

Results of the treatment of papillary thyroid microcarcinoma adapted to risk of recurrence

Resultados del tratamiento del microcarcinoma papilar de tiroides adaptado al riesgo de recurrencia

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Abstract

Background: The incidence of papillary thyroid microcarcinoma (PTMC) is increasing. **Objective:** The objective of the study was to analyze the long-term prognosis of PTMC. **Method:** Study population: patients with a histopathological diagnosis of PTMC (size ≤ 1 cm) treated according to the risk of recurrence of the Latin American Thyroid Society. Inclusion criteria: the following criteria were included in the study: minimum follow-up of 2 years, availability of histopathological samples, and treatment compliance. Exclusion criteria: the following criteria were excluded from the study: previous thyroid surgery, other synchronous malignancies, or ectopic location of the PTMC. Study variables: persistence, recurrences, and mortality. **Results:** Based on the risk of recurrence, PTMC has very low risk in 65.2% ($n = 105$), low risk in 17.4% ($n = 28$), and high risk in 17.4% ($n = 28$). In high-risk patients, total thyroidectomy was performed in all cases, cervical lymphadenectomy in 57.1% ($n = 16$), and metabolic therapy with ^{131}I in all cases. During a mean follow-up of 119.8 ± 65 months, 0.6% ($n = 1$) of recurrences took place. Risk factors associated to recurrence were not identified. No patient died due to MCPT. **Conclusions:** PTMC treated based on its risk of recurrence has a good long-term prognosis, without persistence, with a low number of recurrences and absence of disease-associated mortality.

Keywords: Thyroid cancer. Papillary thyroid carcinoma. Papillary thyroid microcarcinoma. Prognosis. Treatment.

Resumen

Antecedentes: La incidencia del microcarcinoma papilar de tiroides (MCPT) está aumentando. **Objetivo:** Analizar el pronóstico a largo plazo del MCPT. **Método:** Población a estudio: pacientes con diagnóstico histopatológico de MCPT (tamaño ≤ 1 cm) tratados según el riesgo de recurrencia de la Sociedad Latinoamericana de Tiroides. Criterios de inclusión: seguimiento mínimo de 2 años, disponibilidad de las muestras histopatológicas y cumplimiento del tratamiento. Criterios de exclusión: cirugía tiroidea previa, otras patologías malignas sincrónicas o localización ectópica del MCPT. Variables a estudio: persistencias, recidivas y mortalidad. **Resultados:** Según el riesgo de recurrencia, el 65.2% ($n = 105$) tuvo muy bajo riesgo, el 17.4% ($n = 28$) bajo riesgo y el 17.4% ($n = 28$) alto riesgo. En los pacientes de alto riesgo se realizó tiroidectomía total en todos los casos, linfadenectomía cervical en el 57.1% ($n = 16$) y terapia metabólica con ^{131}I en todos los casos. Durante un

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seguimiento medio de 119.8 ± 65 meses hubo un 0.6% ($n = 1$) de recurrencias. No se evidenciaron factores de riesgo asociados a recidiva de la enfermedad. Ningún paciente falleció debido al MCPT. **Conclusiones:** El MCPT tratado en función del riesgo de recurrencia tiene un buen pronóstico a largo plazo, sin persistencias, con una baja cifra de recurrencias y ausencia de mortalidad debida a la enfermedad.

Palabras clave: Cáncer de tiroides. Carcinoma papilar de tiroides. Microcarcinoma papilar de tiroides. Pronóstico. Tratamiento.

Introduction

Papillary thyroid microcarcinoma (PTMC) is that papillary carcinoma that measures ≤ 1 cm¹. Its incidence has been considerably increasing in recent years² not only due to a real increase but also due to better pre-operative clinical examination³⁻⁵ and more accurate histopathological diagnosis in patients who undergo surgery for presumably benign thyroid pathology⁶⁻⁹.

Due to the increase in its incidence, it is important to know its prognosis for being able to implement an adequate treatment, without it being excessive or insufficient. At present, treatment tends to be increasingly less aggressive and more conservative, trying to minimize the risk of post-surgical complications and reduce the number of cases of persistence, recurrence, and disease-related mortality. However, there is no consensus on which is the best treatment¹⁰⁻¹⁵, since there are options that range from highly conservative, especially in Asian centers where only active follow-up is carried out¹⁰, to comprehensive approaches that involve surgery (lobectomy or total thyroidectomy, lymphadenectomy) and radioiodine (¹³¹I)¹¹⁻¹⁵.

In view of this therapeutic variability, the most reasonable approach is still trying to identify those PTMCs that may have a poor prognosis and in which more aggressive treatment should be carried out for the most indolent cases not to be overtreated or most aggressive tumors not to be left without proper treatment. In this sense, increasingly more centers are advising an individualized treatment adapted to the risk of tumor recurrence¹⁶.

The purpose of this study is to analyze PTMC treatment according to the risk of recurrence and long-term prognosis.

Methods

Study population

The population is composed of patients with histopathological diagnosis of PTMC (≤ 1 cm papillary

carcinoma) established in the period comprised between 1995 and 2015, treated according to the risk of recurrence in an endocrine surgery unit. A retrospective analysis of the database collected at the endocrine surgery unit is carried out.

Within the study population, those patients who meet the following inclusion criteria are selected: follow-up for at least 2 years, availability of histopathological samples on anatomical pathology department files, and compliance with the treatment agreed by the endocrine surgery committee based on the risk of recurrence.

Among the selected population, patients with thyroid surgery before PTMC surgery, presence of other synchronous malignant thyroid or extrathyroid pathologies, PTMC ectopic location (sublingual, thyroglossal cyst, struma ovary, etc.), or incomplete medical records are excluded from the study.

Assessment of PTMC recurrence risk

The risk of recurrence is evaluated according to the Latin American Thyroid Society (LATS) classification¹⁶:

- Very low recurrence risk: ≤ 1 cm unifocal tumor with no extension beyond the thyroid capsule and no lymph node or distant metastases.
- Low recurrence risk: ≤ 1 cm multifocal tumor, with no extension beyond the thyroid capsule or lymph node or distant metastases.
- High recurrence risk: tumor with lymph node/regional metastases, persistent disease, extracapsular invasion to locoregional tissues and structures, vascular invasion, distant metastases (M1), aggressive tumor histology (e.g., tall cell, columnar cell, insular types, etc., PTC), or ¹³¹I uptake outside the thyroid cell on first post-treatment scintigraphy.

Treatment adapted to recurrence risk

1) Surgical treatment

Surgical treatment depends on PTMC diagnosis. If diagnosis is clinical and preoperatively established,

the surgical technique is decided depending on PTMC ultrasound characteristics and on the presence of cervical adenopathies suspected of or positive for malignancy. If diagnosis is incidental on the thyroidectomy specimen in patients who are operated on for presumably benign thyroid pathology, whether initial surgical technique is sufficient or should be completed according to histopathological findings are then decided.

2) ¹³¹I treatment assessment

¹³¹I thyroid remnant ablation is carried out in patients who underwent total thyroidectomy, depending on the risk of recurrence, as long as there are no contraindications to its administration (allergy, pregnancy, and breastfeeding):

- In patients with very low risk of recurrence, ¹³¹I is not administered.
- In patients with low risk of recurrence, each case is individually evaluated, analyzing the risks and benefits of ¹³¹I administration. In patients of child-bearing age who want to have offspring, its administration is evaluated.
- In patients at high risk of recurrence, ¹³¹I is always administered.

3) Assessment of thyroid-stimulating hormone suppression therapy

Thyroid-stimulating hormone (TSH) suppression therapy is carried out with levothyroxine (LT4) according to the risk of recurrence, as long as it is not contraindicated (ischemic heart disease, atrial fibrillation, and osteoporosis):

- In patients with very low risk of recurrence, TSH suppression is not carried out.
- In patients with low risk of recurrence and no evidence of locoregional relapse or distant metastases, TSH suppression is carried out maintaining its values at between 0.4 and 1.0 mIU/L.
- In patients with high risk of recurrence, TSH suppression is carried out maintaining its values ≤ 0.1 mIU/L.

Criteria for cure and detection of persistence and relapse

1) Criteria for cure

Criteria for cure are regarded as being met after treatment when at 6 months:

- In patients undergoing lobectomy or total thyroidectomy with no ¹³¹I thyroid remnant ablation:

- There is no clinical evidence of active disease.
- Cervical ultrasound is normal.
- In patients undergoing total thyroidectomy with ¹³¹I thyroid remnant ablation:
 - There is no clinical evidence of active disease.
 - There are one or two negative ¹³¹I scans.
 - Thyroglobulin is < 2 ng/mL (after LT4 withdrawal or after stimulation with recombinant human TSH [rhTSH]) and anti-thyroglobulin antibodies are negative.
 - Cervical ultrasound is normal.

2) Disease persistence

Persistence is defined as the presence of clinical, biochemical, or radiological evidence of disease (ultrasound, computed tomography [CT], full-body ¹³¹I scintigraphy, or positron-emission tomography [PET]) within the first 6 months after surgery. In patients who undergo lobectomy, in whom thyroidectomy is completed within the first 6 months and a PTMC is detected, it is not considered as disease persistence, but as a multifocal PTMC treated with total thyroidectomy.

3) Disease relapse

Relapse is defined as the presence of clinical, biochemical, or radiological evidence of disease (ultrasound, CT, full-body ¹³¹I scintigraphy, or PET) from 6 months after surgery onwards. Three types are differentiated:

- Biochemical relapse: defined as any repeated thyroglobulin measurement > 2 ng/mL (stimulated with rhTSH or after TSH suppression therapy withdrawal), and it is considered only in patients who underwent total thyroidectomy and ¹³¹I thyroid remnant ablation.
- Locoregional recurrence: it is detected on imaging tests (ultrasound, scintigraphy, CT, or PET) and has to be confirmed by histopathological analysis after a fine-needle aspiration (FNA) procedure, biopsy, or surgery.
- Distant relapse: must be confirmed by histological analysis after performing a FNA, biopsy or surgery, or by whole-body ¹³¹I scintigraphy or PET scan.

Study variables

The following variables were analyzed:

- Sociopersonal: age and gender.
- Therapeutic: surgical technique (thyroidectomy and cervical lymphadenectomy), ¹³¹I thyroid remnant ablation and TSH suppression therapy.

- Histopathological: size, focality, laterality, histopathological variants, extracapsular invasion, resection margins, and metastatic adenopathies.
- Follow-up: risk of recurrence, persistence, relapse, overall survival, and disease-related mortality.

Statistical method

Data were collected in a database. For categorical variables, data are expressed by frequencies and percentages, and are compared using Pearson's Chi-square test or Fisher's exact test when appropriate. For continuous quantitative variables, data are expressed as the mean $\pm$ standard deviation. The Kaplan–Meier method was used to analyze overall survival and log-rank test for comparison between groups. $p < 0.05$ is considered to be statistically significant.

Results

Description of the series

Selection criteria were met by 161 patients. Mean age was 46.2 ± 13 years (16-81), and 80.7% ($n = 130$) were female. Eighty-seven cases (54%) were incidental, that is, diagnosed on histopathological analysis of patients operated on for presumably benign thyroid pathology. PTMC histopathological characteristics are detailed in table 1.

According to LATS classification, 65.2% ($n = 105$) of the tumors were of very low risk of recurrence, 17.4% ($n = 28$) of low risk of recurrence, and 17.4% ($n = 28$) of high risk of recurrence.

The number of thyroidectomies, lobectomies, and cervical lymphadenectomies that were performed based on the risk of recurrence is detailed in figure 1.

As for cervical lymphadenectomy, it was carried out more frequently in high-risk patients than in low- and very low-risk patients (57.1 vs. 7.1 vs. 3.8%, respectively; $p < 0.001$).

^{131}I administration according to the risk of recurrence is shown in figure 2. ^{131}I was administered to more patients at high risk of recurrence than to those at low and very low risk of recurrence (100 vs. 82.1 vs. 0%, respectively; $p < 0.001$).

All patients at high risk ($n = 28$) and low risk ($n = 28$) of recurrence received TSH suppression therapy with

Table 1. Papillary thyroid microcarcinoma histopathological characteristics

Histopathological variables	n (%)
Size (mm)	5.3 ± 3 (0.7-10)
Focality	
Unifocal	117 (72.7%)
Multifocal	44 (27.3%)
Laterality	
Unilateral	136 (84.5%)
Bilateral	25 (15.5%)
Histological subtypes	
Classic papillary	82 (51%)
Follicular	76 (47.2%)
Oncocytic	1 (0.6%)
Tall cell	1 (0.6%)
Solid	1 (0.6%)
Extracapsular invasion	
No	143 (88.8%)
Yes	18 (11.2%)
Resection margins	
Uncompromised	154 (95.7%)
Compromised	7 (4.3%)
Metastatic adenopathies	
No	146 (90.7%)
Yes	15 (9.3%)

LT4. Patients at very low risk of recurrence did not receive TSH suppression therapy.

PTMC prognosis

During a mean follow-up of 119.8 ± 65 months (24-271), there were no cases of disease persistence, but one recurrence (0.6%) did occur, which was produced at 96 months of follow-up in a 44-year-old woman with clinical diagnosis of PTMC, who underwent total thyroidectomy plus central-ipsilateral lymph node dissection. On histopathological analysis, a PTMC of the classic variant, unifocal, of 8 mm at its longest diameter, with minimal extracapsular invasion and with 3/11 adenopathies positive for malignancy was described (Fig. 3).

In patients who underwent lobectomy in whom thyroidectomy was not completed ($n = 11$), no relapses in the thyroid remnant were detected during a mean follow-up of 116.8 ± 58.5 months.

No significant differences were observed with regard to overall survival according to the risk of recurrence (very low risk 123.3 ± 6.2 months vs. low risk 121.1 ± 13.1 vs. high risk 120.4 ± 13.4 months; $p = 0.996$) (Fig. 4).

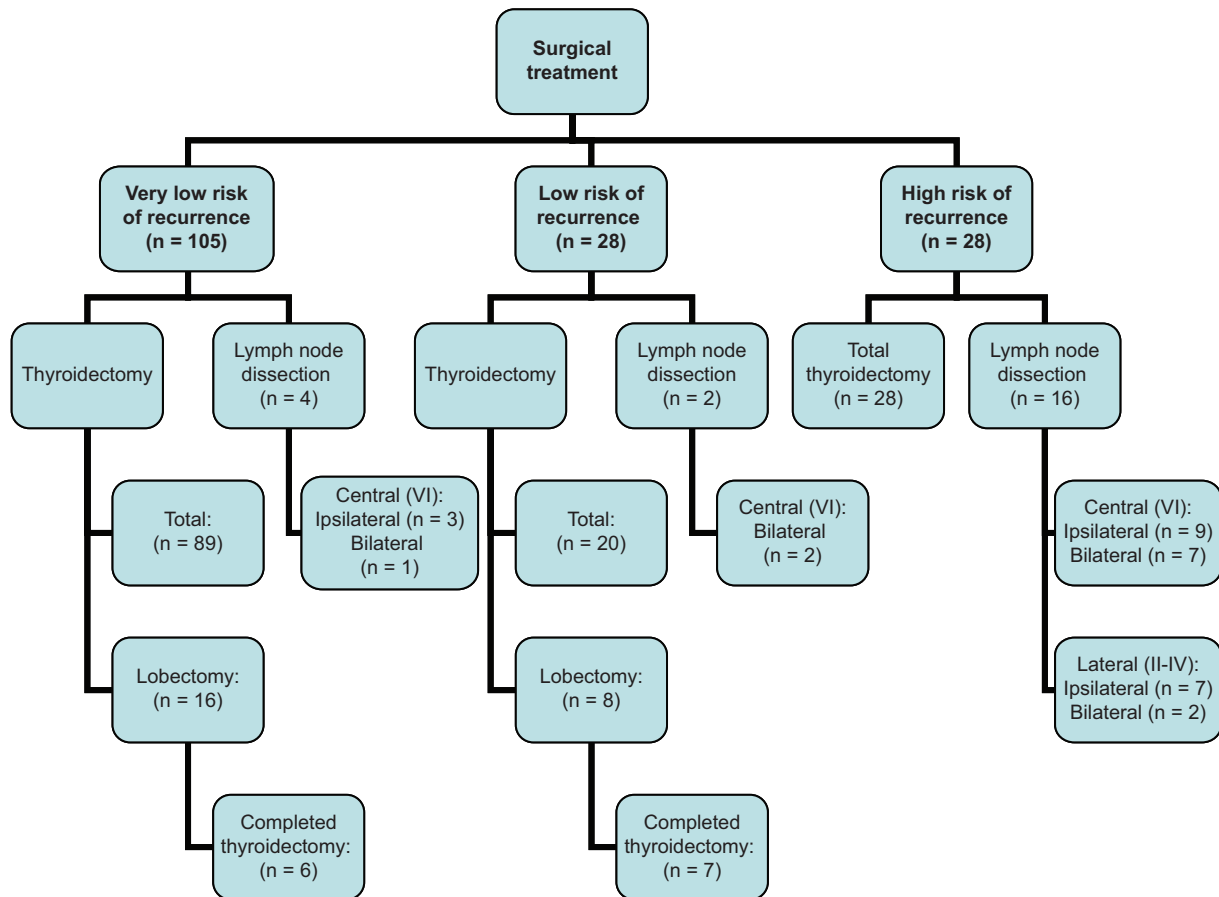


Figure 1. Surgical technique according to the risk of recurrence.

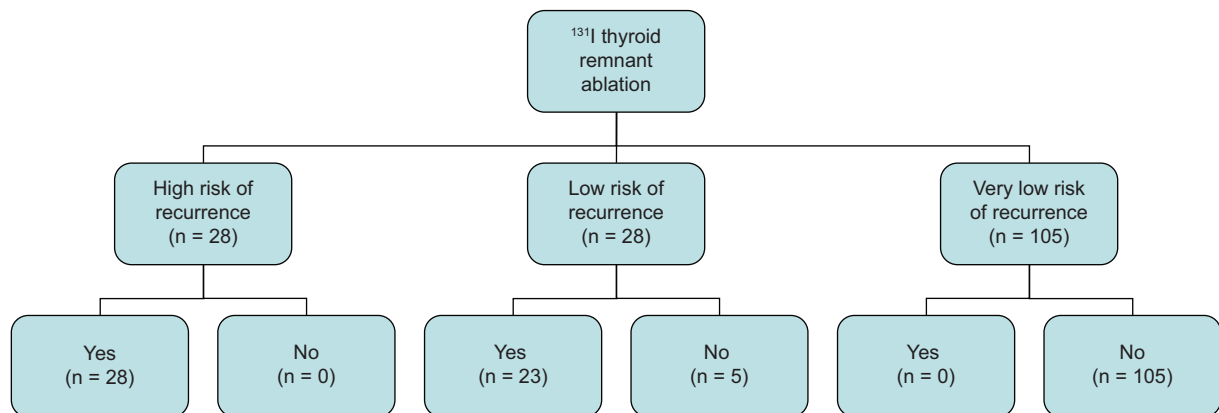


Figure 2. ¹³¹I thyroid remnant ablation according to the risk of recurrence.

Although there was no disease-related mortality, 3.1% (n = 5) of patients died during follow-up from causes unrelated to the disease.

When the factors associated with the presence of relapse were analyzed, no significant differences were found in any of the examined variables (Table 2).

Discussion

The increase in PTMC incidence in recent years², together with its generally favorable prognosis, has led to the establishment of appropriate treatment protocols for initial treatment not to be either too

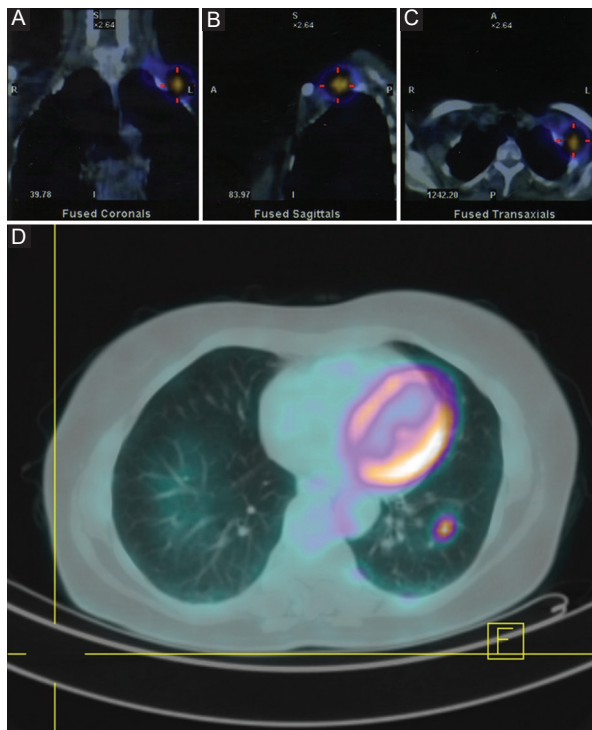


Figure 3. A-C: SPECT coronal, sagittal, and axial sections, in which more intense uptake is observed at left infraclavicular level, which is consistent with relapse on that location. D: PET axial section showing a pathological increase in glucidic metabolism (SUVmax of 6.1) on a 1.2 cm metastatic lesion at left lower lung lobe. SPECT: single photon-emission computed tomography.

Table 2. Factors associated with papillary thyroid microcarcinoma relapse

Histopathological variables	No relapse (n = 160)	Relapse (n = 1)	p
Age			
< 45 years	44.4% (n = 71)	100% (n = 1)	0.447
≥ 45 years	55.6% (n = 89)	0%	
Gender			
Females	80.6% (n = 129)	100% (n = 1)	1.000
Males	19.4% (n = 31)	0%	
Tumor size ≥8 mm			
No	75.6% (n = 121)	0%	0.248
Yes	24.4% (n = 39)	100% (n = 1)	
Focality			
Unifocal	72.5% (n = 116)	100% (n = 1)	1.000
Multifocal	27.5% (n = 44)	0%	
Laterality			
Unilateral	84.4% (n = 135)	100% (n = 1)	1.000
Bilateral	15.6% (n = 25)	0%	
Extracapsular invasion			
No	88.7% (n = 143)	0%	0.112
Yes	11.3% (n = 17)	100% (n = 1)	
Resection margins			
Uncompromised	95.6% (n = 153)	100% (n = 1)	1.000
Compromised	4.4% (n = 7)	0%	
Lymph node metastases			
No	91.2% (n = 146)	0%	0.093
Yes	8.8% (n = 14)	100% (n = 1)	

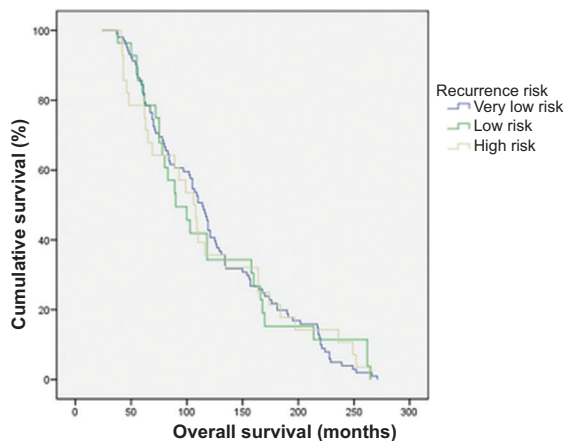


Figure 4. Overall survival according to recurrence risk.

aggressive or insufficient, thus minimizing post-surgical complications, persistence, relapse, and disease-related mortality.

Given that this is a retrospective cohort study, certain aspects that could give rise to several biases should be clarified. First of all, the patients analyzed

in the study are from a specific place, the Murcia Region (Spain). It should be also noted that the period the patients were selected in was long, from 1995 to 2015, and the diagnostic and therapeutic methods could therefore have varied. Diagnostic methods have barely changed since 1995, since by then, cervical ultrasound was already carried out, and if a thyroid nodule or cervical adenopathy was suspicious of malignancy, biopsy was performed by FNA and, depending on malignancy suspicion or confirmation on cytological analysis, surgery was carried out. There are also 54% of incidental cases, that is, those in which PTMC diagnosis was established based on histopathological analysis of samples from patients operated on for presumably benign thyroid pathology. It should only be added that, over the years, high-resolution cervical ultrasound has been introduced, which allows smaller nodules to be identified and better guiding the FNA procedure. As for PTMC treatment, there were no major changes in our hospital either during the time the study took place. In the cases of

PTMC with clinical diagnosis, total thyroidectomy is performed. In addition, central or lateral lymph node dissection, or both, is carried out depending on the presence of metastatic adenopathies (pre-operative diagnosis of a metastatic adenopathy by FNA biopsy or intraoperative diagnosis by freezing when there is high suspicion). Whenever a lateral cervical lymph node dissection is performed, central ipsilateral dissection is also carried out. In cases where diagnosis is incidental, whether initial surgical technique (lobectomy or total thyroidectomy) is sufficient or if it should be completed and is decided based on histopathological findings. Patients with PTMC at very low risk of recurrence are not administered treatments complementary to surgery; those at low risk of recurrence are administered ^{131}I individually assessing the risks and benefits, and TSH suppression therapy is implemented; and those at high risk of recurrence are always administered ^{131}I , and TSH suppression therapy is implemented. On the other hand, it should be noted that all patients diagnosed with PTMC were treated and subsequently followed on an outpatient basis until the end of the study, except for five who died during follow-up due to causes unrelated to the disease. Finally, to avoid information biases, patients with an incomplete medical record and those in whom data on the variables of interest were missing were excluded from the study, which reflects the appropriate validity of data.

The fact that PTMC prognosis is generally indolent does not always justify a little aggressive treatment (with no lymphadenectomy or ^{131}I thyroid remnant ablation). In the series herein presented, only 17.4% of PTMCs were of high recurrence risk, and the results provided in this study, therefore, support a treatment adjusted to the risk of recurrence¹⁶, with good results in terms of relapse and survival, with complex surgeries with lymphadenectomy, ablative treatment with ^{131}I , and TSH suppression therapy being avoided in most cases.

As for persistence, all patients met the criteria for a cure at 6 months and, therefore, had no disease persistence after initial surgical treatment. It should be taken into account, as in other studies¹⁷, that those patients who initially underwent lobectomy in whom thyroidectomy was completed within the first 6 months and had a PTMC detected on the contralateral lobe have not been considered as having local persistence, but rather the lesion has been regarded as part of initial surgery. As in this work, the persistence rates described in scientific literature are low, as in the work

by Kim et al.¹⁸, in which a persistence rate of 0.5% is described.

Regarding PTMC recurrence, two aspects should be taken into account. On the one hand, the follow-up time, since PTMCs can take time to relapse, as it occurred in our case. On the other hand, the criteria to define relapse are not homogeneous between series. This justifies the rather large fluctuation in the relapse percentages documented in the literature, which range from 0.4% to up to 19%^{1,12,17-34}. In the series herein presented, it was 0.6%, corresponding to a single patient from the group at high risk of recurrence, whose relapse took place at 8 years of follow-up. This low number of relapses is possibly due to the high number of incidental cases (which usually have better prognosis)^{1,21}, the high percentage of patients with very low or low risk of recurrence, and the more aggressive treatment of patients at high risk of recurrence, in whom more cervical lymphadenectomy procedures were carried out and ^{131}I was administered more frequently.

In this study, due to the presence of a single case of relapse, no factors associated with disease relapse have been identified. Possibly, a more aggressive treatment according to the risk groups has influenced on this fact. Among the independent risk factors for the development of PTMC recurrence described in scientific literature, clinical diagnosis, the male gender, age younger than 45 years, size > 5-8 mm according to the series, tumor foci diameters sum > 1 cm, absence of tumor capsule, multifocality, bilaterality, capsular invasion, extracapsular invasion, presence of metastatic adenopathies, number of metastatic adenopathies ≥ 4 , metastatic adenopathy ratio (metastatic lymph nodes/total isolated lymph nodes) > 0.44, absence of autoimmune thyroid diseases (absence of Graves' disease and Hashimoto's thyroiditis), solid histological pattern, stimulated thyroglobulin elevation, absence of metabolic therapy with ^{131}I , and follow-up longer duration stand out^{11,12,17-34}.

As for PTMC-associated mortality, a rate of 0-2.2% has been documented, depending on the series^{17,24,27,31,33}. Similarly, in this work, no patient died due to the disease during follow-up, which highlights PTMC good prognosis in the long term when appropriate treatment is implemented.

Conclusions

PTMC treated according to its risk of recurrence has a good long-term prognosis, with no persistence, with

a low percentage of recurrences and absence of disease-associated mortality.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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