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Histological Variants of Papillary Thyroid Cancer in Relation to Clinical and Morphological Parameters and Prognosis

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The correlation of histological features of papillary thyroid cancer with clinical and morphological prognostic factors and cause-specific mortality was analyzed in a case-control study within a cohort of patients from the Altai Regional Oncology Center (25 cases with lethal outcome and 64 follow-up controls). Significant variability was revealed in the histological structure of papillary thyroid cancer with the prevalence of classic (62%) and less frequent follicular (19%), tall cell (8%), and solid (7%) variants. In comparison with the classic variant, the solid variant was more often associated with male sex and large tumor size; follicular and tall cell variant was associated with more frequent metastases to regional lymph nodes; follicular and solid variants were associated with an increased proportion of cases with disease stages III-IV. The main differences reflecting the effect of histological factor on the disease outcome were associated with the solid variant of papillary thyroid cancer that was detected in 21% of lethal cases and only in 2% of control subjects. The detection of this variant can be of importance as an additional prognostic factor of the postoperative survival in papillary thyroid cancer.

Key Words: *papillary thyroid cancer; histological variants; solid variant; tall cell variant; prognosis of postoperative survival*

Papillary thyroid cancer (PTC) is the most common malignant epithelial neoplasm of the thyroid gland (over 70% of all cases in Altai region), usually representing an indolent tumor with a 10-year survival rate over 95% [1,2]. At the same time, papillary carcinomas are characterized by marked clinical and morphological heterogeneity: the 4th edition of the WHO classification of endocrine tumors (2017) has identified 14 histological variants of PTC, among which there is a small group of the so-called "aggressive" subtypes that have a less favorable clinical course [3-7]. Their frequency is generally low – among the relatively common are tall cell, diffuse sclerosing, and solid variants (3-19, 1-6, and 1-3% of cases of PTC); columnar cell and hobnail variants represent not more than 1% of cases [6,7].

All aggressive variants are more or less associated with a higher rate of recurrences and metastases, in some cases with a lack of sensitivity to radioiodine and with lower survival rates [6,7]. At the same time, some studies failed to show statistically significant relationship between tumor histological variant and disease outcome [8-10]. Thus, further analysis is required to consider the possible use of this factor in the comprehensive risk-assessment of adverse outcome in PTC. Such an analysis should also take into account the geographical aspect, since the relative proportion of individual variants and their prognostic value may differ in different populations. Altai region is a territory with one of the highest thyroid cancer incidence rates in Russia [11]. In 1949-1962, it was

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partially exposed to radioactive fallout from the Semipalatinsk nuclear test site [12].

The aim of this work was to analyze the relationship between histological features of PTC and clinical and morphological prognostic factors and cause-specific mortality within 10 years after surgery in a case-control study within a cohort of patients from the Altai Regional Oncology Center.

MATERIALS AND METHODS

The study is based on the results of clinical and morphological examination and treatment of 89 patients with PTC. From January 2003 to December 2015, 3101 patients with PTC underwent surgery at the Altai Regional Oncology Center. Their clinical data were entered into a single database further supplemented with information on outcomes from the Altai regional cancer registry. By the end of retrospective data analysis, 35 (1.1%) patients had died as a result of PTC progression at different time intervals (from 19 days to 9.8 years after surgery). For each of them, 3 patients of the general cohort were randomly selected as controls with the condition that they had survived for at least 10 years of postsurgical follow-up. After screening for the availability and quality of the morphological material, a final sample was formed, which included 25 cases with cause-specific fatal outcome and 64 controls.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki of WMA. All patients signed an informed consent for medical intervention on admission to the Altai Regional Oncology Center. The protocol of the study was approved by the Biomedical Ethics Committee of the Federal Research Center of Fundamental and Translational Medicine (Protocol No. 26, November 1, 2022).

The mean age of PTC patients was 50.4±13.9 years (17-78 years), 66% were aged 30-60 years. Women predominated among the patients — 77 (87%) cases, men — 12 (13%) cases. Surgical procedures included total thyroidectomy (64% patients) or hemithyroidectomy. Expansion of the surgical scope depended on the extent of nodal involvement. Patients with multifocal carcinoma and cases in which treatment of PTC involved the use of radioactive iodine, external irradiation, and chemotherapy were excluded from the study. Clinical and pathological parameters and the stage of the disease were determined according to TNM classification (2010). T1, T2, T3, and T4 tumors were found in 59 (67%), 9 (10%), 13 (14%), and 8 (9%) patients, respectively. Regional lymph node metastases were present in 39 (44%) and distant metastases in 2 (2%) patients. Capsular invasion was found in 42 (47%) cases.

Surgical samples were fixed in 10% neutral formalin and embedded in paraffin using standard tissue processing. Sections (3-5 μm) were stained with hematoxylin and eosin, analyzed in a Leica DM 4000B universal research microscope and microphotographed using an Aperio AT2 scanning microscope (Leica Biosystems). The threshold values of tall cell (30%) and solid (70%) components for the diagnosis of the corresponding histological variants were determined according to the recommendations relevant at the time of the study [5,13].

The results were statistically processed using Statistica 12.0 (StatSoft, Inc.) and SPSS Statistics 26.0 (IBM) software. The distribution of continuous variables was assessed by the Shapiro—Wilk test. Normally distributed parameters were expressed as $M \pm \sigma$, otherwise — as Me (25%-75%). Student's t test or nonparametric Mann—Whitney U test was used to compare quantitative data in two independent groups, one-way ANOVA or Kruskal—Wallis test for three and more groups comparison. Cut points for categorization of continuous variables were based on previously recognized values or results of ROC-analysis. Associations between categorical variables were assessed by Pearson's χ^2 or Fisher's exact test. Cramer's V coefficient and odds ratio (OR) were calculated to measure the strength of associations. The differences were statistically significant at $p<0.05$.

RESULTS

Histopathological analysis revealed the variability of PTC histological patterns with predominance of classic (62%) and follicular (19%) variants, less frequent were tall cell variant (8%), solid (7%), diffusely sclerosing (2%), clear cell (1%), and undifferentiated (1%) (Figs. 1, 2).

The classic variant of PTC had typical architectural and cytomorphological features: randomly oriented papillae with fibrovascular cores, nuclear changes (enlarged, overlapping nuclei with irregular contour, chromatin clearing and margination, nuclear grooves, and pseudoinclusions), numerous psammoma bodies (Fig. 1, *a*, *b*). In the presence of an invasive component, the latter often had a multifocal localization without formation of solid fields. Sometimes we observed marked perivascular invasion (venous or less often lymphatic components) and tumor cell emboli within small vessels. Follicular variant consisted almost entirely of follicles (Fig. 1, *c*, *d*) lined by cells with typical nuclear signs of papillary carcinoma, often with cystic component (in the form of small and large cystic structures) and thickened fibrous capsule. There were single psammoma bodies as well as areas with papillary structure.

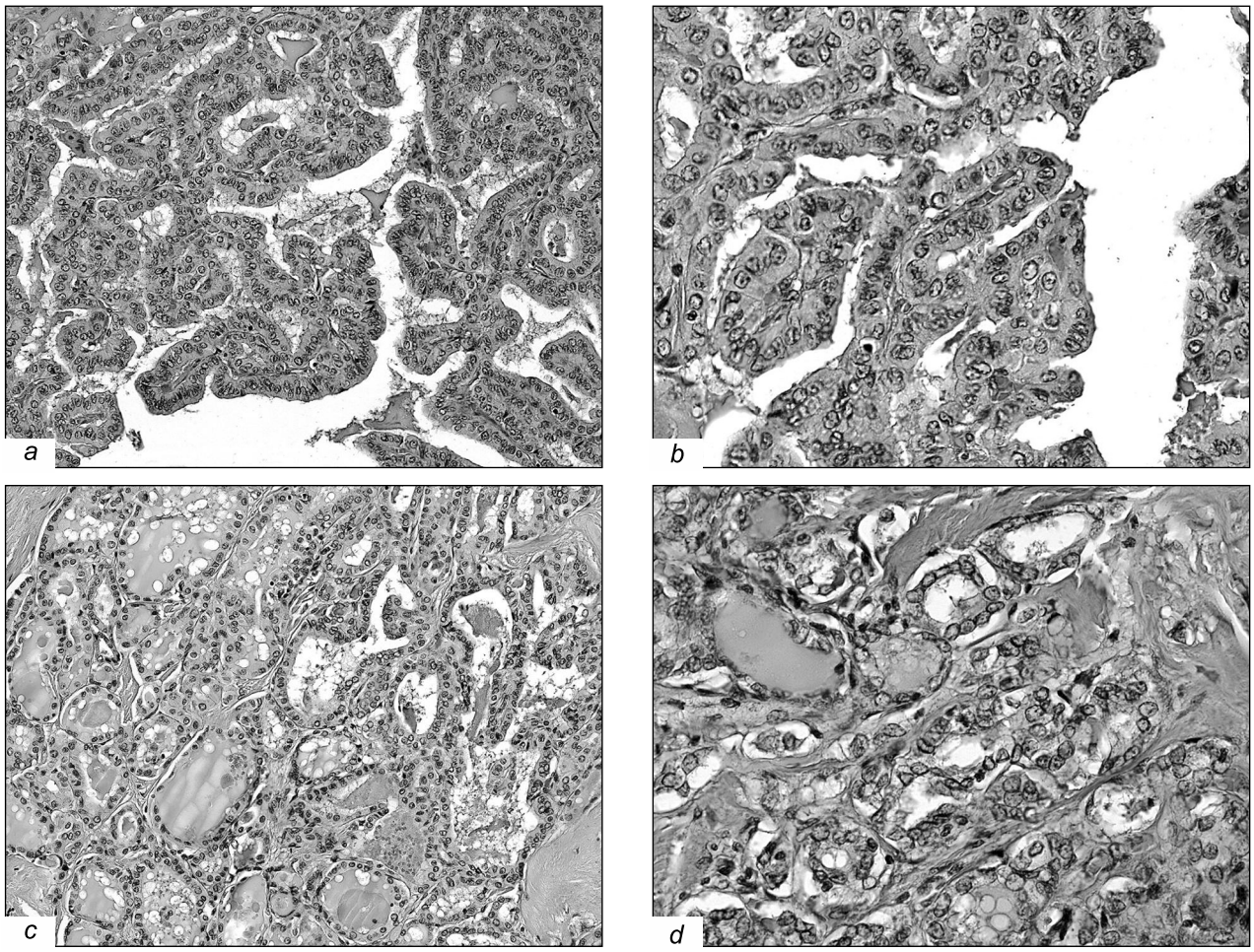

Fig. 1. The most common histological variants of PTC. Hematoxylin and eosin staining, ×100 (*a*, *c*), ×400 (*b*, *d*). *a*, *b*) Classic; *c*, *d*) follicular.

The tall cell variant was characterized by tall (height 3 times greater than thickness) parallel arranged cells with eosinophilic cytoplasm and basally oriented nuclei, which lined the papillary and elongated follicular structures (Fig. 2, *a*, *b*). The nuclear features of PTC were pronounced; in two cases, multiple pseudoinclusions in a single nucleus created a "soap bubble" pattern. The solid variant almost always had no capsule and was characterized by invasive growth. Tumor cells also had typical PTC-like changes, psammoma bodies were extremely rare, fibrous trabeculae were sometimes observed (Fig. 2, *c*, *d*).

In the microscopic picture of diffuse sclerosing variant, along with classical morphology of PTC, there was a predominance of stromal component of fibroplastic cells; foci of squamous cell metaplasia, intensive lymphoid infiltration, numerous psammoma bodies were observed. The clear-cell and undifferentiated variants were characterized by a combination of clear-cell changes and anaplastic carcinoma pattern with classical signs of papillary carcinoma. In our sample, these subtypes were represented by single observations; therefore, along with the diffuse sclerosing variant (2 cases), they were excluded from the analysis.

Associations with clinical and pathological parameters. When evaluating the associations between the most common subtypes of PTC (classic, follicular, tall cell, and solid; n=85) and patient sex, the main differences were related to the significant predominance of classic variant (70%) in women and rarer detection of the solid variant (4%), compared with the corresponding indices for men (33 and 25%; p=0.017). No statistically significant correlations with age were found (Table 1).

Solid tumors were generally characterized by a larger size ($\geqslant$2 cm); the incidence of these cases (83%) as well as the median tumor size in this subgroup (5 cm) were significantly higher than in classic and follicular variants (22 and 12%, p=0.005 and p=0.003; 1.2 and 1.0 cm, p=0.003 and p=0.005, respectively) (Fig. 3). For the tall cell and solid variants of papillary carcinomas, there was some tendency for an increased frequency of capsular invasion (Table 1).

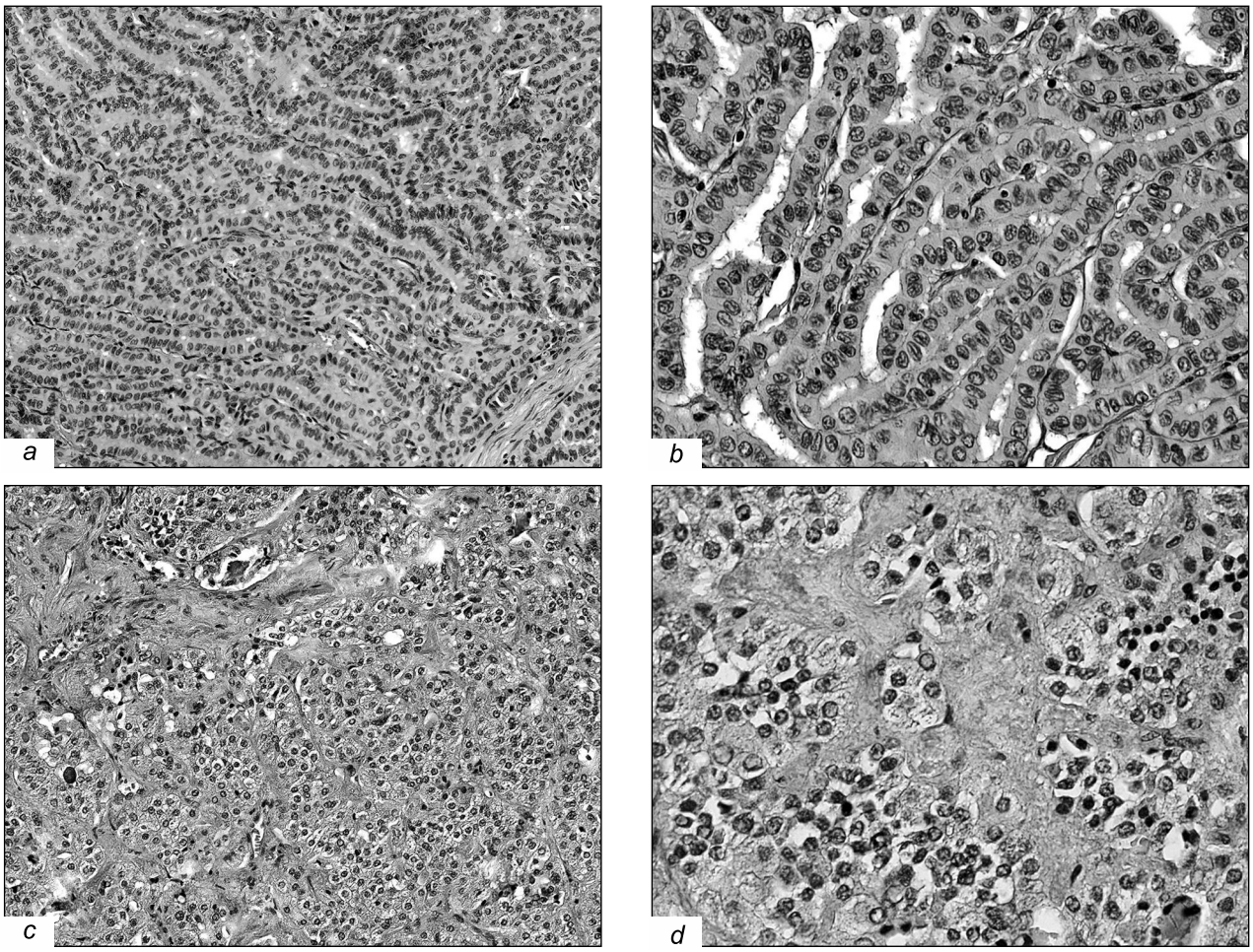

Fig. 2. Aggressive histological variants of PTC. Hematoxylin and eosin staining, ×100 (*a*, *c*), ×400 (*b*, *d*). *a*, *b*) Tall cell variant; *c*, *d*) solid variant.

TABLE 1. Associations between Clinical and Pathological Parameters and the Most Common Histological Variants of PTC

Parameter		Histological variant(*n*=85)				$p_{overall}$	$p_{pairwise}$	Cramer's V
		classical 1	follicular 2	tall cell 3	solid 4			
Sex	female (*n*=73)	51 (70%)	13 (18%)	6 (8%)	3 (4%)	*p*=0.018	p_{1-4}=0.017	0.338
	male (*n*=12)	4 (33%)	4 (33%)	1 (8%)	3 (25%)			
Age, years	$<45_{male}/50_{female}$ (*n*=42)	29 (53%)	9 (53%)	3 (43%)	1 (17%)	*p*=0.409		0.189
	$\geq 45_{male}/50_{female}$ (*n*=43)	26 (47%)	8 (47%)	4 (57%)	5 (83%)			
Size of the tumor node	<2 cm (*n*=64)	43 (78%)	15 (88%)	5 (71%)	1 (17%)	*p*=0.007	p_{1-4}=0.005	0.390
	≥2 cm (*n*=21)	12 (22%)	2 (12%)	2 (29%)	5 (83%)		p_{2-4}=0.003	
Capsular invasion	no (*n*=44)	33 (60%)	7 (41%)	2 (29%)	2 (33%)	*p*=0.204		0.232
	yes (*n*=41)	22 (40%)	10 (59%)	5 (71%)	4 (67%)			
Regional lymph node metastases	no (*n*=47)	38 (69%)	5 (29%)	2 (29%)	2 (33%)	*p*=0.005	p_{1-2}=0.004	0.376
	yes (*n*=38)	17 (31%)	12 (71%)	5 (71%)	4 (67%)		p_{1-3}=0.048	
Stage	I-II (*n*=54)	42 (76%)	8 (47%)	3 (43%)	1 (17%)	*p*=0.003	p_{1-2}=0.025	0.389
	III-IV (*n*=31)	13 (24%)	9 (53%)	4 (57%)	5 (83%)		p_{1-4}=0.007	

TABLE 2. Association of Histological Variant of PTC with Cause-Specific Mortality

Histological variant (*n*=85)	Controls (*n*=61)		Cases (*n*=24)		*p*	Cramer's V	OR (95% CI)
	n	%	*n*	%			
Classic (*n*=55)	42*	69	13*	54	$p_{overall}$=0.028		
Follicular (*n*=17)	13^{+}	21	4^{+}	17			
Tall cell (*n*=7)	5^{x}	8	2^{x}	8			
Solid (*n*=6)	1	2	5	21			
Other[1] (*n*=79)	60	98	19	79	*p*=0.006	0.337	15.8 (1.7-142.9)
Solid (*n*=6)	1	2	5	21			

Note. [1]Classic, follicular, and tall cell variants. $p_{overall}$: significance of differences in overall comparison. *p=0.007, ^{+}p=0.018, ^{x}p=0.078 in comparison with the solid variant of PTC.

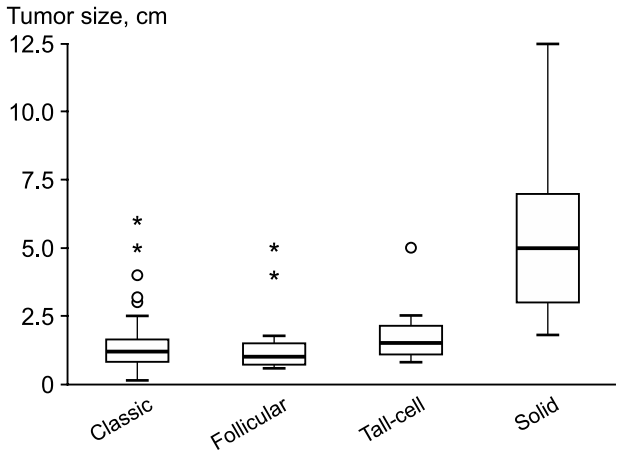

Fig. 3. Tumor size in patients with different histological variants of PTC.

Regional lymph node metastases were more typical for the follicular and tall cell variants of PTC: 70.6 and 71.4% cases *vs* 31% in the classic variant (p=0.004 and p=0.048, respectively). The differences in the incidence of metastasis between the classic (31%) and solid (67%) variants were trending (Table 1).

The stage of PTC is determined on the basis of TNM values, taking into account the age of patients relative to a threshold value of 45 years. According to our findings, the marked predominance of stages I-II (76%) was typical for cases with the classic variant, whereas detection of follicular, tall cell, and especially solid variants was accompanied by an increased proportion of cases with stages III-IV process – 53, 57, and 83%, respectively (Table 1). The most significant differences were observed between the subgroups of classic and solid variants (p=0.007) and were caused by the significant predominance of cases with stage IV disease in the latter (67%).

Associations with cause-specific mortality. When assessing the effect of PTC histological subtype on disease outcome, the main differences were associated with the solid variant, which was detected in 21% of lethal cases and in only 2% of controls (Table 2). As the distributions of classic, follicular, and tall cell variants among lethal cases and controls did not differ significantly, while the differences with the solid variant distribution were statistically significant or showed a clear trend (p=0.007, p=0.018, and p=0.078, respectively), we combined the above three variants into one subgroup for subsequent analysis. The resulting binary variable ("solid/other") demonstrated a medium strength relationship with the disease outcome (V=0.337; p=0.006) with a high odds ratio.

Thus, a considerable variability of histological subtypes of PTC in residents of the Altai region has been registered, with predominance of classic (62%), less frequently follicular (19%), tall cell (8%), and solid (7%) variants. Many researchers have paid attention to certain differences in the course of some histological subtypes, as well as their relationship with other risk factors. Some of them reported the association of tall cell and solid variants with larger tumor size, increased frequency of multifocal lesions and local recurrence, detection of regional and distant metastases [2,4,6,7,13-15]. We have found that the solid variant, in comparison with the classic one, is more often associated with male sex and large tumor size; follicular and tall cell variants are associated with more frequent detection of regional metastases. The detection of follicular and especially solid variant is accompanied by the increase in the proportion of cases with disease stage III-IV.

Some studies suggest that histological variant of tumor can be a significant prognostic factor for PTC [2,6,7]. In our work, the main differences reflecting the impact of this factor on the disease outcome are associated with papillary carcinoma of solid structure. This subtype attracted special attention when its higher frequency was demonstrated among children and young patients with PTC after the Chernobyl accident [13]. Further observations showed that it can occur at any age and without association with radiation

exposure [14]. According to our data, detection of solid PTC variant can be of importance as an additional prognostic factor for postoperative survival, however, larger multicenter studies are required to determine its independent prognostic value.

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REFERENCES

1. Gervald VYa, Klimachev VV, Ivanov AA, Ragulina VD, Avdalyan AM, Bobrov IP, Lazarev AF. Thyroid cancer. Mezhdunarod. Nauch. Issled. Zh. 2014;(8-3):17-18. Russian.
2. Shi X, Liu R, Basolo F, Giannini R, Shen X, Teng D, Guan H, Shan Z, Teng W, Musholt TJ, Al-Kuraya K, Fugazzola L, Colombo C, Kebebew E, Jarzab B, Czarniecka A, Bendlova B, Sykorova V, Sobrinho-Simões M, Soares P, Shong YK, Kim TY, Cheng S, Asa SL, Viola D, Elisei R, Yip L, Mian C, Vianello F, Wang Y, Zhao S, Oler G, Cerutti JM, Puxeddu E, Qu S, Wei Q, Xu H, O'Neill CJ, Sywak MS, Clifton-Bligh R, Lam AK, Riesco-Eizaguirre G, Santisteban P, Yu H, Tallini G, Holt EH, Vasko V, Xing M. Differential clinicopathological risk and prognosis of major papillary thyroid cancer variants. J. Clin. Endocrinol. Metab. 2016;101(1):264-274. doi: 10.1210/jc.2015-2917
3. Bogolyubova AV, Abrosimov AYu, Selivanova LS, Belousov PV. Histopatological and molecular genetic characteristics of clinically aggressive variants of papillary thyroid carcinoma. Arkh. Patol. 2019;81(1):46-51. Russian. doi: 10.17116/patol20198101146
4. Nath MC, Erickson LA. Aggressive variants of papillary thyroid carcinoma: hobnail, tall cell, columnar, and solid. Adv. Anat. Pathol. 2018;25(3):172-179. doi: 10.1097/PAP.0000000000000184
5. Bai Y, Kakudo K, Jung CK. Updates in the Pathologic Classification of Thyroid Neoplasms: a review of the World Health Organization Classification. Endocrinol. Metab. (Seoul). 2020;35(4):696-715. doi: 10.3803/EnM.2020.807
6. Coca-Pelaz A, Shah JP, Hernandez-Prera JC, Ghossein RA, Rodrigo JP, Hartl DM, Olsen KD, Shaha AR, Zafereo M, Suarez C, Nixon IJ, Randolph GW, Mäkitie AA, Kowalski LP, Vander Poorten V, Sanabria A, Guntinas-Lichius O, Simo R, Zbären P, Angelos P, Khafif A, Rinaldo A, Ferlito A. Papillary thyroid cancer-aggressive variants and impact on management: a narrative review. Adv. Ther. 2020;37(7):3112-3128. doi: 10.1007/s12325-020-01391-1
7. Ho AS, Luu M, Barrios L, Chen I, Melany M, Ali N, Patio C, Chen Y, Bose S, Fan X, Mallen-St Clair J, Braunstein GD, Sacks WL, Zumsteg ZS. Incidence and mortality risk spectrum across aggressive variants of papillary thyroid carcinoma. JAMA Oncol. 2020;6(5):706-713. doi: 10.1001/jamaoncol.2019.6851
8. Chang H, Kim SM, Chun KW, Kim BW, Lee YS, Chang HS, Hong SW, Park CS. Clinicopathologic features of solid variant papillary thyroid cancer. ANZ J. Surg. 2014;84(5):380-382. doi: 10.1111/ans.12307
9. Ganly I, Ibrahimpasic T, Rivera M, Nixon I, Palmer F, Patel SG, Tuttle RM, Shah JP, Ghossein R. Prognostic implications of papillary thyroid carcinoma with tall-cell features. Thyroid. 2014;24(4):662-670. doi: 10.1089/thy.2013.0503
10. Russo M, Malandrino P, Moleti M, Vermiglio F, Violi MA, Marturano I, Minaldi E, Vigneri R, Pellegriti G, Regalbuto C. Tall cell and diffuse sclerosing variants of papillary thyroid cancer: outcome and predicting value of risk stratification methods. J. Endocrinol. Invest. 2017;40(11):1235-1241. doi: 10.1007/s40618-017-0688-9
11. Zaridze DG, Stilidi IS, Kaprin AD, Maksimovich DM. Overdiagnosis of thyroid cancer. Prak. Onkol. 2020;21(4):312-326. Russian. doi: 10.31917/2104312
12. Lazarev AF, Shoikhet YaN, Pisareva LF, Petrova VD, Terekhova SA. The factor of ionizing radiation and thyroid cancer in women in the Altai krai. Ross. Onkol. Zh. 2017;22(4):224-228. Russian. doi: 10.18821/1028-9984-2017-22-4-224-228
13. Nikiforov YE, Erickson LA, Nikiforova MN, Caudill CM, Lloyd RV. Solid variant of papillary thyroid carcinoma: incidence, clinical-pathologic characteristics, molecular analysis, and biologic behavior. Am. J. Surg. Pathol. 2001;25(12):1478-1484. doi: 10.1097/00000478-200112000-00002
14. Ohashi R, Kawahara K, Namimatsu S, Igarashi T, Sakatani T, Sugitani I, Naito Z. Clinicopathological significance of a solid component in papillary thyroid carcinoma. Histopathology. 2017;70(5):775-781. doi: 10.1111/his.13132
15. Vuong HG, Odate T, Duong UNP, Mochizuki K, Nakazawa T, Katoh R, Kondo T. Prognostic importance of solid variant papillary thyroid carcinoma: A systematic review and meta-analysis. Head Neck. 2018;40(7):1588-1597. doi: 10.1002/hed.25123