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FAMILIAL NON-MEDULLARY THYROID CARCINOMA

Background. Familial non-medullary thyroid carcinoma (FNMTC) is defined as cancer developing in two or more first-degree relatives if predisposing factors, for example, radiation, are absent. The disease can be either syndromic, when it is a component of complex genetic syndromes, or non-syndromic (95% cases). The genetic basis of non-syndromic FNMTC is unknown; the clinical behavior of tumors is unclear and, at times, contradictory. **Aim:** To analyze clinical manifestations of FNMTC and compare them with the data for sporadic papillary thyroid carcinomas in patients of the same age groups. **Materials and Methods.** We examined 22 patients (a "parents" group and a "children" group) suffering from the non-syndromic FNMTC. For comparison, two groups of sporadic papillary carcinomas patients of the same age were drawn up ("adult" and "young"). We analyzed tumor size and frequency of the distribution by the category of TNM system, invasiveness, multifocality, metastases to lymph nodes, type and extent of surgical and radioiodine treatment, and prognosis according to the MACIS criterion. **Results.** Whether sporadic or familial, the tumor size, metastatic potential, and invasive potential are higher in young people, as already known. There was no significant difference between the "parents" and "adult" groups of patients in terms of tumor parameters. One exception was the higher frequency of multifocal tumors in the FNMTC patients. Meanwhile, compared to the "young" sporadic papillary carcinomas patients, the FNMTC "children" had a higher frequency of T2 tumors, metastasizing (N1a–N1ab), and multifocal tumors, but a lower frequency of carcinomas with intrathyroidal invasions. In the FNMTC "children" compared to FNMTC "parents" was a higher frequency of T2 tumors, metastasizing carcinomas, and tumors with capsular invasion. **Conclusion.** FNMTC carcinomas are more aggressive than sporadic ones, especially in patients who are first-degree relatives in a family with parents already diagnosed with the disease.

Keywords: thyroid cancer, familial non-medullary thyroid cancer, sporadic papillary carcinoma.

Familial non-medullary thyroid cancer (FNMTC), a "black box" of thyroidology, was acknowledged as a separate orphan disease over twenty years ago [1]. Since the first report of an isolated familial papillary thyroid cancer in 24-year-old monozygotic twins [2], many cases have been published of patients with relatives having some kind of differentiated cancer of the thyroid gland (TG), sup-

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porting the existence of this form of FNMTC. It is generally rare, comprising 3 to 15% of TG differentiated cancers; it can manifest itself as papillary carcinoma (more frequent) or follicular carcinoma [3, 4]. FNMTC is defined as cancer developing in two or more first-degree relatives when other predisposing factors (such as radiation) are absent. Some sources also list multinodal goiter in at least three first- or second-degree relatives of the carcinoma patient as a diagnostic criterion [5—7]. The probability of a patient having exactly the FNMTC kind of tumor is over 95% if it was found in three or more first-degree relatives of the patient; if there are two such patients in the family, the probability is 31—38% [8].

Studying the clinical-pathological parameters of the FNMTC led to its subdivision into the non-syndromic kind (a separate familial disease) and the syndromic kind. The latter is a component of several complex genetic syndromes with typical clinical manifestations (familial adenomatous polyposis, ataxia-telangiectasia, Carney complex type 1, and the following syndromes: DICER1, Gardner, Cowden, Werner, Bannayan — Riley — Ruvalcaba, Li — Fraumeni, Peutz — Jeghers, and Pendred) [5, 9—11].

In 95% of cases, FNMTC is non-syndromic. Population studies have shown that the risk of FNMTC development is 8 to 12 times higher in patients with a first-degree relative with thyroid carcinoma, pointing at a so far unidentified predisposing gene [8]. FNMTC has an autosomal dominant inheritance pattern. It is linked to several genes with low, medium, and incomplete penetrance with horizontal transfer in brothers and sisters and a higher fraction of male patients (although this finding remains controversial) compared to the sporadic tumor patients [12—15]. The difficulty of determining the genetic basis of FNMTC is explained by its heterogeneity, which in some families includes homogeneous and polygenic inheritance [15, 16]. A long discussion about how many patients should be in a family to diagnose them with FNMTC with certainty is perhaps over now as genome-wide association studies revealed at least ten loci with odds ratios ~1.2 to ~1.8. Thus, the low-penetrance variants play an important role, and only two patients in a family do not preclude FNMTC. Also, if a tumor grows in a relatively young person, this is an even more important sign of the familial type because familial risks, as a rule, decrease with a proband's age [15, 17].

Among the candidate predisposing genes for FNMTC that can have germline mutations, there are genes responsible for numerous cell processes (transcription and reparation of DNA, processing and splicing of RNA, proliferation, migration, and survival of cells, telomere dysfunction, autophagy, mitochondrial metabolism, chromosomal stability, angiogenesis, hydrogen peroxide metabolism necessary for enzyme activity when thyroid hormones are produced, etc.). Meanwhile, the somatic events are mostly linked to the mitogen-activated protein kinase (MAPK) pathway [10, 16, 18—23]. The presence of germline mutations revealed by sequencing the FNMTC genome underlined the central role played in this cancer by the PI3K/AKT pathway (responsible for apoptosis inhibition, growth, and proliferation of cells) and the MAPK/ERK pathway (participation in the regulation of numerous cellular processes such as control of growth, differentiation, survival, or apoptosis) [16].

However, we have already known that some variants of germline mutations found in some families can be absent in some family members with FNMTC; they can be later unconfirmed in different families [24]. Other mechanisms possibly involved in FNMTC development, e.g., epigenetic ones, still require further study. Recently, gene regulation mechanisms (microRNA and enhancer elements able to affect the genes' expression under FNMTC) are progressively frequently considered to play a role [25]. According to the National Comprehensive Cancer Network, the American Thyroid Association (ATA), and the European Society for Medical Onco-

logy, these findings in their entirety do not allow recommending genetic testing to screen family members in the FNMTC risk group [26—28].

At the germline level, there were not found in FNMTC the classic genetic changes most frequently present in the sporadic papillary or follicular TG carcinomas (point mutations *BRAF* and *RAS*, rearrangements *RET/PTC, PPARγ,* and *TRK*) [15].

There is also controversy regarding the necessity of clinical screening for FNMTC (ultrasound examination (US) of the gland and physical examination of members of families that include at least two first-degree relatives with carcinoma). Thus, a prospective study showed that 4.6% of members of families with two thyroid carcinoma patients per family were also diagnosed with FNMTC. As for the families with three or more first-degree relatives who had cancer, 22.7% of screened people had the same diagnosis [29]. Similar results (5.5%) were obtained in another prospective study, which screened mostly families with two patients [30]. All tumors diagnosed using screening were smaller, had lower incidences of central-cervical lymph node metastases, and required less initial surgical treatment and radioiodine therapy than tumors of patients who already had the clinical disease. Also, the patients found by screening were younger [31, 32].

Proponents of the US screening point to the fact that without screening, tumors are found at a later stage, leading to worse treatment outcomes in such families [33]. Nevertheless, the current ATA protocols do not recommend US screening for the non-syndromic FNMTC [28]. Meanwhile, the current body of research proves the necessity of such screening for families with three or more patients, starting from the age of 20 or even 10 years old [15]. Given the risk of overdiagnosis and overtreatment, the data are insufficient to recommend annual US screening for families with two patients [31, 34].

The data are contradictory about whether the non-syndromic FNMTC is more aggressive than the sporadic form [12]. Thus, according to a meta-analysis, FNMTC is linked to a younger patient age at diagnosis and a higher frequency of multifocal and bilateral tumors, extrathyroidal extension, lymph node metastases, and cancer recurrence [35]. Similar results (younger age at diagnosis, more frequent metastases in cervical lymph nodes) were obtained in a cohort study comparing the data for 78 patients with FNMTC to a large group of patients (53 571) with sporadic thyroid carcinoma, as well as in other studies [6, 14, 15, 36]. Notably, FNMTC carcinomas can be accompanied by benign thyroid gland phenomena (hyperplastic nodes, follicular adenomas) or oncocytic alterations [12, 37]. Meanwhile, there is also evidence of less aggressive FNMTC [38].

Early papers described FNMTC patients as having much shorter life survival than those with sporadic non-medullary thyroid cancer [39]. However, a longitudinal study analyzing spanning ten years found no difference in survival for these two cancers [40]. Likewise, there was no increase in the recurrence and death rates for FNMTC patients [41, 42].

Despite a more aggressive disease at the time of reveal is an argument for a more extensive treatment, the recognized approach to treating FNMTC (surgery, radiotherapy) is that it should not differ from the regimen for sporadic cancers, and the extent of therapy should be determined based on the treatment response and outcome [15].

In Ukraine, there are no studies of the non-syndromic FNMTC, although a pedigree analysis is an important etiological factor for differentiated thyroid cancer. This paper is the first. It aims to analyze the clinical parameters of the disease in FNMTC patients and to compare them with the corresponding patient groups with sporadic papillary carcinomas.

Materials and Methods

We observed 22 FNMTC patients with who had been treated for papillary thyroid cancer in the

surgical clinic of the SI "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine". Among them, there were nine couples of parents and their offspring; of these, the older generation was selected as the "parents" group, and the younger was assigned to the "children" group together with two other couples of brothers and sisters.

For the "parents" group, the mean age of patients diagnosed with thyroid carcinoma was 54.9 ± 1.9 years (averaged for seven women and two men), and for the "children" — 30.2 ± ± 1.9 years (five women and eight men).

When drawing up the comparison groups (patients with sporadic papillary carcinomas), we used the data on patients with differentiated TG cancer (drawn from the clinical database of the Institute's Department of Surgery). From those, we selected a set of patients with comparable main characteristics and compiled comparison groups according to the requirements: the tumors had to be diagnosed as papillary carcinomas; the same age range (it was previously shown that the characteristics of carcinomas depend on the age of patients [43]); the patients had not lived in the regions of Ukraine affected by the accident at the Chornobyl nuclear power plant [44]. The clinical base of the Department of Surgery of the Institute includes records for almost six thousand patients with differentiated thyroid cancer. Of them, 321 adult patients (54.2 ± 0.24 years, the "adults" cohort) and 505 young patients (30.5 ± 0.23 years, the "young" cohort) met our screening requirements. These two cohorts were similar in age to the "parents" and "children", respectively.

We analyzed the following data: tumor size and frequency of distribution according to the TNM system, invasiveness, multifocality, lymph node metastases, nature and extent of the surgical and radiotherapy, and the prognosis according to the MACIS criterion [45].

Statistical treatment included Student's *t*-test (p_t) and Pearson's χ^2 test (p_χ) of distributions. The calculations were done using Statistica 12 software package by StatSoft, Inc. The significance threshold was $p \leq 0.05$.

Results

Since one of the main conditions to diagnose a tumor as FNMTC is non-exposure of the patient to the increased radiation levels, we analyzed the patients' passport records. At the time of the Chornobyl accident, all of the "parents" lived in the regions unaffected by the disaster, and their age then was 21.1 ± 1.3 years. Thus, none of them belonged to the geography- or the age-related (0—18 years) risk groups [44]. Their children had not been born by at least two years after the disaster.

In the FNMTC group of patients, inheritance was more common on the maternal side (7 cases of 9; 77.8%); in three families, the daughters inherited it, and in four families — the sons. In one case, FNMTC was recorded for the father and the daughter, and in another — for the father and the son. In two families, brothers and sisters but not the parents were diagnosed.

The tumors were larger in the "young" cohort than in the "adults" (14.1 ± 0.3 mm *vs.* 11.3 ± ± 0.2 mm, respectively; $p_t < 0.001$). Similarly, they were larger in the "children" than in the "parents" (15.9 ± 1.9 mm *vs.* 10.8 ± 1.3 mm, $p_t < 0.05$).

As for the T category, in the "young", T2—T3 tumors were more frequent compared to the "adults" (see Table 1). They also had more frequent metastasis to cervical lymph nodes (categories N1a and N1ab) and more frequent capsular, intra-, and extrathyroidal invasions. The difference was similar for the FNMTC carcinomas. In the "children" group, the fractions of T2 tumors and metastasizing tumors N1a-N1ab were higher compared to the "parents". As for the invasiveness of FNMTC, in the "children" group, 100% of carcinomas had capsular invasion; in the "parents", it was a third less.

We compared the data on sporadic and familial papillary carcinomas for the corresponding

Table 1. **Frequency of different clinical characteristics of sporadic and hereditary cancer in patients of different ages with sporadic cancer or FNMTC, n (%)**

Indicator	Sporadic cancer		FNMTC	
	«adults», n = 321	«young», n = 505	«parents», n = 9	«children», n = 13
	1	2	3	4
T1	291 (90.7)	354 (70.1) [1]	8 (88.9)	6 (46.2) [3]
T2	0 (0)	44 (8.7) [1]	0 (0)	5 (38.4) [2.3]
T3	19 (5.9)	94 (18.6) [1]	1 (11.1)	2 (15.4)
N1a	31 (9.7)	81 (18.0) [1]	1 (11.1)	2 (15.4)
N1b	19 (5.9)	37 (7.3)	0 (0)	2 (15.4)
N1ab	16 (5.0)	82 (16.2) [1]	1 (11.1)	5 (38.4)
N1a-N1ab	66 (20.6)	200 (39.6) [1]	2 (22.2)	9 (69.2) [2.3]
Multifocality	43 (13.4)	91 (18.0)	4 (44.4) [1]	7 (53.9) [2]
Invasion:				
capsule	254 (79.1)	454 (89.9) [1]	6 (66.7)	13 (100.0) [3]
intrathyroidal	125 (38.9)	374 (74.1) [1]	2 (22.2)	6 (46.2) [2]
extrathyroidal	28 (8.7)	107 (21.2) [1]	1 (11.1)	2 (15.4)
Thyroidectomy	229 (71.3)	368 (72.9)	4 (44.4)	2 (15.4) [2]
Thyroidectomy and lymphodissection	74 (23.1)	96 (19.0)	5 (55.6) [1]	10 (76.9) [2]
Hemithyroidectomy	18 (5.6)	41 (8.1)	0 (0)	1 (7.7)
Radioiodine therapy	304 (94.7)	463 (91.7)	6 (66.7) [1]	13 (100.0) [3]

Note: the difference is significant, $p < 0.05$: [1] — between the "adults" and "young" groups or "adults" and "parents" groups; [2] — between "young" and "children" groups; [3] — between "parents" and "children" groups.

age groups. There were no significant differences between the "adults" and the "parents", except for the greater frequency of multifocal tumors in FNMTC patients (see Table 1). Meanwhile, in the "children", compared to the "young", T2 tumors, N1a—sN1ab tumors, and multifocal tumors were more frequent, whereas carcinomas with intrathyroidal invasion were less frequent.

Among the sporadic papillary carcinoma patients, the most common surgical treatment was limited to total thyroidectomy. Total thyroidectomy with dissection of cervical lymph nodes was much less common. No difference was found for the "adults" and the "young" (see Table). On the contrary, in FNMTC patients, total thyroidectomy was more frequently performed with neck dissection. Most patients required postoperative radiation therapy; it was somewhat less frequent for the "parents" group.

Despite the difference in the parameters of sporadic and familial carcinomas in patients of different ages, all patients had stage I cancer according to their MACIS scores, which remained below 6: "adults" — 4.81 ± 0.03, "young" — 3.88 ± 0.03, "parents" — 3.85 ± 0.13, and "children" — 3.88 ± 0.16.

Discussion

For the FNMTC patients, maternal inheritance is more frequent (female patients with thyroid cancer are much more numerous). However, this tentative conclusion cannot be fully substantiated given the small number of patients examined and the lack of similar findings in the literature. Meanwhile, among the "children", the fraction of male patients was somewhat higher, and there were also two couples of brothers and sisters. This agrees with some reports on increased fractions of males among the affected progeny and with the current views on the possibility of horizontal transfer of cancer [12, 13].

Regardless of whether the carcinoma is sporadic or familial, the tumor size and its metastasizing and invasion potential are higher in young patients. This is in full accordance with the previous findings for sporadic papillary carcinomas [43]. The less profound quantitative changes in the FNMTC patients can be a consequence of the small sample sizes in the "parents" and "children" groups, as expected for an orphan disease; it can also be connected with some of the children diagnosed at an earlier age if they were examined following their parents diagnosed (a kind of accidental screening).

The higher frequency of larger tumors (T2 category), metastases, and multifocal tumors in the "children" compared to the "young" patients, as well as the higher frequency of T2 tumors, metastasizing carcinomas, and tumors with capsular invasion compared to the "parents" are evidence of the more aggressive FNMTC cancer in the young first-degree patients in families with parents already suffering from the disease. As for the "parents" themselves, the more aggressive FNMTC was seen in the higher fraction of multifocal carcinomas compared to sporadic papillary carcinomas in patients of the same age. Previous studies have indicated that for this cancer, multifocal tumors are more frequent and metastasize to the cervical lymph nodes more often [6, 14, 15, 35, 36].

Such features of FNMTC led to neck dissections performed more frequently in both the "parents" and "children" groups (especially in "children") compared to the sporadic papillary carcinoma patients. For the same reason, radioiodine therapy was more frequent for the "children", although according to the current views, the treatment of FNMTC should not be substantially different from the treatment of sporadic papillary carcinomas [15]. Meanwhile, the treatment should be determined individually on the basis of the clinical parameters and therapy response; accordingly, all patients in this study were in good-prognosis groups given the amount of surgical treatment.

To summarize, let us stress that despite all the breakthroughs of the last decades, the genetics of non-syndromic FNMTC is still poorly understood. The genetic mechanisms causing the tumor development are unclear, and the tumor's clinical behavior is contradictory. All of this makes this cancer interesting and important both scientifically and clinically. Further studies of FNMTC are necessary to better understand the genetic factors of the emergence of familial orphan diseases and to discover more aggressive tumors of the patients' relatives in time but without overdiagnosis, personalizing treatment of thyroid cancer [24, 46—48]. Some clinical parameters, such as the relatively young age of the patients and the multicentral and/or bilateral tumors, should attract clinicians' attention to a possible form of familial differentiated thyroid cancer.

Limitation

The study has certain limitations because of the small number of patients with FNMTC, a thyroid cancer rare enough to be an orphan disease.

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REFERENCES

1. Burgess J, Duffield A, Wilkinson S, et al. Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. J Clin Endocrinol Metab 1997; **82**: 345-348. doi: 10.1210/jcem.82.2.3789
2. Robinson D, Orr T. Carcinoma of the thyroid and other diseases of the thyroid in identical twins. AMA Arch Surg 1955; **70**: 923-928. doi: 10.1001/archsurg.1955.01270120131015
3. Xu B, Ghossein R. Evolution of the histologic classification of thyroid neoplasms and its impact on clinical management. Eur J Surg Oncol 2018; **44**: 338-347. doi: 10.1016/j.ejso.2017.05.002
4. Mazeh H, Sippel R. Familial nonmedullary thyroid carcinoma. Thyroid 2013; **23**: 1049-1056. doi: 10.1089/thy.2013.0079
5. Sinclair T, Kebebew E. Chapter 4 - Familial Nonmedullary Thyroid Cancer, Editor(s): A. Shifrin. Advances in Treatment and Management in Surgical Endocrinology. Elsevier, 2020; 35-48. https://doi.org/10.1016/B978-0-323-66195-9.00004-2
6. Capezzone M, Fralassi N, Secchi C, et al. Long-term clinical outcome in familial and sporadic papillary thyroid carcinoma. Eur Thyroid J 2020; **9**: 213-220. doi: 10.1159/000506955
7. Malchoff C, Malchoff D. Familial nonmedullary thyroid carcinoma. Cancer Control 2006; **13**: 106-110. doi: 10.1177/107327480601300204
8. Charkes N. On the prevalence of familial nonmedullary thyroid cancer in multiply affected kindreds. Thyroid 2006; **16**: 181-186. doi: 10.1089/thy.2006.16.181
9. Zhou Y, Luo H, Gou J, et al. Second generation of familial nonmedullary thyroid carcinoma: A meta-analysis on the clinicopathologic features and prognosis. Eur J Surg Oncol 2017; **43**: 2248-2256. doi: 10.1016/j.ejso.2017.09.005
10. Orois A, Mora M, Halperin I, Oriola J. Familial non medullary thyroid carcinoma: Beyond the syndromic forms. Endocrinol Diabetes Nutr (Engl Ed) 2021; **68**: 260-269. doi: 10.1016/j.endinu.2020.08.002
11. Carbone M, Arron S, Beutler B, et al. Tumour predisposition and cancer syndromes as models to study gene-environment interactions. Nat Rev Cancer 2020; **20**: 533-549. doi: 10.1038/s41568-020-0265-y
12. Cameselle-Teijeiro J, Mete O, Asa S, LiVolsi V. Inherited follicular epithelial-derived thyroid carcinomas: from molecular biology to histological correlates. Endocr Pathol 2021; **32**: 77-101. doi: 10.1007/s12022-020-09661-y
13. Dotto J, Nose V. Familial thyroid carcinoma: a diagnostic algorithm. Adv Anat Pathol 2008; **15**: 332-349. doi: 10.1097/PAP.0b013e31818a64af
14. Kim Y, Seo M, Park S, et al. Should total thyroidectomy be recommended for patients with familial nonmedullary thyroid cancer? World J Surg 2020; **44**: 3022-3027. doi: 10.1007/s00268-020-05473-7
15. Capezzone M, Robenshtok E, Cantara S, Castagna M. Familial non-medullary thyroid cancer: a critical review. J Endocrinol Invest 2021; **44**: 943-950. doi: 10.1007/s40618-020-01435-x
16. Srivastava A, Kumar A, Giangiobbe S, et al. Whole genome sequencing of familial non-medullary thyroid cancer identifies germline alterations in MAPK/ERK and PI3K/AKT Signaling Pathways. Biomolecules 2019; **9**: 605. doi: 10.3390/biom9100605
17. Capezzone M, Marchisotta S, Cantara S, et al. Familial non-medullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity. Endocr Relat Cancer 2008; **15**: 1075-1078. doi: 10.1677/ERC-08-0080
18. Gara S, Jia L, Merino M, et al. Germline HABP2 mutation causing familial nonmedullary thyroid cancer. N Engl J Med 2015; **373**: 448-455. doi: 10.1056/NEJMoa1502449
19. Tomsic J, He H, Akagi K, et al. A germline mutation in SRRM2, a splicing factor gene, is implicated in papillary thyroid carcinoma predisposition. Sci Rep 2015; **5**: 10566. doi: 10.1038/srep10566
20. Li J, An C, Zheng H, et al. Leukocyte telomere length and risk of papillary thyroid carcinoma. J Clin Endocrinol Metab 2019; **104**: 2712-2718. doi: 10.1210/jc.2018-02471
21. Sańchez-Ares M, Cameselle-Garćıa S, Abdulkader-Nallib I, et al. Susceptibility genes and chromosomal regions associated with non-syndromic familial non-medullary thyroid carcinoma: some pathogenetic and diagnostic keys. Front Endocrinol 2022; **13**: 829103. doi: 10.3389/fendo.2022.829103
22. Hińcza K, Kowalik A, Kowalska A. Current knowledge of germline genetic risk factors for the development of non-medullary thyroid cancer. Genes 2019; **10**: 482. doi:10.3390/genes10070482
23. Miasaki F, Fuziwara C, Carvalho G, Kimura E. Genetic mutations and variants in the susceptibility of familial non-medullary thyroid cancer. Genes (Basel) 2020; **11**: 1364. doi: 10.3390/genes11111364

24. Kamani T, Charkhchi P, Zahedi A. Akbari M. Genetic susceptibility to hereditary non-medullary thyroid cancer. Hered Cancer Clin Pract 2022; **20**: 9. doi: 10.1186/s13053-022-00215-3
25. Peiling Yang S, Ngeow J. Familial non-medullary thyroid cancer: unraveling the genetic maze. Endocr Relat Cancer 2016; **23**: R577-R595. doi: 10.1530/ERC-16-0067
26. Haddad R, Nasr C, Bischoff L, et al. NCCN guidelines insights: Thyroid carcinoma, version 2.2018. J Natl Compr Cancer Netw 2018; **16**: 1429-1440. doi: 10.6004/jnccn.2018.0089
27. Filetti S, Durante C, Hartl D, et al. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; **30**: 1856-1883. doi: 10.1093/annonc/mdz400
28. Haugen B, Alexander E, Bible K, et al. 2015 American Thyroid Association management guidelines for adult patients with Thyroid nodules and differentiated Thyroid Cancer: the American Thyroid Association guidelines task force on Thyroid nodules and differentiated Thyroid Cancer. Thyroid 2016; **26**: 1-133. doi: 10.1089/thy.2015.0020
29. Furuya-Kanamori L, Bell K, Clark J, et al. Prevalence of differentiated thyroid cancer in autopsy studies over six decades: A meta-analysis. J Clin Oncol 2016; **34**: 3672-3679. doi: 10.1200/JCO.2016.67.7419
30. Ríos A, Rodríguez J, Navas D, et al. Family screening in familial papillary carcinoma: the early detection of thyroid disease. Ann Surg Oncol 2016; **23**: 2564-2570. doi: 10.1245/s10434-016-5149-8
31. Klubo-Gwiezdzinska J, Yang L, Merkel R, et al. Results of screening in familial non-medullary thyroid cancer. Thyroid 2017; **27**: 1017-1024. doi: 10.1089/thy.2016.0668
32. Sadowski S, He M, Gesuwan K, et al. Prospective screening in familial nonmedullary thyroid cancer. Surgery 2013; **154**: 1194-1198. doi: 10.1016/j.surg.2013.06.019
33. Tavarelli M, Russo M, Terranova R, et al. Familial non-medullary thyroid cancer represents an independent risk factor for increased cancer aggressiveness: a retrospective analysis of 74 families. Front Endocrinol 2015; **6**: 117. doi: 10.3389/fendo.2015.00117
34. Rosario P, Mourão G. Ultrasonography screening in children and adolescents who have one parent with familial non-medullary thyroid carcinoma. J Paediatr Child Health 2022. doi: 10.1111/jpc.16215
35. Wang X, Cheng W, Li J, et al. Endocrine tumours: familial nonmedullary thyroid carcinoma is a more aggressive disease: a systematic review and meta-analysis. Eur J Endocrinol 2015. **172**: R253-R262. doi: 10.1530/EJE-14-0960
36. El Lakis M, Giannakou A, Nockel P, et al. Do patients with familial nonmedullary thyroid cancer present with more aggressive disease? Implications for initial surgical treatment. Surgery 2019; **165**: 50-57. doi: 10.1016/j.surg.2018.05.075
37. Maximo V, Botelho T, Capela J, et al. Somatic and germline mutation in GRIM-19, a dual function gene involved in mitochondrial metabolism and cell death, is linked to mitochondrion-rich (Hurthle cell) tumours of the thyroid. Br J Cancer 2005; **92**: 1892-1898. doi: 10.1038/sj.bjc.6602547
38. Sung T, Lee Y, Yoon J, et al. Surgical management of familial papillary thyroid microcarcinoma: A single institution study of 94 cases. World J Surg 2015; **39**: 1930-1935. doi: 10.1007/s00268-015-3064-y
39. Alsanea O, Wada N, Ain K, et al. Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. Surgery 2000; **128**: 1043-1050; discussion 1050-1051. doi: 10.1067/msy.2000.11084.
40. Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, et al. Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. Thyroid 2011; **21**: 43-48. doi: 10.1089/thy.2009.0406
41. Maxwell E, Hall F, Freeman J. Familial non-medullary thyroid cancer: a matched-case control study. The Laryngoscope 2004; **114**: 2182-2186. doi: 10.1097/01.mlg.0000149454.91005.65
42. Cao J, Chen C, Chen C, et al. Clinicopathological features and prognosis of familial papillary thyroid carcinoma — a large-scale, matched, case-control study. Clin Endocrinol (Oxf) 2016; **84**: 598-606. doi: 10.1111/cen.12859
43. Guda B. Associations between prognostic factors determining the survival of thyroid papillary carcinoma patients. Inter J Med Sci Clin Invent 2019; **6**: 4539-4543. doi:10.18535/ijmsci/v6i8.02
44. Tronko M, Shpak V, Bogdanova T, et al. Chapter 3. Epidemiology of thyroid cancer in Ukraine after Chernobyl. Thyroid cancer in Ukraine after Chernobyl: dosimetry, epidemiology, pathology, molecular biology. Editors M Tronko, T Bogdanova, V Saenko, G Thomas, I Likhtarov, S Yamashita. IN-TEX, Nagasaki, Japan. 2014: 39-64. ISBN 4-931481-08-6
45. Hay I, Bergstralh E, Goellner J, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993; **114**: 1050-1057. PMID: 8256208

46. Valerio L, Cantara S, Puxeddu E, Castagna M. Editorial: non-syndromic familial non-medullary thyroid carcinoma: clinical and genetic update. Front Endocrinol (Lausanne) 2022; **13**: 891903. doi: 10.3389/fendo.2022.891903
47. Guilmette J, Nosé V. Hereditary and familial thyroid tumours. Histopathology 2018, **72**: 70-81. doi: 10.1111/his.13373
48. Diquigiovanni C, Bonora E. Genetics of familial non-medullary thyroid carcinoma (FNMTC). Cancers (Basel). 2021; **13**: 2178. doi: 10.3390/cancers13092178

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СІМЕЙНИЙ НЕМЕДУЛЯРНИЙ РАК ЩИТОПОДІБНОЇ ЗАЛОЗИ

Резюме. Сімейний немедулярний рак щитоподібної залози (СНМРЩЗ) визначається як пухлина, що виникає у двох чи більше родичів першого ступеня за відсутності основних чинників ризику, зокрема радіаційного опромінення. Захворювання може бути як синдромальним, у цьому випадку воно є компонентом складних генетичних синдромів, так і несиндромальним (95% випадків). Генетичні механізми, що лежать в основі виникнення несиндромального СНМРЩЗ невідомі, неясна і суперечлива також клінічна та онкологічна поведінка пухлин. **Мета.** провести аналіз клінічних характеристик хвороби у пацієнтів з СНМРЩЗ та порівняти їх з даними відповідних вікових груп хворих зі спорадичними папілярними карциномами. **Матеріали і методи.** Під наглядом було 22 хворих на несиндромальний СНМРЩЗ (групи «батьки» і «діти»). Групи порівняння складено з хворих відповідного віку зі спорадичними папілярними карциномами (групи «дорослі» й «молоді»). Аналізу піддано: розмір пухлин та частота розподілу їх за системою TNM, частота інвазійності, мультифокальності, метастазування до лімфовузлів, характер та обсяг хірургічного й радіойодного лікування, а також прогноз хвороби за критерієм MACIS. **Результати.** Незалежно від природи карциноми (спорадична чи спадкова) розмір пухлин у хворих, їхні метастатичні та інвазійні потенціали вищі у молодих пацієнтів, що відповідає встановленому раніше. Суттєвої різниці у характеристиках пухлин між групами «дорослі» та «батьки» немає, за винятком більшої частоти мультифокальних пухлин у хворих з СНМРЩЗ. Водночас, у групі «дітей» з СНМРЩЗ порівняно з групою «молоді» вищі частота пухлин категорії T2 та метастазуючих (N1a-N1ab) й мультифокальних пухлин і нижча частота карцином з інтратиреоїдною інвазією. У хворих з СНМРЩЗ з групи «діти» була більша частота пухлин T2, метастазуючих карцином та пухлин з капсульною інвазією порівняно з частотою цих показників у групі «батьки». **Висновок.** Карциноми у випадках СНМРЩЗ є більш агресивними, ніж спорадичні, особливо у нащадків першого ступеня спорідненості в родині, де вже є хворі батьки.

Ключові слова: рак щитоподібної залози, сімейний немедулярний рак щитоподібної залози, спорадична папілярна карцинома.