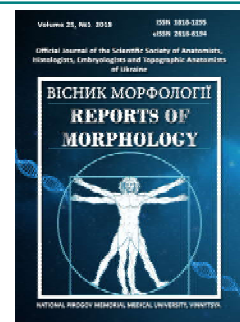




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Morphological features of radioiodine-resistance metastases of thyroid papillary carcinoma

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An important problem in the diagnosis, treatment and prediction of papillary thyroid cancer is radioiodine-resistant metastases, early prediction of which is possible on the condition of determining their cytological and histological characteristics. The purpose of this work was to identify the histological and cytological characteristics of metastases of papillary thyroid carcinomas correlated with their iodine-accumulative capacity, on the basis of which it will be possible to predict the radio-resistance of papillary thyroid carcinomas. A cytological examination of punctates of 30 papillary carcinomas and 45 of their metastases identified in the postoperative period and analysis of the histological characteristics of 100 papillary carcinomas of the general population, 47 primary papillary carcinomas and their radio-resistant metastasis and 17 primary papillary carcinomas of patients with radioiodine-uptake metastases were conducted. Statistical analysis was performed via the non-parametric criterion χ^2 in the package Statistica 11.0. It has been shown a statistically significant difference between presence of sign of follicular structures in the histological material of primary papillary cancer of patients with radioiodine-resistance metastases and between of primary papillary cancer of patients with radioiodine-uptake metastases and common population of papillary thyroid cancer. It has been shown a statistically significant difference between punctuates of radioiodine-resistance and radioiodine-uptake metastases in presence of such cytological characteristics as different subpopulations of thyrocytes. It has been shown that the cytological characteristics of radioiodine-resistant metastases differ from radioiodine-uptake metastases and primary papillary carcinomas by the presence of different subpopulations of thyrocytes, particular structures and oxyphilic changes. It is shown that such histological characteristics as lack of follicular structures in the material of primary papillary carcinomas correlate with radio-resistance and can be prognostic factors of its appearance.

Key words: thyroid papillary carcinoma, fine-needle aspiration puncture biopsy, radioiodine-resistant metastasis, cytological characteristics, histological signs.

Introduction

As a result of the accident at the Chernobyl Nuclear Power Plant, there was a sharp increase in the incidence of thyroid gland (TG) cancer. The highest increase in the level of thyroid cancer was observed among subjects whose age at the time of the accident was 18 years and younger. So, four years after the Chernobyl disaster, the incidence of thyroid cancer in children increased by 4.8 times, and in subsequent years exceeded the accident rate by 10 times [3, 9, 23]. However, in contrast to carcinoma of other localizations, differentiated thyroid cancer in most cases has a favorable prognosis: the survival 5-year rate of patients with thyroid cancer is about 98%, and 20-30

years of survival exceeds 90% [10, 14, 15]. The key to successful treatment of differentiated thyroid cancer and its metastases is the use of radioiodine therapy, a specific highly effective, targeted method of treating this disease. Radioiodine therapy is based on the unique features of the physiology of thyroid cells that are able to accumulate radioiodine and use it in the synthesis of thyroid hormones. But, unfortunately, in some cases (4-20%), in patients with differentiated thyroid carcinoma, on the background of thyroidectomy and radioiodine therapy, metastases whose cells lose the ability to accumulate radioiodine develop appear: this tumor is called metastatic radioiodine-

refractory disease [11, 12, 13]. It is these metastases that cannot be treated with radioiodine therapy and can be uncontrolled to spread in the patient's body and even be the cause of his death [5, 6, 7]. Therefore, it is important to study the immunocytochemical, genetic and morphological features of such metastases. There are some ideas about the histological manifestations of radioiodine resistance [8, 21, 25]. The most aggressive types of thyroid papillary carcinoma (PC) researchers consider high-cellular, columnar-cellular, diffuse-sclerosing, solid and widely invasive follicular variants [19]. According to the literature, some pathomorphological features of primary TG carcinoma correlate with the effectiveness of radioiodine therapy. The loss of sensitivity of the tumor to the radioiodine is thought to result in a reduction in the differentiation of its cells. The manifestation of this phenomenon is the appearance of elements of low degree of differentiation in metastatic tumors of such patients. Such attributes include such pathomorphological characteristics as solid tumor structure, cell oxyphilia, necrotic changes, high numbers of mitoses [20]. Despite the existing literature data on the histological characteristics of thyroid carcinoma with aggressive behavior, there was no clear correlation between histologic peculiarities and thyroid radioiodine resistance.

The earliest possible prediction of radioiodine resistance of papillary thyroid carcinoma is possible on the basis of the determination of the cytological characteristics of the cells of the radioiodine resistant metastases (RIRM). However, no literature data on similar cytological studies have not been found. Therefore, the *purpose* of this work was to study the histological and cytological characteristics of metastases of papillary carcinoma of the thyroid gland (PC TG), correlated with their iodine-accumulation ability, on the basis of which it will be possible to predict the radioiodine resistance of PC TG.

Materials and methods

In this work, the material obtained as a result of performing fine-needle aspiration puncture biopsy in male and female patients from the age of 17 to 40 years old who were examined surgical treatment and radioiodine therapy in the clinic of our institute were used. The specified protocol used to treat patients with thyroid cancer consists of radical thyroidectomy and lymphadenectomy, postoperative radioiodine therapy in 4-6 weeks and the appointment of suppressive hormone therapy with L-thyroxine (2.5 µg/kg). Conducting of scintigraphic and sonographic research allowed to detect in the postoperative period radioiodine-resistant metastases of PC TG and metastases capable of accumulation of radioiodine. In all cases, the diagnosis was confirmed cytologically and histologically (except for radioiodine-sensitive metastases, which were successfully treated with radioiodine and in most cases, they were not surgically removed).

According to the decision of the Bioethics Commission, SI "V.P. Komisarenko Institute of Endocrinology and

Metabolism of NAMS of Ukraine" (No. 28/1-KE of April 12, 2019) found that the study followed ethical and moral requirements, was safe for the patient's health and did not deny the basic bioethical norms of the Helsinki Declaration, the Council of the Convention Europe on human rights and biomedicine, as well as relevant provisions of the WHO and the laws of Ukraine.

Cytological studies were performed on punctures of 30 PC TG detected prior to thyroidectomy and at punctures 45 metastases of PC TG, which arose in the postoperative period following total thyroidectomy and radioiodine therapy. The punctures were fixed with methanol for 5 minutes and stained using the Romanowsky method for 30 minutes. A solution for staining was prepared from a Romanowsky concentrate produced by the Shostka Chemical Reagent Plant consisting of: 20 ml phosphate buffer 0.07 M (pH = 6.4), 1.5 ml of Romanowsky stain.

The analysis of pathological findings of 47 primary PC of patients with RIRM, their RIRM, 17 patients with radioiodine susceptible metastases (RISM) and 100 PC of the general population were carried out. In the group of patients with RIRM, three of them had a diagnosis of "diffuse sclerosing variant of PC TG", 31 with primary thyroid PC (PPC) (66%) had invasive growth in the capsule and beyond, metastases to regional lymph nodes. The histological study was carried out in the laboratory of pathomorphology of the SI "Department of Endocrinology and Metabolism" (head of the department - MD, Prof. Bogdanova T.I.).

The statistical processing of the data was done according to a non-parametric criterion χ^2 , which allows comparing the frequency of occurrence of the qualitative characteristics studied in two samples. The calculations are made in the Statistica package 11. If the sign occurs in any of the comparison groups in less than 10 cases, the Yates correction for continuity was used.

Results

A comparative study was performed on the presence of certain histological characteristics in the pathomorphological findings of the following tumor groups - PPC of patients who developed with time RIRM, the PPC of patients with RISM, the general population of thyroid PC and the RIRM group. The presence of such histological signs, which according to the literature was related to the aggressive behavior of PC-follicular structures (FS), necrotic changes (NC) and oxyphilic-cellular changes (OC), was analyzed.

The presence of FS was noted in the histological conclusions of the PPC TG in 20% of patients, in which developed RIRM. At the same time, RIRM of these patients had a papillary or papillary-solid structure, and FS were found in only 1 case (2%). In this case, in the general population of PC TG, FS were found in 60% of cases (30 times more often than in the group RIRM and 3 times more often than in PPC patients with such metastases). In this case, in the PPC group with RISM, FS were found in 70% of cases. According to the non-parametric criterion χ^2 , a statistically significant

difference at the significance level $p < 0.05$ was confirmed by the presence of a morphological sign - FS between the PPC group of patients with RIRM and PPC in the group of patients with RISM ($p = 0.002$), between the PPC group of patients with RIRM and the general population PC TG ($p = 0.000$), and between the PPC of patients with RIRM and the RIRM group ($p = 0.010$, with the Yates correction for continuity). Thus, the statistically significant difference between the PPC with RIRM and the PPC with RISM and the general group of PC demonstrates that the absence of FS is associated with the development of RIRM and may be a worrying prognostic factor in the development of radioiodine resistance of PC TG.

In the analysis of the presence of the following histological sign, the OC in the pathologist's conclusions, it was found that the frequency of its intolerance in the PPC patients with RIRM (30%) was slightly higher than in the overall population of PC TG (16%), slightly higher such as in the PPC TG of patients with RISM (23%) and RIRM group (21%). There was no statistically significant difference in the incidence of OC between the PPC patients with RIRM and PPC in patients with RISM ($p = 0.859$ with Yeats correction), and in the PPC patients with RIRM and the general population of PC ($p = 0.053$). That is, there was no correlation between the presence of this histological sign and the radioiodine resistance of the tumors under investigation.

Although the presence of histological signs of necrotic changes (NC) of the tumor is associated with the "adverse behavior" of thyroid tumors, the literature does not give a clear idea of its correlation with the ability of thyroid carcinoma precisely to accumulate radioiodine. Therefore, we conducted a comparative analysis of the incidence of NC in all of the above groups of tumors.

As a result of the performed research, it was found that the incidence of NC in the control group of patients with RIRM was higher (2%) than in the general population of PC (1%). In this case, NC did not register in the PPC patients with RISM, and in the group RIRM NC were also noted in 2 cases. The statistical analysis carried out did not reveal a

Table 1. Frequency of occurrence of the following histological signs - FS, NC and OC in primary thyroid PC of patients with RIRM and RISM, the general population of the PC and RIRM.

Sign	PPC patients with RIRM	RIRM	Total population PC	PPC patients with RISM
FS	20% *	2%	60%	70%
NC	2%	2%	1%	0%
OC	30%	21%	16%	23%

Notes: * $p < 0.05$ in comparison with the general population of the PC, the PPC patients with RISM by the criterion χ^2 .

significant difference in the frequency of NC exposure between the PPC patients with RIRM and the PPC with RISM ($p = 0.593$ with Yeats correction), and between the PPC with RIRM and the general population of PC ($p = 0.831$). The results of the research are shown in the table (Table 1).

Thus, the statistical analysis of the research has shown that the factor of absence of FS in the primary PC can be an alarming histological prognostic factor for the appearance of RIRM PC TG. At the same time, the presence of NC and OC in the primary tumor is not associated with the growth of radioiodine resistance.

Since there was no literature data on cytological research of RIRM PC TG, we have conducted comparative studies of cytological characteristics of the thyroid cells population in punctates of RIRM, RISM and the corresponding PPC TG. The performed studies showed that in the punctures of RIRM in 2 times more frequent than in their PPC there are different subpopulations of thyroid cells (which are cytologically different from the general population of thyroid cells), OC are more common, and in 10% - there are specific cellular structures that consist of a psammoma bodies surrounded by a layer of macrophages and vacuolated epithelial cells (Fig. 1).

At the same time, in all cases, the cytological characteristics of RISM are not different from their PPC, their cytograms are represented by regular epithelial layers, which

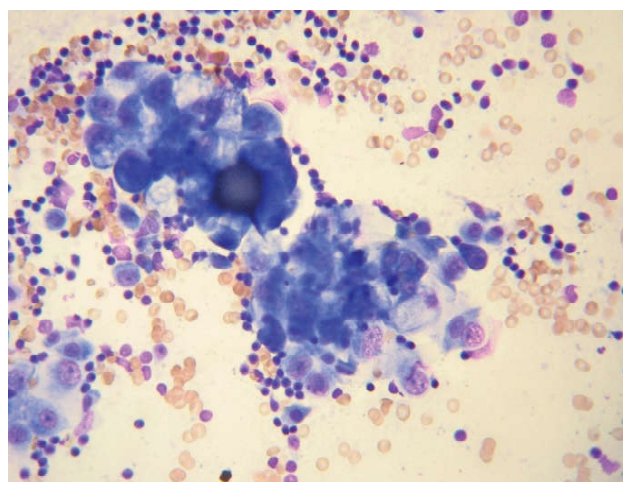
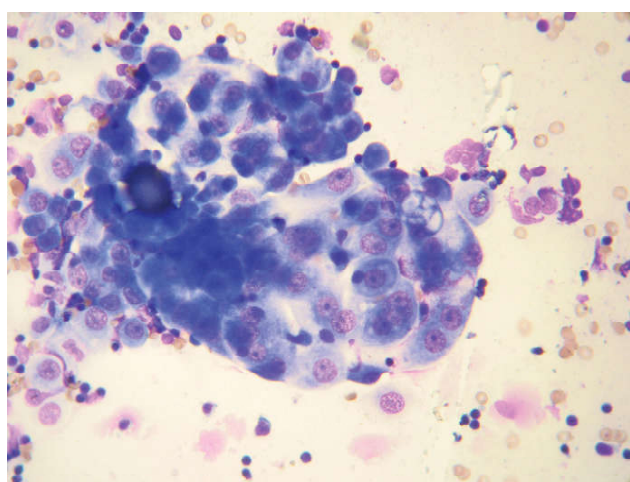


Fig. 1. Special complexes of psammoma bodies and surrounding thyroid cells with signs of expressive vacuolation in RIRM PC TG punctate. Romanowsky staining. Objective x40, eyepiece x3.3.

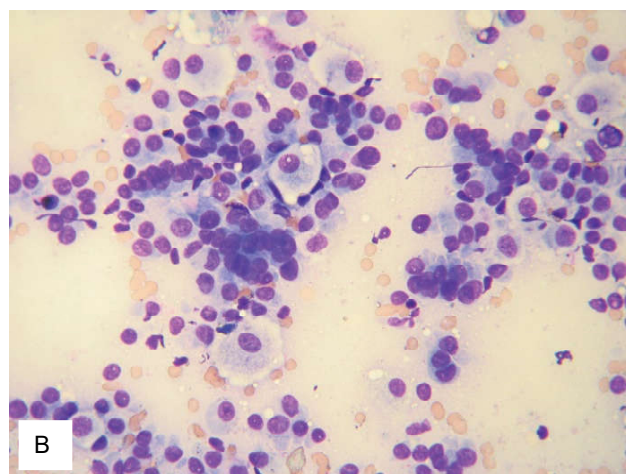
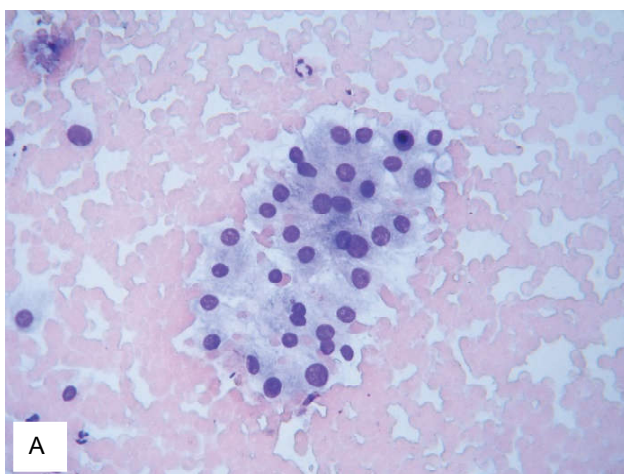


Fig. 2. A - homogeneous population of thyroid cells without expressive signs of atypia in the RISM PC TG punctate. B - different subpopulations of thyroid cells (large rounded cells with clear contour on the background of moderately enlarged thyroid cells) in the RISM PC TG punctate. Romanowsky staining. Objective x40, eyepiece x3.3.

Table 2. The frequency of various cytological signs in the RIRM and RISM PC TG punctates and the punctates of the corresponding PPC.

Types of thyroid cells	Patients with RIRM (n=30)		Patients with RISM (n=15)	
	PPC	RIRM	PPC	RISM
Different subpopulations	36,6% *	79,9% *#	0%	0%
Special complexes	0%	10%	0%	0%
OC	16,6%	26,6% *	0%	0%

Notes: * - $p < 0.05$ in comparison with RISM by criterion χ^2 ; # - $p < 0.05$ in comparison with the PPC by criterion χ^2 .

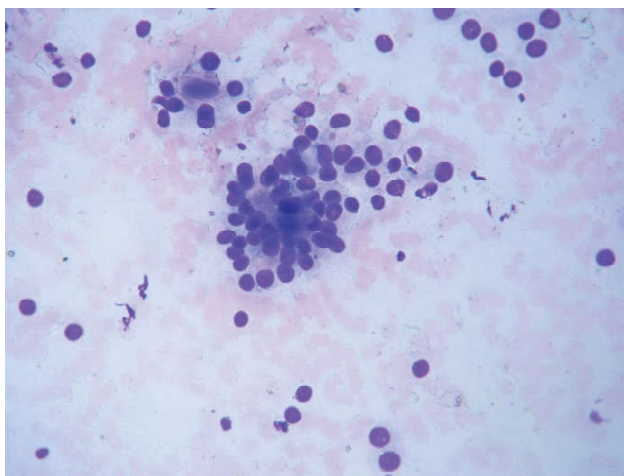


Fig. 3. Follicular structures in the RIRM PC TG punctate. Romanowsky staining. Objective x40, eyepiece x3.3.

consist of homogeneous thyroid cells, in which there are no different subpopulations of cells, OC and special structures. The punctate cells of the PPC and RISM had no signs of a marked atypia, only showing signs of proliferation of the follicular epithelium (Fig. 2, Table 2).

Another interesting observation concerns the follicular structures (FS), the presence of which is considered a

prerequisite for the accumulation of radioiodine. In spite of the fact that in the histological material of RIRM FS were noted only in the first case, we observed FS with colloid within 14% of RIRM punctures, which gives grounds to consider the absence of follicles as a pathomorphological, rather than cytological, manifestation of radioiodine resistance of PC TG (Fig. 3).

Discussion

Radioiodine resistance of PC TG is the biggest problem in the diagnosis and treatment of differentiated thyroid cancer. Since RIRM cannot be detected with a conventional scintigraphic study, it is important to be warned about the possible development of radioiodine resistance of papillary thyroid cancer, which gives the chance to timely use of additional research methods and treatments like carcinoma. Early prediction of the radioiodine resistance of PC TG is possible in the presence of histological and cytological features of such metastases. There are literary data [24] regarding some histological manifestations of aggressive behavior and radioiodine resistance of TG carcinoma, but there are no data on cytological studies of RIRM PC TG.

Complex researches and analysis of cytological and histological characteristics of PPC and their metastases, depending on their iodine accumulation ability, have allowed to reveal morphological peculiarities of metastases associated with radioiodine resistance of PC TG. It is shown that among the studied histological characteristics of tumors, only the absence of FS in the histological material of the PPC is associated with the development of their radioiodine resistance. The fact of loss of FS in the development of RIRM PC TG can be regarded as a manifestation of a reduction in the degree of differentiation resulting in the progression of the tumor. Such data are confirmed in the literature and indicate that TG carcinomas that lose FS, lose the ability to effectively concentrate and store iodine for a long time (for example, solid state metastases) [2]. The absence of FS in

the histological material of the PPC can be considered as an alarming factor in predicting their radioiodine resistance. An interesting phenomenon of the absence of FS in the histological material of RIRM (except for 1 case), when they are registered in 14% of punctures of RIRM can be explained by the fact that when conducting a FNAPB RIRM, even single follicles, which do not mark histologists, can enter into the punctate.

According to literature, tumor necrosis factor is one of the most important histologic markers of poorly differentiated PC and an independent predictor of survival of the patient, even when the histologic tumor architecture corresponds to a well-differentiated PC [14]. At the same time, we did not find a statistically significant difference in the frequency of occurrence in the histological material of such signs as NC and OC between the study groups of tumors. Accordingly, these factors cannot be considered as associated with the development of radioiodine resistance PC TG.

Since the cytological characteristics of the RIRM PC TG were not yet found, we conducted a comparative cytological study of RIRM, RISM and related PPC. It is shown that the RISM cytograms and their control groups have no distinct differences and are represented by homogeneous populations of thyroid cells without expressive signs of polymorphism and atypia. At the same time, RIRM differ in a heterogeneous population of thyroid cells, among which there are different types of cells, including enlarged thyroid cells with a clear cell surface. Different subpopulations of cells are found in punctates of RIRM 2 times more often, and OC is 1.6 times more frequent than in the PPC. The difference in the frequency of the occurrence of different subpopulations of thyroid cells in the punctates between the RIRM and their PPC and RISM is statistically proved. Attention is drawn to the special complexes of psammoma bodies and vacuolated cells that occur in 10% of RIRM and are not found in PPC and RISM. Similar to these complex structures in large numbers are presented in the histological material of the diffuse-sclerosing variant of PC, which, according to literature and our observations, is one of the most aggressive variants of PC TG. It is possible that such special structures may be candidates for the title of cytological prognostic factors of radioiodine resistance PC TG.

The presence in PC TG punctates of the RIRM of a greater diversity of cellular subpopulations and thyroid cells structures compared with the RISM group may be a manifestation of their greater genetic heterogeneity, which may be a "polygon" for the formation of new thyroid cells subclones, aggressive, may eventually lose its accumulation ability for radioiodine and cause the development of radioiodine resistance. These considerations do not contradict contemporary ideas about clonal cellular evolution

and the existence of the phenomenon of intracellular cell heterogeneity, which can be the basis for the development of the resistance of various tumors to therapy [1, 4, 16, 18].

To date, we have not found in available literature data on similar studies of the material of FNAPB of TG in this aspect. In only a few studies in the histological material of the nodal goat, heterogeneity of the thyroid epithelium population was assessed on the basis of cell proliferative activity [22]. In addition, in studies conducted on the cultivation of some lines of anaplastic thyroid carcinoma, researchers have shown that there is a small cellular subpopulation that has some properties of stem cells [17].

As a result of our research, we have received new representations about the cytological and histological characteristics of PC TG associated with their radioiodine resistance, which may be the basis for developing methods for monitoring the radioiodine resistance and developing personalized approaches to each thyroid cancer patient.

The obtained data on the cytological characteristics of RIRM (the presence of various subpopulations of thyrocytes, special cellular structures in comparison with RISM) may become the basis for the development of new methods for preoperative prediction of radioiodine resistance of PC TG. The obtained data on the histological characteristics of the PC, which correlate with their radioiodine resistance, will allow in the future to predict the behavior of the PC in advance.

Conclusions

1. The statistically probable difference in the presence of a histological sign - follicular structures between primary papillary carcinomas of patients with the development of radioiodine-resistant and radioiodine-sensitive metastases and the general population of papillary carcinomas has been proven, which allows us to consider the absence of follicular structures in the histological material of primary papillary carcinoma as an alarming prognostic factor for the appearance of radioiodine-resistant papillary metastases cancers of the thyroid gland. The lack of follicles is a pathomorphological, rather than cytological manifestation of radioiodine resistance.

2. The presence of necrotic and oxyphilic changes in the histological material of the primary thyroid papillary carcinoma cannot be considered as prognostic factors of radioiodine-resistant.

3. Cytological studies of postoperative metastases were performed for the first time in comparison with primary papillary carcinomas of the thyroid gland, which demonstrated the presence of various subpopulations and structures of thyroid cells in radioiodine-resistant metastases, which were absent in radioiodine-sensitive metastases and primary papillary carcinomas.

References

[1] Almendro, V., Marusyk, A., & Polyak, K. (2013). Cellular heterogeneity and molecular evolution in cancer. *Ann. Rev. Pathol.*, 8, 277-302 doi: 10.1146/annurev-pathol-020712-

163923.

[2] Bätge, B., Dralle, H., Padberg, B., Bettina von Herbay, & Sören, Schröder. (1992). Histology and immunocytochemistry of

- differentiated thyroid carcinomas do not predict radioiodine uptake: A clinicomorphological study of 62 recurrent or metastatic tumours. *Virchows Archiv A*, 421, 6, 521-526.
- [3] Bogdanova, T., Zurnadzhy, L., Nikiforov, Y., Leeman-Neill, R., Tronko, M., Chanock, S. ... Brenner, A. (2015). Histopathological features of papillary thyroid carcinomas detected during four screening examinations of a Ukrainian-American cohort. *Br. J. Cancer.*, 113(11), 1556-1564. doi:10.1038/bjc.2015.3723.
 - [4] Brychtova, V., Valik, D., & Vojtesek, B. (2018). Variability in the solid cell population and its consequence for cancer and treatment. *Klin. Oncol.*, 31(2), 255-2513. doi:10.14735/amko2018255.
 - [5] Busaidy, N., & Cabanillas, M. (2012). Differentiated Thyroid Cancer: Management of Patients with Radioiodine Nonresponsive Disease. *J. Thyroid Research*, 2, 1-12. <http://dx.doi.org/10.1155/2012/618985>.
 - [6] June-Key, Chung, & Gi Jeong, Cheon. (2014). Radioiodine Therapy in Differentiated Thyroid Cancer: The First Targeted Therapy in Oncology. *Endocrinol. Metab.* (Seoul), 29(3), 233-239. doi: 10.3803/EnM.2014.29.3.233.
 - [7] Dadu, R., Devine, C., Hernandez, M., Waguespack, S., Busaidy, N., Mimi, I. Hu. ... Cabanillas, M. (2014). Role of salvage targeted therapy in differentiated thyroid cancer patients who failed first-line sorafenib. *J. Clin. Endocrinol. Metab.*, 99, 2086-2094. doi: 10.1210/jc.2013-3588.
 - [8] Deandreis, D., Ghuzlan, A., Leboulleux, S., Lacroix, L., Garsi, J. P., Talbot, M. ... Schlumberger, M. (2011). Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? *Endocr. Relat. Cancer*, 18(1), 159-169. doi: 10.1677/ERC-10-0233.
 - [9] Drozd, V., Branovan, I., Shiglik, N., Biko, J., & Reiners, C. (2018). Thyroid Cancer Induction: Nitrates as Independent Risk Factors or Risk Modulators after Radiation Exposure, with a Focus on the Chernobyl Acciden. *Eur. Thyroid J.*, 7(2), 67-74. doi:10.1159/000485971.
 - [10] Dzepina, D., Zurak, K., Petric, V., & Cupic, H. (2014). Pathological characteristics and clinical perspectives of papillary thyroid cancer: study of 714 patients. *Eur. Arch. Otorhinolarygol*, 271(1), 141-148. doi: 10.1007/s00405-013-2472-6.
 - [11] Francis, Worden. (2014). Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. *Ther. Adv. Med. Oncol.*, 6(6), 267-279. doi: 12.1177/1758834014548188.
 - [12] Haugen, B., Alexander, E., Bible, K., Doherty, G., Mandel, S., Nikiforov, Y. ... Wartofsky, L. (2016). 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*, 26(1), 1-133. doi: 10.1089/thy.2015.0020.
 - [13] Ito, Y., Luster, M., Pitoia, F., Robinson, B., & Wirh, L. (2012). Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. *Expert Rev. Endocrinol. Metab.*, 7(5): 541-554. <https://doi.org/10.1586/eem.12.36>.
 - [14] Lei, S., Ding, Z., Ge, J., & Zhao D. (2015). Association between prognostic factors and clinical outcome of well-differentiated thyroid carcinoma: a retrospective 10-year follow-up study. *Oncol. Lett*, 10(3), 1749-1754. <https://doi.org/10.3892/ol.2015.3416>.
 - [15] Markovina, S., Grigsby, P. W., Schwarz, J. K., DeWees, T., Moley, J. F., Barry, A. Siegel, & Perkins, S. M. (2014). Treatment approach, surveillance, and outcome of well-differentiated thyroid cancer in childhood and adolescence. *Thyroid*, 24(7), 1121-1126. doi: 10.1089/thy.2013.0297.
 - [16] Marusya, A., & Polak, K. (2010). Tumor heterogeneity: causes and consequences. *Biochim. Biophys. Acta*, 1805(1), 105-117.
 - [17] Mitsutake, N., Iwao, A., Nagai, K., Namba, H., Ohtsuru, A., Saenko, V., & Yamashita, S. (2007). Characterization of side population in thyroid cancer cell lines: cancer stem-like cells are enriched partly but not exclusively. *Endocrinology*, 148(4), 1797-1803. doi: 10.1210/en.2006-1553.
 - [18] Le Pennec, S., Konopka, T., Gacquer, D., Fimereli, D., Tarabichi, M., Tom's G. ... Maenhaut, C. (2015). Intratumor heterogeneity and clonal evolution in an aggressive papillary thyroid cancer and matched metastases. *Endocr. Relat. Cancer*, 22(2), 205-216. doi: 10.1530/ERC-14-0351.
 - [19] Ricardo, R. Lastra, Virginia, A. LiVolsi, & Zubair, W. Baloch. (2014). Aggressive variants of follicular cell-derived thyroid carcinomas: A cytopathologist's perspective. *Cancer cytopathology*, 122(7), 484-503. doi:10.1002/cncy.21417.
 - [20] Ricarte-Filho, J. C., Ryder, M., Chitale, D. A., Rivera, M., Heguy, A., Ladanyi, M. ... Fagin J. A. (2009). Mutational Profile of Advanced Primary and Metastatic Radioactive Iodine-Refractory Thyroid Cancers Reveals Distinct Pathogenetic Roles for BRAF, PIK3CA, and AKT1. *Cancer Res.*, 69(1), 4885. doi: 10.1158/0008-5472.CAN-09-0727.
 - [21] Rivera, M., Ghossein, R. A., Schoder, H., Gomez, D., Larson, S. M., & Tuttle, R. M. (2008). Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. *Cancer*, 113(1), 48-56. doi: 10.1002/cncr.23515.
 - [22] Studer, H., Gerber, H., Zbaeren, J., & Peter, H. J. (1992). Histomorphological and immunohistochemical evidence that human nodular goiters grow by episodic replication of multiple clusters of thyroid follicular cells. *J. Clin. Endocrinol. Metab.*, 75(4), 1151-1158.
 - [23] Tron'ko, M., Kravchenko, V., Kvachenyuk, A. & Kaminsky, O. (2016). Chornobyl disaster and thyroid pathology. Health of Ukraine, 34(2):19-20.
 - [24] Vaisman, F., Carvalho, D., & Vaisman, M. (2015). A new appraisal of iodine-refractory thyroid cancer. *Endocrine-related cancer*, 22(1), 301-310. doi:10.1530/ERC-15-0300.
 - [25] Wassermann, J., Bernier, M.-O., Spano, J.-Ph., Lepoutre-Lussey, Ch., Buffet, C., Simon, J.-M. ... Leenhardt, L. (2016). Outcomes and Prognostic Factors in Radioiodine Refractory Differentiated Thyroid Carcinomas. *The Oncologist*, 21(1), 50-58. doi:10.1634/theoncologist.2015-0107.

МОРФОЛОГІЧНІ ОСОБЛИВОСТІ РАДІОЙОДРЕЗИСТЕНТНИХ МЕТАСТАЗІВ ПАПІЛЯРНОГО РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ Зелінська Г.В.

Важливою проблемою діагностики, лікування та прогнозування папілярного раку щитоподібної залози є радіойодрезистентні метастази, раннє прогнозування появи котрих можливо за умовою визначення їх цитологічних та гістологічних особливостей. Метою роботи було дослідження гістологічних та цитологічних характеристик метастазів папілярних тиреоїдних карцином, корелюючих з їх йод-накопичувальною здатністю, на основі котрих стане можливим прогнозування радіойодрезистентності тиреоїдних папілярних карцином. Було проведено цитологічне дослідження пунктів 30 папілярних

карцином та 45 метастазів, виявлених у післяопераційному періоді, проаналізовані гістологічні ознаки 100 папілярних карцином загальної популяції, 47 первинних папілярних карцином та їх радіоїодрезистентних метастазів, а також 17 первинних папілярних карцином у пацієнтів з радіоїодчутливими метастазами. Статистичну обробку отриманих даних проводили в пакеті Statistica 11.0 за непараметричним критерієм χ^2 . Вперше були проведені цитологічні дослідження післяопераційних метастазів у порівнянні з первинними папілярними карциномами щитоподібної залози, котрі виявили наявність різних субпопуляцій та структур тиреоцитів у пунктатах радіоїодрезистентних метастазів, котрі були відсутніми в радіоїодчутливих метастазах та первинних папілярних карциномах. Показана статистично імовірна відмінність в наявності фолікулярних структур в гістологічному матеріалі між первинними папілярними карциномами пацієнтів з радіоїодрезистентними метастазами, первинними папілярними карциномами пацієнтів з радіоїодчутливими метастазами та загальною популяцією папілярних карцином. Не виявлено статистично імовірної відмінності у наявності некротичних та оксифільних змін в гістологічному матеріалі між всіма досліджуваними групами пухлин. Таким чином, цитологічні характеристики радіоїодрезистентних метастазів відрізняються від радіоїодчутливих метастазів та первинних папілярних карцином наявністю різних субпопуляцій тиреоцитів, особливих клітинних структур та оксифільно-клітинних змін. Доведено, що відсутність фолікулярних структур в гістологічному матеріалі первинних папілярних карцином може застосовуватися в якості прогностичного фактору появи радіоїодрезистентних метастазів.

Ключові слова: папілярна карцинома щитоподібної залози, тонкоігольчаста аспіраційна пункційна біопсія, радіоїодрезистентні метастази, цитологічні ознаки, гістологічні ознаки.

МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ РАДИОЙОДРЕЗИСТЕНТНЫХ МЕТАСТАЗОВ ПАПИЛЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Важной проблемой диагностики, лечения и прогнозирования папиллярного рака щитовидной железы являются радиоїодрезистентные метастазы, раннее прогнозирование появления которых возможно при условии выявления их цитологических и гистологических особенностей. Целью данной работы было выявление гистологических и цитологических характеристик метастазов папиллярных тиреоидных карцином, коррелирующих с их йод-накопительной способностью, на основе которых станет возможным прогнозирование радиоїодрезистентности тиреоидных папиллярных карцином. Было проведено цитологическое исследование пунктатов 30 папиллярных карцином и 45 метастазов, выявленных в послеоперационном периоде, проанализированы гистологические характеристики 100 папиллярных карцином общей популяции, 47 первичных папиллярных карцином и их радиоїодрезистентных метастазов, а также 17 первичных папиллярных карцином у пациентов с радиоїодчувствительными метастазами. Статистическую обработку данных проводили по непараметрическому критерию χ^2 в пакете Statistica 11.0. Впервые были проведены цитологические исследования послеоперационных метастазов в сравнении с первичными папиллярными тиреоидными карциномами, которые выявили наличие разных субпопуляций и структур тиреоцитов в пунктатах радиоїодрезистентных метастазов, отсутствующие в радиоїодчувствительных метастазах и первичных папиллярных карциномах. Показано статистически достоверное различие в наличии фолликулярных структур в гистологическом материале между первичными папиллярными карциномами пациентов с радиоїодрезистентными метастазами, первичными папиллярными карциномами пациентов с радиоїодчувствительными метастазами и общей популяцией папиллярных карцином. Не выявлено статистически достоверной разницы в наличии некротических и оксифильных изменений в гистологическом материале между всеми исследуемыми группами опухолей. Таким образом, цитологические характеристики радиоїодрезистентных метастазов отличаются от радиоїодчувствительных метастазов и первичных папиллярных карцином наличием разных субпопуляций тиреоцитов, особых клеточных структур и оксифильно-клеточных изменений. Доказано, что отсутствие фолликулярных структур в гистологическом материале первичных папиллярных карцином можно применять в качестве прогностического фактора появления радиоїодрезистентных метастазов.

Ключевые слова: папиллярная карцинома щитовидной железы, тонкоигольчатая аспирационная пункционная биопсия, радиоїодрезистентные метастазы, цитологические признаки, гистологические признаки.