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Thyroid nodule <1cm and low-risk papillary thyroid microcarcinoma: what are today's management options?

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Opinion

Scientific evidence often does not provide the accurate answers to clinical situations with which doctor's deal. The management of patients with thyroid nodules smaller than 1cm, but with characteristics of malignancy on ultrasonography, is one of those situations where there is great "room for debate".

The American Thyroid Association's (ATA) Guideline defines as suspected malignancy those nodules on ultrasound that present as solid and hypo echoic or as a partially cystic nodule with a solid hypo echoic component, with one of more of the following features: irregular margins (infiltrative, microlobulated), micro calcifications, shape taller than wide, rim calcifications with small extrusive soft tissue component or evidence of extra thyroid extension (ETE).[1]

Regardless of whether the cervical ultrasound in these patients was appropriately ordered or not, once before a patient with a single cervical nodule smaller than 1cm and with malignant characteristics, the endocrinologist must choose to between performing a fine-needle aspiration biopsy (FNAB) as additional workup or following up with periodic sonography evaluation.

The referred ATA Guideline[1] eliminates the biopsy from the management of the sub centimeter nodules, suggesting repetition of sonography every 6-12 months. The committee justified this action, to indicate FNAB only for suspicious nodules above 1cm, by the indolence of the papillary thyroid microcarcinoma (PTMC) and because these tumors rarely present ETE, cervical lymph node or distant metastasis, especially in individuals over 60 years of age [patients younger than 40 years are at increased risk for tumor growth (5.9%) and cervical lymph node metastasis (2.2%), when compared to those over 60 years, 5.3% and 0.4%, respectively; $p < 0.05$].[2]

We, however, advocate the realization of the FNAB in all sub centimeter nodules of suspected malignancy, if technically possible, to guide and optimize the follow-up thereof. Considering the high probability of malignancy of these nodules (70% -90%)[3] not performing FNAB would most likely only delay or hide a probable diagnosis. Furthermore, we consider as the main argument for our conduct, the citological fends off the small but existing possibility of FNAB findings of high-grade malignancy. Similar thought is shared by the Korean guideline,[4] which argues that this strategy can avoid unnecessary long-term active surveillance in 20 to 40% of cases and that the FNAB findings of high-grade malignancy may even change the management strategy from active surveillance to surgery, although such cases are rare.

However, we are aware that over diagnosis has been the source of the alerted thyroid cancer epidemic and agree with the risks associated with the overtreatment of these patients, when conducted in a wreckless manner.[5] Here upon, two Japanese[2,6] prospective studies support the active surveillance as a management strategy of low risk PTMC as an alternative to surgical treatment.

Ito et al.,[2] followed 1235 patients with PTMC for an average of 60 months (18-227 months). They observed tumor growth of >3mm in sonography in 5% (5 years) and 8% (10 years); lymph node metastasis in 1.7% (5 years) and in 3.8% (10 years); need for surgery during follow-up in 15% (191/1235); progression to clinical disease (increase of >12 mm or lymph node metastasis) in 3.5%. Interestingly, the progression rate was inversely proportional to the age of patients, being 8.9% younger than 40 years, 3.5% aged between 40 and 60 years and 1.6% in patients over 60 years-old. Sugitani et al.,[6] followed 230 patients with PTMC for an average of 11 years. The rates of tumor growth, lymph node metastasis and surgical intervention were of 7%, 1% and 7%, respectively, at the end of the period.

More recently, Brito et al.,[7] proposed an interesting decision making approach to assess the applicability of active surveillance, taking into account tumor and patient variables, as well as staff/medical resources. In this study, they reinforce the excellent results seen in active surveillance at the Kuma Hospital as a result of a careful and thorough selection of patients by an experienced team in thyroid cancer with easy access to cytology and quality ultrasound; which is, in our view, also the key to the success of this conduct. They consider the ideal conditions for this patient-management method: patients over 60 years of age, expected to be compliant with the follow-up plans of an experienced multidisciplinary team; with a solitary PTMC with well defined margins, surrounded by ≥2 mm normal thyroid parenchyma and no evidence of ETE, lymph node involvement or metastasis; and a previous ultrasound documenting nodule stability.

In line with this approach, a recent review from Leboulleux et al.,[8] considered active surveillance appropriate only for patients over 40, without previous history of head and neck radiation or

family history of thyroid cancer, nor suspected ETE on ultrasound, without suspected tumor proximity to the recurrent laryngeal nerve and/or the trachea, nor suspected lymph node metastasis and without multinodular thyroid disease. In this case, the group does not even recommend FNAB in sub centimeter nodules with high sonographic suspicion of malignancy. As pointed out above, we do not agree with this approach, especially since we lose the opportunity to ward off the possibility of diagnosing more aggressive subtypes (such as high cells, hobnail, columnar, diffuse sclerosing and solid variant).

Rosai et al.,[9] in an insightful and a precocious manner, suggested changing the PTMC terminology to Papillary microtumor.[9] For them, the word carcinoma in the pathologist's report provides the surgeon and the patient with a message of considerable therapeutic, prognosis, psychological and financial impact, with greater repercussions than those justified by the biological potential of the tumor- indolent in the majority of cases. They argued, and we concur, that this terminology adaptation diminishes the risks of overtreatment, minimizes the anxiety of a cancer diagnosis and maintains unchanged a patient's eligibility for life insurance and similar products.[9]

A more recent Japanese study compared immediate surgical treatment versus active surveillance. 894 females and 259 males aged 15-88 years (median of 56 years) with the diagnosis of PTMC were analyzed prospectively.[10] The patients themselves chose their treatment modality between surgery and active surveillance. The observation period ranged from 12 to 116 months with a median of 47 months. The incidences of unfavorable events were definitely higher in the immediate surgery group when compared to the active surveillance group, but oncological outcomes were similarly excellent. Therefore these authors strongly recommended active surveillance as the best choice for patients with low-risk PTMC.[10] A highlight of this study is the evolution of the understanding and the acceptance by patients in regards of the active surveillance method, since in the initial period of these studies (1993) only 22% chose it, whereas in the period of the study above (2005-2013) 54.8% did.[10] This corroborates the importance of by whom and how the treatment options are explained to patients.

The authors observed, however, some difficulties in the clinical practice of active surveillance, starting with the impact of cancer diagnosis, as well as the patient's cultural resistance to accept the non-interventionist conduct. We need better criteria for monitoring these patients, as to an ideal frequency with which the ultrasonography exam should be performed, the potential role of thyroglobulin in the follow-up, specific surgery criteria, what are a clinically significant lymph node metastasis and other measures used to define clinically significant primary tumor growth. These criteria will certainly be better defined as more prospective studies are published. Surveys are necessary to assess acceptability of this approach among patients, families and medical community. There is need for strict adherence to follow-up, as demonstrated in the Japanese studies, where there was no loss of follow-up after 74 months in the study by Ito et al. and only 3% of loss after 11 years in the Sugitani et al. study.[2,6]

Given these issues, the adoption of active surveillance is not universal and often faces resistance from professional and medical societies. The medico legal responsibility of monitoring a patient knowingly diagnosed with a carcinoma and the barriers these patients face in terms of adherence to life or disability insurance are other problems recently conspicuous.[11]

Studies show that most low-risk PTMC do not grow or do so very slowly, and thus are mostly harmless. The role of active surveillance is to detect the rare cases that are progressive or aggressive (<10%). Some features of the disease may eventually become predictors of the minority of cases that will advance. Abundant tumor vasculature, for example, is a feature associated with higher growth, while scarce vascularization and calcifications are associated with non-progressive tumors.[12] Molecular markers (BRAF, PIK3CA, AKT1, TERT, TP53) may be useful in the future for prognostic stratification, especially the coexistence of these markers[13-16] as well as the expression of the Ki67 protein, which is associated with PTMC size, tumor invasion, lymph node metastasis, and may be used in the future as a monitoring and a clinical decision parameter.[17]

In the group of patients with low-risk PTMC that demand surgery during the follow-up (<10% of cases), it does not impact on the outcome.

Therefore, our conduct for a patient diagnosed with a PTMC and all the low-risk criteria (outlined above), such as over 40 years of age, without history of head and neck radiation, nor family history of thyroid cancer, is active surveillance. In cases where patients opt for surgery, or do not fit the ideal profile for active surveillance (has difficulty following-up, mostly), our treatment of choice is lobectomy, since there is less chance of complications (0% risk of permanent hyperparathyroidism; 0% risk of bilateral lesion of the recurrent laryngeal nerve), small chance of needing complementary surgery (less than 10% of patients will require total tireoidectomy due to recurrence in contra lateral lobe), and even when indicated, does not impact on prognosis.[20] Lobectomy is also less likely to require the use of levothyroxin to maintain the recommended levels of TSH (between 0.5-2.0).[1] Therefore in these cases, lobectomy has a loco regional recurrence rate of 1-4% and requires completion of thyroidectomy in less than 10% of cases, without survival impact[18-20] thus being the treatment method of choice.[1] The lobectomy has the advantage of lower complication rates, even among high-volume thyroid surgeons (7.6% versus 14.5% of total thyroidectomy).[21]

All these points are obviously controversial and the procedures recommended here are not necessarily for all cases. One must always individualize decisions. There is no right or wrong. As said in an old French proverb: Dans la médécine como dans l'amour, ni jamais, ni toujours (in medicine as in love, neither say "never", nor "always" -literal translation).

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Conflicts of interest

The author declares there is no conflict of interest.

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