

DIFFERENTIATED THYROID CARCINOMAS ASSOCIATED WITH CHRONIC THYROIDITIS: BIOLOGICAL AND CLINICAL PROPERTIES

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Aim: To determine biological and clinical features of papillary and follicular thyroid carcinomas associated or not associated with chronic thyroiditis. **Materials and Methods:** The study was conducted by retrospective analysis of medical histories of 2,459 patients with thyroid cancer. Tumor size, its category according to the TNM system, multi-focal properties of tumor growth, carcinoma invasiveness, as well as disease stage, rates of relapses and metastasis, and also cumulative survival rates were analyzed. **Results:** The tumor size in patients with papillary or follicular carcinoma associated with thyroiditis was smaller compared to the patients without thyroiditis. In the first case, the invasion frequency into extrathyroid structure and into the capsule was also lower. Multi-focal growth of both carcinoma types was registered more frequently in the presence of thyroiditis. The frequency of papillary carcinoma metastasis to lateral cervical lymph nodes was lower in the presence of thyroiditis, the frequency being equal for metastasis into lymph nodes of the VI lymph outflow zone in both groups of patients (with and without thyroiditis). In the presence of thyroiditis, the frequency of distant papillary carcinoma metastasis was decreased, no metastases were detected in patients with follicular carcinoma. In the group of patients with papillary carcinoma there was found no relation between the presence of thyroiditis and disease stage, relapse rates, and mortality levels; however, the risk of follicular carcinoma relapse was significantly lower in patients with thyroiditis. **Conclusions:** The presence of chronic thyroiditis in papillary carcinoma patients showed a certain positive impact on the course of the disease, in particular, primary tumor growth, invasion, and metastasis. Such effect is even more expressed in the patients with follicular thyroid carcinoma. **Key Words:** papillary and follicular thyroid carcinomas, autoimmune thyroiditis.

Currently, there is no doubt regarding the intimate association between papillary carcinoma and chronic thyroiditis detected in extratumoral thyroid tissue [1–4]. At the same time, there is no consensus regarding a possible impact of autoimmune process on the prognosis in such patients [5, 6]. While some authors conclude on none relation between biological properties of papillary carcinomas and the disease course with the chronic thyroiditis presence [7–11], there are other opinions suggesting the concomitant thyroiditis to be a factor of more favorable disease course [12–15]. In contrary, some authors insist on negative influence of the chronic thyroiditis on papillary carcinoma course [16–18] dependent on the thyroiditis severity [19].

We have previously shown that the chronic thyroiditis accompanies more frequently papillary carcinoma (these data are in agreement with the results obtained by the majority of authors); this condition is also often found in patients with follicular carcinomas and rarely in cases of anaplastic carcinomas [20]. The aim of this study was to determine the frequency of certain biological and clinical features inherent to papillary and follicular carcinomas in cases of chronic thyroiditis presence in extratumoral tissue.

MATERIALS AND METHODS

In this retrospective study, the medical records of patients who underwent surgical treatment of malignant thyroid neoplasms in the Department of Surgery of the State Institution “V.P. Komisarenko Institute of Endocrinology and Metabolism, National Academy

of Medical Sciences of Ukraine” in 2000–2015 were analyzed. We have analyzed the data of patients whose case histories included not only pathohistological examination of tumors, but also pathomorphological characterization of thyroid extratumoral tissue. The group of comparison (control group) included patients without any significant pathological changes in extratumoral tissue surrounding papillary or follicular carcinoma. The cohort studied enrolled 2,459 patients. This study has been approved by Institute’s Committee on Biological & Medical Ethics.

The data analysis covers real tumor size, tumor category according to the TNM system, multifocal character of tumor growth, invasive properties of carcinoma as well as disease stage, presence of relapses, patients’ risk group, and cumulative survival level using Kaplan — Meyer method.

Data were analyzed statistically using χ^2 -test for comparison between groups. To compare the values of cumulative survival index between the groups, non-parametric log-rank test was conducted. All the statistical calculations were carried out using the software packet Statistica 12 by StatSoft, Inc. Differences were considered significant at $p < 0.05$.

RESULTS

The frequency of tumors with the size ≤ 1 cm was higher among patients with differentiated carcinomas accompanied with chronic thyroiditis in extratumoral tissues, while the larger tumor size was found among such patients with lower frequency (Tables 1, 2). The significant changes regarding larger tumors are registered in the groups of patients with papillary carcinomas (21–40 mm)

and follicular cancer (> 40 mm), the significant difference being found for patients' groups with follicular carcinomas.

Table 1. Clinical characteristics of papillary carcinoma cases with the presence or absence of chronic thyroiditis in extratumoral tissues

Index	Number of patients, n (%)		p
	without thyroiditis (n = 853)	with thyroiditis (n = 1453)	
Tumor size: < 10 mm	239 (28.0)	470 (32.3)	0.0296
11–20 mm	330 (38.7)	577 (39.7)	0.6269
21–40 mm	228 (26.7)	319 (22.0)	0.0092
> 40 mm	56 (6.6)	87 (6.0)	0.5788
Category: T1	463 (54.3)	880 (60.6)	0.0031
T2	141 (16.5)	221 (15.2)	0.4002
T3	206 (24.2)	314 (21.6)	0.6343
T4a	43 (5.0)	37 (2.5)	0.0015
T4b	0 (0.0)	1 (0.1)	0.4434
N0	523 (61.3)	950 (65.4)	0.0495
N1a	135 (15.8)	221 (15.2)	0.6923
N1b	70 (8.2)	94 (6.5)	0.0479
N1ab	125 (14.6)	197 (13.6)	0.3817
M1	32 (3.8)	14 (1.0)	0.0000
Intrathyroid invasion	528 (61.9)	908 (62.5)	0.7769
Invasion into the gland capsule	765 (89.7)	1333 (91.7)	0.3503
Extrathyroid invasion	207 (24.3)	300 (20.6)	0.0427
Multifocal growth	101 (11.8)	291 (20.0)	0.0000
Disease stage: I	708 (83.0)	1197 (82.4)	0.7045
II	53 (6.2)	91 (6.3)	0.9621
III	52 (6.2)	99 (6.8)	0.7874
IV	39 (4.6)	64 (4.4)	0.8509
Risk group: 1	173 (20.3)	299 (20.6)	0.8646
2	273 (32.0)	524 (36.1)	0.0478
3	407 (47.7)	630 (43.3)	0.0423
Relapses	29 (3.4)	45 (3.0)	0.6904
Mortality	3 (0.4)	6 (0.4)	0.8198

Table 2. Clinical characteristics of follicular carcinoma cases with the presence or absence of chronic thyroiditis in extratumoral tissues

Index	Number of patients, n (%)		p
	without thyroiditis (n = 65)	with thyroiditis (n = 88)	
Tumor size: < 10 mm	6 (9.2)	19 (21.6)	0.0409
11–20 mm	20 (30.8)	31 (35.2)	0.5631
21–40 mm	20 (30.8)	30 (34.1)	0.6650
> 40 mm	19 (29.2)	8 (9.1)	0.0012
Category: T1	19 (29.2)	44 (50.0)	0.0098
T2	19 (29.2)	26 (29.5)	0.9663
T3	26 (40.0)	16 (18.2)	0.0027
T4a	1 (1.6)	2 (2.3)	0.7532
T4b	0 (0.0)	0 (0.0)	–
M1	3 (4.6)	0 (0.0)	0.0418
Intrathyroid invasion	29 (44.6)	39 (43.2)	0.9701
Invasion into the gland capsule	61 (93.8)	73 (82.9)	0.0434
Extrathyroid invasion	8 (12.3)	11 (12.5)	0.8616
Multifocal growth	4 (6.1)	15 (17.0)	0.0434
Disease stage: I	54 (83.1)	60 (68.2)	0.0366
II	2 (3.1)	11 (12.5)	0.0387
III	7 (10.7)	15 (17.0)	0.2741
IV	2 (3.1)	2 (2.3)	0.7579
Risk group: 1	5 (7.7)	17 (19.3)	0.0427
2	30 (46.2)	47 (53.4)	0.3749
3	30 (46.2)	24 (27.2)	0.0157
Relapses	3 (4.6)	0 (0.0)	0.0418
Mortality	3 (4.6)	0 (0.0)	0.0418

Generally saying, such a situation was also observed regarding tumor properties according to the TNM system: the relative patients' quantity in the cohort with T1 category tumors was higher in cases of thyroiditis-associated tumors while the quantity of patients with T4a papillary carcinomas and with T3 follicular cancer was lower (see Tables 1, 2).

Number of patients with papillary carcinoma of the N0 category was higher in the case of concomitant (associated) thyroiditis due to the lower number of N1b

cases; this group included also lower number of patients with distant metastases. The latest was true also for patients with follicular carcinomas (see Tables 1, 2).

The analysis of invasive carcinoma properties demonstrated that the percent of patients with tumor invasion into the gland parenchyma was the same in cases with or without thyroiditis; in cases of thyroiditis-associated papillary carcinoma the percent was lower if the invasion was found out of the thyroid structure; in cases of thyroiditis-associated follicular carcinoma this percent was shown to be lower in the case of the invasion into the gland capsule. On the contrary, the multifocal growth of both papillary and follicular carcinomas was more often seen in patients with associated thyroiditis comparing to ones whose extratumoral tissues did not demonstrate concomitant pathological changes (see Tables 1, 2).

The distribution of papillary carcinoma patients according to the disease stage did not detect a dependence on the chronic thyroiditis presence or absence, while a certain re-distribution was found between the groups of patients with follicular carcinomas: the concomitant thyroiditis was accompanied by higher percent of stage II cases and lower percent of patients with stage I. The part of follicular carcinoma patients belonging to the first risk group was higher due to the lower percent of patients belonging to the third risk group. Among patients with papillary carcinoma, such a re-distribution was found between patients of the second and third relapse risk group.

In patients group with chronic thyroiditis-associated follicular carcinomas, there were no cases with the disease relapse; also, there death cases were absent, although these indices reach about 5% among thyroiditis-free patients (see Table 2). Among patients with papillary carcinomas, there were no differences in both relapse percent and mortality rates between the groups with and without thyroiditis (see Table 1). The cumulative survival level in patients with differentiated thyroid carcinomas did not differ between the groups with and without chronic thyroiditis in extratumoral tissues (Table 3).

Table 3. Cumulative survival of patients with differentiated thyroid carcinomas dependently on the presence or absence of chronic thyroiditis in extratumoral tissues

Term, years	Papillary carcinomas, %		Follicular carcinomas, %	
	without thyroiditis	with thyroiditis	without thyroiditis	with thyroiditis
2	99.8	99.8	100.0	100.0
5	99.6	99.7	100.0	100.0
10	99.6	99.4	91.8	100.0
20	99.6	99.4	–	–

p = 0.3812

p = 0.2358

DISCUSSION

In the available current scientific literature, there is an opinion that papillary carcinomas exert less aggressive nature in cases of their association with chronic thyroiditis. It is manifested, firstly, by smaller tumor sizes as well as by less intensive lymph node metastasis and less intensive extrathyroid expansion [8, 13, 15, 21–24]. These conclusions are confirmed by our investigations, their results indicating the tumor sizes in chronic thyroiditis-associated papillary carcinomas to be really somewhat smaller comparing to cases without autoimmune

disease. The frequency of category T2–T4 tumors was also lower as well as the frequency of tumor invasion into extrathyroid structures (it is adequate to the decreased frequency of T4a category tumors being known as invasive ones with marked penetration into sub-dermal soft tissues, larynx, trachea, and esophagus). Other authors' reports indicate also the decreased tumor invasion into blood and lymph vessels [14]. On the contrary, the tumor invasion frequency into the gland parenchyma did not differ between patients' groups with and without chronic thyroiditis (see Table 1), although in children and adolescent cohort (108 persons) the thyroiditis presence was accompanied by almost double quantity of cases with intra-thyroid invasion [17]. Simultaneously, the frequency of cases with multi-focal papillary carcinoma growth was twice higher if chronic thyroiditis was present in the gland simultaneously with papillary carcinoma. These results coincide with the data of other investigators [4, 23] proving the more frequent multi-focal papillary carcinoma growth on the background of thyroiditis to confirm the opinion concerning the thyroiditis role in the carcinogenesis initiation. It is even supposed that the thyroiditis shares a lot of features with carcinoma (morphological, immunohistochemical, and genetic ones) [27] to be, in essence, a microscopic carcinoma analogue [28].

According to our data, the frequency of papillary carcinoma metastases to lateral cervical lymph nodes (N1b) was lower in the presence of thyroiditis, metastases frequency into lymph nodes of the VI zone of lymph outflow (N1a) being the same in patients with and without thyroiditis. These data differ from the results obtained previously: in cases of thyroiditis, the metastases into the central compartment lymph nodes (the VI zone) in thyroiditis cases were rarer. This fact could be explained by possible protective role of autoimmune processes against the tumor expansion [4, 8, 12, 14], or, on the contrary, it occurs significantly more often [16]. The difference of metastases frequency into lateral lymph nodes in patients with multifocal papillary carcinoma with or without thyroiditis was not significant [4, 12]. In some studies, no differences were found regarding tumor size, or TNM category, or metastasis to cervical lymph nodes of thyroiditis-free patients with thyroid papillary carcinomas [9, 25].

It should be emphasized that the tumor size and metastasis rate depend on the presence of IgG4 immunoglobulin subclass in the blood of patients with papillary carcinoma and thyroiditis, and these indexes are higher in IgG4-positive patients comparing with IgG4-negative ones [26]. Possibly, these new data concerning the distribution of patients with Hashimoto thyroiditis on IgG4-positive and IgG4-negative ones may partly explain the contradictory results on the frequency of papillary carcinoma metastasis into lymph nodes of different neck regions in cases of autoimmune process. The presence of IgG4 subclass in patients' blood may lead to worsened clinical consequences, although in general the thyroiditis is thought to be a positive prognostic factor for patients with papillary thyroid cancer [21].

There are certain differences shown for the frequency of described pathomorphological and clinical features

of papillary carcinomas associated or not associated with thyroiditis. However, the patients distribution (taking also in consideration their age) between I–III diseases stages is the same, although there is a conclusion that the chronic thyroiditis may be associated with more favorable stage of tumor process [23]. Besides, it is also shown that the quantity of post-operational relapses in patients with papillary carcinoma associated with thyroiditis is lower than in thyroiditis-free cases, the prognosis being better in the first case [15, 21, 29]. According to our data, the relapse rates in the III high-risk group patients was lower in the subgroup with thyroiditis.

The data on the level of relapse-free cumulative survival are contradictory: in a cohort including 597 patients the survival was significantly higher in papillary carcinoma patients' group with thyroiditis compared to thyroiditis-free one [13], while in a cohort including 388 persons the authors did not find any statistically significant difference between the survival of patients with or without thyroiditis [23]. In the cohort examined in this study (2459 patients) both the mortality rates and the rates of relapse-free survival did not differ between the groups.

The analysis of thyroiditis impact on the thyroid follicular carcinoma features is complicated, such studies are rare. It is ascertained that the chronic thyroiditis co-existence with follicular carcinoma is registered with lower frequency comparing to papillary cancer — in 0–20% of cases [6, 25, 29] and in 33% of cases in our study [20]. However, it is not known if such association could have a significant impact on the course of the disease; it is also unknown if the pathologies possess any common molecular-biological, morphological, immuno-histochemical, or genetic properties.

Follicular and papillary tumors are known to possess a number of common properties allowing to suppose that thyroiditis may possibly have a similar impact on the properties of follicular carcinoma. However, contrary to papillary carcinomas, the follicular cancer is more aggressive, the prognosis being rather poor. The mean age of patients suffering from follicular carcinomas is approximately by 10 years higher compared to papillary carcinoma patients, their gender propensity being the same. For these differentiated carcinomas, the latent period for induction of carcinogenic transformation due to radioactive exposure is different [30, 31]; this fact may be associated with different types of genetic damages being found in cells of these carcinomas.

The tumor size of both follicular and papillary carcinomas was smaller in the cases of chronic thyroiditis. The significantly increase number of small tumors (< 10 mm) is due to three-fold decreased number of large neoplasms (> 40 mm) corresponding to the re-distribution of T1 and T3 category carcinomas; the latest fact was caused by the decreased percent of tumor invasion into the capsule. It should be noted the quantitative parameters of such re-distribution are similar to those of papillary carcinomas. No distant metastases were detected in the patients with thyroiditis-associated follicular carcinomas, these data being in agreement with other reports [29]. However, in cases of both papillary and follicular thyroiditis-associ-

ated carcinomas, multifocal tumor growth was observed more often, especially in cases of follicular carcinomas.

Instead, in spite of certain “positive” features of chronic thyroiditis-associated follicular carcinomas, the percent of the I stage patients was lower in thyroiditis-associated cases, the percent of the II stage cases being higher compared to thyroiditis-free patients; it may be due to older age of patients with thyroiditis [20]. However, the disease relapse risk (as well as the relapse rate) in patients with thyroiditis-associated follicular carcinomas was significantly lower compared to patients without thyroiditis. Of note, the survival rates in both groups of patients were similar without lethal outcomes in the group of patients with thyroiditis.

Thus, the presence of chronic thyroiditis in papillary carcinoma patients demonstrated a certain positive effect on the course of the disease, in particular, primary tumor growth, invasion, and metastasis. Such effect was even more expressed in the patients with thyroid follicular carcinoma, more aggressive thyroid cancer.

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