Accepted Preprint first posted on 31 March 2016 as Manuscript EJE-15-1223

"Incidental" and "non-incidental" thyroid papillary microcarcinomas are two different entities

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Short Title: TSH and thyroid microcarcinoma

Key words: TSH, Papillary Thyroid Cancer, Thyroid Microcarcinomas, Goiter

Word count: 3316

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Abstract

Objective: papillary thyroid microcarcinomas (microPTC) may be "incidental" (Inc-microPTC), occasionally found at histology after surgery for benign disease or "non-incidental" (Non-Inc-microPTC), diagnosed on clinical grounds. It is unclear whether these different microPTC reflect the same disease. The aim of the study was to compare Inc-microPTC and Non-Inc-microPTC for clinical and histological features as well as for serum TSH, a known factor involved in PTC development.

Design: We evaluated histology and serum TSH levels of consecutive patients submitted to thyroidectomy for goiter with compressive symptoms or for cytological diagnosis suspicious/indicative of PTC.

Methods: 665 consecutive patients (259 with a single thyroid nodule, SN and 406 with a multinodular gland, MN) were included in the study. According to histology, patients were classified as: benign nodular goiter (Benign, n= 291); Inc-microPTC (n=92); Non-Inc-microPTC (n= 67); PTC ≥ 1 cm (macroPTC, n = 215).

Results: Inc-microPTC were significantly more frequent in MN than in SN (66/406, 16.2% vs 26/259,10.0%, p = 0.02). Patients with Inc-microPTC compared to Non-Inc-microPTC were older (mean age 53.3±13.2 years vs 44.9±14.8 years, p=0.0002), had a smaller tumor size (median 4 mm vs 9 mm, p<0.0001), a higher frequency of multifocality (70/92, 76.1% vs 35/67, 52.2% p=0.001) and lower levels of TSH (median 0.6 mU/L, IR 0.4-1.0 mU/L vs value 1. mU/L, IR 0.6-1.4 mU/L vs p=0.0001).

Conclusion: Incidental and Non-incidental papillary thyroid microcarcinomas appear to be two different entities

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53 **Introduction**

54 Thyroid cancer is the most common malignant tumor of the endocrine system and
55 papillary thyroid cancer (PTC) accounts for more than 80% of all thyroid malignancies.
56 The frequency of PTC has been increasing in last years, mainly due to the diagnosis of
57 small cancers (1-4). The increased incidence of thyroid cancer is likely related to an
58 increased diagnosis due to the use of ultrasound and fine needle aspiration (5). Some
59 authors have attributed this to the increasing identification of thyroid nodules during
60 routine imaging for non thyroid-related conditions (e.g. radiological evaluations for carotid
61 disease or magnetic resonance imaging for cervical disease) and the wide spread use of
62 ultrasound guided fine needle aspiration cytology (6). As a result of this phenomenon, the
63 frequency of papillary thyroid microcarcinomas (microPTC), defined by the World Health
64 Organization as a PTC of 10 mm or less in the largest dimension (7), has increased
65 considerably during the past two decades (8). The clinical significance of microPTC is still
66 debated, and many authors consider it as non-progressive disease that has no effect on
67 survival (1), (9-16). On clinical and histological grounds there are two different
68 presentations of microPTC (6): a) “incidental” microPTC identified postoperatively at
69 histological examination of thyroid specimens following thyroid surgery for benign disease,
70 (i.e.compressive goiter) ; b) “non-incidental” microPTC, diagnosed before surgery at fine
71 needle aspiration (FNA) of small thyroid nodules detected at neck ultrasound or at other
72 diagnostic procedure, or for the presence of nodal metastasis.
73 According to some studies, “incidental” microPTC have an overall excellent prognosis
74 and there is nearly no risk of recurrence or death (17,18), while “non incidental”
75 microPTC show a more aggressive behaviour, eventually associated with lymph-node
76 metastases at presentation, neck loco-regional recurrences during follow-up and/or
77 multifocality of the tumor (6,10,16,19,20).However conflicting results are present in
78 literature to date. Thus it is unclear whether these different presentations reflect the same
79 disease or express two different entities with their own underlying pathophysiology
80 (17,21-25).
81 In the last few years it has been reported that, in patients with nodular thyroid disease,
82 the risk of thyroid malignancy increases with increasing concentrations of serum thyroid-

stimulating hormone (TSH) and, even within normal ranges, higher serum TSH levels are associated with a higher frequency and more advanced stage of thyroid cancer (26). Furthermore, it has been shown that thyroid diseases, that affect thyroid function, influencing pituitary secretion of TSH, are associated with a different risk of PTC, being the likelihood of thyroid malignancy reduced when TSH is lower, as in nodular goiter with thyroid autonomy (27) and increased when TSH is higher, as in nodular Hashimoto's thyroiditis (28). Moreover, in patients with nodular thyroid disease, L-thyroxine (L-T4) treatment, reducing serum TSH, is associated to a significantly lower risk of developing clinically detected thyroid cancer (28). The relationship between serum TSH and microPTC is not clear, results reported in the literature being discrepant and relying only on retrospective studies (29-35).

We designed a prospective study with the aim to analyze clinical and histological presentation of "incidental" and "non incidental" microPTC and the possible role of serum TSH in each of these two entities.

Subjects and Methods

Patients

In this study we included consecutive patients submitted to thyroid surgery in our Institution from march 2013 to march 2014 for goiter with compressive symptoms or for nodule(s) with a cytological diagnosis suspicious or indicative of cancer. We included in the study only patients with all clinical data available (previous treatment, use of medicine affecting TSH values) and who underwent to all the diagnostic procedures described below before surgery in our Institution.

The diagnostic management of patients included: thyroid ultrasound, technetium-99m-pertechnetate scintiscan in patients with serum TSH lower than 0.4 mU/L, FNA of dominant cold nodules in multinodular goiter, of cold single nodules larger than 1 cm and of nodules smaller than 1 cm with suspicious findings (e.i microcalcifications, a taller-than-wide shape, irregular borders and marked hypoechogenicity) at thyroid ultrasound. TSH, free thyroid hormones, serum thyroid autoantibodies (TAb) and calcitonin (CT) were measured immediately before surgery. As one aim of the study was to evaluate the role of serum TSH, patients were excluded if they were taking L-T4 or methimazole or

drugs that may affect serum TSH levels (such as corticosterois). We also excluded from the study patients with Graves' disease, diagnosed according to the standard criteria and those with a non papillary thyroid tumors, e.g. follicular, anaplastic cancer, lymphoma and those who had high levels of CT suspicious of medullary thyroid carcinoma. All patients included in the study were submitted to total thyroidectomy. Patients included in the study were 665 (males 202, females 463, mean age 50.1 $\pm$13.8 years). All patients gave their informed consent to the study.

Before surgery thyroid ultrasound was performed to determine thyroid volume and the presence of single or multiple nodules. Thyroid volume was calculated according to the formula of the ellipsoid model: (width x length x thickness x 0.52 for each lobe). A thyroid volume greater than 20 mL in males and 15 mL in females was considered as goiter (36).

Patients were grouped as follows:

- patients with multiple thyroid nodules (MN = 406): in a gland of normal size (MN-no goiter n= 71) or in goiter (MN-goiter n= 335).

-patients with a single thyroid nodule (SN = 259): in a gland of normal size (SN-no goiter, n= 122) or in goiter (SN-goiter n= 137)

The indication for surgery are summarized in table 1. In MN goiter group patients were submitted to thyroidectomy because of a large goiter with compressive symptoms (n=141) or a goiter with one or more nodules with an indeterminate (TIR3, n= 143) or suspicious or indicative of cancer (TIR4/5, n= 51) cytology. In MN-no goiter group patients had one or more nodules with an TIR3 (n= 41) or TIR4/5 (n= 29) cytology. In this group 1 patient was submitted to surgery because of a clinically suspicious thyroid nodule with a non diagnostic cytology (TIR1), increased in size during the follow up. In SN goiter group the indications for surgery were the presence of a large nodule with compressive symptoms (n=31) or a nodule with a TIR3 (n=77) or TIR4/5 (n= 29) cytology. In SN-no goiter group patients had one nodule with an TIR3 (n= 72) or TIR4/5 (n= 50) cytology

Thyroid function tests

Serum free T4 (FT4) and triiodothyronine (FT3) were measured by chemiluminescent immunometric assay (VITROS 3600, Siemens, Buckinghamshire, UK FT4– normal values 0.7–1.7 ng/dl; FT3–normal values 2.7-5.7 pg/ml) and expressed as ng/dl and

pg/ml respectively. Serum TSH was measured by a solid-phase, two-site chemiluminescent immunometric assay (IMMULITE 2000 Third Generation, DPC 5700 Los Angeles, USA– normal values 0.4–3.4 mU/L) and expressed as mU/L. TgAb and TPOAb were measured by an immunoenzymatic assay (AIA-Pack TgAb, and TPOAb, Tosoh, Tokyo, Japan) and expressed as UI/ml. Normal values were <30 UI/ml for TgAb and <10 UI/ml for TPOAb. CT was measured by chemiluminescent immunometric assay (IMMULITE 2000, Siemens Healthcare , Llanberis, Gwynedd LL55 4EL, UK, normal values <10 pg/ml) and expressed as pg/ml.

FNA and cytological diagnosis

FNA was performed under echo guidance using a 23-gauge needle attached to a 10 ml syringe. The material was air-dried, stained with Papanicolaou and Giemsa. Cytological results were classified according to the criteria of the Italian Consensus for the classification and reporting of thyroid cytology (37).

Histopathologic examination

All specimens were accurately described (weight, shape, color and cut surface) and sampled for histology by two independent pathologists. The entire circumference of nodules was sampled. Samples were also made for each centimeter of extra nodular parenchyma. Formalin-fixed, paraffin-embedded tissues obtained from thyroid sampling of each case were stained by hematoxylin and eosin (38). The histological diagnosis was made according to the World Health Organization guidelines 7).

Statistical analysis

All variables were described by statistical characteristics: categorical data were described by frequency and percentage and quantitative data by median value and interquartile range . To evaluate “the normality” of the quantitative variables distributions, the *Kolmogorov-Smirnov test* was applied. *Two-tailed Mann-Whitney* and *Kruskall-Wallis tests* were employed for quantitative data and *Chi square test* for the categorical variable. Differences were considered significant at $p<0.05$. The statistical analysis was performed using the statistical software JMP 10 (SAS Institute, Cary, North Carolina, USA).

Results

Classification of patients according to thyroid ultrasound and histology

According to thyroid ultrasound data, cytological diagnosis and results at histology, patients were subdivided as follows (Table 1):

a) “Incidental” microPTC (Inc-microPTC, n= 92) identified postoperatively at histological examination of thyroid of patients submitted to surgery for large multinodular goiter with compressive symptoms and/or incidentally detected in the extra-nodular parenchyma of thyroid gland of patients submitted to surgery for nodules with an “indeterminate” cytological diagnosis and with a final histological diagnosis of benign nodules;

b) “Non-incidental” microPTC (Non-Inc-microPTC n = 67) diagnosed before surgery as small thyroid nodule incidentally detected at thyroid ultrasound and submitted to FNAC because of the presence of “suspicious” signs at ultrasound

c) PTC larger than 1 cm (macroPTC): n = 215

d) Benign nodular goiter (Benign): n= 291;

Inc-microPTC were significantly more frequent in multinodular glands being detected in 66/406 (16.2%) patients with MN and in the extra-nodular parenchyma of 26/259 (10.0%, p = 0.02) patients with SN. On the other hand, Non-Inc microPTC were more frequent in patients with SN (33/259, 12.7%) than in MN (34/406, 8.4%, p = 0.04).

Patients with Inc-microPTC were significantly older compared to Non-Inc-microPTC (mean age 53.3 $\pm$13.2 years vs 44.9 $\pm$14.8 years p = 0.0002). Age was not significantly different between Inc-microPTC and Benign (51.8 $\pm$12.7 years) and between Non-Inc-microPTC and macroPTC (46.7 $\pm$14.8 years).

No statistically significant differences were found between males and females in the 4 groups of patients, although females were prevalent in all groups.

No statistically significant differences were found in the frequency of positive serum thyroid autoantibodies in the 4 groups of patients.

Tumor size and node metastasis at histology

Inc-microPTC were significantly smaller (4 mm, IR 2-7 mm) compared to Non-Inc-microPTC, (9 mm, IR 7-10 mm, Mann-Whitney p <0.0001). Median size of macroPTC was 19 mm (IR 15-30 mm).

We perform node neck dissection only in patients with suspicious node detected at neck ultrasound before surgery. At histology node metastases were found in 17/67 (25.4%) patients with Non-Inc-microPTC and in 0 of 92 patients with Inc-microPTC (χ^2 p < 0.0001). The frequency of node metastases in patients with Non-Inc-microPTC was not significantly different compared to that found in macroPTC (42/215, 19.5%, p=ns).

Histological variants

Out of 374 patients with micro and macroPTC, less aggressive variants were diagnosed in 285 (76.2%) patients: classic variant in 119, follicular variant in 166. More aggressive variants were found in 89/374 (23.7%): 32 tall cell, 5 solid and 52 mixed variants (including classic and follicular variants with solid areas, diffuse sclerosing, trabecular and solid variants). The frequency of the different histological variants in Inc-microPTC, Non-Inc-microPTC and macroPTC is reported in Table 2.

More aggressive variants were more frequent in Non-Inc-microPTC (18/67, 26.9 %) than in Inc-microPTC (11/92, 11.9%; χ^2 p = 0.016), and not statistically significant differences were found between Non-Inc-microPTC and macroPTC (60/215, 27.9%)

Multifocality

Out of the 374 patients with a micro or macro PTC, a multifocal cancer was detected in 192 (51.3%).

As reported in Figure 1, multifocal PTC were more frequent in Inc-microPTC (70/92, 76.1%) compared to Non-Inc-microPTC (35/67, 52.2%, p=0.001) and to macroPTC (87/215, 40.5%, p<0.0001) and were not statistically different in Non-Inc-microPTC compared to macroPTC.

The frequency of multifocal PTC was higher in patients with MN (121/212, 57.1%) than in SN (71/162, 43.8%, p=0.01). No significant difference in the frequency of a multifocal PTC was observed between patients with or without goiter both in MN (91/163, 55.8% vs 30/49, 61.2%) and in SN (34/72, 47.2% vs 37/90, 41.1%) groups (data not shown).

Serum TSH levels

All patients had normal FT4 and FT3. In the whole study group median TSH was 0.8 mU/L (IR 0.5-1.2 mU/L). As reported in Figure 2, TSH was significantly higher in Non-Inc-microPTC than in Inc-microPTC (1.1 mU/L, IR 0.6-1.4 mU/L vs 0.6 mU/L, IR 0.4-1.0 mU/L, Mann Whitney p=0.0001) and in macroPTC than in Benign (0.9 mU/L, IR 0.6-1.4 mU/L vs 0. 7 mU/L, IR 0.3-1.1 mU/L, Mann Whitney p<0.0001). No significant difference was observed between Benign and Inc-microPTC and between macroPTC and Non-Inc-microPTC.

When patients were subdivided according to the median TSH level (0.8 mU/L), as reported in Figure 3, Inc-microPTC were significantly more frequent than Non-Inc-microPTC in patients with TSH≤ 0.8 mU/L (58/92, 63.0% vs 22/67, 32.8%, p<0.0001); while Non-Inc-microPTC were significantly more frequent than Inc-microPTC (34/92, 36.9% vs 45/67, 67.1%, p<0.0001) in patients with TSH >0.8 mU/L.

As expected, serum TSH was lower in MN than in SN (0.6 mU/L, IR 0.3-1.1 mU/L vs 0.9 mU/L, IR 0.6-1.5 mU/L, Mann Whitney p<0.0001) as consequence of development of thyroid autonomy in the first group.

Discussion

In the last 10–15 years, several epidemiological studies have reported an increased incidence of PTC, mainly due to tumors smaller than 1 cm in size, while the incidence of larger tumors is stable (1-4). Among newly diagnosed PTC the average prevalence of microPTC is around 39%, although different series in the same country report significantly different prevalence, pointing toward methodological or selection bias (12).

The increased incidence of thyroid cancer is likely related to an increased diagnosis due to the use of ultrasound and fine needle aspiration (5) and the clinical benefit of diagnosing small thyroid cancers remains uncertain. The average rate of recurrences and deaths is 3.3% and 0.2%, respectively, cumulating different series (12). The low frequency of recurrences is not surprising in view of the evidence that several risk factors for recurrence and death (mutifocality, extrathyroidal extension, lymph node metastases, distant metastases) are dependent on the size of the primary tumor and are thus very low

in microPTC (12-16). Higher rate of multicentricity, bilaterality, invasiveness, and lymph node metastases have been reported in several series in Non-Inc-microPTC compared to Inc-microPTC (16,19,20). Thus, to date it is unclear whether "incidental" and "non-incidental" microcarcinomas reflect the same disease or two different entities.

In the present study, we observed clinical and histological differences between Inc-microPTC and Non-Inc-microPTC. Inc-microPTC, like benign nodular thyroid disease, were more frequent in older subjects and in multinodular goiter, while Non-Inc-microPTC, similarly to macroPTC, were more frequent in younger subjects and in single nodules. Non-Inc-microPTC with respect to Inc-microPTC were larger and associated with a higher frequency of lymph node metastases at histological examination (25.4% vs 0%), similarly to macroPTC. The majority of microPTC presented a classic or a follicular histological variant. However more aggressive variants (such as tall cell, solid variant etc.) were more frequent in Non-Inc-microPTC (18/67, 26.9%), than in Inc-microPTC (11/92, 11.9%).

It as been shown that in patients with nodular thyroid disease, the risk of papillary thyroid cancer clinically detected increases with increasing concentrations of TSH (26) and, in a mouse animal model with a thyroid-specific knock-in of oncogenic Braf, serum TSH was shown to play a key role in the development of papillary thyroid carcinoma (39). Results obtained in the present series of patients confirm our previous data (27), TSH levels being significantly higher in macroPTC with respect to benign nodular disease. Conflicting results have been reported about the relationship between serum TSH and microPTC. In a recent study Shi et al. (29) found that TSH is not a good risk predictor for carcinomas smaller than 1 cm. Similar data were found by Gerschpacher et al. (30) and Shon et al. (31), who did not observe significant associations between serum TSH and the risk of malignancy in patients with thyroid nodules <1 cm. However, in the last study, there was a significant association between serum TSH and malignancy in patients with thyroid nodules > 1 cm in diameter (31). On the other hand, an association between TSH and microPTC was found by Moon et al. (32), Haymart et al. (33) and Zafon et al.(34) even if in these last studies statistical significance of analysis was not reached because of the small number of enrolled patients. Published studies on microPTC are all retrospective and those analyzing the relationship between microcarcinoma and serum TSH do not distinguish between clinically overt and incidental microcarcinoma. Our study was aimed

not only at evaluating clinical differences between incidentally discovered and clinically diagnosed microcarcinoma, but also at investigating the possible relationship with serum TSH. For this reason patients under treatment with L-T4 or methimazole as well as those with Graves' disease were excluded. TSH levels were significantly lower in Inc-microPTC with respect to Non-Inc-microPTC. On the other hand, TSH levels were not statistically different between Inc-microPTC and benign nodular disease and between Non-Inc-microPTC and macroPTC. In particular, in patients with serum TSH lower than the median value (0.8 mU/L), Inc-microPTC were more frequent than Non-Inc-microPTC, while in patients with TSH higher than 0.8 mU/L, Non-Inc-microPTC were more frequent.

On clinical grounds the presence of lower levels of serum TSH in Inc-microPTC , more frequently associated with multinodular goiter, than Non-Inc-microPTC, usually presented as single nodule, is likely related to the development of thyroid autonomy in the first group of patients (27). It is more complicated to explain the higher frequency of multifocality at histology in Inc-microPTC with respect to Non-Inc-microPTC (76.1% vs 52.2%, p=0.001). Conflicting results are reported in literature on this matter, multifocal PTC being more commonly found in Non-Inc-microPTC in some studies (6), but not in one more recent study (35). At difference with previous papers, our study is prospective and multiple PTC foci have been accurately looked for in patients submitted to thyroidectomy and were found more frequently in MN glands than in SN. These data suggest the hypothesis that genetic and environmental factors that lead to multinodular thyroid disease may favour the occurrence of somatic mutations in follicular thyroid cells that initiate the neoplastic process of multiple little foci of papillary cancer. Support to this hypothesis is given by the observation that, in multinodular goiter, also activating mutations of TSH receptors or GS alfa, responsible for the development of functioning adenomatous nodules, are common (40).

In this study we have found a statistically significant association between higher TSH levels and frequency of Non-Inc-microPTC compared to Inc-microPTC. We are aware that this observation per se does not demonstrate a pathogenetic role of TSH, but we support the hypothesis that TSH may play a role in the progression of PTC. Two different phenomena could be operating in multinodular goiter: on one site a more frequent occurrence of oncogenic mutations and, on the other, the development of thyroid

autonomy, reducing TSH levels, could slow down cancer progression of the multiple little foci of PTC, thus preventing the occurrence of clinically detectable carcinoma. This hypothesis can explain the relatively higher frequency of microPTC incidentally detected in older patients with multinodular goiter submitted to thyroid surgery. On the other hand in SN the probability of cancer initiation is lower, but higher TSH levels may favour the progression of small PTC that can eventually be detected at ultrasound exam and that show, at diagnosis, histological features (such as frequency of node metastases) similar to those observed in macroPTC. Own features of the tumor, e.g. more aggressive histological variants, may also have a role together with serum TSH to explain the faster growth, the larger size, and the higher frequency of node metastasis of clinically overt with respect to clinically occult microPTC.

In conclusion Non-Inc-microPTC and Inc-microPTC appear to be two different entities and serum TSH has probably a critical role in these two kinds of tumor.

343 **Declaration of interest**

344 The authors declare that there is no conflict of interest that could be perceived as prejudicing
345 the impartiality of the research reported

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347 **Funding**

348 This work was supported by Italian Ministry of Education, University and Research (MIUR),
349 grant n° I58C13000360001/2012 “Is there a link between thyroid cancer and thyroid
350 autoimmunity? A clinical, molecular, immunological and cell biology approach”

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Legend of Figures

Figure 1

Frequency of multifocality in Inc-microPTC , Non-Inc-microPTC and macroPTC.

Multifocal PTC were significantly more frequent in Inc-microPTC (black column) (70/92, 76.1%) with respect to Non-Inc-microPTC (gray column) (35/67, 52.2%, p=0.001) and macroPTC (white column), (87/215, 40.5%, p<0.0001), and not statistically different between Non-Inc-microPTC and macroPTC.

Figure 2

Box-whiskers plot of TSH levels in patients with Benign (white box), Inc-microPTC (gray box), Non-Inc-microPTC (striped box) and macroPTC (dotted box). Results are reported as median values, interquartile (25^{th} -75^{th} percentiles) ranges (IR) and 10^{th} -90^{th} percentiles; the statistical differences between groups were evaluated using the Mann-Whitney test. TSH was significantly higher in Non-Inc-microPTC than in Inc-microPTC (1.1 mU/L, IR 0.6-1.4 mU/L vs 0.6 mU/L, IR 0.4-1.0 mU/L, p=0.0001) and in macroPTC than in Benign (0.9 mU/L, IR 0.6-1.4 mU/L vs 0.7 mU/L, IR 0.3-1.1 mU/L, p<0.0001). No significant difference between Benign and Inc-microPTC and between macroPTC and Non-Inc-microPTC.

Figure 3

Frequency of Inc-microPTC and Non-Inc-microPTC according to TSH levels

Patients were subdivided according to the median TSH value (0.8 mU/L). Inc-microPTC (black columns) were significantly more frequent than Non-Inc-microPTC (white columns) in patients with TSH≤ 0.8 mU/L (58/92, 63.0% vs 22/67, 32.8%, p <0.0001); while Non-Inc-microPTC was significantly more frequent than Inc-microPTC (34/92, 36.9% vs 45/67, 67.1%, p<0.0001) in patients with TSH >0.8 mU/L.

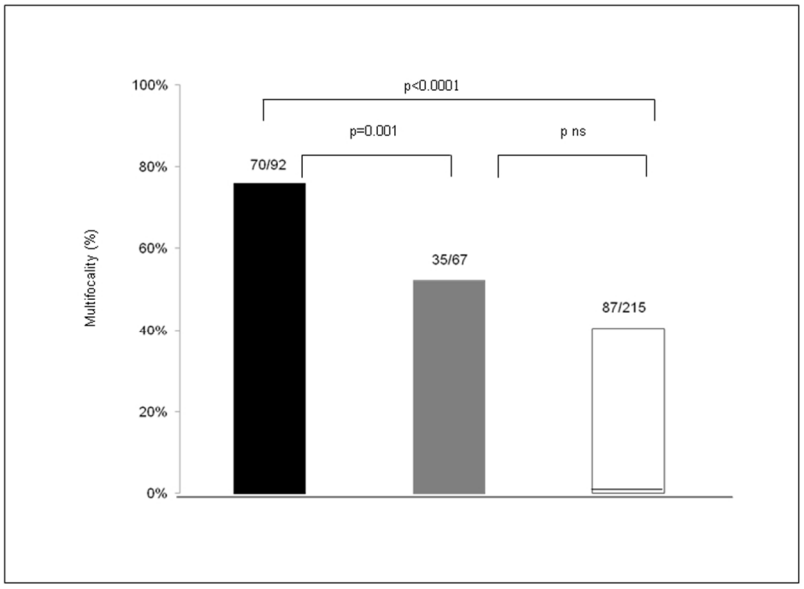
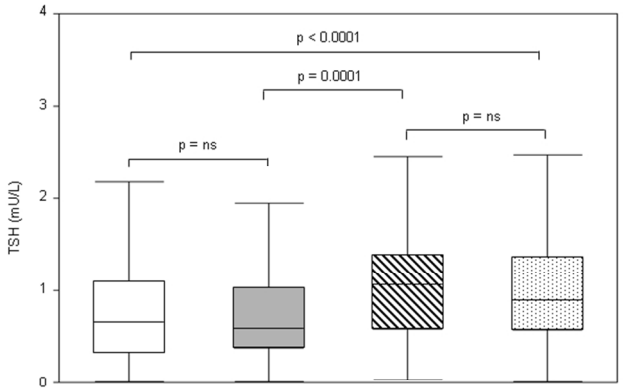


Figure 1. Frequency of multifocality in Inc-microPTC , Non-Inc-microPTC and macroPTC. \r\nMultifocal PTC were significantly more frequent in Inc-microPTC (black column) (70/92, 76.1%) with respect to Non-Inc-microPTC (gray column) (35/67, 52.2%, p=0.001) and macroPTC (white column), (87/215, 40.5%, p<0.0001), and not statistically different between Non-Inc-microPTC and macroPTC. \r\n
254x190mm (96 x 96 DPI)



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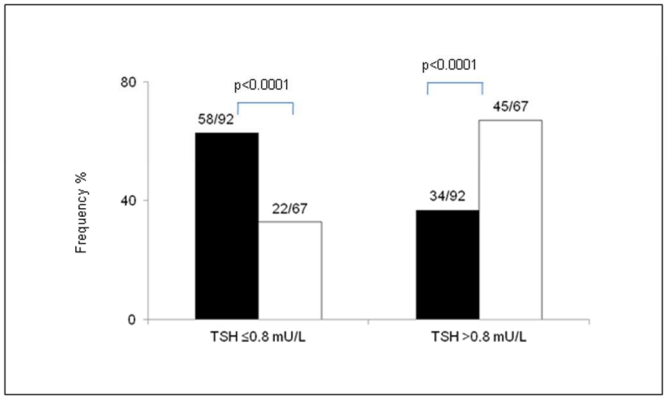

Figure 3. Frequency of Inc-microPTC and Non-Inc-microPTC according to TSH levels \r\nPatients were subdivided according to the median TSH value (0.8 mU/L). Inc-microPTC (black columns) were significantly more frequent than Non-Inc-microPTC (white columns) in patients with TSH≤ 0.8 mU/L (58/92, 63.0% vs 22/67, 32.8%, p <0.0001); while Non-Inc-microPTC was significantly more frequent than Inc-microPTC (34/92, 36.9% vs 45/67, 67.1%, p<0.0001) in patients with TSH >0.8 mU/L. \r\n
254x190mm (96 x 96 DPI)

Table 1: Indication to surgery according to clinical and cytological diagnosis and histology

Surgical Indications		**Histology**			
		Benign (291)	Inc-microPTC (92)	Non-Inc-microPTC (67)	macroPTC (215)
MN-goiter (335)					
	Compressive symptoms (141)	104	30	0	7[a]
	TIR3 (143)	68	29	6	40
	TIR4/5 (51)	0	0	8	43
MN-no goiter (71)					
	TIR1 (1)	1[b]	0	0	0
	TIR3 (41)	21	7	4	9
	TIR4/5 (29)	0	0	16	13
SN-goiter(137)					
	Compressive symptoms (31)	24	5	0	2 [c]
	TIR3 (77)	41	8	2	26
	TIR4/5 (29)	0	0	4[d]	25
SN-no goiter (122)					
	TIR3 (72)	32	13	5	22
	TIR4/5 (50)	0	0	22	28

[a] In 3 cases the PTC nodule was not submitted to FNAB, in 2 cases false negative cytology
[b] TIR 1 nodule increased in size during follow up
[c] 1 false negative cytology
[d] In 2 cases PTC was detected by the presence of clinical lymphadenopathy

Table 2: Histological variants in Inc-microPTC, Non-Inc-microPTC and macroPTC

	Inc-microPTC (n = 92)	Non-Inc-microPTC (n = 67)	macroPTC (n = 215)
Less aggressive variants (a) (n = 285)	81 (88.1%)*	49 (73.1%)*	155 (72.1%)
More aggressive variants (b) (n = 89)	11 (11.9%)	18 (26.9%)	60 (27.9%)

[a)] Less aggressive variants: classic and follicular
[b)] More aggressive variants: tall cell, solid an mixed
* p = 0.016