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Determinants of Structural Recurrence in Papillary Thyroid Carcinoma: A 10-Year Single-Center Cohort Study

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ABSTRACT

Well-differentiated papillary thyroid carcinoma (PTC) is generally tied to an exceptionally good outlook; nonetheless, a handful of pathological traits—most notably macroscopic extrathyroidal extension and tumor size reaching or exceeding 2 cm—have been linked with structural reappearance of disease. The present study aimed to determine which clinical and histopathological features most strongly predict disease-free survival in patients undergoing total thyroidectomy for PTC. A retrospective review of records was conducted, drawing on 750 subjects who underwent total thyroidectomy, either alone or accompanied by neck dissection, at a tertiary academic cancer referral institution from 2014 to 2024. Data covering clinical presentation, pathology reports, and oncologic follow-up were evaluated over a maximal tracking period of 100 months. The statistical framework comprised Kaplan–Meier survival plots, log-rank comparisons, and Cox proportional hazards regression. A structural recurrence occurred in 4% of the cohort, and overall survival was 99%. When subjected to multivariate testing, the sole factors that persisted as independent correlates of recurrence were macroscopic extrathyroidal extension (HR 3.29; P = 0.008) and tumor diameter (HR 1.32; P = 0.013). Neither age, smoking history, perineural nor vascular invasion, nor central neck node involvement showed a statistically meaningful relationship with structural relapse. Macroscopic extrathyroidal extension, together with increasing tumor diameter, emerged as the dominant prognostic factors for structural recurrence in the PTC population. Collaborative multi-institutional studies are called for to authenticate these patterns across the broader Brazilian populace.

Keywords: Thyroid neoplasms, Cancer recurrence, Thyroidectomy, Extrathyroid extension, Papillary thyroid carcinoma, Differentiated thyroid cancer

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Introduction

Well-differentiated papillary thyroid carcinoma makes up close to 84% of all cancers arising in the thyroid gland. Even with its high rates of occurrence and prevalence, overall survival hovers near 98.5%, as the preponderance of tumors is discovered at dimensions under 1 cm [1]. Within Brazil, the yearly projection for 2023 to 2025 anticipates 16,660 new cases, corresponding to roughly 7.68 cases per 100,000 people [2].

The proportion of individuals who remain free of disease (DFS) after surgical removal approximates 85.8% at 3 years, with structural recurrence predominantly manifesting in the cervical lymphatics and lung parenchyma [3].

Several factors have been implicated in structural recurrence, including lymph node spread, multicentric growth, lymphovascular space involvement, and extrathyroidal extension (ETE). Within this group, ETE is the most impactful on recurrence probability [4].

The 2015 guidance document from the American Thyroid Association (ATA) on differentiated thyroid cancer names histological subtype, molecular markers, lateral compartment lymph node engagement, and extrathyroidal extension as central harbingers of disease recurrence. ETE, specifically, is underscored as a principal contributor to an adverse prognosis [5].

Earlier reports have suggested that tumor diameters exceeding 2 cm correlate with shorter disease-free survival when other risk factors are present. In contrast, they do not shift overall survival or recurrence-free survival curves independently [6-8].

While systemic agents—sorafenib, lenvatinib, and cabozantinib among them—have diversified the management options for advanced thyroid cancer, their application remains reserved for scenarios involving unresectable tumors, widely disseminated disease, or high-grade histological variants [5].

As a result, surgical excision via thyroidectomy remains the first-line definitive treatment for well-differentiated papillary thyroid cancers, affording the strongest chance of sustained disease suppression [5].

The present study aimed to determine which clinical and histopathological features most strongly predict disease-free survival in patients undergoing total thyroidectomy for PTC.

Materials and Methods

This retrospective cohort analysis was conducted at the Dr. Arnaldo Cancer Institute (Instituto de Câncer Doutor Arnaldo), a tertiary-level center in São Paulo, Brazil. Spanning April 2014 through November 2024, the dataset comprised 750 consecutive persons who received total thyroidectomy, with or without a neck dissection, for histopathologically proven well-differentiated papillary thyroid carcinoma. Postoperative observation windows ranged from 6 to 100 months.

The primary outcome of interest centered on evaluating influences on disease-free survival (DFS) among individuals diagnosed with well-differentiated papillary thyroid carcinoma who were managed with total thyroidectomy.

A secondary aim was to pinpoint clinical and histopathological parameters associated with structural disease recurrence.

Structural recurrence was operationalized as thyroid tissue identified via cytologic sampling or core needle biopsy at any stage of surveillance following total thyroidectomy.

Criteria for study entry included: age > 18 years, treatment under the Brazilian publicly funded health network (SUS), thyroid nodule categorization according to the Bethesda System for Reporting Thyroid Cytopathology, and total thyroidectomy performed at the Dr. Arnaldo Cancer Institute.

For nodules classified as benign on cytology (Bethesda II), the decision to operate was based on compressive symptoms or cosmetic distress; the presence of malignancy was ultimately established on definitive histopathologic sections.

The investigation relied on the initial cytologic interpretation, without recourse to slide re-review or repeat fine-needle aspiration at the study institution.

When cytology was nondiagnostic or of uncertain significance (Bethesda I or III), molecular assays were not pursued because they were unavailable through the public system. Therefore, enrollment was restricted to patients furnishing two Bethesda I/III reports obtained no more than 6 months apart.

All histopathological evaluations adhered to standardized operating procedures, employed identical equipment, and were interpreted by a single dedicated pathology team throughout the entire duration of the study, a measure that ensured diagnostic uniformity.

Exclusion criteria encompassed histopathological confirmation of medullary carcinoma, anaplastic carcinoma, or any other poorly differentiated thyroid neoplasm, together with a background of hyperthyroidism or any thyroid resection previously conducted at an outside facility.

Data processing, statistical testing, and graphical rendering were performed using the Python programming language (version 3.12.1) and the pandas, numpy, matplotlib, and seaborn libraries.

The statistical plan incorporated Pearson correlation coefficients, chi-square tests, and logistic regression to probe associations between categorical explanatory variables and the binary endpoint. Linear regression was additionally applied to disentangle inter-variable relationships in the multivariate setting. Statistical meaningfulness was accepted at a P-value of < 0.05.

Results and Discussion

Over the interval spanning 12 April 2014 through 24 November 2024, the study enrolled 750 consecutive individuals who underwent total thyroidectomy with histopathologically proven well-differentiated papillary thyroid carcinoma **(Table 1)**, and the postoperative observation period ranged from 6 months to 100 months.

Table 1. Clinical and histopathological categorical variables.

Variable	Category	Relative frequency (%)	Absolute frequency
Gender	Female	60.9	457
Gender	Male	39.1	293
Age	17–29	6.7	50
Age	30–39	19.1	143
Age	40–49	25.5	191
Age	50–59	25.5	191
Age	≥ 60	23.3	175
Smoking	No	86.4	648
Smoking	Yes	13.6	102
Alcoholism	No	94.8	711
Alcoholism	Yes	5.2	39
FNA (Bethesda)	I	1.2	9
FNA (Bethesda)	II	4.5	34
FNA (Bethesda)	III	19.3	145
FNA (Bethesda)	IV	12.5	94
FNA (Bethesda)	V	34	255
FNA (Bethesda)	VI	28.4	213
pT staging	1	65.1	488
pT staging	2	18.4	138
pT staging	3	16.5	124
pN staging	0	84.1	631
pN staging	1a	9.9	74
pN staging	1b	6	45
Extrathyroidal Extension	Absent	87.1	653
Extrathyroidal Extension	Present	12.9	97
Perineural Invasion	No	93.9	704
Perineural Invasion	Yes	6.1	46
Vascular Invasion	No	89.9	674
Vascular Invasion	Yes	10.1	76
Radioiodine Therapy	No	73.2	549
Radioiodine Therapy	Yes	26.8	201

Female patients constituted 457 of the total sample (60.93%). The average age at the time of surgery was 49.14 years (SD = 13.14). One hundred and two participants (13.6%) identified as active smokers, and 39 individuals (5.2%) acknowledged habitual alcohol intake.

Cytological assessment of thyroid nodules via preoperative fine-needle aspiration (FNA) produced results that were either suspicious for malignancy or definitively malignant in 62.4% of instances **(Table 1; Figure 1).**

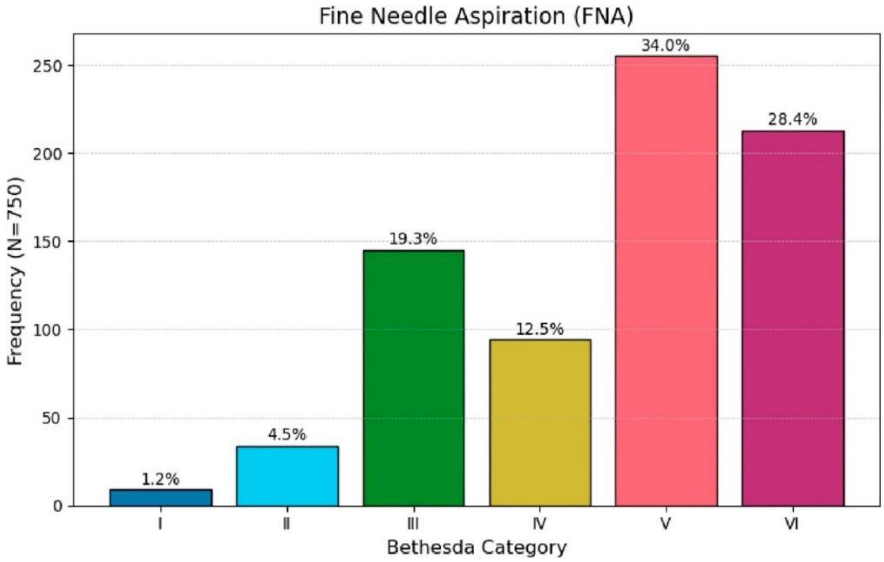

Figure 1. Distribution of Bethesda System categories for thyroid cytopathology in 750 patients.

Ultrasound-based TIRADS categorization was retrievable from the records of merely 235 subjects (31.3%), a circumstance that precluded its inclusion in the exploratory statistical evaluations.

Pathological tumor size ranged widely, from 0.2 cm to 11.0 cm, yielding a mean of 1.8 cm and a standard deviation of 1.4 cm **(Table 2).** Breaking the series into dimensional groupings revealed that the preponderance of nodules (69.5%) fell within the ≤ 2 cm bracket; 24.8% measured between 2 and 4 cm, and the remaining 5.7% exceeded 4 cm **(Figure 2).**

Table 2. Descriptive statistics for continuous histopathological variables.

Variable	Max	P75	P25	Min	SD	Mean
Resected lymph nodes	74	3	0	0	8.2	3.3
Metastatic lymph nodes	51	2	0	0	5.8	2.5
Tumor diameter (cm)	11	2.4	0.9	0.2	1.4	1.8

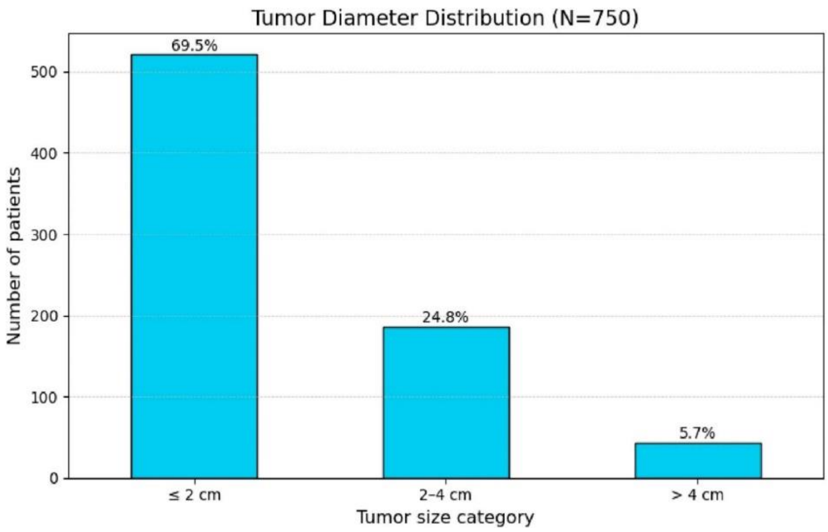

Figure 2. Frequency distribution of tumor size categories (diameter in cm) in 750 patients.

The microscopic features of the resected specimens were systematically examined. All enrolled subjects carried a confirmed diagnosis of papillary thyroid carcinoma. According to the eighth edition of the AJCC TNM staging manual, 488 patients (65.1%) were pT1. The relative frequencies of pT2 and pT3 stages were 18.4% and 16.5%, respectively.

Lymph node clearance of the central compartment was undertaken in 233 patients, while lateral neck dissection was carried out in 45 cases. The majority—472 individuals—had no form of cervical lymphadenectomy performed. Consistent with this, 84.1% of the overall cohort showed no pathological evidence of nodal metastatic deposits.

Extrathyroidal extension was not identified in 653 specimens (87.1%), whereas it was documented in the remaining 97 specimens (12.9%). Perineural invasion was encountered in 33 patients (5.9%), and vascular invasion was present in 68 instances (12.2%).

The overall survival probability at the 100-month time point equaled 99% **(Figure 3).** The relationship linking histopathological parameters to disease-free survival was subsequently investigated. During the entire surveillance period, structural disease relapse was diagnosed in 30 cases, amounting to 4% of the study population. Mortality was an exceedingly rare event, occurring in just two patients.

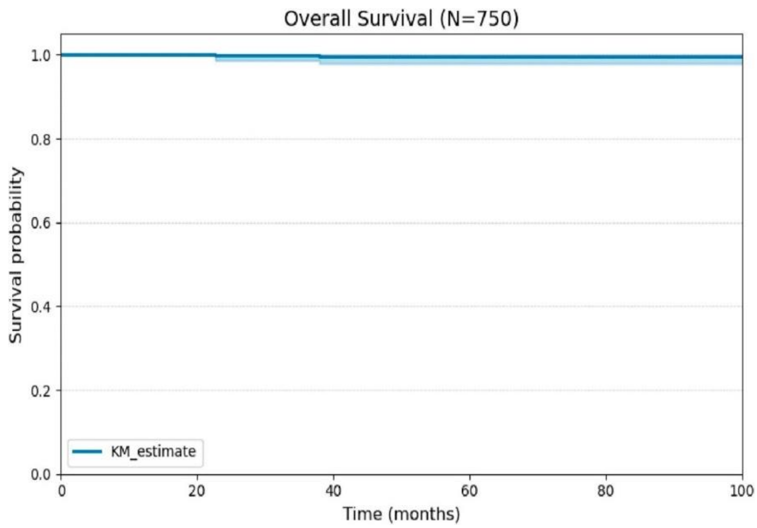

Figure 3. Kaplan-Meier curve for Overall Survival (OS) of the cohort of 750 patients over 100 months of follow-up.

Univariate analyses were then applied to the remaining dichotomous histopathological variables. Vascular invasion and perineural invasion displayed broadly analogous behavior, with neither reaching statistical significance for disease-free survival **(Figures 4 and 5).**

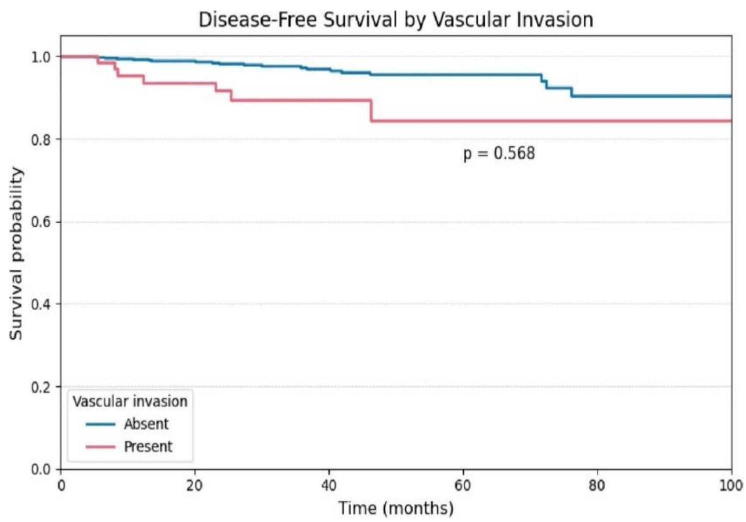

Figure 4. Kaplan-Meier curve for disease-free survival stratified by the presence or absence of extrathyroidal extension in 750 patients.

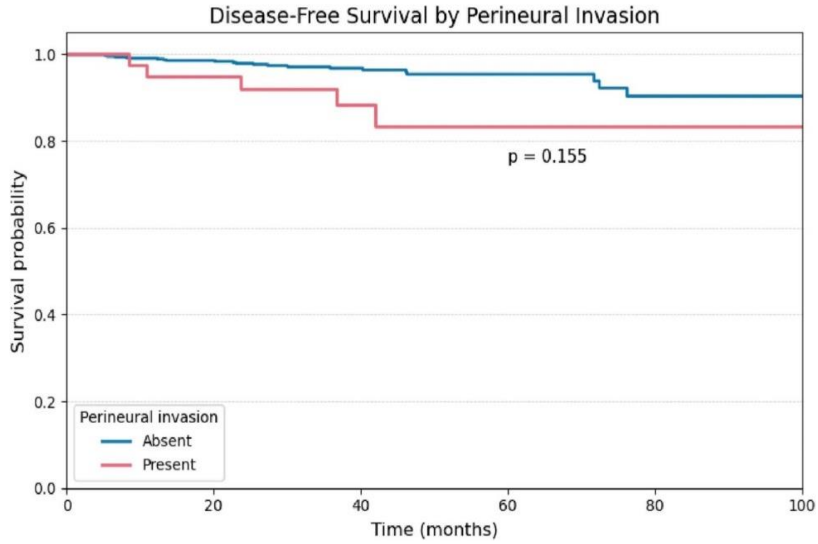

Figure 5. Kaplan-Meier curve for disease-free survival stratified by the presence or absence of vascular invasion.

Constraining the dataset to patients staged as pN0 or pN1a (n = 705), the presence of central neck nodal disease was associated with a statistically significant decrement in disease-free survival (P = 0.03), as shown in **Figure 6**.

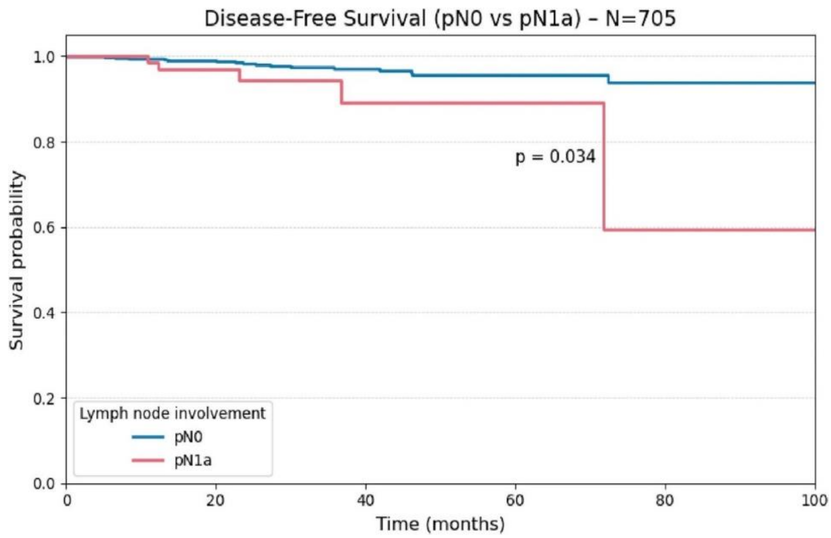

Figure 6. Kaplan-Meier curve for disease-free survival stratified by perineural invasion status.

When log-rank testing was employed for pairwise contrasts, both central compartment (pN1a; P = 0.034) and lateral compartment (pN1b; P = 0.010) lymph node metastases were associated with a statistically significant shortening of disease-free survival relative to patients classified as node-negative (pN0), underscoring the adverse prognostic implications of nodal spread. In contrast, the disease-free survival trajectories of the pN1a and pN1b subsets were virtually indistinguishable (P = 0.982), as illustrated in **Figure 7**.

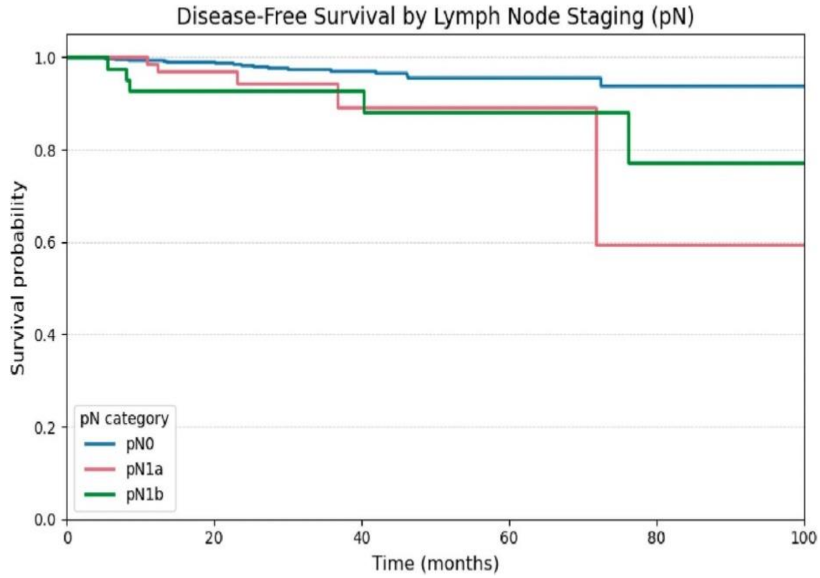

Figure 7. Kaplan-Meier curve for Disease-Free Survival comparing patients with central lymph node involvement (pN1a) versus absence of lymph node involvement (pN0) (n = 705).

Focusing on the histopathologically determined tumor dimension, the primary lesion diameter was subdivided into three bands: 2 cm or smaller (n = 501), between 2.1 and 4.0 cm (n = 164), and greater than 4.0 cm (n = 40). Those whose tumors did not exceed 2 cm had the most favorable disease-free survival among the three groups. The survival curves diverged significantly across these size categories (global log-rank test, $\chi 2 = 10.58$; P = 0.01), as shown in **Figure 7.**

From the survival plots **(Figure 7),** subjects with tumors > 4 cm had a substantially greater likelihood of structural recurrence than the reference group with tumors ≤ 2 cm (P = 0.001). The comparison of ≤ 2 cm lesions against the intermediate 2.1–4.0 cm category approached but did not firmly cross the threshold of significance (P = 0.05), and no reliable difference emerged when contrasting the 2.1–4.0 cm and > 4.0 cm strata (P = 0.13).

Because detailed information on radioactive iodine (RAI) activity administered and the timing of therapy was missing for a sizable fraction of records, RAI exposure was deliberately excluded from the core adjusted regression models. In a supplementary, unadjusted Cox regression performed for exploratory purposes that compared participants who received RAI at any point (n = 201) against those with no history of RAI treatment (n = 549), the instantaneous risk of structural recurrence appeared substantially higher in the RAI-treated subset (HR = 6.79, 95% CI = 2.89–15.97; P < 0.005; concordance 0.74). This result very likely reflects confounding by indication and possible differential misclassification of the exposure over the course of follow-up, and it must not be ascribed a causal interpretation. These numbers are reported solely to ensure full transparency.

Upon fitting the multivariate Cox proportional hazards model **(Table 3)**, only tumor diameter and extrathyroidal extension remained independently associated with structural recurrence. The effect of tumor diameter remained statistically significant (HR: 1.30; 95% CI: 1.04–1.63; P = 0.019), alongside the independent contribution of extrathyroidal extension (HR: 3.21; 95% CI: 1.32–7.77; P = 0.010).

Table 3. Univariate and multivariate analysis of disease-free survival. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a Cox regression model.

Variable	P multivariate	HR (95% CI) multivariate	P univariate	HR (95% CI) univariate
Age	0.074	0.98 (0.95–1.00)	0.047	0.97 (0.95–1.00)
Tumor diameter (cm)	0.019	1.30 (1.04–1.63)	< 0.001	1.37 (1.14–1.61)
Extrathyroidal extension	0.01	3.21 (1.32–7.77)	< 0.001	4.94 (2.36–10.34)
Perineural invasion	0.858	0.91 (0.30–2.71)	0.014	3.13 (1.26–7.76)
Vascular invasion	0.571	1.32 (0.50–3.49)	0.007	2.85 (1.34–6.06)
pN1a	0.639	1.31 (0.42–4.04)	0.074	2.43 (0.92–6.41)
pN1b	0.253	1.88 (0.64–5.52)	0.027	2.86 (1.12–7.27)

After multivariable adjustment, perineural invasion (HR: 0.91; 95% CI: 0.30–2.71; P = 0.858), vascular invasion (HR: 1.32; 95% CI: 0.50–3.49; P = 0.571), and lateral lymph node metastasis, designated pN1b (HR: 1.88; 95% CI: 0.64–5.52; P = 0.253), all lost the statistical signals they may have shown in unadjusted testing.

Advancing age demonstrated a weak, borderline inverse association with structural recurrence (HR: 0.97; 95% CI: 0.95–1.00; P = 0.047), a pattern compatible with a modest protective effect among older individuals. Central lymph node metastasis (pN1a) fell short of conventional significance levels in the univariate context (HR: 2.43; 95% CI: 0.92–6.41; P = 0.074).

Following full adjustment within the multivariable Cox proportional hazards framework, only tumor diameter (HR: 1.30; 95% CI: 1.04–1.63; P = 0.019) and extrathyroidal extension (HR: 3.21; 95% CI: 1.32–7.77; P = 0.010) stood as independent prognostic markers for structural recurrence.

The apparent predictive value that several other variables displayed in unadjusted univariate analyses was no longer detectable after controlling for confounders: perineural invasion (HR: 0.91; 95% CI: 0.30–2.71; P = 0.858), vascular invasion (HR: 1.32; 95% CI: 0.50–3.49; P = 0.571), central compartment nodal disease coded as pN1a (HR: 1.31; 95% CI: 0.42–4.04; P = 0.639), and lateral cervical lymph node involvement coded as pN1b (HR: 1.88; 95% CI: 0.64–5.52; P = 0.253). Even when point estimates indicated heightened risk, none of these factors achieved statistical significance after entering the multivariate model.

The present retrospective cohort analysis set out to uncover the dominant clinical and histopathological drivers of structural disease recurrence in subjects carrying a diagnosis of well-differentiated papillary thyroid carcinoma. A structural recurrence occurred in 4% of the sample (30 instances), making it an uncommon outcome within the range of figures reported internationally. The experience reported by Medas *et al*. [4] indicates a 5-year structural reappearance rate of 6.2% in a retrospective cohort of 579 patients with differentiated thyroid carcinoma. Likewise, Iizuka *et al*. [3] chronicled relapses in 13.7% of 284 subjects stratified as intermediate or high risk over a 3-year postoperative window following radioiodine administration.

Every operation in this series was performed by a highly specialized surgical group embedded within a tertiary-referral academic oncology program. This reality plausibly contributed to the comparatively low recurrence rates we documented. This line of reasoning is supported by the findings of Loyo *et al*. [9], who analyzed a large data repository comprising 871,644 thyroidectomy recipients and found materially better short- and long-term outcomes when care was concentrated in centers with high operative throughput.

Lesion size emerged as a meaningful predictor of structural relapse in both crude and covariate-adjusted analyses **(Figure 8; Table 3)**. This result is broadly consonant with contemporary scholarship, including contributions by Can *et al*. [10] and Kurtom *et al*. [6], both of which further cement the notion that papillary thyroid microcarcinomas carry an especially indolent disease trajectory.

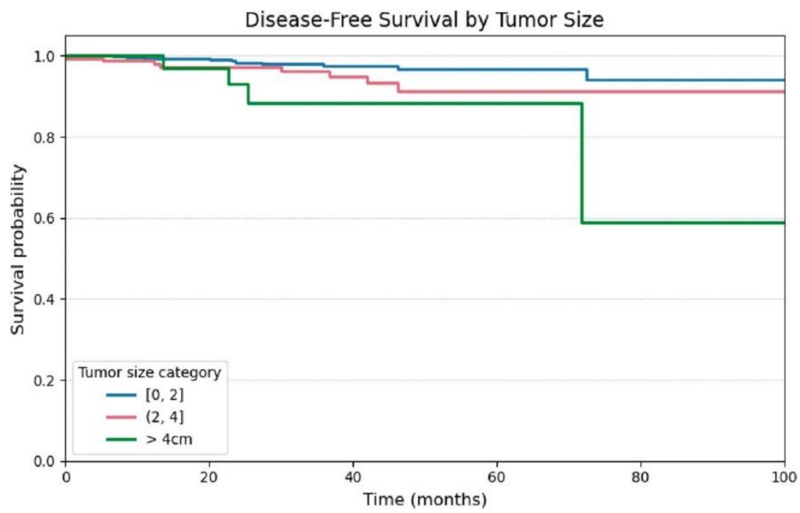

Figure 8. Kaplan-Meier curve for disease-free survival stratified by pathological lymph node staging (pN0, pN1a, pN1b).

It is noteworthy that, although Kaplan-Meier graphical analysis supplemented by the log-rank test did not disclose a statistically compelling separation in disease-free survival curves contingent on the presence versus absence of extrathyroidal extension (P = 0.40); **(Figure 9)**, this selfsame pathological feature surfaced as the single most potent correlate of recurrence within the Cox regression framework, generating a hazard ratio of 4.94 in univariate space and 3.21 upon incorporation of other covariates. One plausible account for this divergence lies in the contrasting mathematical underpinnings of the two approaches: the log-rank procedure effectively contrasts aggregate survival distributions, whereas the Cox formulation estimates the instantaneous influence of each explanatory factor on the hazard function over continuous time and tends to outperform in scenarios where the tally of outcome events remains modest [6].

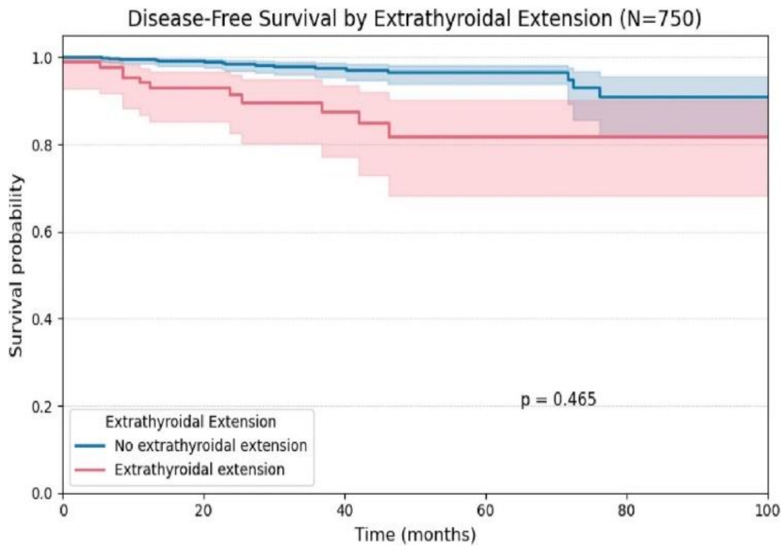

Figure 9. Kaplan-Meier curve for disease-free survival stratified by tumor size categories (≤ 2 cm, > 2 to 4 cm, > 4 cm).

The lean event yield (30 recurrences among 750 participants; 4.0%) has direct implications for inferential capacity. A Schoenfeld-type event-driven projection—premised on a 12.9% prevalence of extrathyroidal extension, a target HR of 1.70, two-sided alpha fixed at 0.05, and 80% desired power—would necessitate roughly 248 events, approximating 6,200 enrolled patients under the assumption of a 4% event fraction. With only 30 events, the present investigation's ability to estimate a hazard ratio of 1.70 is only 16%, a constraint that both rationalizes an intentionally lean multivariable model and warrants privileging the interpretation of effect magnitudes and interval estimates over rigid reliance on p-value cutoffs.

The strong prognostic signal associated with extrathyroidal extension reinforces its designation as an adverse risk indicator in the 2015 American Thyroid Association management framework. It bolsters its standing as a catalyst for recommending adjuvant radioiodine therapy [5, 11]. Anwar *et al*. [12], deploying a closely parallel analytic strategy on a smaller collection of 312 individuals, concurrently identified extrathyroidal extension as the paramount independent determinant of disease recurrence. Population-scale corroboration comes from Weis *et al*. [13], who, in a systematic exploration of 101,087 registrants in the SEER (Surveillance, Epidemiology, and End Results) database, reached similar conclusions. In contradistinction, perineural invasion, lymphovascular space involvement, central neck nodal metastases, and chronological age all fell conspicuously short of exerting a statistically reliable effect on disease-free survival across both unadjusted and adjusted specifications—a constellation of null findings that resonates with earlier published work. Echoing our own data, a Japanese patient series analyzed by Ito *et al*. [14] found that advancing age does not independently predict recurrence, though it remains closely linked with poorer overall survival once disease reaches an advanced stage.

In a complementary vein, Xing *et al*. [15], through a retrospective dissection of 1,849 cases, ascertained that neither central compartment lymphatic involvement nor vascular invasion retained independent predictive value for recurrence within multivariable frameworks, particularly when the analysis was circumscribed to neoplasms smaller than 4 cm. It bears mentioning that, while the investigation conducted by Xing *et al*. [15] integrated BRAF V600E mutational profiling into its prognostic modeling alongside conventional clinicopathologic descriptors, such molecular characterization is not yet systematically accessible through the Brazilian public healthcare apparatus for either pretreatment risk estimation or postoperative triaging [15].

Even though particular attributes may hold prognostic salience in carefully demarcated patient niches, one must remain mindful that statistical formulations built to capture survival and recurrence dynamics inherently reflect the properties of relatively cohesive populations. The expectation that a singular predictive instrument could faithfully anticipate structural relapse across widely dissimilar clinical landscapes is therefore largely unrealistic. Given the profound ethnic, cultural, and socioeconomic mosaic that defines the Brazilian populace, a meaningful prospect emerges to cultivate resilient, regionally nuanced predictive schemas that can differentiate patients poised to gain the most from supplementary therapy or protracted surveillance protocols. Extending the footprint of this inquiry to encompass additional high-volume thyroid cancer management referral centers distributed across the national territory is a logical and necessary next step to amplify the transportability of these observations.

Conclusion

Spanning 750 patients submitted to total thyroidectomy for well-differentiated papillary thyroid carcinoma, this retrospective appraisal identified structural recurrence as an uncommonly encountered event, with a cumulative rate of merely 4% despite lengthy surveillance. The variables that independently conferred a heightened hazard of structural relapse were extrathyroidal extension and primary tumor diameter exceeding 2 cm, both of which maintained statistical robustness across unadjusted and adjusted analyses, in close alignment with the broader body of evidence.

Demographic and pathological factors, including age at presentation, perineural invasion, and lymphovascular infiltration, did not significantly affect recurrence-free survival.

We strongly endorse the design and execution of multicenter investigative collaborations to verify these patterns in other high-volume reference institutions across Brazil and to develop locally calibrated statistical tools for stratifying recurrence risk.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: The Ethics Committee of the Arnaldo Vieira de Carvalho Cancer Institute approved the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement for written informed consent for participation from participants or their legal guardians/next of kin because the data used in this study are retrospective and derived from clinical outpatient consultations. As the study poses no risk to the participants, the Ethics Committee that reviewed the protocol granted a waiver of the Informed Consent Form (ICF).

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