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Review

Controversies in the surgical management of thyroid follicular neoplasms. Retrospective analysis of 721 patients

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ABSTRACT

The most appropriate surgical management of "follicular neoplasm/suspicious for follicular neoplasm" lesions, is still controversial. Analysing and comparing the experience of two units for endocrine surgery, we retrospectively evaluated 721 patients, surgically treated after a follicular neoplasm diagnosis. Total thyroidectomy was routinely performed in one Institution, while in the other one it was selectively carried out. The main criteria leading to hemythyroidectomy were a single nodule, the age ≤45 years, the absence of thyroiditis or clinical/intraoperative suspicion of malignancy.

Total thyroidectomy was performed in 402/721 patients (55.7%), hemythyroidectomy in 319/721 cases (44.2%) and a completion thyroidectomy in 51/319 cases (15.9%). The overall malignancy rate was 24% (176/721 patients), respectively 16% (51/319 patients) following hemythyroidectomy, and 31% (125/402 patients) following total thyroidectomy. Definitive recurrent laryngeal nerve paralysis and permanent hypoparathyroidism were not reported in hemythyroidectomy patients in which lower mean hospitalization and costs were observed. Considering the low-risk of follicular neoplasm solitary lesions, hemythyroidectomy is still the safest standard of care with lower hospitalization and costs. In case of multiglandular disease or thyroiditis, that might be associated with a higher risk of cancer, total thyroidectomy should be recommended. Further investigation is warranted to achieve a better preoperative follicular neoplasm diagnostic accuracy in order to reduce the amount of unnecessary surgical operations with a diagnostic aim.

1. Introduction

In the last decade, the extensive use of thyroid ultrasound (US) guided FNC (fine needle cytology), has determined a surprisingly increased detection of differentiated cancer and in about 15–30% of cases of "follicular neoplasm/suspicious for follicular neoplasm" lesions (FN), whose undetermined nature requires pathologic examination [1–4]. Papillary variants are the most frequent thyroid neoplasms, followed by follicular, medullary cancer, often part of the MEN-2 syndrome [5,6], and anaplastic carcinoma, associated with an unfavourable prognosis similar to that observed in sarcomatoid carcinomas of other districts [7]. The recent National Cancer Institute "Thyroid FNA Conference" specified consistent criteria to diagnose FNs, in most cases including lesions such as hyperplastic nodular goiter (HN), or follicular adenoma (FA) [8]. Identification of capsular or vascular invasion is necessary to achieve a definitive diagnosis and less frequently a well differentiated thyroid carcinoma, papillary thyroid cancer (PTC), typically in its follicular variant (FVPTC) and less commonly follicular carcinoma (FTC), is postoperatively diagnosed [1]. According to literature data, the increased number of FN diagnoses has led to more thyroid surgical procedures, demonstrating that malignancy rate (MR) associated with FN is low (10–30%) [8,9]. Nonetheless, neither preoperative US features nor molecular markers, nor intra-operative

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consultation [10] are so accurate to predict malignancy, and, an increased number of diagnostic thyroidectomies have been reported. On the other hand, in several patients who underwent lobectomy, a completion thyroidectomy was required. Despite several studies, management guidelines are controversial, endocrine, head and necks surgeons are divided between supporters and detractors of routine total thyroidectomy (TT), and FN surgical treatment differs from one institution to another. HT was considered as an adequate procedure in 96% of FN cases [11] and moreover, according to American Thyroid Association (ATA) guidelines, thanks to its limited operative risks, is well indicated in the treatment of small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas, in absence of clinical lymph nodes metastases [12]. On the contrary, the frequent presence of a contralateral occult microcarcinoma, the increased healthcare costs in managing the remnant lobe and increasing complication rates of reinterventions are the main arguments evocated in favour of TT, the operation of choice in most thyroid diseases [13–16]. Available evidence data confirm the need of a better preoperative evaluation of patients with a FN to avoid unnecessary diagnostic surgery. Analysing the data reported in one of the largest reported series and describing the results of a multicentric study by two academic Units of endocrine surgery, this controversial issue is here investigated. In addition, a review of more recent literature papers was performed. The analysis of different surgical procedures – TT vs HT – and histological outcomes was the main objective of the study.

2. Study design

We analysed, by a retrospective multicenter study, the clinical experience of two university Units of endocrine surgery, of Sardegna and Campania, at medium risk for thyroid cancer. 800 patients (pts) treated between January 2000 and December 2008, after cytological evidence of FN, were selected by computerized search. All patients provided written consent for the treatment of data. In order to uniform the different classification adopted for all the FNCs, a centralized review, conducted by two experienced endocrine pathologists of the Cytology Service of Biomorphologic and Functional Sciences Department of "Federico II" University of Naples and of Department of Cytomorphology of University of Cagliari, using at least two smear layers for each case, was performed. The Bethesda NCI Conference criteria for FN were adopted: a moderate/high cellularity, the microfollicular 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. Age, gender, associated thyroiditis and nodule size were compared along with definitive pathology. Pathological examination, surgical complications and long-term progression 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.

3. Materials and methods

From 800 selected pts, only 721 cases, 524 female (72.6%), 197 male (27.3%) with a mean age of 47.93 years, fully responding to the reported criteria according to study design, were included in the series. In Institution A (VII Division of General and Endocrine Surgery – Second University of Naples, Italy) TT was performed in bilateral thyroid disease cases or in patients with high-risk clinical features (thyroiditis, fixity or infiltration of cervical structures) and familiarity with thyroid cancer (154/721). A single nodule, the age ≤45 years, the absence of thyroiditis or radiological, clinical and intraoperative suspicion of malignancy were the main criteria leading to HT (319/721). Frozen section examination was not performed, and in case of cancer confirmed by definitive pathology, completion thyroidectomy was undertaken. In Institution B (Department of Surgical Sciences University of Cagliari, Italy), TT was routinely performed and frozen section examination was not used (248/721). An intraoperative nerve monitoring was not utilized. Routine pre and post-operative fibrolaryngoscopy was performed; vocal fold paresis was considered definitive (paralysis) 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 dosed on post-operative day 1. An iPTH serum level <1.06 pmol/L was considered for postoperative hypoparathyroidism (definitive 6 months after surgery). After HT, levothyroxine was administered in the majority of cases (mean dose 75 ± 25 μg).

3.1. Statistical analysis

Data were analysed using descriptive statistics: for the categorical variables, the Pearson chi-squared (exact) test and, for the quantitative variables, the independent *t*-Student test was 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.

4. Results

4.1. Cyto-histological correlation

Institution A: HN was diagnosed in 172 (36.4%) cases at the pathological examination, FA in 211 (44.7%) cases, whereas malignancy was diagnosed in 89/472 pts (18.8%) (Fig. 1). PTC was found in 69/89 (77.5%). Most of the PTC cases were follicular variant subtype (58/69). 15/89 (16.8%) patients were diagnosed of FTC, whereas in 5 (5.6%) cases were Hürthle cell carcinoma.

Institution B: HN was diagnosed in 107 (42.9%) cases at the pathological examination, FA in 55 (22.1%) cases, whereas malignancy was diagnosed in 87/249 patients (34.9%) (Fig. 1). PTC was found in 67/87 (77%); 32/67 belonged to the follicular variant subtype. 17/87 (19.5%) patients were diagnosed of FTC, whereas 2 (2.3%) cases were Hürthle cell carcinoma.

4.2. Clinical data and histological diagnosis

Institution A: Thyroiditis co-existed in 99/472 pts (21%). It was associated with cancer in 17 pts (17/89; 19%) while to benign pathology in 82/383 pts (21.4%). Mean age of 37.8 ± 14.1 years, female gender (F/M = 6.4/1), and a mean nodule size of 16.4 ± 6.9 mm were associated to malignancy. While patients affected by benign disease are characterized by a mean age of 47.3 ± 12.5 year and a mean nodule size of 16.9 ± 7.6 mm, with a female/male ratio of 1.85/1. Age <40 years and female gender were statistically associated to malignancy (Table 1)

Institution B: Thyroiditis co-existed in 119/249 pts (47.7%). It was associated with cancer in 40 patients (40/87; 45.9%) and to benign pathology in 79/162 patients (48.7%). A solitary FN lesion was diagnosed in only 140/249 patients (56.2%), while in the remaining cases a multinodular disease or thyroiditis were associated. In cancer patients mean age of 51.5 ± 14.9 years, female gender (F/M = 4.11/1), and a mean nodule size of 18.6 ± 11.4 mm were associated to malignancy. In patients affected by benign disease, a mean age of 52.9 ± 12.9 year and a mean nodule size of