THE ASSOCIATION OF THE BETHESDA REPORTING SYSTEM AND THE AACE/ACE/AME US CLASSIFICATION SYSTEM FOR IMPROVING THE DIAGNOSTIC ACCURACY OF THYROID NODULES. AN INSTITUTIONAL PROSPECTIVE COHORT STUDY

Giuseppina Orlando[1], Alessandro Corigliano[1], Sergio Mazzola[2], Irene Vitale[1], Riccardo Guercio[1], Marco Dominici[1], Claudia Carolla[1], Giulia Rotolo[1], Roberto Gullo[1], Giuseppe Carollo[1]

[1]Unit of General and Emergency Surgery, Department of General, Emergency and Transplant Surgery, Policlinico "P. Giaccone", University of Palermo, Via L. Giuffré 5, 90100 Palermo, Italy - [2]Unit of Clinical Epidemiology and Tumor Registry, Department of Laboratory Diagnostics, Policlinico "P. Giaccone", University of Palermo, Via L. Giuffré 5, 90100 Palermo, Italy

ABSTRACT

Introduction: The Bethesda system is widely accepted for reporting thyroid cytopathology. Its association with ultrasounds (US) leads thyroid nodules' diagnosis, expecially by using an efficacious US reporting system. Aim of our study is to evaluate if the association between the Bethesda system and a 3-categories US risk stratification system, proposed by American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE) / Associazione Medici Endocrinologi (AME), improves the diagnostic performance compared to the cytology alone, decreasing the risk of false negatives.

Materials and methods: 574 patients suffering from thyroid nodules that underwent US, cytology and thyroidectomy were prospectively recruited. We included: benign lesions, papillary thyroid carcinoma (PTC), follicular or Hürtle cells carcinoma (both included in FTC), aggressive tumors (AT). All patients were stratified and grouped according to definitive histology as a reference. In each group the cytology and the US risk were intersected each other. The chi-square test was applied to verify the concordance US/cytology. Negative and positive predictive values (NPV and PPV) were also calculated, as well as the false negatives (FN) with 95% confidence interval (CI). Rstudio IDE (33) software version 3.4.1 (2017-06-30) was used.

Results: Among 231 benign, chi-square test showed a p-value = 0,2 (non-significant), that means an overlapping US/cytology non-useful in improving diagnosis; NPV=58%. In 293 PTC, chi-square test resulted in p<0,05; PPV = 57%, FN = 14% (95% CI = 7%-15%). In 31 FTC PPV was 68%, FN 12,9% (95% CI = 1%-25%), in 19 AT PPV = 89%, FN = 5,3% (95% CI = 0-10%). In Bethesda 3 examined isolatedly, we found predictive values indicating risk of malignancy in intermediate and even more in high US risk. In Bethesda 4, predictive values indicated high risk of malignancy in all US risk classes.

Conclusion: The US risk stratification system proposed is easy to apply. Its association with cytology is useful expecially for reducing underestimated malignancies: a reduced rate of FN and a satisfying accuracy were observed in PTC and even more in aggressive tumors. In Bethesda 3 and 4 categories, the risk of malignancy could be stratified in different levels.

Keywords: Ultrasounds, Bethesda system, Thyroid cytology, Risk stratification.

DOI: 10.19193/0393-6384_2021_2_123

Introduction

Thyroid US plays a role of primary importance in diagnostic algorithm of thyroid nodules. Its widespread adoption carries favourable effects: notwithstanding the increase in prevalence of thyroid nodules (in which the risk of cancer is no more than 5-15%) in the population, it gives the opportunity of identifying the "suspected" lesions that should be addressed to fine-needle aspiration biopsy (FNAB) for cytological exam[1-3]. As first "side effect" could increase in addressing to unnecessary FNAB and surgery a number of benign nodules, an US "risk stratification" is desirable in each reporting. Then, the lesion considered "at risk" should be screened for surgery according to the results of cytology.

Several systems have been proposed by scientific societies or individual research groups for the assessment of US risk stratification of thyroid nodules[4-7]. Once the risk of a thyroid nodule has been assessed, FNAB could improve diagnostic accuracy and, in some cases, specify its malignancy. Concerning this, Bethesda system for reporting thyroid cytopathology represented a step forward in systematizing the interpretation of cytological specimens[8]. In fact, the sixth class of this reporting system corresponds to a malignancy with a probability near the 100% of cases, although this result is found in a minority of thyroid carcinomas[7,8]. If Bethesda system has a widespread consensus due to its easy application in clinical practice, US risk stratification systems generally appear more complex to use and apply in clinical routine[9].

More recently, three scientific societies, the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE) and the (Italian) Associazione Medici Endocrinologi (AME) proposed a new US rating system of the risk of malignancy for thyroid nodules[10]. This three-class system appears easy to apply in the practice.

Stated that both US and cytopathology have an excellent but not absolute diagnostic accuracy, it could be hypothesized that their association could be useful in increasing the number of true diagnoses, although to date a combined system have not validated yet[7, 9, 11-13].

Aim of the present study is to investigate if the association of Bethesda system for reporting thyroid cytopathology and AACE/ACE/AME US reporting system is able to increase the diagnostic accuracy of the thyroid nodules.

Materials and methods

Patients selection

The present institutional prospective study involved 574 consenting patients (448 females, 126 males) scheduled and operated on for thyroidectomy (thyroid lobectomy or total thyroidectomy ± any lymph node dissection) at the Unit of General and Emergency Surgery of "Policlinico Paolo Giaccone" University Hospital, in Palermo from January 2012 to December 2017. All patients were recruited after an outpatient evaluation and most of these were previously selected for surgery during endocrinology outpatient evaluation performed at our Institution or outside.We included in the study any patient suffering from any thyroid nodular disease (single nodule, multinodular goiter) and excluded Grave's disease. We also excluded all patients for which a complete clinical record concerning the entire clinical pathway, from the enrolment to the discharge, including the definitive histology, was not available. In particular, we considered exclusion criteria the US reports not in agreement with the AACE/ACE/AME standards. The second exclusion criteria was the absence of cytopatological report, or its incomplete description according to the Bethesda system. Finally, we excluded medullary thyroid carcinomas, since its diagnosis is strongly connected with specific laboratory tests, mesenchymal tumors, lymphomas and metastases to thyroid gland. Institutional Ethics Committee approval was not needed for this study the protocol of which conformed to the ethical guidelines of the 1975 Declaration of Helsinki and agreed with Italian regulations.

Thyroid US: technique and interpretation

All US imaging exams were performed with three high-resolution US machines endowed with a 10-12 MHz linear transducer. The procedure provided cranial-caudal and transverse scanning. The most indicative images were archived and a descriptive report was written. It described the thyroid nodules and the lymph nodes. The description of nodules concerned margins (regular, lobulated, spiculated), echogenicity (hyper-iso-hypoechoic), halo sign (present or absent), shape (ovoid, round, taller than wide), intralesional calcifications (absent, presence of gross calcifications or microcalcifications), vascularization (absent, peripheral, intralesional regular, intralesional irregular). The lymph nodes were described according to the level and to its characteristics as regular (ovoid, ilum preserved, size ≤ 1 cm), enlarged, suspicious (round, absence of ilum, irregular margins, confluent, hypoechoic, cystic changes).

Thyroid US was performed by endocrinologists or surgeons, all with an experience of at least 5 years in the specific field. Two supervisors, one endocrinologist and one surgeon, with an experience of respectively 25 and 15 years in thyroid and parathyroid US, revised all exams by analysing the recorded images and all reports. The reports produced before June 2016 were carefully re-examined and systematically reclassified according to the AACE/ACE/AME system. The thyroid US performed later were directly formulated according to this system. Table 1 shows the US risk stratified into the three risk categories.

• *Class 1. Low-risk (expected risk of malignancy about 1%)*
- Mostly cystic (>50%) nodules with reverberating artifacts that are not associated with suspicious US signs
- Isoechoic spongiform nodules confluent or with regular halo
• *Class 2. Intermediate-risk* (expected risk of malignancy: 5-15%)
- Slightly hypoechoic nodules (cf. surrounding thyroid tissue) and isoechoic nodules with ovoid-to-round shape and smooth or ill- defined margins.
- Intranodular vascularization, elevated stiffness at elastography, macro- or continuous rim calcifications, or hyperechoic spots of uncertain significance may be present.
• *Class 3. High-risk* (expected risk of malignancy 50-90%)
Nodules with at least 1 of the following suspicious features:
- Marked hypoechogenicity (cf. prethyroid muscles)
- Spiculated or microlobulated margins
- Microcalcifications
- Taller-than-wide shape
- Evidence of extrathyroidal growth or pathologic adenopathy

Table 1: AACE/ACE/AME US risk categorization.

Thyroid cytopathology: technique and interpretation

A preoperative cytopathology sampling was always performed with at least two punctures under US guidance per each thyroid nodule examined. A 25-gauge needle performed all samplings, without syringe aspiration. In presence of multinodular goiter, the prevalent nodules (more suspected in terms of US findings or > 3 cm) were sampled. The specimens, not fixed, were examined within a few hours according to Bethesda categorization, from B1 to B6[8]. If the specimen resulted in B1 (non-diagnostic) the sampling was repeated once. If it resulted in non-diagnostic once again, the patient was informed about the possible risk of an undiagnosed malignancy and operated on for thyroidectomy according to its choice. Cytological diagnosis was performed by one of four experienced (10 years or more) thyroid cytopathologists.

Thyroidectomy and analysis of specimen

The surgical procedure (hemithyroidectomy/total thyroidectomy) was chosen according to the institutional protocols. In particular, the unilateral thyroidectomy was offered in the presence of solitary nodules resulted Bethesda 1, 2, 3 or 4 after cytology, after a clear and complete patient's information that concerned the possibility of complications and sequelae[14-19] and the risk of malignancy that needs a completion thyroidectomy within approximately 3 months. The surgical technique was conventional extracapsular thyroidectomy or minimally invasive video-assisted thyroidectomy[20]. The neck dissection was performed when indicated according to the current or institutional guidelines[21-23]. The specimen was analysed from experimented institutional pathologists. The definitive result was stratified in four categories: benign lesion, papillary carcinoma including classic and follicular variant, follicular carcinoma / Hürtle cells carcinoma, aggressive

tumor (including tall cells carcinoma, insular carcinoma, anaplastic or undifferentiated carcinoma) groups.

Statistical analysis

With the aim of evaluating the performance of combined US + cytology, we highlighted the concept of "prevalence" of thyroid carcinoma that is real in the present study, since we analysed and stratified the results of definitive pathology exam. Each pathological result was included in a table for each group, and then crossed according to the US risk and Bethesda category. The chi-squared test was then applied for verifying the concordance of the two diagnostic exams: the most the two exams were concordant, the less these were supplementary. Once the four tables were obtained, negative predictive value (NPV) in the table of benign nodules, and positive predictive value (PPV) in the three tables of malignancies, where calculated. NPV and PPV were considered as probability of true negative and true positive results of US and cytology combination. Moreover, the interval estimation of false negative (FN) results was calculated in each group of malignancies with the aim of completing the evaluation of the concurrent use of both cytology and US. The Rstudio IDE[33] software version 3.4.1 (2017-06-30) was used for this analysis.

Results

The demographics of the 574 consecutive patients, agreeing with the inclusion/exclusion criteria included in the study, are reported in table 2. In the tables 3-6 we stratified the patients in four groups: 231 with a definitive pathology of benign nodules (table 3), 293 papillary thyroid carcinomas (table 4) 31 follicular or Hürtle cell carcinomas (table 5), 19 aggressive tumors (table 6). Concerning the first group (table 3), first we calculated if US and cytology gave results similar or complementary. Chi-square test showed a p-value = 0,2 (non-significant) that means an overlap US/cytology non-useful in improving diagnosis. The goal of the diagnostic exams in this group of nodules should be a true negative result: so, the cross nearer to the result negative for malignancy (highlighted with a star) are the higher (near the US risk 1-2 lines) and the left sided (Bethesda 1, 2 or 3).

The results considered negatives were (9+17+32+24+56) = 138. The NPV, calculated as a reference result for this group was 0,58.

Variable	M	%	F	%	Total
Gender	126	22%	448	78%	574
	Mean		Median		SD*
Age	49		49		14
	Yes	%	No	%	Total
Familiarity	237	41%	337	59%	574
	Multinodular goiter		Solitary nodule		Total
Case history	322 (56%)		252 (44%)		574
	1	2	3	4	Total
Pathology	231 (40%)	293 (51%)	31 (6%)	19 (3%)	574 (100%)

Table 2: Demographics.
SD = standard deviation. Pathology: 1= benign; 2 = papillary carcinoma; 3 = follicular or Hürtle Cell carcinoma; 4 = aggressive tumor.

	Bethesda category					
US risk	1	2	3	4	5	Total
1	9*	32*	24*	5	1	71
2	17*	56*	52	14	2	141
3	3	10	3	1	2	19
Total	29	98	79	20	5	231

Table 3: Benign Nodules: correlation with US risk and Bethesda category.
The results highlighted with were considered true negatives and used for calculating the NPV.*

	Bethesda category						
US risk	1	2	3	4	5	6	Total
1	0	14	4	5	1	0	24
2	8	13	63	41*	26*	11*	162
3	8*	9	8*	17*	23*	42*	107
Total	16	36	75	63	50	53	293

Table 4: Papillary thyroid carcinomas: correlation with US risk and Bethesda category.
The results highlighted with were considered true positives and used for calculating the PPV.*

On the contrary, for the malignancies we considered the PPV as a reference result. In particular, in the group of papillary carcinomas the chi-square test was 0,05. This difference statistically significant means that US and cytology were not concordant, in other words complementary. Moreover, we found (41+26+11+8+8+17+23+42) = 168 of true positive results, with a PPV = 0,57. We also calculated the interval estimation of false negative (FN) results that was 7%-15%. In the group of follicular/Hürtle cell carcinomas we found (10+3+2+2+2+1+1) = 21 true positive results (PPV=0,69).

	Bethesda category						
US risk	1	2	3	4	5	6	Total
1	0	1	2	1	1	0	5
2	0	1	4	10*	3*	0	18
3	2*	0	2*	2*	1*	1*	8
Total	2	2	8	13	5	1	31

Table 5: Follicular or Hürtle cell carcinomas: correlation with US risk and Bethesda category.
The results highlighted with were considered true positives and used for calculating the PPV.*

	Bethesda category						
US risk	1	2	3	4	5	6	Total
1	0	0	0	1	0	0	1
2	0	0	1	3*	2*	0	6
3	1*	0	3*	0	2*	6*	12
Total	1	0	4	4	4	6	19

Table 6: Aggressive tumors: correlation with US risk and Bethesda category.
The results highlighted with were considered true positives and used for calculating the PPV.*

	Benign	Malignant	Total Bethesda 3	Predictive Value	C.I.*
US risk class 1	24	6	30	NPV = 0,80	0,73-0,87
US risk class 2	52	68	120	PPV = 0,57	0,53-0,61
US risk class 3	3	13	16	PPV = 0,81	0,71-0,91
TOTAL	79	87	166		

Table 7: NPV and PPV in the three US risk classes in Bethesda 3 cytologic category.

The FN intervallar estimation was 1%-25%. In the group of aggressive tumors we found (3+2+1+3+2+6) = 17 true positive results, with a PPV = 0,89 and a FN interval estimation = 0 - 10%. In a second step, we considered the Bethesda 3 and 4 groups isolatedly (tables 7 and 8). In Bethesda 3, the NPV in the US low risk was 0,80 and the PPV in the intermediate and high-risk groups were respectively 0,57 and 0,81. In Bethesda 4, we found NPV = 0,41 in US risk class 1, and a PPV of respectively 0,79 and 0,95 in US risk classes 2 and 3 (tables 8).

	Benign	Malignant	Total Bethesda 4	Predictive value	C.I.*
US risk cass 1	5	7	12	NPV = 0,41	0,27-0,55
US risk lass 2	14	54	68	PPV = 0,79	0,74-0,84
US risk class 3	1	19	20	PPV = 0,95	0,91-0,99
TOTAL	20	80	100		

Table 8: NPV and PPV in the three US risk classes in Bethesda 4 cytologic category.

Discussion

In the last years, most of prominent international societies of thyroidology and also radiology published different US risk score systems

concerning thyroid nodules. American Thyroid Association (ATA) proposed a US risk stratification system in four class of suspicion (from "very low" to "high") plus the "benign" nodules, considered only cystic nodules without solid component[24]. The ATA score system does not consider vascularization and elastography as suspicion criteria (recommendation 8), although it includes the vascularity among the nodule characteristic that should be described (recommendation 6). The British Thyroid Association proposed a 5-classes suspicion scale (U1= normal; U2 = benign; U3 = indeterminate/ equivocal; U4 = suspicious; U5 = malignant) and takes into consideration vascularity (peripheral in benign nodules; mixed/central in U3; intranodular in U5) but not the elastographic findings[25].

Previously, a system derived from the Breast Imaging Reporting and Data System that the American College of Radiology had proposed was published[26]. The so-called TIRADS is a 6-level score system (From 1: benign to 6: category included biopsy proven malignant nodules) with an optional subdivision of TIRADS 4 (suspicious nodules) in a (malignancy risk 5-10%) and b (malignancy risk 10-80%). This is a specific and sensitive score system, but the ranges of malignancy risk appear too large. The Korean Society of Thyroid Radiology proposed a modified TIRADS score, so-called K-TIRADS, a five classes of risk score that takes into consideration among other signs, the elastography[7, 27].

The AACE/ACE/AME system appears simple (3 risk categories) and reliable. It showed in general good performances, being inferior to ATA system only concerning sensitivity when the size of nodules was considered[13]. Although these efforts in highlighting US risk categorisation, cytology remains the gold standard in identifying thyroid malignancies, even though this technic alone presents a high number of non-diagnostic, indeterminate or only suspected results and, on the contrary, only a few results, that accord to the Bethesda 6, could be considered certainly malignant[8]. For this reason, several studies based on combined US and cytology risk stratification have been published, each of those have some limits, such as a retrospective perspective[11, 12] or absent or incomplete surgical verification of real nature of nodules[28, 29].

The present prospective study included only patients that underwent thyroidectomy, then the histologic confirmation of the real nature of the nodules was trustworthy. In this point of view, the association US cytology seems to offer grounded informa-tions concerning the risk of malignancy of thyroid nodules. In particular, a remarkable step forward is the improvement of predictive value in Bethesda 3 cytological category, which interpretation is nowadays a debated topic.

Recent studies found that the two subcategories of Bethesda 3, Follicular Lesion of Undetermined Significance (FLUS) and Atypia of Undetermined Significance (AUS) had a different risk of cancer, with a predominance of malignancy in the second one[30, 31]. These studies indicate that malignant nodules at final histology had higher rate of suspicious US features and, as a result, a relevant role of US in identifying different classes of risk.

Our study was draw up considering the malignancy proved on the pathologic exam as a reference, the true negative result as a goal in Bethesda 2 and "low risk" US and the true positive one the goal in Bethesda 3 or more suspected cytological findings and "intermediate" or "high risk" US findings. In a first step we applied chi-square test looking for a difference statistically significant between cytological exam and US in reaching the true diagnosis (benign/ malignant) in benign nodules and different groups of malignancy (papillary, follicular/Hurtle cell, aggressive carcinomas).

A second step was dedicated to a Bayesian statistical analysis aimed to determining the predictive values (positive or negative) of each class of US risk in the Bethesda categories 3 and 4 (follicular lesions or atypia of undetermined significance). In the presence of a Bethesda 3 result, our study clearly suggests follow up in the presence of a class 1 risk on US. If the same result is connected to class 2 and even more 3, the probability of malignancy increases to respectively 57 and 81%, so the surgical approach is suggested especially in the more suspected US pattern. Applying the same method of evaluation to Bethesda 4 category, we found results even more interesting. In this latter cytology reporting category, the predictive value is always in favour of the surgery, moderately in the US class 1 (NPV = 0,41) and strongly in the 2 and 3 classes (PPV respectively 0,79 and 0,95). It means that the association of Bethesda cytology and AACE/ACE/AME US reporting systems is very useful, moreover seems to indicate a strong recommendation for surgery even in Bethesda 3 cytological category, in the presence of advanced US risk classes: on the contrary, in this Bethesda category thyroidectomy could be avoided in the presence of low US risk. Moreover our study confirmed that in the presence of a Bethesda

4 cytology surgical choice is always preferable, and mandatory in the presence of US risk intermediate or high. These findings have relevant implications for patient care and could direct the indications for surgery. Of course, molecular tests such as BRAF (V600E), RAS, RET/ PTC, PAX 8-PPAR-c rearrangement, Galectin 3, etc., improve the results of cytology by giving several informations especially concerning the undetermined (Bethesda 3 and 4) diagnostic categories. However, they are expensive and non-widely diffused tests[32], then they are not taken into consideration in the present study.

Our study has some limitations: first of all, the selection bias. In fact, all patients came from a surgical series collected in a high volume context[33-38]. This could have given a pre-selection of patients, showed from the high prevalence of the Bethesda 3 and 4 cytological categories in the overall series. Moreover, the sample size relatively small did not allow of enrol a high number of Bethesda 5 cases (only fifteen). Finally, our statements in considering benign or malignant the crosses US/cytology for the predictive values calculations, expecially in Bethesda 1 category, are not supported by literature data although appeared us reasonable.

Anyway, it is a prospective study that involved only 2 US operators (the US interpretation should be homogeneous enough) and the US and cytology reporting criteria were applied with stringent method. On the other hand, the results are in line with those of another recent study, conducted in our institution and referred to the more limited field of Bethesda III and IV nodules, in which the ability of US and cytology to integrate in the improvement of the diagnosis is clearly demonstrated[39].

Conclusions

AACE/ACE/AME US categorization system is a reliable and easily reproducible method for reporting thyroid US results. Our study was performed with classical as well as "Bayesian" statistical methods focused on the false results (positive and negative) and predictive values. Evaluating the diagnostic power of two diagnostic methods applied in association, it allowed us to conclude that US and cytology associated each other can improve the performance of diagnostic pathway and lead decision-making. It is capable to reduce underestimated malignancies. Moreover, the rate of FN and the accuracy observed in PTC were satisfying and increased in tumors that are more aggressive. In particular, it seemed us very

significant that the predictive values in the three classes of US risk in Bethesda 3 cytology indicated different surgical choices in each class; on the contrary in Bethesda 4 a more "aggressive" surgical choice was strengthened from the results in each US class of risk. These findings earn in-depth evaluations and could lead to further studies that seem to be needed for implementing informations in these cytological categories.

References

1) Ianni F, Campanella P, Rota CA, et al: A meta-analysis-derived proposal for a clinical, ultrasonographic, and cytological scoring system to evaluate thyroid nodules: the "CUT" score. Endocrine, 2016; 52(2): 313-21.

2) Tan GH, Gharib H: Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Int Med, 1997; 126: 226-231.

3) Ha EJ, Baek JH, Na DG: Risk Stratification of Thyroid Nodules on Ultrasonography: Current Status and Perspectives. Thyroid, 2017; doi: 10.1089/thy.2016.0654.

4) Park, JY, Lee HJ, Jang HW, et al: A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. Thyroid, 2009; 19, 1257-64.

5) Brito JP, Gionfriddo MR, Al Nofal A, et al: The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab, 2014; 99:1253- 63.

6) Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ, Hahn SY, Jeon SJ, Jung SL, Kim DW, Kim EK, Kwak JY, Lee CY, Lee HJ, Lee JH, Lee JH, Lee KH, Park SW, Sung JY, Korean Society of Thyroid R, Korean Society of R (2016) Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol, 2016; 17:370-395.

7) Hong MJ, Na DG, Baek JH, Sung JY, Kim JH: Cytology-Ultrasonography Risk-Stratification Scoring System Based on Fine-Needle Aspiration Cytology and the Korean-Thyroid Imaging Reporting and Data System. Thyroid, 2017; 27(7): 953-9

8) Cibas ES, Ali SZ: The Bethesda system for reporting thyroid cytopathology . Thyroid, 2009, 19(11):1159-65

9) He YP, Xu HX, Zhao CK, et al: Cytologically indeterminate thyroid nodules: increased diagnostic performance with combination of US TI-RADS and a new scoring system. Sci Rep 2017, 7(1) doi: 10.1038/s41598-017-07353-y.

10) Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P, AACE/ACE/AME task force on thyroid nodules: American association of clinical endocrinologists, american college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update. Endo-

cr Pract, 2016; 22(5) 622-39.

11) Liu ZW, Fox R, Unadkat S., Farrel R : A retrospective study of ultrasound and FNA cytology investigation of thyroid nodules: working towards combined risk stratification. Eur Arch Otorhinolaryngol doi , 2017; 10.1007/s00405-017-4488-9.

12) Lee SW, Lee HJ, Kim HJ, Lee J, Park JY, Kim SH, Kim J: Combined categorical reporting systems of US and cytology findings for thyroid nodules: guidance on repeat fine-needle aspiration cytology. Radiology, 2013, 266(3): 956-63.

13) Trimboli P, Fulciniti F, Zilioli V, Ceriani L, Giovanella L: Accuracy of international ultrasound risk stratification systems in thyroid lesions cytologically classified as indeterminate. Diagn. Cytopathol, 2017; 45(2): 113-7.

14) Lee JC, Breen D, Scott A, Grodski S, Yeung M, Johnson W, Serpell J: Quantitative study of voice dysfunction after thyroidectomy. Surgery,2016; 160(6): 1576-1581. doi: 10.1016/j.surg.2016.07.015.

15) Dedivitis RA, Aires FT, Cernea CR: Hypoparathyroidism after thyroidectomy: prevention, assessment and management. Curr Opin Otolaryngol Head Neck Surg, 2017; 25(2):142-146. doi: 10.1097/MOO.0000000000000346.

16) Scerrino G, Inviati A, Di Giovanni S, Paladino NC, Di Paola V, Lo Re G, Almasio PL, Cupido F, Gulotta G, Bonventre S: Esophageal motility changes after thyroidectomy; possible associations with postoperative voice and swallowing disorders: preliminary results. Otolaryngology-Head and Neck Surgery, 2013; 148(6): 926-32

17) Scerrino G, Inviati A, Di Giovanni S, et al: Long-term esophageal motility changes after thyroidectomy: associations with aerodigestive disorders. G Chir, 2017; 37(5): 193-199.

18) Scerrino G, Tudisca C, Bonventre S, et al: Swallowing disorders after thyroidectomy: What we know and where we are. A systematic review. Int J Surg 2017; 41 Suppl 1:S94-S102. doi: 10.1016/j.ijsu.2017.03.078.

19) Scerrino G, Melfa G, Raspanti C, et al: The prevalence of post-thyroidectomy chronic asthenia: a prospective cohort study. Langenbecks Arch Surg, 2017; 15. doi: 10.1007/s00423-017-1568-7.

20) Scerrino G, Paladino NC, Di Paola V, et al: Minimally invasive video-assisted thyroidectomy: four-year experience of a single team in a General Surgery Unit. Minerva Chir, 2013; 68(3): 307-14.

21) Conzo G, Docimo G, Ruggiero R, et al: Surgical treatment of papillary thyroid carcinoma without lymph nodal involvement. G.Chir, 2012; 33 (10): 339-42.

22) Scerrino G, Attard A, Melfa GI, Role of prophylactic central neck dissection in cN0-papillary thyroid carcinoma: results from a high-prevalence area. Minerva Chir, 2016; 71(3): 159-67.

23) Attard A, Paladino NC, Lo Monte AI, et al: Skip metastases to lateral cervical lymph nodes in differentiated thyroid cancer: a systematic review. BMC Surg. 2019; Apr 24;18(Suppl 1):112. doi: 10.1186/s12893-018-0435-y.

24) Haugen BR, Alexander EK, Bible, et al: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid, 2016; 26(1):1-133. doi: 10.1089/thy.2015.0020.

25) Perros P, Colley S, Boelaert K, et al: British Thyroid Association Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxford), 2014; 81(suppl. 1):1–122.

26) Horvath E, Majlis S, Rossi R, et al: An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical man- agement. J Clin Endocrinol Metab 2009; 94: 1748–1751.

27) Ha EJ, Moon WJ, Na DG, et al: A Multicenter Prospective Validation Study for the Korean Thyroid Imaging Reporting and Data System in Patients with Thyroid Nodules. Korean J Radiol, 2016; 17(5): 811-21. doi: 10.3348/kjr.2016.17.5.811.

28) Lee YH, Kim DW, In HS, et al: Differentiation between benign and malignant solid thyroid nodules using an US classification system. Korean J Radiol, 2011; 12(5): 559-67. doi: 10.3348/kjr.2011.12.5.559.

29) Park SY, Ahn SY, Shin JH, Ko EY, Oh YL: The Diagnostic Performance of Thyroid US in Each Category of the Bethesda System for Reporting Thyroid Cytopathology. Plos One, 2016; 27 DOI:10.1371/journal.pone.0155898

30) Lee JH, Han K, Kim EK, et al: Risk Stratification of Thyroid Nodules With Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) Cytology Using Ultrasonography Patterns Defined by the 2015 ATA Guidelines. Annals of Otology, Rhinology & Laryngology, 2017; DOI: 1d0o.i.1o1rg7/71/00.10107374/08090431487974197477192472 journals.sagepub.com/home/aor.

31) Onder S, Firat P, Ates D: The Bethesda system for report- ing thyroid cytopathology: an institutional experience of the outcome of indeterminate categories. Cytopathology, 2014; 25(3): 177-84.

32) Baser H, Cakir B, Topaloglu O, et al: Diagnostic accuracy of thyroid imaging reporting and data system in the prediction of malignancy in nodules with atypia and follicular lesion of undetermined significance cytologies. Clin. Endocrinol, 2016; doi: 10/1111/cen.13274.

33) Scerrino G, Melfa G, Raspanti C, et al: Minimally Invasive Video-Assisted Thyroidectomy: Analysis of Complications From a Systematic Review. Surg Innov. 2019; 26(3): 381-387. doi: 10.1177/1553350618823425.

34) Scerrino G, Paladino NC, Di Paola V, et al: The use of haemostatic agents in thyroid surgery: efficacy and further advantages. Collagen-Fibrinogen-Thrombin Patch (CFTP) versus Cellulose Gauze. Ann Ital Chir. 2013; 84(5): 545-50.

35) Romano G, Scerrino G, Profita G, et al: Terminal or truncal ligation of the inferior thyroid artery during thyroidectomy? A prospective randomized trial. Int J Surg. 2016; 28 Suppl 1:S13-6. doi: 10.1016/j.ijsu.2015.05.057.

36) Melfa G, Porello C, Cocorullo G, et al: Surgeon volume and hospital volume in endocrine neck surgery: how many procedures are needed for reaching a safety level and acceptable costs? A systematic narrative review. G Chir. 2018; 39(1):5-11. doi: 10.11138/gchir/2018.39.1.005.

37) Scerrino G, Melfa G, Raspanti C, et al: Mapping the centers performing endocrine neck surgery in Italy. G Chir. 2019; 40(5): 389-397.

38)   Iacobone M, Scerrino G, Palazzo FF: Parathyroid surgery: an evidence-based volume-outcomes analysis : European Society of Endocrine Surgeons (ESES) positional statement. Langenbecks Arch Surg. 2019; 404(8): 919-927. doi: 10.1007/s00423-019-01823-9.

39)   Scerrino G, Cocorullo G, Mazzola S, et al: Improving diagnostic performance for thyroid nodules classified as Bethesda category III or IV: how and by whom ultrasonography should be performed. J Surg Res, 2021; doi: 10/1016/j.jss.2020.12.009.

————

Corresponding Author:
Giuseppina Orlando MD
Unit of General and Emergency Surgery, Department of
General, Emergency and Transplant Surgery, Policlinico
"P. Giaccone", University of Palermo, Via L. Giuffré 5, 90100
Palermo, Italy
Email: giusi_orlando@hotmail.it
(Italy)