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Original Research

# Risk of malignancy in thyroid nodules classified as TIR-3A: What therapy?

Fabio Medas [a], Enrico Erdas [a], Luca Gordini [a], Giovanni Conzo [b], Claudio Gambardella [b], Gian Luigi Canu [a], Giuseppe Pisano [a], Angelo Nicolosi [a], Pietro Giorgio Calò [a, *]

[a] Department of Surgical Sciences, University of Cagliari, Cittadella Universitaria, SS554, Bivio Sestu, 09042, Monserrato, CA, Italy
[b] Università degli Studi della Campania "Luigi Vanvitelli" - School of Medicine, Division of General Surgery and Surgical Oncology, Via Gen.G.Orsini 42, 80132 Naples, Italy

## HIGHLIGHTS

- Thyroid nodules with TIR3A cytology have a lower risk of malignancy than TIR3B cases.
- The new SIAPEC classification has proved accurate and effective.
- Malignancy rates in nodules with TIR3A cytology are higher than expected.
- The accurate definition of the risk of TIR3A nodules is extremely difficult.
- A careful assessment of risk factors and ultrasound characteristics is always needed.

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## ABSTRACT

*Background:* The aim of the present study was to assess the clinical applicability of the TIR3A category in managing thyroid nodules, to examine the malignancy rates of TIR 3A and TIR 3B nodules, and to suggest management guidelines for these nodules.
*Materials and methods:* Thyroid cytologies performed in patients referred to our Department between January 2014 and August 2016 were classified according to the guidelines published by the SIAPEC. 102 cases were included in this retrospective study and were divided into two groups: 19 TIR3A were included in group A and 83 TIR3B in group B.
*Results:* In group A, malignancy was diagnosed in 4 (21.1%) cases, papillary thyroid cancer was found in 3 patients and follicular thyroid cancer in 1; one case was classified as microcarcinoma, in two cancer was multicentric and bilateral and in one central node metastases were observed. In Group B malignancy was diagnosed in 48 (57.8%) patients, papillary thyroid cancer was found in 36 patients and follicular cancer in 12; microcarcinoma was observed in 25 cases, 12 were unilateral multicentric and 7 bilateral multicentric; in 3 cases central node metastases were present.
*Conclusion:* Thyroid nodules with TIR3A cytology have a lower risk of malignancy than TIR3B cases, for which the new SIAPEC classification has proved accurate and effective. Malignancy rates in nodules with TIR3A cytology are higher than expected, although the real and accurate definition of the risk is extremely difficult. The recommendation to perform an accurate follow-up and repeat the fine-needle aspiration still appears the best option. For better management of patients with TIR3A cytology a careful assessment of risk factors and ultrasound characteristics is always needed. Further multicenter

* Corresponding author. Department of Surgical Sciences, University of Cagliari, S.S. 554 Bivio Sestu 09042, Monserrato, CA, Italy.
*E-mail addresses:* fabiomedas@gmail.com (F. Medas), enricoerdas@medicina.unica.it (E. Erdas), lucagordini@aol.com (L. Gordini), Giovanni.CONZO@unina2.it (G. Conzo), claudiog86@hotmail.it (C. Gambardella), gianlu_5@hotmail.it (G.L. Canu), gpisano@unica.it (G. Pisano), nicolosi@unica.it (A. Nicolosi), pgcalo@unica.it (P.G. Calò).

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studies with longer follow-up are needed to better define the efficacy of this classification, the actual cancer risk, and the best management of these lesions.



## 1. Introduction

Thyroid nodules are common, being present by palpation in up to 5% of individuals and by ultrasonography (US) in up to 50% [1,2]. While the overwhelming majority are benign, it is estimated that the incidence of cancer in clinically apparent thyroid nodules is between 5 and 15% [1,3].

Thyroid fine-needle aspiration (FNA) has been in use for many years and is now the mainstay of preoperative diagnosis of thyroid lesions [1,4–8]. FNA is clinically safe, cost-effective, quick and minimally invasive, and the diagnostic success depends on the performance and right interpretation [2,9,10]. Limitations of FNA arise for nodules which are reported as having indeterminate cytology. While the majority of these cases transpire to be benign, surgical excision with histological examination is frequently necessary to make a definitive diagnosis [1].

In the recent years, a variety of four-to six-tiered reporting schemes for thyroid cytology have been proposed by different societies and institutions, with the aim of improving the communication between cytopathologists and clinicians [11].

In 2007 the United States National Cancer Institute (NCI) has proposed "The Bethesda System for Reporting Thyroid Cytology " (BSRTC) which provided well-defined criteria with exhaustive explanatory notes [11]. Category III of the BSRTC, described as "atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)," is defined as cases with thyroid FNA cytology results that are neither convincingly benign nor definitely suspicious for malignancy [9,12]; AUS/FLUS has been the most controversial category of the BSRTC [10,13]. A recommendation was made to avoid overuse of the AUS/FLUS diagnosis to <7% of thyroid FNA cytologies; the malignancy risk for this category is expected to be in the range of 5–15% [9,10,12–19]. For this subset of nodules, there is no firm consensus regarding clinical management [20]. The BSRTC recommends performing a repeat FNA for decision of management. However, even after repeat cytology, 20–48.6% of nodules may remain indeterminate [13,20]. Recent studies have showed that malignancy rates in nodules with AUS/FLUS cytology are higher than previously estimated, such as 5–48% [9,12,13,15–17].

In the UK, the system currently in use is the British Thyroid Association/Royal College of Pathologists (BTA/RCPath) terminology, first published in 2002 and modified in 2009 [2,7,11,21,22]. In order to enhance the sophistication of the British Thy system in dealing with indeterminate cytology results and to facilitate the triage of such cases into those which require immediate surgical excision and those which can be followed without immediate surgery, the Royal College of Pathologists (RCP) in 2009 proposed the subclassification of Thy-3 aspirates into Thy-3a (atypia) and Thy-3f (follicular neoplasm) [1]. Thy3a category was introduced to describe lesions with cellular atypia in the form of a mixed micro- and macro-follicular pattern. It also covers lesions with features that raise the possibility of neoplasm, for example sparse colloid, yet insufficient to be placed into the Thy4 or Thy5 category [2]. The Thy3a category has an undetermined risk of malignancy, which makes it difficult for clinicians to advise patients [2].

In Italy, a 5-tiered classification, proposed in 2007 by the Italian Society for Anatomic Pathology and Cytology joint with the Italian Division of the International Academy of Pathology (SIAPEC-IAP), was used by most institution [11]. In 2014, on the basis of architectural and cytological alterations and of the background component, two sub-classes at different risk of malignancy were distinguished: TIR 3A (low-risk indeterminate lesion, LRIL) and TIR 3B (high-risk indeterminate lesion (HRIL) [11]. Currently, no published data are available about both the frequency of the TIR 3A subcategory and its risk of malignancy. A recommendation was made to keep the TIR 3A frequency <10% and its cancer risk <10% [11]. The subdivision of the diagnostic category TIR 3 in two subcategories with different risk of malignancy and different clinical action is similar to the subdivision of BSRTC (III-IV) and to the Thy 3a and 3f of BTA-RCPath [11]. Yet, the Italian classification includes in the subcategory TIR 3B those cases with "mild/focal nuclear atypia" at expected higher risk of malignancy [11].

The aim of the present study was to assess the clinical applicability of the TIR 3A category in managing thyroid nodules, to examine the malignancy rates of TIR 3A and TIR 3B nodules at our institution, and to suggest management guidelines for these nodules.

## 2. Materials and methods

Thyroid FNA cytologies performed in patients referred to the Department of Surgical Sciences of the University of Cagliari (a tertiary care referral endocrine surgical center) between January 2014 and August 2016 were classified according to the guidelines published by the SIAPEC as: non diagnostic (TIR1), non-diagnostic-cystic (TIR1C), benign (TIR2), low-risk indeterminate (TIR3A), high-risk indeterminate (TIR3B), suspicious of malignancy (TIR4), or malignant (TIR5). FNA cytologies were performed with US guidance, using either a 22-gauge needle attached to a 10-mL disposable plastic syringe or an aspirator. Samples were stained with hematoxylin and eosin and evaluated by our Pathology Department.

Only patients presenting TIR3 cytology were included in the study. The study has been performed in accordance with the Declaration of Helsinki. All patients provided written informed consent for their involvement in this study and for the storage and use of their data. According to the classification, 102 cases with indeterminate nodules were included in this retrospective study. The patients were divided into two groups according to cytological diagnosis: 19 TIR3A were included in group A and 83 TIR3B in group B. All the patients underwent surgical intervention consisting in total thyroidectomy or hemithyroidectomy. Intraoperative frozen section examination was not used. Age, gender, familiarity, presence of thyroiditis and nodule size were compared with definitive pathology.

Surgical complications were assessed over a follow-up period that ranged between 6 and 35 months. Routine pre- and post-operative fibrolaryngoscopy were performed in all cases; vocal fold paresis was considered definitive (paralysis) if persisting for more than 6 months after surgery. Serum calcium (normal value = 2.09–2.54 mmol/L) and iPTH (intact parathyroid hormone) levels (normal value = 1.06–6.89 pmol/L) were assessed on post-operative day 1. An iPTH serum level <1.06 pmol/L was used to determine postoperative hypoparathyroidism (considered

definitive if present 6 months after surgery).

### 2.1. Statistical analysis

Statistical analysis were performed with MedCalc vers. 16.8. Chi-squared test was used for categorical data and T-Test for continuous variables. Results were considered statistically significant if p value was $\leq 0.05$. Continuous data are reported as the mean value ± standard error of the mean.

## 3. Results

Patients in group A were 5 (26.3%) males and 14 (73.7%) females; those in group B were 22 (26.5%) males and 61 (73.5%). females. Autoimmune thyroiditis was present in 6 (31.6%) patients in group A and 32 (38.5%) in group B (Table 1).

All but one patients in group A were submitted to total thyroidectomy (TT), in 5 (26.3%) cases a central compartment lymph node dissection (CLND) was associated. In the same group one patient underwent hemithyroidectomy. All the patients in group B underwent TT, in 8 (9.7%) cases associated to CLND.

In group A there were 6 (31.6%) cases of transient hypoparathyroidism, 1 (5.3%) of definitive hypoparathyroidism, 1 (5.3%) of transient paresis. In group B transient hypoparathryrodism was reported in 27 (32.5%) patients, permanent hypoparathyroidism in 4 (4.8%), transient recurrent laryngeal nerve paresis in 2 (2.4%) and definitive paralysis in 1 (1.2%). Full data regarding surgical treatment and follow up are reported in Table 2.

Among the patients in group A, histological diagnosis was multinodular goiter in 4 (21.1%) cases, follicular adenoma in 7 (36.8%), and thyroiditis in 4 (21.1%), while malignancy was diagnosed in 4 (21.1%) cases (see Table 3). In particular, papillary thyroid cancer was found in 3 patients and follicular thyroid cancer in 1 case. Among these, one case was classified as microcarcinoma, in two cases cancer was multicentric and bilateral and in one case central node metastases were observed. In all patients with cancer another thyroid pathology co-existed: in 2 cases a thyroiditis, in 1 a multinodular goiter and in 1 Graves' disease.

In Group B histological diagnosis was multinodular goiter in 4 (4.8%) cases, follicular adenoma in 18 (21.7%), thyroiditis in 11 (13.3%), and Graves' disease in 2 (2.4%), while malignancy was diagnosed in 48 (57.8%) patients. In particular, papillary thyroid cancer was found in 36 patients and follicular cancer in 12; microcarcinoma was observed in 25 cases, 12 were unilateral multicentric and 7 bilateral multicentric; in 3 cases central node metastases were present. In 41 over 48 cases with diagnosis of carcinoma another thyroid pathology co-existed: in 19 a thyroiditis, in 8 a follicular adenoma, and in 14 a multinodular goiter.

Statistical analysis revealed a significant difference in malignancy rate in group B *vs* group A ($p < 0.01$) and in association of CLND to TT in group A *vs* group B ($p = 0.013$).

## 4. Discussion

FNA cytology has been widely accepted as the diagnostic procedure of choice in the evaluation of patients presenting with nontoxic nodules [21]. The primary objective is both to triage patients, that is, to determine whether or not surgical intervention is indicated, and to assist in deciding the appropriate surgical procedure when necessary [7,21].

The risk of malignancy for patients undergoing surgery with Bethesda category III nodules has been reported higher than expected (37.8%–55.5%) [13]. Ho et al. [15] reported a 26.6% combined malignancy rate for all Bethesda category III nodules managed with surgery, repeat FNA, or observation, and a 37.8% malignancy rate for nodules managed by surgery alone. Kim [17] reported a malignancy rate of 36.2%. Nagarkatti et al. [23] observed an incidence of 16%, whereas VanderLaan et al. [24] reported a prevalence of 46% and Yoo et al. [13] a risk of malignancy of 59.5%. In the opinion of some authors, these results suggest that AUS/FLUS nodules may warrant reconsideration of current recommendations [15]. However, the actual risk for malignancy is difficult to determine, because a pathologic diagnosis is only available in the subset of patients selected for surgery [22].

Rosario et al. [25] reported 48.6% of repeat Bethesda category III nodules on a second FNA in their prospective repeat FNA study without surgery. Other studies showed a wide range of 19%–48.6% for classification as repeat Bethesda category III nodules on repeat FNA [13]. The risk of malignancy of repeat Bethesda category nodules was 73.1% in the study of Yoo [13], which was significantly higher than that of thyroid nodules classified initially as Bethesda category III.

Several sources of bias might lead to overestimation of the risk of malignancy, specifically, the tendency of tertiary-care centers to be referred higher risk cases, the tendency of surgically operated cases to be higher risk, the possibility of incidental papillary thyroid cancers elsewhere in the gland inflating the malignancy rate, and publication bias with certain findings more likely to be published [16].

With regard to the British classification, the results of Brophy [1] showed a slightly higher malignancy rate in Thy-3f cases (17.9%) than in Thy-3a cases (13.4%). However, the difference was not statistically significant. In the study of Wong [2], 50% of operated

**Table 1**
Demographic data.

| | Group A (n = 19) | Group B (n = 83) | p value |
|---|---|---|---|
| Sex (M:F) | 5:14 | 22:61 | 0.79 |
| Age (years) | 59 ± 15.5 | 52 ± 14.6 | 0.06 |
| Autoimmune thyroiditis | 6 (31.6%) | 32 (38.5%) | 0.76 |
| Familial thyroid cancer | 0 | 6 (7.23%) | 0.50 |

**Table 2**
Surgical treatment, outcomes and follow up.

| | Group A (n = 19) | Group B (n = 83) | p value |
|---|---|---|---|
| Surgical procedure | | | |
| TT | 13 (68.4%) | 75 (90.4%) | 0.013 |
| TT + CLND | 5 (26.3%) | 8 (9.7%) | |
| Lobectomy | 1 (5.3%) | 0 | |
| Operative time (minutes) | 85.2 ± 19.8 | 92.9 ± 24.5 | 0.22 |
| Postoperative stay (days) | 3.2 ± 1.2 | 3 ± 1.3 | 0.62 |
| Transient hypoparathyroidism | 6 (31.6%) | 27 (32.5%) | 0.84 |
| Permanent hypoparathyroidism | 1 (5.3%) | 4 (4.8%) | 0.61 |
| Recurrent nerve injury | 1 (5.3%) | 3 (3.6%) | 0.75 |
| Cervical haematoma | 0 | 2 (2.4%) | 0.81 |

TT: total thyroidectomy. CLND: central compartment lymph node dissection.

**Table 3**
Pathologic data.

| | Group A (n = 19) | Group B (n = 83) | p value |
|---|---|---|---|
| Nodule size (mm) | 26.7 ± 14.7 | 23.4 ± 12.7 | 0.33 |
| Histological diagnosis | | | |
| - Benign disease | 15 (78.9%) | 35 (42.2%) | <0.01 |
| - Malignancy | 4 (21.1%) | 48 (57.8%) | |
| Node metastases | 1 (5.3%) | 3 (3.6%) | 0.75 |

Thy3a lesions were found to be malignant on histopathological examination. This reduces to 33.9% if the authors adopt "best case scenario" and assume all Thy3a left unresected are benign [2].

A recently published interobserver reproducibility study for reporting thyroid FNA using the UK RCPath classification showed a good agreement between 6 experienced cytopathologists for diagnosing Thy1, Thy2, Thy3f, and Thy5 categories and no agreement for diagnosing categories Thy3a and Thy4 [21,26]. In the study of Kocjan [7], the interobserver reproducibility of class Thy3a was poor. In contrast with Thy3 a, Thy3f achieved moderate to good agreement.

Unfortunately there are no reported studies in the literature on the rate of malignancy related to the Italian SIAPEC classification.

Our results has confirmed the validity of the new SIAPEC classification pointing out a significant difference in risk of malignancy among TIR3A and TIR3B (21.1% *vs* 57.8%). However, also in our experience, cancer incidence in TIR3A patients was higher (about twice) than expected. The bias already reported by Iskandar [16] can surely get an impact on these results, in particular ours is an institutional referral center in which the most suspicious cases are addressed. Another important point already highlighted by various authors [16,22] is that the group of operated patients is selected and probably includes more suspicious cases. The third point to consider is the high rate of incidental carcinomas: in our experience microcarcinomas were observed in one case of TIR3A (5.3%) and 25 cases of TIR3B (30.1%). However we have also to consider that in two TIR3A cases cancer was multicentric and bilateral and in one case central node metastases were present at time of diagnosis.

Given the unexpectedly high rate of malignancy, several studies have examined clinical risk factors associated with malignancy in patients with indeterminate nodules. Age (over 40 years), male sex, nodules larger than 2 cm in diameter, and suspicious US characteristics such as hypoechogenicity, irregular margin, microcalcification, solid structure, taller-than-wide shape, nodule size, and increased vascularization of the nodule on Doppler US have been reported by several studies as the predictive factors for malignancy in indeterminate nodules [5,17,19,20,27]. Our numerically small sample did not allow to obtain statistically significant results on the possible cancer risk factors. However, on the basis of our previous observations [5,27], we believe that the study of these factors is helpful for selecting patients to be operated.

In the case of surgical treatment, hemithyroidectomy can be considered an appropriate treatment [28–30].

Important limitations of this study appear to be the short follow-up and the low numerical sample; again, the high incidence of microcarcinomas represents another possible bias. However, in the absence of other reports in the literature, there still seems an interesting first contribution on the new SIAPEC classification.

Possible future directions for the further work-up of indeterminate nodules may include the use of genetic analysis panels, including testing for BRAF-V600E mutation [1,12,13,31,32] and immunocytochemistry [1,31,33].

## 5. Conclusions

Thyroid nodules with TIR3A cytology have a lower risk of malignancy than TIR3B cases, for which the new SIAPEC classification has generally proved accurate and effective. However, malignancy rates in nodules with TIR3A cytology are higher than expected, although the real and accurate definition of the risk is extremely difficult.

The recommendation to perform an accurate follow-up and repeat the FNA still appears the best option.

For better management of patients with TIR3A cytology a careful assessment of the risk factors and US characteristics as well as of the eventual growth of the lesion over time is always needed.

Further multicenter studies with a longer follow-up are needed to better define the efficacy of this classification, the actual cancer risk, and the best management of these lesions.

## Ethical approval

Ethical approval was requested and obtained from the University of Cagliari ethical committee.

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## Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Fabio Medas: Partecipated substantially in conception, design, and execution of the study and in the collection, analysis and interpretation of data; also partecipated substantially in writing, drafting, and editing of the manuscript.

Enrico Erdas: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luca Gordini: Partecipated substantially in conception and execution of the study and in the collection, analysis and interpretation of data.

Giovanni Conzo: Partecipated substantially in execution of the study and in the analysis and interpretation of data.

Claudio Gambardella: Partecipated substantially in conception and design of the study and in the interpretation of data.

Gian Luigi Canu: Partecipated substantially in conception and execution of the study and in the collection and interpretation of data.

Giuseppe Pisano: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Angelo Nicolosi: Partecipated substantially in conception and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Pietro Giorgio Calò: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in writing, drafting, and editing of the manuscript.

## Conflicts of interest

All Authors have no conflict of interests.

## Guarantor

Prof. Pietro Giorgio Calò.

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## References

[1] C. Brophy, R. Mehanna, J. McCarthy, A. Tuthill, M.S. Murphy, P. Sheahan, Outcome of subclassification of indeterminate (Thy-3) thyroid cytology into Thy-3a and Thy-3f, Eur. Thyroid. J. 4 (2015) 246–251.

[2] G. Wong, Z. Awad, P.Y. Wong, S. Wood, R. Farrell, Clinical applicability of the Thy3a cytological category in thyroid nodules aspirates. Our experience in one hundred and fifty-seven patients with Thy3 cytology, Clin. Otolaryngol. 39 (2014) 393–396, http://dx.doi.org/10.1111/coa.12307.

[3] R. Mehanna, M. Murphy, J. McCarthy, G. O'Leary, A. Tuthill, M.S. Murphy, P. Sheahan, False negatives in thyroid cytology: impact of large nodule size and follicular variant of papillary carcinoma, Laryngoscope 123 (2013) 1305–1309, http://dx.doi.org/10.1002/lary.23861.

[4] P.G. Calò, M.L. Lai, E. Guaitoli, G. Pisano, P. Favoriti, A. Nicolosi, G. Pinna, S. Sorrenti, Difficulties in the diagnosis of thyroid paraganglioma: a clinical case, Clin. Ter. 164 (2013) e35–39, http://dx.doi.org/10.7417/CT.2013.1519.

[5] P.G. Calò, F. Medas, R. Santa Cruz, F. Podda, E. Erdas, G. Pisano, A. Nicolosi, Follicular nodules (Thy3) of the thyroid: is total thyroidectomy the best option? BMC Surg. 14 (2014) 12, http://dx.doi.org/10.1186/1471-2482-14-12.

[6] V. Cantisani, H. Grazhdani, P. Ricci, K. Mortele, M. Di Segni, V. D'Andrea, A. Redler, G. Di Rocco, L. Giacomelli, E. Maggini, C. Chiesa, S.M. Erturk, S. Sorrenti, C. Catalano, F. D'Ambrosio, Q-elastosonography of solid thyroid nodules: assessment of diagnostic efficacy and interobserver variability in a large patient color, Eur. Radiol. 24 (2014) 143–150, http://dx.doi.org/10.1007/s00330-013-2991-y.

[7] G. Kocjan, A. Chandra, P.A. Cross, T. Giles, S.J. Johnson, T.J. Stephenson, M. Roughton, D.N. Poller, The interobserver reproducibility of thyroid fine-needle aspiration using the UK Royal College of Pathologists' classification system, Am. J. Clin. Pathol. 135 (2011) 852–859, http://dx.doi.org/10.1309/AJCPZ33MVMGZKEWU.

[8] A. Marrazzo, P. Taormina, M. David, I. Riili, L. Casà, A. Noto, G. Romano, E. Marrazzo, G. Buscemi, Il carcinoma della tiroide: dalla diagnosi alla terapia, Chir. Ital. 60 (2008) 685–695.

[9] E.S. Cibas, S.Z. Ali, The Bethesda system for reporting thyroid cytopathology, Am. J. Clin. Pathol. 132 (2009) 658–665, http://dx.doi.org/10.1309/AJCPPHLWMI3JV4LA.

[10] A. Stanek-Widera, M. Biskup-Frużyńska, E. Zembala-Nożyńska, T. Kącik, M. Śnietura, D. Lnge, Clinical importance of follicular lesion of undetermined significance (diagnostic category III according to Bethesda System) diagnosed from Fine-Needle Aspiration Biopsy, Endokrynol. Pol. 67 (2016) 12–16, http://dx.doi.org/10.5603/EP.2016.0002.

[11] F. Nardi, F. Basolo, A. Crescenzi, G. Fadda, A. Frasoldati, F. Orlandi, L. Palombini, E. Papini, M. Zini, A. Pontecorvi, P. Vitti, Italian consensus for the classification and reporting of thyroid citology, J. Endocrinol. Invest. 37 (2014) 593–599, http://dx.doi.org/10.1007/s40618-014-0062-0.

[12] S. Lee, J.H. Shin, Y.L. Oh, S.Y. Hahn, Subcategorization of Bethesda system category III by ultrasonography, Thyroid 26 (2016) 836–842, http://dx.doi.org/10.1089/thy.2015.0637.

[13] M.R. Yoo, H.M. Gweon, A.Y. Park, K.E. Cho, J.A. Kim, J.H. Youk, E.J. Son, Repeat diagnoses of Bethesda category III thyroid nodules: what to do next? PLoS One 10 (2015) e0130138, http://dx.doi.org/10.1371/journal.pone, 0130138.

[14] H.M. Gweon, E.J. Son, J.H. Youk, J.A. Kim, Thyroid nodules with Bethesda system III cytology: can ultrasonography guide the next step? Ann. Surg. Oncol. 20 (2013) 3083–3088, http://dx.doi.org/10.1245/s10434-013-2990-x.

[15] A.S. Ho, E.E. Sarti, K.S. Jain, H. Wang, I.J. Nixon, A.R. Shaha, J.P. Shah, D.H. Kraus, R. Ghossein, S.A. Fish, R.J. Wong, O.Lin, L.G.T. Morris, Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS), Thyroid 24 (2014) 832–839, http://dx.doi.org/10.1089/thy.2013.0317.

[16] M.E. Iskandar, G. Bonomo, V. Avadhani, M. Persky, D. Lucido, B. Wang, J.L. Marti, Evidence for overestimation of the prevalence of malignancy in indeterminate thyroid nodules classified as Bethesda category III, Surgery 157 (2015) 510–517, http://dx.doi.org/10.1016/j.surg.2014.10.004.

[17] D.W. Kim, E.J. Lee, S.J. Jung, J.H. Ryu, Y.M. Kim, Role of sonographic diagnosis in managing Bethesda class III nodules, AJNR Am. J. Neuroradiol. 32 (2011) 2136–2141, http://dx.doi.org/10.3174/ajnr.A2686.

[18] B. Kuru, A. Atmaca, M. Kefeli, Malignancy rate associated with Bethesda category III (AUS/FLUS) with and without repeat fine needle aspiration biopsy, Diagn. Cytopathol. 44 (2016) 394–398, http://dx.doi.org/10.1002/dc.23456.

[19] B. Kuru, A. Atmaca, I.A. Tarim, M. Kefeli, K. Topgul, S. Yoruker, M. Elmali, M. Danaci, Risk factors associated with malignancy and with triage to surgery in thyroid nodules classified as Bethesda category III (AUS/FLUS), Eur. J. Surg. Oncol. 42 (2016) 87–93, http://dx.doi.org/10.1016/j.ejso.2015.09.026.

[20] O. Norlén, A. Popadich, S. Kruijff, A.J. Gill, L.M. Sarkis, L. Delbridge, M. Sywak, S. Sidhu, Bethesda III thyroid nodules: the role of ultrasound in clinical decision making, Ann. Surg. Oncol. 21 (2014) 3528–3533, http://dx.doi.org/10.1245/s10434-014-3749-8.

[21] C. Lobo, A. McQueen, T. Beale, G. Kocjan, The UK Royal College of Pathologists thyroid fine-needle aspiration diagnostic classification is a robust tool for the clinical management of abnormal thyroid nodules, Acta Cytol. 55 (2011) 499–506, http://dx.doi.org/10.1159/000333234.

[22] K. Şenol, K. Katar, C. Yüksel, B. Saylam, M. Tez, Prediction of malignancy in Bethesda category III nodules: application of thyroid imaging reporting system, Am. Surg. 81 (2015) E351–E352.

[23] S.S. Nagarkatti, W.C. Faquin, C.C. Lubitz, D.M. Garcia, G. Barbesino, D.S. Ross, R.A. Hodin, G.H. Daniels, S. Parangi, Management of thyroid nodules with atipica cytology on fine-needle aspiration biopsy, Ann. Surg. Oncol. 20 (2013) 60–65.

[24] P.A. VanderLaan, E. Marqusee, J.F. Krane, Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated FNA be the preferred initial approach? Am. J. Clin. Pathol. 135 (2011) 770–775.

[25] P.W. Rosario, Thyroid nodules with atipia or follicular lesions of undetermined significante (Bethesda Category III): importance of ultrasonography and cytological subcategory, Thyroid 24 (2014) 1115–1120, http://dx.doi.org/10.1089/thy.2013.0650.

[26] C.G. Theoharis, K.M. Schofield, L. Hammers, R. Udelsman, D.C. Chhieng, The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution, Thyroid 19 (2009) 1215–1223, http://dx.doi.org/10.1089/thy.2009.0155.

[27] P.G. Calò, F. Medas, F. Boi, G. Pisano, G. Baghino, S. Mariotti, A. Nicolosi, Predictive factors of malignancy in follicular thyroid nodules (THY3): our experience on 324 patients, Minerva Chir. 69 (Suppl. 1) (2014) 53–59.

[28] P.G. Calò, E. Erdas, F. Medas, L. Gordini, A. Longheu, G. Pisano, A. Nicolosi, Differentiated thyroid cancer: feasibility of loboisthmectomy in an endemic region, G. Chir. 36 (2015) 257–262.

[29] G. Conzo, N. Avenia, G.L. Ansaldo, P. Calò, M. De Palma, C. Dobrinja, G. Docimo, C. Gambardella, M. Grasso, C.P. Lombardi, M.R. Pelizzo, A. Pezzolla, L. Pezzullo, M. Piccoli, L. Rosato, G. Siciliano, S. Spiezia, E. Tartaglia, F. Tartaglia, M. Testini, G. Troncone, G. Signoriello, Surgical treatment of thyroid follicular neoplasms: results of a retrospective analysis of a large clinical series, Endocrine (2016 Apr 13), http://dx.doi.org/10.1007/s12020-016-0953-2 [Epub ahead of print].

[30] G. Conzo, P.G. Calò, C. Gambardella, E. Tartaglia, C. Mauriello, C. Della Pietra, F. Medas, R. Santa Cruz, F. Podda, L. Santini, G. Troncone, Controversies in the surgical management of thyroid follicular neoplasms, Int. J. Surg. 12 (Suppl 1) (2014) S29–S34, http://dx.doi.org/10.1016/j.ijsu.2014.05.013. Retrospective analysis of 721 patients.

[31] P. Caria, T. Dettori, D.V. Frau, A. Borghero, A. Cappai, A. Riola, M.L. Lai, F. Boi, P. Calò, A. Nicolosi, S. Mariotti, R. Vanni, Assessing RET/PTC in thyroid nodule fine-needle aspirates: the FISH point of view, Endocr. Relat. Cancer 20 (2013) 527–536, http://dx.doi.org/10.1530/ERC-13-0157.

[32] S.J. Johnson, S.A. Hardy, C. Roberts, D. Bourn, U. Mallick, P. Perros, Pilot of BRAF mutation analysis in indeterminate, suspicious and malignant thyroid FNA cytology, Cytopathology 25 (2014) 146–154, http://dx.doi.org/10.1111/cyt.12125.

[33] E. Baldini, C. Tuccilli, N. Prinzi, S. Sorrenti, L. Falvo, C. De Vito, A. Catania, F. Tartaglia, R. Mocini, C. Coccaro, S. Alessandrini, S. Barollo, C. Mian, A. Antonelli, E. De Antoni, M. D'Armiento, S. Ulisse, Deregulated expression of Aurora Kinases is not a prognostic biomarker in papillary thyroid cancer patients, PLoS One 10 (2015) e0121514, http://dx.doi.org/10.1371/journal.pone.0121514.