

Original Research Article

The impact of ipsilateral central neck dissection on the 2015 American thyroid association risk stratification system and TNM staging in papillary thyroid carcinoma

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ABSTRACT

Background: In patients with classic papillary thyroid carcinoma (PTC) and no clinical evidence of lymph node metastasis (cN0), elective central neck dissection remains controversial. This study evaluates whether elective ipsilateral central neck dissection (eICND) along with total thyroidectomy could modify the staging of these patients. Additionally, we aim to assess pN1 risk factors, the incidence of post-operative complications, and the correlation between pN1 and change in tumor classification according to the risk stratification score of the American thyroid association 2015 (ATA 2015-RSS) and the TNM Score.

Methods: This is a prospective, observational study, involving 46 patients with cN0 PTC who underwent eICND along with total thyroidectomy. The number of metastatic lymph nodes, the largest lymph node metastasis, and the extra-nodal extension were assessed.

Results: 22 out of 46 patients (47.8%; CI 32.9–63.1) presented lymph node metastasis. Seventeen out of the 45 patients initially classified as low or intermediate ATA 2015-RSS upgraded their risk staging (37.8%; CI 23.8–53.5). Fourteen out of these reclassified patients had their initial ATA 2015-RSS changed due to lymph node metastasis larger than 2 mm (mostly between 3 mm and 4 mm). Ten out of 46 (21.7%; CI 10.49–36.4) patients had their TNM staging reviewed. General complication rate was 17.4% (8/46).

Conclusions: Elective dissection of levels VI ipsilateral and VII showed the ability to upgrade the initial ATA 2015-RSS and TNM staging in patients with cN0 PTC. However, further studies are necessary to evaluate the clinical impact of lymph node micro-metastasis.

Keywords: Thyroid, Neoplasm staging, Recurrence, Papillary carcinoma, Neck dissection

INTRODUCTION

Therapeutic lymph node dissection is consensually recommended as the initial surgical approach for patients diagnosed with papillary thyroid carcinoma (PTC) and lymph node metastasis, detected by pre-operative ultrasound or intra-operative inspection.^{1,2} In particular,

in these cases, bilateral cervical lymphadenectomy of the central compartment is commonly performed. However, this procedure is associated with a higher incidence of complications, especially hypoparathyroidism, when compared to thyroidectomy alone. In patients with no clinical suspicion of lymph node metastasis (cN0), elective central neck dissection (eCND) remains

controversial. Many authors argue that this procedure should be performed in all patients with PTC.² Their idea is supported by extensive demonstrations that most cN0 patients present with micro-lymph node metastasis; and that intra-operative inspection and pre-operative ultrasound have low accuracy for detecting metastasis on lymph nodes in the cervical compartment.³⁻⁷

The finding of a lymph node metastasis—even when clinically in apparent and confined to the central compartment (cN0pN1a)—can modify the patient's initial risk stratification and influence the clinical decisions subsequent to surgery. In cN0 patients, not every lymph node involvement can upgrade the initial recurrence risk. According to the American thyroid association (ATA), cN0 patients with up to 5 lymph nodes with metastatic lesions smaller than 2 mm are still considered to have low recurrence risk.⁸ However, larger lesions that may be found in cN0 patients, can alter the initial risk stratification. The understanding of how often this occurs is essential to establish the convenience of an elective central neck dissection (eCND), which is recommended by the latest ATA guideline.⁸

Although there are many studies quantifying the incidence of clinically occult or sonographically negative lymph node metastases, they did not answer whether eCND is able to modify initial risk stratification in cN0 patients.⁹⁻¹⁴ Moreover, most of these studies have considered only the negative pre-operative evaluation in defining the patient as having cN0, rather than the equally effective intra-operative inspection.⁹⁻¹⁴ The majority of studies also evaluated only whether cN0 patients turn into pN1 after elective lymph node dissection, without assessing the number and the histologic characteristics of the involved nodes.⁵ Answering these questions would require a prospective study, with uniform and pre-defined dissection extension, as well as pre-operative ultrasound examination and surgery performed by only one professional each, in order to avoid intra-professional variations.

In the present study, we aim to evaluate whether and how frequently elective ipsilateral central neck dissection (eICND) could modify initial the 2015 Risk Stratification Score of the American Thyroid Association (ATA 2015-RSS) in patients with PTC and without previously diagnosed lymph node metastasis, defined as negative pre-operative ultrasound and intra-operative inspection.

METHODS

Study design: A prospective single-centered study conducted at Life Center Hospital, Belo Horizonte, Brazil with patients who sequentially underwent eICND between 2014 and 2016. The inclusion criterion were as follows: (a) patients above 18 years of age, (b) cytologic classification of Bethesda V or VI, (c) absence of suspicion for lymph node metastasis both in pre-operative ultrasound examination and intra-operative inspection,

(d) elective lymphadenectomy (level VI ipsilateral and level VII), and (e) histologic confirmation of classic PTC. Patients who were not-agreement in joining the study and not fulfilling the inclusion criteria were excluded from the study.

Patients underwent clinical evaluation, followed by cervical ultrasound examination, surgical procedure, and histologic analysis of thyroid and lymph node tissues. Each stage of the evaluation was performed by a single specialist of each area with extensive experience in thyroid carcinoma.

Sonographic pre-operative assessment of thyroid and cervical compartments: The equipment used was a Siemens Acuson S2000, using high resolution linear transducers, with frequencies varying between 4 and 18 MHz. Thyroid nodules were evaluated for their dimensions, texture, echogenicity, borders, presence of calcifications, and micro-calcifications, anteroposterior, and transverse diameter ratio, free margins from the glandular capsule, location, and vascularization pattern. Lymph nodes at IIA, IIB, III, IV, VA, VB, VI and VII cervical levels were assessed regarding their texture, dimensions, and diameter ratio between the major and minor axis, as well as their vascularization pattern. The following signs were considered to be suggestive of metastasis: rounded shape (major axis/minor axis <2), hyper-echogenicity, calcifications, presence of cystic areas, lack of an echogenic hilum, presence of micro-calcifications or foci of dense colloid, and a peripheral vascularization pattern to the Doppler.

Surgical procedure: Classic total thyroidectomy with the Kocher cervicotomy technique, and visual and palpatory inspection of lymph nodes at levels VI and VII were performed. Hard nodes, irregular outlines or swollen nodes were considered to be suggestive of metastasis. Routine level VI ipsilateral and level VII (mediastinal) lymphadenectomy was added. Level VI dissection was performed ipsilaterally to the dominant nodule in cases of multinodular disease. Patients who presented any clinical suspicion of metastatic disease were not included in this study and were treated with bilateral central compartment resection.

The ipsilateral level VI encompasses the prelaryngeal, pretracheal and paratracheal lymph nodes, limited by the carotid sheath, the hyoid bone, the middle line and the suprasternal notch. Level VII encompasses the upper mediastinal lymph nodes. The anatomic boundaries are the carotid arteries, the aortic arch and the suprasternal notch.

Post-operative evaluation: In-hospital follow-up was performed during the first 24 hours after surgery. Possible morbidities, including vocal cord paralysis and hypoparathyroidism, were assessed and eventually treated in this period. Hospital discharge was allowed with oral

diet, in addition to calcium and levothyroxine replacement therapies, when necessary.

Pathologic anatomy reports: The thyroid and the resected lymph nodes were immediately fixed in buffered formaldehyde 10% solution. Levels VI and VII lymph nodes were dissected from the adipose tissue. The gland was measured and weighed, and its surface was embedded in Indian ink for better identification and assessment of surgical margins. The right and left lobes, as well as the isthmus, were sectioned and identified. The thyroid nodes were also measured. All the materials were processed and embedded into paraffin blocks, and hematoxylin and eosin stain was applied to the paraffin sections. Microscopic analysis assessed the nature of the nodules (neoplastic or not). If neoplastic, the tumor was classified; only classic PTC was included in this study. The presence of extra-thyroidal extension, surgical margin status (free, partially or fully compromised), and vascular or capsular invasion was also observed. In the lymph nodes affected by neoplasia, the following characteristics were analyzed: the lymph node size, the size of the largest focus of metastasis, the presence or absence of extra-capsular extension, the number of lymph nodes affected, and the total number of dissected lymph nodes.

Statistical analysis and sample calculation: Data were collected using Microsoft Office Excel, and statistical analysis was performed using IBM SPSS Statistics 20.0 software. Quantitative variables were described with mean, standard deviation, and range (minimum-maximum). Categorical variables were described considering their absolute and percentage frequencies, in univariate analysis. The relationships between the observed features (presence of metastatic disease and the change in the ATA 2015-RSS initial risk stage) and the demographic, clinical, and surgical characteristics were evaluated performing the Mann-Whitney, Chi-Square, and Fisher's Exact Tests. Multivariate analysis was performed using the binary logistic regression method. Statistical significance was attained whenever the observed *p*-value of a statistic test was less than 0.05.

Considering the 36.6% of migration observed in a study established by Lin et al and the 14.1% margin of error, this study requires a sample of 45 patients.¹⁵

RESULTS

In the present study, 46 patients were included, from which 36 were females and 10 were males, aged from 20 to 72 years. Observed clinical and surgical characteristics are described in Table 1.

There were 40 patients with low, 5 with intermediate, and 1 with high ATA 2015-RSS initially. The patient with high ATA 2015-RSS was excluded from the univariate and multivariate analysis, since he was not considered at risk of migration. After eICND, 37.8% of patients (17/45;

95% CI: 23.8–53.5) were reclassified with a higher ATA 2015-RSS. All stage migrations were from low to intermediate ATA 2015-RSS. Among these patients, 9 (52.9%) were females, 7 (41.2%) were 45 years old or higher, and 6 (35.3%) had microscopic multifocal disease.

Table 1: Clinical and surgical characteristics of all the included patients.

Tumor size in surgical specimen (mm±SD)	14.44±12.11 (4-65)
Removed lymph nodes (range)	8.78±4.29 (3-21)
Metastasis n (%)	22 (47.8)
T stage, n (%)	
1a/1b/2/3/4	21 (41.7)/14 (30.4)/4 (8.7)/6 (13.0)/1 (2.2)
Microscopic multifocal disease, n (%)	13 (28.3)
Complications, n (%)	8 (17.4)
Vascular invasion, n (%)	3 (6.5)

SD: Standard deviation.

The univariate analysis indicated that female gender (*p*=0.003) was significantly correlated with a lower risk of alteration of the ATA 2015-RSS stage; while tumor size in the surgical specimen (*p*=0.147), the number of removed lymph nodes (*p*=0.786), microscopic multifocal disease (*p*=0.511), age over 45 years (*p*=0.912), vascular invasion (*p*=0.279), and extra-thyroidal extension (*p*=0.281) were not significantly correlated with ATA 2015-RSS alteration. In the multivariate analysis, a logistic regression model found that the female gender was related with a lower rate of migration of the ATA 2015-RSS stage (Table 2). Nine (25.7%) out of the 36 female patients developed higher ATA 2015-RSS versus 8 (80.0%) out of the 10 male patients.

Table 2: Factors associated with migration of ATA 2015-RSS.

	OR	P value	95% CI for OR	
			Lower	Upper
Female Gender	0.042	0.011	0.004	0.489
Age >= 45	1.786	0.492	0.342	9.332
RLN	1.133	0.210	0.932	1.378
VI	0.000	0.999	0.000	
PTS	1.032	0.281	0.975	1.092
EE	0.000	0.999	0.000	
MMD	3.598	0.191	0.528	24.519

OR: odds ratio. CI: confidence interval. RLN: removed lymph nodes (range); VI: vascular invasion, PTS: tumor size in surgical specimen (mm); EE: extra-thyroidal extension; MMD: microscopic multifocal disease. Method: logistic regression. Constant exp (b) 1.208 and *p*-value 0.897.

After eICND, 22 out of 46 cN0 patients (47.8%) presented with lymph node metastasis. The univariate analysis indicated that gender ($p=0.004$) was significantly correlated with the incidence of metastasis, while pathological tumor size ($p=0.056$), the number of removed lymph nodes ($p=0.706$), microscopic multifocal disease ($p = 0.068$), age ($p=0.725$), vascular invasion ($p=1.000$), and extra-thyroid extension ($p=0.659$) were not significantly correlated with metastasis. Pathological tumor sizes associated with and without positive lymph nodes were 11.96 mm and 17.14 mm, respectively (Median 9 mm and 13 mm, SD 12 mm and 11.7 mm).

In the multivariate analysis, a logistic regression model found female gender to be related to a lower rate of metastasis, and microscopic multifocal disease to be associated with a higher rate of metastasis (Table 3). Thirteen (36.1%) female patients had metastasis versus 9 (90.0%) male patients (increase of 149% in risk). Sixty-nine percent (9/13) of the patients with microscopic multifocal disease had metastasis versus 39% (13/33) of those without (increase of 75% in risk). Fourteen out of 27 (51.8%) patients under 45 years of age presented cervical lymph node metastasis and 8 out of 19 (42.1%) patients aged 45 years or more presented lymph node metastasis in the central compartment.

Table 3: Factors associated with pN1.

	OR	P value	95% CI for OR	
			Lower	Upper
Female Gender	0.042	0.012	0.004	0.494
Age (>=45)	1.305	0.730	0.287	5.932
RLN	1.119	0.257	0.921	1.359
VI	0.215	0.543	0.002	30.528
PTS	1.037	0.209	0.980	1.097
EE	2.140	0.499	0.235	19.463
MMD	6.655	0.043	1.063	41.658

OR: odds ratio. CI: confidence interval. RLN: removed lymph nodes (range); VI: vascular invasion, PTS: tumor size in surgical specimen (mm); EE: extra-thyroidal extension; MMD: microscopic multifocal disease. Method: logistic regression. Constant exp (b) 1.368 and p-value 0.832.

Forty-one (89.1%) patients with cN0 were in TNM stage I, 2 (4.3%) in TNM stage II, and 3 (6.5%) in TNM stage III. After dissection, 10 patients (21.7%; 95% CI: 10.49–36.4) were observed with upgraded TNM stage. The univariate analysis indicated that female gender ($p=0.666$), age ($p=0.067$), extra-thyroidal extension ($p=0.061$), microscopic multifocal disease ($p=1.000$), vascular invasion ($p=1.000$), tumor size in surgical specimen ($p=0.058$), and the number of removed lymph nodes ($p=0.254$) were not significantly correlated with the alteration of the TNM stage. In a multivariate analysis, a logistic regression model found age equal or over 45 years and presence of extra-thyroidal tumor extension to be related to a higher rate of migration of the TNM stage (Table 4). Seven (36.8%) patients aged 45

years or more developed higher TNM stage versus 3 (11.1%) patients aged less than 45 years. Sixty percent (3/5) of patients with extra-thyroidal tumor extension developed higher TNM stage versus 17.1% (7/41) of those without extra-thyroidal tumor extension.

Table 4: Factors associated with cN1.

	OR	P value	95% CI for OR	
			Lower	Upper
Female Gender	0.182	0.103	0.023	1.415
Age (>=45)	12.651	0.021	1.477	108.388
MMD	2.673	0.314	0.394	18.145
ETE	25.267	0.018	1.733	368.319

OR: odds ratio. CI: confidence interval. ETE: extra-thyroid tumor extension; MMD: microscopic multifocal disease. Method: logistic regression. Constant exp (b) 0.004 and p-value 0.006.

DISCUSSION

Although the current ATA guideline had expanded the recommendation of elective central neck compartment dissection to patients with PTC, which can provide information required for future therapeutic directions, there is still controversy concerning its potential risks and benefits.⁸ A randomized controlled study showed that eCND did not improve outcomes in cN0 patients, in addition to being associated with a higher prevalence of transient hypoparathyroidism.¹⁶ Nevertheless, other study had previously demonstrated that eCND plays a role in redefining the stages and optimizing the clinical decision of additional radioiodine therapy, which improves the 10-year survival rate without changing increasing morbidity.¹⁷ Given this lack of consensus regarding eCND, we adopted an ipsilateral approach (eICND), which has been shown to be safe-no increase in surgical morbidity-and effective-it allows a more reliable evaluation of lymph nodes and adequate post-operative staging and treatment.^{2,18}

It has been demonstrated that even in the context of a pre-operative negative ultrasound and per-operative non-remarkable inspection lymph node micro-metastasis can be found in the central neck compartment.⁴⁻⁷ Vergez et al showed that the largest lymph nodes found in the central neck compartment were ≤ 5 mm in 66% of cases and < 1 cm in 95% of cases.¹⁹ Mirallie et al reported that 38–90% of lymph node metastases are not clinically diagnosed.²⁰ Ito et al and Sagitani et al showed that ultrasound sensitivity for diagnosis of metastasis in the central lymph node compartment ranges from 10.5% to 29%, while other authors have found higher sensitivity, ranging from 30% to 64%.^{3,4,21-23}

Being aware of the limitations of the pre-operative ultrasonography, as well as the per-operative inspection to detect metastatic lymph nodes smaller than 5 mm, the eICND allowed us to assess histologically the lymph

nodes regarding the presence or lack of metastasis, the size of the metastatic focus (when present), the number of metastatic lymph nodes, and the extranodal extent of the tumor. All the previous criteria are already consolidated as relevant for the adequate staging of the recurrence risk.⁸ Randolph et al have raised the need for better tools to predict the risk of recurrence in pN1 patients.⁵

Previous studies have found significant association between the tumor size, male gender, extra-thyroidal tumor extension, and lymph node metastasis. In the present study, we found that male gender and multifocal carcinoma (the latter after multivariate analysis) were significant risk factors for lymph node metastasis.^{15-17,24,25} We also observed a trend towards tumor size as being a significant risk factor ($p=0.056$). Contrary to previous studies, age younger than 45 years was not significantly associated with lymph node metastasis.^{10,15}

The average number of dissected lymph nodes was 8.78 ± 4.29 , higher than that previously reported in other studies.^{19,24,26} There was no predefined minimal or maximal number of lymph node resected per specimen. General complication rate was 17.4% (8/46). The bulk of it, six out of 46 (13.04%) patients developed transient hypoparathyroidism, one (2%) patient developed permanent hypoparathyroidism and another patient (2%) had transient vocal cord paralysis, with full recovery after 6 weeks. In the only case of permanent hypoparathyroidism, 4 glands were identified and preserved during surgery, while no parathyroid tissue was identified in the specimen sent for anatomopathological study. However, the patient had been diagnosed with chronic thyroiditis, a factor that may have contributed to the occurrence of this complication. General and specific complication rates were lower than those found in the studies with bilateral (23–58%) or unilateral (32%) dissection and comparable to those found in studies with total thyroidectomy alone (17%).^{15-17, 25}

The percentage (37.8%) of patients with ATA 2015-RSS upstaging resembles previous studies that, nevertheless, conducted elective bilateral and/or lateral chain dissections, and showed upstaged rates between 26% and 36.6%.^{2,15,24} Meanwhile, 10 out of 46 (21.7%) cN0 PTC patients were observed with upgraded TNM stage, which was higher than the 9.8% found in an earlier study.¹⁵ It is important to point out that TNM stage upgrade has a fundamental impact on the clinical follow-up of a good percentage of patients, concerning the therapeutic complementation with radioiodine, the thyroid-stimulating hormone suppression, and the timing of medical visits. Additionally, the chosen procedure—eICND—does not offer additional risk for complications, when compared with thyroidectomy alone.

Fourteen out of 17 patients who had their ATA 2015-RSS upgraded presented with lymph node metastasis larger than 2 mm (most of them between 3 mm and 4 mm). A new stratification risk according to the presence of lymph

node metastasis was included in the latest ATA 2015-RSS review. In the earlier risk stratification score of the American thyroid association 2009 (ATA 2009-RSS), all patients with lymph node metastasis were staged as having an intermediate risk of recurrence, regardless the number of involved lymph nodes and/or the size of the metastatic lesions.²⁷ According to the new ATA guideline, lymph node metastatic lesions larger than 3 cm are considered to have high risk of recurrence.⁸ Patients with cN0pN1a, up to 5 lymph nodes, with lesions smaller than 2 mm are considered to have low risk of recurrence. More than 5 lymph nodes, with lesions smaller than 3 cm, and a patient with cN1 are considered to have intermediate risk. This raises the following query: in which risk group would the patients with less than 5 involved lymph nodes and any metastatic lesion between 2 mm and 3 cm be included?

In their latest classification, ATA 2015-RSS made an “additive” postulate.⁸ It stated that in order to be included in the low risk stage, it is necessary to have less than 5 involved lymph nodes and all of them must have lesions smaller than 2 mm. Patients with more than 5 involved lymph nodes with lesions smaller than 3 cm are classified in the intermediate risk group. Patients with less than 5 involved lymph nodes with lesions sized between 2 mm and 3 cm were missed in this classification.

We claim that these patients would be classified with intermediate risk based on the following reasons. The ATA 2015-RSS tried to exclude two extreme situations that would undoubtedly be low and high risk, which are up to 5 lymph nodes with metastatic foci <2 mm and any lymph node with a lesion >3 cm, respectively; all the other situations remain as before, with no evolution in the N1 classification. Thus, those patients with less than 5 lymph nodes with metastatic foci between 2 mm and 3 cm are considered of intermediate risk.

Within this group of patients, it is possible to have patients with from only one lymph node with a metastasis of 3 mm, to 4 affected lymph nodes, one being of 2.5 cm in size. There is no doubt that the latter should be considered of intermediate risk and not low risk. Once these two different patterns are classified within the same group, both of them have to be considered of intermediate risk.

Finally, by selecting lymph nodes smaller than 2 mm as the cut-off point the ATA ensures that the neck ultrasound and inspection will be necessarily negative (cN0), so that there is no risk of any patient being cN1 and at the same time being considered of low risk. Accordingly, all our 14 patients with less than 5 lymph nodes affected by at least 1 metastatic lesion between 2 mm and 3 cm were considered of ATA 2015-RSS intermediate risk.

On the other hand, we wonder if our finding of 82.4% (14/17) of patients that upgraded from low to intermediate risk due to the size of the lymph node

lesions (between 2 mm and 5 mm) could be exaggerated. In order to answer this question, more studies are needed to evaluate whether patients currently staged as ATA 2015 RSS pN1 intermediate risk with less than 5 involved lymph nodes and any metastatic lesion between 2 mm and 5 mm have similar behavior to those patients currently staged as low risk. A possible study design is the one used by Lee et al, who evaluated the risk of relapse in 258 patients; those patients were in ATA 2009-RSS intermediate stage and became low risk in ATA 2015 RSS. They observed only a 1% risk, equal to the low risk patients, which validates the staging modification by ATA.²⁸

This evaluation could shift the cut-off point of lymph node lesions from <2 mm to <5 mm or even <1 cm. Randolph et al showed that metastatic lymph node lesions smaller than 1 cm appear to have the similar recurrence rate of 5–6% as cN0 patients or patients with micro-metastasis (<2mm).^{5,29-32} Other study has shown that remission rates after re-operation were diminished only when lymph node metastatic lesions were larger than 1.5 cm.³³ Thus, we may infer smaller positive lymph nodes imply low risk of recurrence and we should address a better reassessment and definition of the cut-off for the size of the metastatic focus in patients with less than 5 affected lymph nodes in the ATA 2015-RSS.

CONCLUSION

This study was prospective, with a pre-defined dissection extension, a pre-operative ultrasound and a histologic analysis, performed by a blinded single professional, avoiding inter-observer variations. However, the sample size is one possible limitation of our study. Larger samples could demonstrate other significant associations, such as the relationship between tumor size and lymph node metastasis, and would reinforce the associations already identified.

We conclude that eICND is safe and efficient in improving recurrence risk stratification and TNM staging in patients with PTC with no clinical evidence of lymph node metastasis at the moment of diagnosis and it leads to no changes in surgical morbidity. However, further studies are needed to evaluate the clinical impact of less than 5 metastatic lymph nodes with lesions in between 2 mm and 5 mm. It would be also helpful to assess the need of changing the cut-off point in size of lymph node metastatic lesions from <2 mm to <5 mm in the low risk of recurrence group in the ATA 2015-RSS.

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