to clinical evaluation of thyroid pathology, a progressive increase in the prevalence of ITC has been observed [25]. Some authors estimated ultrasound features of increased malignancy risk of thyroid nodules, such as microcalcifications, low echogenicity of lesions or predominance of the anterior-posterior dimension over the lateral dimension of lesions [1, 4, 26, 27]. In the opinion of many authors, large nodules or dominant ones have higher risk for malignancy than small lesions, but it is not the rule. Some, very small nodules might turn out to be microcarcinomas and be discovered after surgery as ITC. Pelizzo *et al.* [28] noted that the prevalence of carcinoma less than or equal to 5 mm compared with those measuring 6–10 mm increased in the period between 1990 and 2001. The same situation might exist in the remaining TCs, larger than 1 cm in diameter. The majority of them are diagnosed as ITC, so some authors try to estimate the clinical factors of high risk for malignancy of TNs [1, 4, 29, 30]. The most often analyzed are age, gender, type of thyroid nodule (solitary or multiple), enlarged lymph nodes and diameter of the tumor. If there are any suspicions of malignancy in some nodules (lymph node involvement, ultrasound features of increased malignancy risk or high blood level of calcitonin), each of them should be further evaluated and UG-FNAB should be performed [1, 4, 29].

In our study we analyzed retrospectively 3,241 patients surgically treated due to TNs. Among them we identified 235 (7.25%) cases with TC. The prevalence of ITC was lower than that observed in some other studies [31], and in our study it was estimated at 2.3%. These differences probably are due to different geographical regions, populations, ultrasound examination accuracy and reliability of FNAB. ITCs are in the great majority papillary type, and a lot of them are less than 1 cm in diameter. In our study in the group of patients with ITC papillary type occurred in 62 (82.7%) patients, and in the group with NITC this type occurred in 134 (84.8%) cases. We also did not observe a statistically significant difference in tumor size of ITC and NITC. In the ITC group the majority of nodules were below stage pT1b (according to AJCC/UICC 2010 7th Edition) (51; 70.8%), and in the NITC group there were 103 (65.0%) such nodules ($p > 0.05$). Most ITCs are diagnosed after surgery due to multinodular goiter, fewer due to other benign thyroid pathologies. In our study we found that solitary TN is an independent predictor of TC presence, so this characteristic was observed more often in patients with NITC compared to patients with ITC (85% vs. 38.7% respectively, $p < 0.0001$).

Some authors suggest that small ITCs have benign behavior and will never spread to the regional or distant lymph nodes or organs [32]. In contrast, others have described very small TCs,

Table I. Demographic and clinicopathological characteristics of patients with incidental and nonincidental thyroid cancer (TC). Descriptive data are presented as number (percent)

Parameter	Incidental TC (n = 75)	Nonincidental TC (n = 160)	χ² test	P-value
Age:			0.82	0.366
< 45	20 (26.7)	52 (32.5)		
≥ 45	55 (73.3)	108 (67.5)		
Gender:			0.04	0.850
Female	64 (85.3)	138 (86.2)		
Male	11 (14.7)	22 (13.8)		
Type of thyroid nodules:			52.41	< 0.0001
Solitary	29 (38.7)	136 (85)		
Multifocal	46 (61.3)	24 (15)		
Type of resection:			92.91	< 0.0001
Radical	16 (21.3)	137 (85.6)		
No radical	59 (78.7)	23 (14.4)		
Reoperation needed:			113.02	< 0.0001
No	17 (22.7)	146 (91.3)		
Yes	58 (77.3)	14 (8.7)		
Type of cancer:			1.719	0.787
Papillary	62 (82.7)	134 (84.8)		
Follicular	8 (10.7)	10 (6.3)		
Medullary	2 (2.7)	5 (3.2)		
Undifferentiated	2 (2.7)	7 (4.4)		
Sarcoma	1 (1.3)	2 (1.3)		
pTNM stage:			4.34	0.226
I	53 (70.7)	107 (66.9)		
II	14 (18.7)	22 (13.8)		
III	6 (6.7)	12 (7.5)		
IV	3 (4.0)	19 (11.9)		
pT:			8.70	0.121
pT1a	36 (50)	60 (38.0)		
pT1b	15 (20.8)	43 (27.0)		
pT2	11 (15.3)	24 (15.2)		
pT3	7 (9.7)	10 (6.3)		
pT4a	0 (0.0)	11 (7.0)		
pT4b	3 (4.2)	10 (6.3)		
pN:			140.04	< 0.0001
pN0	4 (5.3)	106 (66.3)		
pN1a	1 (1.3)	23 (14.4)		
pN1b	1 (1.3)	12 (7.5)		
pNx	69 (92.0)	19 (11.9)		
pM:			144.03	< 0.0001
pM0	5 (6.7)	136 (85.0)		
pM1	0 (0.0)	5 (3.1)		
pMx	70 (93.3)	19 (11.9)		

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Table II. Logistic regression model assessing independent predictors of thyroid cancer (TC) presence (NITC/ITC, 1/0). Total: χ^2 = 53.28, p < 0.0001

Variables	OR	95% CI	Wald test	P-value
Type of thyroid nodules: for solitary	8.88	4.63–17.02	43.65	< 0.0001*
Type of thyroid nodules: for multifocal	−2.22	−2.87–(−1.58)	45.91	< 0.0001*
Gender: for female	0.94	0.37–2.37	0.02	0.895
Age: for < 45 years	1.60	0.77–3.33	1.60	0.206

*NITC – non-incidental thyroid cancer, ITC – incidental thyroid cancer, *statistically significant.*

less than 1 cm in diameter, that gave local lymph node and distant metastases at the time of diagnosis [25, 33, 34]. In our study the prevalence of lymph node involvement was significantly higher in the group of patients with NITC compared to the group with ITC (p < 0.0001).

Pellegriti *et al.* [21] emphasize that some ITCs and NITCs have clinical and histopathological characteristics which determine poor prognosis. The most important are age of the patient at the time of TC diagnosis, nodule size, lymph node involvement and the presence of distant metastases. The nodule size in ITC is a very important prognostic factor. A lot of studies report low cancer recurrence rates in patients with low histopathological degree, especially less than pT1b [28, 33, 35–37]. Of course, there are some others who do not confirm this observation [21, 25]. Disease-related mortality has been observed very rarely [25, 35]. Multifocality and dimensions of ITC are also very important information, because according to them, further evaluation is planned.

In our study we noted that multifocality was observed more often in patients with ITC than in patients with NITC (61.3% vs. 15%). We did not observe significant differences in age, gender or stage of disease at the time of diagnosis between groups. Some authors emphasize a very important aspect of multifocality of ITC [33, 34]. They suggest that this specific feature may be connected with aggressiveness of this tumor. However, others have demonstrated that various intrathyroidal carcinoma foci had different RET/PTC gene rearrangements and independent clonal origins. It rather suggests that they arise as distinct tumors [38]. Some authors confirm our results and report higher prevalence of multifocality (32–40%) in ITCs [21, 25].

In our study the prevalence of NITC was two times higher than ITC (31.91% vs. 68.09%). In the opinion of some researchers, this situation is caused by the phenomenon of overdiagnosis of TC [39]. They noted that TC fulfills all criteria for overdiagnosis, but they also added that this is supported by the geographical region where the analyzed population lives.

It is still a matter of debate what surgical procedure is sufficient for ITC. Ito *et al.* [32] reported their own 3.8-year observation period of the non-operated patients with proven papillary thyroid carcinoma at a stage below pT1b. During this period they did not develop any sign of progression. In our study papillary type was dominant in patients with ITC (82.7%). Some authors suggest that surgery extension is not crucial in patients with a tumor at a stage below pT1b [32]. Other researchers propose partial thyroidectomy as a sufficient surgical procedure in cases of ITC but with a tumor at a stage below pT1b [37]. Others say that total or near total thyroidectomy in patients with ITC should be performed [21, 25, 28]. In our study in the group of patients with ITC we performed 16 (21.3%) radical (total thyroidectomy) and 59 (78.7%) non-radical procedures (subtotal thyroidectomy). After histopathological examination 58 (77.3%) individuals with ITC needed reoperation due to an insufficient primary procedure. Therefore some authors suggest that total thyroidectomy may be considered as the treatment of choice for both malignant and benign thyroid disease [40]. They add that total thyroidectomy eliminates the risk of completion thyroidectomy for ITC.

In conclusion, there are no differences in gender, age or histopathological type of cancer in patients with ITC and NITC. Papillary TC is the predominant type in patients with ITC and NITC. Incidence of TC in a solitary nodule is significantly higher in patients with NITC compared to ITC. Solitary type of TC is an independent predictor of NITC. The prevalence of ITC is associated with multifocal type of TC.

Conflict of interest

The authors declare no conflict of interest.

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