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MULTIFOCAL DIFFERENTIATED THYROID CANCER

Aim: *the purpose of the paper is to determine the frequency of multifocal thyroid cancer wide-spreading for tumors with different characteristics.* ***Materials and Methods:*** *a retrospective study of patients' cohort has been carried out including persons operated because of thyroid cancer. The patients were divided into groups according to such characteristics as uni- and multifocality. While analyzing patients' age and sex, as well as histological types of carcinomas, their sizes, tumor characteristics according to the TNM (tumor, nodus, metastasis) classification and invasive properties, clinical stage of disease, volume of surgical intervention, prognosis according to the MACIS scale, and mortality levels have been taken into account.* ***Results:*** *the significant difference between unifocal and multifocal papillary and follicular carcinomas was observed in the elderly (above 60 years) patients, whereas multifocal follicular carcinomas are almost absent in patients below 18. It has been found that the wide-spreading of papillary multifocal carcinomas with aggressive characteristics is higher comparing to unifocal carcinoma. The changes among cohort patients' percent with follicular carcinomas when multifocal growth is present or absent are similar to papillary carcinomas-associated changes. But the degree of these probability changes is not so marked, especially concerning the changes of patients percent with follicular carcinomas of different sizes, different T categories, different clinical stages. Simultaneously, the mortality of patients with multifocal follicular carcinomas exceeds this index for cases with multifocal papillary carcinomas. It may be due to two times higher percent of elderly patients with multifocal follicular carcinomas comparing to patients with papillary. This is a cause of higher risk degree for relapse development and frequency, of poorer prognosis as well as of differences for patients treatment tactics with multifocal tumors.* ***Conclusion:*** *multifocality is an important factor determining the survival prognosis for patients with differentiated thyroid carcinomas.*

Papillary thyroid carcinoma (PTC) is a multifocal one in cases when two or more separated malignant growth foci are found in a tumor. During last several decades the morbidity due to multifocal PTC has increased [1–3]. These cancer forms are mostly presented as multiple microcarcinomas, although malignant foci sizes may also be larger, exceeding 10 mm [4]. The last version of clinical recommendations presented by the American Thyroid Association attributes multifocal microPTC to a group of low risk degree contrary to the same tumors with extra-thyroid invasion (a middle risk group) [5]. In cases of two-sided multifocal PTC the prognosis is usually poorer [6, 7].

More often, multifocal thyroid PTC is diagnosed as an «occasional» tumor found during surgical intervention or pathohistological studies [4, 8]. According to different data available, the wide-spreading (prevalence) of such pathologies varies from 18.0% up to 87.0% depending on some epidemiological and methodological factors [9]. Although recently multifocal carcinomas (especially papillary ones) are in the center of research attention, the problems concerning long-term results of such tumors treatment as well as of their treatment tactics are still unresolved [10] and require further efforts permitting to understand clinical characteristics of multifocal tumors. Available data found in scientific literature suggest the multifocal character of tumor growth is associated more often with capsular invasion, metastases into lymph nodes, and tumors of the T2–T4 category [11]. We have earlier demonstrated that survival of patients with multifocal differentiated carcinomas was significantly poorer comparing to unifocal tumors [12].

The aim of this retrospective analysis was to investigate the wide-spreading frequency of thyroid multifocal carcinomas with different characteristics.

MATERIALS AND METHODS

A retrospective study of a patients' cohort having been operated because of differentiated thyroid tumors at the Institute of Endocrinology and Metabolism during the 1995–2014 period. Total quantity of patients is 5526 persons including 1068 men (19.3%) and 4458 women (80.7%). The mean patients' age is 40.9 years (from 10 to 84 years). The papillary carcinoma (PC) has been detected in 4956 persons (89.7%), follicular carcinoma (FC) having been found in 570 ones (10.3%). Multifocal carcinoma have been diagnosed in 999 (18.1%) patients.

Patients' groups have been analyzed according to the following indices: patients' age and sex, histological type of carcinoma, size, their characteristics according to the TNM classification (7th version) and invasive characters, clinical stage of disease, volume of surgical intervention, risk group, quantity of relapses and courses of radio-iodine therapy, scores quantity according to the MACIS scale, as well as mortality level.

The statistical evaluation of data obtained was made using Pearson's criterion of distribution concordance (χ^2), the critical significance level taken here being 0.05.

RESULTS AND DISCUSSION

The multifocal PTC frequency among patients of the cohort studied here reaches 18.6% (922/4956); these data coincide with previous results of some authors [10], being, however, lower than results of other ones (32.3%) [9]. The significant difference between unifocal and multifocal PTC was observed only in the elderly (above 60 years) patients (Table 1). No gender difference has been found in our patients' cohort, concerning multifocal PTCs frequency — 18.8% (750/3982) and 17.7% (172/974), for women and men, respectively.

Table 1

Percent of different age patients among cohort patients with unifocal and multifocal thyroid carcinoma (n, %)

Index	PC		FC	
	unifocal (n = 4034)	multifocal (n = 922)	unifocal (n = 493)	multifocal (n = 77)
Below 18 years	413 (10.2)	93 (10.1)	47 (9.5)	1 (1.3)*
19–40 years	1641 (40.7)	354 (38.4)	113 (22.9)	11 (14.3)
41–60 years	1573 (39.0)	343 (37.2)	246 (49.9)	43 (55.8)
Above 60 years	407 (10.1)	132 (14.3)*	87 (17.6)	22 (28.6)*

*Difference with data for the unifocal group is significant ($p < 0.05$).

The multifocus PTC growth is usually associated with tumors above 20 mm (Table 2) that completely coincides with results of analysis concerning the widespreading of patients-carriers of multifocal PTCs belonging to T1, T3, and T4 categories. Total multifocal tumor size is thought to be used as a parameter for detection of patients with increased risk of disease persistence, and the T1a category of multifocal PTC may be re-classified as T1b [13].

The multifocal PTC growth has no effect on the widespreading frequency of tumors with metastases into I–VI zones of lymph outflow, however, the percentage of patients with unifocal PTCs of the Nab category is almost half comparing to patients with multifocal tumor growth (see Table 2). The data available suggest that PTC multifocality closely associated with metastases and is an independent risk factor of metastases development in both central and lateral lymph nodes [10, 14–18], the metastases being mostly lateral [19] or mostly central [20–23]. The last case is thought to be due to large carcinoma size [24]. It is emphasized that multifocal PTC growth significantly increased the risk of tumor metastases to central lymph nodes, however, if such growth is accompanied by current capsular invasion, Hashimoto thyroiditis or metastases into central lymph nodes, it is necessary to pay attention to the risk of metastases into lateral nodes [14, 25, 26]. Other authors also indicate that multifocality is associated with PTC metastases into lymph nodes on the background of lymphocytic infiltration of glandular tissue [27]. Our data show that tumors associated with thyroiditis in extra-tumor tissue were also mostly multifocal [28]. The multifocality association with metastases to central lymph nodes in cases of Hashimoto thyroiditis was mostly observed in patients of 25–45 years old [29]. A wide meta-analysis has demonstrated that the PTC with two tumor foci (presenting also as metastases prognostic factor) are less important for metastatic process comparing to greater quantity of tumor foci. The understanding of the prognostic role of at least two tumor-growing centers for metastases penetration to central lymph nodes may be useful for clinicians helping them to take the optimal treatment strategy and surgical intervention volume for patients with multifocal PTCs [30].

Table 2

Percent of patients with unifocal and multifocal thyroid carcinoma with different characteristics among the cohort patients (n, %)

Index	PC		FC	
	unifocal (n = 4034)	multifocal (n = 922)	unifocal (n = 493)	multifocal (n = 77)
Tumor size				
Up to 10 mm	1303 (32.3)	203 (22.0)**	119 (24.1)	9 (11.7)*
11–20 mm	1492 (36.8)	343 (37.0)	151 (30.6)	33 (42.9)*
21–40 mm	940 (23.3)	271 (29.4)**	139 (28.2)	25 (32.5)
Above 40 mm	299 (7.4)	105 (11.4)**	84 (17.1)	10 (12.9)
TNM category				
T1	2374 (58.8)	422 (45.8)**	238 (48.3)	34 (44.2)
T2	644 (16.0)	156 (16.9)	118 (23.9)	18 (23.4)
T3	816 (20.2)	245 (26.6)**	117 (23.7)	18 (23.4)
T4a	192 (4.8)	91 (9.8)**	19 (3.9)	6 (7.8)
T4b	8 (0.2)	8 (0.9)*	1 (0.2)	1 (1.3)
N1a	518 (12.8)	131 (14.2)	30 (6.1)	6 (7.8)
N1b	295 (7.3)	75 (8.1)	21 (4.3)	2 (2.6)
Nab	497 (12.3)	220 (23.9)**	20 (4.1)	8 (10.4)*
M1	76 (1.9)	54 (5.9)**	3 (0.6)	4 (5.2)**
Invasive characters of tumors				
Capsular invasion	3463 (85.8)	856 (92.8)**	399 (80.9)	71 (92.2) *
Intra-thyroid invasion	2243 (55.6)	679 (73.6)**	190 (38.5)	50 (64.9)**
Extra-thyroid invasion	819 (20.3)	295 (32.0)**	60 (12.2)	19 (24.7)*

Difference with data for the unifocal group is significant: *< 0.05; **< 0.001.

In the patients' cohort with distant metastases the wide-spreading of multifocal PTC is higher comparing to patients with unifocal PTC (see Table 2). These data coincide with conclusions suggesting the higher frequency of distant metastases in patients with multifocal PTCs [10].

The invasive properties of multifocal PTCs are more markedly expressed — the percent of patients with multifocal PTCs accompanied by capsular, intra- and extra-thyroid invasions is higher comparing to the patients with invasive tumors without multifocal growth (see Table 2). The existence of significant association between multifocal tumor character and capsular and extra-thyroid invasion [11] or between tumor multifocality and intra-thyroid or lymphovascular, but not intra-thyroid invasion [20] has been also demonstrated in some studies. Thus, the combination of invasive PTC properties and its multifocal growth character are factors determining tumor's aggressive behavior [16, 25, 26]. It is confirmed by higher frequency of patients with multifocal PTCs in our cohort having more severe clinical course: higher percent of patients with disease stages II–IV and lower one with the stage I that coincide with other authors data [10]. Also higher percent of patients

included by risk groups 2 and 3 comparing to group 1 — there are more patients with registered post-operation relapses (Table 3). It should be noted our data on widespreading of post-operation relapses demonstrate significantly lower frequency comparing to the data obtained by other authors (19.8% and 13.6%, respectively for multi- and unifocal PTCs [31]), although we have found in this study the increased relapse frequency is seen in the first case. At the same time, the data of multifactorial analysis do not confirm the conclusion on the multifocality impact on the relapse development. Consequently, the authors conclude that the multifocality has no prognostic value for clinical results of the PTC treatment. Thus, multifocality should not be recognized as an independent relapse risk factor making a doctor to use a more aggressive treatment tactics [31]. Simultaneously, other investigators underline on the contrary that multifocality belongs to a series of clinically important factors stipulating for a possibility of disease relapse development (together with the tumor size, quantity of metastases-affected lymph nodes (>5), intra- or extrathyroid invasion as well as the prognostic value (quantity of scores according to the MACIS scale) in PTC patients belonging to the N0/N1a category) [19, 32, 33]. This factor is thought to be taken into consideration to resolve the problem concerning a more aggressive tactics for surgical intervention to avoid possible relapses during the post-operation period [16].

Table 3

Percent of patients with unifocal or multifocal thyroid carcinoma with different clinical characteristics among patients of the cohort (n, %)

Index	PC		FC	
	unifocal (n = 4034)	multifocal (n = 922)	unifocal (n = 493)	multifocal (n = 77)
Clinical stage				
I	3241 (80.3)	628 (68.1)**	358 (72.6)	41 (53.2)**
II	263 (6.5)	100 (10.8)**	42 (8.5)	14 (18.2)*
III	276 (6.8)	86 (9.3)*	56 (11.4)	11 (14.3)
IV	254 (6.3)	108 (11.7)**	37 (7.5)	11 (14.3)
Risk group				
1	1079 (26.7)	16 (1.7)**	111 (22.5)	2 (2.6)**
2	1256 (31.1)	386 (41.9)**	210 (42.6)	46 (59.7)**
3	1699 (42.1)	520 (56.4)**	172 (34.9)	29 (37.7)
Relapse	116 (2.9)	56 (6.1)**	3 (0.6)	3 (3.9)*
Surgical intervention volume				
TE	2773 (68.7)	688 (74.6)**	326 (66.1)	61 (79.2)*
TE+dissection	882 (21.9)	204 (22.1)	87 (17.6)	12 (15.6)
HemiTE	379 (9.4)	30 (3.3)**	80 (16.2)	4 (5.2)*
Radio-iodine therapy				
0 course	421 (10.4)	38 (4.1)**	89 (18.1)	5 (6.5)*
1 course	3198 (79.3)	741 (80.4)	378 (76.7)	67 (87.0)*
2 courses	259 (6.4)	65 (7.0)	14 (2.8)	3 (3.9)
3–5 courses	135 (3.3)	52 (5.6)**	9 (1.8)	2 (2.6)
Above 5 courses	21 (0.5)	26 (2.8)**	3 (0.6)	0 (0.0)
MACIS				
Below 5.99 scores	3641 (90.3)	753 (81.7)**	415 (84.2)	57 (74.0)*
6–6.99 scores	238 (5.9)	77 (8.3)	45 (9.1)	12 (15.6)
7–7.99 scores	90 (2.2)	43 (4.7)**	14 (2.8)	4 (5.2)
Above 8 scores	65 (1.6)	49 (5.3)**	19 (3.9)	4 (5.2)

Difference with data for the «unifocal» group is significant: *< 0.05; **< 0.001. TE – thyroidectomy; hemiTE – hemithyroidectomy.

The analysis of our patients' cohort suggests that the surgical intervention tactics is only slightly different in cases with multi- and unifocal PTCs: hemithyroidectomy has been made in the first case by three times rarer comparing to patients with unifocal PTCs. However, the frequency of thyroidectomy accompanied by lymph nodes dissection is the same for both patients group (see Table 3). At the same time, it is thought that the surgical intervention has to be more aggressive for PTC patients being 45 years old and belonging to the cN0 category and to be combined with central cervical lymph nodes dissection [21, 34].

In cases of multifocal PTC, it was necessary to carry out 3 and more radio-iodine therapy courses for patients' healing comparing to persons whose tumors had no multifocal growth (see Table 3). The post-operative prognosis calculated using the MACIS prognostic system is worse for patients with multifocal PTCs (see Table 3), the mortality among them was also higher comparing to patients with unifocal tumors — 3.1% (29/922) and 0.7% (29/4034), respectively ($p < 0.001$). In other studies, patients' mortality in cases of multifocal papillary tumors is similar (4.4%) [10]; however, no difference has been found for patients with multi- or unifocal PTCs [10, 31].

While discussing the aggressiveness of multifocal PTCs, it is necessary to mention the data on the association of genetic changes inducing the carcinomas development and the wide-spreading of exactly multifocal ones. For example, the presence of *RET*/PTC3 rearrangements, but not of the gene $BRAF^{V600E}$ mutations is associated with not only greater tumor size, but also with its multifocal growth [35, 36]. The study results on clonal multifocal PTCs origin are not clear [37–40]. If the authors are inclined to recognize the existence of a single precursor in cases of two-sided PTCs and those with metastases, it is not so for multifocal PTCs foci [41].

Multifocal FC among our patients cohort were somewhat more rare comparing to PTC cases: 13.5% (77/570) and 18.6% (922/4956), respectively ($p < 0.01$). Earlier we have obtained close data, analyzing the frequencies of multifocal FC and PTC in cases of presence or absence of chronic thyroiditis in extra-tumor tissue (12.4% and 17.0 %, respectively) [28]. As in PTC cases, no difference has been registered for FC wide-spreading in our cohort among men and women 13.9% (66/476) and 11.7% (11/94), respectively. Of interest, multifocal FC are almost absent in patients below 18; their highest part is found among patients of the age group 41–60 years. The percent of multifocal FC in group of elderly patients significantly exceeds the level of unifocal ones (see Table 1).

The changes among cohort patients' percent with FC when multifocal growth is present or absent are similar to PTC-associated changes (see Tables 2 and 3). At the same time, the degree of these probability changes is not so marked, especially concerning the changes of patients percent with FC of different sizes, different T categories, different clinical stages. This may be due to lower patients quantity with FC. Other authors have also found FC multifocality to be of less importance for these tumors aggres-

sive properties comparing to PTCs [42]. Simultaneously, the mortality of patients with multifocal FC exceeds this index for cases with multifocal PTCs. It may be due to two times higher percent of elderly patients with multifocal FC comparing to PTC patients — 28.6% and 14.3% (see Table 1) and higher percent of patients with unifocal FC — 9.1% (7/77) and 3.2% (16/493), respectively.

Therefore, in cases both of PTC and FC the presence of multifocal tumor growth is a factor being often accompanied by aggressiveness characters. This factor is an unfavorable one for clinical prognosis and (it goes with saying) requires an adequate treatment tactics. Some authors leaning on their data refuse the multifocality impact on patients' survival, at least on their survival during the term up to 10 years [23]. At the moment, according to the data presented by the American Thyroid Association as well as according to our own results, multifocality (together with other tumor characters, such as extrathyroid invasion, tumor size, presence of metastases, relapse risk etc.) is an independent and important factor determining the survival prognosis for patients with differentiated thyroid carcinoma [28, 43].

CONCLUSIONS

Multifocal FC is rare comparing to PTC cases, but the changes among cohort patients' percent with FC when multifocal growth is present or absent are similar to PTC-associated changes.

Multifocality is an important factor determining the survival prognosis for patients with differentiated thyroid carcinomas, which defines of differences for patients treatment tactics with multifocal tumors.

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МУЛЬТИФОКАЛЬНИЙ ДИФЕРЕНЦІЙОВАНИЙ РАК ЩИТОПОДІБНОЇ ЗАЛОЗИ

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Резюме. ***Мета:*** *встановити частоту поширеності мультифокальних карцином щитоподібної залози (ЩЗ), яким притаманні різні характеристики.* ***Об'єкт і методи:*** *проведено ретроспективне дослідження когорти прооперованих з приводу раку ЩЗ пацієнтів, які були розділені на групи за такою характеристикою пухлин, як уні- чи мультифокальність. При проведенні аналізу враховували вік і стать пацієнтів, гістологічний тип карцином, їх розмір, характеристику пухлин за класифікацією TNM (tumor, nodus, metastasis) та інвазійними властивостями, клінічну стадію хвороби, обсяг оперативного втручання, групу ризику, кількість рецидивів і курсів радіойодного лікування, прогноз за шкалою MACIS, а також рівень смертності.* ***Результати:*** *мультифокальні папілярні та фолікулярні карциноми частіше виявляли у хворих віком понад 60 років; мультифокальні фолікулярні карциноми майже не виникали у хворих молодше 18 років. Встановлено, що папілярні мультифокальні карциноми з агресивними характеристиками більш поширені, ніж уніфокальні. Зміна частки хворих з наявністю чи відсутністю багатофокусного росту аналогічна такій пацієнтів з фолікулярними та папілярними карциномами. Проте ступінь вірогідності їх менш виражений, особливо це стосується змін відсотка хворих з фолікулярними карциномами різного розміру та категорії T, а також частки пацієнтів, які мали різні клінічні стадії хвороби. Водночас смертність у групі хворих із мультифокальними фолікулярними карциномами була вищою, ніж серед пацієнтів із мультифокальними папілярними карциномами. Це може бути пов'язано з переважанням (у 2 рази) в цій групі хворих похилого віку. Зазначене зумовлює вищий ступінь ризику виникнення та частоту рецидивів, гірший прогноз захворювання, а також різницю у тактиці лікування хворих із мультифокальними пухлинами.* ***Висновки:*** *мультифокальність є важливим чинником, який визначає прогноз виживаності пацієнтів з диференційованими карциномами ЩЗ.*

Ключові слова: мультифокальні диференційовані карциноми щитоподібної залози, інвазивність, метастази, рецидиви, MACIS.

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