



Papillary thyroid microcarcinoma: is selection suitable for active surveillance protocol?

Microcarcinoma papilar de tiroides: ¿es adecuada la selección para protocolo de vigilancia activa?

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Abstract

Introduction. Papillary thyroid microcarcinomas are tumors up to 10 mm in greatest diameter. Its treatment is the subject of debate, and it is proposed from clinical follow-up to early surgical intervention. This aim of the study was to identify risk factors related to lymph node involvement, which allow a better selection of patients in our setting, in whom immediate surgical management or active surveillance is proposed, in accordance with the classification of risk of progression.

Methods. Ambispective analytic cohort study that included patients with papillary thyroid microcarcinoma who underwent thyroidectomy and central dissection. The population was characterized and a multivariate logistic regression analysis was performed to define preoperative factors associated with lymph node involvement. Additionally, the eventual assignment to progression risk groups, according to the Miyauchi criteria, and their nodal state.

Results. 286 patients with papillary thyroid microcarcinoma were included. Among them, 48.9% had lymph node disease, from which 33.5% had a significant lymph node disease that increased their relapse risk classification. Of the latter, 59.5% could have had a conservative treatment, under Miyauchi's criteria. For ages < 55 years old, suspect nodes in ultrasound and nodules > 5 mm were identified as related to significant lymph node involvement.

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Discussion. Immediate surgical management appears to be an appropriate option for patients with suspected lymph node involvement on preoperative ultrasound, patients younger than 55 years and nodules larger than 5 mm. It is possible that the current criteria for defining active surveillance do not adequately select patients in our setting.

Keywords: lymphatic metastasis; thyroidectomy; neck dissection; thyroid cancer; papillary.

Resumen

Introducción. Los microcarcinomas papilares de tiroides son tumores de hasta 10 mm en su diámetro mayor. Su tratamiento es sujeto de debate, y se propone desde seguimiento clínico, hasta intervención quirúrgica temprana. Este estudio buscó identificar factores de riesgo relacionados con compromiso ganglionar, que permitan una mejor selección de los pacientes en nuestro medio, en quienes se propone manejo quirúrgico inmediato o vigilancia activa, en consonancia con la clasificación del riesgo de progresión.

Métodos. Estudio de cohorte analítica ambispectiva que incluyó pacientes con microcarcinoma papilar de tiroides llevados a tiroidectomía más vaciamiento central. Se caracterizó la población y se realizó un análisis de regresión logística multivariado para definir factores preoperatorios asociados al compromiso ganglionar. Adicionalmente, se evaluó de manera retrospectiva la eventual asignación a grupos de riesgo de progresión, según los criterios de Miyauchi, y su comportamiento respecto al estado nodal.

Resultados. Se incluyeron 286 pacientes. El 48,9 % presentó compromiso ganglionar, y de estos, el 33,5 % presentó compromiso ganglionar significativo, que modificó su clasificación de riesgo de recaída. De estos últimos, el 59,5 % hubiesen sido manejados con vigilancia activa, según los criterios propuestos por Miyauchi. Se identificó que la edad menor de 55 años, los ganglios sospechosos en la ecografía y los nódulos mayores de 5 mm, se relacionan con compromiso ganglionar significativo.

Discusión. El manejo quirúrgico inmediato parece ser una opción adecuada para pacientes con sospecha de compromiso ganglionar en ecografía preoperatoria, pacientes menores de 55 años y nódulos mayores de 5 mm. Es posible que los actuales criterios para definir vigilancia activa no seleccionen adecuadamente a los pacientes en nuestro medio.

Palabras clave: neoplasias de la tiroides; cáncer papilar tiroideo; carcinoma papilar; metástasis linfática; tiroidectomía; disección del cuello.

Introduction

The term papillary thyroid microcarcinoma (PTMC) refers to tumors up to 10 mm in size in their greatest diameter, which represent more than 50% of all thyroid cancer cases¹⁻⁴. It has an apparently benign course and, despite its high prevalence, the specific mortality of this type of tumors is less than 1%, locoregional recurrence is 2 to 6%, and distant recurrence occurs between 1 and 2% of patients^{5,6}. In Colombia, we found a single report of distant metastasis in a 49-year-old male patient, who presented with metastasis to the femur⁷.

Nowaday, the management of PTMCs is not fully established, which is why it is subject to debate including a wide variety of behaviors, ranging from active surveillance strategy to early surgical treatment. Regarding the surgical option, the optimal extension and the role of elective lymph node resections of levels VI and VII are discussed^{6,8}.

It has been shown that PTMC tend to have an indolent course in most cases⁸. In a clinical follow-up of 340 patients with PTMC, it was found that only 6.4 and 15.9% of the patients had tumor growth of 3 mm or more, at 5 and 10 years, respectively. In the same study, nodal involvement was identified

in 1.4 and 3.4% of the patients, at 5 and 10 years, respectively. Based on these results, it is proposed not to carry out immediate surgical management and to initiate strict clinical follow-up in those patients with PTMC who do not have high-risk characteristics, which are: extracapsular extension on ultrasound, clinical or imaging lymph node involvement, cytology with aggressiveness findings, or nodule growth in follow-up⁹. The lack of these characteristics has been called by multiple authors as papillary thyroid microtumor to define a tumor whose behavior is of a more predictable course¹⁰.

In Colombia, a study of a prospective cohort of 102 patients was reported, in which the experience of active surveillance in low-risk thyroid carcinoma was evaluated, including patients with encapsulated tumors, smaller than 1.5 cm and without evidence of nodal commitment, regardless of gender or age¹¹. The mean follow-up was 13.9 months, and 32.3% of the patients had a follow-up longer than 24 months. The patients who had a tumor growth greater than 3 mm represented 10.8%, 14.7% a growth greater than 30% in its largest diameter, and 25.5% presented a growth greater than 50% of its volume during active surveillance. These data are in similar ranges to those of other international studies and suggest the possibility of safe clinical follow-up of patients with PMPT in our environment^{12,13}.

A descriptive study carried out in Bogotá, Colombia, which included 509 patients with thyroid cancer, concluded that the lack of a preoperative classification to establish the risk of relapse or mortality, the presence of an aggressive histological variable and the deficiencies of the health system, do not allow adequate follow-up of patients with thyroid tumor pathology, therefore, may justify aggressive surgical management as initial treatment¹⁴.

When opting for early surgical treatment, the extent of thyroid resection and the need for central lymph node dissection must be defined. The regional lymph node involvement of PTMC ranges between 14 and 46%, which is why the role of systematic central resection is debated¹⁵⁻¹⁷. Both the ATA 2015 guidelines, as well as other authors, recommend performing a central lymph node

dissection only in T3 and T4 tumors^{18,19}, however, some authors affirm that performing systematic central lymph node dissection in T1 and T2 tumors can reduce locoregional recurrence from 4.5 - 8.6% to 2.5 - 5.9%²⁰.

The objective of this study was to identify preoperative clinical or paraclinical risk factors related to general central lymph node involvement and significant central lymph node involvement in our population, as well as to analyze nodal involvement, based on the retrospective assignment of patients to risk groups progression, according to the criteria proposed by Miyauchi²⁰.

Methods

Ambispective cohort study of patients with thyroid disease, taken to surgery by the head and neck surgery service, at the National University Hospital of Colombia, in the city of Bogotá, DC, Colombia, from January 2017 to July 2020. For practical purposes, the term low-risk PTMC was used in this study as it has been defined globally.

All patients older than 18 years of age, with a diagnosis of papillary thyroid carcinoma, with tumors of up to 10 mm according to the pathological anatomy report, underwent total thyroidectomy and central lymph node dissection, operated for the first time in the institution and that they would have rejected the active surveillance proposal if they were candidates for this management. Patients in whom distant metastasis or lateral lymph node involvement was identified upon admission and patients who did not sign the informed consent were excluded for the use of data in the prospective phase of data collection, which began in February 2020. Information was collected through an instrument where the variables of interest were included in sequential moments of patient care, from the pre-surgical consultation, including surgery and pathology report, to post-operative controls.

A descriptive analysis of the characteristics of the population was carried out with measures of frequency and central tendency, which included sociodemographic, clinical and outcome variables. Additionally, a retrospective classification of the risk of progression was performed in the follow-up

of all patients, according to the Miyauchi criteria for active surveillance of the PTMC¹⁷. A bivariate analysis was performed for the outcome of lymph node involvement and possible associated factors according to the literature. Patients with any of the following findings were considered to have significant lymph node involvement: metastasis greater than 3 cm, more than 5 lymph nodes involved, and extranodal extension; characteristics changes in the subsequent classification of risk of relapse, according to the ATA 2015 guidelines¹⁶. Finally, for this outcome of interest, a multivariate logistic regression model was performed that included all significant variables in the bivariate analysis or that were of clinical relevance. There were used 95% confidence intervals and all analyzes were performed with Stata 15.0 (StataCorp LP, College Station, TX).

Results

Of 1513 patients operated on for thyroid disease between January 2017 and July 2020 at our institution, 384 patients (25.3%) had papillary tumors of up to 10 mm in diameter, and 286 were managed with total thyroidectomy plus central resection, being this the study population.

Regarding the clinical characteristics, 254 patients (88.8%) were women, and 219 patients (76.5%) were 55 years old or younger (Table 1). In the presurgical studies, 43 patients (15%) had suspicious lymph nodes and one patient (0.3%) had suspicion of extrathyroid involvement on ultrasound, and the presence of multiple nodules was reported in 48.9% of the patients. In none of the cases was a high-grade histological variable reported in fine needle biopsy.

According to the pathology report, it was found that 280 patients (97.9%) had tumors classified as pT1a, two patients (0.7%) were classified as pT3b and four patients (1.4%) as pT4a. All patients under 55 years of age were classified as stage I of the disease. Among patients 55 years of age or older, 70.2% were classified as stage I, 28.3% as stage II, and 1.5% as stage III. Patients with nodules up to 5 mm in diameter were 17.1%, and 82.9% nodules larger than 5 mm, 38.1% had multifocality, and 19.9% had involvement of both lobes.

The predominant histological variant was classic in 212 patients (74.1%), followed by follicular in 62 patients (21.7%), and infiltrating follicular in 38 (13.3%). One-hundred forty (48.9%) patients presented lymph node involvement in the pathology, and of these, 47 patients (33.6%) had more

Table 1. Clinicopathological characteristics of patients with papillary thyroid microcarcinoma. (n=286)

Parameter	Frequency (%)	
Sex	Women	254 (88.8%)
	Men	32 (11.2%)
Age	Under 55 years old	219 (76.5%)
	55 years or older	67 (23.4%)
Presurgical findings on ultrasound *		
Suspicious nodes	43 (15.0%)	
Extrathyroid extension	1 (0.3%)	
Multiple nodules	140 (48.9%)	
Post-surgical pathological findings		
Primary tumor (T)		
T1a	280 (97.9%)	
T3b	2 (0.7%)	
T4a	4 (1.4%)	
Lymph nodes (N)		
Nx	5 (1.7%)	
N0	140 (48.9%)	
N1	141 (49.3%)	
TNM stage	< 55 years	≥ 55 years
Stage I	219 (76.5%)	47 (16.4%)
Stage II	0 (0%)	19 (6.6%)
Stage III	NA	1 (0.3%)
Tumor size	≤ 0.5 mm	49 (17.1%)
	> 0.5 mm	237 (82.9%)
Bilateralism	Sí	57 (19.9%)
	No	229 (80.1%)
Multifocality	Sí	109 (38.1%)
	No	177 (61.9%)
Papillary histological variant		
Classic	212 (74.1%)	
Follicular	62 (21.7%)	
Infiltrating follicular	38 (13.3%)	
Encapsulated follicular	10 (3.5%)	
High cell	5 (1.7%)	
Others	8 (2.8%)	

* High-risk predictors for disease progression: suspicious lymph nodes on ultrasound, extrathyroid extension on ultrasound, high-grade histological variant on cytological

than five lymph nodes involved or extranodal extension. No patient reported metastasis greater than 3 cm.

Regarding complications, 21 patients (7.3%) presented postoperative dysphonia and one patient required a tracheostomy. In the one-year follow-up, definitive hypoparathyroidism was identified in 0.8% of the patients, and relapse of the disease was reported in 11 patients (3.8%).

In the logistic regression analysis, both bivariate and multivariate, it was identified that, for the age younger than 55 years, the finding of suspicious nodes on ultrasound and nodules larger than 5 mm was associated with the presence of both general lymph node involvement and of significant lymph node involvement (Tables 3 and 4). This risk increased proportionally, according to the size of the tumor, for every millimeter above 5 mm (OR= 1.22; 95% CI 1.03-1.44; p= 0.019).

Discussion

Unlike numerous malignant pathologies in which it is preferred to intervene in early stages, the trend in PTMC is expectant management through the active surveillance strategy, as was proposed

by Miyauchi since 1993, who found that 8% of patients presented an increase in size greater than 3 mm and only 3.8% had lymph node progression in more than 10 years of follow-up²¹.

This approach depends on the presence or absence of pre-surgical clinical characteristics of the patient, such as the finding of high-grade histological variants, evidence of regional or distant lymph node involvement, extrathyroid involvement, or documented growth in follow-up²¹. This configures a group at high risk of progression, to which early surgery is offered, leaving the remaining population with PTMC in the low-risk group, where clinical and imaging follow-up is feasible. However, the evidence available in the literature is not conclusive and leaves the door open for discussion.

Although the global trend is to reduce over-treatment in thyroid cancer, clinical follow-up protocols are difficult to apply in our environment, in part, due to the scarce supply of head and neck surgeons in our country, especially outside of large cities, which frequently limits timely medical care. On the other hand, due to the fear of patients and the surgeon of loss of follow-up due to administra-

Table 2. Nodal involvement in patients with papillary thyroid microcarcinoma

Relationship of risk classification for progression in follow-up and lymph node involvement (n=286)			
Centra compartments evaluated n=286 ^γ	N0 no node involvement	N+ nodal involvement present	
		General lymph node involvement	Significant involvement*
Total:	146 (51%; 95% CI: 45.1-56.9)	Total: 140 (48.9%; 95% CI: 43.0-54.8)	47/140 (33.5%; 95% CI: 25.9-42.1)
Low risk n=243	132 (54.3%; 95% CI: 47.8-60.6)	111 (45.7%; 95% CI: 39.3-52.1)	28/111 (25.2%; 95% CI: 17.6-34.5)
High risk n=43	14 (32.6% 95% CI: 19.5-48.6)	29 (67.4%; 95% CI: 51.3-80.4)	19/29 (65.5%; 95% CI: 45.6-81.4)
Significant lymph node involvement*			
- Risk groups for progression under follow-up			
	Total: 47 (100%)	Low risk (n=28)	High risk (n=19)
		59.5% (95% CI: 44.3-73.2)	40.5% (95% CI: 26.7-55.6)

^γ : Patients taken to lymph node dissection of the central compartment.

*: Metastasis > 3 cm, > 5 involved nodes, extranodal involvement.

Table 3. Bivariate and multivariate analysis of risk factors related to lymph node involvement in patients with papillary thyroid microcarcinoma

Factor studied	Bivariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age < 55 years	2.92	1.59 - 5.37	0.001	3.14	1.63 - 6.05	0.001
Sex	Women	1.26	0.60 - 2.65	0.533		
	Men				0.74	0.31 - 1.79
Suspicious nodes on ultrasound	2.46	1.24 - 4.89	0.010	2.75	1.32 - 5.74	0.007
Multiple nodules on ultrasound	0.74	0.46 - 1.20	0.229	0.88	0.53 - 1.48	0.651
Nodule size > 5 mm	3.19	1.61 - 6.33	0.001	3.37	1.64 - 6.90	0.001

Table 4. Bivariate and multivariate analysis of risk factors related to significant lymph node involvement in papillary thyroid microcarcinoma

Factor studied	Bivariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age < 55 years	3.44	1.18 - 10.00	0.023	3.84	1.24 - 11.85	0.019
Sex	Women	0.66	0.27 - 0.12	0.381		
	Men				1.53	0.52 - 4.43
Suspicious nodes on ultrasound	6.07	2.96 - 12.47	0.000	6.56	3.02 - 14.23	0.000
Multiple nodules on ultrasound	1.19	0.63 - 2.24	0.591	1.60	0.78 - 3.27	0.191
Nodule size > 5 mm	3.49	1.03 - 11.75	0.043	4.34	1.19 - 15.74	0.025

tive issues of their health provider companies and other social conditions typical of the population of developing countries, due to the suspicion of thyroid cancer, surgical management is frequently chosen.

Currently, the role of division by progression risk groups is discussed in patients who have been found to have PTMC, as in the present study, since the absence of high-risk characteristics does not exclude significant lymph node involvement, which directly affects the prognosis of the patient²². The foregoing suggests that these groups may not be applicable to all populations, and presents the need for local studies to determine the best approach in these patients.

By applying the criteria and classifying by groups, as proposed by Miyauchi et al.⁹, in our population of 286 patients, only 43 patients would

have had an indication for surgical management, due to a high-risk pre-surgical classification, of which 29 (67.4%) had general lymph node involvement and 19 (65.5%) had significant lymph node involvement, which increased their classification for risk of relapse according to ATA 2015.

On the other hand, of the 243 patients who, as proposed by Miyauchi⁹, had no indication for surgical management due to their low risk of progression, 111 patients (45.7%; 95% CI: 39.3-52.1) had lymph node involvement, of which 28 (25.2%; 95% CI: 17.6-34.5) corresponded to significant lymph node involvement, which increases their relapse risk classification, thus changing adjuvant therapy. The foregoing reflects that, if only the ultrasound and cytology findings had been taken into account to define which patients with PTMC should be taken to surgery in our population, a

large proportion of patients would not have undergone surgical management since the time of surgery, who since diagnosis had significant lymph node involvement.

Of the 6 patients in whom the extrathyroid extension of the PTMC was documented in the pathology, only one of them was suspected by preoperative images. Similarly, no high-risk histological variant was identified on cytology in any patient, so neither of these two variables could be taken into account in the logistic regression analysis of the present study. There are no major doubts in the literature that patients with extrathyroid extension of the PTMC, or in whom an aggressive histological variant is documented preoperatively, should be managed surgically^{9,19}.

Based on the above, when analyzing the postoperative results, we observed that the correlation between the risk groups for follow-up progression and lymph node involvement is not good, since low-risk patients present lymph node involvement in up to 45.7%, and when discriminating the data by significant nodal involvement, 59.5% of the patients with significant involvement were classified in the low-risk group to which active surveillance of the nodule had been assigned.

Our findings allow debate regarding the usefulness of the primary surgical management of patients with PTMC associated with prophylactic central resection (pCND), since the substaging presented with the proposed clinical characteristics classification is reduced. by Miyauchi *et al.*⁹, and the implications this has for the prognosis of patients. Our findings are consistent with other studies evaluating pCND, in which, in patients with differentiated thyroid carcinoma (DTC), performing prophylactic dissection leads to changes in the staging of patients in up to 35%, to going from N0 to N1a, especially in carcinomas smaller than 1 cm, among which our population is included²³. In addition, it was found that patients taken to pCND have a lower local recurrence rate in the central cervical area (1% vs 3.6%; $p < 0.01$), which avoids reoperations with high technical difficulty and risk postoperative complications, such as recurrent laryngeal nerve injury and definitive hypocalcemia.

The head and neck surgery group that developed this study systematically performed elective central lymph node dissection in patients with a highly suspected diagnosis of thyroid cancer; however, this is another point of controversy, in relation to the higher risk of postoperative complications derived from a greater extension of the surgery. In our institution, for this group of patients, transient or definitive global dysphonia was detected in 7.3% and definitive hypoparathyroidism in 0.8%, which is within international standards²⁴. This allows us to conclude that, in this population, patient safety was not compromised by increasing the extent of surgery.

Although it has been shown that expectant management of PTMC is feasible and safe in our setting, it is necessary to adequately define the selection criteria for the active surveillance protocol and thus avoid delaying treatment in patients presenting with tumor disease and significant nodal commitment. It is important to investigate the clinical characteristics that guide the surgical decision in our population. The findings in the bivariate and multivariate analysis yielded statistically significant data that relate the suspicion of lymph node involvement in preoperative ultrasound, age less than 55 years and nodules greater than 5 mm, as independent factors that increase the risk of general and significant lymph node involvement.

Although more studies are required, the findings found in our population suggest that patients with the aforementioned characteristics could benefit from early surgical management, which may additionally include pCND at the discretion and experience of the treating group, which provides benefits in terms of optimizing staging and reducing the risk of local relapse, as long as patient safety is not compromised.

Limitations

This is an ambispective single-center analysis, which decreases the external validity of the results. Additionally, not all patients with a diagnosis of PTMC were included, since not all were managed with total thyroidectomy plus central resection, which constitutes a selection bias. Adequate control of the information bias was carried

out since the database was designed and directed to the study, with the optimal recording of the variables described.

Conclusions

The findings of this study suggest that early surgical management appears to be an appropriate option in patients with papillary thyroid microcarcinoma who have suspected lymph node involvement on preoperative ultrasound, age less than 55 years, and nodules larger than 5 mm. Additionally, in our sample, the classification into progression risk groups proposed by Miyauchi⁸ did not adequately select patients who benefit from active surveillance, which was demonstrated by the behavior of significant lymph node involvement and its distribution in our patients. The implementation of prospective studies is required for the application and validation of the results obtained in this report.

Compliance with ethical standards

Informed consent: This study is in compliance with the standards for research in humans, the protocol and its amendments were approved by the Research Ethics Committee of the institution. Informed consent was obtained from the patients. The confidentiality and security of the information was guaranteed using the RedCap tool and no information related to the identification of patients was shared in the preparation of this article.

Conflict of interest: None declared by the authors.

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- Conception and design of the study: Sergio Fabián Zuñiga-Pavia, David Mauricio Figueroa-Bohórquez, Pilar Carola Pinillos-Navarro.
- Data acquisition: Research group of the Department of General Surgery, Universidad Nacional de Colombia.
- Data analysis and interpretation: David Mauricio Figueroa-Bohórquez, Giancarlo Buitrago.
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- Critical review: Sergio Fabián Zuñiga-Pavia, Diego Alejandro Ardila-Torres, Giancarlo Buitrago.

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