Surgical approach to TIR3 cytology class
A prospective evaluation

Ann. Ital. Chir., 2014 85: 537-543
pii: S0003469X14022349

Nicola D'Alessandro*, Giovanni Michele Fasano*, Francesco Gilio*, Giovanni Iside*, Maria Lucia Izzo*, Andrea Loffredo*, Margherita Pinto*, Salvatore Tramontano*, Giuseppe Tramutola*, Giuseppe Citro**

**Unità Operativa Complessa di Chirurgia Generale, Azienda Ospedaliera Regionale "S. Carlo", Potenza, Italy*
***Unità di Endocrinologia e Diabetologia Pediatrica. Ambulatorio di Endocrinologia, Azienda Sanitaria Potenza, Italy*

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AIM: *Fine-needle aspiration (FNA) has proven to be a safe and reliable method of investigation of thyroid lesions. Referencing to European classification, the associated risk of malignancy for TIR3, category reserved for aspirates that contain architectural and/or nuclear atypia, is variable in such studies. Aims of study were evaluating safety of surgical approach, assessing perioperative parameters surgically related, and estimating neoplastic rate for TIR3 group.*
MATERIAL AND METHODS: *A prospective evaluation of all TIR3 submitted to thyroidectomy was conducted by assessing histopatohologic results between January 2005 and December 2012, considering two categories, positive (neoplastic) and negative (not neoplastic) group. Intraoperative and complication rate was analyzed on TIR3 population.*
RESULTS: *A total of 1514 total thyroidectomy was performed from 2005 to 2012: a total of 148 cases was considered on TIR3 group. Positive cases amounted to 64 (43.2%), 29 of which were carcinoma (19.6% of total population) and 35 of which were adenoma, while negative cases amounted to 84 (56.8%). Sensitivity and specificity of TIR3 as neoplastic screening was 43.2% and 82.1%. A total of 32 linfectomies was performed (21.6% of group). Positive group presented a significant lower mean age than negative group (42.1 vs 56.2 years)*
CONCLUSIONS: *TIR3 group represents a various category, with probably different malignancy risk. Our results and neoplasms rate confirmed that surgical option should be gold standard, in order to define atypical pattern and reduce delayed diagnoses. Choice of a second FNA or a imaging monitoring should be adopted for specific condition.*

KEY WORDS: Fine-needle aspiration, Thyroidectomy, TIR3, Thyroid cancer

Introduction

Thyroid nodules are a common detection in general population and can be detected by ultrasound in up to 60% of the general population[1]. For the initial evaluation of patients with such nodules, thyroid fine-needle aspiration (FNA) has proven to be a rapid, cost-effective, safe and reliable method of investigation [2]. This procedure is the most appropriate diagnostic tool to distinguish between patients that require clinical management or surgical excision. Its application, combined with ultrasound examination, has been proven to increase the malignancy yield [3,4].

A 5-diagnostic classes classification has been applied from 2001 in Europe to all thyroid FNAs [5]. Since 2007, a new classification, similar to previous but with descriptive chapters and specific cellular patterns, was proposed by the Working Group for the cytologic classification of thyroid lesions of the Italian Society of Anatomic Pathology and Cytology (SIAPEC) and the Italian Division of the International Academy of pathology

Pervenuto in Redazione Dicembre 2013. Accettato per la pubblicazione Aprile 2014.
Correspondence to: Dr. Salvatore Tramontano, Unità Operativa Complessa di Chirurgia Generale, Azienda Ospedaliera Regionale "S. Carlo", Potenza (e-mail: salvytra@libero.it)

(IAP), based on the Guidelines for Management of Thyroid Cancer of the British Thyroid Association (BTA) [6,7]. This guideline repeated five categories, with same cytological patterns, in order to homologate results of European pathologic results. SIAPEC classification, synthetized in table I, reflects modern pathological concepts about neoplastic growth.

On the same plan, in an effort to establish standard terminology and a uniform approach for the reporting of thyroid cytology, the National Cancer Institute (NCI) and American Association of Clinical Endocrinologists (AACE), standardized a new classification, according to suspicious for malignancy risk, defined Bethesda System (BS) [8]. These recommendations included 6 diagnostic categories for thyroid FNA cytology, similar to European classification, except for intermediate classes, including report with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), different from follicular neoplasm, suspicious for malignancy, and positive for malignancy groups.

Referencing to SIAPEC classification, the TIR3 category is reserved for aspirates that contain follicular, lymphoid, or other cell types with architectural and/or nuclear atypia that is more pronounced than that observed in benign/reactive lesions, yet not sufficient to be classified as suspicious for malignancy or malignant. Based on available studies, the associated risk of malignancy for TIR3 was anticipated to be in the range of 5% to 15% [3,6].

As with other diagnostic categories of uncertainty (such as "atypical squamous cells of undetermined significance" for cervical cytology), TIR3 has the potential to be overused. Similarly, for BS classification, authors recommended that intermediate category should not exceed 7% of thyroid FNA diagnoses [8].

TIR3 cases, such as intermediate groups of other classifications, remains the most controversial category due to heterogeneity in its use among institutions and follow-up. This is due to the fact that it is nearly impossible to establish distinct morphological criteria for diagnosing atypia among cytopathologists.

According with these evaluations, we prospectively evaluated intermediate/indeterminate group, until 2005, and TIR3 category, since 2007, surgically treated and followed by comprehensive pathological study.

Aims of study were evaluating safety of surgical approach in these patients, assessing perioperative parameters surgically related, with specific prognostic characters of this subgroup, and confirming neoplastic rate for intermediate cytological group.

Material and Method

A prospective evaluation of all TIR3 submitted to surgery was conducted by assessing histopatohologic results on the thyroid gland between January 2005 and December 2012. Anthropometric data were obtained in this population, including mean size of nodules and presence/absence of goiter or thyroiditis. The data set was then analyzed, considering two categories in TIR3 population, *positive* and *negative* group: first consisted of cases not included as neoplasms by cytologic examination and in which a neoplasm was discovered, second included cases that were confirmed as benign. Intraoperative data and postoperative complication rate were analyzed in all TIR3 population treated, to perform a descriptive analysis.

All the patients underwent thyroid ultrasonographic (US) examination using a 10-Mhz linear transducer. US-guided FNA was performed using a free hand fine needle technique, according to characteristic, dimension of nodule and evolution during follow-up.

Mean age, sex and maximum diameter of major nodule detected at US were compared among benign and neoplastic groups, to detect significant difference.

Regard to TIR3 diagnosis, we evaluated positive and negative predictive value in comparation with all cases of nodular thyroid surgically treated at our Department in the same period. Positive result was estabilished as neoplastic cases (benign and malign).

The obtained samples were processed according to liquid-based cytology technique. All the materials were rinsed into a methanol-based preservative solution (a transport reagent), containing haemolytic and mucolytic agents, and sent to the laboratory for examination. Thyroid aspirates were examined in the Department of Human Pathology. The specimen samples were resuspended in a preservative solution and processed according to the manufacturer's instructions. Pathological evaluation was performed with habitual coloration, adding immunohistochemical analysis for neoplastic confirmation and typification, according with international evidence [9].

Thyroidectomy was performed according with standard of our surgical team, binding all polar vessels and in all cases detecting recurrent nerve and parathyroids on both side. Drain and suture points were removed in first postoperative day, except for haemorrhages or other complications [10].

The follow-up data included only reported histopathologic follow-up. Any detected lesions in the surgical resection specimens was included in results, because incidental lesions represents a common detection of multinodular goiter and enhance value and need for surgical approach.

Results

A total of 1514 total thyroidectomy was performed at our Department from January 2005 to December 2012. Patients treated before 2007 reporting an intermediate result (group 3) at FNA, and cases treated from 2007,

including inTIR3 category, were included. A total of 148 cases was considered for prospective evaluation. Anthropometric data are syntethized in Table II: entire population did not differ from all patients treated for thyroid pathologies.

Intraoperative data, reported in Table II, did not distance from general population treated during the same period, either for complication rate, either for postoperative hospitalization. *Positive* cases amounted to 64 (43.2% of cases), 29 of which were carcinoma and 35 of which adenoma; *negative* cases amounted to 84 (56.8% of cases). Histopathologic results, synthetized in Table III, reported a malignancy rate of 19.6% of total population (29 cases). Malignant lesions accounted of 19 cases of papillary carcinoma (65.6 % of neoplastic cases), 7 of follicular carcinoma (24.1% of neoplastic cases), and 3 of Hurtle cell carcinoma (10.3% of neoplastic cases). In six cases (10.5 % of *positive* cases), all papillar lesions, a microcarcinoma was detected (under 10 mm of maximum diameter). A prevalence of follicular type was detected for adenoma (Table III).

Sensitivity of TIR3 detection as neoplastic screening was 43.2%; specificity was 82.1%. Positive predictive value of TIR3 diagnosis resulted of 20.8%, while negative predictive value 93.0%

A total of 32 linfectomies was performed during thyroidectomy (21.6% of group), generally for incidental finding of suspect node, in 24 cases for positive group.

TABLE I - *Classification of thyroid FNA, according to European and American guidelines.*

European Classification		**Bethesda System**	
TIR1	Non-diagnostic	I	Non diagnostic
TIR2	Benign/ non neoplastic	II	Benign
TIR3	Indeterminate. Follicular lesion/follicular neoplasms/cytological and architectural atypia (descriptive text)	III	Atypia of undetermined significance/ follicular lesion of undetermined significance
		IV	Follicular neoplasm or suspicious for follicular neoplasm
TIR4	Suspicious for malignancy	V	Suspicious for malignancy
TIR5	Diagnostic for malignancy	VI	malignant

TABLE II - *Antropometric, intraoperative and postoperative parameters of TIR3 group*

	Num. cases	**% of total TIR3 cases**	**M/F**	**Mean age (range)**	**Mean hospital stay**	**Mean operative time**	**Complication rate Total Major - Minor**	**Mean maximum diameter (range)**
Positive cases	64	43.2	22/43	42.1°(22-71)	1,4	75 (60-130)	7,8% 0,15%* 5%**	28 mm (4-50)
Benign tumors	35	23.6	10/25	38.2 (29-71)	1,2	72.5 (50-100)		35 mm (4-50)
Malign tumors	29	19.6	11/24	46.4 (22-69)	1,5	80.4 (60-130)		25 mm (8-30)
Negative cases	84	56.8	30/54	56.2° (24-70)	1,2	75 (40-120)	15,4% 0,3%*** 11,9%****	30.5 mm (5-80)
All TIR3 cases	148		52/96	48.4 (22-71)	1,2	78.5 (40-130)	14,8% 0,2% 12,1%	22 mm (6-50)

Legend: °p<0.05; *one case of recurrent nerve monolateral lesion; **temporary postoperative hypocalcemia (4 cases) and surgical site infection (1 case); ***recurrent nerve monolateral lesion (2 cases) and recurrent nerve bilateral lesion (1 case); ****temporary postoperative hypocalcemia (10 cases), prolonged postoperative hypocalcemia (3 cases), and surgical site infection (2 case).

TABLE III - *Histologic results of TIR3 group.*

Hystotipes	Number of cases	%	Central linfectomies	Radical cervical linfectomies	Linfatic metastasis
Follicular adenomas	28	80%	0	0	
Hurtle cell adenomas	7	20%	2	0	
Papillary carcinoma	19	65.6	9	10	1 (0,5% of the group)
Follicular carcinoma	7	24.1	1	0	
Hurtle cell carcinoma	3	10.3	1	1	
Total	64		13	11	1 (0,4% of all linfectomies)

In one case, pathologic study resulted positive for metastasis (1,6% of positive group). Mean number of resected lymphnode was 4,4 (range 1-22).
The mean size of major lesion detected in TIR3 group was 22 mm (range: 6 - 50 mm); comparing *negative* and *positive* group, no statistical difference was observed.
Thyroiditis rate amounted to 14.2% of entire group (21 patents), without difference for neoplastic detection; a multinodular goiter was detected in 65.5% of cases (91 patients).
TIR3 patients were in the majority female (F vs M: 96 vs 52) ; this prevalence was constant for *positive* and *negative* groups, with similar rates. TIR3 cases including in *positive* group presented a significant lower mean age than negative group (42.1 vs 56.2 years); adenomatous cases (35 cases; mean age: 38.2; range: 29 - 71), in addition, were younger than neoplastic cases (29 cases; mean age: 46.4; range: 22-69), without significant difference.

Discussion and Comments

Analysis of TIR3 population submitted to surgical excision at our Department confirmed that this group is heterogeneous; risk of neoplasm is underestimated by patients and, in some cases, by same specialists.
The validity of SIAPEC classification, such as BTA and BS ones, is justified by an acceptable correlation between each category and the histological prediction, although risk of malignancy is not completely defined [3]. The overall incidence of intermediate FNA categories (AUC/FLUS for BS, THY3 and TIR3 for European classifications) varied from 9 to 25% in literature [6,9,10]. As evidenced by many pre- and post- classification edition publications on this topic, these groups, despite differences for inclusion criteria, represent the 'gray zone' in thyroid cytopathology for many reasons [5]. This is also due to different therapeutic approach, that determined a different surgery rate and, consequently, incomplete histological confirm.
Pathological evaluation is another conditioning variable. Layfield et al [11], Ohori et al [12], Muddegowda et al [13], and Shi et al [14], for example, have reported low reproducibility for AUS/FLUS, with marked interobserver and intraobserver variations. The level of experience of the clinician/pathologist performing the thyroid FNA, the methods used for specimen preparation and staining, the number of FNA passes performed, and the availability of onsite rapid interpretation may all be contributing factors to this variation.
Moreover, the results of this large thyroid FNA study reinforced most of the common knowledge regarding the usefulness of this diagnostic tool: most of the reported sensitivity and specificity of thyroid FNA ranges, in literature, between 80% and 100% [2,5]. While the diagnosis of a benign thyroid lesion should be made only on adequate samples, the presence of atypical cells or cellular patterns always should be addressed regardless of cellularity. The most important objective, for a pathologist, consists of separating cases of compromised quality/quantity of specimen from those where a real cytological atypia is difficult to include in neoplasms. Moreover, risk of a miscellaneous category, that does not quite fulfil that goal, is remarked by many authors. Renshaw, for example, considered different types of atypical follicular cells with significantly different risks of malignancy [15].
Enhancement of FNA diagnosis during years reduced rate of thyroidectomy for benign cases without other indications to surgery (compression or tracheal deviation) [8,10]. Instead, rate of TIR3 has progressively increased, either for detection either for recourse to surgical approach.
Because of high percentage of TIR3 cases undergoing surgery, in many publications, we might ask if this category is perceived as a 'positive test', more than 'indeterminate results' that require repeated FNA, such as indicated by American pathologists. In approximately 20% to 28% of intermediate groups (mostly AUS/FLUS) cases [8,16], a repeat thyroid FNA will again be interpreted as intermediate. In addition, Shi et al[14] and Yang et al[8] have shown that if TIR3 cases are forced into either lower or higher diagnostic risk categories, the latter results in diminished sensitivity for detecting thyroid neoplasms, with increased false-negative and false-positive rates, making thyroid FNA a less effective screening test.
For this reason, some authors have recommended a further subdivision to better reflect the malignancy risk, but this new approach is not validated [17-19]. Spliting into

two categories, atypia of undetermined significance and suspicious for follicular neoplasm, management might change, by repeat FNA for the first, and by surgical options, for the second group. New Italian SIAPEC Consensus includes two subclasses for TIR3 class (a and b), according with proliferation risk of cellular pattern described. This new partition harmonizes today international cytological reporting.

Introducing a second intermediate category is still debating because a potential different risk of malignancy should dilute the categorization, diminishing impact of a benign cytologic diagnosis: however, an adequate clinical and instrumental follow-up is mandatory, and an absolute negative predictive value of this cytological evaluation should be a mistake in follow-up of an atypical pattern.

The question arises how one can prevent the overuse of the intermediate category in a clinical practice. At present, a lot of molecular tests, which consist of mutation panels or RNA analysis, are being offered at both institutional and commercial levels with good predictability; combined analysis of multiple markers, such as BRAF mutations, PAZ8-PPAR chimeric oncogene and RET/PTC mutations, associated with thyroid cancer, is likely to hold the greatest clinical utility in order to reduce the rate of unnecessary surgical procedures[20-22]. HBME-1, galectina-3, CK19, Ki67, p27 and 4ß12 have been also described as malignancy indicators, suitable also on cell blocks.

Diagnostic accuracy in cytologic patterns may be implemented also by identification of clinical risk factors and by using imaging techniques. However, recent evidence did not found clinical or ultrasound patterns, either alone or combined, warranting a sure diagnosis regarding malignancy risk in TIR3 [23].

In order to obtain histological evaluation and prognostic significance of a specific category, we chose submitting to surgery all patients with TIR3 report, in accord with referred endocrinologists. Neoplastic rate observed in our group, was about 20% of entire population, rate amounting to 43.2% adding adenomatous cases; it resulted higher than majority of international publications. This leads to define our opinion about TIR3, that represents a high-risk group, in which street observation and early advancing surgical option is maybe actually a safe approach. This probably also determined our high rate of *positive* cases. An audit of FNA across five hospitals looking all TIR3 results, demonstrated that until 75% of cases go on surgical excision, with a 35% malignancy rate on histological analysis; data strongly suggest that the use of surgical follow-up, while most precise in providing an unequivocal end-point of malignancy, probably overestimates the risks of malignancy provided by certain diagnostic categories as a result of selection bias [24]. Heterogeneity of TIR3 group represents actually a reason for a more aggressive approach, with a safe and reproducible surgical procedure. Moreover, review of the data in the literature shows that most of the data available are based on retrospective level III studies that have used follow-up thyroidectomy to calculate the probability of finding a thyroid malignancy after thyroid FNA[25]; for example, for AUS/FLUS category of BS, risk of malignancy is comparable to non-diagnostic cases in much studies [26].

Our data confirmed accountability of this categorization and enhanced need of an accurate evaluation of malignancy risk, mostly for multinodular goiters and for high risk US-patterns [24]. The most common malignant diagnosis made at the time of surgery in cases initially diagnosed as TIR3 is papillary carcinoma; majority of these lacked nuclear inclusions and grooves, the characteristic chromatin pattern was not evident, and lacked often papillary structures (comparable to microfollicular pattern). Values of sensitivity, specificity and positive predictive value were not high: for this reason TIR3 detection can not be considered as test screening for cancer. An acceptable negative predictive value can hypothesize an acceptable role of this FNA category to exclude cancer cases (TIR1 or TIR2 detection).

Our malignant and adenomatous cases amounted almost to half of population; considering unpredictable risk of evolution of adenomas not treated, neoplastic risk is really considerable. It has been reported a malignancy rate until to 50% for patients with atypia at FNA: in almost all studies considered, related to TIR3 cases, the malignant rate was higher than that observed in patients who had thyroid nodules in the benign category [6]. Despite the undoubted role for an indeterminate group, there is uncertainty regarding the management of these patients. A repeated aspiration, as proposed for AUS/FLUS by American endocrinolgists [27], is unlikely in most cases to resolve this issue, since a second intermediate FNA result, in our opinion, is a risk of underestimate risk of cancer or switch to diagnosis of benign lesion [28]. In addition, a not irrelevant rate of incidental thyroid cancer (until to 10%) [29], with possible multifocality, support that a low grade of suspicion, for intermediate FNA categories, and a benign recurrent disease, as multinodular goitre, should be treated with total thyroidectomy.

Comparing international FNA classifications, we can postulate BTA and SIAPEC ones are assimilable, while TIR3 may be compared either to AUS/FLUS or to association of this with follicular neoplasms group. In this latter case, also adding malignancy risks of two intermediate BS groups (until to 30%), we did not obtain neoplasm rate observed in our TIR3 population.

These evidences, according to the guidelines of Papanicolaou Society of Cytopathology and the AACE, confirmed thyroid nodules within the indeterminate cytologic category should be managed by surgical removal, analogous to the recommendation for management in the malignant category [30]. Choice of total thyroidectomy is based, in our experience, on standardization of procedure, timing of operation and postopera-

tive management, reducing risk of complications, mostly related to voluminous goiter or to infiltrating lesions. Our patients take into account that risks of a second operation and of residual proliferating tissue are abolished [31].

Conclusions

In summary, the current study demonstrated that thyroid FNA is an accurate and relatively precise tool for the diagnosis of thyroid malignancy. The diagnostic categories of thyroid cytology are very useful for triaging patients with thyroid nodules for clinical management, according with all international classification standardized by multidisciplinary groups, permitting comparisons and performance evaluations on a large scale.
TIR3 group represents a various category, with probably different malignancy risk. Our neoplasms rate (benignant and malignant) confirmed that surgical option, with total thyroidectomy, should become gold standard, in order to completely define atypical pattern and reduce risk of delayed diagnosis. Choice of a second FNA or a imaging monitoring should be adopted case by case, for specific condition.
An extensive surgical evaluation should complete comprehension about cytological groups, and precise role for neoplastic predictability, in association with a routine recourse to molecular markers.

Riassunto

INTRODUZIONE: Il riscontro di lesioni tiroidee rappresenta un evento frequente nella popolazione generale, fino ad oltre il 60% dei controlli ecografici. Rispetto ai limiti degli studi di imaging, l'aspirazione con ago sotttile (FNA) è risultata una metodica sicura, ripetibile e dotata di sensibilità e specificità elevate per predire la natura di tali lesioni nodulari, riducendo il ricorso alla chirurgia negli ultimi venti anni ai casi sospetti o francamente positive per neoplasia. Secondo la classificazione citologica europea, la categoria intermedia (TIR3), il rischio di malignità non dovrebbe superare il 15%; sempre più evidenze, tuttavia, stanno modificando tale stima, al punto che un atteggiamento sempre più aggressivo è consigliato da diversi endocrinologi ed endocrinochirurghi.Sulla base di tali valutazioni, abbiamo valutato prospetticamente tutti i pazienti con diagnosi citologica di atipia di incerto significato, dal 2005, e classificati come TIR3, dal 2007, afferiti presso il Nostro ambulatorio, candidandoli a tiroidectomia totale, al fine di ottenere uno studio istopatologico completo.
MATERIALI E METODI: Sono stati considerati i pazienti operati da gennaio 2005 a dicembre 2012. Di questi, abbiamo incluso nella nostra valutazione tutti i pazienti con riscontro di TIR3 ad esame citologico, dal 2007, mentre prima del 2007 abbiamo arruolato i pazienti con riscontro di atipia all'esame (gruppo intermedio, secondo la vecchia classificazione). Tutti i pazienti sono stati sottoposti a tiroidectomia totale secondo tecnica standardizzata, con visualizzazione ed isolamento delle paratiroidi e dei nervi ricorrenti su entrambi i lati.
RISULTATI: Sono stati sottoposti a tiroidectomia totale da gennaio 2005 a dicembre 2012 totale di 1514 pazienti. Di questi, 148 presentavano un riscontro citologico TIR3 e sono stati valutati prospetticamente.
I dati intraoperatori e postoperatori di questo sottogruppo non differivano dal totale della popolazione operata, riguardo ai parametri antropometrici, alla degenza media post-operatoria e al tasso di complicanze. Il riscontro di neoplasie (gruppo positivo) si è osservato in 64 casi (43.2%), con un tasso di neoplasie maligne pari al 19.6% del totale dei TIR3 analizzati (29 casi); il tasso di adenoma era pari a 23.6% (35 casi). Il gruppo dei negativi, con riscontro di sola patologia multi nodulare, di tipo prevalentemente follicolare, si è osservato in 84 pazienti (56.8% della popolazione TIR3). Confrontando i pazienti con precedente citologia TIR3, rispetto al totale della popolazione chirurgica sottoposta a tiroidectomia, abbiamo ottenuto, per tale parametro, una sensibilità pari al 43.2%, una specificità dell'82.1%, mentre il valore predittivo positivo era pari al 20.8%, ed il valore predittivo negativo al 93%. In 32 casi è stata effettuata una linfectomia, per linfonodi sospetti all'esplorazione chirurgica (21.6% di tutto il gruppo TIR3), e solo in un caso di carcinoma papillare, l'esame istologico definitivo ha confermato la presenza di metastasi.
CONCLUSIONI: Il gruppo citologico intermedio dei TIR3 rappresenta ancora una categoria eterogenea, con rischio di malignità ancora non definito. I nostri risultati chirurgici, in termini di tasso di neoplasia (benigna e maligna) confermano che l'approccio chirurgico al momento è il più esaustivo nella comprensione di questo sottogruppo di pazienti e, come approccio terapeutico, una scelta sicura dal punto di vista oncologico e preventivo, in attesa che marker molecolari incrementino il valore di tale studio ed entrino nella pratica clinica. In casi isolati, la scelta di una stretta sorveglianza o di un secondo FNA, anche in accordo con il patologo di riferimento, può ulteriormente precisare la condotta terapeutica di ciascun caso.

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