International Journal of Surgery 12 (2014) S29–S34

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

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

Giovanni Conzo [a,*], Pietro Giorgio Calò [b], Claudio Gambardella [a], Ernesto Tartaglia [a], Claudio Mauriello [a], Cristina Della Pietra [a], Fabio Medas [b], Rosa Santa Cruz [b], Francesco Podda [b], Luigi Santini [a], Giancarlo Troncone [c]

[a] Department of Anesthesiologic, Surgical and Emergency Sciences, VII Division of General and Endocrine Surgery, Second University of Naples, Via Gen. G. Orsini 42, 80132 Napoli, Italy
[b] Department of Surgical Sciences University of Cagliari, Italy
[c] Department of Biomorphologic and Functional Sciences, "Federico II" University of Naples, Italy

ARTICLE INFO

Article history:
Received 23 March 2014
Accepted 3 May 2014
Available online 22 May 2014

Keywords:
Fine needle cytology
Follicular neoplasm
Hemithyroidectomy
Total thyroidectomy
Thyroid cancer

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

* Corresponding author.
E-mail address: giovanni.conzo@unina2.it (G. Conzo).

http://dx.doi.org/10.1016/j.ijsu.2014.05.013
1743-9191/

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

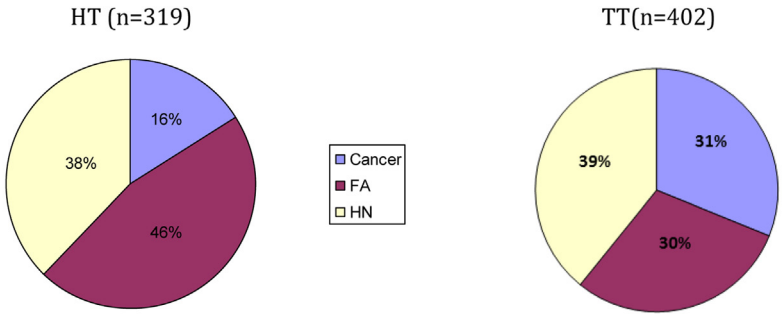
Institution A: HN was diagnosed in 172 (36.4%) cases at the pathological examination, FA in 211 (44.7%) cases, whereas malignancy was diagnosed in 89/472 pts (18.8%) (Fig. 1). PTC was found in 69/89 (77.5%). Most of the PTC cases were follicular variant subtype (58/69). 15/89 (16.8%) patients were diagnosed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



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

Fig. 1. Relationship between surgical treatment and histological diagnosis of 721 FN patients.

17.9 ± 9.1 mm were observed, with a female/male ratio of 3.76/1. None of the characteristics was associated to malignancy with a statistical significance (Table 2)

4.3. Surgical treatment and histological diagnosis

Institution A: HT was performed in 318/472 (67.3%) pts, including 239 female (75.2%), 79 male (24.8%), with a mean age of 43.4 ± 13.8 years. Histology revealed HN in 121/318 (38%), FA in 146/318 (46%), including 8 Hürthle cell FA, and 51/318 (16%) cancers; these latters underwent completion thyroidectomy (Fig. 1). TT was performed in 154/472 (32.6%) pts, 87 female (56.5%), 67 male (43.5%), with a mean age of 49.9 ± 11.1 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.

Institution B: TT was performed in 248/249 (99.6%) patients, HT in 1/249 (0.4%, that resulted FA at the pathological examination). HN was diagnosed in 107 (42.9%) cases, FA in 55 (22.1%) cases, whereas malignancy was diagnosed in 87/249 patients (34.9%) (Fig. 1). Considering the MR and surgical operation in a high rate of patients affected by a solitary FN nodule TT could be considered as an overtreatment.

4.4. Surgical treatment and outcomes

Institution A: Definitive complications were not observed after HT (Table 3). Conversely, 2 TT cases reported definitive recurrent laryngeal nerve (RLN) paralysis (1.3%). RLN transient paresis rates were similar between HT (1.2%; 4/318 pts) and TT (3.2%; 5/154 pts) ($p = 0.13$). On the contrary, we reported a transient hypoparathyroidism in HT (1.2%; 4/318 pts), lower than in TT (8.4%; 13/154 pts; $p \leq 0.0001$), with a statistically significant difference. Permanent hypoparathyroidism occurred after TT in 1.94% (3/154 pts). A cervical haematoma occurred in 3/318 HT (0.9%) and in 2/154 TT (1.3%); of these latter, only one case required reintervention for bleeding control. Wound infection only occurred in one HT patient (0.3%). Mean hospitalization was 1.9 ± 0.7 days for HT and 3.2 ± 1.3 for TT and was associated with lower costs in HT group ($p < 0.001$).

Institution B: RLN transient paresis rates were 0.8% (2/249 pts). Permanent hypoparathyroidism occurred in 1.6% (4/249 pts). A cervical haematoma occurred in 3/249 HT (1.2%); of these, 2 cases required reintervention for bleeding control. Wound infection only occurred in one patient (0.4%) (Table 4).

4.5. Completion thyroidectomies

Institution A: a completion thyroidectomy was performed whenever ($n = 51$) pathology revealed malignancy on the HT surgical specimen, that was a microcarcinoma in 6/51 cases (11.7%); the mean time between HT and second surgery was 35.1days ± 14.1. Preoperative ultrasound features "suspected" for cancer (margins features, vascularization, microcalcifications) have been identified in 16/51 pts (31.3%). 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 ± 30.4 months mean follow-up, data showed contralateral nodular relapse in 18 cases (5.6%). Compressive symptoms led to surgical removal; histological examination showed HN in all cases, which was associated to thyroiditis in one case.

4.6. Comparison between the two institutions

Patient characteristics of the two institutions differ significantly (Table 4). Differences in Female/Male Ratio, age, incidence of thyroiditis and of malignancy were statistically significant. In particular, the incidence of carcinoma was significantly higher in the institution B (34.9% vs 18.8%, $p < 0.01$ (0.000002)). Moreover, in the latter the incidence of thyroiditis (47.7% vs 21%, $p < 0.01$) was

Table 1
Clinical and pathological data of Institution A patients.

	Benign pathology (383/472 pts)	Cancer (89/472 pts)	*p*
Age (years)[a]	47.3 ± 12.5	37.8 ± 14.1	<0.05
Female/Male ratio	1.8	6.4	0.001
Tumour size (mm)[a]	16.9 ± 7.6	16.4 ± 6.9	n.s.
Associated thyroiditis	21.4%	19%	n.s.

$p \leq 0.05$ was considered statistically significant.
n.s. = not significant.
pts = patients.
[a] Mean value ± standard deviation.

Table 2
Clinical and pathological data of institution B patients.

	Benign pathology (162/249 pts)	Cancer (87/249 pts)	*p*
Age (years)[a]	52.9 ± 12.9	51.5 ± 14.9	0.19
Female/male ratio	3.7	4.1	0.91
Tumour size (mm)[a]	17.9 ± 9.1	18.6 ± 11.4	0.27
Associated thyroiditis	48.7%	45.9%	0.77

$p \leq 0.05$ was considered statistically significant.
pts = patients.
[a] Mean value ± standard deviation.

Table 3
Institution A complications.

	HT%	TT%	*p*
Transient hypopara	1.3	8.4	<0.0001
Permanent hypopara	–	1.9	–
Transient RLN palsy	1.3	3.2	0.13
Permanent RLN palsy	–	1.3	–
Cervical haematoma	0.9	1.2	0.7
Wound infection	0.3	–	–

HT: hemithyroidectomy; TT: total thyroidectomy; Hypopara: hypoparathyroidism. RLN: recurrent laryngeal nerve.
$p \leq 0.05$ was considered statistically significant.

significantly greater. In the surgical unit B the mean age was greater (52.4 ± 13.6 years vs 45.5 ± 13.3, $p < 0.01$ (0.0000000003)) and this could also explain the higher incidence of cancer.

5. Discussion

This study analyses two different surgical procedures – TT vs HT – in FN patients. According to our knowledge, the presented series is one of the largest reported. The overall MR associated with undetermined FNCs was low (24%, 176/721 cases), resulting significantly different between the considered regions, respectively higher in Sardegna (34.9%) than in Campania (18.9%), and in TT than in HT group. Nevertheless, considering the low MR following routine TT, this surgical approach may represent an "overtreatment" in a high number of cases. Two elements have to be certainly underlined: Sardegna has proved to be an area of endemic goiter and presents a very high incidence of autoimmune diseases, in particular Hashimoto's thyroiditis, probably determining a more elevated rate of malignant neoplasms, justifying the wide diffusion of TT. Therefore, the characteristics of the population at risk and the clinic-pathological features of cancer itself may be significantly different according to ethnicity and geographical location [17]. The cytological classification may not be uniform in different geographical areas and therefore a centrally review of all FNCs was systematically performed. The age<40 years and female gender resulted statistically associated with cancer in Institution A, while it was not confirmed in the other institution. Therefore, the most effective surgical procedure following FN diagnosis is still controversial and, analysing the preoperative predictive value of several clinical, radiological and molecular variables, the debate is not solved [18–20].

In the last decades an increasing precocious diagnosis of "low-risk" thyroid carcinomas (<2 cm) and microcarcinomas has been reported and more favourable oncological outcomes are expected [21]. So, planning a multimodal therapeutic protocol, an "overtreatment" with risk of morbidity should be avoided suggesting a "tailored" and less "aggressive" management [16]. Nevertheless, according to available evidence data, HT and TT maintain both an important role in the current approach to thyroid neoplasms, remaining matter of intensive research [22]. In case of small (≤1 cm) FN solitary low-risk lesions, HT, avoiding the possibility of bilateral recurrent laryngeal nerve paresis and definitive lifelong opotherapy, may represent the most accurate procedure [23] and the safest standard of care [1]. In our series, a low associated MR, a low long-term incidence of completion thyroidectomy (5.6%), and finally a low rate of contralateral unexpected PTC (9.8%) in HT patients were observed. Moreover, in case of small papillary cancers (<1 cm), the need of TT remains controversial. Revised ATA guidelines consider HT a sufficient treatment for incidental, small (<1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas, in absence of clinical lymph nodes metastases [12]. Our series confirmed the absence of definitive complications, also following a completion thyroidectomy, the lower mean hospitalization and costs in the HT group. Transient recurrent nerve paralysis was similar in the two groups of patients while transient hypoparathyroidism rate was lower following HT. According to literature, the majority of FNs are diagnosed as benign, and it may be considered that most patients could benefit more from a watchful waiting rather than from surgery. A surgical treatment performed only for a diagnostic purpose increases healthcare costs, may cause distress to patients and can be a source of litigations. On the contrary, TT, associated with a low morbidity rate, similar to that reported in parathyroid surgery [24–27], should be recommended both in patients affected by multinodular pathology and in cases of thyroiditis, as frequently reported in Sardegna, where a more elevated cancer risk has been observed. Furthermore the presence of contralateral occult microcarcinoma, described with a different incidence in various series, the increased healthcare costs in managing the remnant lobe and increasing complication rates of reinterventions are evocated in favour of TT [15,28,29]. Moreover, the performance of TT associated with prophylactic central compartment neck dissection in clinically node-negative patients is still debated [30]. Further randomized prospective trials could contribute to the standardization of cytologic classifications and treatment profiles, identifying the patients risk and the best surgical procedure. Moreover, sex, age, lesion size, serum thyroglobulin levels, US findings, molecular and genetic markers have been intensively investigated in making management decisions but the analysis of available evidence data supply controversial results. In the attempt to better classify thyroid nodules a more accurate US assessment (echogenicity, margins features, vascularization, microcalcifications, elastography) is promising, but not still definitively diagnostic [3,9,31]. Similarly, most of the proposed immunocytochemical (galectin 3, CK19 and HBME-1), genetic markers (BRAF, RET/PTC, PAX 8/PPRY and NRAS) or thyroglobulin serum level, may be very useful, but not widely validated [2,32–39]. The choice of the most suitable surgical procedure is also related to many different parameters, and a multifactorial clinical analysis, similar to that considered for differentiated thyroid cancer [40], could be useful. Nevertheless, each single factor did not reach predictive power and, moreover clinical series are unfortunately retrospective. Historical high-risk findings such as hoarseness of the voice, nodule fixation to the surrounding structures or previous exposure to radiations are rarely observed; more attention should be focused on patient age, sex or nodule size. Our data showed a difference in predictive factors. In one Institution the age >50 years was related with cancer, while in the other, the age <40 years and female gender were statistically associated to malignancy. Tyler, Davis [40] and Baloch [41], suggested thyroidectomy in >50 years old patients, conversely to the evidence reported by other authors [23,42,43]. Several studies highlighted the influence of the hard consistency on clinical palpation and the US hypoechoic pattern [44] on cancer risk. In our series, a cancer mean size less than 20 mm was observed even if according to literature data nodules

Table 4
Comparison between clinico-pathological data of FN patients observed at the two different Institutions.

	Institution A	Institution B	*p*
Patient number	472	249	–
Female/male ratio	2.23	3.88	<0.01
Age (years)[a]	45.5 ± 13.3	52.4 ± 13.6	<0.01
Associated thyroiditis (%)	21	47.8	<0.01
Tumour size (mm)[a]	16.8 ± 7.5	18.1 ± 9.9	>0.05
Malignancy disease (%)	18.9	34.9	<0.01

$p \leq 0.05$ was considered statistically significant.
[a] Mean ± standard deviation.

>4 cm in diameter are more frequently diagnosed as malignant lesions [8,41,43–45]. These clinical features still remain a controversial issue [41,9]. Even if the series is one of the largest reported, according to the high number of cases and the long-term follow-up, the different FN surgical approach of the two Institutions and the different epidemiological and pathological features of the analysed patients were the main limitations of the retrospective study. Nevertheless, it should be considered an outcomes analysis of surgical treatment in FN patients with different characteristics rather than a comparison between two different surgical procedures (HT vs TT) performed in similar cases.

6. Conclusions

Definitive FN MR was low and most surgical procedures had only a diagnostic significance. MR was higher after TT, especially in patients with thyroiditis. Even if some clinical features were cancer associated, malignancy could not be reliably predicted before surgery.

In solitary small low-risk lesions, HT, thanks to its lower complication rates, is still the safest standard of care, avoiding unnecessary morbidity. In our series in HT patients a lower mean hospital stay and costs were also reported.

TT should be recommended in case of multiglandular disease or in presence of thyroiditis that might be associated with a higher risk of cancer.

Even if a more conservative surgical approach might be suggested in FN patients, more prospective randomized trials based on multi-institutional, and multivariate analysis are requested to achieve a better preoperative diagnostic accuracy reducing the amount of unnecessary surgical operations with a diagnostic aim.

Funding

All Authors have no source of funding.

Ethical approval

This is a retrospective study based only on the analyses of recorded data and then no Ethical Approval was necessary.

Author contribution

Giovanni Conzo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Piero Giorgio Calò: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Claudio Gambardella: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Ernesto Tartaglia: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Claudio Mauriello: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Cristina Della Pietra: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Fabio Medas: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Rosa Santa Cruz: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Francesco Podda: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Luigi Santini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giancarlo Troncone: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflict of interest

The authors have no conflict of interest or any financial support.

References

[1] G. Conzo, G. Troncone, G. Docimo, et al., Cytologically undetermined follicular lesions: surgical procedures and histological outcome in 472 cases, Ann. Ital. Chir. 84 (2013) 251–256.
[2] G. Troncone, M. Volante, A. Iaccarino, et al., Cyclin D1 and D3 overexpression predicts malignant behavior in thyroid fine-needle aspirates suspicious for Hurtle cell neoplasms, Cancer Cytopathol. 117 (2009) 522–529.
[3] E. Baldini, S. Sorrenti, C. Di Gioia, et al., Cervical lymph node metastases from thyroid cancer: does thyroglobulin and calcitonin measurement in fine needle aspirates improve the diagnostic value of cytology? BMC Clin. Pathol. 13 (2013) 7.
[4] P.G. Calò, M.L. Lai, E. Guaitoli, et al., Difficulties in the diagnosis of thyroid paraganglioma: a clinical case, Clin. Ter. 164 (1) (2013) e35–e39.
[5] G. Conzo, L. Circelli, D. Pasquali, et al., Lessons to be learned from the clinical management of a MEN 2A patient bearing a novel 634/640/700 triple mutation of the RET proto-oncogene, Clin. Endocrinol. (Oxf) 77 (6) (2012) 934–936.
[6] G. Conzo, M. Musella, F. Corcione, et al., Laparoscopic adrenalectomy, a safe procedure for pheochromocytoma. A retrospective review of clinical series, Int. J. Surg. 11 (2) (2013) 152–156.
[7] D. Di Vizio, L. Insabato, G. Conzo, et al., Sarcomatoid carcinoma of the colon: a case report with literature review, Tumori 87 (6) (2001) 431–435.
[8] J. Smith, R.E. Cheifetz, N. Schneidereit, K. Berean, T. Thomson, Can cytology accurately predict benign follicular nodules? Am. J. Surg. 189 (5) (2005 May) 592–595.
[9] K.H. Lee, J.H. Shin, E.S. Ko, S.Y. Hahn, J.S. Kim, J.H. Kim, Y.L. Oh, Predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm of thyroid nodules, Int. J. Surg. 11 (9) (2013) 898–902.
[10] C.R. McHenry, C. Raeburn, T. Strickland, J.J. Marty, The utility of routine frozen section examination for intraoperative diagnosis of thyroid cancer, Am. J. Surg. 172 (6) (1996 Dec) 658–661.
[11] S.M. Wiseman, C. Baliski, R. Irvine, et al., Hemithyroidectomy: the optimal initial surgical approach for individuals undergoing surgery for a cytological diagnosis of follicular neoplasm, Ann. Surg. Oncol. 13 (3) (2006 Mar) 425–432.
[12] D.S. Cooper, G.M. Doherty, B.R. Haugen, et al., Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, Thyroid 19 (2009) 1167–1214.
[13] G. Docimo, R. Ruggiero, A. Gubitosi, et al., Ultrasound scalpel thyroidectomy: prospective randomized study, Ann. Ital. Chir. 83 (6) (2012) 491–496.
[14] A. De Bellis, G. Conzo, G. Cennamo, et al., Time course of Graves' ophthalmopathy after total thyroidectomy alone or followed by radioiodine therapy: a 2-year longitudinal study, Endocrine 41 (2012) 320–326.
[15] P.G. Calò, G. Pisano, G. Piga, et al., Postoperative hematomas after thyroid surgery. Incidence and risk factors in our experience, Ann. Ital. Chir. 81 (5) (2010) 343–347.
[16] G. Conzo, D. Pasquali, G. Bellastella, et al., Total thyroidectomy, without prophylactic central lymph node dissection, in the treatment of differentiated thyroid cancer. Clinical retrospective study on 221 cases, Endocrine 44 (2) (2013 Oct) 419–425.
[17] Seong Hyeon Lee, Jeong Su Baek, et al., Predictive factors of malignancy in thyroid nodules with a cytological diagnosis of follicular neoplasm, Endocr. Pathol. 24 (4) (2013 Dec) 177–183.
[18] J.B. Vander, E.A. Gaston, T.R. Dawber, The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy, Ann. Intern Med. 69 (1968) 537–540.

[19] S. Ezzat, D.A. Sarti, D.R. Cain, G.D. Braunstein, Thyroid incidentalomas. Prevalence by palpation and ultrasonography, Arch. Intern Med. 154 (1994) 1838–1840.
[20] G.M. Sclabas, G.A. Staerkel, S.E. Shapiro, et al., Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients, Am. J. Surg. 186 (6) (2003 Dec) 702–709.
[21] F. Sorrentino, J. Atzeni, G. Romano, G. Buscemi, M. Romano, Differentiated microcarcinoma of the thyroid gland, G. Chir. 31 (6–7) (2010 Jun-Jul) 277–278.
[22] C. Dobrinja, G. Trevisan, L. Piscopello, M. Fava, et al., Comparison between thyroidectomy and hemithyroidectomy in treatment of single thyroid nodules identified as indeterminate follicular lesions by fine-needle aspiration cytology, Ann. Ital. Chir. 81 (2010) 403–410.
[23] C.M. Antunes, A. Taveira-Gomes, Lobectomy in follicular thyroid neoplasms' treatment, Int. J. Surg. 11 (9) (2013) 919–922.
[24] G. Conzo, A.F. Perna, A.A. Sinisi, et al., Total parathyroidectomy without autotransplantation in the surgical treatment of secondary hyperparathyroidism of chronic kidney disease, J. Endocrinol. Investig. 35 (2012) 8–13.
[25] G. Conzo, A. Perna, N. Avenia, et al., Evaluation of "putative" role of intraoperative intact parathyroid hormone assay during parathyroidectomy for secondary hyperparathyroidism. A retrospective study on 35 consecutive patients, Endocrine 42 (3) (2012) 606–611.
[26] R.M. De Santo, M.G. Esposito, C.M. Cesare, et al., Parathyroidectomy improves the quality of sleep in maintenance hemodialysis patients with severe hyperparathyroidism, J. Nephrol. 21 (Suppl. 13) (2008) S92–S96.
[27] G. Conzo, A.F. Perna, V. Savica, et al., Impact of parathyroidectomy on cardiovascular outcomes and survival in chronic hemodialysis patients with secondary hyperparathyroidism. A retrospective study of 50 cases prior to calcimimetics era, BMC Surg. 13 (Suppl. 2) (2013) 1–8.
[28] P.M. Spanheimer, S.L. Sugg, G. Lal, et al., Surveillance and intervention after thyroid lobectomy, Ann. Surg. Oncol. 18 (2011) 1729–1733.
[29] M.A. Rafferty, D.P. Goldstein, L. Rotstein, et al., Completion thyroidectomy versus total thyroidectomy: is there a difference in complication rates? an analysis of 350 patients, J. Am. Coll. Surg. 205 (2007) 602–607.
[30] Giovanni Conzo, Pietro Giorgio Calò, Antonio A. Sinisi, et al., Impact of prophylactic central compartment neck dissection on locoregional recurrence of differentiated thyroid cancer in clinically node-negative patients: a retrospective study of a large clinical series, Surgery 155 (6) (2014 Jun) 998–1005.
[31] P. Trimboli, S. Ulisse, M. D'Alò, et al., Analysis of clinical, ultrasound and colour flow-Doppler characteristics in predicting malignancy in follicular thyroid neoplasms, Clin. Endocrinol. 69 (2008) 342–344.
[32] A. Bartolazzi, F. Orlandi, E. Saggiorato, et al., Galectin-3-expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine-needle aspiration cytology: a prospective multicentre study, Lancet Oncol. 9 (2008) 543–549.
[33] D. Finley, B. Zhu, C.B. Barden, T. Fahey, Discrimination of benign and malignant thyroid nodules by molecular profiling, Ann. Surg. 240 (2004) 425–436.
[34] M.E. Herrmann, V.A. LiVolsi, T.L. Pasha, et al., Immunohistochemical expression of galectin-3 in benign and malignant thyroid lesions, Arch. Pathol. Lab. Med. 126 (2002) 710–713.
[35] A. Carpi, A.G. Naccarato, G. Iervasi, et al., Large needle aspiration biopsy and galectin-3 determination in selected thyroid nodules with indeterminate FNA-cytology, Br. J. Cancer 95 (2006) 204–209.
[36] M. Mekel, C. Nucera, R.A. Hodin, S. Parangi, Surgical implications of B-RafV600E mutation in fine-needle aspiration of thyroid nodules, Am. J. Surg. 200 (1) (2010 Jul) 136–143.
[37] D. Pasquali, A. Santoro, P. Bufo, et al., Upregulation of endocrine gland-derived vascular endothelial growth factor in papillary thyroid cancers displaying infiltrative patterns, lymph node metastases, and braf mutation, Thyroid 21 (4) (2011) 391–399.
[38] G. Conzo, G. Docimo, D. Pasquali, et al., Predictive value of nodal metastases on local recurrence in the management of differentiated thyroid cancer. Retrospective clinical study, BMC Surg. 13 (Suppl. 2) (2013).
[39] E.K. Alexander, G.C. Kennedy, Z.W. Baloch, et al., Preoperative diagnosis of benign thyroid nodules with indeterminate cytology, N Engl. J. Med. 367 (8) (2012 Aug 23) 705–715.
[40] N.L. Davis, M. Gordon, E. Germann, et al., Clinical parameters predictive of malignancy of thyroid follicular neoplasms, Am. J. Surg. 161 (1991) 567–569.
[41] Z.W. Baloch, S. Fleisher, V.A. LiVolsi, P.K. Gupta, Diagnosis of "follicular neoplasm": a gray zone in thyroid fine-needle aspiration cytology, Diagn. Cytopathol. 26 (2002) 41–44.
[42] J.M. Zdon, A.J. Fredland, P.H. Zaret, Follicular neoplasms of the thyroid: predictors of malignancy? Am. Surg. 67 (2001) 880–884.
[43] A. Belfiore, G.L. La Rosa, G.A. La Porta, et al., Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity, Am. J. Med. 93 (1992) 363–369.
[44] W. Raber, K. Kaserer, B. Niederle, H.T. Vierhapper, Risk factors for malignancy of thyroid nodules initially identified as follicular neoplasia by fine-needle aspiration: results of a prospective study of one hundred twenty patients, Thyroid 10 (2000) 709–712.
[45] C.R. McHenry, S.R. Thomas, S.J. Slusarczyk, A. Khiyami, Follicular or Hürthle cell neoplasm of the thyroid: can clinical factors be used to predict carcinoma and determine extent of thyroidectomy? Surgery 126 (1999) 798–802.