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### Original research

# THY3 cytology: What surgical treatment? Retrospective study and literature review



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#### ABSTRACT

*Introduction:* THY3 nodules collects 20% of cytological examinations, with a rate of malignancy by about 20–30%, and represent one of the most controversial topics of scientific debate. In fact, differential diagnosis of follicular lesions, is very difficult, due to the inability of cytology to differentiate between adenomas and carcinomas. Surgery represents the only possible diagnostic and therapeutic approach, but on the type of surgery there is still absolute discordance of opinions.

*Methods*: We retrospectively analyzed 230 patients undergoing total thyroidectomy for THY3 cytology between May 2007 and September 2013. Subsequently we re-evaluated our results assuming a conservative surgical approach in patients without preoperative contralateral pathological evidence.

Results and Discussion: Our results indicate an incidence of malignancy in THY3 cytology of 29.6% (n=68/230), in line with literature data; multifocal bilateral carcinoma in 26.5% of patients; 37 incidental carcinomas (16.5%), 15 of which located contralateral at THY3 nodule; nodular hyperplasia in 52.2% of patients. So, according to a conservative surgery, among patients ideally underwent lobectomy (n=110), we wouldn't recognize 10 of overall 105 malignancies (9.5%) (including bilateral tumors on THY3 and contralateral incidental carcinomas). Thus, these malignancies would be neither diagnosed nor removed during surgery.

Conclusions: We believe these results allow to state that total thyroidectomy is oncologically the most appropriate intervention to make the patient "disease-free". Moreover, our study could serve as a motivation for further research, but maybe is needed a new Consensus Conference to define a surgical protocol universally recognized.

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#### 1. Introduction

The cytology THY3 class represents one of the most difficult and controversial topics of scientific discussion, as a nosological entity since to date undefined, according to universally recognized parameters, nor supported by any unique and unanimously approved protocol.

Within the large group of nodular thyroid diseases, cytology THY3 class forms the focal point of a long scientific debate: collects

20% of cytological examinations, with a rate of malignancy by about 20–30% at final histology [1–3] and may include a wide variety of follicular lesions (adenomatous hyperplasia, follicular adenoma and carcinoma, follicular variant of papillary carcinoma, Hurtle cell adenoma and carcinoma) and not (Tables 1–2). In cases of lesions with follicular pattern, fine needle aspiration biopsy (FNAB) alone does not differentiate adenomas from carcinomas, characterization allowed only by the histology, after surgical excision of the lesion.

Due to the nosologic polymorphism that characterizes the THY3 class, in recent years most of the guidelines introduced two subclasses that identify two groups of lesions with different degree of malignancy: the revision by Royal College of Pathologists (RCPath) [2] of the previous British Thyroid Association (BTA) classification identifies two subclasses, THY3a (atypia/non-diagnostic) and

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**Table 1**Diagnostic categories of FNA reports (British Thyroid Association — Royal College of Physicians, Guidelines for the management of thyroid cancer, 3rd Edition, 2014) [3].

Classification	Description	Clinical action
THY 1	NON-DIAGNOSTIC	Repeat FNAB
	(inadequate or non-representative)	_
	Due to technical mistakes or to poorly cellular samples	
THY 2	BENIGN (or NON-NEOPLASTIC)	Follow up
	(endemic goitre, hyperplastic nodules, Hashimoto's autoimmune thyroiditis, De Quervain's granulomatous thyroiditis)	-
THY 3	NEOPLASM POSSIBLE	
	(follicular proliferation)	
	FNA can't discriminate benign follicular lesions (adenomas) from malignant lesions (carcinomas)	
THY3 a	Follicular lesion/atypia	Repeat FNAB
THY3 f	Follicular neoplasm	Surgery
THY 4	SUSPICIOUS OF MALIGNANCY	Surgery
	There are not enough cytological atypia or neoplastic cells to make a certain diagnosis (usually suspicious papillary carcinomas)	
THY 5	DIAGNOSTIC OF MALIGNANCY	Surgery, other treatments
	Cytological aspect of certain malignancy	

**Table 2** Comparison between cytological classifications of thyroid nodule [1,3,4,15].

BTA 2014	SIAPEC 2007 (rev. 2013)	Bethesda 2009	ATA 2006 (rev. 2010 AACE/AME/ ETA)
THY1 Non-diagnostic/ inadequate	Tir1 Non-diagnostic	I Unsatisfactory	Non-diagnostic/ unsatisfactory
THY2 Benign	Tir2 Negative for malignant cells	II Benign	Benign
THY3a Atypia	Tir3a Low risk follicular proliferation	<ul><li>III Atypia of undetermined significance (AUS) – Follicular lesion of undetermined significance (FLUS)</li></ul>	l Follicular lesion
THY3b Follicular lesion	Tir3b High risk follicular proliferation	IV Follicular neoplasm	
THY4 Suspicious for malignancy	Tir4 Suspicious for malignancy	V Suspicious for malignancy	Suspicious for malignancy
THY5 Malignant	Tir5 Malignant	VI Malignant	Malignant

THY3f (follicular lesion/suspect follicular neoplasia) (Table 1). This subclassification has been accepted by the scientific community, spreading widely in common nomenclature and finding similar designations in other international systems (Table 2) [1,4].

These indications of method, rather than facilitate the diagnostic approach to the problem, they paradoxically burdened side effects linked to the subjectivity of interpretation of data. Those relating to the incidence of THY3 nodules on cytology and rate of malignancy [1,3] suggest that many patients who in retrospect will be benign histologically diagnosed, undergo unnecessary surgery and *de facto* not devoid of risks and complications.

The optimization of differential diagnosis is a prerequisite for a surgical approach more effective and less risky and remains the cornerstone of the solution: the recent years have seen experimenting with alternative and complementary techniques to FNAB, with encouraging results from genetic analysis supplemented by immunocytochemistry [5,6]. Were identified several genetic [7,8] and molecular markers [9–11] indicative of degree of cellular differentiation and biological aggressiveness of a nodular lesion, but none has proven so far unable to deliver, on its own, the differential diagnosis of follicular proliferations. The majority of scientific studies in progress [12,13] has deposed in favor of combined analysis of multiple molecular markers such as complementary to FNAB, in order to create a panel of monoclonal antibodies to facing the main markers, each of which add its own sensitivity and specificity to minimize the risk of misdiagnosis, thus avoiding unnecessary and expensive surgical approaches.

Surgery is the diagnostic and therapeutic approach universally recognized by the international community for the THY3 nodules, but on the type of surgery there is absolute discordance of opinions:

most international guidelines [1,3,14-16] agree that total thyroidectomy is the best action for lesions of THY4 and THY5 class larger to 1 cm, in the presence of at least one of the risk factors. For patients with unifocal papillary microcarcinoma (some even in cases of minimally invasive follicular carcinoma) and in the absence of risk factors, it is frowned a conservative treatment such as lobectomy. Similar indications are provided in relation to the treatment of THY3 nodules, but in view of the lack of a precise protocol universally applied, it is customary to choose a "reasonable compromise", a preliminary lobectomy followed by a completion thyroidectomy only against an histology that suggests a diagnosis of malignancy. It should be noted that this behavior is purely indicative and represents the best suggestion accepted by the operators, as none of the guidelines contemplates Grades of Recommendation A or B, or Levels of Evidence 1 or 2, for treating this type of lesion. It is therefore advisable, to protect the success of treatment and then the patient's welfare, discuss each case as part of a multidisciplinary team and conduct a thorough interview with the patient, in order to assess his preferences [1,3,15,16]. The most recent scientific discoveries in oncology and the higher level of awareness and information required by patients have inevitably influenced the choices of the entire surgical field, with a tendency to prefer less invasive treatments, preserving the maximum value of oncological radicality. Thyroid surgery is not subtracted at this trend of minimally invasive [17–19] and robotic techniques [20,21], as much as demonstrates the increase of their application in other fields of surgical oncology. All the problems described above, show how the scientific debate concerning the treatment of the THY3 nodules is particularly heated and still requires the commitment of all high volume centers, with the hope that the scientific discussion

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