Incidentally discovered papillary thyroid microcarcinoma in patients undergoing thyroid surgery for benign disease

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Abstract

Introduction  The incidence of thyroid carcinoma has grown significantly over the last few decades. A possible explanation is the increased diagnosis of small thyroid microcarcinoma (TMc). TMc reach a maximum diameter of ≤1 cm, identified during histopathology examination following a thyroidectomy performed for reasons not pertaining to malignancy. This study aims to investigate the prevalence of papillary thyroid microcarcinoma (PTMc) according to the benign pathology that refers patients to surgery and its trend evolution.

Methods  Retrospective cohort analysis of 1815 patients who underwent total thyroidectomy for non-malignant diseases in the 2005–2020 period.

Results  The mean age of the subjects was 53.5 years, with a higher proportion of women (1481, 82.1%). A total of 167 PTMc (9.3%) were incidentally discovered. A multivariate logistic regression analysis was performed, showing no differences in prevalence according to sex or age in patients with PTMc compared to 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 in the 2017–2020 vs. 2005–2008 period (p = 0.005).

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

Keywords  Benign thyroid disease · Thyroid surgery · Papillary thyroid microcarcinoma · Incidental

Introduction

Thyroid carcinoma (TC) is responsible for 2% of all tumors and is considered the most frequent neoplasm of the endocrine system. The incidence has been rapidly increasing in recent decades in many countries, with a female-to-male ratio of 3:1 [1]. However, mortality has remained stable or even declined in most areas, at 0.6/100,000 women and 0.3/100,000 men per year [2]. These trend changes may be influenced by the overdiagnosis of small subclinical tumors [3, 4]. Approximately 90% are differentiated cancers originating from thyroid follicular cells. The most common histological subtype is papillary thyroid carcinoma (PTC), followed by follicular thyroid carcinoma [5].

Papillary thyroid microcarcinoma (PTMc) is a PTC with a maximum diameter of 1 cm. There are three other ways of referring to PTMc: occult sclerosing carcinoma, occult papillary carcinoma, and non-encapsulated sclerosing tumor [6]. This carcinoma can be solitary or detected in multiple foci [7]. The term incidental is used for tumors identified unexpectedly in the anatomopathological study.
after conducting a thyroidectomy for a benign reason or identified randomly while undergoing cervical examinations performed for another purpose [8]. The majority of these incidental carcinomas are PTMc [9]. It is rare to find in this casual way medullary thyroid cancer since its prevalence is a mere 0.3% [10]. The incidence of incidental carcinoma in autopsy series ranges from 0.5 to 36% [6]. The approximate prevalence in our area in autopsies is at the upper end, with a prevalence of 22% [11]. The natural history and growth kinetics of the majority of low-risk intrathyroidal small PTC presents a favorable evolution [12]. As a result of their indolent evolution, they rarely or never progress [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 prevalence according to the type of underlying pathology: Graves’ disease (GD), multinodular goiter (MNG), chronic lymphocytic thyroiditis (CLT). Finally, we attempt to detail the evolution of PTMc in surgeries from 2005 to 2020.

Materials and methods

We enrolled all patients referred to thyroid surgery in a high-volume tertiary hospital, the Hospital Universitario de Navarra (Pamplona, Spain). The inclusion criteria were patients who underwent total thyroidectomy for benign disease between 2005 and 2020 with a histologically confirmed PTMc (largest diameter ≤ 10 mm) that had been diagnosed incidentally. We excluded all patients with reported irradiation of the head or neck, subjects with genetic syndromes predisposing to PTC, operated for suspicion of nodular malignancy, and histologic confirmation of TC with a diameter exceeding 1 cm. Patients undergoing hemithyroidectomy and subjects with final histology that differ from PTMc were also excluded.

Database recorded information regarding clinical, laboratory tests, imaging, indication for surgery, surgery performed, cytological and histopathological. The patients were classified according to the reason for the surgical indication: CLT, GD, and MNG.

The presence of compressive symptoms is an indication of surgery in CLT and MNG. Thyroidectomy was performed on GD patients with relapse or lack of response to antithyroid drugs. All patients had pre-surgical thyroid ultrasound, performing a study of the dominant nodule if indicated. We excluded subjects with cytological analysis compatible with Bethesda III, IV, V, and VI. The thyroidectomy specimens were sent together with the patient’s clinical information, to two expert thyroid pathologists. The specimen was stained, and sections were made every 1 cm parallel to the sagittal plane and fixed in formol for 24–48 h. During the process, each nodule was identified and analyzed individually. The morphology, size, color, consistency, presence of capsule, calcifications, and location within the gland were recorded for each nodule. Subsequently, the microscopic analysis of all the nodules identified was performed and a report was issued with the histopathological diagnosis, following WHO classification [14]. The same standard protocol was used for all patients from the beginning of the study. 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. A Kolmogorov–Smirnov test was carried out to ensure the normality of the data distribution. Categorical variables were expressed as numbers and frequencies and compared using the \( \chi^2 \) test. The data are presented as mean – standard deviation. The proportions were analyzed with a \( \chi^2 \) test, and logistic regression with 95% confidence intervals (CI) was calculated. The continuous variables were compared using a parametric or non-parametric test, as required. In addition, we conducted 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 statistically significant. All tests were two-sided.

Results

We enrolled a total of 2920 consecutive patients who underwent thyroid surgery for benign disease. However, 1105 subjects were excluded: 618 with TC larger than 1 cm, 487 who underwent hemithyroidectomy, and 13 with a histological analysis different from PTMc. Finally, 1802 patients met the inclusion criteria. The flowchart is illustrated in Fig. 1. The overall prevalence of PTMc in patients undergoing total thyroidectomy for benign indication was 9.3% (167 patients). We also detected microcarcinomas of other histological variants: six follicular carcinomas (3.3%), five medullary (2.8%), one Hürthle (0.6%), and one non-invasive follicular thyroid neoplasm with papillary-like nuclear features (0.6%).

The baseline characteristics of the sample are presented in Table 1. Demographic and clinical parameters were analyzed to detect differences (Table 2). In the univariate analysis, age and gender were not statistically associated with cancer. Nevertheless, cancer rates according to benign thyroid pathology for surgery resulted as follows: CLT 6.5% (3/46), GD 4.9% (17/349), MNG 10.5% (147/1406). The pathological characteristics of incidental PTMc are presented in Table 3.
We noted a higher and statistically significant ($p = 0.001$) proportion of PTMc in MNG vs. CLT/GD. The 4-year prevalence of PTMc and benign histology is shown in Fig. 2. A progressively and significantly increasing trend of diagnosed PTMc has been detected over the years ($p = 0.010$).

On multivariate analysis, we found no association between gender and age. By contrast, the 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 results in the 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 4).

Regarding surgery dates, subjects who underwent intervention after the first 4-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 4-year period.

### Discussion

PTMc is the most frequently discovered thyroid neoplasm [15]. The prognosis of PTMc is excellent, with a recurrence rate of 0.5% and mortality as low as 0% [16]. In this direction, it has been observed that PTMc shows an alternative rearrangement gene expression pattern compared to PTC. Therefore, that specific microenvironment is responsible for the different phenotypic and clinical expressions [17, 18]. Consequently, American Thyroid Association guidelines and the 8th AJCC/TNM system suggest less aggressive therapeutic approaches [19, 20]. It has even been proposed active surveillance for low-risk PTMc is the best first-line treatment, particularly in the elderly [21, 22].

Some clinical characteristics modify this indolent evolution of PTMc, conferring a subgroup of patients a higher risk. These modifiers are youth (under 19 years), multifocality, microscopic features of aggressiveness (tall cell, blood vessel infiltration), and incidental diagnosis in patients with clinical metastases [6]. Some authors have proposed a subdivision according to size, with a cut-off point of 7 mm in diameter, as this seems to be related to tumorigenic behavior [23]. Three different subtypes of PTMc have been identified: type I (incidentally detected PTMc with no symptoms, harmless the life expectancy), type II (associated with small lymph node metastasis and/or minimal invasion with no progression), and type III (high-risk for presenting data of aggressiveness) [24].

Recent studies have shown a growing prevalence of PTC over the last decades, with uncertainty if this is a real increase or an increased detection [1]. The local thyroid cancer registry of the Community of Navarre (Spain) is consistent with this trend. The track record demonstrated an increase of TC diagnosed in both sexes. It is the result of a gradual rise of T1a PTC due to a higher diagnosis of microcarcinomas [25]. The frequency of PTMc found in surgical series differs depending on the cohort reviewed, ranging from 2 to 40% [26]. An interpretation of this inter-study variability could be explained by geographical factors (e.g., environmental features, iodine status, diet, medical healthcare access) and underlying pathology of the subjects that lead them to surgery. The first study that proved a greater incidental thyroid cancer risk in patients referred to surgery was carried out by Smith et al. [27], with an overall prevalence of 15.6%. The prevalence of PTMc in our cohort was 9.3% (167/1802), which places us near the lower limit of other series [27–30]. A possible explanation could be that there are no environmental exposures that increase the risk of PTMc in our region. The exclusion criteria were strict because the main objective was to include only patients with truly incidentally discovered PTMc and avoid selection bias. Therefore, all patients with a suspicion of TC confirmed by histologic examination were not included.

Our analysis found a higher prevalence of PTMc in MNG, followed by other benign pathologies such as CLT

### Table 3

Pathological characteristics of incidental PTMc (\( n = 167 \))

| Characteristic                  | Mean (standard deviation) |
|---------------------------------|----------------------------|
| Size (mm)                       | 4.65 mm (2.09)             |
| Multifocality                   | Yes 26.3% (\( n = 44 \))   |
|                                 | No 73.7% (\( n = 123 \))   |
| Extensión extratiroidea         | Yes 3.6% (\( n = 6 \))     |
|                                 | No 96.4% (\( n = 161 \))   |
| Node                            | Yes 0% (\( n = 0 \))       |
|                                 | No 100% (\( n = 167 \))    |
| Metastasis                      | Yes 0% (\( n = 0 \))       |
|                                 | No 100% (\( n = 167 \))    |
| Papillary histological subtypes | Follicular 43.7% (\( n = 73 \)) |
|                                 | Classic 33.5% (\( n = 56 \)) |
|                                 | Tall cell 13.2% (\( n = 22 \)) |
|                                 | Others 9.6% (\( n = 16 \)) |

### Table 4

Results of a multivariate logistic regression analysis to test the association between benign thyroid pathology and surgery date

| Characteristic | 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   |

Fig. 2 Total surgeries, cases of papillary thyroid microcarcinoma, and benign histology
and finally GD. The leading indication for surgery in our center was MNG, probably due to the relatively high prevalence in our environment, which is at endemic levels [31]. Moreover, thyroid nodules are the most frequent thyroid disease. Overall, 10.5% of the MNG operated (147/1406) presented an incidental microcarcinoma, similar to the 12% risk described by Fama et al. [26] and 14% of Taşova et al. [32], but lower than the 29.2% of the cohort of Ajarma et al. [33]. This percentage is comparable to the pre-surgery probability of malignancy of nodules, which ranges from 7 to 15%, depending on age, sex, radiation history, or family history [19].

Opposite to our findings, other authors have reported a greater prevalence of cancer in patients with underlying thyroiditis. Nevertheless, the relationship between thyroid autoimmunity and cancer remains controversial. Some studies have demonstrated a link between lymphocytic infiltration of the thyroid parenchyma and PTC, a histologic feature described in Hashimoto’s disease [34]. The pathophysiological mechanism responsible is not fully understood. Virchow, in 1863, speculated about the link between chronic inflammation and neoplastic transformation of normal tissue [35]. Some of the triggered mechanisms proposed for carcinogenesis are stimulation due to the action of TSH, an expression of specific proto-oncogenes, and chemokines produced by tissue-infiltrating lymphocytes [36]. The autoimmune role of antibodies and chronic lymphocyte infiltration may predispose to dysplastic evolution of the follicular epithelium, creating a pre-neoplastic area progressing toward the existence of a tumor [37]. It has been reported that Hashimoto’s thyroiditis increases the risk of PTC in euthyroid individuals and those with partially preserved thyroid function [38]. High TSH levels lead to cellular hypertrophy and hyperplasia by constitutive activation of this pathway, triggering genetic abnormalities. In this direction, Fiore and Vitti [39] demonstrated that the risk of malignancy is associated with increased TSH values. The microenvironment and molecular investigation of thyroid cancer are crucial because they may explain why two carcinomas with the same histological subtype have different behaviors. Research has shown that PTC is less frequent and aggressive in GD as compared to CLT and non-autoimmune thyroid disease [40]. Nevertheless, it has been considered that cancer and autoimmunity are extremes of immune responses [41].

Our cohort reported one of the lowest prevalence of PTMc in CLT (3/46 = 6.5%), compared to other series. Slijepcevic et al. [30] described a different distribution of incidental PTMc concerning the underlying thyroid pathology for which surgery is recommended, with the highest prevalence in Hashimoto’s thyroiditis (22.7%). Bircan et al. [42] 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 can give the sonographic appearance of intermediate or high suspicion nodules [43, 44]. This pre-surgical suspicion can lead to the performance of cytological studies by fine-needle aspiration biopsy. If malignancy is confirmed by histological analysis of the specimen, these subjects are excluded.

The current study found the lowest risk in GD, with a frequency of PTMc of around 4.9% (17/349). The reported prevalence ranges from 0.5 to 15%, with many cohorts submitting rates below 5%. Dănilă et al. [45] performed a retrospective study on 92 consecutive patients operated on with GD. They conclude that the 2.2% prevalence of PTMc was similar to other benign diseases. The lower distribution of PTMc in autoimmune disorders compared to MNG suggests that thyroid autoimmunity does not affect tumorigenesis [46].

Age was not associated with the risk of malignancy. Our results are in concordance with Luo et al. [47] who reported that age is not a strong independent factor for predicting malignancy (OR 0.97, 95% CI 0.960–0.987, p < 0.001) because its odds ratio is close to 1. Consequently, age is not helpful for predicting malignancy. However, it seems to influence the progression and prognosis of PTMc [22].

In our study, we did not detect sex as a risk factor for predicting PTMc, with a male prevalence of 11.1% (36/323) compared to 17.3% (131/759) in females. Slijepcevic et al. [30] reported no gender differences in his 2466 cohort. Roti et al. [48] corroborated this theory. This phenomenon does not seem to occur in larger carcinomas. This overall increase in the prevalence of PTC in women suggests the promoter role of estrogen, stimulating the genesis of carcinoma. [49]. At the onset of puberty, the prevalence of PTC increases only in females, decreasing again after menopause, an effect attributable to the growth mediated by membrane-bound estrogen receptors [50].

The increase in the prevalence of PTMc in recent decades in our cohort [25] is consistent with other series [15]. Leenhardt et al. [51] described a rise in the prevalence of 8.1% and 6.2% per year in women and men, respectively, with 43% of total operated PTMc measuring less than 1 cm. Rego-Iraeta et al. [52] support the previous results. This Spanish descriptive epidemiological study proved that the increase was exclusive to PTMc. Besides PTMc, they did not identify significant variations in tumor size over time. The iodization situation in Navarre could have influenced this increase in incidence. There has been a progressive change in recent decades from an iodine-deficient to an iodine-sufficient community. Since 2004, the WHO has included Spain in the countries with optimal iodine nutrition [53, 54]. There is an apparent “U-shaped” association between iodine exposure and thyroid disease.
Lee et al. [11] performed a 16 studies metaanalysis demonstrating a statistical relationship favoring more exposure to iodine in patients diagnosed with PT compared to the control group. However, the final pathophysiological mechanism is not fully understood. Another factor to consider is the increase over the years in the number of histological slides studied from the samples. An over-exposure to ionizing radiation sources through the decades may also contribute to this effect.

Our study is limited by the classification of patients according to the surgical indication and its retrospective nature.

In conclusion, we found a prevalence of 9.3% of PTMc, similar to other European cohorts. The highest rates have been detected in MNG followed by CLT and lastly in GD. Similar to other European cohorts. The highest rates have been detected in MNG followed by CLT and lastly in GD. Surgical findings of PTMc in total thyroidectomy for the benign disease have increased significantly over the years, particularly in the 2017–2020 period.

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Author contributions J.d.C. was in charge of analysis, writing up the article, and interpreting the data. A. Erмага was responsible for overseeing the project, data collection, and manuscript correction. A.I. was responsible for the data analysis, data collection, and its critical revision. J.J.P. was responsible for follow-up patients, data acquisition, and intellectual production. A. Echegoyen was responsible for the histological study of the sample and study designs. P.S. was responsible for the data analysis, data collection, and its critical revision. A.I. coordinated the study. All authors discussed previous versions of the manuscript and agreed to the submission of the final version.

Compliance with ethical standards

Conflict of interest All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Ethics approval and consent to participate Ethical principles for medical research involving human subjects under the World Medical Association Declaration of Helsinki have 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).

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