Genetic Testing in Differentiated Thyroid Carcinoma – Important or Not?

ANDRA BURUIANA[1]*, NICOLETA DUMITRU[1], ADINA GHEMIGIAN[1,2], EUGENIA NEDELTCHEVA PETROVA[1,2]

[1]C.I. Parhon National Institute of Endocrinology,Department of Endocrinology I, 32-24 Aviatorilor Blvd., 011863, Bucharest, Romania

[2]Carol Davila University of Medicine and Pharmacy, Clinical Department No.2, 37 Dionisie Lupu Str., 030167, Bucharest, Romania

Thyroid carcinoma is the most common endocrine cancer representing 1-1.5% of all cancers diagnosed annually. Differentiated thyroid carcinoma (DTC) with the 2 main subtypes, papillary (PTC) and follicular (FTC), is the most common. DTC incidence has increased significantly in recent years, mainly due to increased and early use of imaging techniques (thyroid ultrasonography) and fine needle biopsy of thyroid nodules. Although after radical treatment, DTC is considered to be curable, histologic and clinical presentation is very diverse, the recurrence rate being 10-30%, while 5% of patients are resistant to conventional therapy, and some are even incurable. In recent years, there has been progress in terms of describing genetic changes in thyroid carcinoma, genetic testing providing important information that may influence therapeutic decision. The practical importance of these genetic mutations (for example, BRAF V600E, RAS, etc.) and their roles in tumorigenesis, the clinical features, treatment and prognosis of thyroid carcinoma is still controversial and incompletely elucidated.The increase knowledge of molecular pathogenesis and tumorigenesis in thyroid cancer lead to the emergence of new therapies with targeted antitumor effect and minimal toxicity. Patient selection should be made taking into account the risk stratification and tangible benefits, molecular tests being expensive and inaccessible.

Keywords: differentiated thyroid carcinoma, genetic mutations, BRAF V600E

Thyroid carcinoma is the most common endocrine cancer, representing 1-1.5% of all cancers diagnosed annually and 5-10% of all thyroid nodules [1,2]. Papillary and follicular carcinomas are the two differentiated tumor-derived entities of follicular cells [3]. The incidence of small differentiated thyroid carcinomas (DTCs) (<2 cm) has increased significantly in recent years, mainly due to the intensive and early use of imaging screening techniques (thyroid ultrasound) and fine needle biopsy of thyroid nodules [3,4]. The histological appearance of papillary thyroid carcinoma (PTC) is vast, with multiple forms being described: papillary microcarcinoma (< 1 cm), classical PTC, follicular infiltrative type, high cells type, diffuse sclerosing, solid, columnar cell type, *Hobnail* variant, Hurthle cells, Warthin-like, cribriform and morular type. The increasing incidence is mainly due to the follicular variant of PTC (FVPTC). The encapsulated variant of FVPTC (EFVPTV) represents between 10-20% of all thyroid cancers. Due to its indolent character and genetic differences to infiltrating tumors, this form of cancer has been renamed and reclassified as non-invasive thyroid follicular neoplasia with papillary features (NIFTP) [3,5].

The diagnosis of certainty in thyroid carcinoma is performed by fine needle biopsy (FNAB), and the cytological results are classified according to the Bethesda system, which includes 6 categories by which cancer risk can be estimated (table 1) [6,7].

Main genetic mutations in DTC

RET/PTC rearrangements

RET (rearranged during transfection) protooncogene represents a 21 exon gene located on chromosome 10q11-2 encoding a tyrosine kinase membrane receptor [3]. It is the most common genetic modification in papillary carcinoma, having at least 10 subtypes, of which RET / PTC1 and RET / PTC3 represent > 90%. These rearrangements are found with a higher frequency in patients with radiation exposure history. RET / PTC1 is associated with papillary microcarcinomas with favorable evolution, and RET / PTC3 with the solid variant of PTC and a more aggressive tumor phenotype [8,9].

TRK rearrangements

TRK (tyrosine receptor kinase) protooncogene is located on chromosome 1 and encodes a membrane receptor for nerve growth factor (NGF). These rearrangements are found in 1-5% of PTC cases with a higher frequency in case of exposure to radiation [3]. TrkA, TrkB and TrkC kinase proteins are encoded by NTRK1, NTRK2 and NTRK3, respectively. The association between RET and NTRK in PTC is considered to have an unfavorable prognosis, suggesting the need for targeted therapy in this situation [10].

ALK rearrangements

The ALK (anaplastic lymphoma kinase) gene is found in 9% of poorly differentiated thyroid cancers, 4% of anaplastic and 1% papillary carcinomas. This mutation is considered more common in the diffuse sclerosing variant of PTC but does not predict the degree of tumor aggression [3, 11].

PAX8/PPARγ rearrangements

This rearrangement consists of a fusion of the Pax-8 coding region (Paired Box 8), an important transcription factor in thyroid ontogenesis and the Peroxisome Proliferator-Activated gamma receptor (PPARγ) coding region, a transcription factor belonging to the nuclear

* *email:andra_buruiana@yahoo.com; Phone:+4021.31.77.430*

Table 1
BETHESDA CLASSIFICATION [6,7]

Category	Risk of malignancy %	Management
I. Nondiagnostic or unsatisfactory	1-4	Repeat FNAB
II. Benign	0-3	Clinical follow-up
III. Atypia or follicular lesion of undetermined significance	5-15	Repeat FNAB
IV. Follicular neoplasm or suspicious for follicular neoplasm	15-30	Surgical treatment (lobectomy)
V. Malignancy suspicious	60-75	Surgical treatment (total thyroidectomy of lobectomy)
VI. Malignant	97-99	Surgery treatment (total thyroidectomy)

receptors family. PAX8/PPARγ was described in 30-35% of follicular carcinomas but also with a lower incidence in the follicular variant of PTC and follicular adenomas [12,13]. Therefore, preoperative detection of PAX8/PPARγ provides an increased risk of malignancy in a thyroid nodule, particularly well-differentiated thyroid carcinoma suggesting the need for total thyroidectomy. However, a small proportion of positive tumors may be benign and amenable to lobectomy, especially in small nodules or those without ultrasonography invasion signs [14].

RAS mutation

It is the second frequent mutation in thyroid carcinoma. The RAS gene encodes three isoforms: NRAS, HRAS and KRAS. These 21-kDa membrane proteins are essential in the transducing signals from G protein-coupled tyrosine kinase receptors to MAPK (mitogen-activated protein kinase) and PI3K-AKT (Phosphatidylinositol-3-Kinase) signaling pathway effectors that mediate cellular differentiation, proliferation and survival. RAS gene mutations occur in 30-45% of follicular thyroid carcinomas, in a proportion of 30-45% in the follicular variant of papillary carcinoma, 20-40% of poorly differentiated thyroid carcinomas, 10-20% in the anaplastic and rare in classical PTC. The RAS mutation is also described in 20-25% of benign follicular adenomas [15,16]. Regarding RAS utility as a molecular prognostic factor, it was not associated with tumor aggression. Even when the malignancy of the RAS-positive tumor has been histologically demonstrated, it has not been associated with extra-thyroid extension with regional or remote lymphatic metastasis, these tumors having an excellent rate of curability and excellent prognosis. Aggressiveness for RAS mutation is given by association with BRAF V600E or TERT (Telomerase reverse transcriptase)[15-17].

BRAF mutation (v-raf murine sarcoma viral oncogene homolog B)

It is the most frequent genetic mutation in patients with PTC, recurring in 45% of cases. It is located on chromosome 7 and represents the most potent activator of MAPK. The BRAF V600E mutation at nucleotide position 1799 consists of a change of valine in glutamate. Studies on the utility of this mutation as a prognostic factor are controversial. Carrier patients are prone to more aggressive forms of thyroid cancer, extra-thyroidal invasion, lymphatic metastases, the presence of BRAF V600E being associated with PTC mortality, invasive phenotype, and the progression of papillary carcinoma [18,19].

Results and discussions

There is increased evidence that different carcinomas (e.g. neuroendocrine tumors, ovarian cancer etc), including the thyroid carcinoma, remained underdiagnosed because of the enhanced number of their variants types [20-24]; additionally, the association of various comorbidities, such as diabetes mellitus, osteoporosis, renal impairment (including peritoneal dialysis and hemodialysis population) can influence the overall outcome in this group of patients [25-30].

Thyroid nodules are very common, being found in about 50% of adults. Biopsy is performed to exclude thyroid cancer. However, in 10-20% of cases cytology is undiagnosed and the decision of surgery becomes difficult. The risk of thyroid cancer in a nodule with such a FNAB result is between 10-75% [31].

When DTC is diagnosed by biopsy (Bethesda VI), the amplitude of surgery (total hemithyroidectomy or thyroidectomy) must be determined. This decision is based on the risk factors associated with tumor aggression such as the patient's sex, tumor size and the presence of lymphatic or metastatic metastases. Some genetic mutations are considered aggression markers (e.g. RAS, PIK3CA, ALK and BRAF). Once genetic testing has been performed, the results have to be taken into account in establishing the subsequent therapeutic course, although there are no specific recommendations from this point of view [6,32].

Conclusions

Due to the increasing incidence of DTC, additional information is needed regarding the molecular pathogenesis of thyroid carcinoma in order to develop new strategies, respectively, to improve those available for its

management. Further studies are needed to establish consistency between genetic diagnosis, treatment, and clinical outcome.

References

1.PELLEGRITI, G., FRASCA, F., REGALBUTO, C., SQUATRITO, S., VIGNERI, R., J. Cancer. Epidemiol., 2013:965212, 2013

2.CHOI, K.U., KIM, J.Y., PARK, D.Y., LEE, C.H., SOL, M.Y., HAN, K.T., KIM, Y.G., ANZ. J. Surg., **75**, nr. 7, 2005, p. 537

3.SCHLUMBERGER, M., PACINI, F., TUTTLE, R.M., Thyroid Tumors, Estimprim, Roche Lez Beaupre, 2016

4.RAUE, F., FRANK-RAUE, K., Clin. Cancer. Res., **22**, nr. 20, 2016, p. 5012

5.NIKIFOROV, Y.E., SEETHALA, R.R., TALLINI, G., BALOCH, Z.W., BASOLO, F., THOMPSON, L.D., BARLETTA, J.A., WENIG, B.M., AL GHUZLAN, A., KAKUDO, K., GIORDANO, T.J., ALVES, V.A., KHANAFSHAR, E., ASA, S.L., EL-NAGGAR, A.K., GOODING, W.E., HODAK, S.P., LLOYD, R.V., MAYTAL, G., METE, O., NIKIFOROVA, M.N., NOSE, V., PAPOTTI, M., POLLER, D.N., SADOW, P.M., TISCHLER, A.S., TUTTLE, R.M., WALL, K.B., LIVOLSI, V.A., RANDOLPH, G.W., GHOSSEIN, R.A., JAMA. Oncol., **2**, nr. 8, 2016, p. 1023

6.ZOLOTOV, S., Rambam. Maimonides Med. J., **7**, nr. 1, 2016

7.RENUKA, I.V., SAILA BALA, G., APARNA, C., KUMARI, R., SUMALATHA, K., Indian J. Otolaryngol. Head Neck Surg., **64**, nr. 4, 2012, p. 305

8.NIKIFOROV, Y.E., Endocr. Pathol., **13**, nr. 1, 2002, p. 3

9.ROMEI, C., ELISEI, R., Front. Endocrinol. (Lausanne), **3**, 2012, p. 54

10.SCIAVOLINO, P.J., http://www.targetedonc.com/publications/targeted-therapy-news/2016/september-2016/ntrk-fusions-in-papillary-thyroid-cancer-expanding-targetable-treatment-options, accessed May 2017

11.CHOU, A., FRASER, S., TOON, C.W., CLARKSON, A., SIOSON, L., FARZIN, M., CUSSIGH, C., ANISS, A., O'NEILL, C., WATSON, N., CLIFTON-BLIGH, R.J., LEAROYD, D.L., ROBINSON, B.G., SELINGER, C.I., DELBRIDGE, L.W., SIDHU, S.B., O'TOOLE, S.A., SYWAK, M., GILL, A.J., Am. J. Surg. Pathol., **39**, nr. 5, 2015, p. 652

12.KROLL, T.G., SARRAF, P., PECCIARINI, L., CHEN, C.J., MUELLER, E., SPIEGELMAN, B.M., FLETCHER, J.A., Science, **289**, nr. 5483, 2000, p. 1357

13.PLACZKOWSKI, K.A., REDDI, H.V., GREBE, S.K., EBERHARDT, N.L., MCIVER, B., PPAR. Res., 2008:672829, 2008

14.ARMSTRONG, M.J., YANG, H., YIP, L., OHORI, N.P., MCCOY, K.L., STANG, M.T., HODAK, S.P., NIKIFOROVA, M.N., CARTY, S.E., NIKIFOROV, Y.E., Thyroid, **24**, nr. 9, 2014, p. 1369

15.HOWELL, G.M., HODAK, S.P., YIP, L., Oncologist, **18**, nr. 8, 2013, p. 926

16.XING, M., BMC. Med., **14**, 2016, p. 12

17.GUPTA, N., DASYAM, A.K., CARTY, S.E., J. Clin. Endocrinol. Metab., **98**, nr. 5, 2013, p. E914

18.KEBEBEW, E., WENG, J., BAUER, J., RANVIER, G., CLARK, O.H., DUH, Q.Y., SHIBRU, D., BASTIAN, B., GRIFFIN, A., Ann. Surg., **246**, nr. 3, 2007, p. 466

19.YARCHOAN, M., LIVOLSI, V.A., BROSE, M.S., J. Clin. Oncol., **33**, nr. 1, 2015, 7

20.POIANA, C., NEAMTU, M.C., AVRAMESCU, E.T., CARSOTE, M., TRIFANESCU, R., TERZEA, D., NEAMTU, O.M., DANCIULESCU MIULESCU, R., Rom. J. Morphol. Embryol., **54**, nr. 1, 2013, p. 201

21.CARSOTE, M., PAUN, S., NEAMTU, M.C., AVRAMESCU, E.T., IOSIF, C., TERZEA, D., CONSTANTINOIU, S., DANCIULESCU MIULESCU, R., NEAMTU, O.M., POIANA, C., Rom. J. Morphol. Embryol., **53**, nr. 2, 2012, p. 401

22.POIANA, C., NEAMTU, M.C., AVRAMESCU, E.T., CARSOTE, M., TRIFANESCU, R., TERZEA, D., NEAMTU, O.M., FERECHIDE, D., DANCIULESCU MIULESCU, R., Rom. J. Morphol. Embryol., **54**, nr. 3 Suppl, 2013, p. 717

23.GHEORGHISAN-GALATEANU, A., TERZEA, D.C., CARSOTE, M., POIANA, C., J. Ovarian Res., **6**, nr. 1, 2013, p. 28

24.SINESCU, R.D., NICULAE, A., PERIDE, I., VASILESCU, F., BRATU, O.G., MISCHIANU, D.L., JINGA, M., CHECHERITA, I.A., Rom. J. Morphol. Embryol., **56**, nr. 2, 2015, p. 601

25.CAPATINA, C., GHINEA, A., DUMITRASCU, A., POIANA, C., Int. J. Diabetes. Dev. Ctries., **36**, nr. 4, 2016, p. 393

26.CHECHERITA, I.A., MANDA, G., HINESCU, M.E., PERIDE, I., NICULAE, A., BILHA, S., GRAMATICU, A., VORONEANU, L., COVIC, A., Int. Urol. Nephrol., **48**, nr. 3, 2016, p. 373

27.ISVORANU, I., RADULESCU, D., PERIDE, I., NICULAE, A., SINESCU, R.D., CHECHERITA, I.A., Rev. Chim.(Bucharest), **66**, no. 8, 2015, p. 1239

28.ISVORANU, I., PERIDE, I., RADULESCU, D., NICULAE, A., SINESCU, R.D., CHECHERITA, I.A., Rev. Chim.(Bucharest), **66**, no. 9, 2015, p. 1316

29.JINGA, M., CHECHERITA, I.A., BECHEANU, G., JINGA, V., PERIDE, I., NICULAE, A., Rom. J. Morphol. Embryol., **54**, nr. 3 Suppl, 2013, p. 863

30.POIANA, C., RADOI, V., CARSOTE, M., BILEZIKIAN, J.P., Bone Res., **1**, nr. 3, 2013, p. 260

31.SABRA, M., Clinical Thyroidology for the Public, **7**, nr. 5, 2014, http://www.thyroid.org/wp-content/ uploads/publications/ctfp/volume7/issue5/ct_public_v75_8.pdf, accessed May 2017

32.POIANA, C., VIRTEJ, I., CARSOTE, M., BANCEANU, G., SAJIN, M., STANESCU, B., IOACHIM, D., HORTOPAN, D., COCULESCU, M., Gynecol. Endocrinol., **26**, nr. 8, 2010, p. 617

Manuscript received:14.01.2017