Thieme

Papillary Thyroid Microcarcinoma: Insights from a Cohort of 257 Thyroidectomized Patients

Authors
Henrique Cabral Scherer[1], Paula Martins Fernandes[1], Rafael Selbach Scheffel[1,2], André Borsatto Zanella[1,3], Ana Luiza Maia[1], Jose Miguel Dora[1]

Affiliations
1 Thyroid Unit, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
2 Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
3 Endocrinology, Hospital São Lucas da PUCRS, Porto Alegre, Brazil

Key words
thyroid cancer, diagnosis, treatment

received 14.10.2022
accepted after revision 21.12.2022
published online 16.02.2023

Bibliography
Horm Metab Res 2023; 55: 161–168
DOI 10.1055/a-2008-0824
ISSN 0018-5043

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Prof. Jose Miguel Dora
Hospital de Clinicas de Porto Alegre, Tireoide
Porto Alegre
Brazil
Tel.: 55-51-3359.7858
jdora@hcpa.edu.br

Supplementary material is available under https://doi.org/10.1055/a-2008-0824

ABSTRACT

Papillary thyroid microcarcinoma management evolved, and less aggressive strategies are now considered. Questions, however, remain on these tumors' behavior, particularly on developing countries' real ground healthcare scenarios. Our aim is to gather insights on the natural history of papillary thyroid microcarcinoma on patients treated with thyroidectomy in Brazil. Consecutive patients diagnosed with papillary thyroid microcarcinoma had their clinical characteristics, interventions, and outcomes described. Patients were classified as incidental or nonincidental based on the diagnosis after or before surgery, respectively. A sum of 257 patients were included, 84.0 % of which were women, and the mean age was of 48.3 ± 13.5 years. The mean tumor size was of 0.68 ± 0.26 cm, 30.4 % were multifocal, 24.5 % had cervical metastasis, and 0.4 % distant metastasis. The nonincidental and incidental tumors differed in tumor size (0.72 ± 0.24 and 0.60 ± 0.28 cm, respectively, p = 0.003) and in presence of cervical metastasis (31.3 % and 11.9 %, respectively, p < 0.001). Male sex, nonincidental diagnosis, and younger age were independent predictors of cervical metastasis. After 5.5 years (P25–75 2.5–9.7) of follow-up, only 3.8 % of patients had persistent structural disease (3.4 % cervical). Predictors of persistent disease at multivariate analysis included cervical metastasis and multicentricity. In conclusion, incidental and nonincidental papillary thyroid microcarcinoma patients of the population studied displayed excellent outcomes. Cervical metastasis and multicentricity were frequent findings and prognostic factors for persistent disease.

Introduction

In the last decades, thyroid cancer incidences increased worldwide [1–5], up to 15-fold in countries that adopted screening programs [3], and with substantial variability between and within populations. Mortality rates, however, remained stable or even decreased in most countries [1–3, 6]. Papillary thyroid carcinoma (PTC), the histologic type that accounts for more than 85 % of thyroid carcinomas, has been shown to be responsible for most of thyroid cancer incidence's growth [1, 2]. Almost half of new PTC cases can be due to small tumors with 10 mm or smaller diameter, called microcarcinomas (PTMC) [1]. Possibly due to enhanced healthcare access and increased sensitivity of diagnostic imaging methods [7, 8], this data raised concerns on the risk of overdiagnosing PTC [5, 9], especially in PTMC cases, in which the tumors present favorable prognosis.

Given the surgical risks and potential consequences associated with thyroidectomies – such as vocal cord paralysis (VCP), hypoparathyroidism (Hypo-PT), and need for levothyroxine substitution – current recommendations point to the increasing relevance of more conservative treatment options. In this context, thyroid

lobectomy and active surveillance (AS) emerge as safe and effective options for selected cases, with excellent clinical outcomes in long-term follow-up [10, 11]. Moreover, these new approaches brought relevant discussion of PTMC decision-making process and its impact in several issues, including quality of life and healthcare costs [12, 13]. Nevertheless, current PTMC treatment approaches are predominantly aggressive worldwide, regarding surgical decisions and radioiodine (RAI) use, despite new evidence and guidelines [14]. The applicability, patient selection, and decision-making between treatment options according to prognostic factors and potential benefits and risks, especially in real clinical care settings, are still a matter of study.

In this study, we aim to gather insights on PTMC management and treatment perspectives in a cohort study of PTMC patients who underwent total thyroidectomy. We also explored if the clinical course and outcomes were different in PTMC classified as incidental and as nonincidental based on the diagnosis after and before surgery, respectively.

Patients and Methods

Patients and study design

Patients from a cohort of differentiated thyroid cancer (DTC) were followed at a tertiary care, university teaching hospital in southern Brazil. From 2000 to 2019, all consecutive patients with a histological diagnosis of PTC with a tumor size ≤ 10 mm were included. Patients were classified with nonincidental diagnosis when the index nodule investigated had malignancy confirmed by fine needle aspiration biopsy or high suspicion for malignancy prior to surgical intervention decision, with confirmatory histopathological results. Incidental diagnosis was defined as diagnosis of PTC made in histopathological examination after thyroid surgery for other reasons.

The study was approved by the ethics committee of the institution (CAAE 3095.4520.600005327/GPPG 2020–0182). A preprint for this study is available at https://doi.org/10.21203/rs.3.rs-1880064/v1.

Treatment protocol and follow-up

All patients underwent thyroidectomy, some of them were referred to our Thyroid Unit after undergoing surgery in other institutions. Decisions regarding cervical lymph node dissection were made at the discretion of the surgical team at the Institution where the procedure was performed. At our hospital, lymphadenectomy is indicated for patients with lymph node (LN) metastasis identified before the surgery or in the presence of suspicious LN during the surgery. The radioiodine (RAI) administration protocol used activities prescribed at the attending physician's discretion. RAI was administered in a stimulated thyrotropin (TSH) condition of endogenous hypothyroidism (TSH > 30 mUI/l), after withdrawing levothyroxine for at least 3–4 weeks [15]. A post-treatment whole body scan (post-treatment WBS) was performed seven to ten days after RAI administration [16].

In the first evaluation, the following data were recorded for each patient: demographics, tumor characteristics including histological features, extension and lymph node involvement, and treatment (e. g., surgery, RAI remnant ablation, and other interventions). Each patient was classified using the 8th edition of the TNM/AJCC staging system (I, II, III, or IV) [17]. The "no evidence of lymph node metastasis" (N0) status was determined by preoperative cytological evaluation of LN or pathological examination of patients with LN resection (TNM 8th Edition N0a) or preoperative and/or postoperative neck US imaging (TNM 8th Edition N0b).

Distant metastasis (M1) was considered present when there was a lesion outside the cervical bed on imaging computed tomography (CT), or scintigraphy with histological confirmation, or post-treatment WBS uptake and/or elevated thyroglobulin (Tg). The risk of persistent/recurrent disease was assessed based on the proposed risk stratification system by the 2009 American Thyroid Association (ATA) guidelines, with patients classified into three risk groups: low, intermediate, and high [18].

The follow-up protocol called for an initial assessment at 3 to 6 months after the initial treatment, which included a physical examination of the neck and measurements of the serum Tg levels under TSH suppression and anti-thyroglobulin antibody (TgAb). In a second evaluation, 6 to 12 months after the initial treatment, physical examination of the neck and serum TSH, Tg and TgAb were reassessed. Some patients also had the serum level of Tg evaluated under stimulated TSH condition of endogenous hypothyroidism (TSH > 30 mIU/l) (sTg) at the end of the first year of follow-up. Neck US was performed in this first year of follow-up. At this point, the patient was classified according to disease response to initial therapy (see below in the outcomes section). Patients classified as having an excellent response were scheduled for annual visits, during which a physical examination of the neck and measurements of TSH, Tg, and TgAb were performed. Patients with indeterminate response or persistent disease were scheduled for the same examination at least twice a year. Additional imaging studies (e. g., X-ray, bone scintigraphy, CT) were performed, as needed, whenever the clinical or laboratory findings raised the suspicion of persistent or recurrent disease. Duration of follow-up was defined as the time between the first surgery and the last medical visit to the clinic.

Outcomes

Dynamic response stratification (DRS) status after treatment was defined based on clinical examination, Tg and/or sTg levels, neck US, post-RAI WBS (when available), and additional imaging exams when indicated. Patients were classified into four categories: excellent response, indeterminate response, biochemical incomplete response, or structural incomplete response [19, 20].

In patients submitted to RAI, excellent response was defined as negative imaging and Tg < 0.2 ng/ml or sTg < 1.0 ng/ml. Biochemical incomplete response was defined as negative imaging and Tg > 1.0 ng/ml or sTg > 10.0 ng/ml or rising TgAb levels. Structural incomplete response was defined as structural or functional evidence of disease with any Tg or TgAb level. Indeterminate response was defined as non-specific findings on imaging studies or Tg between 0.2 to 1.0 ng/ml, sTg between 1.0 and 10.0 ng/ml, or positive TgAb with stable or declining levels [19].

In patients who underwent total thyroidectomy (TT) but did not receive RAI, excellent response was defined as negative imaging and Tg < 0.2 ng/ml or sTg < 2.0 ng/ml. Biochemical incomplete response was defined as negative imaging and Tg > 5.0 ng/ml, sTg > 10.0 ng/ml, or increasing Tg levels over time or rising TgAb levels. Structural incomplete response was defined as structural or

functional evidence of disease with any Tg or TgAb level. Indeterminate response was defined as non-specific findings on imaging studies or Tg between 0.2 to 5.0 ng/ml, sTg between 2.0 and 10.0 ng/ml, or positive TgAb with stable or declining levels [19].

For patients who underwent lobectomy, excellent response was defined as negative imaging and stable Tg level < 30 ng/ml with undetectable TgAb. Biochemical incomplete response was defined as negative imaging and Tg level > 30 ng/ml, increasing Tg level values over time with similar TSH levels, or increasing TgAb levels. Structural incomplete response was defined as structural or functional evidence of disease with any Tg or TgAb level. Indeterminate response was defined as non-specific findings on imaging studies, positive TgAb levels stable, or declining in the absence of structural or functional disease [20].

For treatment response analysis, persistent disease was defined as either incomplete biochemical, cervical structural incomplete, or distant structural incomplete responses. Indeterminate response was combined with excellent response outcome, due to their similar prognosis after treatment, with 80–85 % of these patients remaining either stable or improving to excellent response [21, 22].

Regarding surgical complications, permanent Hypo-PT was defined as hypocalcemia and low parathormone levels (PTH < 20 pg/ml) for more than one year after surgery; this period was chosen, rather than the six months period of current guidelines [23], aiming for more conservative and accurate event rate report of long-term complications. Patients with no preoperative voice symptoms who presented with complaints of deficiency or quality alterations on voice for more than one year after surgery were considered to have persistent subjective voice disturbance (PSVD). Any surgical complication was defined as permanent Hypo-PT and/or PSVD.

Laboratory analysis

Serum Tg measurements were conducted using immunoradiometric assays: radioimmunoassay (COBRA II) from 2000 to 2002; electrochemiluminescence (ELECSYS 2010, Elecsys TG, Roche, Switzerland – analytical sensitivity of 1.0 ng/ml) from 2002 to 2005; electrochemiluminescence (MODULAR E-170, Elecsys TG, Roche, Switzerland- analytical sensitivity of 1.0 ng/ml) from 2005 to 2010; and chemiluminescence (Immulite XPI 2000, Siemens, Germany – analytical sensitivity of 0.2 ng/ml) from 2010 until the present. Serum TgAb levels were measured using the passive agglutination method from 2000 to 2010 (U-shaped microplates, Serodia-ATG, Japan – analytical sensitivity of 1/100); chemiluminescence from 2010 to 2018 (Architect ci 4100, Abbott, United States – analytical sensitivity 1.0 UI/ml); and chemiluminescence from 2019 until the present (DXI UNICEL 800, Beckman Coulter, United States – analytical sensitivity < 0.9 UI/ml). TSH levels were measured by chemiluminescence assay from 2000 to 2006 (Immulite 2000 SIEMENS, Munich, Germany), electrochemiluminescence from 2006 to 2010 (Modular E ROCHE, Basel, Switzerland), chemiluminescence assay from 2010 to 2014 (Centaur XP SIEMENS, Munich, Germany), electrochemiluminescence from 2014 to 2019 (Cobas E602 ROCHE, Basel, Switzerland), and chemiluminescence immunoassay (Abbot, Chicago, USA) from 2019 until the present, with RV 0.35–4.94 mUI/l.

Serum PTH was evaluated by chemiluminescent microparticle immunoassay method through the ARCHITECT ci 4100 equipment (Abbott Diagnostics, Abbott Park, IL, USA), with reference values (RV) of 15.0–68.3 pg/ml; intra-assay and inter-assay coefficients of variation were 6.1 and 6.4 %, respectively. Total serum calcium was evaluated by the NM-BAPTA method and corrected by albumin levels [corrected calcium = 0.8 × (4.0 – serum albumin) + serum calcium] with RV 8.6 to 10.0 mg/dl. Serum phosphorus was evaluated by the Molybdate UV and colorimetric (xylidyl blue) methods, with RV 2.5–4.5 mg/dl. The electrolyte tests were made using Cobas 8000 c702 equipment (Roche Diagnostics, Indianapolis, IN, USA).

After each new assay had been implemented, the necessary procedures for standardization and validation were performed.

Statistical analysis

The clinical and laboratory data are reported as the mean ± standard deviation (SD) values or as the median and percentiles 25 and 75 (P25–75) for continuous variables, and as absolute numbers and percentages for categorical variables. Statistical analyses were performed using Pearson chi-square and Fisher's exact test for categorical variables, and Student's *t*-test and Mann–Whitney U-test for continuous variables, as appropriate. For multivariate analysis models, Poisson regression was used, in which relative risk (RR) represented likelihood of associated events with a confidence interval (CI) of 95 %.

All tests were two-tailed, and all analyses were performed using the Statistical Package for Social Science Professional software version 20.0 (IBM Corp., Armonk, NY). A two-tailed $p < 0.05$ was considered statistically significant. The e!Sankey software (iPoint-systems Gmbh., Reutlingen, Germany) was used to build figures.

Results

Patients

A total of 257 (23.5 %) patients amongst the 1091 patients of the institutional DTC cohort had PTC smaller or equal to 10 mm. Of these 257 PTMC patients, 84.0 % were females, and the mean age of diagnosis was 48.3 ± 13.5 years (▶ **Table 1**). The mean tumor size was 0.68 ± 0.26 cm, and 30.4 % of them presented multicentric disease. 63 (24.5 %) patients had nodal dissemination of the disease, and only 1 patient had distant metastasis (0.4 %), which occurred in the lungs. The work-up of the 153 patients negative for LN metastasis was surgical (N0a) in 67 (43.8 %) cases, while 86 (56.2 %) were stratified clinically/radiologically (N0b). Most patients, n = 241 (93.8 %), were classified as TNM Stage I, and 16 (6.2 %) as TNM Stage II. Regarding 2009 ATA Risk Stratification System, 170 (66.1 %) were classified as low risk, 86 (33.5 %) as intermediate risk, and 1 (0.4 %) as high risk. All patients underwent TT, with exception of two lobectomies. A set of 156 (60.7 %) patients received RAI therapy, with a mean RAI activity of 88.3 ± 34.5 mCi.

Nonincidental versus incidental diagnosis

The pre-surgical clinical evaluation was available for 207 patients: 115 (55.6 %) were classified as nonincidental diagnosis, and 92 (44.4 %) as incidental (▶ **Table 1**). Nonincidental diagnosis, when compared with incidental diagnosis, was associated with larger

▶ **Table 1** Characteristics of the 257 patients with PTMC who underwent total thyroidectomy and 2 who underwent lobectomy, compared by the modality of diagnosis.

Characteristics	All patients (n = 257)[a]	Incidental diagnosis (n = 92)	Nonincidental diagnosis (n = 115)
Female – n (%)	216 (84.0)	81 (88.0)	93 (80.9)
Age at diagnosis (years)	48.3 ± 13.5	50.4 ± 12.4	49.3 ± 14.0
Tumor size (cm) *	0.68 ± 0.26	0.60 ± 0.28	0.72 ± 0.24
Multicentric – n (%)	78 (30.4)	26 (28.3)	33 (28.9)
Lymph node metastasis – n (%) *			
N0a	67 (26.1)	22 (23.9)	37 (32.2)
N0b	86 (33.5)	46 (50.0)	28 (24.3)
N1	63 (24.5)	11 (11.9)	36 (31.3)
Nx	41 (16.0)	13 (14.1)	14 (12.2)
Distant metastasis – n (%)	1 (0.4)	0 (0.0)	1 (0.9)
TNM AJCC stage – n (%) *			
I	241 (93.8)	91 (98.9)	104 (90.4)
II	16 (6.2)	1 (1.1)	11 (9.6)
American Thyroid Association 2009 Risk Stratification System – n (%)			
Low	170 (66.1)	69 (75.0)	73 (63.5)
Intermediate	86 (33.5)	23 (25.0)	41 (35.7)
High	1 (0.4)	0 (0.0)	1 (0.9)
Radioiodine – n (%)	156 (60.7)	49 (55.7)	66 (58.9)
Radioiodine activity (mCi)	88.3 ± 34.5	82.2 ± 32.5	91.8 ± 33.8
Adverse Surgical Outcomes – n (%)			
Permanent hypoparathyroidism	20 (7.8)	3 (3.3)	9 (7.9)
Persistent subjective voice disturbance	14 (5.4)	3 (3.4)	7 (6.3)
Any surgical complication	31 (12.1)	5 (5.6)	15 (13.5)
Dynamic response to therapy stratification after initial treatment – n (%)			
Excellent response	130 (58.0)	44 (55.0)	57 (55.3)
Indeterminate response	74 (33.0)	30 (37.5)	35 (34.0)
Biochemical incomplete response	10 (4.5)	4 (5.0)	5 (4.9)
Cervical structural incomplete response	9 (4.0)	2 (2.5)	5 (4.9)
Distant structural incomplete response	1 (0.4)	0 (0.0)	1 (1.0)
Dynamic response to therapy stratification at last follow-up - n (%)			
Excellent response	147 (63.1)	49 (59.8)	66 (63.5)
Indeterminate response	66 (28.3)	25 (30.5)	30 (28.8)
Biochemical incomplete response	11 (4.7)	5 (6.1)	4 (3.8)
Cervical structural incomplete response	8 (3.4)	3 (3.7)	3 (2.9)
Distant structural incomplete response	1 (0.4)	0 (0.0)	1 (1.0)
Follow-up (years)	5.5 (2.5–9.7)	5.2 (1.8–8.7)	5.0 (2.5–7.6)

[a] We could not classify 50 patients as incidental or nonincidental diagnosis. Data are shown as number (%), mean ± SD and median (P25–P75). * A significant statistical difference between diagnosis modality groups ($p < 0.05$). ATA: American Thyroid Association; N0: No evidence of lymph node metastasis; N1: Metastasis to lymph nodes; Nx: Regional lymph nodes not accessed; TNM/AJCC: TNM staging system of the American Joint Committee on Cancer.

tumors (0.72 ± 0.24 and 0.60 ± 0.28 cm, respectively, p = 0.003), more frequent LN metastasis [36 (31.3 %) and 11 (11.9 %), respectively, p = 0.001], and a larger proportion of TNM stage II classification [11 (9.6 %) and 1 (1.1 %), respectively, p = 0.009]. No difference in the proportion of RAI prescription was observed between incidental and nonincidental groups [49 (55.7 %) and 66 (58.9 %), respectively, p = 0.685]; The RAI activity dose was also similar between the groups (82.2 ± 32.5 and 91.8 ± 33.8 mCi, respectively, p = 0.144).

Clinical outcomes and lymph node metastasis predictors

The DRS after initial treatment was defined in 224 patients (▶ **Table 1**), with an excellent response observed in 130 (58.0 %) patients, indeterminate response in 74 (33.0 %), biochemical incomplete response in 10 (4.5 %), cervical structural incomplete response in 9 (4.0 %), and distant structural incomplete response in 1 (0.4 %). The patient with M1, classified as ATA high-risk, was a 40-year-old male with a 0.4 cm (larger nodule) multicentric tumor, who presented lateral cervical LN and distant lung metastasis.

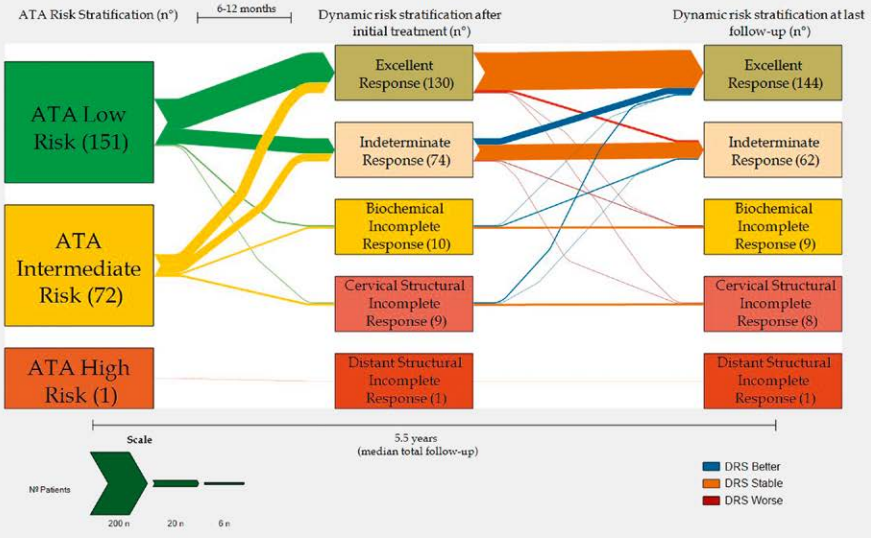
After a median follow-up of 5.5 years (P25–P75 2.6–9.7), the DRS at last follow-up of the cohort was defined for 233 patients: excellent response was observed in 147 (63.1 %) patients, indeterminate response in 66 (28.3 %), biochemical incomplete response in 11 (4.7 %), cervical structural incomplete response in 8 (3.4 %), and distant structural incomplete response in only 1 (0.4 %). ▶ **Fig. 1** depicts the patients' DRS evolution between initial response to treatment and at last follow-up. During this period, 27 (12.0 %) patients improved their DRS status, 185 (82.5 %) remained in the same stratum, and 12 (5.3 %) worsened DRS status. Among the 233 patients with DRS stratification at last follow-up, 109 (46.7 %) underwent TT only and 122 (52.3 %) underwent TT with lymphadenectomy. Persistent disease was observed in 5 (4.6 %) patients of the TT only group and in 14 (11.4 %) of the TT with lymphadenectomy group, whereas an excellent or indeterminate response was observed in 104 (95.4 %) and 108 (88.5 %) patients of these groups, respectively.

The characteristics and tumor features of the 20 patients with persistent disease – incomplete biochemical, cervical structural incomplete, and distant structural incomplete responses – are listed in the Supporting Information **Table 1S**. Predictors of persistent disease at univariate analysis for the 20 patients with this classification at last follow-up included male sex ($p = 0.041$), LN metastasis ($p < 0.001$), more advanced ATA risk stratification system classification ($p < 0.001$), and persistent disease after initial treatment ($p < 0.001$) (▶ **Table 2**). No difference in RAI activity was observed between patients with excellent or indeterminate response versus persistent disease. No differences in DRS were observed between the incidental and the nonincidental diagnosis groups. Regarding nodal dissemination, younger age at diagnosis ($p < 0.0001$), male sex ($p < 0.001$), and multicentricity ($p = 0.048$) were associated with higher rates of LN metastasis (**Table 2S**).

In multivariate analysis – regarding sex, age, tumor size, multicentricity, LN metastasis, and type of diagnosis – LN metastasis ($p = 0.004$; RR = 4.48, 95 % CI 1.6–12.3) and multicentricity ($p = 0.039$; RR = 2.42, 95 % CI 1.04–5.6) remained as predictors of persistent disease (▶ **Table 3**). Nonincidental diagnosis was associated with a tendency of persistency of the disease ($p = 0.078$; RR = 2.19, 95 % CI 0.91–5.26), as well as younger age ($p = 0.089$; RR = 1.05, 95 % CI 0.99–1.11). Predictors of LN metastasis in the multivariate models included male sex ($p < 0.001$; RR = 2.30, 95 % CI 1.51–3.52), younger age ($p < 0.001$; RR = 1.03, 95 % CI 1.01–1.04) and nonincidental diagnosis ($p = 0.010$; RR = 2.17, 95 % CI 1.20–3.92). Each reduction in 1 year in age was associated with an increased risk of 3 % for LN metastasis. ▶ **Fig. 2** depicts the distribution of LN metastasis in different age groups.

Surgical complications

A total of 20 (7.8 %) patients developed permanent Hypo-PT, and 14 (5.4 %) suffered from PSVD. Any long-term surgical complication, occurred in 31 (12.1 %) patients, and three patients suffered from both permanent Hypo-PT and PSVD. Notably, there was a tendency to more long-term surgical complications in the nonincidental diagnosis than in the incidental diagnosis group (15 (13.5 %) and 5 (5.6 %), respectively, $p = 0.062$). LN resection data was available for 216 patients. Permanent Hypo-PT was more frequent in patients who underwent LN resection compared to those who did not



▶ **Fig. 1** Evolution of 224 PTMC patients stratified by ATA risk for recurrence and dynamic response to therapy, both at initial treatment and at last follow-up. Line's trajectory represents patient evolution and thickness represents the number of patients. ATA: American Thyroid Association, DRS: Dynamic risk stratification.

▶ **Table 2** Univariate analysis of predictors of persistent disease.

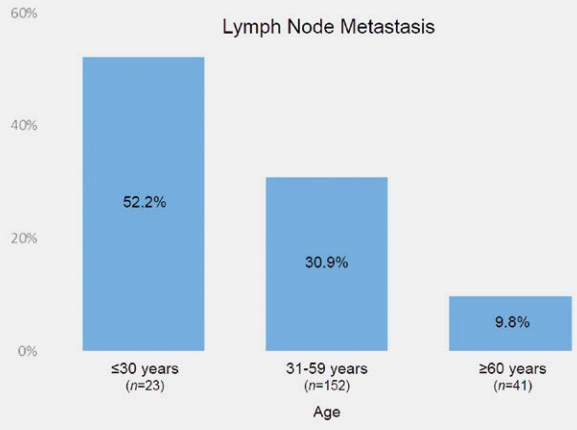
	Disease Status		
	Excellent/ Indeterminate (n = 213)	**Persistent disease (n = 20)**	**p**
Male – n (%)	28 (13.1)	6 (30.0)	0.041
Age at diagnosis (years)	49.1 ± 12.7	42.6 ± 14.3	0.110
Tumor size (cm)	0.69 ± 0.25	0.60 ± 0.25	0.659
Multicentricity – n (%)	61 (28.6)	9 (45.0)	0.135
Nodal metastasis – n (%)	44 (20.7)	12 (60.0)	< 0.001
TNM AJCC stage – n (%)			0.133
I	200 (93.9)	17 (85.0)	
II	13 (6.1)	3 (15.0)	
American Thyroid Association Risk Stratification System 2009 – n (%)			< 0.001
Low	151 (70.9)	5 (25.0)	
Intermediate	62 (29.1)	14 (70.0)	
High	0 (0.0)	1 (5.0)	
Radioiodine use – n (%)	132 (62.0)	13 (65.0)	0.388
Radioiodine activity (mCi)	86.9 ± 34.2	89.8 ± 39.6	0.775
Dynamic response to therapy after initial treatment – n (%)			< 0.001
Excellent	128 (60.1)	2 (10.0)	
Indeterminate	72 (33.3)	3 (15.0)	
Biochemical incomplete response	4 (1.9)	6 (30.0)	
Cervical structural incomplete response	3 (1.4)	6 (30.0)	
Distant structural incomplete response	0 (0.0)	1 (5.0)	
Unknown	7 (3.3)	2 (10.0)	
Nonincidental diagnosis – n (%)	96 (45.1)	8 (40.0)	0.883

Data are shown as number (%), mean ± SD and median (P25–P75). ATA: American Thyroid Association; TNM/AJCC: TNM staging system of the American Joint Committee on Cancer.

▶ **Table 3** Multivariate analysis of predictors of lymph node metastasis and persistent disease.

	RR [95% CI]	p
Predictors of lymph node metastasis[a]		
Male sex	2.30 [1.51–3.52]	< 0.001
Age at diagnosis (years)	0.97 [0.96–0.99]	< 0.001
Tumor size	0.60 [0.93–1.14]	0.599
Multicentricity	1.00 [0.62–1.62]	0.970
Nonincidental diagnosis	2.17 [1.20–3.92]	0.010
Predictors of persistent disease[b]		
Male sex	1.75 [0.59–5.15]	0.304
Age at diagnosis (years)	0.95 [0.90–1.01]	0.089
Tumor size	0.82 [0.64–1.06]	0.135
Multicentricity	2.42 [1.04–5.60]	0.039
Nodal metastasis	4.48 [1.60–12.30]	0.004
Nonincidental diagnosis	2.19 [0.91–5.26]	0.078

[a] A total of 179 patients with complete available variables were included for this analysis. [b] A total of 168 patients with complete available variables were included for this analysis. CI: confidence interval; RR: Relative risk.



▶ **Fig. 2** Percentage of lymph node metastasis stratified by age groups.

(14 (10.8%) and 2 (2.3%), p = 0.02), but no association of LN resection with PSVD [6 (4.8%) and 5 (5.9%), p = 0.72] or any surgical complication [18 (14.3%) vs 8 (9.4%), p = 0.291] was observed.

Discussion and Conclusions

We studied a cohort of patients with PTMC who underwent thyroidectomy at the Brazilian public health system. Among the 1091 PTC patients of our cohort, we found a PTMC proportion similar to the literature report [24]. Moreover, we observed that 30.4% of them presented multicentric disease and 24.5% had LN metastasis at diagnosis. Another interesting finding is that most of the patients were disease-free after a median follow-up of 5.5 years.

The LN is the main site of metastasis of PTC. In our PTMC cohort we observed in multivariate analysis that nonincidental diagnosis, male sex and younger age were predictors of LN metastasis. This is consistent with previous reports that found male sex, multicentricity, and younger age to be associated with LN metastasis [25]. Younger age is usually associated with more advanced PTMC disease [26, 27]. In accordance with this observation, we found an association of younger age with nodal dissemination, but not with worse treatment response. Interestingly, in published AS strategies, younger age is the most significant predictor of tumor growth and development of LN metastasis [27]. All these data point to a pattern of more extensive and progressive disease in younger patients.

Most PTMC patients were classified as excellent response after the initial treatment and at last follow-up. DRS status remained stable over time for most patients, while some demonstrated status improvement and very few progressions of disease. These findings support the long-term excellent prognosis of PTMC tumors in different healthcare scenarios. Both ATA risk classification ($p = 0.006$) and DRS at initial treatment ($p < 0.001$) were predictors of excellent response in the last follow-up, reassuring these tools as useful methods for PTMC management. Multifocality and LN metastasis, were associated with persistent disease at last follow-up. Although associated with larger tumors and lymph node dissemination in our cohort, nonincidental diagnosis was not associated with worse response to treatment, a finding that may be due to underpower. Notably, a recent meta-analysis found significative higher risk of recurrence in nonincidental PTMC [28]. In our study, we observed 3.8 % of structural persistent disease at last follow-up (3.4 % cervical) in our cohort, and available reports of structural persistence/recurrence range from 1 to 6 % [24, 29].

We also observed high rates of surgical complications, represented by permanent Hypo-PT and PSVD, totaling 12.1 % of any adverse event in these patients. These surgical complications have been associated with increased treatment costs within the health system [12] and worse quality of life outcomes [13], especially for permanent Hypo-PT regarding the former (due to costs of exams, hospital outpatient and inpatient visits, and pharmacological treatment) and voice disturbance regarding the latter. Since these are key factors in treatment decision-making [30], we further encourage physicians to consider local surgical complication rates to perform patient-shared and patient-centered decisions in PTMC diagnosis, aiming for better quality of life outcomes and healthcare costs.

In this scenario of excellent clinical PTMC outcomes, AS emerges as a safe and effective option for selected cases [10, 11]. Miyauchi et al. demonstrated in a low-risk PTMC cohort the good prognosis of these tumors when managed with AS. Tuttle et al. also expanded this finding to PTC with a size up to 1.5 cm. These cohorts and others have shown that a minority of these patients evolve to surgery due to disease progression, and in these cases, despite postponement of the surgical treatment, oncological outcomes were excellent and non-different from immediate surgery management [27, 31]. In addition, AS can effectively reduce adverse events related to the management of these generally indolent tumors [32]. This is especially significant in a healthcare scenario containing a large proportion of PTMC cases and a significant risk associated with surgical treatment, such as ours. Patient selection to this approach, however, would demand careful evaluation due to the expressive rates of LN metastasis in this population – an exclusion criterion to this strategy – which is especially important in males and young patients. Since most AS cohorts were conducted in high-resource settings, Latin-American patients' acceptability and engagement on AS strategy should also be considered and clarified during treatment for a shared decision-making [33].

Some limitations of our study should be acknowledged. Due to its retrospective nature, inherent bias may be present. Moreover, since only patients of a single thyroid cancer reference center were studied, selection bias cannot be ruled out. Our institution represents a real-ground clinical practice in Latin America – where data is still needed to understand PTMC patient presentation and evolution. To our knowledge, this is the first Latin American cohort that comprised PTMC patient profile, tumor characteristics, DRS both after initial treatment and long-term, and adverse events associated with treatment. Due to the historic nature of the cohort, which comprises a period from 2000 to 2019, many patients were treated following previous protocols – 245 patients underwent TT and only 2 underwent lobectomy, with a substantial portion receiving RAI therapy (60.9 %). These modalities of treatment for PTMC are considered overtreatment in the light of most recent evidence and guidelines for this tumor management. As we are a regional reference center for Thyroid Cancer, many patients are referred to our institution after the initial surgery. Decisions regarding cervical lymph node dissection were made at the discretion of the surgical team at the institution where the procedure was performed, which could be a factor that contributed to overtreatment. Additionally, given that a significant portion of our cohort was operated outside our institution, perioperative clinical, ultrasonographic and pathological information is not consistently available. This especially applies to type of diagnosis – incidental or nonincidental, which was not available for 50 patients of the cohort – perioperative US data, and pathological micro/macroinvasion. Although less aggressive treatment approaches have already been demonstrated as equally effective alternatives in selected cases, aggressive treatment approaches remain common worldwide. TT is still extensively overused, being the treatment modality in up to 80 % of tumors ≤ 2 cm; RAI therapy, with current limited indications by the ATA 2015 guidelines, persists widely used in patients with low-risk disease [34]. Considering that up to 80 % of recurrences occur during 3–5 years after initial treatment, our median follow-up of 5.5 years seems adequate to evaluate long-term disease status [35].

In conclusion, we found a significant proportion of PTMC in a DTC cohort from a tertiary public hospital in Brazil. The PTMC excellent outcomes occurred despite type of diagnosis, and at the expense of high rates of surgical complications. Since nonincidental diagnosis, male sex, and younger age were predictors of LN metastasis (which, in turn, is a predictor of persistent disease) we believe that this group of patients must be evaluated more carefully before AS be considered. Comprehensive consideration of tumor and patient profile, treatment prognosis, and treatment-related adverse effects should, altogether, be considered and conveyed during the shared decision-making process with PTMC patients.

Funding Information

Fundo de Incentivo à Pesquisa e Eventos do Hospital de Clínicas de Porto Alegre. Programa Institucional de Bolsas de Iniciação Científica da Universidade Federal do Rio Grande do Sul. Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul.

Acknowledgements

We would like to thank the funders of the study and the iPoint-systems for providing the resources to conduct this study and for providing the software to build the images, respectively.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164

[2] Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngology Head Neck Surg 2014; 140: 317–322

[3] Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic" — screening and overdiagnosis. N Eng J Med 2014; 371: 1765–1767

[4] La Vecchia C, Malvezzi M, Bosetti C et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer 2014; 136: 2187–2195

[5] Vaccarella S, Dal Maso L, Laversanne M et al. The impact of diagnostic changes on the rise in thyroid cancer incidence: a population-based study in selected high-resource countries. Thyroid 2015; 25: 1127–1136

[6] Li M, Brito JP, Vaccarella S. Long-term declines of thyroid cancer mortality: an international age-period-cohort analysis. Thyroid 2020; 30: 838–846

[7] Morris LGT, Sikora AG, Tosteson TD et al. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid 2013; 23: 885–891

[8] Haymart MR, Banerjee M, Reyes-Gastelum D et al. Thyroid ultrasound and the increase in diagnosis of low-risk thyroid cancer. J Clin Endocrinol Metab 2018; 104: 785–792

[9] Vaccarella S, Franceschi S, Bray F et al. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Eng J Med 2016; 375: 614–617

[10] Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. World J Surg 2016; 40: 516–522

[11] Tuttle RM, Fagin JA, Minkowitz G et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. JAMA Otolaryngol Head Neck Surg 2017; 143: 1015

[12] Oda H, Miyauchi A, Ito Y et al. Comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid. Endocrine J 2017; 64: 59–64

[13] Kong SH, Ryu J, Kim MJ et al. Longitudinal assessment of quality of life according to treatment options in low-risk papillary thyroid microcarcinoma patients: active surveillance or immediate surgery (Interim Analysis of MAeSTro). Thyroid 2019; 29: 1089–1096

[14] Moten AS, Zhao H, Willis AI. The overuse of radioactive iodine in low-risk papillary thyroid cancer patients. Surg Oncol 2019; 29: 184–189

[15] Scheffel RS, Zanella AB, Dora JM et al. Timing of radioactive iodine administration does not influence outcomes in patients with differentiated thyroid carcinoma. Thyroid 2016; 26: 1623–1629

[16] Nava CF, Scheffel RS, Zanella AB et al. Reappraising the diagnostic accuracy of post-treatment wole-body scans for differentiated thyroid carcinoma. Horm Metab Res 2020; 52: 834–840

[17] Nava CF, Zanella AB, Scheffel RS et al. Impact of the updated TNM staging criteria on prediction of persistent disease in a differentiated thyroid carcinoma cohort. Archiv Endocrinol Metab 2019; 63: 5–11

[18] Cooper DS, Doherty GM, Haugen BR et al. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19: 1167–1214

[19] Haugen BR, Alexander EK, Bible KC et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1–133

[20] Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. Endocrinol Metab Clin North Am 2014; 43: 401–421

[21] Tuttle RM, Tala H, Shah J et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American thyroid association staging system. Thyroid 2010; 20: 1341–1349

[22] Vaisman F, Momesso D, Bulzico DA et al. Spontaneous remission in thyroid cancer patients after biochemical incomplete response to initial therapy. Clin Endocrinol 2012; 77: 132–138

[23] Brandi ML, Bilezikian JP, Shoback D et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab 2016; 101: 2273–2283

[24] Roti E, degli Uberti EC, Bondanelli M et al. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 2008; 159: 659–673

[25] Liu LS, Liang J, Li JH et al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. Eur Archiv Oto-Rhino-Laryngoly 2016; 274: 1327–1338

[26] Zhang L, Wei W, Ji Q et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. J Clin Endocrinol Metab 2012; 97: 1250–1257

[27] Ito Y, Miyauchi A, Kihara M et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 2014; 24: 27–34

[28] Mehanna H, Al-maqbili T, Carter B et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. J Clin Endocrinol Metab 2014; 99: 2834–2843

[29] Leboulleux S, Tuttle RM, Pacini F et al. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? Lancet Diabetes Endocrinol 2016; 4: 933–942

[30] Sawka AM, Ghai S, Yoannidis T et al. A prospective mixed-methods study of decision-making on surgery or active surveillance for low-risk papillary thyroid cancer. Thyroid. 2020; 30: 999–1007

[31] Sasaki T, Miyauchi A, Ito Y et al. Marked decrease over time in conversion surgery after active surveillance of low-risk papillary thyroid microcarcinoma. Thyroid 2020; 31: 217–223

[32] Oda H, Miyauchi A, Ito Y et al. Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery. Thyroid 2016; 26: 150–155

[33] Smulever A, Pitoia F. Active surveillance in papillary thyroid carcinoma: not easily accepted but possible in Latin America. Archiv. Endocrinol Metab 2019; 63: 462–469

[34] Welch HG, Doherty GM. Saving thyroids – overtreatment of small papillary cancers. N Eng J Med 2018; 379: 310–312

[35] Durante C, Montesano T, Torlontano M et al. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 2013; 98: 636–642