

Clinical Science

# Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology



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## KEYWORDS:

Indeterminate cytology;  
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Predictive marker;  
Thyroidectomy

## Abstract

**BACKGROUND:** We investigated the efficacy of thyroglobulin antibodies (TgAb) in detecting malignancy in indeterminate thyroid nodules and evaluated the possible association between TgAb and autoimmunity in papillary thyroid carcinoma (PTC).

**METHODS:** This retrospective, nonrandomized study included 1,646 patients who had undergone preoperative fine-needle aspiration biopsy to evaluate their thyroid nodules, and then standard total thyroidectomy. Of 194 patients (11.8%) with indeterminate nodules, 61 (31.4%) had PTC and 133 (68.6%) had benign nodules at the final histologic examination.

**RESULTS:** Univariate analysis showed that multifocality ( $P = .002$ ), bilaterality ( $P = .003$ ), lymph-node metastasis ( $P = .030$ ), and capsule penetration ( $P = .003$ ) were significantly associated with positive TgAb in patients with indeterminate cytology and histopathologic diagnosis of PTC. The multivariate analysis showed that TgAb positivity ( $P < .001$ ) and preoperative thyroid-stimulating hormone levels ( $P = .022$ ) were independent predictive factor for PTC diagnosis in patients with indeterminate cytology.

**CONCLUSIONS:** Preoperative TgAb could be a marker for PTC in patients with indeterminate thyroid nodules, increasing diagnostic accuracy. TgAb positivity could also influence the clinical assessment and subsequent selection of total thyroidectomy.

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Thyroid nodules are a common clinical problem. The incidence of thyroid nodules detected with ultrasound is 19% to 67% in the general population and exceeds 50% in patients older than 65 years.<sup>1,2</sup>

Estimates of the rate of malignancy in thyroid nodules are subject to several biases because not all nodules undergo surgical resection and confirmatory pathological analysis. However, histopathologic findings have revealed that significant numbers of nodules (up to 15%) display malignant biological behavior, so adequate evaluation is essential.<sup>3,4</sup> The gold standard technique for evaluating thyroid nodules remains ultrasonographically guided fine-needle aspiration biopsy (FNAB), which yields cellular material suitable for cytological analysis.<sup>3</sup> When adequate material is available, cytology provides a reliable diagnosis of benign nodules at a rate that ranges from 62% to 85% of patients.<sup>5</sup> Approximately, 5% of nodules are cytologically malignant and are typically papillary thyroid carcinoma (PTC), which represents 70% to 80% of all thyroid carcinomas.<sup>5</sup>

Currently, 15% to 30% of biopsied nodules are characterized as “indeterminate”, as defined by the Bethesda criteria, (Bethesda III: atypia of undetermined significance or follicular lesion of unknown significance; Bethesda IV: follicular neoplasm or suspected follicular neoplasm; Bethesda V: suspected malignancy).<sup>2</sup> These indeterminate nodules have an approximate risk of malignancy of more than 25%. According to American Thyroid Association guidelines, malignancy cannot be confirmed with FNAB and cytological analysis because the diagnostic hallmarks of thyroid carcinoma, such as vascular and capsular invasion, are not detectable with cytology.<sup>3</sup> Although in patients with atypia or follicular lesion of undetermined significance, a repeat FNAB is recommended in 6 to 12 months, thyroid nodules with indeterminate features cause a significant problem for the clinician, and at present, only surgical excision and histopathologic analysis can provide a final diagnosis.<sup>6,7</sup>

The current guidelines recommend surgical resection of these nodules to permit their pathological evaluation, although only 15% to 30% of these nodules prove malignant (usually either a follicular variant of PTC or follicular carcinoma).<sup>5,8,9</sup>

The diagnosis of indeterminate FNAB cytology has been associated with thyroid autoimmunity and not with malignancy in a group of patients with thyroid nodules.<sup>10</sup> In contrast, in a previous study, we showed a positive correlation between thyroglobulin antibodies (TgAb) and PTC in patients with indeterminate nodules.<sup>11</sup>

Indeterminate thyroid nodules represent a difficult challenge for clinicians, and their clinical assessment, evaluation, and surgical treatment in different series of patients are still contentious.<sup>12,13</sup> The aims of this study were 2 fold: (1) to investigate whether TgAb are a potential predictive marker of PTC in patients with indeterminate thyroid nodule cytology; and (2) to examine the possible

association between preoperative TgAb and autoimmunity in patients with PTC.

## Methods

This was a retrospective cohort study. We reviewed 1,646 patients who had undergone preoperative FNAB and standard total thyroidectomy during the period between January 2001 and December 2010 at the Department of Otolaryngology in Venizeleio General Hospital, Heraklion, Crete. The TgAb levels of all patients were measured before surgery.

The inclusion criteria were adult age, indeterminate cytology on FNAB, standard total thyroidectomy, and preoperative measurement of TgAb. The 6th edition of the UICC TNM Classification of Malignant Tumors (2002) was used to describe and categorize the cancer stages and progression. The exclusion criteria were previous thyroid or parathyroid surgery, Graves disease, previous neck surgery, a family history of cancer, and a history of neck radiation. Nodules with lesions suspected of malignancy on FNAB (Bethesda V) were also excluded to increase the sensitivity of TgAb as a potential marker of PTC. In addition, 14 patients with indeterminate nodules had a follicular or Hürthle cell carcinoma at the histologic examination. We excluded these 14 patients from our study because the aim was to investigate the correlation of PTC and TgAb and not the different and more aggressive clinical course of follicular and Hürthle cell thyroid carcinoma.

Based on the Bethesda criteria for FNAB, indeterminate nodules were subdivided into 2 categories: (a) follicular lesions of undetermined significance or atypia of undetermined significance; and (b) follicular neoplasms or lesions suspected to be follicular neoplasms.<sup>3</sup> All thyroid nodules with U/S features suspicious for thyroid malignancy (microcalcifications, hypervascularity, ill-defined and irregular margins, hypoechoic rim) were subjected to FNAB regardless of their size ( $>10$  mm or  $\leq 10$  mm).

All thyroidectomies were performed by 4 surgeons at our hospital based on the American Thyroid Association guidelines taskforce on thyroid nodules. Surgical management of the patients was recommended on referral to our hospital for heterogeneous reasons, such as malignant or suspicious thyroid nodules by U/S features and FNAB, multinodular goiter, hyperthyroidism, or compression of neighboring structures. The thyroid specimens were histopathologically evaluated by 3 pathologists at our hospital, and the entire gland and additional nodal tissue were evaluated as 1-mm thick anatomical slices. The histopathologic diagnoses were made blindly by 2 independent pathologists, according to the guidelines of the World Health Organization. The patients' records, containing their clinical data and circulating TgAb levels, were not available to these pathologists.

Our database included the age at the time of surgery, sex, surgical treatment, preoperative TgAb, and

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