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How many patients with TIR3 FNA really have a thyroid neoplasm?

Dear Editor,

When a patient presents a thyroid nodule, the primary concern is whether it is benign or malignant. Nodules are usually benign; however, 5% to 15% prove to be malignant.^{1, 2} Fine-needle aspiration (FNA) has become the primary diagnostic tool in the initial evaluation of thyroid nodules with a sensitivity and specificity ranges between 80% and 100%.³ The preoperative characterization of some thyroid nodules is still a challenge and many lesions, which diagnosis remain indeterminate after FNA cytology, are referred to surgery. About 80% of these thyroid nodules are classified as benign at histology.

We evaluated 179 patients with “indeterminate2 FNA, according to SIAPEC classification, undergoing surgery. Five patients chose lobectomy and 174 patients underwent thyroidectomy.

In 48 patients (26.8%) histological examination confirmed thyroid cancer. In 29 patients, the nodule underwent FNA was benign, but one or more carcinomas were diagnosed in different locations. In 102 patients, the indeterminate nodule was benign and has not been diagnosed any “incidental” cancer. Ultimately, in 131 patients, 73.2% of cases, there was no correspondence between cytology and histological examination.

We have considered sex, age (>or< of 65 years), the presence of thyroiditis and nodule dimension (>or< 1 cm) and have found a significant association between male sex and histological malignancy with an odds ratio male/female of 3.28, but there was not a relationship between age, the presence or absence of thyroiditis, dimension and carcinoma. A combination of clinical factors (age, sex, exposure to radiation, familial traits) and US features determines whether the clinician should proceed with further tests or observation.¹ US-FNA usefulness has increased significantly in recent years, especially for the possibilities it offers, to aspire smaller and deep-seated nodules³ whose management is based on data correlating a specific cytological reading with the probability of malignancy. The marked hypoechogenicity, the microlobulated or irregular margins, the microcalcifications, the anteroposterior diameter greater than the transverse, the intra-nodular vascularization may indicate which nodules undergo FNA. In preoperative time, US-FNA has been shown to classify 62 to 85% of thyroid nodules as benign,² then the main role of thyroid FNA is to triage patients for either surgery or conservative management.³ The Italian Society of Anatomic Pathology and Cytology classification (SIAPEC)

includes 5 categories: unsatisfactory, benign, indeterminate (Tir3), suspicious and positive for malignancy. Tir3 are associated with an approximately 25% risk of malignancy.¹ Despite a low risk of malignancy, a Tir3 diagnosis usually leads to surgical treatment, although clinical (age, performance status) and personal variables may change the final therapeutic option.⁴

Thyroidectomy is preferable in patients who have bilateral nodular disease, thyroiditis, nodules >4 cm, marked atypia or in patients who prefer it to avoid the possibility of requiring future surgery. For isolated nodules, lobectomy may be proposed. Postoperative diagnosis of malignant would lead to a completion thyroidectomy in some case, but two stage surgery has higher morbidity and increase cost if compared with initial total thyroidectomy. The possibility of more exhaustive preoperative evaluation might reduce unnecessary surgery; then, there is a need for alternative or adjunctive diagnostic tools. Scintigraphy, CT scan, elastography are not able to solve the problem of differential diagnosis. Recent studies on thyroid lesions detected incidentally at PET or PET/CT in the follow-up for non-thyroid neoplasms, showed higher Fluorine-18 fluorodeoxyglucose uptake in neoplastic nodules compared to benign. Some authors proposed repeat FNA but, once the cytological diagnosis “indeterminate” is made, patients and surgeons will decide for surgery because the second diagnosis does not necessarily cancel the validity of the first. When a Tir3 nodule has no suspicious malignant US features, intra operative frozen section can help surgeons determine the extent of surgery. The nodule size is not a useful means of distinguishing malignant from benign nodules. Sex, age, laboratory data (thyroglobulin, TSH, thyroid hormone, the presence or absence of autoantibodies) were taken into account by the various authors, but are not considered sure predictors of malignancy. In our experience, only male sex is a negative prognostic factor. On the basis of the above, there are no prognostic factors for malignancy in Tir3 nodules; therefore, current studies are trying the possible additional introduction of a genetic panel or other biomarkers which can determine a more accurate risk of malignancy and more precise preoperative selection of thyroid nodules, but many of these molecular markers are too complex or expensive for routine clinical use or are still poorly standardized.⁵ Galectin-3, telomerase, thyroid peroxidase, RET-PTC, and p53 showed relatively high accuracy for detecting malignancy. Recent reports focused on the diagnostic value of panel of microRNAs or single microRNAs in indeterminate FNA. BRAF mutational analysis is commonly used to assess the malignancy of thyroid nodules but, in some cases, it still leaves indeterminate diagnoses, because only positive results can be used to guide the decision for surgery. Clusterin isoforms, sCLU and nCLU, play an important role in the regulation of proliferation and cell death: a specific increase of sCLU is observed in papillary carcinoma, compared with a decrease of nCLU.

Ultimately, the thyroid nodule with indeterminate cytology still remains a challenge for the surgeon, because for the patients with postoperative benign disease,

this surgery would be unnecessary if the diagnosis were established preoperatively. Although rare, complications from thyroid surgery — recurrent nerve injury, postoperative bleeding, hypoparathyroidism and infection — can be serious or even life-threatening.

Surgery is necessary in TIR3 cases because we have no other parameters to select malignant from benign nodule and in this we are comforted by the lack of long-term complications in our patients. Surgeon's experience is an important factor which can influence the onset of these complications; the use of ultrasonic dissector can only help surgical action but cannot replace the experience. We do not consider acceptable the risk of leaving a tumor that certainly has low aggressive behavior, but that often presents infiltration of the thyroid capsule. The potential of molecular diagnostics is promising, but they should be used judiciously until further data guide us as to their precise value as well as their limitations.

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