Incidentally Discovered Papillary Thyroid Microcarcinoma in Patients Undergoing Thyroid Surgery for Benign Disease

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Abstract

Introduction

Incidence of thyroid carcinoma (TC) has grown significantly over the last few decades worldwide, partly due to the increase detection of small thyroid microcarcinoma (TMc). TMc are tumors with a maximal diameter ≤ 1 cm, identified during histopathology examination following a thyroidectomy performed for reasons not pertaining to malignancy. The aim of this study is to investigate the prevalence of papillary thyroid microcarcinoma (PTMc) according to the nature of benign pathology that submit patients to thyroid surgery and its trend evolution.

Methods

Retrospective cohort analysis of 1815 patients who underwent total thyroidectomy for non-malignant disease from 2005 to 2020.

Results

The mean age of subjects was 53.5 years, with a higher proportion of women (1481, 82.1%). A total of 167 PTMc (9.3%) were incidentally discovered. Multivariate logistic regression analysis shows no differences in prevalence according to sex or age in patients with PTMc compared to those with final benign histology. Multinodular goiter increases the risk of PTMc with an odds ratio of 2.2 (p=0.001) compared to Hashimoto's thyroiditis and Graves´ disease (GD). There is a statistically significant increase in the incidence of PTMc in the group operated between 2017-2020 vs. 2005-2008 (p=0.005)

Conclusion

Overall prevalence of PTMc in patients who underwent thyroid surgery for benign disease was 9.3%. Thyroid nodular hyperplasia was the most frequent benign pathology associated to this occult cancer as compared to Hashimoto or GD. Gender and age were not correlated with prevalence of TMc. Over the years, surgical findings of PTMc have grown, particularly in the 2017-2020 period.

Introduction

Thyroid carcinoma (TC) is responsible over 2% of all tumors, being considered the most frequent neoplasm of the endocrine system. Incidence has been rapidly increased in recent decades around many countries worldwide, with a female-to-male ratio of 3:1 (1). However, mortality has remained stable or even declining in most areas, at 0.6/100.000 women and 0.3/100.000 men per year (2). This phenomenon is partly due to overdiagnosis of small and subclinical tumors (3)(4). Approximately 90% are differentiated cancers originating from thyroid follicular cells, being papillary thyroid carcinoma (PTC) the most common histological subtype, followed by follicular thyroid carcinoma (5).

Papillary thyroid microcarcinoma (PTMc) also called occult sclerosing carcinoma, occult papillary carcinoma and non-encapsulated sclerosing tumor, is a PTC variant defined by measuring 1 centimeter (cm) or less in diameter (6). This carcinoma could be solitary or detected in multiple foci (7). The term incidental is used for tumors identified unexpectedly at the anatomopathological study after thyroidectomy carried out for benign reason or identified randomly while undergoing cervical examinations performed for another purpose (8), the majority of them are PTMc (9). Occult medullary thyroid cancer (MTC) is an uncommon entity with a prevalence of approximately 0.3%, most of them are small and confined to the gland (10)(11). Occult carcinoma is significantly prevalent in population, being reported in autopsy series with an incidence of 0.5-36% with an increased occurrence from birth to adulthood (6). Due to his indolent evolution, it has been proposed to be renamed as “papillary microtumor” (6). Natural history and growth kinetics of the majority of clinical low risk intrathyroidal small PTC is excellent (12). So, natural history of PTMc incidentally detected have an indolent evolution, that rarely or never progresses (13).

We performed a study to define the prevalence of PTMc in patients undergoing total thyroidectomy for benign disease. Secondly, we aimed to detect whether there are different rates according to the type of underlying pathology: Graves' disease (GD), multinodular goiter (MNG), chronic lymphocytic thyroiditis (CLT). Finally, it is intended to detail the evolution of the number of surgeries and PTMc findings from 2005 to 2020.

Materials And Methods

All patients referred to thyroid surgery in a high-volume tertiary referral hospital, Hospital Universitario de Navarra (Pamplona, Spain) were enrolled. Inclusion criteria were patients who underwent total thyroidectomy between 2005 to 2020 with histologically confirmed papillary thyroid microcarcinoma (largest diameter ≤ 10 mm) diagnosed incidentally in subjects undergoing to thyroid surgery for benign disease. We exclude all patients with reported irradiation of head or neck, subjects with genetic syndromes predisposing to the development of PTC, subjects operated for suspicion of nodular malignancy and histologic confirmation of TC with a diameter exceeding 1 cm. Patients who underwent hemithyroidectomy and subjects with final histology that differs from PTMc were also excluded. Distant or nodal metastasis from thyroid cancer could not have been the reason for the surgical procedure.

Database recorded clinical, laboratory, imaging, indication for surgery, surgery performed, cytological and histopathological information. Patients were classified according to pathology for which the indication of surgery was performed: CLT, GD and MNG.

The presence of compressive symptoms was the indication of surgery in CLT and MNG. The operation was performed on GD in patients that require definitive treatment due to relapse or lack of response to antithyroid drugs.

Histological study was carried out by expert thyroid pathologists, carrying out a routine study of the thyroid nodules, capsular parenchyma and defining whether vascular invasion was present. The same

standard protocol was used to examine the surgical specimen in all patients. Surgery was conducted by general surgeons with expertise in thyroid pathology.

SPSS software (version 16.0.2: SPSS, Inc., Chicago, Illinois, USA) was used to perform the statistical analysis of the registry. Kolmogorov–Smirnov test was carried out to ensure the normality of the data distribution. Categorical variables were expressed as number and frequencies and compared using chi-squared test. Data is presented as mean – standard deviation. Proportions were analyzed with chi-squared test, logistic regression with 95% confidence intervals (CI) were calculated. Continuous variables were compared using parametric or non-parametric test, as required. Additionally, we performed a multivariate logistic regression model to test the association of age, sex, CLT, MNG, GD and year of surgery with the development of PTMc. P-values of <0.05 were considered to be statistically significant. All tests were two-sided.

Results

A total of 2920 consecutive patients who have undergone to thyroid surgery for benign disease in our center were enrolled. However, 1105 subjects were excluded: 618 with TC larger than 1 cm, 487 who underwent hemithyroidectomy and 13 with histology different to PTMc. Finally, 1802 satisfied the inclusion criteria, flow chart of study is illustrated in Figure 1.

Overall papillary microcarcinoma prevalence in patients treated by total thyroidectomy for benign indication were 167 cases (9.3%), classified as occult PTMc. We also detect microcarcinomas of other histological variants, such as 6 follicular carcinoma (3.3%), 5 medullary (2.8%), 1 Hürthle (0.6%) and 1 non-invasive follicular thyroid neoplasm with papillary like nuclear features (0.6%) (NIFTP).

Baseline characteristics of the sample are presented in Table 1. Demographic and clinical features were analyzed to evaluate any significant associations comparing PTMc versus patients with benign disease (Table 2). In the overall univariate analysis, age and gender were not statistically associated with cancer. Median age of presentation of cases without PTMc was 53.5± 12.9 vs 55.5± 13.9 in non PTMc (p=0.970). The percentage of men that presented with PTMc was 21.5% (36), compared to 17.6% (287) without PTMc (p=0.199). Nevertheless, cancer rates according to benign thyroid pathology for surgery were as follows: CLT 6.5% (3/46), GD 4.9% (17/349), MNG 10.5% (147/1406). We noted a higher proportion of PTMc in MNG, resulting statistically significant (p=0.001) vs CLT/GD. The four-year period prevalence of incidental PTMc and benign histology is shown in Figure 2. It has been noted a progressively and significant increasing trend of diagnosed PTMc over the years (p=0.010).

Table 1
Demographic and clinical characteristics of the cohort.

Total population	**1802**
Age at diagnosis, years (mean ± standard deviation)	53.5 ± 13.8
Sex, n (%):	
- Female (%)	1481 (82.1%)
- Male (%)	321 (17.9%)
Benign indication for surgery:	
- Chronic lymphocytic thyroiditis	46 (2.5%)
- Graves' disease	350 (19.4%)
- Nodular hyperplasia	1406 (78.0%)
Presence of incidental papilar microcarcinoma	167 (9,3%)

Table 2
Incidence of PTMc in relation to sex, age, benign thyroid disease, and time of diagnosis.

	Cases without PTMc	**Cases with PTMc**	**p**
Age at diagnosis, years (mean ± standard deviation)	55.5 ± 13.9	53.5 ± 12.9	0.970
Age ≥ 55	784 (48.0)	79 (47.3)	0.874
Sex:			0.199
- Male (%)	287 (31.4%)	36 (21.6)	
- Female (%)	628 (68.6%)	131 (78.4)	
Benign indication for surgery:			**0.001**
- Chronic lymphocytic thyroiditis (%)	**43 (2.6)**	**3 (1.8)**	
- Graves' disease (%)	**332 (20.3)**	**17 (10.2)**	
- Multinodular goiter (%)	**1259 (77.1)**	**147 (88.0)**	
Surgery date:			**0.010**
- 2005-2008	**340 (93.1)**	**25 (6.9)**	
- 2009-2012	**465 (91.5)**	**43 (8.5)**	
- 2013-2016	**448 (91.6)**	**41 (8.4)**	
- 2017-2020	**382 (86.8)**	**58 (13.2)**	

On multivariate analysis, we found no association with gender and age. By contrast, MNG disease was significantly associated with incidental thyroid cancer with an odds ratio of 2.2 (CI 95%, 1.4-3.5; p=0.001). This reflects a strength of the association between the development of PTMc in MNG. The risk of PTMc is 120% higher in MNG compared with the observed prevalence in the combination of CLT/GD patients (Table 3). Regarding surgery dates, subjects who underwent intervention after the first four-year period (2005-2008) had an increased risk of developing PTMc. This increase was significant in the group treated in 2017-2020, which has an OR of 2.03 (CI 95%, 1.24-3-33; p=0.005) when compared to the first four-year period.

Table 3
Results of a Multivariate logistic regression analysis to test the association of benign thyroid pathology and surgery date.

	Odds ratio	95% CI	p
Multinodular goiter	2.2	1.4-3.5	0.001
Surgery date:			
- 2005-2008	1		
- 2009-2012	1.23	0.75-2.06	0.424
- 2013-2016	1.21	0.72-2.04	0.463
- 2017-2020	2.03	1.24-3.33	0.005

Discussion

PTMc is the most frequently incidentally discovered thyroid neoplasm because of its indolent and asymptomatic course (14). Prognosis of incidental PTMc is excellent, with recurrence rate of 0.5% and mortality as low as 0% (15). In this direction, it has been observed that PTMc show an alternative rearrangement gene expression pattern compared to PTC. Therefore that specific microenvironment is responsible for the different phenotypic and clinical expression (16)(17). Consequently American Thyroid Association (ATA) guidelines and the 8th AJCC/TNM system, suggest less aggressive therapeutical approaches (18, 19). It has even been proposed active surveillance of low-risk PTMc as the best first-line treatment, particularly in elderly (20) (21).

There are some clinical characteristics that modify the indolent evolution of PTMc, conferring those patients a higher risk. These modifiers are youth (under 19 years), multifocality, microscopic features of aggressiveness (tall cell, blood vessel permeation), incidental diagnosis in patients with clinical metastases (6). Some authors have proposed a subdivision according to size, with a cut-off point of 7mm, as this seems to be related with tumorigenic behavior (22). Three different subtypes of PTMc have been identified: type I (incidentally detected PTMc with no symptoms, harmless the life expectancy), type II (accompanied by small lymph node metastasis and/or minimal invasion with no progression) and type III (high-risk for presenting data on aggressiveness) (23). Recent studies have shown a growing prevalence of PTC over the last decades (1). Our local thyroid cancer registry of the Community of Navarre (Spain) is consistent with this trend. It demonstrated an increase of TC diagnosis in both sexes, as a result of a gradual rise of T1a papillary carcinoma probably due to a higher diagnosis of microcarcinomas over the years (24).

Frequency of incidentally PTMc found in surgical series differs depending on the cohort reviewed, ranging from 2–40% (25). Interpretation of this inter-study variability could be explained by geographical

factors (environmental features, diet, medical healthcare access) and underlying pathology of the subjects that leads them to surgery. The first study that proved a grater incidental thyroid cancer risk in patients referred to surgery was carried out by Smith *et al.* (26), with an overall prevalence of 15.6%. PTMc prevalence in our cohort was 9.3% (167/1802), which places us near the lower limit of other series (27)(28)(26)(29). A possible explanation of this results could be that there are no environmental exposures that increase risk of PTMc in our region. Exclusion criteria were strict because the main objective was to include only patients with truly incidentally discovered PTMc and avoid selection vias. Therefore, all patients with a suspicion of thyroid carcinoma confirmed by histologic examination were not included.

Our analysis found a higher prevalence of occult PTMc in MNG, followed by other benign pathologies such as CLT and finally GD. Leading indication for surgery in our center was MNG, probably due to the relatively high prevalence in our environment, which is at endemic levels (30). Moreover, thyroid nodules are the most frequent thyroid disease. The term of MNG is currently used when there are several nodules in the thyroid gland. Overall, 10.5% of the MNG operated (147/1406) had an occult microcarcinoma, similar to the 12% risk described by Fama *et al* (25) and 14% of Taşova *et al* (31), but lower than the 29.2% of the cohort of Ajarma *et al* (32). This percentage is comparable to pre-surgery probability of malignancy of nodules, ranging from 7–15%, depending on age, sex, radiation history or family history (18).

Opposite to our findings, other authors have reported a greater prevalence of cancer in patients with underlying thyroiditis. Nevertheless, relationship between thyroid autoimmunity and cancer remains controversial. Some studies have demonstrated that there is a link between lymphocytic infiltration of the thyroid parenchyma and PTC, an histologic feature described in Hashimoto's disease (33). The pathophysiological mechanism responsible is not fully understood, however Virchow in 1863 had speculated the link between chronic inflammation and neoplastic transformation of normal tissue (34). Some of trigged mechanisms proposed for carcinogenesis are stimulation due to the action of TSH, expression of specific proto-oncogenes and chemokines produced by tissue-infiltrating lymphocytes (35). Autoimmune role of antibodies and chronic lymphocyte infiltration may predispose for dysplastic evolution of the follicular epithelium, creating a pre-neoplastic area progressing toward the existence of a tumor (36). Hashimoto’s thyroiditis has been reported that only increases the risk of PTC in euthyroid individuals and in those that partially preserve the function (37). High TSH levels leads to cellular hypertrophy and hyperplasia by a constitutive activation of this pathway, tiggering genetic abnormalities. In this direction, Fiore E. *et al* (38), showed that risk of malignancy is associated with increased in TSH values. Microenvironment and molecular investigation of thyroid cancer is crucial because it may explain why the same histological subtype have different behavior. Research have found that PTC is less frequent and aggressive in GD as compared to CLT and non-autoimmune thyroid disease (39). Nevertheless, it has been considered that cancer and autoimmunity were extremes of immune-responses (40).

Our cohort reported one of the lowest prevalence of PTMc in CLT (3/46=6.5%), compared to other series. Slijepcevic *et a*l (29) show a different distribution of incidental PTMc in relation to the benign thyroid disease to undergoing surgery, with the highest prevalence in Hashimoto thyroiditis (22.7%). Bircan *et al* (41) noted around 39%. Notably, the indication for CLT surgery is the lowest of all in our cohort. This may be due to the strict inclusion criteria. Probably, areas of thyroiditis in the parenchyma may form nodules with an ultrasound appearance that mimics nodules with intermediate or high suspicion (42)(43). This pre-surgical suspicion could lead to perform cytological studies by fine needle aspiration biopsy (FNAB) and, if malignancy is confirmed by histological analysis of the specimen, these subjects would be excluded.

The current study found the lowest risk in GD, with a frequency of PTMc around 4.9% (17/349). Prevalence reported range from 0.5–15%, with many cohorts submitting rates below 5%. Dănilă R. *et al*. (44), in a retrospective study performed on a consecutive 92 patients operated with GD, conclude that the 2.2% prevalence of incidental thyroid microcarcinoma was similar to other benign disease. Lower distribution of PTMc in autoimmune disorders compared to MNG, suggest that thyroid autoimmunity does not affect tumorigenesis (45).

Age was not found to affect the risk of malignancy. Our results are in concordance with Luo *et al.* (46) who reported that age was not a very strong independent factor for predicting malignancy (OR 0.97, 95%CI 0.960–0.987, $p < 0.001$) due to an odds ratio approached to 1. Consequently, age is not helpful for predicting malignancy. However, it seems to influence on progression and prognosis of PTMc (21).

In our study we did not find sex as a risk factor to predict PTMc, with a male prevalence of 11.1% (36/323) compared to 17.3% (131/759) in females. Slijepcevic N. *et al*. (29), did not report gender differences in his cohort of 2,466 patients. Roti E. *et al*. (47), corroborated this same theory. This phenomenon does not seem to occur in cancers of a larger size, since the overall higher prevalence of papillary PTC in women suggests a role in promoting malignancy transformation attributable to estrogen stimulation (48). At the onset of puberty, the prevalence of PTC increases only in females, decreasing again after menopause, possibly due to the growth-promoting effect mediated by membrane-bound estrogen receptors (49).

Rising prevalence of PTMc in our cohort over decades (24), is a fact that is consistent with other series (14). Leenhardt L. *et al*. (50), described an increase of 8.1% and 6.2% per year in women and men, due to papillary type with an epidemic tumors measuring less than 1 centimeter (43% of total operated cancers). Rego-Iraeta A. *et al.* (51), support these results. This Spanish descriptive epidemiological study found that this rise exclusive of PTMc. Besides PTMc, they do not identify significant variations in tumor size over time. One possible explanation that may have influenced in this increasing incidence in the population of Navarre is the change in the iodization situation. There has been a progressive change in recent decades from an iodine-deficient to an iodine-sufficient community, although the association between increased iodine intake and thyroid cancer is controversial. Another factor to take into is that the number of pathologic slides from each surgical specimen has increased over the years, contributing to the detection

of PTMC specimens. Overexposure to ionizing radiation sources through the decades may also contribute to this effect.

In conclusion, we found a prevalence of 9.3% of incidental PTMc, that is comparable to rates of other European cohorts. Age and gender are not independent predictors for PTMc, with a higher prevalence of incidental PTMc in MNG followed by CLT and lastly in GD. Surgical findings of PTMc in total thyroidectomy for benign disease has increased significantly over the years, particularly in the 2017-2020 period.

Statements And Declarations

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Statement of Ethics

Ethical principles for medical research involving human subjects in accordance with the World Medical Association Declaration of Helsinki has been conducted. The study protocol has been approved by the ethics committee of the Government of Navarre (Spain). This study has been granted an exemption from requiring written informed consent by the ethics of the Government of Navarre (Spain).

Consent to participate and to publish

Ethics committee of the Government of Navarre (Spain) has authorized the retrospective study of the patients' medical files.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. de Carlos was in charge of analysis, writing up the article and interpretation of data. Dr. Ernaga was responsible for overseeing the project, data collection and manuscript correction. Dr. Irigaray was responsible of data analysis, data collection and revising it critically. Dr. Pineda was responsible of follow-up patients, data acquisition and intellectual producer. Dr. Echegoyen was responsible of the histological study of the sample and study designs. Dr. Salvador was responsible of surgery, literature

search and follow-up patients. Dr. Anda overall coordinator of the entire study. All authors discussed previous versions of the manuscript and agreed to the submission of the final version.

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Figures

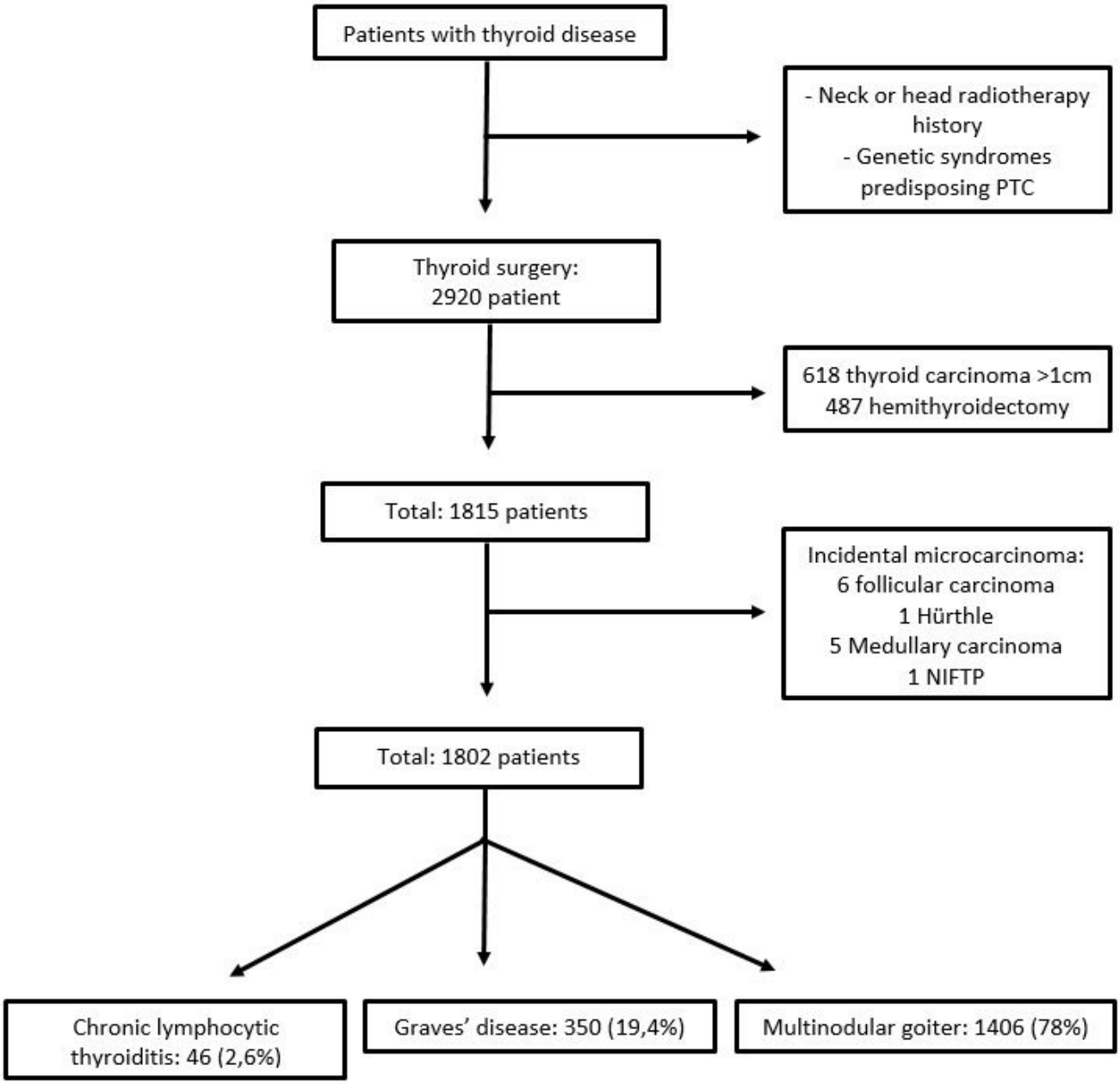

Figure 1

Flow chart for the selection of patients, with inclusion and exclusion criteria.

NIFTP, Non-invasive follicular thyroid neoplasm with papillary like nuclear features.

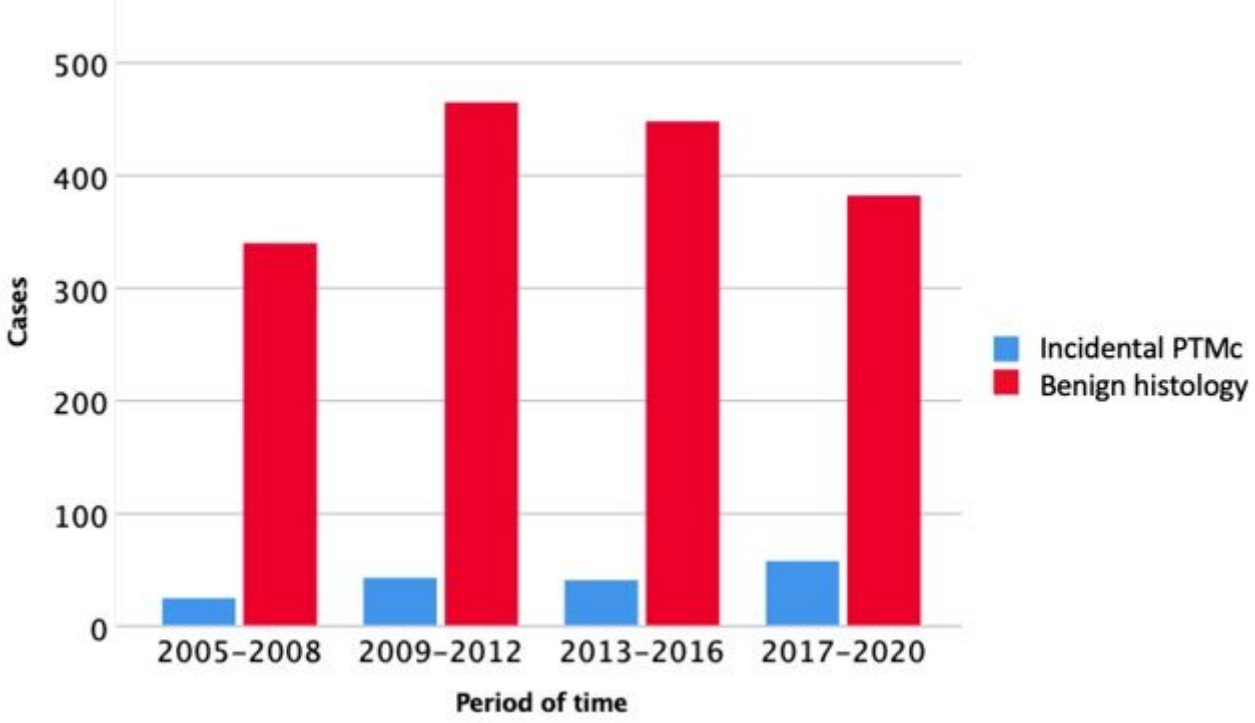

Figure 2

Total surgeries, cases of papillary thyroid microcarcinoma and benign histology.