Editorial Commentary

Metastases free thyroid cancer patients harbouring *TERT* mutations may benefit from a more intensive treatment and follow-up

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The telomerase reverse transcriptase (TERT) was discovered in the beginning of 1980s. This enzyme is able to preserve the chromosomes integrity by adding to their ends a specific nucleotide sequences called "telomeres" (1,2). To date, it is also well established that TERT plays a crucial role in the immortalization and proliferation of malignant cells in several type of cancers, thyroid cancer (TC) included (3,4). The most common *TERT* mutations identified among TC are *C288T* and *C250T*. A recent review has shown that 10% of evaluated TC, of different types, harboured *TERT* mutations: 86.1%, *C228T*; 12%, *C250T*; 2.1% other types. The prevalence was higher among the most aggressive subtypes of TC with the highest value in the anaplastic TC (56.8%). In fact a significant association has been reported between *TERT* mutations and: older age, larger tumor size, extrathyroidal invasion, lymph node or distant metastases, TNM stage, or recurrence. *TERT* promoter mutations might also be present in *BRAF V600E* positive TC. Patients affected by tumors with these two combined mutations have poorer prognosis and outcomes (5). These data are supported by a meta-analysis, which showed that papillary thyroid cancers (PTCs) harbouring both *BRAF* and *TERT* promoter mutations, are more aggressive than those with *BRAF*, or *TERT* promoter mutations, alone. By specifying the *BRAF* and *TERT* promoter mutations status, PTCs can be classified into four distinct risk groups with decreasing aggressiveness as follows: *BRAF* and *TERT* mutations, *TERT* mutation only, *BRAF* mutation only, or absence of both (6).

Through the cellular samples obtained by fine needle aspiration (FNA) of thyroid nodules, it is possible to define the molecular profile of the sampled thyroid nodules, improving their diagnosis and management. *BRAF V600E* is the most studied and experienced mutation of cancer for thyroid nodule due to its high specificity. The diagnostic yield can be augmented testing FNA samples for more mutations associated with TC such as *TERT*, *BRAF*, *PAX8/PPARγ*, *RAS*, and *RET/PTC*: thyroid nodules found with any of these mutations have a higher chance to be malignant. Thus the molecular profiling of thyroid nodules, especially if with indeterminate cytology at the FNA, is a helpful tool for their clinical management (7,8).

Bournaud *et al.* (9) studied the prognostic value of *TERT* promoter mutations in TC. They enrolled in a prospective study [2010–2013], 173 patients affected by differentiated TC [pT3 >20 mm, pT4 or M1; 2004 World Health Organization]. All patients were treated with total (or near total) thyroidectomy, plus lymph node dissection, (when indicated) and radioiodine (RAI) therapy. Follow-up and therapies adhered to American

Thyroid Association (ATA) guidelines [2009] (10,11). The subjects were restaged according to system defined by Tuttle *et al.* (12), and the new ATA guidelines [2016] (13). Patients were considered: (I) in remission when classified as excellent, or indeterminate response, after the first treatment; (II) whereas as having persistent disease, in those having biochemical, or structural incomplete response. Subsequently, once a year, thyroglobulin (Tg), and cervical ultrasonography (and when appropriate also other imaging), were obtained to update the oncological status of patients, up to 5 years. The patients were classified as having: (I) no evidence of disease (NED) (Tg <1 mg/L, negative AbTg, no structural evidence of TC) (13); (II) recurrent disease (biological; morphological; local; or metastatic). Deaths due or not to cancer, were registered. Mutations of *TERT* promoter, of *BRAF* exon 15, *HRAS* exon 3, *NRAS* exon 3 were evaluated in all tumors. *TERT* promoter mutations were present in 20.2% TC (the prevalence was higher in tumors with histological aggressive features, than in non-aggressive: 32.7%, *vs.* 15.3%, respectively). *TERT* mutations were also more frequently reported among patients older than 45 years, pT4 stage cancers, metastatic, or with extrathyroidal invasion. A poor prognosis was associated with *TERT* mutations in all the patients (P<0.001), but not in non-metastatic. In particular, in non-metastatic patients event-free survival was related with age ≥45, histological aggressive features and vascular invasion.

BRAF mutation was detected in 50 tumors (28.9%) with no significant difference between aggressive (24.5%) and non-aggressive tumors (30.6%), whereas *RAS* mutation was found in 27 TC (15.6%) (*NRAS*, 17; *HRAS*, 10). The association of *TERT* and *BRAF* was found in 7.5% TC, and of *RAS* and *TERT* 5.2%. Event-free survival was not related with these mutations in all patients. In multi-variate analysis, histological aggressive characteristics were linked to worse event-free survival. *TERT* mutations were strongly associated with a poorer prognosis in subjects with no metastases and aggressive histological features (9); but not *BRAF*, or *RAS*.

BRAF V600E has been associated, by several data, with aggressive behavior of PTC: recurrence; RAI refractory TC; extrathyroidal extension; and lymph node metastases (14,15). PTC-specific mortality was associated with *BRAF V600E* in a study on 1,849 patients (16). These and other studies suggested an important tumorigenic role of *BRAF V600E* in the aggressiveness, or progression, of PTC. However, other studies were also reported that did not find any association with features of TC aggressiveness (4,17,18).

Most of previous studies assessed the impact of *TERT*, on long-term outcomes, finding an association with high death risk, or of RAI courses (19,20). On the other hand, the Bournaud's study had evaluated the patient status every year, during the follow-up (9). With their study, Bournaud *et al.* showed that *TERT* mutations were related with incomplete response (after the initial therapy), and a lower NED after 5 years, even in initially non-metastatic patients, supporting a closer monitoring and more aggressive treatment of these patients (9). According to these data, few years ago, Xu *et al.* reported a retrospective study of patients with PTC, with initial low-risk histological features, and *TERT* mutations, subsequently developing metastatic disease (21).

In conclusion, *TERT* mutations may do not have a better prognostic value than histology, but they have been linked to a worse prognosis in metastasis-free patients without aggressive histological characteristics. For this reason patients affected by TC harbouring *TERT* mutations may benefit from a more intensive follow-up, and treatment. More studies in larger number of TC patients are needed to confirm the results of the Bournaud's paper, but its research could represent a promising advancement in identifying metastasis free TC patients deserving a more intensive follow-up, and treatment (9).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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