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ORIGINAL ARTICLE

Prognostic factors and follow-up of patients with differentiated thyroid carcinoma with false negative or nondiagnostic FNAC before surgery. Comparison with a control group

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Abstract Since the clinical implementation of fine needle aspiration cytology (FNAC) to diagnose thyroid carcinoma, few patients remain misdiagnosed and little is known about their clinical outcomes. An observational retrospective study was carried out to analyse prognostic factors and follow-up of patients with differentiated thyroid carcinoma (DTC) not disclosed by FNAC before surgery, compared to a control group. From October 2003 to July 2010, 308 patients underwent surgery as treatment for nodular goitre and 53 had DTC. Cases were 12 subjects with DTC and benign ($n = 7$) or nondiagnostic ($n = 5$) FNAC. Controls were 39 subjects with DTC and suspicious ($n = 19$) or malignant ($n = 20$) FNAC. Prognostic factors, recurrence and survival rates were compared. Cases had longer time from FNAC to surgery than the control group (86.8 ± 74.1 vs. 16.4 ± 23.8 weeks; $P < 0.001$), higher prevalence of follicular carcinoma (33.3 vs. 2.6%; $P = 0.009$), and of two-time total thyroidectomy (75 vs. 30.8%; $P = 0.016$). Average follow-up was 42.7 ± 25.3 months (2–86 months). There were no deaths. Disease-free survival for cases was 66.9 ± 5.8 months, and for controls 78.7 ± 3.9 months (*P*: ns). In patients with DTC, the result of the FNAC performed before surgery was not an independent predictor of recurrences or mortality in the first 7 years of follow-up. Thus, false negative or nondiagnostic FNAC in a patient with DTC does not seem to be a primary prognostic factor, but it may reveal other adverse prognostic factors such as longer time to therapy and higher prevalence of follicular carcinoma that may influence long-term outcomes.

Keywords Thyroid neoplasm · Prognostic factors · Thyroid carcinoma · Neoplasm recurrence

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Introduction

Differentiated thyroid carcinoma (DTC) is a rare condition that accounts for approximately 5% of patients with nodular goitre [1, 2]. This corresponds to an incidence of 1.2–3.8 per 100,000 people per year [3, 4]. Fine needle aspiration cytology (FNAC) is a cost-effective procedure that provides specific diagnosis rapidly with minimal complications, and it is routinely performed to diagnose thyroid carcinoma in a thyroid nodule before surgery. Overall, it is accepted that FNAC has high diagnostic accuracy (85% approximately) with a positive predictive value of up to 99% and a usually low rate of false negative results (1–11%, mean 5%) [2]. However, in nondiagnostic FNAC results (unsatisfactory smears) which represent 5–20% of cases [2], the prevalence of thyroid carcinoma in patients subsequently submitted to surgery is about 11% [5]. Thus, it is reasonable to think that in patients with nodular goitre, once FNAC is performed, only few patients

with thyroid carcinoma are misdiagnosed. Because little is known about the prognosis and follow-up of these patients with thyroid carcinoma not diagnosed by FNAC, we have focused our interest on this group of patients.

The purpose of this study is to analyse prognostic factors and follow-up of patients with DTC and a false negative or nondiagnostic FNAC performed before surgery, and to compare them with a control group of patients with DTC that underwent surgery due to a FNAC that was positive or suspicious for malignancy.

Materials and methods

Cases and control group

Between October 2003 and July 2010, a total of 308 patients underwent surgery at our institution as treatment for nodular goitre. Of these, 53 patients had a histopathologic diagnosis of DTC. There were 46 papillary carcinomas, five follicular carcinomas, one tall cell variant of papillary carcinoma, and one columnar cell variant of papillary carcinoma. Another 41 cases of patients with incidental thyroid papillary microcarcinoma (less than 1 cm) found at histopathologic analysis of a benign goitre were not included in the study.

Among the 53 confirmed diagnoses of thyroid carcinoma, FNAC results before surgery on the neoplastic nodule were nondiagnostic in five, benign in seven, suspicious in 19, and malignant in 22 cases. All cases considered as nondiagnostic FNAC had been aspirated on two consecutive occasions with the same result. Therefore, the cases group was composed of those patients with nondiagnostic or benign (false negative) FNAC ($n = 12$). The control group was composed of those patients with suspicious or malignant FNAC excluding the two cases of specific variants, tall cell and columnar cell carcinoma (both with malignant FNAC), because there was no similar tumour in the cases group ($n = 39$).

Cases underwent surgery when the size of the dominant nodule was greater than 4 cm, they had cystic recurrence after needle evacuation, the nodule showed an increase in size of more than 30% in ultrasound control at 6–12 months, or when surgical treatment was preferred because cosmetic and/or compressive symptoms were present.

FNAC

FNAC was performed by the palpation method. Diagnostic categories of the Bethesda System [6] allowed us to group results as: benign (including smears with atypia of indeterminate significance), malignant, suspicious of malignancy (including categories of follicular neoplasm and suspicious for malignancy), and nondiagnostic when there were not at least two satisfactory smears containing six or more groups of well-preserved follicular cells, each group composed of at least 10 cells [6, 7]. Exceptions to this numeric requirement of follicular cells were any specimen that contained abundant colloid, which was considered benign and not unsatisfactory [6]. Likewise, whenever a specific diagnosis could be rendered (lymphocytic thyroiditis, etc.) and whenever there was any atypia, the specimen was considered satisfactory for evaluation [6, 8].

During the period between October 2003 and July 2010, we performed a total of 1083 consecutive FNAC in 883 patients. Results were benign in 68.2%, suspicious in 10%, malignant in 2%, and nondiagnostic in 19.8%. Of the 308 operated patients in this time (20 patients with malignant FNAC, 86 patients with suspicious FNAC, 41 patients with nondiagnostic FNAC, and 161 patients with benign FNAC), FNAC had a sensitivity of 82.9%, specificity of 98%, positive predictive value of 91.9% and negative predictive value of 95.6% (for calculations, patients with nondiagnostic FNAC were excluded, and patients with malignant and suspicious FNAC were taken together). The rate of false negative results for carcinoma was 17.1%, and the rate of false positive results for carcinoma was 1.9%. The rate of carcinoma in suspicious FNAC was 19.7%.

Surgical approach

Total thyroidectomy in one time was considered the treatment of choice for patients with a preoperative diagnosis of DTC, and also for patients with multinodular goitre and a suspicious FNAC. Hemithyroidectomy was performed in patients with single nodular goitre and a FNAC that was benign, nondiagnostic or suspicious of DTC. However, if the diagnosis of a thyroid carcinoma was reached at intraoperative frozen section analysis, then total thyroidectomy was performed. When definitive histopathological examination showed a DTC (a papillary thyroid carcinoma greater than 10 mm or multifocal, or with lymph node metastases, and any follicular carcinoma) in a patient with hemithyroidectomy, the thyroidectomy was completed in a second time after 2 weeks or else after 3 months (two-time total thyroidectomy).

In our centre, lymph node dissection of the central compartment has been performed with increased frequency in recent years in patients with papillary thyroid carcinoma in whom total thyroidectomy was performed. Laterocervical node dissection was carried out only if nodes were found enlarged at physical or ultrasound examination and/or at intraoperative palpation. Usually, for the statistical analysis, the histological nodal stage was used when available. The clinical nodal stage was used for the remaining patients.

Histopathological analysis

All surgical specimens were fixed with 10% neutral buffered formalin solution. After 48 h, each nodule was totally or subtotally sampled (with at least ten sections comprehensive of capsule) and embedded in paraffin. Serial slides stained with hematoxylin and eosin were examined. The presence of benign or malignant neoplasm, as well as non-neoplastic lesions, was confirmed following established criteria.

Follow-up of patients

According to our protocol, extent of the carcinoma was evaluated by presurgical ultrasonography, intraoperative findings, histopathologic analysis of the excised tissue and a postoperative (3–4 weeks) diagnostic 131-I whole body scan (WBS) performed 48 h after administration of a diagnostic dose of 2–5 mCi in overt hypothyroid condition (serum TSH higher than 30 mcU/ml), or after the administration of recombinant-human TSH (rh-TSH). Before administering 131-I, a blood sample for thyroglobulin (TG), antithyroglobulin antibodies (TGAb), and TSH was drawn. Serum TG values above 2 ng/ml in this condition, with concomitant negative TGAb (levels below 100 UI/ml), were considered abnormal. One week later, cases and controls received treatment with radioiodine to achieve ablation of thyroidal rests and metastases. The choice of each radioiodine dose was based on the extent of the carcinoma and radioactive iodine uptake in the diagnostic WBS preceding treatment. If 131I WBS showed a small cervical uptake, a 131I dose of 30–100 mCi was administered; if cervical lymph nodes were infiltrated, the dose of 131-I was 125–150 mCi, and if pathological uptake with elevated TG suggested distant metastases, a dose of 150–200 mCi was administered after surgical resection of the metastases if feasible. A post-therapeutic 131I WBS was acquired. All patients received TSH-suppressive levothyroxine therapy thereafter.

Six to nine months after radioiodine treatment, a new 131I WBS was performed and the levels of serum TG and TGAb were measured after levothyroxine withdrawal or after administration of rh-TSH. If 131I WBS was negative, and TG < 2 ng/ml, this procedure was repeated after 1 year, and if results were again negative, then TG was measured yearly under levothyroxine treatment. If a result of TG greater than 2 ng/ml was obtained, and 131I WBS showed pathological uptakes, surgical treatment was performed if possible, and a new therapeutic dose of radioiodine was administered according to the above procedure. When there was an absence of agreement between 131I WBS and TG levels (the 131I WBS was negative and TG levels higher than 2 ng/ml, or the 131I WBS showed pathological uptake but TG levels were less than 2 ng/ml), other imaging techniques such as chest X-ray, neck ultrasonography, magnetic resonance, computed tomography, 18-fluordeoxyglucose positron emission tomography-computed tomography, and FNAC or biopsy of suspicious lesions, were performed to detect locoregional recurrence or distant metastases. If these imaging techniques and procedures failed to localize the disease, and TG was higher than 10 ng/ml or showed increasing levels, a therapeutic dose of 100–150 mCi of radioidine was administered.

If a value of TG beyond 1 ng/ml under levothyroxine treatment was obtained, a new 131I WBS and measurement of TG after levothyroxine withdrawal or after administration of rh-TSH was performed.

Prognostic factors

The variables considered as prognostic factors were:

- Patient and tumour features: age at surgery, gender, type of tumour, tumour size, presence of lymphocytic thyroiditis, multicentricity (more than one tumoral focus in the gland), and stage (graded according to the Sixth Edition of the UICC/AJCC TNM classification) [9].
- Treatment factors: time to therapy (fragmented in time from first tumour manifestation to FNAC, and time from FNAC to surgery), surgical therapy (extent of thyroidectomy, lymph node dissection), and radioiodine treatment.

Recurrences and survival

Remission was defined as a negative 131I WBS, and a serum TG < 2 ng/ml, with concomitant negative TGAb and TSH higher than 30 mcU/ml after levothyroxine withdrawal or by administration of rh-TSH. Disease-free survival was defined as the length of time, expressed in months, during which the subject remained in remission.

Persistence of the disease was defined as absence of remission. Recurrence was defined as serum TG greater than 2 ng/ml, with concomitant negative TGAb and TSH higher than 30 mcU/ml after levothyroxine withdrawal or by administration of rh-TSH, after a period of remission. Only the first tumour recurrence for each patient was included in our study.

Cause-specific survival was defined as a net survival measure representing cancer survival in the absence of other causes of death. Individuals who died of causes other than thyroid carcinoma were considered censored.

Time of follow-up (months) was computed starting from first surgical treatment.

Statistical analysis

Comparisons of the means of the variables between groups were performed with *U*-Mann–Whitney test, and comparisons of the frequencies between groups with Fisher exact test. Logistic regression analysis was performed with the forward stepwise method, with Wald statistics for contrasts, in order to examine the influence of independent variables between groups (cases and controls). Odds ratio and their 95% confidence interval were determined for significant variables. A two-sided P value less than 0.05 was considered statistically significant.

Survival curves were estimated with the Kaplan–Meier method. Mean time, typical error of the mean and 95% confidence interval of the mean were registered. Univariate differences between cases and controls were examined with a log-rank test. A P value less than 5% was regarded as significant.

Results

Prognostic factors

Values for the recorded variables in cases and controls are summarized in Table 1. Univariate analysis showed significant differences in time from FNAC to surgery (cases 86.8 ± 74.1 weeks, controls 16.4 ± 23.8 weeks; $P < 0.001$), distribution of the type of carcinoma (cases: 66.6% of papillary carcinoma and 33.3% of follicular carcinoma; controls: 97.4% of papillary carcinoma and 2.6% of follicular carcinoma; $P = 0.009$) and extent of the thyroidectomy (cases: 25% one-time total thyroidectomy, and 75% two-time total thyroidectomy; controls: 69.2% one-time total thyroidectomy, and 30.8% two-time total thyroidectomy; $P = 0.016$). Multivariate analysis by logistic regression including all the above significant univariate variables showed that only the time from FNAC to surgery was independently associated with the group of subjects (cases or controls)($P = 0.003$; odds ratio 0.971; 95% confidence interval: 0.952–0.990).

A model of multivariate analysis by means of logistic regression was constructed to explore variables that might explain differences in results of FNAC obtained before surgery in cases (FNAC benign or nondiagnostic) and controls (FNAC suspicious or malignant) (Table 2). After inclusion of the type of carcinoma, (follicular vs. papillary) ($P = 0.013$; odds ratio: 19; 95% confidence interval: 1.867–193.4) no other variables remained significant.

In the cases group, there was a tendency towards a more prevalent follicular carcinoma type in patients with benign FNAC as compared to patients with nondiagnostic FNAC, although differences were not statistically significant (Table 3).

Recurrences and survival

Average follow-up from first surgical treatment was 42.7 ± 25.3 months (range 2–86 months), without differences between cases and controls. In this period there were no deaths related to thyroid carcinoma, either in the control group or in the cases group.

Among the cases, only one subject had a recurrence (8.3%). She was a 31-year-old woman with a benign FNAC, a time from FNAC to surgery of 114 weeks, and a solitary 53 mm papillary of follicular pattern carcinoma with pulmonary metastases (stage II), who underwent a one-time total thyroidectomy and central lymph node dissection, received 425 mCi of 131I radioiodine, and experienced a cervical lymph node recurrence 6 months after she had achieved remission.

In the control group, there were three subjects with recurrences (7.7%). The first was a 49-year-old woman, with a suspicious FNAC, a time from FNAC to surgery of 48 weeks, and a multicentric classic papillary carcinoma with a dominant nodule of 40 mm, without nodal or distant metastases seen either at thyroidectomy or after therapeutic (100 mCi) 131I WBS (stage III), who had a cervical nodal recurrence after 18 months of remission. The second case was a 52-year-old man, with a malignant FNAC, a time from FNAC to surgery of 8 weeks, and a multicentric classic papillary carcinoma with a dominant nodule of 25 mm, with metastatic nodes at unilateral cervical level (stage IVA), who received 150 mCi of radioiodine, and had a cervical lymph node recurrence after 44 months of achieved remission. The final subject with a recurrence was a 33-year-old woman, with a malignant FNAC, a time from FNAC to surgery of 7 weeks, and a multicentric classic papillary carcinoma with a dominant nodule of 15 mm with minimal extrathyroidal extension, lymph node involvement at cervical unilateral level, without distant metastases (stage I), who received 150 mCi of radioiodine, and had a cervical homolateral lymph node recurrence after 9 months of achieved remission.

In the Kaplan–Meier analysis, average disease-free survival was 66.9 ± 5.8 months (95% confidence interval 55.5–78.3 months) for cases versus 78.7 ± 3.9 months (95% confidence interval 70.9–86.5 months) for controls (Fig. 1). The difference between groups was not significant with log-rank test.

Discussion

We compared prognostic factors for DTC and clinical outcomes (recurrences and survival) between patients with DTC not diagnosed before surgery by FNAC because of a false negative result or a nondiagnostic FNAC and a

Table 1 Prognostic factors for cases and controls

Number of cases:	Cases 12	Controls 39	*P* value
At surgery			
Age (years)	42.5 ± 18 (21–72)	42.1 ± 13.6 (12–76)	ns
$n \geq 45$ years	6 (50%)	18 (46.1%)	ns
Female gender	10 (83.3%)	29 (74.4%)	ns
Time to therapy (weeks)			
From first tumour manifestation to FNAC	88.2 ± 155.9 (1–520)	83.2 ± 119.2 (2–520)	ns
From FNAC to surgery	86.8 ± 74.1 (8–228)	16.4 ± 23.8 (2–114)	<0.001
Total time	175 ± 193 (14–668)	101.2 ± 121.9 (4–544)	ns
Type of carcinoma			
Papillary classic	4 (33.3%)	25 (64.1%)	0.009*
Papillary of follicular pattern	4 (33.3%)	13 (33.3%)	
Follicular minimally invasive	3 (25%)	1 (2.6%)	
Follicular widely invasive	1 (8.3%)	0 (0%)	
Size of the carcinoma (mm)			
Total	35.4 ± 19.3 (12–80)	26.6 ± 11.2 (10–50)	ns
>4 cm	4 (33.3%)	7 (17.9%)	ns
≥1.5 cm	11 (91.7%)	34 (87.2%)	ns
Multicentricity	2 (16.7%)	17 (43.6%)	ns
Lymphocytic thyroiditis	5 (41.7%)	6 (15.4%)	ns
Extent of thyroidectomy			
One-time total thyroidectomy	3 (25%)	27 (69.2%)	0.016
Two-time total thyroidectomy	9 (75%)	12 (30.8%)	
Lymph node dissection			
Bilateral	0 (0%)	3 (7.7%)	ns
Unilateral	2 (16.7%)	6 (15.4%)	
Central	3 (25%)	9 (23.1%)	
Not done	7 (58.3%)	21 (53.8%)	
Tumour diameter[a]			
T1	3 (25%)	11 (28.2%)	ns
T2	6 (50%)	16 (41%)	
T3	2 (16.7%)	8 (20.6%)	
T4a	1 (8.3%)	4 (10.2%)	
Metastatic nodes[b]			
N0	10 (83.3%)	23 (58.9%)	ns
N1a	0 (0%)	8 (20.5%)	
N1b	2 (16.7%)	8 (20.5%)	
Distant metastases[c]			
M0	11 (91.7%)	30 (100%)	ns
M1	1 (8.3%)	0 (0%)	
Stage UICC/AJCC TNM 6th ed			
Stage I	7 (58.3%)	26 (66.7%)	ns
Stage II	1 (8.3%)	5 (12.8%)	
Stage III	2 (16.7%)	4 (10,2%)	
Stage IVA	2 (16.7%)	4 (10,2%)	
Radioiodine treatment	12 (100%)	39 (100%)	ns
Cumulative dose of radioiodine (mCi)	143.7 ± 98.3 (100–425)	138.6 ± 63.8 (50–330)	ns

Table 1 continued

	Cases	Controls	*P* value
Number of cases:	12	39	
Months of follow-up after surgical treatment	45.4 ± 23.4 (3–73)	41.9 ± 26.1 (2–86)	ns

Numeric values are expressed as mean ± standard deviation. Ranges are expressed in brackets

* Grouped papillary versus follicular

[a] *T1* 2 cm or smaller; *T2* >2–4 cm; *T3* >4 cm or minimal extrathyroidal extension; *T4a* tumour invades subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve

[b] *N0* no metastases nodes; *N1a* metastases to level VI; *N1b* metastases to unilateral, bilateral, contralateral cervical or superior mediastinal nodes

[c] *M0* no distant metastases; *M1* distant metastases

Table 2 Logistic regression to analyse the influence of independent variables on results of FNAC obtained in cases and controls

Variables in the equation	*P* value	Odds ratio	95% confidence interval
Type of carcinoma (follicular vs. papillary)	0.013	19	1.867–193.4
Variables not in the equation			
Age at surgery	0.844		
Age at surgery greater than 44 years	0.672		
Gender	0.939		
Size of the carcinoma	0.088		
Size of the carcinoma greater than 4 cm	0.192		
Size of the carcinoma greater than 1.5 cm	0.960		
Stage	0.229		
Multicentricity	0.303		
Lymphocytic thyroiditis	0.098		

Table 3 Distribution (number of cases) of the type of differentiated thyroid carcinoma in the cases group (*P*: ns)

	Papillary carcinoma	Follicular carcinoma	Total
Benign FNAC	4	3	7
Nondiagnostic FNAC	4	1	5
Total	8	4	12

control group composed of patients with DTC because of a suspicious or malignant FNAC before surgery. In univariate analysis, cases had a longer time from FNAC to surgery, a more prevalent type of follicular carcinoma, and a less frequently performed one-time total thyroidectomy as surgical treatment, as compared to the control group. Of these variables, with multivariate analysis only time from FNAC to surgery remained as a significant independent variable. Analysis of the candidate variables to explain the results of FNAC showed that the follicular carcinoma type was associated with the false negative and nondiagnostic FNAC results (cases group). In 7 years of follow-up there was no death. Recurrences occurred in one case (8.3%)

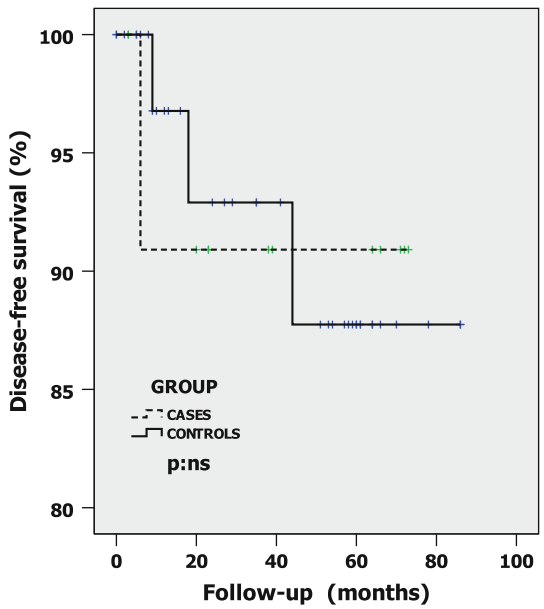

Fig. 1 Kaplan–Meier curves of disease-free survival of the cases and the controls

6 months after remission, and in three controls (7.7%) at 9, 18, and 44 months after remission. The time of disease-free survival for cases and controls was similar. The principal

limitation of the study is the small number of cases that were included.

The prognosis of patients with DTC is usually favourable, with a high survival rate. However, a subset of patients can develop local recurrence or distant metastases and may subsequently die of the disease [10, 11]. Several prognostic factors have been suggested as influencing the patient's outcome. Advanced age at diagnosis (greater than 45 years), male gender, large tumour size ($\geq$1.5 cm and $>$4 cm), some histologic subtypes, longer time to therapy, lesser extent of primary surgical treatment, absence of postoperative administration of 131I, greater extrathyroidal extension, lymph node metastases, distant metastases, and some molecular and genetic factors are associated with higher rates of persistence, recurrence and mortality [10–22]. In contrast, the presence of autoimmune thyroid disease or lymphocytic infiltration may exert a protective effect on the outcome of differentiated thyroid carcinoma patients [15, 23, 24]. Our study has investigated some of these clinically prognostic factors, but unfortunately we did not measure molecular and genetic factors.

We focused our attention on the group of patients with false negative and nondiagnostic FNAC because they are usually observed, and surgery is not initially considered. The false negative results of FNAC constitute a serious limitation of this technique since malignant lesions would go untreated. The prevalence of false negative results of FNAC in some series may be as high as 20–31% [25–27], depending on the quality of smears and the experience of the cytologist in interpreting the findings [26–29]. But another determining factor in the rate of false negative results of FNAC is the number of patients with benign FNAC who undergo surgery [30]. In our study, the false negative rate of FNAC was relatively high, 17.1%, which could be in relation to a relatively high number of patients with benign FNAC who underwent surgery (161 of 650 patients; 24.7%) since other series only have a modest 5% [30].

Another factor for discrepancies between thyroid FNAC and the surgical resection diagnosis is size differences between the targeted nodule and the tumour in the thyroidectomy specimen. This may explain an inadequate FNAC sampling due to the heterogeneity of the nodule that may combine areas of non-papillary carcinoma coexisting with areas of papillary carcinoma [31]. But this last reason seems to be relevant only for carcinomas that measured less than 1 cm [31]. In other cases, papillary thyroid carcinomas that did not show typical features, such as marked nuclear enlargement, pale chromatin and intranuclear inclusions, have been misdiagnosed [32]. In our study, there was a higher prevalence of follicular carcinoma in the cases group than in the control group. In logistic regression analysis, the type of carcinoma was the only significant variable that conferred a 19-fold higher risk for a false negative or nondiagnostic FNAC result in cases of follicular carcinoma compared to papillary carcinoma (this odds ratio may have been overestimated due to the small number of cases). Since in the cases group most follicular carcinoma (75%) was in the subgroup of subjects with benign (false negative) FNAC, the type of carcinoma may play an important role in the cytological error in these cases. Although it is well known that follicular carcinoma can only rarely be diagnosed on the basis of preoperative cytology, follicular neoplasm has been recognized as a possible source of false negative cytological diagnosis because these lesions bleed easily on aspiration, and the cellular sample is usually diluted with blood [28]. Repeating FNAC in patients with benign cytology about 1 year later could reduce the rate of misdiagnosed carcinomas [33].

Nondiagnostic FNAC is another obstacle to identifying thyroid carcinoma. Our rate of this result was 19.8%, similar to other series [5]. We performed FNAC by palpation method so the rate of nondiagnostic results could be 3–16% higher than if FNAC had been performed by ultrasound-guided method [5]. Nondiagnostic FNAC is frequently found in complex thyroid nodules, in which malignancy, especially cystic papillary carcinomas, can be detected in about 11% of cases [5]. In our series, there were five cases with nondiagnostic FNAC, and four of them (80%) had papillary thyroid carcinoma, while in cases with benign (false negative) FNAC this rate was a little lower (57.1%).

As expected, we found that patients with false negative or nondiagnostic FNAC before surgery have a longer time from FNAC to surgery than patients with suspicious or malignant FNAC. Cases also had a more frequently performed two-time total thyroidectomy, according to our protocol of surgery procedure. The time from the first tumour manifestation to surgery has been reported as a prognostic factor for DTC, and a delay of 1 year or more has been associated with a 130% increased 30-years cancer mortality rate [14]. In our study, the time from the first tumour manifestation to FNAC and the time from the first tumour manifestation to surgery were very variable and showed no differences between groups. As most differentiated cancers have few symptoms or signs to distinguish them from benign tumours [34], it is likely that in some subjects with multinodular goitre, these estimations included the time from the patient's perception of the benign portion, while in other cases, the goitre may have gone unnoticed for some time. In patients with false negative or nondiagnostic FNAC, the delay in receiving treatment is obviously influenced by the FNAC result, so the time from FNAC to surgery is clearly prolonged. The time from FNAC to surgery in these patients might be a better indicator of the delay in surgical treatment.

Considering the relatively low incidence of DTC in the general population and the favourable prognosis in most

patients, clinical trials to investigate the impact of prognostic factors in disease recurrence and survival rates will need thousands of patients and follow-up for some decades [10, 12–14]. In a retrospective study by Shah et al. [12], a series of 931 consecutive patients with DTC treated over a 50-year period had an overall 87% 10-year survival rate. Hay et al. [13] reported a 10-year survival of about 95.3% in a cohort of 1,779 patients with papillary thyroid carcinoma, treated between 1940 and 1989. Mazzaferri et al. [14] evaluated a prospective series of 1,355 patients with DTC and found that after 30 years the survival rate was 76%, the recurrence rate 30% and the cancer death rate 8%. Pelizzo et al. [10], in a group of 1,858 patients with papillary thyroid carcinoma, reported a 10-year survival rate of 90.2% for males and 96.1% for females, and a 20-year survival rate of 81.9% for males and 86.2% for females. In this latter series, with an average follow-up of 21.4 years (range 5–34 years) after surgery, the rate of recurrences was 6.1% for males and 4.6% for females. The more recent series have better outcomes due to more effective treatments (total thyroidectomy vs. subtotal thyroidectomy, radioiodine treatment, TSH-suppressive treatment). However, almost half of the recurrences occur in the first 5 years of follow-up [12, 14, 35, 36]. In our series, follow-up time was relatively short (about 7 years) and the recurrence rate was similar in the two groups: 8.3% in cases and 7.7% in controls. Survival was 100% in both groups. The long-term impact of the delayed treatment on recurrences and survival, as a prognostic factor derived from a long time from FNAC to surgery, probably requires longer follow-up to be more accurately evaluated.

Nowadays authors continue searching for prognostic variables in DTC to formulate an optimal therapeutic approach [10, 11]. Many prognostic scores have been proposed in the literature, but to our knowledge, no study has been performed taking into account whether patients with DTC have been diagnosed by FNAC or not. Our study was addressed to explore the differences in prognostic factors between patients according to results of their FNAC, and we may conclude that patients with DCT not disclosed by FNAC suffer delayed therapy and a higher prevalence of follicular carcinoma. However, the results of FNAC before surgery were not an independent predictor of recurrence in the first 7 years of follow-up. Then, false negative or nondiagnostic FNAC in a patient with DTC seems not to be a primary prognostic factor, but it may be seen in other adverse prognostic factors such as longer time to therapy and higher prevalence of follicular carcinoma that may influence long term outcomes.

We acknowledge potential concerns related to our study methods that should be kept in mind. First, there is the retrospective design of the study. Second, subjects of the cases group submitted for surgery were not selected randomly, allowing for potential physician or patient preferences. Finally, our sample size was relatively small because patients with misdiagnosed thyroid carcinoma after FNAC are rarely found in clinical practice. In this study, the lack of association between some prognostic factors and recurrence or survival rates previously described in larges series of patients with overt thyroid carcinoma may have resulted from this limitation in sample size.

Ethical standards The study was reviewed and approved by the ethical committee of the Hospital Universitari Mútua de Terrassa. Written informed consent was obtained from all the patients.

Conflict of interest The authors declare that they have no conflict of interest.

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