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Multi- and Unifocal Thyroid Microcarcinoma: Are There Any Differences?

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Abstract

Background. Thyroid microcarcinoma (TMC) often occurs as two or more separate *foci*, therefore a completion of primary surgery might be necessary.

Objectives. To evaluate and compare the incidence, diagnostic accuracy, clinicopathological characteristics and surgical treatment of unifocal and multifocal thyroid microcarcinoma (UTMC vs. MTMC).

Material and Methods. We retrospectively analyzed 3,218 medical records of patients consecutively admitted and surgically treated in one center due to thyroid pathology.

Results. In the end, we evaluated 246 (7.64%) patients with thyroid malignancy. Ninety-seven of them (39.43%) were diagnosed as TMC: 84 (86.59%) UTMC and 13 (13.41%) MTMC ($p < 0.0001$). All MTMC were unilateral tumors. The papillary type of cancer was found in 82 (97.62%) patients with UTMC and in 12 (92.31%) with MTMC ($p = 0.8661$). In the UTMC group, 1 (1.19%) patient had follicular and 1 (1.19%) the medullary type of TMC. 1 (7.69%) individual in the MTMC group had tumors composed of papillary and follicular cancer. The number of younger patients (age < 45) was comparable in both groups ($p = 0.825$). The trend was observed that ultrasound guided fine needle aspiration biopsy (UG-FNAB) revealed malignant processes before surgery in a greater number of patients with MTMC than UTMC (84.62% vs. 58.33%, $p = 0.131$). In the MTMC group, the number of larger tumors (> 5 mm) was greater (84.62% vs. 65.48%), however the difference was not statistically significant. Thirteen percent of patients with UTMC presented cervical lymph node involvement, compared to nearly 8% of patients with MTMC ($p = 0.298$). Disease-related mortality was not observed in either group.

Conclusions. The prevalence of UTMC was significantly higher than MTMC. The majority of UTMC and MTMC were composed of the papillary type of cancer. MTMC and UTMC were equally frequent in both age groups. The accuracy of UG-FNAB was higher in patients with MTMC. The dimensions of most UTMC and MTMC was above 5 mm. The involvement of the cervical lymph node at the time of diagnosis in both groups is comparable and not infrequent (*Adv Clin Exp Med* 2016, 25, 3, 485–492).

Key words: cancer, thyroid, multifocal, microcarcinoma.

Over the last few decades, numerous studies have described a specific type of thyroid malignancy, known as thyroid microcarcinoma (TMC). This small tumor very often occurs as two or more separate foci and unlike unifocal thyroid microcarcinoma (UTMC), is defined as a multifocal tumor, i.e. multifocal thyroid microcarcinoma (MTMC) [1].

The incidence of MTMC ranges from 15% to 36.1% of all TMC [2, 3] and, as some authors suggest, may increase [1].

The widespread use of ultrasound examination of the thyroid gland, followed by ultrasound-guided fine-needle aspiration biopsy (UG-FNAB), in the general population led to an increase in the detection of very small thyroid carcinomas [4].

The accuracy of preoperative ultrasound examination of TMC, in the opinion of some authors, is, however, still unsatisfactory [3].

Although the prognosis for TMC is thought to be excellent, the clinical importance of this tumor remains in debate. Some authors suggest a benign course of these tumors [5], but the others describe cases with local lymph node and distant metastases at the time of diagnosis [6] as well as cancer-related deaths [7]. It is considered that multifocality may be an important predictor of recurrence [8–10]. In cases of incidental MTMC, completion of primary surgery and lymph node dissection may be necessary. Moreover, the extent of surgery in unilateral MTMC is still not defined clearly [11, 12].

Because TMC is being diagnosed with increasing frequency, it seems very important to evaluate and compare the incidence, diagnostic accuracy, clinicopathological characteristics and surgical treatment of unifocal and multifocal thyroid microcarcinoma (UTMC vs. MTMC).

Material and Methods

Patient Cohort and Study Design

We retrospectively analyzed 3218 medical records of patients consecutively admitted and surgically treated due to thyroid pathology in the 1st Department of General, Gastroenterological and Endocrine Surgery, Wroclaw Medical University, between 2008 and 2013. All of the patients were staged in accordance with TNM staging criteria (tumor-node-metastasis) proposed by AJCC/UICC 2010 7th Edition [13]. Preoperative thyroid ultrasonography, UG-FNAB and cytological examinations were performed in all cases. After surgery, the final histopathological classification was performed according to World Health Organization Guidelines. Serial 2 mm sections were prepared from histopathologic specimens, and suspicious lesions were examined microscopically. Two pathologists experienced in thyroid lesions examined all of the pathology specimens to confirm the diagnosis, features of the tumor and extent of the malignant process. Patients were diagnosed as TMC if the largest tumor diameter was equal to or less than 1 cm. Subsequently, patients were categorized as UTMC if only one malignant *foci* in the thyroid gland was found during histopathological examination, or as MTMC if there were two or more foci present.

Data Analysis

The following data was compared between the two analyzed groups (UTMC vs. MTMC): Incidence, diagnostic accuracy (UG-FNAB), demo-

graphic information such as gender and age at the time of diagnosis, clinicopathological characteristics, surgical treatment and postoperative staging of tumors. For MTMCs, the dimension of the largest tumor was defined as the primary tumor size.

Statistical Analysis

The statistical analysis was conducted with the use of STATISTICA (StatSoft, Inc., USA) data analysis software, v. 12, based on the license owned by Wroclaw Medical University. In this trial, the following statistical measures were used: Arithmetical mean ($\bar{x}$) and standard deviation (SD). The Shapiro-Wilk test was used to confirm the consistency of the analyzed sample's age distribution with the normal distribution. As the distribution of the analyzed samples was not significantly different from the normal distribution of statistically identical variance, to assess eventual differences, the t -test was used. The intergroup frequency assessment was performed with the use of a χ^2 test. If the expected frequency was less than 5 or the total count was less than 50, Yate's correction or Fisher's exact test were applied.

The importance of selected independent clinical parameters as the predictive factors for explanatory variables "TC diagnosis by FNAB", "total thyroid resection" and "need of reoperation", was tested with the use of multiple logistic regression analysis.

A p -value < 0.05 was considered statistically significant, while a p value from 0.05 to < 0.10 was regarded as on the borderline of statistical significance.

Results

Among all the studied cases, 246 (7.64%) patients with thyroid malignancy (thyroid carcinoma, TC) were selected for further evaluation. Ninety-seven (39.43% of TC) were diagnosed as TMC (Table 1). There were 84 (86.59%) patients with UTMC and 13 (13.41%) with MTMC ($p < 0.0001$). The mean age of the patients with UTMC was 48.7 ± 14.8 , and with MTMC was 48.4 ± 14.0 ($p = 0.942$). All MTMCs were diagnosed as unilateral tumors. Eighty-two (97.62%) patients with UTMC had the papillary type of cancer compared to 12 (92.31%) patients with MTMC ($p = 0.864$). In the group of UTMC, 1 (1.19%) patient had follicular and 1 (1.19%) the medullary type of TMC. One (7.69%) individual in the group of MTMC had a tumor composed of papillary and follicular types. The number of younger patients (age < 45) was comparable in both groups ($p = 0.825$). The trend

Table 1. Demographic and clinicopathological characteristics of patients with unifocal and multifocal thyroid microcarcinoma. Descriptive data is presented as number (n), percentage (%) and mean $\pm$ standard deviation ($\pm$ SD)

Parameter	Unifocal thyroid microcarcinoma (n = 84)	Multifocal thyroid microcarcinoma (n = 13)	χ^2 test	p-value
Age (years)	48.7 $\pm$ 14.8	48.4 $\pm$ 14.0	T = 0.07	0.942
Age: < 45 $\geq$ 45	26 (30.95) 58 (69.05)	5 (38.46) 8 (61.54)	0.05	0.825
Gender: female male	78 (92.86) 6 (7.14)	12 (92.31) 1 (7.69)	0.25	0.614
Prediction of thyroid cancer by FNAB: yes no	49 (58.33) 35 (41.67)	11 (84.62) 2 (15.38)	2.28	0.131
Type of resection: total not total	50 (59.52) 34 (40.48)	12 (92.31) 1 (7.69)	3.92	0.047*
Reoperation needed: no yes	75 (89.29) 9 (10.71)	13 (100.0) 0 (0.0)	0.53	0.468
Type of cancer: papillary follicular papillary/follicular in one patient medullary	82 (97.62) 1 (1.19) 0 (0.0) 1 (1.19)	12 (92.31) 0 (0.0) 1 (7.69) 0 (0.0)	0.29	0.864
pTNM stage: I II III IV	83 (98.81) 0 (0.0) 1 (1.19) 0 (0.0)	13 (100.0) 0 (0.0) 0 (0.0) 0 (0.0)	1.17	0.280
pT: pT1 pT2 pT3 pT4 pTm	84 (100.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	13 (100.0) 0 (0.0) 0 (0.0) 0 (0.0) 13 (100.0)	–	–
pN: pN0 pN1a pN1b pNx	41 (48.81) 10 (11.90) 1 (1.19) 32 (38.10)	10 (76.92) 1 (7.69) 0 (0.0) 2 (15.38)	3.68	0.298
pM: pM0 pM1 pMx	43 (51.19) 1 (1.19) 40 (47.62)	11 (84.62) 0 (0.0) 2 (15.38)	5.12	0.077**
Tumor size 1–5 mm 6–10 mm	29 (34.52) 55 (65.48)	2 (15.38) 11 (84.62)	1.12	0.290

FNAB – fine-needle aspiration biopsy; * – statistically significant difference; ** – on the border of statistical significance.

Table 2. Characteristics of patients with FNAB diagnosis (cancer yes/cancer no) in two groups: Unifocal and multifocal thyroid microcarcinoma. Descriptive data is presented as number (n), percentage (%) and mean $\pm$ standard deviation ($\pm$ SD)

Parameter	Unifocal thyroid microcarcinoma			Multifocal thyroid microcarcinoma		
	FNAB – “cancer yes” n = 49	FNAB – “cancer no” n = 35	p-value	FNAB – “cancer yes” n = 11	FNAB – “cancer no” n = 2	p-value
Age (years)	45.53 $\pm$ 15.72	51.74 $\pm$ 12.87	0.111	48.72 $\pm$ 13.9	46.50 $\pm$ 20.5	0.921
Age:			0.263			0.670
< 45	18 (36.73)	8 (22.86)		4 (36.36)	1 (50.0)	
$\geq$ 45	31 (63.27)	27 (77.14)		7 (63.64)	1 (50.0)	
Gender:			0.669			0.318
female	46 (93.88)	32 (91.43)		11 (100.0)	1 (50.0)	
male	3 (6.12)	3 (8.57)		0 (0.0)	1 (50.0)	
Type of resection			< 0.00001			0.318
total	42 (85.71)	8 (22.86)		11 (100.0)	1 (50.0)	
not total	7 (14.29)	27 (77.14)		0 (0.0)	1 (50.0)	
Reoperation needed:			0.211			–
no	46 (93.88)	5 (82.86)		11 (100.0)	2 (100.0)	
yes	3 (6.12)	3 (17.14)		0 (95.2)	0 (0.0)	
Type of cancer:			0.481			–
papillary	47 (97.91)	35 (97.22)		10 (90.91)	2 (100.0)	
follicular	0 (0.0)	1 (2.78)		0 (0.0)	0 (0.0)	
papillary/follicular						
in one patient	0 (0.0)	0 (0.0)		1 (9.09)	0 (0.0)	
medullary	1 (2.09)	0 (0.0)		0 (0.0)	0 (0.0)	
pTNM stage:			0.864			–
I	48 (97.96)	35 (100.0)		11 (100.0)*	2 (100.0)	
II	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
III	1 (2.04)	0 (0.0)		0 (0.0)	0 (0.0)	
IV	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
pT:			–			–
pT1	49 (100.0)	35 (100.0)		11 (100.0)	2 (100.0)	
pT2	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
pT3	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
pT4	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
pTm	0 (0.0)	0 (0.0)		11 (100.0)	2 (100.0)	
pN:			< 0.00001*			0.001*
pN0	39 (79.59)	2 (5.71)		10 (90.91)	0 (0.0)	
pN1a	10 (20.41)	0 (0.0)		1 (9.09)	0 (0.0)	
pN1b	0 (0.0)	1 (2.86)		0 (0.0)	0 (0.0)	
pNx	0 (0.0)	32 (91.43)		0 (0.0)	2 (100.0)	
pM:			< 0.00001*			0.011*
pM0	41 (83.67)	2 (5.71)		11 (100.0)	0 (0.0)	
pM1	0 (0.0)	1 (1.19)		0 (0.0)	0 (0.0)	
pMx	8 (16.33)	32 (91.43)		0 (0.0)	2 (100.0)	
Tumor size			< 0.00001*			0.682
1–5 mm	7 (14.29)	22 (62.86)		2 (18.18)	0 (0.0)	
6–10 mm	42 (85.71)	13 (37.14)		9 (81.82)	2 (100.0)	

FNAB – fine-needle aspiration biopsy; * – statistically significant difference.

was observed that ultrasound-guided fine-needle aspiration biopsy (UG-FNAB) revealed malignant processes before surgery in a greater number of patients with MTMC than UTMC (84.62% vs. 58.33%, $p = 0.131$). In the group of patients with MTMC, the number of larger tumors (6–10 mm) was higher than in the UTMC group (84.62% vs. 65.48%), however the difference was not statistically significant ($p = 0.290$). Thirteen percent of patients of the UTMC group presented cervical lymph node involvement, compared to nearly 8% of patients with MTMC ($p = 0.298$). The characteristics of patients with FNAB diagnosis in the groups with unifocal and multifocal thyroid microcarcinoma are presented in Table 2. Only in the group of patients with unifocal thyroid microcarcinoma there is statistically significant difference in the choice of surgical procedure between microcarcinomas confirmed by FNAB and unconfirmed ones ($p < 0.00001$). Multiple logistic regression analysis showed that positive results of FNAB were not dependent on the patient's age or gender in both analyzed groups (Table 3). The results of the logistic regression analysis for the prediction of total thyroid resection in TC patients with unifocal and multifocal microcarcinoma are presented in Table 4. In the group of patients with multifocal thyroid microcarcinoma, a positive result of FNAB was the only predictor of radical procedure ($p < 0.0001$). The risk of reoperation in patients

with multifocal thyroid microcarcinoma was not statistically significant for age, gender or thyroid microcarcinoma confirmation in FNAB (Table 5). Disease-related mortality was not observed in either group. Detailed results of the clinical characteristics of the patients with TMC diagnosis are presented in the tables (Table 1–5).

Discussion

The prevalence of UTMC and MTMC in the last decades has increased [14]. Moreover, as some authors suggest, the number of TMC in the general population will equal the incidence of occult TMC diagnosed at autopsy, reaching the prevalence rate of 36% [15].

About 47 years ago, Iida et al. [16] noticed that multifocality of thyroid cancer was a result of intrathyroid metastases of a single primary tumor via lymphatic vessels. It was the main argument concerning multifocal lesions as very aggressive tumors. Currently, thanks to the results of studies using advanced molecular techniques, MTMC is considered as a multiple synchronous primary tumor arising from different cell clones [17]. In 2010 it has to be noticed however, that some relatively new findings indicate multifocality of TMC as a consequence of intraglandular metastases of a primary tumor, which in such case has to

Table 3. Multiple logistic regression analysis for the prediction of TC by FNAB (cancer yes/cancer no) in the two groups of patients: with unifocal thyroid microcarcinoma and multifocal thyroid microcarcinoma

	Unifocal thyroid microcarcinoma			Multifocal thyroid microcarcinoma		
	OR	95% CI	p-value	OR	95% CI	p-value
Age: for < 45	0.571	0.028–11.849	0.7175	1.960	0.736–5.220	0.1783
Gender: for “male”	0.000	0.000	0.9966	0.696	0.132–3.669	0.6688

Table 4. Multiple logistic regression analysis for the prediction of total thyroid resection (total resection/resection not total; 1/0) in the two groups of patients: with unifocal thyroid microcarcinoma and multifocal thyroid microcarcinoma

	Total resection for unifocal thyroid microcarcinoma			Total resection for multifocal thyroid microcarcinoma		
	OR	95% CI	p-value	OR	95% CI	p-value
Age: for < 45	17303609.520	0.000	0.9973	0.713	0.280–1.818	0.4786
Gender: for “male”	0.000	–	–	0.313	0.054–1.812	0.1946
Prediction of thyroid cancer by FNAB: for “cancer yes”	254550706.197	0.000	0.9968	20.250	6.583–62.295	< 0.0001*
Type of cancer: for papillary	–	–	–	2344023.58	–	–

* – statistically significant difference.

Table 5. Multiple logistic regression analysis for the prediction of reoperation (yes/no; 1/0) in the two groups of patients: With unifocal thyroid microcarcinoma and multifocal thyroid microcarcinoma

	Reoperation needed in unifocal thyroid microcarcinoma			Reoperation needed in multifocal thyroid microcarcinoma		
	OR	95% CI	p-value	OR	95% CI	p-value
Age: for ≤ 45	–			1.130	0.260–4.918	0.8702
Gender: for “male”	–			1.750	0.181–16.909	0.6287
Prediction of thyroid cancer by FNAB: for “cancer yes”	–			0.315	0.073–1.360	0.1216
Type of cancer: for papillary	–			–		

be considered as aggressive and therefore requires a radical treatment [18]. These contrary observations justify further investigation of the clinical and pathological characteristics of TMC. What is more, as some authors recommend, a more aggressive surgical approach for MTMC (contrary to UTMC) seems to be worthwhile and useful [19]. The next important issue is the very low sensitivity of all diagnostic tools for presurgical diagnosis of MTMC and its prognosis, which is not clearly established. Therefore, an estimation of prognostic factors of multifocality of these specific tumors is needed.

In the study by Kuo [20], as in our survey, the size of a primary tumor exceeding 5 mm in diameter occurred more often in MTMC. What is more, the suggestion that MTMC is more frequent in patients above 45 years of age [21] can be supported by our study, however in our study the same clinical feature concerns UTMC patients.

UG-FNAB procedures performed in all the analyzed patients before surgery revealed malignancy in more than 84% of MTMC patients and only in 58% of UTMC cases. This is a completely new observation as far as this aspect of presurgical diagnostics of MTMC and UTMC.

Recent findings suggest that the incidence of recurrence or persistence was higher in patients with multifocality of TC compared to unifocal lesions, even if they underwent more aggressive treatment [10]. It might be suspected that this clinical scenario may be the consequence of the fact that patients with MTMC have higher rates of lymph node metastases, soft tissue invasion and distant metastases at the time of diagnosis and treatment. Therefore, some authors recommend total aggressive thyroidectomy and postoperative radioiodine ablation treatment in cases of MTMC [22].

Although multifocality of thyroid carcinoma is strongly associated with the lymph node and distant metastases in cases of MTMC [23], in our study we did not observe a higher incidence of lymph node (pN) or distant (pM) metastases at the time of diagnosis and treatment in patients

with MTMC compared to patients with UTMC (7.69% vs. 13.09%). One has to remember, though, that the number of the patients with MTMC analyzed in our study is small, therefore the conclusions must be careful.

Some authors suggest total thyroidectomy in all cases of MTMC diagnosed preoperatively and completion of initial non-radical surgery for incidentally diagnosed MTMC due to the high probability of contralateral tumor foci and rather poorer prognosis [3]. They add that if a partial thyroidectomy is performed, accurate follow-up is obligatory. Barczyński et al. [24] additionally suggest prophylactic central lymph node dissection in MTMC.

Other authors suggest that subtotal thyroidectomy followed by radioiodine therapy without completion of primary surgery and lymphadenectomy might be an acceptable option in the management of incidental MTMC [2]. They observed patients with MTMC after subtotal thyroidectomy during the 24- to 120-month follow-up period. All patients after primary surgery received an ablative dose of 131I, and during the follow-up period all of them remained free from relapse of the disease or metastasis.

So et al. [3] concluded that multifocality of TMC localized in one lobe carried a higher chance of bilateral *foci*. Therefore, they recommended more extensive surgery in cases of MTMC. In our study, all analyzed patients with MTMC were classified as unilateral tumors. The results of other studies showed that the clinicopathological characteristics did not differ between patients with multifocal-unilateral and multifocal-bilateral thyroid carcinomas [10]. It was confirmed, however, that multifocality and bilaterality are both connected with aggressive pathologic features. Furthermore, no association between bilaterality and disease recurrence or persistence was found.

Other findings suggest that the factors which may influence disease recurrence are: age, sex, tumor dimension, extrathyroidal invasion and cervical lymph node metastasis [25, 26]. In our study, we did not confirm such observations. Chow et al. [27]

noticed that multifocality predicted locoregional recurrence of TMC. In the current study, we did not observe distant and regional metastases, however the duration of the follow-up was not long (12–36 months). For this reason, we focused on the clinicopathological characteristics of multifocal and unifocal tumors to improve their early diagnosis and treatment. Our plan is to increase the study group and elongate the follow-up period in order to estimate the long-term influence of multifocality on disease persistence and recurrence.

The authors concluded that the prevalence of UTMC was significantly higher than MTMC. The majority of UTMC and MTMC were composed of papillary type of cancer. A younger age of patients was equally frequent in both groups (MTMC and UTMC). The accuracy of UG-FNAB was higher in patients with MTMC. The dimensions of most UTMC and MTMC were above 5 mm. The involvement of cervical lymph node at the time of diagnosis in both groups is comparable and not infrequent.

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