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ORIGINAL ARTICLE

Predictors for papillary thyroid cancer persistence and recurrence: a retrospective analysis with a 10-year follow-up cohort study

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Summary

Objective We aimed to determine outcome predictors of papillary thyroid cancer (PTC) persistence and recurrence, separately.

Context The factors contributing to either persistence or recurrence of PTC are poorly defined, as both outcomes are usually evaluated together.

Design and patients In this 10-year follow-up cohort study, 190 PTC patients were evaluated (18–85 years old; registered from 1 January 1990 to31 December 1999 at a Brazilian Cancer Care referral Hospital). After initial surgery, we examined persistence (disease detected up to 1 year), recurrence (disease detected after 1 year) and PTC-free status (disease absence during follow-up).

Measurements Outcome predictors were modelled using multinomial logit regression analysis.

Results The univariate analysis showed that persistence and recurrence were significantly associated with lymph node metastasis (OR = 12·33; OR = 2·84, respectively), local aggressiveness (OR = 5·22; OR = 3·35) and extrathyroidal extension (OR = 5·07; OR = 7·11). Persistence was associated with male sex (OR = 3·49), age above 45 years old at diagnosis (OR = 1·03), macroscopic lymph node metastasis (OR = 5·85), local aggressiveness (OR = 5·22), each 1-cm tumour size increase (OR = 1·34), a cancer care referral hospital as the place of initial surgery (OR = 2·3), thyroidectomy or near total thyroidectomy (OR = 3·03) and neck dissection (OR = 3·19). Recurrence was associated with the time of radioactive iodine (^{131}I) therapy (OR = 3·71). After data modelling, persistence was associated with macroscopic lymph node metastasis (OR = 6·17), 1-cm increases in tumour size (OR = 1·30) and thyroidectomy or near total thyroidectomy (OR = 3·82), while recurrence was associated with surgery at referral hospital (OR = 3·79).

Conclusions The best predictors of persistence were tumour size and macroscopic lymph node metastasis; when the initial surgery is of quality, the recurrence depends more on tumour's biology aspects.

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Introduction

Predictors are used to support medical decisions regarding the initial treatment and the clinical follow-up for papillary thyroid cancer (PTC).[1–4] In the past, the analyses were fundamentally focused on predictors for mortality;[1,5] however, the staging systems have improved for estimating PTC persistence and recurrence, which are two major concerns regarding treatment.[4,6–8] Usually, the outcome predictors for PTC do not estimate persistence and recurrence independently. However, predicting each outcome individually would provide additional information to facilitate tailored treatment. Although one French study analysed predictors for PTC persistence and recurrence separately,[9] we have not found any other similar studies.

A properly designed and reported outcome predictor study is of interest, mainly due to the fact that the identification of factors that predict PTC relapse within the first year of follow-up might be useful to ameliorate clinical care.[10] To overcome the current limitations, our study aims to assess predictors for persistence separately from recurrence, based on data collected during initial treatment.

Subjects and methods

Study design characteristics and hospital setting

We conducted a hospital-based cohort study of PTC patients registered at a tertiary hospital in Brazil, which is a centre of excellence in cancer care that offers complex diagnostic and therapeutic capabilities. The hospital is part of the National

Cancer Institute (Inca) in Rio de Janeiro, Brazil. The entry point for the beginning of follow-up was the day of the initial surgical treatment and finished or (i) the date of the first relapse (persistence or recurrence), (ii) the last follow-up (dropped out). Patients were initially operated in either tertiary hospital or in another secondary hospital (operated by general surgeons, not in cancer hospitals).

Ethics

This study was approved by the Inca HC-1 Ethics and Research Committees, protocol no. 86/2010, and was conducted in accordance with the principles of the Declaration of Helsinki [11] and the Good Clinical Practice Guidelines.

Study participants, outcome measures and exploratory variables

We included 393 patients admitted to the hospital between 1 January 1990 and 31 December 1999, with a diagnosis of PTC as per the International Classification of Diseases for Oncology (ICD-O) codes 83 403, 82 603 or 80 503 (follicular variant of PTC, thyroid papillary adenocarcinoma (SOE) and papillary thyroid carcinoma, respectively) in the hospital cancer register from the centre's database, which was available in 2010. The eligible patients had undergone thyroid surgical approach to treat PTC and were aged 18 years old or more at time of initial surgery. Of these potentially eligible patients, 175 patients were not included because no further consultation was registered in the medical database, and 28 were excluded: 22 due to a follow-up for less than 1 year, without presenting any of the study outcomes; four had a pathology report showing anaplastic cells and two died during surgery. Data were, therefore, available for 190 patients.

The three main outcome variables of interest were persistence, recurrence and PTC-free status. Another outcome studied was death as a result of PTC and/or from any other cause. PTC persistence was defined as evident structural and/or biochemical residual disease (active disease status) until 1-year after initial surgery. PTC recurrence was considered when the first event of active disease occurred after 1-year follow-up. We considered only the event first experienced by the patient, so that the patients who had persistent PTC were not considered at risk of recurrence. Only PTC followed for at least 1 year who did not show active structural and/or biochemical disease were considered PTC-free patients. Active PTC disease was indicated when one or more of the following was observed: (i) structural disease evidenced by positive imaging findings (ultrasound, radiography, ^{99}mTc sestamibi scintigraphy, tomography or nuclear magnetic resonance) or after radioactive iodine (^{131}I, RAI) administration for diagnostic or therapeutic purposes; and (ii) biochemical evidence of disease was evaluated based on serum Tg levels, serum TSH and the serum anti-Tg levels. In thyroidectomized patients (total or near total thyroidectomy), suppressed serum Tg above 1 μg/l or stimulated serum Tg above 2 μg/l was considered. In patients with subtotal thyroidectomy or positive serum anti-Tg antibodies, only structural disease analysis was conducted. The functional sensitivity of serum Tg measurements were 1 μg/l from 1990 to 1998, 0·5 μg/l from 1998 to 2003 and 0·2 μg/l from 2003 to 2010.

We considered the following factors: (i) patient demographic data (sex, age); (ii) surgical pathology findings [tumour size, histological variants, multicentricity, extrathyroidal extension, vessel invasion, pathological lymph node status for metastasis (pN)]; (iii) clinical disease status assessed by loco regional or distant metastasis and lymph node metastasis (TNM) stage [local aggressiveness status of the tumour based on a (pT) assessment and macroscopic lymph node status for metastasis defined as the presence of clinically visible or palpable lymph nodes (cN1) before surgery and a confirmed diagnosis of pathological lymph node metastasis (pN1)]; (iv) hospital of initial surgery (establishment of the cancer care referral hospital as a proxy variable for a higher quality level of service); and (v) medical treatments (type of initial thyroid surgery [total thyroidectomy (TT) or near-TT in relation to others, and RAI therapy.

Data sources and data collection

The main sources for data collection were medical charts and the clinical intranet system for obtaining the examination results. Using the cancer death registry of the hospital, we determined the date of death during 10 years of follow-up and assessed the causes. All surgical pathology reports were reviewed, and all macroscopic lymph nodes (cN1) were confirmed as positive in the pathology report. We built a database specifically for this study, and data were assessed and analysed for clinical course and PTC outcomes from June 2010 to May 2012.

Statistical analyses

Descriptive information is presented for categorical variables, such as frequency (percentage). For continuous variables, the mean, standard deviation (SD) and *t*-tests were used. Kernel density estimation was used for describing the details of influence of tumour size as a continuous variable for outcome status. Only the first morbidity outcome for each patient was included in the analysis.

As analytical tools, we used multinomial logit regression analysis only for patients without distant metastasis at presentation (n = 172), and the PTC-free group was considered as the reference group. Univariate multinomial regression analysis included all candidate exploratory variables and calculated the crude odds ratio (OR) and confidence interval (CI), with a significance level of 95%.[12] For the multinomial logit model, we had previously tested all categorical candidate predictors for multicollinearity. Candidate predictors were selected for inclusion in the logit model based on the theoretical relevance of clinical outcomes, regardless of the univariate results. The PTC variant, multicentricity, extrathyroidal extension, vessel invasion and pathological lymph node were not included in the model due to missing data (>20%). The candidate variables for modelling the outcome

predictors were age, sex, macroscopic lymph node, tumour size, local aggressiveness, TNM stage, hospital of initial surgery (proxy of quality), type of thyroid surgery, neck dissection and RAI therapy. Age and tumour size were considered continuous variables.[10,13]

Exploratory, automatic, stepwise and manual approaches were used to compare scenarios with two sets of candidate predictors. The best-fit model was selected considering the approximation of the goodness' values from the Akaike information criterion (AIC), CI and taking into account the association's plausibility. The final model was tested for interactions. Analyses were conducted using the R software package version 2.15.3.[14] For practical inferences, the logit estimated coefficients (β) were used to calculate the OR when the *P*-value was <0·05. Once a final model was chosen, the inferences were made based on a hypothesis test of parameters, CI, interactions, parameters and parameter errors. This study complies with the methodological recommendations for clinical prediction research,[10] observational studies (STROBE) [13] and reported prognostic studies on cancer.[15]

Results

Characteristics of study population

In the study population of 190 PTC patients, the female–male ratio was 4:1, and the mean age was 47 years old (SD = 17·35) with a median of 43 years old (range of 18–85 years old). The PTC-free and recurrence groups presented a similar age [mean of 44 years old (SD = 14·20), median of 40 years old (range of 19–74) and mean of 44 years old (SD = 20·67), median of 39 years old (range of 18–85), $P = 0{\cdot}893$, respectively], and the persistent group showed a higher mean age of 53 years old (SD = 19·09; median of 57 years old; range of 18–83; $P = 0{\cdot}002$).

The median cohort time of follow-up was 11 years for all the study population; by outcome group, the median time of follow-up time was of 12 years for PTC-free, 11 years for recurrence and 6·5 years for persistence.

Outcomes and the association of exploratory variables

Persistence and/or recurrence were significantly associated with nine of the sixteen exploratory variables tested (Table 1). Regarding the demographic data, sex was associated with outcome ($P = 0{\cdot}022$). Among the surgical pathology findings, the extrathyroidal extension was the only variable that significantly influenced the outcomes ($P < 0{\cdot}001$).

The PTC-free group presents a higher frequency of smaller tumours compared with the recurrent and persistent groups, but only persistence showed a significant difference in relation to the outcome ($P = 0{\cdot}005$). Tumour size was not associated with outcome when a cut-off of 4 cm was used ($P = 0{\cdot}372$, Table 1); however, when tumour size is analysed as a continuous variable, the outcomes of persistence, recurrence or PTC-free can be better predicted, as shown in Fig. 1, for tumours below 2·5 cm.

In relation to the patient clinical disease status (Table 2), local aggressiveness was present in 39% of the whole sample, and 66% of these aggressive tumours evolved with persistence (49%) or recurrence (17%). We found macroscopic lymph node metastasis (clinical) in 33% of cases ($n = 63$), and advanced TNM stage (TNM-high-risk) in 38% (59 of 156) of cases at baseline, which became persistent in 63% and recurrent in 17%. TNM-low-risk status was found in 62% of cases, of which 18% became persistent and 20% recurrent. All patients who were at high-risk TNM stage and <45 years of age (TNM stage II) at baseline evolved into persistence, and 78% of those aged ≥45 years (TNM stages III–IV) became persistent (60%) or recurrent (18%; Table 2). All these parameters were statistically significant ($P < 0{\cdot}001$).

The initial morbidity burden was higher in patients submitted to the first surgery at the referral hospital. It is noteworthy that the patients followed at reference hospital had a significantly higher prevalence of high-risk TNM stages ($P = 0{\cdot}003$) and distant metastasis ($P = 0{\cdot}051$) at baseline than those initially treated in secondary hospitals.

On the other hand, extensive surgeries were more frequent in the referral hospital than in the secondary hospitals (TT or near-TT, $P = 0{\cdot}018$, 71% *vs* 55% and neck dissection, $P = 0{\cdot}004$, 44% *vs* 22%, respectively). In relation to using RAI, there was no difference between the hospitals ($P = 0{\cdot}752$). Neck dissection ($n = 55$) was performed in 43%, 31% and 21% of persistent, recurrent and the PTC-free groups, respectively.

Most of the neck dissections (lateral = 56·4%; central = 12·7%; lateral and central = 27·3%) were therapeutic (75%; cN1, $n = 41$), while prophylactic neck dissections were performed in 10% (cN0, $n = 6$) of cases, and the type of dissection was not assessed in 15% (cNx, $n = 8$). Prophylactic neck dissection occurred only in patients initially treated at the cancer care referral hospital.

The lateral was the most performed type of neck dissection in both groups of hospitals (53% in cancer care hospital and 65% in secondary hospitals), while lateral and central neck dissections were performed in 29% and 24% of surgeries in cancer care hospital and secondary hospitals, respectively. Central neck dissection was only performed in cancer care referral hospital (18%).

All the 25 persistent patients who were submitted to neck dissection had pathological lymph node metastasis (1 to 39 lymph nodes) varying from 0·6 to 4·5 cm of diameter, and seven of them had 10 or more positive lymph nodes. All the 10 recurrent patients who were submitted to neck dissection had pathological lymph node metastasis (1 to 20 lymph nodes) varying from 0·6 to 4·4 cm of diameter, and two of them had 10 or more positive lymph nodes. In the PTC-free patients who were submitted to neck dissection, 90·5% ($n = 19$) had pathological lymph node metastasis (1 to 11 lymph nodes) varying from 0·75 to 4·5 cm of diameter, and three of them had 10 or more positive lymph nodes.

The progression into either persistence ($n = 56$) or recurrence ($n = 32$) was detected by imaging in 54% ($n = 30$) of persistent and 56% ($n = 18$) of recurrent patients, while both biochemical and structural diseases were diagnosed in 46% ($n = 26$) of

Table 1. Prevalence of persistent and recurrent PTC and their associations with patient demographic data and surgical pathology findings at baseline (n = 190)

	Outcome groups						
	PTC-free n = 102 (54%)		Persistent PTC n = 56 (29%)		Recurrent PTC n = 32 (17%)		
Variable	No.	%	No.	%	No.	%	P-value
Sex							
Female (n = 152)	88	86	36	64	28	88	0·002**
Male (n = 38)	14	14	20	36	4	12	
Age at baseline, categorical *years*							
≥45 (n = 91)	44	43	34	61	13	41	0·071
<45 (n = 99)	58	57	22	39	19	59	
Tumour size†							
>4 cm (n = 23)	8	8	11	20	4	12	0·138
≤4 cm (n = 131)	73	72	38	68	20	63	
Unknown (n = 36)	21	20	7	12	8	25	
Histological variants							
Classical (typical; n = 34)	16	15	10	18	8	25	0·455
Others (n = 33)	19	19	10	18	4	12	
Unknown variant type (n = 123)	67	66	36	64	20	63	
Multicentricity							
Yes (n = 61)	31	30	22	39	8	24	0·538
No (n = 77)	44	44	21	38	12	38	
Unknown (n = 52)	27	26	13	23	12	38	
Extrathyroidal extension							
Yes (n = 61)	16	16	34	61	11	46	<0·001**
No (n = 47)	31	30	13	23	3	12	
Unknown (n = 82)	55	54	9	16	18	42	
Vessel invasion							
Yes (n = 26)	10	9	13	23	3	9	0·203
No (n = 33)	16	16	9	16	8	25	
Unknown (n = 131)	76	75	34	61	21	66	
Lymph node metastasis *pathology stage (pN)*							
Positive (n = 81)	28	27	36	64	17	53	0·372
Negative (n = 10)	6	6	3	5	1	3	
Unknown (n = 99)	68	67	17	30	14	44	

PTC, papillary thyroid cancer.
The P-value refers to the chi-square test.
**The P-value is significant.
†Fisher's exact test

persistent patients and 41% (n = 13) of recurrent cases. In one recurrent patient, only biochemical disease was diagnosed.

RAI therapy did not lead to significant differences in terms of outcomes (Table 3). The initial dose of radioiodine was identical for the three outcome groups (median of 100 mCi); however, the accumulated dose differed among them (median accumulated dose: PTC-free = 100 mCi; Persistence = 150 mCi; Recurrence = 219 mCi).

Multinomial logit analyses

Univariate analysis. The univariate multinomial logit regression analysis indicates the chances of recurrence or persistence separately and summarizes the results for each assessed candidate predictor, except for distant metastasis (Table 4). In this analysis, the chance of both outcomes increased with three candidate predictors: extrathyroidal extension, local aggressiveness and high-risk TNM stage.

The persistence-only group was positively associated with seven candidate predictors: male sex; age; macroscopic lymph node metastasis; tumour size; hospital of initial surgery; TT or near-TT as the initial surgery; and neck dissection. Males had a greater chance of persistent disease. Additionally, patients aged 45 years or older were more likely to experience disease persistence. Macroscopic evidence of lymph node metastasis was significantly associated with persistence and was nearly significant in relation to recurrence (P = 0·056). The chance of disease persistence increased for each 1-cm increase in mean tumour size at baseline (Table 4).

Mortality within 10 years was associated with disease persistence (OR = 27·55, 95% CI = 3·47–218·4, P = 0·002), but not with recurrence (OR = 6·73, 95% CI = 0·58–6·85, P = 0·125).

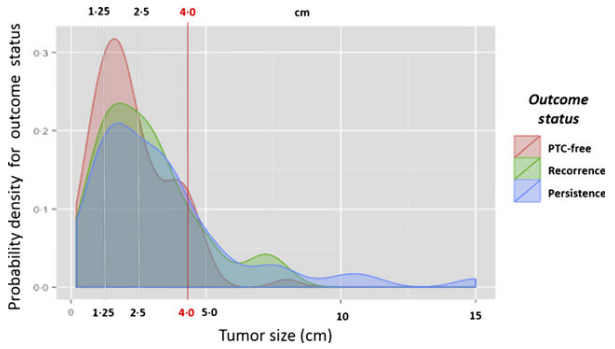

Fig. 1 Tumour size distribution according to probability of persistence, recurrence and papillary thyroid cancer (PTC)-free outcomes. The probability of PTC relapse (persistence or recurrence) overcomes PTC-free when tumour sizes are above 2·5 cm, and it was not negligible when tumour sizes were above 1·5 cm.

Modelling data sets and the best-fit model. We preselected three candidate models to determine the best-fit model, in which the presence of macroscopic lymph node, tumour size ≥1 cm, initial surgery in the cancer care referral hospital, TT or near-TT surgery did not show any interaction with each other (AIC = 216·18). The model showed that tumour size ≥1 cm, and the presence of macroscopic lymph node metastasis were identified as independent predictors of persistence when adjusted for the hospital of initial surgery and type of surgery (Table 4). The patients submitted to TT or near-TT had significantly increased chance of persistence compared with the PTC-free survival group (Table 4). For the recurrence-only group, the model revealed that the cancer care referral hospital was an independent predictor.

Discussion

Our study emphasizes the importance of distinguishing specific predictors for PTC persistence and recurrence. Tumour size and macroscopic lymph nodes appear to be independent predictors for persistence, while the hospital of initial surgery, which was used as a proxy for the quality of care effectiveness, is a predictor for recurrence.

Some authors have reported that different cut-off points for tumour size can predict recurrence and death.[8, 20–22] Previous reports show that recurrence and lethality rates increase linearly except with tumours <1 cm,[23] and tumour size greater than 2 cm has been identified as a predictor of persistence compared with tumours smaller than 1 cm (RR = 2·8; $P < 0·01$).[21] A tumour larger than 3 cm is a predictor of a 6% increase in both

Table 2. Clinical disease status at baseline and their associations with persistent and recurrent PTC (n = 190)

	PTC-free n = 102 (54%)		Outcome groups Persistent PTC n = 56 (29%)		Recurrent PTC n = 32 (17%)		
Variable	No.	%	No.	%	No.	%	*P*-value
Local aggressiveness							
Locally aggressive (pT3 + pT4) (n = 74)	25	25	36	64	13	41	<0·001**
Locally limited (pT1 + pT2) (n = 83)	58	57	16	29	9	28	
Unknown (pTx) (n = 33)	19	18	4	7	10	31	
Macroscopic lymph node metastasis *(pN1 and clinical, cN1)*							
Yes (n = 63)	22	22	31	56	10	31	<0·001**
No (n = 76)	54	53	13	23	9	28	
Unknown (n = 51)	26	25	12	21	13	41	
TNM stage at initial treatment							
Advanced High-risk TNM (n = 59)	12	12	37	66	10	31	<0·001**
III–IV (n = 55)	12	–	33	–	10		
II (<45 years) (n = 4)	–	–	4	–	–		
Low-risk TNM (n = 97) (base)	60	59	18	32	19	60	
II (≥45 years) (n = 1)	1	–	–	–	–		
I (n = 96)	59	–	18	–	19		
Unknown: n = 34 (all aged ≥45 years.)	30	29	1	2	3	9	
Distant metastasis (M) at initial treatment							
Yes (n = 18)	–	–	18	32	–	–	<0·001**
No (n = 171)	102	100	38	68	31	97	
Unknown (n = 1)	–	–	–	–	1	3	

The left column shows the absolute frequency of variables in the study cohort at baseline.
PTC, papillary thyroid cancer. p, pathological; c, clinical. Assessments based on the disease status of the tumour (pT), lymph node (pN, cN) and distant metastasis (M) stated in the seventh edition of the tumour node metastasis (TNM) system UICC/AJCC.
The *P*-value refers to the chi-square test.
**The *P*-value is significant.

Table 3. Hospital of initial surgery and treatment interventions at baseline and their associations with persistent and recurrent PTC (n = 190)

	Outcome groups PTC-free n = 102 (54%)		Persistent PTC n = 56 (29%)		Recurrent PTC n = 32 (17%)		
Variable	No.	%	No.	%	No.	%	*P*-value
Hospital of initial surgery							
Cancer care referral hospital (n = 91)	41	40	34	61	16	50	0·046**
Others (n = 99)	61	60	22	39	16	50	
Medical treatments							
Type of thyroid surgery							
Total or near-total thyroidectomy (n = 119)	58	57	44	79	17	53	0·007**
Others (n = 70)*	44	43	11	20	15	47	
Unknown (n = 1)	–	–	1	1	–	–	
Neck dissection during initial surgery							
Yes (n = 55)	21	21	24	43	10	31	0·008**
No (n = 109)	67	66	24	43	18	56	
Unknown (n = 26)	14	13	8	14	4	13	
RAI therapy at any time							
Yes (n = 128)	62	61	41	73	25	78	0·102
No (n = 62)	40	39	15	27	7	22	
RAI therapy and time interval before first dose							
Yes, ≤1 year (n = 81)	42	41	27	48	12	38	0·102
Yes, >1 year (a) (n = 47)	20	20	14	25	13	41	
No iodine (n = 62) (reference)	40	39	15	27	7	21	

The left column shows the absolute frequency of variables in the study cohort at baseline.
PTC, papillary thyroid cancer. RAI, radioactive iodine.
*Others (n = 70): partial thyroidectomy: 61; tracheostomy: 2; others: 4.
The *P*-value refers to the chi-square test.
***P*-value is significant.

recurrence and death compared with a tumour less than 1 cm in size.[23] In 1994, Mazzaferri and Jhiang claimed that the 30-year lethality risk increased 17 times when the tumour size increased up to 2·5 cm, compared with a tumour size <1·5 cm.[23] Tumour sizes $1 < T \leq 4$ cm, tumours >4 cm and tumours with extrathyroidal invasion had higher relative risks for recurrence, when compared with tumour size <1 cm, adjusted for age and sex in a Cox regression model of DTC.[22] Leboulleux *et al.* [9] were the first to assess outcome predictors separately and identified tumour size as a predictor of persistence and lymph nodes as a predictor of both persistence and recurrence. These findings are very similar to ours and endorse the use of tumour size as a predictor of persistence, as we concur that tumour size ≥1 cm revealed an increased chance of persistence per each 1-cm enlargement of tumour size.

Macroscopic lymph node metastasis is a predictor that is specifically associated with PTC persistence (early relapse) in our model, but not recurrence (late relapse). Several previous studies have confirmed the relevance of macroscopic lymph node metastasis as a classical predictor of persistence or recurrence.[23–26] However, our findings differ from these studies concerning lymph nodes as predictors of PTC recurrence, although data were almost significant.[8,9]

The hospital of initial surgery acts mainly as a proxy for other variables [16] related to the quality of service, and it is a plausible predictor, not a risk factor in the epidemiological theoretical framework.[17–19] The setting of initial surgery at cancer care referral hospital was associated with recurrence after being adjusted to the model. It appears that specialized cancer care hospitals offer better treatment, which could decrease the chance of early relapse (persistence), as the head and neck surgery specialists are highly skilled at performing complex PTC surgical procedures due to their ability to explore neck structures more extensively and appropriately compared with surgeons from local hospitals.[2,27–31] In the present study, the patients without initial distant metastasis who used the cancer care referral hospital for their initial surgery had more initial morbidity burden (high-risk TNM stages), but were treated with a higher standard of care during the initial surgery, leading to PTC recurrence instead of persistence.

The lack of association of outcome with age, sex and use of RAI contrasts with the results of many studies,[23,32–35] and we report that RAI therapy is only associated with recurrence through the univariate analysis.

Of note, according to the American Thyroid Association (ATA) Management Guidelines, the low-risk category includes intrathyroidal PTC of all sizes;[34] however, we show herein that tumour size is highly associated with persistence, mainly depending on the hospital of initial surgery. The study of predictors will certainly add discretionary value regarding the initial

Table 4. Multinomial logit analysis: univariate analysis and final best-fit multivariable predictor model for PTC outcomes of persistence (up 1-year relapse) and recurrence (1–10 year relapse)

	Univariate analysis						Multivariable analysis§					
	Persistent group *vs* PTC-free group			Recurrent group *vs* PTC-free group			Persistence			Recurrence		
Variables	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Sex (male)	3·49	1·59; 7·66	0·001**	0·90	0·27; 2·95	0·859						
Age year ≥ 45	2·04	1·05; 3·96	0·036**	0·90	0·4; 2·02	0·802						
Age year (mean age cases)	1·03	1·01; 1·05	0·002**	1·00	0·98; 1·03	0·893						
Surgical pathology findings												
Tumour size (T) (cm, mean)	1·34	1·09; 1·63	0·005**	1·2	0·94; 1·54	0·153	1·30	1·01; 1·67	0·043**	1·23	0·90; 1·67	0·187
Histological variants (classical)	1·19	0·4; 3·57	0·760	2·38	0·6; 9·37	0·217						
Multicentricity (Yes)	0·67	0·32; 1·43	0·303	1·06	0·39; 2·89	0·914						
Extrathyroidal extension (Yes)	5·07	2·1; 12·21	<0·001**	7·11	1·73; 29·19	0·007**						
Vessel invasion (Yes)	2·31	0·72; 7·38	0·157	0·6	0·13; 2·81	0·517						
Pathological lymph node metastasis*	0·39	0·09; 1·69	0·208	0·27	0·03; 2·48	0·250						
Clinical disease status												
Local aggressiveness (pT3 + pT4)†	5·22	2·46; 11·08	<0·001**	3·35	1·27; 8·84	<0·001**						
Macroscopic lymph node metastasis-	5·85	2·59; 13·23	<0·001**	2·73	0·98; 7·62	0·056	6·17	2·40; 15·88	<0·001**	2·47	0·76; 8·01	0·134
High-risk TNM stage at initial treatment‡	12·33	5·14; 29·58	<0·001**	2·84	1·01; 8·02	0·040**						
Medical treatments												
Initial surgery in cancer care referral hospital	2·30	1·18; 4·48	0·014**	1·49	0·67; 3·30	0·329	2·53	0·96; 6·67	0·061	3·79	1·07; 13·44	0·039**
TT or near-TT during initial surgery	3·03	1·41; 6·54	0·005**	0·86	0·39; 1·91	0·710	3·82	1·12; 12·99	0·032**	0·61	0·19; 2·03	0·422
Neck dissection (Yes)	3·19	1·51; 6·74	0·002**	1·77	0·71; 4·43	0·220						
RAI Yes, ≤1 year study population (n = 190)	1·71	0·80; 3·69	0·168	1·64	0·58; 4·56	0·350						
RAI Yes, >1 year study population (n = 190)	1·87	0·76; 4·61	0·176	3·71	1·28; 10·77	0·016**						
RAI Yes ≤1 year; initial TT or nTT, n = 119	1·14	0·44; 2·95	0·793	5·46	0·65; 45·87	0·118						
RAI Yes >1 year, initial TT or nTT (n = 119)	1·35	0·41; 4·50	0·625	6·00	0·58; 61·84	0·132						

PTC, papillary thyroid cancer; RAI**,** Radioactive iodine; TT or near-TT (nTT), *Total thyroidectomy or near total thyroidectomy* during initial surgery.
*Presence of pathological lymph node metastasis stage (pN1) for shorter interval.
†,‡Local aggressiveness based on tumour pathology stage (pT3 + pT4) and high-risk tumour node metastasis (TNM) stage defined in the seventh edition of the TNM system UICC/AJCC.
§There were no interactions, including between type of surgery and tumour size.
**The *P*-value is significant.

management of thyroid cancer when uncertainty is present, such as for patients younger than 45 years assessed by the TNM stage system.[30] The independent increased chances for persistence as a result of the presence of macroscopic lymph node metastasis and tumour size bigger than 1 cm might guide a deep consideration for planning a more extensive initial surgery to prevent persistence. Furthermore, the pre-operative predictors were designed to assess persistence separately from recurrence and do not conflict with the ATA guidelines postoperative risk stratification for recurrence.[34]

In the present report, the selection of our patients corresponds to an unbiased population study, which was confirmed by the similarity of sex and age profiles among patients who were included and those excluded. The excluded patients (n = 28) had similar characteristics compared with the whole population, regarding sex and age profile (female: male =4·6:1;

mean age of 46 years old; median age of 44·5 years old). The census (all the population comprised of adults with PTC between 1990 and 1999 followed up at a hospital setting) offers advantages over the study of a sample for estimating predictors for PTC persistence and recurrence. Another advantage of this study population was the possibility to estimate predictors due to the high rate of relapse events.

One of the limitations of the present study was the lack of data to properly assess the microscopic pathological characteristics of tumours, including the extrathyroidal extension, which is a potential predictor for both outcomes. Although several studies have shown a significant association between pN and recurrence,[9,35] it was not possible for us to analyse this association, due to missing data and the low frequency of neck dissections. However, regarding lymph nodes, Ito *et al.* [25] have claimed that cN is a better predictor than pN.

The study population size likely limited the chance to assess small effects, such as RAI therapy for the entire data set or its association with recurrence. In addition, the low number of patients with recurrence might have limited the statistical analysis about its association with the presence of macroscopic lymph node, as suggested by the large CI.

In future studies, we suggest persistence to be examined separately from recurrence. Based on our results, persistence might be associated with late diagnosis and surgical approach. Recurrence is still a concern after initial PTC surgery at a cancer hospital and suggests that recurrence could be connected to tumour biology itself.

Practical implications of study findings for the clinic and research

Macroscopic lymph node metastasis and tumour size act as predictors of increased likelihood of persistence. As an easily assessed predictor marker at baseline that is required for the TNM system, cN1 could be used to tailor the treatment for a specific patient's need.

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Authors contributions

Taciana Padilha de Castro, William Waissmann, Taynãna César Simões, Rossana Corbo R. de Mello and Denise Pires de Carvalho studied the design. Taciana Padilha de Castro collected the data. Taciana Padilha de Castro and Denise Pires de Carvalho analysed the data. William Waissmann gave scientific advice. Taciana Padilha de Castro, Rossana Corbo R. de Mello and Denise Pires de Carvalho discussed the results. William Waissmann and Taynãna César Simões discussed the data. Taciana Padilha de Castro and Denise Pires de Carvalho wrote the manuscript. Taynãna César Simões performed statistical analysis.

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