When Is Thyroidectomy the Right Choice? Comparison between Fine-Needle Aspiration and Final Histology in a Single Institution Experience

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Keywords

Thyroid cancer · Fine-needle aspiration · Thyroid nodules · Surgery · Thyroid cytology

Abstract

Objectives: The aim of this study was to compare SIAPEC-IAP-based cytological reports with their corresponding histological diagnoses to establish when thyroidectomy is the right choice in the management of thyroid diseases. **Study Design:** This is a retrospective review of all the consecutive thyroidectomies/lobectomies performed at Maria Vittoria Hospital during the 10-year period between January 2005 and December 2015. Patients who underwent both fine-needle aspiration (FNA) and surgical procedures in our institution were included in the study. **Results:** A total of 260 patients underwent both FNA and a thyroid surgical procedure at Maria Vittoria Hospital; 111 (42.69%) had a malignant histological report. The final cytological diagnosis was nondiagnostic (TIR-1) in 19 cases (7.31%), benign (TIR-2) in 83 cases (31.92%), indeterminate (TIR-3) in 96 cases (36.92%), suspicious for malignancy (TIR-4) in 22 cases (8.46%), and diagnostic for malignancy (TIR-5) in 40 cases (15.38%). Among the 96 cases with TIR-3 cytology, after the review, 44 (16.92%) were classified as TIR-3A and 52 (20%) as TIR-3B. The preva-

lence of malignancy among TIR-3A cases was 20.45% (9/44) and among TIR-3B cases 53.85% (28/52). The difference was statistically significant ($p = 0.0007$). **Conclusions:** Our data suggest that follow-up alone is not sufficient in TIR-3A patients given the high prevalence of malignancy within that diagnostic category (20.45%) and the low sensitivity (75.68%) and specificity (59.32%) in the distinction between TIR-3A and TIR-3B. Regarding patients with a multinodular goiter and TIR-2 at FNA, the surgical approach should not be excluded.

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Introduction

According to the National Institutes of Health (USA), approximately 1.1% of men and women will be diagnosed with thyroid cancer at some point during their lifetime. The critical issue in the management of patients with thyroid disease is to find a way to distinguish preoperatively benign nodules (>90%) from cancers [1–4]. The management of thyroid diseases has significantly changed over the past 30 years due to the widespread availability of novel diagnostic and therapeutic resources [5, 6]. Thyroid fine-needle aspiration (FNA) cytology has proven to be

the most accurate, safe, efficient, and cost-effective screening and diagnostic tool for the preoperative distinction of benign from malignant nodules [3, 4]. It is critical that cytopathologists communicate thyroid FNA results to referring physicians in terms that are concise, unambiguous, and clinically helpful [7]. To address terminology and other issues related to thyroid FNA, in 2007 the Italian Societies of Endocrinology (SIE and AME) and Pathology (SIAPEC-IAP), recommended the “5-tiered TIR system” (TIR for “tiroide” [thyroid in Italian]) as a resource to improve the accuracy of thyroid cytopathology [8]. Although this classification has achieved its aim of standardizing thyroid-reporting cytopathology, the TIR-3 category remains the most controversial. “Indeterminate” lesions have been associated with a variable risk of malignancy, ranging from 5 to 30% [7]. For this reason, in 2012 the Italian Thyroid Association (AIT), the Italian Association of Clinical Endocrinologists (AME), the Italian Society of Endocrinology (SIE), and the SIAPEC-IAP appointed a working panel of experts to update the former consensus. One of the most important changes brought by the new SIAPEC-IAP classification was the distinction between TIR-3A and TIR-3B [9]. This subdivision is similar to those developed by The Bethesda System for Reporting Thyroid Cytopathology (AUS/FLUS-FN/SFN) and by the British Thyroid Association Royal College of Physicians (Thy3 “a” and “f”) [7, 10, 11].

The aim of this study was to compare SIAPEC-IAP-based cytological reports with their corresponding histological diagnoses. In particular, we focused on the distinction between TIR-3A and TIR-3B to verify their associated cancer risk and, consequently, their clinical management.

Materials and Methods

Collection of Data

This is a retrospective review of the medical records of all the consecutive patients who underwent thyroidectomy/lobectomy at Maria Vittoria Hospital during the 10-year period from January 2005 to December 2015. Only those patients who underwent both FNA and the surgical procedure in our institution were included in this study. Demographic data such as age, sex, nodule size, and treatment were obtained for each specimen.

FNA Procedures

All thyroid FNAs were performed under ultrasound (US) guidance by dedicated thyroid specialists (endocrinologists, pathologists, or endocrine surgeons). In most cases, thyroid nodules were aspirated using a 21-G needle on a 20-mL syringe attached to a pistol-type handle; 2–4 smears were prepared by cytotechnologists for each FNA pass and fixed in 90% ethanol for Papanicolaou or

hematoxylin-eosin stains, and air-dried for Giemsa staining. The needle was optionally rinsed in saline and the rinsings were processed with a cytocentrifuge and stained with Papanicolaou stain as an adjunct to conventional smears [12]. In this way, each case comprised of a range of 3–8 glass slides each, usually a combination of Giemsa- and Papanicolaou-stained slides. Cell blocks were also made when sufficient material was obtained.

Cytological Classification

Interpretation was made by evaluating all slides with diagnostic material, irrespective of the staining method used. Adequacy was evaluated according to guidelines published by the Papanicolaou Society [13] and Goellner et al. [14]. Aspirates that fell short of the adequacy criteria were designated “nondiagnostic.”

All slides were interpreted by the team of cytopathologists at the Maria Vittoria Hospital. FNA results were reported according to the 2007 SIAPEC-IAP classification [4, 5, 7, 8, 15].

In order to meet the aim of this study, cytological smears diagnosed as TIR-3 were reviewed and reclassified by an experienced cytopathologist (S.T.) into TIR-3A and TIR-3B, according to the 2014 SIAPEC-IAP classification:

- The TIR-3A (low-risk indeterminate lesion) subcategory included:
 - samples with increased cellularity with numerous microfollicular structures and poor colloid amount;
 - sparsely cellular samples containing microfollicular groups, also with oxyphilic features (“Hürthle cells”), in a background of scant colloid.

The TIR-3A subcategory frequency should be lower than 10% and its cancer risk should be <10% [9].

- The TIR-3B (high-risk indeterminate lesion) subcategory included:
 - specimens with high cellularity in a monotonous and repetitive microfollicular/trabecular arrangement, with scant or absent colloid;
 - samples composed exclusively or almost exclusively of Hürthle cells [10];
 - samples characterized by nuclear alterations suggestive of papillary carcinoma, but too mild or focal to be included in the TIR-4 category [16].

The TIR-3B subcategory should have a frequency lower than 10% and its cancer risk between 20 and 30% [9].

When performing the review of these specimens, our expert pathologist did not know the surgical pathology so as not to be influenced in his interpretation. In cases in which more than 1 FNA was performed, the patient’s worst FNA category was given. In multinodular goiters, we biopsied the nodule with an echographic pattern more suggestive for malignancy (tumor capsular invasion, a “taller-than-wide” shape, microcalcifications, hypoechogenicity, border irregularity, and Doppler central flow).

Indications for FNA and Surgery

Thyroid-stimulating hormone (TSH) was almost always measured before proceeding with FNA. If TSH was lower than 0.8 mU/L the patient underwent a ^{99m}Tc thyroid scan; in the case of a hot nodule, the patient did not undergo FNA. Whereas, if the nodule was cold, the patient underwent FNA. As a rule, patients underwent FNA on 1 or 2 nodule(s); nodules were biopsied either if the diameter was 1 cm or more, if there was an echographic indication, or if the nodule was cold at ^{99m}Tc thyroid scan.

Table 1. Diagnostic categories, expected risk of malignancy, and suggested management in 2014 SIAPEC-IAP classification (modified by Nardi et al. [9])

Code	Cytological diagnosis	Risk of malignancy, %	Suggested actions
TIR-1	Nondiagnostic	Not defined	Repeat US-guided FNA after at least 1 month
TIR-2	Benign	<3	Follow-up
TIR-3	Low-risk indeterminate lesion	<10	Repeat FNA/clinical follow-up
TIR-3b	High-risk indeterminate lesion	15–30	Surgery
TIR-4	Suspicious for malignancy	60–80	Surgery
TIR-5	Malignant	>95	Surgery

Table 2. Characteristics of the study population

Surgical procedure	Sex, <i>n</i> (%)		Mean age, years (range)	Malignant histological report, <i>n</i> (%)	Mean diameter of neoplasm, cm (range)
	male	female			
Thyroidectomy	53	151	51.78 (15–85)	97 (46.57)	1.97 (0.1–8)
Lobectomy	22	29	50.82 (22–79)	9 (17.65)	2.27 (0.3–6)
Other surgical procedure ^a	3	2	61 (39–79)	5 (100)	1.75 (1.5–2)
Total	78 (30)	182 (70)	51.71 (15–85)	111 (42.69)	1.99 (0.1–8)

^a Among these 5 cases, 1 was the removal of a papillary carcinoma inside a thyroglossal duct cyst, and the remaining 4 were removals of thyroid tissue in the left (*n* = 1)/right (*n* = 3) thyroid lodge in patients treated in other hospitals with a local recurrence.

In our series, until 2014, the surgical indication was based on the 2007 National SIAPEC-IAP guidelines [8], so all patients with TIR-3, TIR-4, and TIR-5 at FNA were referred to surgery. From 2014, the surgical indication was based on the 2014 National SIAPEC-IAP guidelines [9] (Table 1), so all patients with TIR-3B, TIR-4, and TIR-5 at FNA were referred to surgery. All patients with TIR-3A at FNA (*n* = 13) were referred to surgery; however, 3 were not operated on due to comorbidities or refusal of the surgical procedure, and were excluded from the study.

TIR-1 and TIR-2 patients were referred to surgery based on compressive goiter, and/or uncertainty for malignancy at US (tumor capsular invasion, a “taller-than-wide” shape, microcalcifications, hypoechogenicity, border irregularity, and Doppler central flow). TIR-1 patients were referred to surgery also when there was high risk of a nondiagnostic result with a repeat FNA.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 6. The 2-tailed Fisher exact test was used to compare 2 × 2 contingency tables, while the Student *t* test was used to test for significant differences in normally distributed data.

The 2 × 2 contingency tables were created considering thyroid FNA as a “screening test.” First, a comparison between benign FNAs (TIR-2) and malignant FNAs (TIR-4 and TIR-5) was performed. True positives (TP) were defined as nodules with malignant cytology and a corresponding malignant postoperative histology result. True negatives (TN) had both a benign cytology and

histology. False negatives (FN) were defined as nodules with a benign cytology and malignant histology. False positives (FP) had a malignant cytology and benign histology.

The remaining categories, TIR-3A and TIR-3B, were then added considering:

- TIR-3A as TN with a benign histology and FN with a malignant histology;
- TIR-3B as TP with a malignant histology and FP with a benign histology.

The TIR-1 category was excluded from the statistical analysis because these diagnoses usually led to either a repeat FNA or, if the clinical suspicion was strong, a surgical procedure.

Finally, when the histological report found a microcarcinoma (papillary carcinoma ≤1 cm in diameter) associated with a TIR-2-cytological report, we considered it to be FN only if the area of the FNA included the area in which the cytopathologist found the carcinoma.

Results

From January 2005 through to December 2015, 260 patients underwent both FNA and a thyroid surgical procedure at Maria Vittoria Hospital. For each specimen, demographic data such as age, sex, nodule size, and treat-

Table 3. Final histological diagnoses associated with the relative cytological report

Histological report	TIR-1	TIR-2	TIR-3a	TIR-3b	TIR-4	TIR-5
Hürthle cell adenoma	1	1	3	2	1	0
Microfollicular adenoma	5	2	11	13	0	1
Papillary carcinoma						
Classical	2	6 ^a	1	5	4	24
Follicular	2	1	1	5	2	4
Hürthle cell	1	0	0	3	0	0
Cystic	0	2	0	1	3	3
Diffuse sclerosing	0	2	1	2	3	6
Follicular carcinoma	0	1	6	11	4	2
Medullary carcinoma	0	2	0	1	0	0
Struma	6	65	14	7	4	0
Thyroiditis	0	0	6	1	0	0
Other benign pathologies ^b	2	1	1	1	1	0

^a Among these 6 cases, all were microcarcinomas and they were not in the biopsied area.

^b This category includes: cavernous hemangioma, hemorrhagic pseudocyst, c-cell hyperplasia, amyloid goiter, and oxyphilic cell metaplasia.

Table 4. Prevalence of malignancy among the 5 categories

Category	Prevalence of malignancy, <i>n</i> (%)
TIR-1	5/19 (26.32)
TIR-2	14 ^a /83 (16.87)
TIR-3A	9/44 (20.45)
TIR-3B	28/52 (53.85)
TIR-4	16/22 (72.73)
TIR-5	39/40 (97.5)

^a Among these 14 cases, 11 were microcarcinomas and they were not in the biopsied area.

ment were obtained. During the same period, 2,742 patients underwent FNA, but not surgical follow-up, in our institution.

Our population was composed by 182 females (70%) and 78 males (30%), and the mean age was 51.71 years (range 15–85). Of the 260 cases, 111 (42.69%) had a malignant histological report and the mean diameter of neoplasms was 1.99 cm (range 0.1–8.0); 204 (78.46%) patients underwent a total thyroidectomy, 51 (19.62%) a lobectomy, and the remaining 5 (1.92%) different surgical procedures.

Lobectomy was proposed for patients with a TIR-2/TIR-3A result at FNA and a US pattern not suggestive of malignancy (absence of capsular invasion, ovoid-to-

round shape, macrocalcifications, hyperechogenicity, distinct nodule borders).

Table 2 shows the characteristics of our population, and the 2014 SIAPEC-IAP classification is described in Table 1. Among the 260 cases, the final cytological diagnosis was nondiagnostic (TIR-1) in 19 cases (7.31%), benign (TIR-2) in 83 cases (31.92%), indeterminate (TIR-3) in 96 cases (36.92%), suspicious for malignancy (TIR-4) in 22 cases (8.46%), and diagnostic for malignancy (TIR-5) in 40 cases (15.38%). Among the 96 cases with TIR-3 cytology, following review, 44 (16.92%) were classified as TIR-3A and 52 (20%) as TIR-3B. Table 3 shows the final histological diagnoses according to cytological subcategory, while Table 4 summarizes the prevalence of malignancy among the 6 categories. It is important to underline that the prevalence of malignancy was 20.45% (9/44) among TIR-3A and 53.85% (28/52) among TIR-3B, and this difference was statistically significant ($p = 0.0007$). In both categories, there was no significant difference between patients with and those without cancer in terms of age (TIR-3A: 58.78 vs. 53.31 years, $p = 0.31$; TIR-3B: 50.68 vs. 52.33 years, $p = 0.65$).

A 2×2 contingency table was created to compare TIR-2 versus TIR-4/5 in order to set a benchmark; we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. A Fisher exact test was also performed in order to verify the statistical significance. Moreover, we performed an additional statistical analysis including the TIR-3A and TIR-

Table 5. Main diagnostic indicators of the 2014 SIAPEC-IAP classification

2×2 table	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %	<i>p</i> value
TIR-2 vs. TIR-4/5	91.67	91.76	88.71	93.98	91.72	<0.0001
TIR 2/3A vs. TIR 3B/4/5	85.57	78.47	72.81	88.98	81.33	<0.0001
TIR-3A vs. TIR-3B	75.68	59.32	53.85	79.55	65.63	0.0014

3B categories, and calculated sensitivity, specificity, PPV, NPV, and diagnostic accuracy. The main diagnostic indicators are presented in Table 5.

Discussion

Since thyroid disorders are among the most prevalent of medical conditions, it is becoming essential to identify diagnostic methods that distinguish preoperatively benign nodules (>90%) from cancers [3, 4, 17]. When we encounter thyroid nodules in our institution, we almost always use the TSH level as a first tool to stratify patients: those with a TSH level lower than 0.8 mU/L will undergo a ^{99m}Tc thyroid scan, while those with a TSH level higher than 0.8 mU/L will undergo thyroid FNA. If the ^{99m}Tc thyroid scan identifies a cold nodule, the patient will undergo thyroid FNA, while if the ^{99m}Tc thyroid scan identifies a hot nodule, the patient will not undergo FNA. This approach is largely approved in the literature [18–24] and is justified by the fact that most functional thyroid nodules are follicular adenomas and hyperplasia, and in these cases FNA is often not conclusive. This could be used as a first tool to reduce the number of FNAs with a TIR-3 diagnosis, which is the most controversial and clinically complex FNA category.

The aim of this study was to determine if the SIAPEC-IAP distinction between TIR-3A and TIR-3B could help in the clinical management of patients with an indeterminate cytological report. First of all, the prevalence of malignancy among TIR-3A and TIR-3B was calculated as 20.45% (9/44) and 53.85% (28/52), respectively. The difference was statistically significant ($p = 0.0007$). Our prevalence of malignancy was higher than outlined by the 2014 National SIAPEC-IAP guidelines [9], The Bethesda System [7] (where the TIR-3A category is considered analogous to AUS/FLUS, and the TIR-3B category is considered analogous to FN/SFN), and the British Thyroid Association Royal College of Physicians guidelines [11] (in which the TIR-3A category corresponds to THY-3a, and TIR-3B category to THY-3f). This discrepancy is

rather frequent in the international literature [25–29], suggesting that TIR-3A and TIR-3B should be both considered as intermediate/high-risk categories. For this reason, a surgical approach should be considered for both categories rather than only for TIR-3B, as is recommended by the most important international guidelines [7, 9, 11]. We are conscious that referring all patients with TIR-3A to surgery would lead to overtreatment in 4/5 patients, but until a more sensitive and specific method is found, we believe that it is mandatory to protect the 20.45% of patients with a TIR-3A at FNA and a malignant histology.

Moreover, as Nardi et al. [9] reported that the majority of the samples in the TIR-3 category are characterized by “a microfollicular pattern (‘follicular proliferation’) that may correspond at histology to adenomatous hyperplasia, follicular adenoma and follicular carcinoma.” The only way to distinguish a follicular adenoma from a follicular carcinoma is by analyzing blood vessel invasion and penetration of the tumor capsule, which can be done only with a histological analysis [30].

A further analysis showed that among TIR3A and TIR3B there is no significant difference between patients with and those without cancer in terms of age (TIR-3A: 58.78 vs. 53.31 years, $p = 0.31$; TIR-3B: 50.68 vs. 52.33 years, $p = 0.65$), as already shown by Brophy et al. [16].

In order to better analyze the impact of the subclassification in TIR-3A and TIR-3B, a 2 × 2 contingency table was created including only TIR-2 and TIR-4/5 with the aim of setting a benchmark. TIR-3A and TIR-3B were then added in the second contingency table. As shown in Table 5, the sensitivity decreased from 91.67 to 85.57%, corresponding to a 73.22% increase in the FN rate (from 8.33 to 14.43%). Although the second contingency table showed statistical significance ($p < 0.0001$), we believe that TIR-3A patients should not be placed in a low-risk category, but further analysis should be performed. For example, cytologic samples may be evaluated using a panel of molecular tests for BRAF, RET/PTC, PAX8/PPARG1, and Ras [6, 31]. This panel is able to identify a group of patients with virtually a 100% probability of malignancy, thus helping to reduce the FN rate. Another option should

be the use of immunocytochemical techniques, such as the galectine-3-expression analysis, which reduces the rate of unnecessary thyroidectomy [2]. Another option could be that suggested by Pyo et al. [32], who believe that core needle biopsy has a higher conclusive rate than repeat FNA when the initial FNA gave an AUS/FLUS result.

An interesting finding that arose from this analysis is the prevalence of malignancy in the TIR-2 category (14/83; 16.87%), which is higher than in the literature [9]. Since in our institution only those patients with a multinodular or compressive goiter are referred to surgery, the high prevalence of malignancy could be explained by the fact that papillary carcinoma appears to be associated with long-standing multinodular goiter, with a prevalence that ranges from 4.6 to 23.1% [33–37]. As shown in Table 3, all of the 6 cases of papillary carcinoma with a TIR2 cytology were microcarcinomas and were not in the biopsied area. Among the remaining 8 cases of TIR2 with a malignant histology, 5 were microcarcinomas, and 3 were challenging cases. Indeed, we had a papillary carcinoma follicular variant that lacked cytological and nuclear atypia at FNA, a cystic papillary carcinoma, and a follicular carcinoma with a macrofollicular pattern.

Conclusion

In our clinical series, a significant difference ($p < 0.0001$) was found between TIR-3A and TIR-3B regarding the risk of malignancy. However, our data do not allow suggesting only follow-up in TIR-3A patients given: (1) the high prevalence of malignancy in TIR-3A (20.45%), and (2) the low sensitivity (75.68%) and specificity (59.32%) in the distinction between TIR-3A and TIR-3B. Therefore, until a more sensitive and specific method is found, we believe that it is advisable to refer all TIR-3A patients to surgery.

Regarding patients with multinodular goiter and TIR-2 at FNA, we found an important prevalence of papillary carcinoma (Table 4). This was probably because it is not possible to biopsy all nodules and we usually focus either on the biggest or on the most suspicious at US. For these reasons, the surgical approach should not be excluded.

Disclosure Statement

The authors declare they have no potential conflict of interest with respect to this manuscript.

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