Cytologically undetermined thyroid's follicular lesions: surgical procedures and histological outcome in 472 cases

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BACKGROUND: *Fine needle cytology (FNC) of thyroid nodules is not always diagnostic. Most of FNCs undeterminated for malignancy belong to the cytological class of "follicular neoplasm/suspicious for follicular neoplasm" lesions (FN). In this group only 10-30% of cases are malignant and the most appropriate surgical management is still controversial. Here, this issue was addressed and the more reliable predictive criteria of malignancy were also evaluated.*
METHODS: *We retrospectively evaluated 472 patients, surgically treated after a FN diagnosis in a tertiary care referral center. In patients affected by bilateral thyroid disease with a cytological diagnosis of FN, or when high-risk clinical features and familiarity for thyroid cancer were present, total thyroidectomy (TT) was performed. Conversely, hemithyroidectomy (HT) was preferred when the nodule was single and when the age was ≤ 45 years. Frozen section examination was not used, and if cancer was diagnosed by definitive pathology of the HT specimen, the remnant thyroid* lobe *was removed. Histological features, surgical complications, and long-term outcomes of the remnant lobe were reported. Clinical features predictivity was also evaluated.*
RESULTS: *TT was performed in 154/472 pts (32.62%), while HT was carried out in 318/472 cases (67.37%). The overall malignancy rate (MR) was 18.85% (89/472 pts), respectively 16% (51/318pts) following HT, and 24.6% (38/154pts) following TT, with a statistically significant difference. Similarly, the rates of transient and definitive hypoparathyroidism and the mean hospital stay following TT were higher than after HT (and statistically significant). Age < 45years and female gender were more frequently associated to malignancy. The rate of complications following second surgery was comparable to that of primary HT. In the HT group incidence of unexpected contralateral papillary thyroid cancer (PTC) was 9.8% and, after 88.2 ± 30.42 months mean follow-up, completion surgery for benign pathology was carried out in 6.7% of cases.*
CONCLUSIONS: Our data show that histology following a cytological FN diagnosis is malignant only in a *low percentage of cases (89/472, 18.85%). Following TT, a MR higher than in HT was observed. Even if some clinical features are cancer associated, malignancy cannot be reliably predicted before surgery. Thus, in solitary low-risk lesions, HT is still the standard of care. Its lower complication rates makes HT the safest procedure. In case of multiglandular disease TT may be recommended. Further investigation is warranted to achieve a better preoperative diagnostic accuracy in order to reduce the amount of surgical operations with diagnostic aim.*

KEY WORDS: Fine needle cytology, Follicular neoplasm, Hemithyroidectomy, Total thyroidectomy, Thyroid cancer.

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Introduction

The extensive use of thyroid FNC (fine needle cytology) has determined an increased detection of "follicular neoplasm/suspicious for follicular neoplasm" lesions (FN), whose undetermined nature requires pathologic examination. The recent National Cancer Institute "Thyroid FNA Conference" specified consistent criteria to diagnose FN. According to Baloch, FN is a "gray-zone" [1], that includes a number of lesions such as hyperplastic nodular goiter (HN), follicular adenoma (FA) and well differentiated thyroid carcinomas. These are most frequently represented by papillary thyroid cancer (PTC), typically in its follicular variant (FVPTC) and less commonly by follicular carcinoma (FTC).

In the last years, the increased number of FN diagnoses has led to more thyroid surgical procedures. However, histology is malignant only in the 10-30% of cases. Nonetheless, neither US features nor molecular markers are so accurate to predict malignancy before surgery. Moreover, it is widely believed that also intra-operative consultation is ineffective too [2,3]. As a consequence, FN surgical management differs from one institution to another.

Hemithyroidectomy (HT), thanks to its limited operative risks, may be a rational approach in absence of contralateral nodules or thyroiditis. Total thyroidectomy (TT), however, might be preferred for different reasons. This controversial issue is here investigated. A retrospective analysis of a 472 patients series, surgically treated following the FNC diagnosis of FN, is reported. Pathological examination, surgical complications, and long-term evolution of the remnant lobe, represent the main parameters of this analysis. Our aim was to identify the most appropriate surgical treatment and the most reliable predictive criteria of malignancy. Our data showed that HT is the standard of care in patients with "solitary low-risk" lesions, whilst, in multiglandular diseases, TT should be recommended, expecially in case of a well-grounded malignancy risk. In addition, the age < 45 years and female gender were more frequently associated to malignancy.

Materials and Methods

In our Institution, a tertiary care referral endocrine surgical center, clinical records of patients, undergoing surgery between January 2000 and December 2008, after cytological evidence of FN, were selected by computerized search. A total of 551 patients was identified. Since not all of FNCs were performed in our Institution, and since diagnostic terminology embraced different classification schemes adopted trough several years, we decided to centrally review all FNCs. Consequently, at least two smears for each case were jointly reviewed by two experienced endocrine pathologists (GT, CB) at the Cytology Service of Biomorphologic and Functional Sciences Department of "Federico II" University of Naples-Italy. The Bethesda NCI Conference criteria for FN were adopted: a moderate/high cellularity, the micro-follicular pattern in a little or absent colloid background were the main diagnostic criteria. Conversely, cells with overlapping and crowding patterns, and/or nuclear atypia (vesicular nuclei, micro nucleoli and irregular cell membrane), which raised the suspect for PTC, were excluded. In conclusion, 472 cases, 326 female pts (69,06%), 146 male pts (30,9%) with a mean age of 45.56 ± 13.36 years were included in the study (Fig. 1).

In our Institution, total thyroidectomy (TT) is gener-

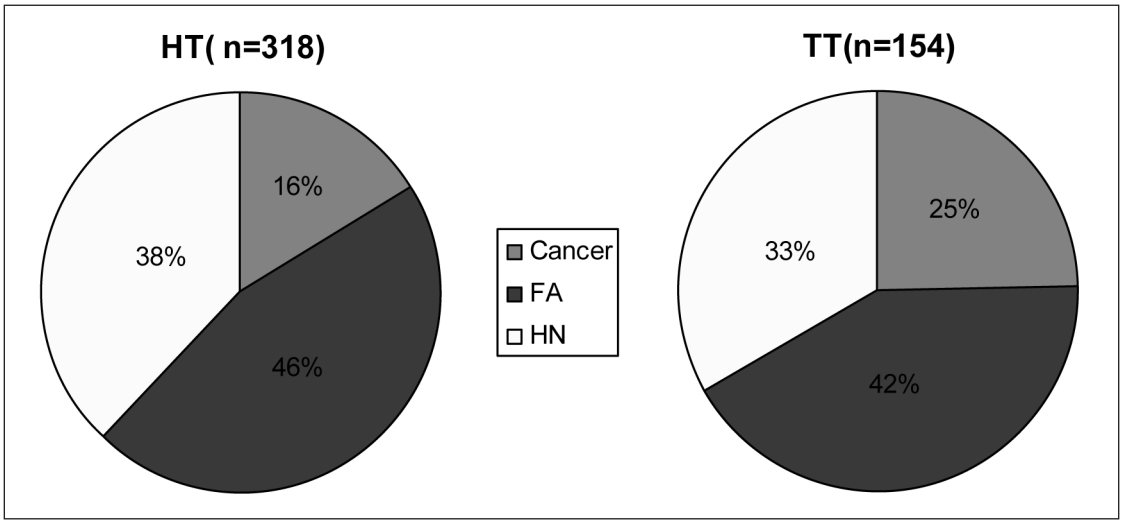

Fig. 1: Relationship between surgical treatment and histological diagnosis of 472 FN patients.

FN: follicular neoplasm; HT : hemithyroidectomy; TT : total thyroidectomy; FA : follicular adenoma; HN : hyperplastic nodular goiter.

ally performed when thyroid disease is bilateral or when high-risk clinical features (fixity or infiltration of cervical structures) and familiarity for thyroid cancer occur. Conversely, a single nodule, the age ≤ 45 years, the absence of thyroiditis or clinical/intraoperative suspicion of malignancy are the main criteria leading to HT. We do not use frozen section examination, and if cancer was diagnosed by definitive pathology, removal of the remaining thyroid lobe was undertaken. Age, gender, consensual thyroiditis and nodule size were compared along with definitive pathology. Surgical complications and remnant lobe evolution were assessed during a 88.2 ± 30.42 months mean follow-up.

Routine pre and post-operative fibrolaryngoscopy were performed in each case; vocal fold paresis was considered definitive (paralysis) after 6 months from 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 dosed on postoperative day 1. A iPTH serum level < 1.06 pmol/L was considered in determining postoperative hypoparathyroidism (definitive after 6 months from surgery). After HT, levothyroxine was administered in the majority of cases (mean dose 75 ± 25 μg).

Statistical analysis

Data were analyzed using descriptive statistics: for the categorical variables, the Pearson chi-squared (exact) test and for the quantitative variables the independent t-Student test were used. Data were reported as the mean value ± standard error of the mean (SEM). All calculations were performed using the software package GraphPad Prism, Version 5.0 for Windows (GraphPad Software, San Diego, CA, USA). Our values were considered statistically significant if p was ≤ 0.05.

Results

Cyto-Histological correlation

The mean time between FNC and surgical treatment was 40.45 ± 14.75 days. HN was diagnosed in 172 (36.4%) cases at the pathological examination (Fig. 1), FA in 211 (44.7%) cases, whereas malignancy was diagnosed in 89/472 patients (18.8%). In particular, PTC was found in 69/89 (77.5%). Most of the PTC cases belonged to the follicular variant subtype (58/69). FTC was found in 15/89 (16.8%) cases, whereas Hürthle cell carcinoma lesions were found in 5 (5.6%) cases.

Clinical data and histological diagnosis.

Thyroiditis co-existed in 99/472 pts (21%), where it was associated to cancer in 17 patients (17/89; 19%) and to benign pathology in 82/383 patients (21.4%). In Table 1, patients' cancer features are reported. Mean age of 37.89 ± 14.19 years, female gender (F/M=6.4/1), and a mean nodule size of 16.49 ± 6.99 mm were associated to malignancy.

In the patients affected by benign disease, a mean age of 47.35 ± 12.55 year and a mean nodule size of 16.94 ± 7.66 mm were observed, with a female/male ratio of 1.85/1. Age < 45 years and female gender were associated to malignancy with a statistical significance.

Surgical treatment and histological diagnosis

HT was performed in 318/472 (67.37%) patients, including 239 female pts (75,2 %), 79 male pts (24.8 %), with a mean age of 43.45 ± 13.86 years. Histology showed HN in 121/318 (38%), FA in 146/318 (46%), including 8 Hürthle cell FA, and 51/318 (16%) cancers; these latter underwent completion thyroidectomy (Fig. 1). TT was performed in 154/472 (32.62%) patients, 87 female pts (56.5 %), 67 male pts (43,5%), with a mean age of 49.93 ± 11.17 years. Histology showed HN in 51/154 (33.1%), FA in 65/154 (42.2%), including 8 Hürthle cell FA, and 38/154 (24.6%) carcinomas (Fig. 1).

Surgical treatment and outcomes

Definitive complications were not observed after HT (Table II). Conversely, 2 TT cases reported definitive recurrent laryngeal nerve (RLN) paralysis (1.3%). RLN transient paresis rates were similar between HT (1.25%; 4/318 pts) and TT (3.24%; 5/154 pts) (p=0.13). On the contrary, we reported a transient hypoparathyroidism in HT (1.25%; 4/318 pts), lower than in TT (8.4%; 13/154 pts; p= <0.0001), with a statistically significant difference. Permanent hypoparathyroidism occurred after TT in 1.94% (3/154 pts). A cervical haematoma was reported in 3/318 HT (0.94%) and in 2/154 TT (1.3%); of these latter, only one case required reintervention for

Table I - *Clinical data of 472 cytologically undetermined follicular lesions*

	Benign pathology (383/472 pts)	**Cancer (89/472 pts)**	p
Age (years)*	47.34 ± 12.55	37.89 ± 14.19	<0.05
Female / Male ratio	6.4	1.85	0.001
Tumour size (mm)*	16.93 ± 7.66	16.49 ± 6.99	n.s.
Consensual thyroiditis%	21.4	19	n.s.

*mean value ± standard deviation; p ≤0.05 was considered statistically significant; n.s.= not significant

TABLE II - *Complications*

	HT %	TT %	P
t Hypopara	1.3	8.4	<0.0001
p Hypopara	–	1.9	–
t RLN palsy	1.3	3.2	0.13
p RLN palsy	–	1.3	–
Cervical haematoma	0.9	1.2	0.7
Wound infection	0.3	–	–

HT: hemithyroidectomy; TT: total thyroidectomy; t: transient; p: permanent; Hypopara: hypoparathyroidism; RLN: recurrent laryngeal nerve; p ≤0.05 was considered statistically significant

bleeding control. Wound infection only occurred in one HT patient (0.3%). Mean hospital stay was 1.91 ± 0.74 days for HT and 3.24 ± 1.30 for TT (p<0.001).

COMPLETION THYROIDECTOMIES

A completion thyroidectomy was performed whenever (n= 51) pathology revealed malignancy on the HT surgical specimen; the mean time between HT and second surgery was 35.17 days ± 14.17. Apart from only one (1.9%) transient RLN paresis, no relevant complications occurred. Histological examination showed PTC in 5 (9,8%) cases, with microcarcinomas in most cases (4/5). In benign HT (n= 267), after a 88.2 ± 30.42 months mean follow-up, data showed contralateral nodular relapse in 18 cases (6.7%). Compressive symptoms led to surgical removal; histological examination showed HN in all cases, which was associated to thyroiditis in 1 case.

Discussion

Data generated in this study are relevant because a large FN patient series was analysed. We report that the malignancy rate (MR) associated to undeterminated FNCs is low (18.8%), being significantly different between HT and TT patients. Considering its very low morbidity rate, the low long-term incidence of completion thyroidectomy (6.7%), and also contralateral unexpected PTC (9.8%), HT may represent the standard of care in patients with solitary low-risk lesions.

The most effective surgical procedure following a FN diagnosis is controversial [4-8]. Since the majority of these lesions are diagnosed at pathology as benign, patients could more benefit from a long-term follow-up rather than from surgery. A surgical treatment performed only for a diagnostic purpose increases healthcare costs, causes distress to patients and can sometimes be a source of litigations. A more sensitive US evaluation, based on the accurate assessment of the echogenic patterns (margins features, vascularisation, microcalcifications) is promising, but not still definitively diagnostic [9].

Similarly, most of the proposed immunocytochemical (galectin 3, CK19 and HBME-1) and genetic markers (BRAF, RET/PTC, PAX 8/PPRY and NRAS) have not been validated for clinical use yet [10-21].

There are few doubts that TT is indicated in the bilateral diseases, as in the treatment of Graves' disease [22] whilst the most suitable surgical treatment for the solitary cytological undetermined nodule, is still intensively investigated. As suggested by our data, HT is supported by the low MR associated to FN, its low morbidity, the low incidence of long-term completion thyroidectomy [23], and, according with previous studies, it may be considered the preferred procedure for underminated FNCs [8,24]. This is especially true in case of small (< 1 cm) PTCs, whose low aggressiveness does not require TT. Nevertheless, TT might be suggested given: its slightly higher morbidity; the possibility to diagnose a contralateral occult microcarcinoma [25]; the ineffectiveness of HT in preventing hypothyroidism, and the increased healthcare costs in managing the remnant lobe. Moreover, a completion thyroidectomy for benign disease is often necessary (6.7% in our series), sometimes increasing complication rates [26,27]. According to Rosato [28], HT shows the lowest morbidity and remains the safest surgical procedure. This is confirmed by the absence of definitive complications in our series, also after completion thyroidectomy. As previously reported, TT had a higher morbidity rate than HT, even if it was not significant in every series [29-31].

The choice of the most suitable surgical procedure is also related to many different parameters and a multifactorial clinical analysis could be useful. Our data also show that age < 45 years and female gender are more frequently associated to malignancy, with statistical significance. Tyler (32), Davis [33] and Baloch [1], suggested thyroidectomy in >50 years old patients, conversely to the evidence reported by other authors [34-37]. Several studies confirmed that age, sex and size were less related to cancer risk than the hard consistency on clinical palpation and the US hypoechoic pattern [8,38]. In our series, a cancer mean size of 16.49 ± 6.99 mm was observed even if, according to literature data nodules > 4 cm in diameter are more frequently diagnosed as malignant lesions [1,34,37,39,40]. This clinical feature still remains a controversial issue [8,35,41-43].

In conclusion, our data show that pathology following a cytological FN diagnosis is malignant only in a low percentage of cases. In our series, TT, mostly performed in bilateral disease, was followed by an higher MR irrespective to HT, routinely indicated in solitary "low risk" lesions, with statistical significant difference. Even if some clinical features are cancer associated, malignancy cannot be reliably predicted before surgery. Thus, HT is still the standard of care. Its lower complication rates makes HT the safest procedure in solitary low-risk lesions, while TT should be recommended in case of multiglandular disease. Further investigation is warranted to achieve a better preoperative diagnostic accuracy in order to reduce the number of surgical operations with a diagnostic aim.

Riassunto

La citologia con ago sottile dei noduli tiroidei non è sempre diagnostica. La maggior parte dei casi che risultano "indeterminati" per patologia maligna appartengono alla classe citologica delle "neoplasie follicolari" (FN), cosiddette tir 3, che richiedono una verifica istologica. In questo gruppo mediamente il 10-30% dei casi risulta maligno e pertanto il trattamento chirurgico più appropriato resta ancora oggetto di controversie. Gli Autori hanno esaminato tale problematica valutando inoltre l'affididabilità di alcuni criteri predittivi di malignità. Nel lavoro retrospettivo sono stati analizzati i risultati relativi a 472 pazienti operati in seguito a diagnosi citologica di FN. Nei pazienti affetti da patologia tiroidea bilaterale, o in presenza di caratteristiche cliniche di rischio o familiarità per cancro tiroideo, è stata eseguita una tiroidectomia totale (TT)-154/472 pazienti (32.62%). Al contrario, nei pazienti con nodulo singolo ed età ≤ 45 aa è stata preferita una emitiroidectomia (HT) - 318/472 casi (67.37%), seguita da totalizzazione in caso di carcinoma. Venivano così analizzate le caratteristiche istologiche all'esame definitivo, le complicanze chirurgiche e l'evoluzione a lungo termine del lobo residuo in caso di HT. Il tasso di malignità complessivo (MR) è stato pari a 18.85% (89/472), rispettivamente 16% (51/318) dopo HT, e 24.6% (38/154) dopo TT, con una differenza statisticamente significativa. Allo stesso modo l'ipoparatiroidismo transitorio e definitivo e l'ospedalizzazione media in seguito a TT risultavano superiori rispetto alla HT. Dall'analisi statistica inoltre, solo l'età <45 anni ed il sesso femminile apparivano associati al cancro in maniera significativa. La morbilità dei reinterventi risultava sovrapponibile a quella osservata dopo HT. L'analisi dei dati osservati dimostra che in seguito a diagnosi citologica di FN l'istologia definitiva risulta maligna in una bassa percentuale di casi (89/472 -18.85%) ed inoltre che i criteri predittivi di malignità sono ancora oggetto di discussione. Pertanto, nei pazienti con noduli solitari a basso rischio, la HT, caratterizzata da una trascurabile morbilità, resta il trattamento di scelta. Al contrario, nei casi di patologia multinodulare va raccomandata una TT. Ulteriori studi sono tuttavia necessari per una migliore accuratezza diagnostica preoperatoria, al fine di ridurre il numero di interventi chirurgici a scopo diagnostico.

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