

ORIGINAL ARTICLE

Multifocality of papillary thyroid carcinoma with low risk of recurrence: Prevalence, predictive markers, prognostic significance and initial surgical treatment



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KEYWORDS

Papillary thyroid carcinoma;
Multifocal tumour;
Predictive markers

Abstract

Background and objective: The impact of multifocality on the prognosis of patients with papillary thyroid cancer is relevant when considering the choice of initial surgical treatment by hemithyroidectomy or total thyroidectomy. The aim of the study is to determine the prevalence of multifocality in our setting, its predictive markers and the rates of persistence, recurrence and mortality associated with papillary thyroid cancer with a low risk of recurrence in order to infer the most appropriate initial surgical treatment.

Patients and method: Retrospective observational cross-sectional study of 85 total thyroidectomies.

Results: Prevalences: unifocal carcinoma: 68.2%; multifocal: 31.8%. Predictive markers of multifocality: multinodular ultrasound pattern (OR:17.069, 95% CI:2.989–97.454) and non-incidental finding (OR:7.569, 95% CI:2.363–24.242). In 66.6% of multifocal cases there was bilateral involvement, all of them had a bilateral multinodular ultrasound pattern. Multifocal cases received postoperative radioiodine more frequently ($p < 0.001$). During the follow-up of 95.5 ± 32.2 months there was one case of persistence and one of recurrence, both in the multifocal group (p:ns), at 12 and 71 months of follow-up. There was no mortality.

Conclusions: This is the first study in our country to estimate the prevalence of multifocality in papillary carcinoma with a low risk of recurrence and to show an excellent prognosis, with no differences compared to unifocal cases, considering that all cases have been treated with total thyroidectomy, but multifocal cases with radioiodine more frequently. Hemithyroidectomy could offer a similar prognosis to total thyroidectomy in cases with an ultrasound pattern of a single or unilateral multinodular nodule, but not in cases of bilateral multinodular thyroid.

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PALABRAS CLAVE

Carcinoma papilar de tiroides;
Tumor multifocal;
Marcadores predictivos

Multifocalidad del carcinoma papilar de tiroides con bajo riesgo de recurrencia: prevalencia, marcadores predictivos, significado pronóstico y tratamiento quirúrgico inicial

Resumen

Antecedentes y objetivo: El impacto de la multifocalidad sobre el pronóstico de pacientes con cáncer papilar de tiroides es relevante al considerar la elección del tratamiento quirúrgico inicial mediante hemitiroidectomía o tiroidectomía total. El objetivo del estudio es conocer en nuestro entorno la prevalencia de multifocalidad, sus marcadores predictivos y las tasas de persistencia, recurrencia y mortalidad asociadas al cáncer papilar de tiroides con bajo riesgo de recurrencia para inferir el tratamiento quirúrgico inicial más adecuado.

Pacientes y método: Estudio retrospectivo observacional transversal sobre 85 tiroidectomías totales.

Resultados: Prevalencias: carcinoma unifocal: 68,2%; multifocal: 31,8%. Marcadores predictivos de multifocalidad: patrón ecográfico multinodular (OR:17,069, IC al 95%:2,989-97,454) y hallazgo no incidental (OR:7,569, IC al 95%:2,363-24,242). El 66,6% de los casos multifocales tuvo afectación bilateral, todos con un patrón ecográfico multinodular bilateral. Los casos multifocales recibieron radioyodo postquirúrgico más frecuentemente ($p < 0,001$). Durante el seguimiento de $95,5 \pm 32,2$ meses hubo un caso de persistencia y uno de recurrencia, ambos del grupo multifocal (p :ns), a los 12 y 71 meses de seguimiento. No hubo mortalidad.

Conclusiones: Es el primer estudio en nuestro país que cifra la prevalencia de multifocalidad del carcinoma papilar con bajo riesgo de recurrencia y demuestra un excelente pronóstico, sin diferencias respecto a los unifocales, considerando que todos han sido tratados con tiroidectomía total, aunque los multifocales con radioyodo más frecuentemente. La hemitiroidectomía podría ofrecer un pronóstico similar a la tiroidectomía total en los casos con patrón ecográfico de nódulo único o multinodular unilateral, pero no en los casos de tiroides multinodular bilateral.

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Introduction

Thyroid carcinoma ranks ninth in cancer frequency worldwide, representing 3.1% of all cancers, is the fifth leading cause of cancer in women, and is the most frequent endocrine neoplasm.¹⁻⁵ Its incidence rate ranges between 1998 and 2012 in Spain was 16.2 cases per 100,000 person-years in women and 4.5 cases per 100,000 person-years in men. In recent decades, there has been a notable increase related to a higher number of diagnoses facilitated by a greater frequency of use of high-resolution imaging modalities, such as ultrasound.⁶⁻⁹

The most frequent histological type of thyroid cancer is papillary, accounting for 85–90% of all cases.^{3,5,8-10} Although up to 30% may have recurrences and distant metastases, its survival prognosis is very good, with a mortality rate of less than 5%. For this reason, especially in cases of low recurrence risk, which also represent most new diagnoses, less aggressive treatment with fewer complications, such as hemithyroidectomy instead of total thyroidectomy, is increasingly proposed.^{3,5,11-14} To consolidate this procedure, it is important to know if, as frequently occurs, the tumor is multifocal, as this circumstance can be pre-

dictive of persistence, recurrence, and survival. On this basis, some authors recommend more extensive surgical treatment, even supplemented with radioiodine, and more intensive postoperative monitoring in cases of multifocal papillary carcinoma.^{1,3,5,7,8,10,15-19}

The prevalence of multifocality of papillary thyroid carcinoma described in the literature ranges from 18 to 87%.^{2,5-8,10,14-22} This is such a wide percentage range that it is necessary to know the specific figure in each territory. Similarly, data on its influence on persistence, recurrence, and mortality are inconsistent.^{2,5,6,8,10,14,16,18,19} In our environment, there is no data on this. This knowledge would help make therapeutic decisions in cases of papillary carcinoma with low recurrence risk, allowing us to assess when a hemithyroidectomy could be considered with the same prognostic outcome as a total thyroidectomy, but with fewer postoperative complications.

The objective of this study is to determine in our setting the prevalence of multifocality in cases of papillary thyroid carcinoma with low recurrence risk, evaluate predictive markers, and determine the rate of persistence, recurrence, and associated mortality to infer the most appropriate initial surgical treatment.

Material and methods

We conducted a retrospective observational study in a single hospital center to compare cases of unifocal tumors with multifocal tumors in patients with papillary thyroid carcinoma with low recurrence risk. Adult patients who underwent total thyroidectomy in one or two stages (with an interval of less than 6 months to be considered part of the initial surgical treatment)² between 2011 and 2020, with the anatomopathological diagnosis of papillary thyroid carcinoma meeting the low recurrence risk criteria previously defined in the literature¹¹ and with a minimum follow-up of 4 years after the initial surgical treatment, were included. Cervical lymphadenectomy concomitant with thyroidectomy was performed when there was radiological evidence, with or without cytological confirmation, of metastatic involvement. With some exceptions, radioiodine treatment was administered 1–1.5 months after thyroidectomy to patients with carcinoma larger than 1 cm, those with multifocal tumors, and/or metastatic lymphadenopathy. The study was approved by the Clinical Research Ethics Committee of the Fundació Assistencial Mútua de Terrassa.

Patients with a history of cervical radiotherapy, radioiodine treatment for hyperthyroidism, thyroid surgery, and a history of papillary thyroid carcinoma in two or more first-degree relatives²³ were excluded due to their possible influence on carcinoma multifocality. Patients with tumors of the non-invasive follicular neoplasm type with papillary-like nuclear features who had been previously diagnosed with non-invasive encapsulated follicular variant papillary carcinoma were also excluded.

The variables collected from the medical history were: age, sex, weight, height, and body mass index (BMI) at the time of intervention, preoperative thyroid ultrasound pattern (single or multiple nodular thyroid, unilateral or bilateral), preoperative blood test values of thyroid-stimulating hormone (TSH), free thyroxine (T4I), thyroid antibodies (anti-thyroperoxidase and/or anti-thyroglobulin), the indication for thyroidectomy (clinical suspicion of carcinoma: indeterminate or malignant cytology – Bethesda III, Bethesda IV, Bethesda V, or Bethesda VI–, or growth in the previous 6–12 months > 50% of one or more diameters if the nodule is <10 mm, or >20% in two or more diameters if >10 mm with Bethesda I or Bethesda II cytology; cervical compressive symptoms; hyperthyroidism), histological type (classic papillary or follicular variant papillary), number of foci, size and location of carcinomas in the thyroidectomy specimen, and whether metastatic cervical lymphadenopathy was found, the dose of radioiodine received post-thyroidectomy, postoperative analytical values of TSH, T4I, thyroglobulin (TG), and anti-thyroglobulin antibodies, the findings of imaging modalities performed, and the follow-up time.

Based on the preoperative ultrasound examination, the preoperative ultrasound pattern was established. Since the appearance of microcarcinomas is relatively frequent in the context of patients with papillary thyroid carcinoma, multinodular thyroid was considered when more than one thyroid nodule was observed on ultrasound, regardless of size, with the exception of purely cystic nodules without a visible solid portion, which were not taken into account.

The main thyroid lobe was established where the largest carcinoma was found. The multinodular thyroid pattern was classified as unilateral when lesions were present only in one thyroid lobe, and bilateral when they were observed in both lobes. In general, cytological study of thyroid nodules was performed on those in which ultrasound suspicion of malignancy was observed and those that were dominant due to their substantially larger size than the others.

Patients were grouped according to the number of carcinomas found in the anatomopathological study into cases of unifocal carcinoma or multifocal (uni or bilateral) when more than one focus of carcinoma was present simultaneously in the thyroidectomy specimen, regardless of location.^{2,8,14}

The carcinoma was established as an incidental finding when the indication for thyroidectomy did not include the clinical suspicion of carcinoma previously defined, and when, although the indication for thyroidectomy was due to suspicion of carcinoma, the histopathological examination did not confirm it but found an unsuspected carcinoma.

The main evaluation variables were:

- Prevalence of cases with unifocal and multifocal tumors.
- Disease persistence rate at the end of the first year of follow-up in unifocal and multifocal cases.
- Disease recurrence rate in unifocal and multifocal cases.
- Carcinoma-associated mortality rate in unifocal and multifocal cases.

The secondary evaluation variable was the possible predictive markers associated with multifocality.

Complete remission of the disease was considered when the following criteria were met^{11,24}:

- Imaging modalities (131I Na or 123I Na scan and cervical ultrasound) without lesions suggestive of local or distant neoplasm, and
- Serum thyroglobulin, measured beyond 4 weeks after initial treatment, under thyroxine treatment, at undetectable levels according to the assay applied in each period, or <0.2 ng/mL, and
- Serum thyroglobulin when stimulated, by suppression of levothyroxine treatment for at least 3 weeks or instead by administration of recombinant human TSH, measured beyond 4 weeks after initial treatment, at undetectable levels according to the assay applied in each period or less than 1 ng/mL if radioiodine was applied in addition to total thyroidectomy, and less than 2 ng/mL if radioiodine was not applied, and
- Absence of anti-thyroglobulin antibodies.

Persistence of the disease was considered if complete remission was not achieved after the first year of initial surgical treatment, and recurrence of the disease was considered when one or more of the previous criteria for complete remission were not met after a period of complete remission. Dynamic risk stratification into excellent response to treatment, incomplete biochemical response, incomplete structural response, or indeterminate response was performed as described in the literature.^{11,24}

Furthermore, we conducted a descriptive analysis of the collected variables. The univariate analysis of differences

Table 1 Distribution of unifocal and multifocal papillary carcinomas in the thyroid lobes.

Type	n	Affected Lobes	Main Lobe (Unifocal)	Main Lobe (Multifocal)	Contralateral Lobe (Unifocal)	Contralateral Lobe (Multifocal)
Unifocal	58	Unilateral	58	–	–	–
Multifocal	27	Unilateral	–	9	–	–
		Bilateral	11	–	8	3
			–	7	3	4

between continuous and categorical variables was analyzed with the Student's *t*-test or Mann-Whitney U test, as appropriate; the relationship between categorical variables, with the chi-square or Fisher's F test, and the relationship between continuous variables, with Pearson's or Spearman's correlation coefficient. A forward stepwise binary logistic regression analysis was performed to investigate the predictive variables of multifocality, including as independent variables those clinically relevant variables that had statistical significance in the univariate analysis. Independent variables with lower statistical significance were eliminated from the model when they were correlated with another independent variable. The predictive validity of the logistic regression model was verified by evaluating calibration with the Hosmer-Lemeshow test. Internal reproducibility was checked by generating 1000 samples with the bootstrapping technique. Statistical significance was set at $p < 0.05$ (2-tailed). Statistical analysis was performed with IBM SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 85 patients were included, 67 (78.8%) women and 18 (21.2%) men, with a mean age of 49.4 ± 14.8 years. Of these, 58 (68.2%) had unifocal carcinoma and 27 (31.8%) multifocal carcinoma. Their distribution in the thyroid lobes is shown in Table 1. We highlight that 18 of the 27 multifocal cases (66.6%) were bilateral: 11 with unifocal tumor in the main lobe and 7 with multifocal involvement of the main lobe.

The characteristics of the unifocal and multifocal groups are shown in Table 2. All patients had tumors <4 cm. In the comparison between unifocal and multifocal cases, a higher frequency of the solitary nodule ultrasound pattern in unifocal cases (29.3% vs 7.4%, $p = 0.02$) and also a higher frequency of incidental finding (65.5% vs 40.7%, $p = 0.028$) are highlighted.

Only one case of neoplasm persistence was recorded at the end of the first year since initial surgical treatment, in the form of incomplete biochemical response, in a patient with an ultrasound multinodular thyroid, carrying a 16 mm multifocal and bilateral follicular variant papillary carcinoma diagnosed incidentally, who received a second dose of radioiodine, achieving complete remission (excellent response to treatment). There was only one case of recurrence at 71 months in another patient with an ultrasound multinodular thyroid, in the form of indeterminate

response, carrying a 15 mm multifocal and bilateral classic papillary carcinoma diagnosed preoperatively by cytology and who is under active follow-up. Mortality due to neoplasm was zero.

In the logistic regression (Table 3), the multinodular ultrasound pattern and the non-incidental finding of carcinoma were confirmed as predictors of multifocality. The model correctly classified 76.5% of the subjects. The distribution of unifocal or multifocal and unilateral or bilateral involvement of cases according to preoperative ultrasound pattern and incidental or non-incidental finding of carcinoma is shown in Table 4. We highlight that all cases with a solitary thyroid nodule ultrasound pattern with incidental or non-incidental finding of carcinoma were unilateral, although two of the 16 non-incidental cases were multifocal in the main lobe. In these two cases with preoperative ultrasound of a solitary thyroid nodule, the anatomopathological examination of the specimen showed multifocal carcinoma of 7 and 0.5 mm in one case and 23 and 1 mm in the other. Cases with a multinodular thyroid ultrasound pattern had 17.4% or 50% bilateral involvement depending on whether the finding was incidental or not, respectively, but in all cases with bilateral involvement, the multinodular ultrasound pattern was bilateral, whether incidental or non-incidental (Table 5).

Discussion

We have reviewed 85 cases of total thyroidectomy, in which a papillary carcinoma that met the characteristics of low recurrence risk¹¹ was found, to evaluate the prevalence of unifocal and multifocal cases, identify predictive markers of multifocality, and assess whether multifocal cases had a worse prognosis than unifocal cases. With this, we aimed to obtain epidemiological data in our environment to consider in which cases the initial surgical treatment could be a hemithyroidectomy with the same prognostic guarantees as a total thyroidectomy.

Various studies have reported between 18% and 87% of papillary carcinoma cases appearing as multiple nodules within the gland^{2,5–8,10,14–22,25,27}; in our study, it was 31.8%. This wide percentage range may be due to different environmental factors occurring in each territory, but it may also be related to the origin of the tumor foci. It is debated whether multifocality is the result of multiple independent tumors of polyclonal origin (multicentricity) or of intraglandular lymphatic extension of an

Table 2 Patient characteristics according to unifocal or multifocal carcinoma.

	Total	Unifocal Carcinoma (n = 58)	Multifocal Carcinoma (n = 27)	p-value
No. of cases, n (%)	85 (100)	58 (68.2)	27 (31.8)	
Sex				
Women, n (%)	67 (78.8%)	48 (82.8%)	19 (70.4%)	ns
Men, n (%)	18 (21.2%)	10 (17.2%)	8 (29.6%)	
Age (mean $\pm$ SD, years)	49.4 $\pm$ 14.8	48.5 $\pm$ 14.8	51.2 $\pm$ 14.9	ns
> 45 years old, n (%)	55 (64.7%)	36 (62%)	19 (70.4%)	ns
Weight (mean $\pm$ SD, kg)	72.6 $\pm$ 15.4	70.5 $\pm$ 15	77 $\pm$ 15.6	ns
BMI (mean $\pm$ SD, kg/m ²)	27.1 $\pm$ 4.96	26.43 $\pm$ 4.54	28.52 $\pm$ 5.58	ns
Preoperative TSH (mIU/L)	2.33 $\pm$ 2.95	2.04 $\pm$ 1.75	2.92 $\pm$ 4.49	ns
Preoperative T4I (ng/dL)	1.22 $\pm$ 0.39	1.24 $\pm$ 0.44	1.19 $\pm$ 0.24	ns
Positive antithyroid antibodies	15 (17.6%)	9 (15.5%)	6 (22.2%)	ns
Ultrasound Pattern				
Single nodule	19 (22.3%)	17 (29.3%)	2 (7.4%)	0.02
Multiple nodules	66 (77.7%)	41 (70.7%)	25 (92.6%)	
Clinical suspicion of cancer	48 (56.4%)	32 (55.2%)	16 (59.3%)	ns
Incidental finding	49 (57.6%)	38 (65.5%)	11 (40.7%)	0.028
Histopathological Data				
Right main thyroid lobe	63 (74.1%)	41 (70.7%)	19 (70.4%)	ns
Multiple foci in main lobe	15 (17.6%)	0 (0%)	16 (59.3%)	<0.001
Size of main focus (mm)	12.81 $\pm$ 12.24	11.7 $\pm$ 11.7	15.1 $\pm$ 13.2	ns
Main focus > 10 mm	33 (38.8%)	19 (32.7%)	14 (51.8%)	ns
Total number of foci	1.72 $\pm$ 1.41	1 $\pm$ 0	3.26 $\pm$ 1.68	<0.001
Lymphocytic thyroiditis	23 (27.1%)	16 (27.6%)	7 (25.9%)	ns
Metastatic lymph nodes	7 (8.2%)	4 (6.9%)	3 (11.1%)	ns
Main Focus Histology				
Classic papillary	61 (71.8%)	42 (72.4%)	19 (70.4%)	ns
Follicular variant	24 (28.2%)	16 (27.6%)	8 (29.6%)	
Different histologies	8 (9.4%)	–	8 (29.6%)	–
Postoperative RAI Therapy				
Patients	56 (65.9%)	31 (53.4%)	25 (92.6%)	0.001
RAI dose (mCi)	65.5 $\pm$ 30.7	60.8 $\pm$ 26.8	71.4 $\pm$ 34.6	ns
1-Year Follow-up				
Complete remission	84 (98.8%)	58 (100%)	26 (96.3%)	ns
Persistent disease	1 (1.2%)	0 (0%)	1 (3.7%)	
Post 1-Year Follow-up				
Persistence	0 (0%)	0 (0%)	0 (0%)	ns
Recurrence	1 (1.2%)	0 (0%)	1 (3.7%)	
Mortality	0 (0%)	0 (0%)	0 (0%)	
Follow-up time (months)	95.5 $\pm$ 35.2	99 $\pm$ 35.6	87.9 $\pm$ 33.8	ns

SD, standard deviation; BMI, body mass index; RAI, radioactive iodine.

Table 3 Variables independently associated with multifocal papillary carcinoma in a binary logistic regression model (vs unifocal cases).

Significant independent variables	β coefficient	Standard error (β)	p-value	Odds Ratio	95% Confidence interval
<i>Multifocal Carcinoma</i>					
Multinodular ultrasound pattern	2.837	0.889	0.001	17.069	2.989–97.454
Non-incidental finding	2.024	0.594	0.001	7.569	2.363–24.242
Constant	–4.001	0.948	<0.001	0.018	–

Table 4 Distribution of unifocal or multifocal and unilateral or bilateral involvement in papillary carcinoma cases according to ultrasound pattern and whether the finding was incidental.

Ultrasound pattern	Incidental finding	n	Unifocal	Multifocal	Unilateral	Bilateral
Solitary Nodule	Yes	3	3 (100%)	0 (0%)	3 (100%)	0 (0%)
	No	16	14 (87.5%)	2 (12.5%)	16 (100%)	0 (0%)
Multinodular	Yes	46	35 (76.1%)	11 (23.9%)	38 (82.6%)	8 (17.4%)
	No	20	6 (30%)	14 (70%)	10 (50%)	10 (50%)

Table 5 Patients with Multinodular Thyroid Ultrasound Pattern. Distribution of Unifocal or Multifocal and Unilateral or Bilateral Involvement According to Whether the Finding Was Incidental and the Ultrasound Pattern Was Unilateral or Bilateral.

Incidental finding	Multinodular ultrasound pattern	n	Unifocal n (%)	Multifocal n (%)	p-value	Unilateral n (%)	Bilateral n (%)	p-value
Yes	Unilateral	3	3 (100%)	0 (0%)	ns	3 (100%)	0 (0%)	ns
	Bilateral	43	32 (74.4%)	11 (25.6%)		35 (81.4%)	8 (18.6%)	
No	Unilateral	5	3 (60%)	2 (40%)	ns	5 (100%)	0 (0%)	0.01
	Bilateral	15	3 (20%)	12 (80%)		5 (33.3%)	10 (66.7%)	

original tumor.^{4,5,8,18,20,28} We speculate that the main or only etiopathogenesis is multicentricity, given that multifocality is a characteristic of papillary carcinoma and not of other varieties of carcinoma that occur in the thyroid, and that lymphatic ganglion involvement is often scarce in cases of papillary carcinoma with low recurrence risk, even if they are multifocal.^{2,5,6,8,10,16-19,21} This phenomenon of multicentricity could be promoted by the paracrine effects of a substance generated by the original tumor and modulated by the environment of each area. Even those cases where the multiple foci have a different histology (about 30% of multifocal cases) could fit into this hypothesis, if the already known situation of a heterogeneous distribution of mutated genes²⁸ occurs, giving rise to different histopathological variants promoted under the same paracrine effect.

Regarding the identification of predictive factors of multifocality, in the meta-analysis by Zhang et al.⁴ on 9665 patients, none were found. In a different meta-analysis of 12 studies, it was observed that tumor size > 1 cm had an OR of 2.75 associated with multifocality.⁸ In the series by Markovic et al.¹⁸ on 153 patients with 28% multifocal cases, age greater than 45 years and dominant tumor size > 4 cm were associated with a higher incidence of multifocality. In the study by Wang et al.,¹⁷ conducted in 11 centers in 6 countries including 2638 patients, neither age nor tumor size were predictive of multifocality. Sapuppo et al.,⁵ on 2814 cases of low-risk papillary carcinoma, found that multifocal cases occurred preferentially in men, at an older age (46.4 vs 44.5 years), with smaller tumors and with greater cervical ganglion involvement. In our study, we have not found that age, sex, main focus size, or the presence of metastatic lymphadenopathy, in addition to other variables collected in Table 2, were predictors of multifocality. In contrast, multifocality was

associated with a more frequent multinodular thyroid pattern on preoperative ultrasound and a lower frequency of incidental finding, possibly because it was more evident due to having a greater number of neoplastic foci. These predictive markers have not been considered in the previously cited studies, although they are clinically considered relevant when evaluating patients with papillary thyroid carcinoma.

A debate that has persisted for some decades focuses on what should be the extent of the initial surgery in papillary thyroid carcinoma. In cases of low recurrence risk, whether microcarcinomas or not, where hemithyroidectomy is recommended, the question is whether possible multifocality has an impact on prognosis.^{1,2,26,27} There is controversy on whether multifocal forms, which are often associated with greater extrathyroidal extension with greater locoregional ganglion involvement at diagnosis, even in the case of microcarcinomas, can confer a higher rate of persistence, recurrence, and mortality, so in that case, they would be candidates for total thyroidectomy instead of hemithyroidectomy.^{2,5,6,8,10,14,16,18,19} In the meta-analysis by Joseph et al.⁸ on 178,550 patients, multifocality resulted in greater recurrence. In the series by Harries et al.²² on 849 lobectomies, the recurrence and mortality rate at nearly 5 years of follow-up was similar between multifocal and unifocal cases. When total thyroidectomy is performed and subsequent radioiodine treatment is administered, the prognosis has the lowest rates of recurrence, distant metastasis, and mortality.^{5,15,25} If total thyroidectomy is performed without subsequent radioiodine treatment, the recurrence rate and mortality may be higher in cases of multifocality.¹⁸ In other studies of patients with low-risk papillary carcinoma, those treated with hemithyroidectomy had a higher rate of locoregional recurrences than those who underwent total thyroidectomy, supposedly due to residual contralateral

eral neoplastic involvement inadvertently left behind.^{1,7,12} In the meta-analysis by Kim et al.³ on 33,976 patients, multifocality is related to a higher recurrence rate, more frequent when the main tumor is >10 mm, the number of foci is >2, and patients are older, without higher mortality, but it is not specified whether patients were treated with total thyroidectomy and radioiodine. On the other hand, in the multicenter study by Wang et al.,¹⁷ the higher recurrence rate in the multifocal group ceased to be significant when the model was adjusted for other confounding variables, and there was no increase in distant metastasis or mortality either. In the series by Geron et al.²¹ on 1039 patients followed for 10.1 years, cases with multifocal disease had greater initial extension of the neoplasm, a higher percentage of persistence at the first year of follow-up, subsequent recurrences, and mortality. However, multifocality did not make a difference in recurrence or mortality when these were adjusted for confounding variables. In the study by Feng et al.¹⁹ on 635 patients, 226 with hemithyroidectomy and 409 with total thyroidectomy, multifocality was associated with a higher risk of recurrence; the effect of surgical extension or administration of radioiodine treatment was not analyzed. In the meta-analysis by Zhang et al.,⁴ multifocality was associated with greater initial extension of the neoplasm and a higher rate of persistence and recurrence, but not all patients underwent total thyroidectomy, and it is also unclear whether these patients received radioiodine treatment. In the meta-analysis by Cui et al.,¹⁰ which included 41,616 patients, multifocality was found to be a risk factor for extrathyroidal extension, lymphovascular invasion, cervical lymph node metastasis, distant metastasis, and greater recurrence, but not greater mortality. In the series by Cho and Kim¹³ on 1684 hemithyroidectomies, multifocality was not associated with a worse prognosis during a 7-year follow-up, but it was associated with greater ganglion involvement. In the recent review by Ai et al.²⁹ on 9387 multifocal papillary microcarcinomas, the survival of patients treated with total thyroidectomy was compared with those treated with hemithyroidectomy, without finding differences. We could summarize that with 8–10 year follow-ups, the recurrence rate in papillary thyroid cancer with low recurrence risk ranges from 1% to 10%, and the mortality rate, from 0% to 4%, probably related to multifocality, tumor size, treatment with total thyroidectomy or hemithyroidectomy, and postoperative radioiodine.^{11,12,14,24} When total thyroidectomy is performed and then radioiodine treatment is administered, 10-year survival in low-risk recurrence cases is 98–99%, and recurrences are 1–3%.¹¹ In our study, with a mean follow-up of almost 8 years, the persistence rate at the end of the first year was 1 case (1.2%), and the recurrence rate was 1 case (1.2%), both in the multifocal group, and the mortality rate was 0%. It should be considered that all patients were treated with total thyroidectomy, and that multifocal cases received complementary radioiodine treatment almost entirely, more frequently than unifocal tumor cases, which may have contributed to initial complete remission and may have also minimized recurrences. We highlight that, in our series, all cases of carcinoma with a solitary thyroid nodule ultrasound pattern were unilateral, both those found incidentally and the two multifocal cases found non-incidentally, where the second tumor was not appreciated

on ultrasound, probably due to its small size, 1 and 0.5 mm. On the other hand, a considerable percentage (27%) of cases with multinodular thyroid were bilateral carcinomas; all of them had a multinodular ultrasound pattern with bilateral lesions. Of note, multifocality has been a previously recognized predictive factor of bilaterality,^{7,14,15,20,25,27} and that a recent study shows that ultrasound assessment using the ACR TI-RADS criterion underestimates malignancy in the contralateral lobe.³⁰ Therefore, hemithyroidectomy could have the same prognostic guarantees as total thyroidectomy in cases of a solitary thyroid nodule ultrasound pattern, both in the case of an incidental finding of unifocal papillary carcinoma and if it is non-incidentally and multifocal, if it meets the low recurrence risk criteria, since this procedure could completely eradicate the tumor just like total thyroidectomy. In contrast, hemithyroidectomy could offer a worse prognosis in many cases with a bilateral multinodular thyroid ultrasound pattern, with incidental or non-incidentally findings of papillary carcinoma, due to residual tumor left in the contralateral lobe.

The study has limitations that should be taken into consideration. It was conducted in a single hospital center, which could lead to selection bias. Ultrasound evaluation in the early years was performed with equipment with lower image resolution, which may have overlooked the appreciation of some lesions. The follow-up period may have been insufficient to detect all cases of recurrence and mortality. Lymphadenectomy was performed only in patients where involvement was suspected, which may have underestimated the true prevalence of ganglion extension and, therefore, the persistence and recurrence rate. The finding of multifocality was probably related to the adequacy of the thyroid sample, the thickness of the cross-section, and the pathologist's interpretation, as has been cited on other occasions,^{7,10,14,18,19,22} factors that we have not been able to control. The inference we make about the initial surgical treatment of papillary thyroid carcinoma with low recurrence risk should be verified in future studies.

In conclusion, in patients with papillary thyroid carcinoma with low recurrence risk treated with total thyroidectomy, we have found a prevalence of multifocal tumors of 31.8%, associated with a multinodular ultrasound pattern and diagnosed less frequently incidentally than unifocal tumors. Their prognosis was excellent and similar to that of unifocal cases, which may have been influenced by a higher frequency of postoperative radioiodine treatment in multifocal cases. Therefore, total thyroidectomy associated with postoperative radioiodine treatment is very effective for cases of multifocal papillary thyroid carcinoma with low recurrence risk. Since all cases with a solitary thyroid nodule ultrasound pattern were unilateral, and a significant percentage of cases with a multinodular thyroid ultrasound pattern in both thyroid lobes showed bilateral involvement, hemithyroidectomy could be relegated to those cases with a single thyroid nodule or unilateral multinodular ultrasound pattern, whether unifocal papillary carcinoma has been diagnosed incidentally or if it is a unilateral multifocal carcinoma found non-incidentally, with low recurrence risk characteristics, if there are no other conditions for which total thyroidectomy is preferable, such as tumor size >4 cm, a history of familial papillary carcinoma or cervical radiotherapy, and extrathyroidal extension.

CRedit authorship contribution statement

Each author has materially contributed to the research and preparation of the article. Specifically: Luis García Pascual: conception and design of the study, acquisition and analysis of data, interpretation of results, writing of the draft, and approval of the final version.

Andreu Simó-Servat, Carlos Puig-Jové, and Lluís García-González: conception and design of the study, interpretation of results, critical review, and approval of the final version.

Ethical considerations

Protection of People and Animals. The authors declare that no experiments with humans or animals have been carried out in this research.

Data Confidentiality. The authors declare that they have complied with the protocols of their workplace for the publication of patient data.

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Declaration of competing interest

None declared.

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