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Management of biopsy proven lymph node metastases from papillary thyroid cancer under active surveillance protocols

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Abstract

Introduction:

Cervical lymph node metastases (LNM) from papillary thyroid carcinoma (PTC) often remain stable over time, supporting conservative management in selected patients. Minimally invasive techniques have emerged as alternatives to surgery. However, evidence comparing these strategies and identifying predictors of progression is limited. This study evaluates the safety of active surveillance in biopsy-proven LNM and aims to identify factors associated with disease progression while exploring the role of minimally invasive treatments.

Materials and Methods

We conducted a retrospective multicentric cohort study including patients with PTC and biopsy-proven LNM followed on an active surveillance protocol at three Latin American centers. Eligible patients had lymph nodes < 2 cm and located away from vital structures. Disease progression and protocol discontinuation were defined as new lymph node disease or enlargement ≥ 3 mm.

Results

The cohort included 72 patients, most were female (82%) with an average age of 40.3 years. After a mean follow-up of 62.8 months, 47 patients (65%) remained under active surveillance, while 25 discontinued surveillance and required intervention, due to disease progression (n = 14) or patient/surgeon´s preference (n = 11). Progressive cases usually happened in older patients. No other variables predicted progression.

Discussion

Active surveillance is safe in properly selected patients with small, non-threatening LNM. Age appears to be the most relevant predictor of structural progression. These findings reinforce the need of a more personalized approach and risk based for the management of lymph node metastasis in differentiated thyroid cancer and that active surveillance is also possible in patients in Latin American cancer centers, providing real-world data from a population that is underrepresented in the current literature.

Title:

Management of biopsy proven lymph node metastases from papillary thyroid cancer under active surveillance protocols

Introduction

Growing evidence suggests that cervical lymph node metastases (LNM) detected after thyroidectomy often remain stable over time. In a cohort of 83 papillary thyroid carcinoma (PTC) patients with at least one malignant lymph node, Tomoda *et al* (1) reported that only 20.5% increased ≥ 3 mm/year after a median follow-up of 7.2 years, almost same value (20%) found by Robenshtok et al (2). These findings highlight the potential for conservative management in selected cases.

The 2025 American Thyroid Association (ATA) guidelines (3) recommend fine-needle aspiration biopsy (FNA) for cytology and thyroglobulin (Tg) measurement in aspirated fluid for suspicious lymph nodes ≥8mm in the central compartment or ≥ 10 mm in the lateral neck, provided that the results are expected to influence therapeutic decisions (3) as opposed to a more interventional proposal in the past that was more commonly advocated for such findings (4). Importantly, Lang et al (5) demonstrated no significant difference in morbidity between patients undergoing reoperative central neck dissection for lymph nodes < 10 mm versus 10–15 mm. In their multivariate analyses, only nodes > 15 mm was independently associated with biochemical incomplete response after reoperative central neck dissection, suggesting that 15 mm may represent a more clinically relevant size threshold (5).

A recent meta-analysis (6) including 486 patients with metastatic nodal differentiated thyroid carcinoma followed for 28–86 months reported lymph node growth ≥ 3 mm in 21% of cases and the emergence of new metastatic nodes in 19%, suggesting that lymph node active surveillance (AS) may represent a suitable strategy for selected patients with small nodal disease, potentially avoiding or delaying surgical reintervention. Surgical reintervention is associated with major complications in 5-8.6% of cases (7–9), and after a mean follow-up of 59.4–60 months, just 53-59.3% achieve an excellent response (8–9).

Beyond identifying which patients may safely avoid immediate surgery, an important unresolved issue is the limited evidence regarding clinical and ultrasonographic predictors of lymph node progression during surveillance. In the context of papillary thyroid microcarcinoma, diffuse thyroid disease and intratumoral vascularity have been associated with a higher risk of tumor progression (10). However, data specifically addressing metastatic lymph nodes are scarce. A single-center study including 50 patients identified a rise in thyroglobulin levels ≥ 0.5 ng/mL as a predictor of lymph node enlargement (11), whereas another single-center study with 40 patients found no demographic, oncologic, or biochemical factors associated with disease progression (12).

Against this background of limited comparative evidence and uncertain predictors of progression, this study aims to evaluate the safety of active surveillance for biopsy-proven metastatic lymph nodes from PTC in three centers in South America, located in different countries (National Cancer Institute—INCA, Brazil, Hospital de Especialidades Carlos Andrade Marín HECAM and Clinica Tiroids – Quito, Ecuador. We also seek to identify predictors of disease progression.

Materials and Methods

Study design and population

This retrospective cohort study included DTC patients who underwent initial total thyroidectomy and subsequently presented with locoregional disease confirmed by FNA cytology and/or by Tg measurement in aspirated fluid. Eligibility criteria for lymph node active surveillance was age > 18 years, persistent or recurrent LNM < 2.0 cm in maximum diameter, located away from vital cervical structures (trachea, recurrent laryngeal nerve, major cervical vessels), and who fully understood and consented to AS.

Exclusion criteria included aggressive histological variants, lymph node disease near vital structures (trachea, recurrent laryngeal nerve or major cervical vessels), prior cervical radiotherapy or systemic therapy, presence of another primary cervical malignancy, and insufficient data in the medical records.

The study was approved by the Institutional Ethics Committee of all participating centers (INCA, Brazil: CAAE 44999521.4.0000.5274), and was performed in accordance with Declaration of Helsinki (2013 revision)

This study included patients with biopsy-proven metastatic cervical lymph nodes from papillary thyroid carcinoma managed at the participating centers. This was a phased study with both retrospective and prospective patient inclusion. The retrospective phase consisted of a review of the institutional cytology database to identify patients with positive FNA results for metastatic lymph nodes, among whom those managed with active surveillance rather than surgical reintervention were selected. From 2017 onward, patient inclusion proceeded prospectively using identical eligibility criteria, with consecutive enrollment of all newly diagnosed patients with biopsy-proven metastatic lymph nodes who were managed with active surveillance. Starting around 2021, radiofrequency ablation (RFA) became available as a minimally invasive therapeutic alternative. From that time onward, a subset of eligible patients underwent RFA according to multidisciplinary team recommendation, patient preference, and the availability of ablation needles and procedural resources.

Clinical data review

Medical records were retrospectively reviewed using a standardized data collection form. Extracted variables included demographic characteristics, histopathological findings, laboratory values, ultrasonographic features, and treatment-related information.

Definitions

Suspicious lymph nodes: postoperative surveillance included neck ultrasound at 3–6 months after thyroidectomy, followed by repeat evaluation every 6–12 months in cases of elevated Tg or anti-thyroglobulin antibodies (TgAbs), or when suspicious sonographic findings were identified. Lymph nodes were considered suspicious when at least one of the following ultrasonographic features was present: microcalcifications, cystic change, peripheral vascularity, hyperechogenicity, or a rounded shape.

Eligibility criteria for lymph node active surveillance: AS was offered to adult patients (> 18 years) with DTC and persistent or recurrent LNM < 2.0 cm in maximum diameter, located away from vital cervical structures (trachea, recurrent laryngeal nerve, major cervical vessels), and who fully understood and consented to AS.

Lymph node active surveillance protocol: Patients enrolled in lymph node active surveillance were evaluated at 6-month intervals with clinical assessment, laboratory testing [thyroid-stimulating hormone (TSH), free thyroxine (fT4), Tg, TgAbs], and confirmation of informed consent. Suppressive levothyroxine therapy was prescribed with a target TSH level < 0.1 mIU/L, unless contraindicated. Neck ultrasonography was performed every 6 months during the first year and annually thereafter if disease stability was maintained.

Criteria for discontinuation of lymph node active surveillance: AS was discontinued if there was evidence of disease progression (LNM growth ≥ 3 mm in any dimension or occurrence of new cervical metastases) or upon patient preference for definitive treatment. Surgery or RFA were offered according to criteria, indication and availability in the service.

Structural incomplete response evaluation: Patients with structural incomplete disease at the end of follow up had the volume calculated with ellipsoid formula ($volume = \frac{\pi}{6} x\ length\ x\ width\ x\ depth$) and were classified as partial response (≥ 30% reduction in volume), stable disease (reduction < 30% or < 20% of increase in volume), and disease progression (> 20% increase in volume).

Ultrasonographic evaluation and FNA biopsy.

In this study, cervical ultrasonography (USG) was systematically performed across all neck compartments by radiologists with established expertise in thyroid imaging or by medical residents under direct specialist supervision in all centers. Examinations were conducted using a high-resolution ultrasound system. All FNAs were performed by experienced radiologists under high-resolution USG guidance and cytology analyzed by an experienced pathologist.

Laboratory evaluation

Between 1986 and 1997, a variety of Tg assays were used with functional sensitivities of approximately 1 µg/L. From 1998 and 2001, an assay of Tg with functional sensitivities of 0.5 µg/L was used. Then, starting in 2001, serum Tg was quantified by immunometric assay (Immulite® 1000 Immunoassay System; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) with a functional sensitivity of 0.2 µg/l. From 2014 onward, we began instead using an immunometric assay approach (Immulite® 1000 Immunoassay System; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) with a functional sensitivity of 0.1µg/L.

Regarding anti-thyroglobulin antibodies Between 1986 and 2009, a variety of TgAb assays were used with functional sensitivities of approximately 60UI/L. From 2009 to 2013, an assay of TgAb with

functional sensitivities of 20/L was used. Then, starting in 2014, serum TgAb was quantified by electrochemiluminescence assay (with a functional sensitivity of 10 UI/L.

Statistical methods

Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables are expressed as frequencies and percentages. Comparisons between groups were performed using the unpaired Student's *t* test or the Mann–Whitney test for parametric and nonparametric quantitative variables analysis, respectively. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Time-to-event analyses were performed using the Kaplan–Meier method. P values less than 0.05 were considered statistically significant.

Patients with positive TgAb, central hypothyroidism or TSH > 0.4mUI/L were excluded from analysis involving Tg measurements. Patients known to be alive at the end of follow-up were censored at the date of last contact. The IBM SPPS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Patients

A total of 72 patients were included, of whom 54 were from Brazil and 18 from Ecuador, all of whom underwent lymph node active surveillance at some point during follow-up. The cohort was predominantly female (81.9%, n = 59), with males accounting for 18.1% (n = 13), and had an average age of 40.32 years at first surgery (range, 19–66) and 51.58years (range 24–86) at AS protocol entering. The majority of patients presented with TNM stage I disease (80.6%) and were classified as having an intermediate-high or high ATA risk (76.4%) (Table 1).

Table 1
Baseline demographic, clinicopathological, and treatment characteristics of patients under AS.

Age at first surgery, years (average ± SD)	**Total cohort (n = 72)**
	40.32 ± 11.95
Age at AS, years (average ± SD)	51.58 ± 12.26
Female sex, n (%)	59 (81.9%)
Histology, n (%)	
PTC	69 (95.8%)
FVPTC	2 (2.8%)
PTC+FVPTC	1 (1.4%)
TNM 8 staging (UICC, 2017), n (%)	
I	58 (80,6%)
II	8 (11.1%)
III	1 (1.4%)
IVa	5 (6.9%)
ATA risk (2025), n (%)	
Low	3 (4.2%)
Low-intermediate	14 (19.4%)
Intermediate-high	24 (33.3%)
High	31 (43.1%)
LN minimum diameter (cm)	0.72
LN maximum diameter (cm)	1.15
Previous RAI ablation	65 (90.3%)
Previous lymphadenectomy for recurrent/persistent disease, n (%)	21 (29.2%)

Initial surgical management consisted of total thyroidectomy in 54.2% of patients (n = 39), total thyroidectomy with central-compartment neck dissection in 27.8% (n = 20), total thyroidectomy with central and ipsilateral-compartment neck dissection in 15.3% (n = 11), and total thyroidectomy with central and bilateral-compartment neck dissection in 2.7% (n = 2).

The most frequent histological type was the classic PTC in 95.8% (n = 69) of the patients. Two patients had follicular variant PTC and one patient had both classic and follicular variant PTC. The largest

diameter of the initial tumor averaged 2.8 (0,4–6) cm. ATA recurrence risk (2025) was low in 3 patients (4.1%), low-intermediate in 14 patients (19.5%), intermediate high in 24 patients (33.3%) and high in 31 patients (43.1%). According to the 8th edition of the tumor, node, metastasis stage (TNM8) staging system for DTC (13), the patients were distributed as follows: 58 (80.6%) in stage I, 8 (11.1%) in stage II, 1 (1.3%) in stage III and 5 (7%) in stage IVa.

Following primary surgical treatment, 65 (90.3%) underwent radioactive iodine (RAI) therapy. After initial surgery, 21 patients (29.2%) required a second surgical intervention consisting of lymph node dissection; among these, 4 patients (6%) underwent a third lymphadenectomy before entering the lymph node active surveillance protocol. The mean time to enter the protocol was 77,35 months (SD, 64,24), ranging from 3.4 to 255.6 months after initial surgery. Four patients were not seen at follow-up during the last year: one died of sudden death, and three did not attend the scheduled follow-up visit.

Cervical disease progression

Of the 72 patients included in the lymph node active surveillance protocol, 47 remain under surveillance, whereas 25 discontinued AS. Discontinuation occurred due to patient preference in 8 cases, lymph node enlargement ≥ 3 mm in 6 cases, the appearance of new lymph nodes in 1 case, combined lymph node enlargement ≥ 3 mm and new lymph nodes in 7 cases, and surgeon decision in 3 cases (Fig. 1).

Among the 25 patients who discontinued AS, 11 underwent lymphadenectomy and one was awaiting surgery by the time this manuscript was written. At last follow-up, response to treatment was classified as excellent in 3 patients, indeterminate in 5, and biochemical incomplete in 1 patient; 2 patients had not yet undergone postoperative ultrasonographic and laboratory evaluation and the patient waiting surgery was not classified. Additionally, 11 patients were treated with RFA. At last follow-up, 6 RFA-treated patients had persistent structural disease: 1 achieved complete response of the ablated lymph node but subsequently developed new nodal disease and is currently awaiting surgery, 2 demonstrated partial response (≥ 30% reduction in volume), 3 had stable disease, and 2 had biochemical incomplete response and 3 evolute with excellent response. Another patient underwent percutaneous ethanol ablation and continues to show disease progression but declined surgical intervention. One additional patient was initially treated with RFA and subsequently underwent surgery 6 months later due to enlargement of another cervical lymph node and presented excellent response at the end of follow-up (Fig. 1).

Among the 47 patients who remained under lymph node AS, one had a biopsy-proven metastatic lymph node measuring 0.9 cm diagnosed in 2008. This patient had previously undergone total thyroidectomy in 2000 and received a cumulative radioactive iodine dose of 250 mCi, with the last administration in 2003. The lymph node has not been visualized on imaging since 2013, and Tg levels have remained < 0.1 ng/mL with negative TgAbs and the patient was classified as excellent response. At the last follow up 2 patients had indeterminate response. Among the remaining 44 patients with structural incomplete response, 9 demonstrated partial response (≥ 30% reduction in volume), 32 had stable disease, and 3 experienced disease progression (> 20% increase in volume). Of the patients with disease progression,

two remained under lymph node AS due to slow progression and one has progressive locoregional disease and lung metastases, high thyroglobulin (302 ng/ml), high volume doubling time (54,5 months) but refuses surgery (Fig. 2).

Among the 72 patients, 6 underwent radioactive iodine (RAI) therapy after entering the lymph node AS protocol. One patient received 150 mCi after the initial surgery and an additional 200 mCi following a positive fine-needle aspiration biopsy, due to persistent radioiodine uptake in lateral cervical lymph nodes and the lungs. The remaining 5 patients had not received RAI after initial surgery and subsequently underwent RAI therapy a mean of 8.2 months after a positive FNAB (range, 1.8–18.8 months).

The mean duration of follow-up was 62.8 months. All patients were alive at the end of follow-up

Nodal disease behavior

Among the 47 patients who remained under AS, only one Brazilian and one Ecuadorian patient demonstrated slow disease progression and elected to continue AS. One Ecuadorian patient had rapid progressive disease but refused surgery.

Of the 25 patients who discontinued AS, 14 did so due to disease progression. Among these, six presented lymph node enlargement ≥ 3 mm, one developed new nodal disease, and seven exhibited both lymph node enlargement and new disease. Management after AS discontinuation included surgery in nine patients, RFA in two, combined RFA and surgery in one, ethanol ablation in one patient who declined surgery, and one patient is waiting surgery. Persistent disease progression was observed in only two patients: one who underwent ethanol ablation and refused surgery, and another who initially underwent RFA but developed new disease four years later and was awaiting surgical treatment at the time of manuscript preparation.

In total, seventeen patients presented with progressive disease. Fourteen discontinued AS, while three chose to remain under surveillance (two due to slow disease progression and one who declined surgery).

Patients with progressive disease were significantly older at first surgery (48.67 ± 13.78 vs. 37.74 ± 10.27 years, $p < 0.01$) and at lymph node metastasis diagnosis (60.99 ± 15.04 vs 48.68 ± 9.85), and more frequently male (35.3% vs. 12.7%, $p = 0.045$). They had also received higher cumulative RAI doses (223.53 ± 149.07 vs. 154.18 ± 107.66, $p = 0.038$). The mean time to progression was 44.28 ± 19.73 months. No other demographic, oncologic, or biochemical variables were significantly associated with disease progression. Moe details shown in Table 2.

Table 2
Comparison of demographic, clinicopathological, biochemical, and ultrasonographic characteristics between patients with stable and progressive disease during lymph node active surveillance. * Fourteen patients discontinued AS because of disease progression and the three who elected to remain on AS despite progression.

Age at first surgery, years (average ± SD)	**Stable Disease (n = 55)**	**Progressive Disease (n = 17*)**	**p**
	37.74 ± 10.27	**48.67 ± 13.78**	**< 0.01**
Age at AS, years (average ± SD)	48.68 ± 9.85	60.99 ± 15.04	0.005
Female sex, n (%)	48 (87.3%)	11 (64.7%)	0.045
Tumor maximum diameter, average ± SD	2.49 ± 1.45	3.76 ± 3.14	0.123
LNM in initial surgery, n (%)	35 (63.6%)	9 (52.9%)	0.429
Central LNM, n	26	8	0.659
Lateral LNM, n	9	1	0.659
Extranodal extension	12	1	0.240
TNM 8 staging (UICC, 2017), n			0.234
I	46	12	
II	6	2	
III	1	0	
IVa	2	3	
ATA risk (2025), n			0.411
Low	3	0	
Low-intermediate	12	2	
Intermediate-high	16	8	
High	24	7	
Time to recurrence, months	77.66 ± 68.94	70.58 ± 50.63	0.697
LN recurrence minimum diameter, cm	0.73 ± 0.34	0.71 ± 0.30	0.799
LN recurrence maximum diameter, cm	1.13 ± 0.40	1.23 ± 0.47	0.368
Central LNM, n	22	4	0.217
Lateral LNM, n	33	13	0.217
US characteristics			

Age at first surgery, years (average ± SD)	Stable Disease (n = 55)	Progressive Disease (n = 17*)	p
	37.74 ± 10.27	**48.67 ± 13.78**	**< 0.01**
Microcalcifications, n	25	6	0.580
Cystic aspect, n	17	4	0.719
Peripheral vascularity, n	15	3	0.147
Hyperechogenicity, n	3	0	0.139
Round shape, n	34	9	0.146
Central hilum absence, n	31	7	0.073
Heterogenicity, n	38	14	0.562
Lobulated margins, n	30	7	0.709
RAI dose before FNAB, mCi	154.18 ± 107.66	223.53 ± 149.07	0.038
Tumor volume doubling time, months	-44.45 ± 206.46	8.4 ± 38.79	0.301
Thyroglobulin doubling time, months	-41.22 ± 107.21	-2.04 ± 36.82	0.244
Basal thyroglobulin, average (ng/ml) ± SD	9.25 ± 24.18	10.35 ± 16.46	0.884
Tg elevation ≥ 0.5ng/ml, n (%)	9 (16.4%)	5 (29.4%)	0.044
Thyroglobulin tendence, n			0.099
Stable (> 24months)	5	1	
Elevation (0–24 months)	6	6	
Reduction (negative DT)	24	4	
Previous RAI ablation, n	48	17	0.187
Previous lymphadenectomy for recurrent or persistent disease, n	15	6	0.525
Time under lymph node active surveillance, months	55.25 ± 47.28	83.33 ± 33.41	0.026

The Kaplan-Meier analysis was performed using the time from the malignant FNAB to disease progression or last follow-up for patients with stable disease. The mean progression-free survival was 139.4 months (95% CI 113.8-164.9) Fig. 3.

Tumor volume doubling time and thyroglobulin doubling time did not differ significantly between patients with progressive and stable disease. The median tumor volume doubling time was 8.4 months in the progressive disease group and − 44.5 months in the stable disease group (p = 0.301), whereas the

median thyroglobulin doubling time was − 2.0 months and − 41.2 months, respectively (p = 0.244). Baseline thyroglobulin levels were also comparable between groups, with median values of 10.35 ng/mL in patients with progressive disease and 9.25 ng/mL in those with stable disease (p = 0.884). In contrast, an absolute increase in thyroglobulin of at least 0.5 ng/mL during follow-up was significantly more frequent among patients with progressive disease than among those with stable disease (29.4% vs. 16.4%, p = 0.044).

TNM staging and ATA risk stratification were comparable between groups, and no ultrasonographic features were predictive of disease progression. However, as shown in Table 3, multivariate analysis failed to show significance, except for age.

Table 3
Binary Logistic Regression Analysis of Factors Associated with Progression During Active Surveillance

Variable	No. analyzed	Progression events	Univariable OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Age at AS entry code	72	17	5.37 (1.67–17.22)	0.005	5.71 (1.11–29.40)	0.037
Female sex	72	17	0.27 (0.07–0.95)	0.042	0.46 (0.07–2.84)	0.401
Extranodal extension	48	11	0.18 (0.02–1.61)	0.126	—	—
Largest tumor diameter code	70	17	2.08 (0.63–6.89)	0.229	—	—
ATA high risk	72	17	0.97 (0.32–2.94)	0.963	—	—
ATA intermediate-high risk	72	17	1.99 (0.65–6.03)	0.226	—	—
Tg increase ≥ 0.5	53	9	4.86 (1.08–21.90)	0.039	3.02 (0.58–15.56)	0.187

Abbreviations: AS, active surveillance; ATA, American Thyroid Association; CI, confidence interval; OR, odds ratio; Tg, thyroglobulin.

**Adjusted model included variables with p < 0.10 in univariable analysis (age at AS entry code, female sex, and Tg increase > 0.5). The complete multivariable model with all seven predictors was not reported because it did not converge reliably due to sparse events/missingness.*

Discussion

In cohort from three different Latin American referral centers including patients with DTC and biopsy-proven metastatic cervical lymph nodes managed initially with lymph node active surveillance, we observed that the majority of patients remained stable over a median follow-up of more than five years, with no disease-specific mortality.

Our findings reinforce accumulating evidence that small-volume nodal metastases in DTC frequently demonstrate indolent behavior (2). In our cohort, the majority of patients remained without structural progression during lymph node active surveillance. An additional 15% discontinued AS for reasons unrelated to disease progression, while 4.2% experienced progression but opted not to undergo intervention. Overall, around 20% of patients developed progression requiring therapeutic intervention, most of them due to enlargement and fewer due to new cervical metastases. Importantly, no thyroid cancer–related deaths were recorded. These results are consistent with prior observational studies demonstrating that most suspicious lymph nodes remain stable for years, with approximately 20% showing measurable growth (1–2). Our progression rate aligns closely with the 21% nodal growth rate reported in the recent meta-analysis by Scheinpflug *et al*. (6) and 23% of Lim *et al* (14), further validating lymph node active surveillance as a viable management strategy in appropriately selected patients. Other Brazilian cohort (12) showed disease progression in 35% patients: 7 (17.5%) due to enlargement ≥ 3 mm, and 7 (17.5%) had new cervical metastasis, also showing the indolent nature of disease progression in properly selected patients.

Notably, the mean time to progression in our series was approximately 44 months, underscoring the slow kinetics of disease evolution and supporting the safety of structured active surveillance protocols. In comparison, Walter *et al*. (12) reported a median time to progression of 15.5 months. Furthermore, the progression-free survival observed in our cohort (139.4 months) was longer than the 79 months reported by Jerkovich F *et al*. (11). This variability likely reflects small number of patients included on all cohorts (40 and 50 patients respectively) and duration of follow up. But ultimately, the high rate of disease stability across diverse cohorts supports lymph node AS as delayed surgical intervention or RFA had not been associated with higher mortality or loss of regional control.

Among all clinicopathologic, biochemical, and ultrasonographic variables evaluated, only age was associated with disease progression. Consistent with our findings, Kim *et al*. (15) and Tomoda *et al*. (1) identified age as a predictor of progressive disease. These findings suggest that while older age may help identify a subset of patients at higher risk for progression, a personalized approach is essential for guiding intervention decisions in patients managed with lymph node AS

Patients who developed progressive disease had received higher cumulative doses of radioactive iodine (RAI). These findings likely reflect a clinical perception of more aggressive disease in this subgroup, prompting more intensive evaluation and treatment. However, despite these differences in management, no significant differences were observed in baseline tumor characteristics, including ATA risk category, TNM stage, primary tumor size, or the presence of extranodal extension. This suggests that conventional

clinicopathologic risk stratification systems may have limited ability to identify patients at risk of progression when dealing with small-volume lymph node disease.

Interestingly, Tg doubling time did not predicted structural progression in our cohort. These findings question the clinical utility of Tg kinetics as a decision-making tool in patients with small-volume structural disease, particularly in those under TSH suppression. Previous studies have reported an association between rising Tg levels and structural progression (2, 11, 16), although this relationship has not been consistently confirmed (12,15) and the positive predictive value is too low to be clinically reliable for individual management decisions (2). Moreover, the biological significance of Tg kinetics remains incompletely understood. In this context, Andress et al. (17) evaluated 42 patients with lymph node metastases from differentiated thyroid carcinoma and undetectable serum Tg; notably, 11 patients (26%) were TgAb-negative. This finding suggests that, in a subset of patients with metastatic lymph node disease, the absence of detectable serum Tg—both by immunoassay and mass spectrometry—cannot be fully explained by analytical limitations of Tg assays or interference from Tg antibodies, highlighting the complex and heterogeneous biology of Tg production in metastatic DTC.

Robenshtok *et al*. (2) demonstrated that while features such as increased vascularity may be statistically associated with growing lymph nodes, no specific sonographic characteristic possessed a positive predictive value high enough to be clinically useful in identifying which lesions would progress. This lack of predictive capability has been consistently echoed in other cohorts. Jerkovich *et al* (11), Tomoda *et al*. (1) and Walter *et al.* (12) also didn´t identify any specific sonographic predictors of progression, reinforcing the concept that ultrasound characteristics identify malignancy but do not reliably predict biological behavior.

This study has limitations inherent to its retrospective design. The small sample size and follow-up, although longer than many published series, remains insufficient to evaluate very late progression. In addition, the absence of molecular profiling and standardized quality-of-life assessment represents areas for future research. However, even in three different Latin American Countries, results were consistent, and disease AS was safe.

In conclusion, our findings support that lymph node AS is safe in carefully selected patients with small (< 2 cm), non-threatening metastatic lymph nodes. Age should be considered risk factor for disease progression. Tg kinetics and ultrasonographic characteristics alone should not drive intervention decisions. These observations reinforce a personalized, risk-adapted approach to nodal disease management in differentiated thyroid carcinoma.

Finally, prospective multicenter studies are needed to better define objective size thresholds for intervention. And evaluate patient-reported outcomes and cost-effectiveness. Given the increasing recognition of conservative management in DTC, algorithms including active surveillance should be further explored in the management of lymph node recurrence disease in DTC.

Declarations

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Author Contribution

MYT collected and analyzed data, and drafted the manuscript.,RJST analyzed data and drafted the manuscript, RG colledted and analyzed data, TLM collected data, HG collected data and critically reviewed the manuscript FAA analyzed data and critically reviewed the manuscript, PAAJ analyzed data and critically reviewed the manuscript, DAB critically reviewed the manuscript, ICS and MA nalyzed data and critically reviewed the manuscript, RC critically reviewed the manuscript, FLD critically reviewed the manuscript, F.V. conceived and designed the study, collected and analyzed data, and critically

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Figures

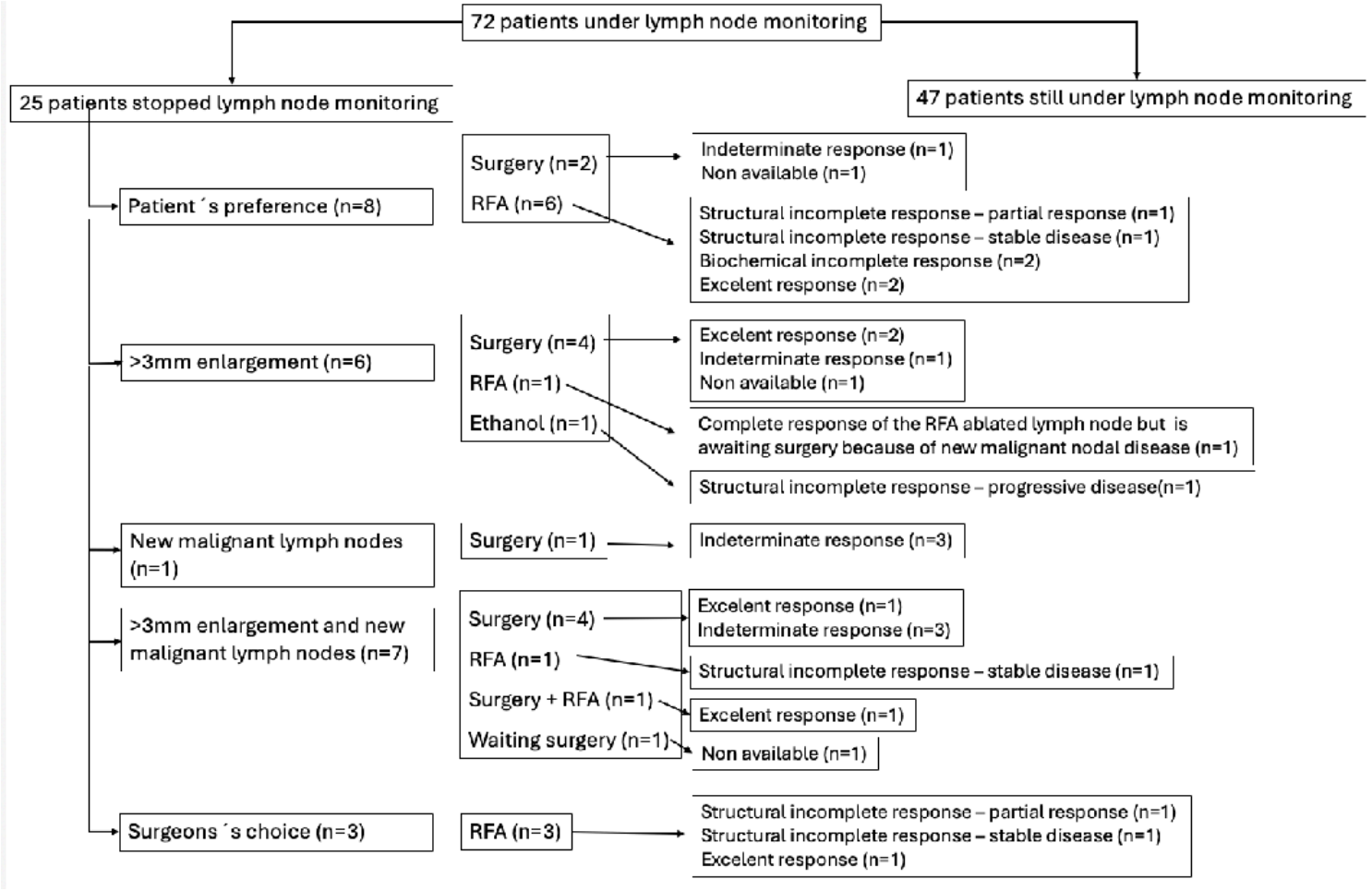


Figure 1

Treatments performed during follow-up of patients under lymph node active surveillance protocol and last follow-up response to treatment. RFA radiofrequency ablation

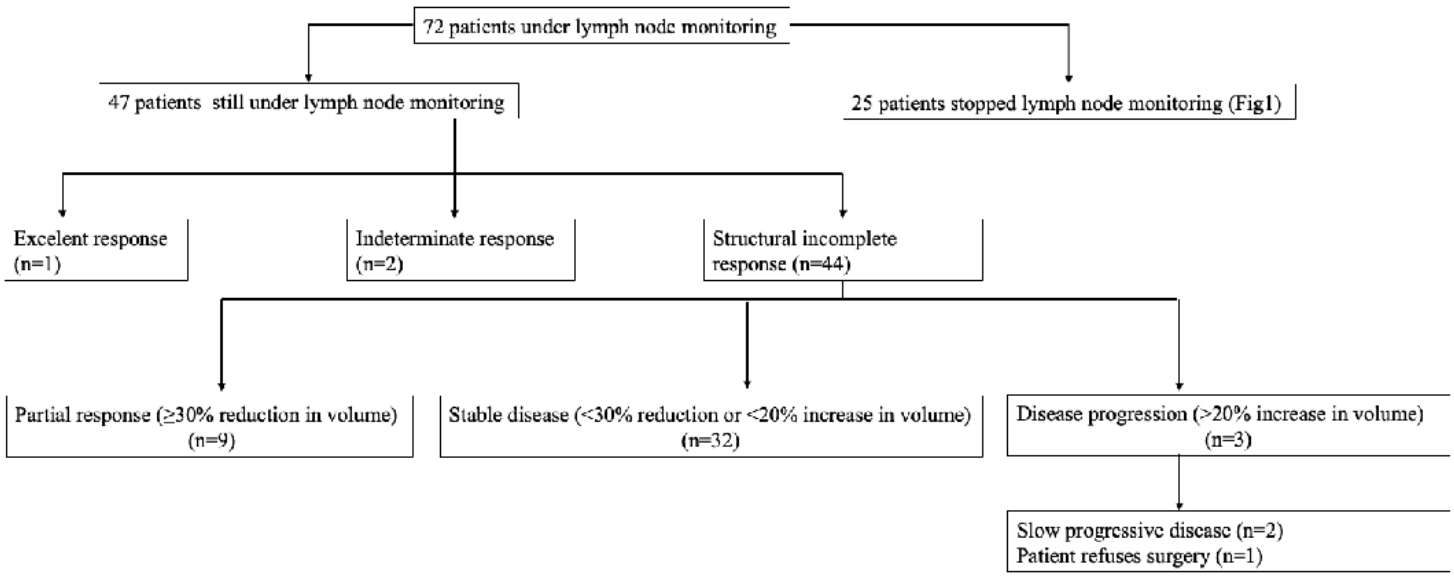


Figure 2

Response criteria after lymph node active surveillance

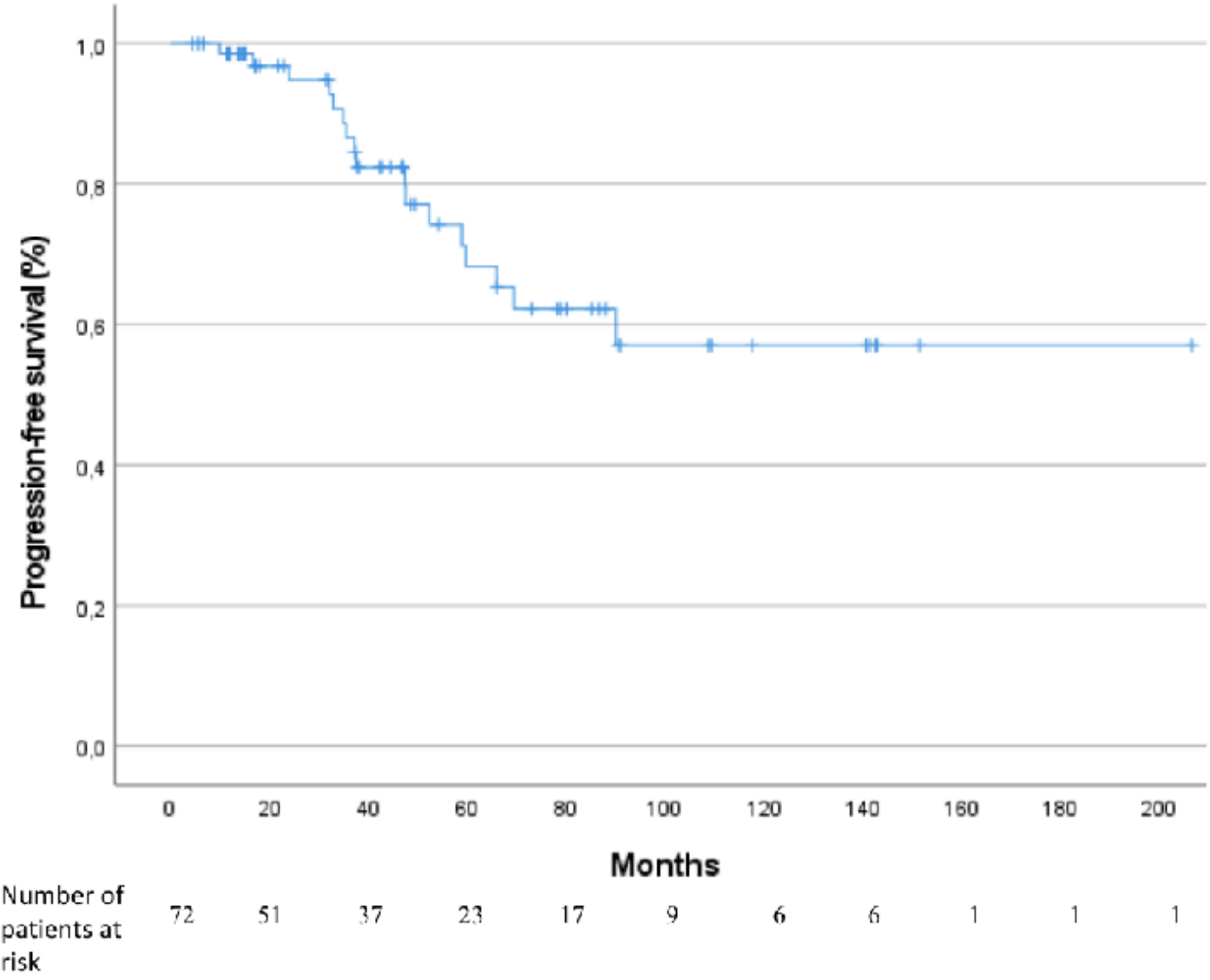


Figure 3

Kaplan-Meier analysis of cervical progression-free survival (months) from positive FNAB until disease progression or last follow-up for patients with stable disease.