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Original Article

Impact of microscopic extra-nodal extension (ENE) on locoregional recurrence following curative surgery for papillary thyroid carcinoma

Running head: Microscopic ENE increases recurrence

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SYNOPSIS

The finding of microscopic extranodal extension in any involved lymph nodes may elevate the risk of locoregional recurrence in patients with papillary thyroid carcinoma following curative total thyroidectomy, therapeutic neck dissection and radioactive iodine ablation.

ABSTRACT

Background:

The presence of microscopic extranodal extension (ENE) may increase locoregional recurrence (LRR) in papillary thyroid carcinoma (PTC). We aimed to evaluate the association between microscopic ENE, response to initial therapy and LRR risk following total thyroidectomy, therapeutic neck dissection and radioactive iodine (RAI) ablation in PTC.

Methods:

Of the 369 eligible PTC patients, 264 (71.5%) did not have microscopic ENE (group I) while 105 (28.5%) did (group II). All presented with clinical nodal metastasis (cN1) and underwent therapeutic neck dissection and RAI ablation. Biochemical incompleteness meant post-ablation stimulated thyroglobulin (sTg) >10ng/mL. Multivariate analyses were conducted to identify independent factors for LRR.

Results:

Biochemical incompleteness was significantly more common group II (43.8% vs. 17.4%,$p<0.05$). The 10-year locoregional free-survival was significantly worse in group II than I (52.0% vs. 86.2%, $p=0.005$). After adjusting for other significant factors, age<45 ($p<0.05$), multifocality ($p<0.05$), presence of ENE ($p=0.027$) were independent risk factors of LRR. The number and size of positive lymph nodes were not independent factors.

Conclusions:

Patients with microscopic ENE were significantly more likely to have biochemical incompleteness after initial therapy. After adjusting for other significant primary and nodal characteristics, microscopic ENE was an independent factor for LRR in patients with cN1.

Keywords: Papillary thyroid carcinoma; nodal metastasis; distant metastasis; TNM staging; ATA risk stratification

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma and its age-adjusted incidence has doubled in the last 25 years [1]. However, despite its excellent prognosis, locoregional recurrence (LRR) is common after curative surgery [2]. Cervical nodal metastasis (N1) is one of the most significant risk factors for LRR and studies have shown that in addition to N1, the nodal characteristics such as the number, size and ratio of positive lymph nodes (i.e. lymph node ratio or LNR) at surgery also carry prognostic significance [3-7]. In fact, under the new (2015) American Thyroid Association (*ATA*) guidelines, patients with N1 are stratified into one of three risk groups according to the total number and size of positive lymph nodes (LNs) retrieved at the initial surgery [8]. Under this newly-revised system, in the absence of other risk factors, a patient with ≤ 5 pathologic N1 micrometastasis (<0.2cm in largest dimension) would be in the low-risk group while a patient with >5 pathologic nodes with all involved LNs (<3cm in their largest dimension) would be in the intermediate-risk group. A patient with one or more involved LNs measuring ≥3cm in largest dimension would be classified as high-risk.

However, despite this change, the modified *ATA* risk stratification system did not specifically include the presence of microscopic extra-nodal extension (ENE) as a factor for nodal risk stratification [8]. One reason for this omission is because it is believed that ENE is often tightly linked to other risk factors like the number of positive lymph nodes and extrathyroidal extension (ETE) of the primary tumor [8]. Furthermore, although gross or macroscopic ENE is known to predict poorer outcomes, microscopic ENE as an independent risk factor appears less certain especially when other inter-related risk factors like the number and size of positive LNs and extrathyroidal extension (ETE) of the primary tumor have been considered [8]. However, given the growing evidence showing the prognostic significance of ENE [9-11], we hypothesized microscopic ENE could be an independent risk factor for LRR. Therefore, our study aimed to evaluate the association between microscopic ENE and response to initial therapy as well as risk of LRR following a standardized total thyroidectomy, simultaneous therapeutic neck dissection and radioactive iodine (RAI) ablation.

PATIENTS AND METHODS

From 1980 – 2011, 1915 consecutive PTC patients underwent surgery at our institution. Of these, 407 (21.3%) had simultaneous lateral N1 that was either clinically palpable or visible on preoperative ultrasound (USG) and later confirmed by fine needle aspiration cytology (FNAC) (i.e. clinical N1b or cN1b). Patients with distant metastasis (n=21), unresectable gross primary or nodal disease (n=3), ≤2 levels of lateral cervical nodes dissected (n=5) or gross extra-nodal invasion to surrounding structures (like the overlying sternocleidomastoid muscles, internal jugular vein, carotid artery or vagus nerve) at surgery (n=9) were excluded. Therefore, 369 (20.3%) patients were eligible. Among these, 36 (9.8%) were follicular-variant, 3 (0.8%) were tall-cell variant and 6 (1.6%) were columnar-variant. All excised LN specimens were subjected to similar histological examination by our group of pathologists. Microscopic ENE was defined as the presence of tumor cells outside the capsule of a LN that harbored metastatic PTC (see Figure 1) without any evidence of macroscopic invasion to surrounding structures as judged by the operating surgeon. Based on microscopic examination of the harvested LNs, 264 (71.5%) patients were found not to have ENE (group I) while 105 (28.5%) patients were found to have ENE in at least one positive LN (group II). Relevant clinical, laboratory, radiologic, and perioperative data were collected prospectively and follow-up data were updated in a computerized database. Since this study spanned over a long period of time, initial tumor risk estimate and response to initial therapy (i.e. dynamic risk stratification) were retrospectively recoded according to the newly-revised *ATA* risk stratification system [8]. Clinicopathological features (including number, size of positive LNs and LNR), postoperative stimulated thyroglobulin (sTg), response to therapy and LRR were compared between the two groups. LNR (%) was defined as the number of metastatic LNs divided by the total number of LNs retrieved and multiplied by 100.

Management of PTC

Details of surgical treatment, criteria for radioactive iodine (RAI) ablation, postoperative and follow-up protocol had been described previously [12]. Total thyroidectomy and simultaneous therapeutic unilateral central (level VI) and lateral (levels II-V) selective neck dissections were performed for cN1b. Concomitant bilateral central dissection was only performed when there was clear evidence of disease within the central compartment. Two months after initial surgery,

an ablative RAI dose was given after LT4 withdrawal or with recombinant TSH. This was followed by the post-therapy scan 4-7 days later. sTg was defined as a Tg level measured when serum TSH >30 mIU/L either by 4-week thyroxine withdrawal or recombinant TSH injections. The pre-ablation sTg level was taken approximately 2-3 months after surgery (i.e. at the time of RAI ablation) while the post-ablation level was taken approximately 9-12 months after surgery (at the time of the diagnostic whole body scan (WBS)). Tg autoantibodies were measured at the same time. The decision for RAI ablation was based on the presence of 2 or more risk factors such as tumor size >1.5cm, N1, age >45 years old and extrathyroidal extension. TSH suppression to <0.1 ug/L was recommended for all patients with cN1.

Postoperative and follow-up protocol

All post-surgical patients were followed up within 4 weeks in a specialized combined oncology clinic. A follow-up visit was conducted at 6-month intervals in the first 2 years, 6 to 9-month in the subsequent 3 years and annually thereafter. Clinical examination, neck USG and non-stimulated Tg level were done during follow-up visits. Response to initial therapy was assessed based on post-ablation sTg values obtained 9-12 months after surgery [8]. LRR was defined as an identifiable neck lesion on USG which was confirmed on FNAC and/or histology.

Laboratory methods

All postoperative sTg levels were measured at the same laboratory using the same immunometric assay. The assay used was the Immulite 2000 (Diagnostic Products Corp. Roche, Los Angeles, CA). This was calibrated against the CRM- 457 standard. Normal reference range was <0.5 – 55 ug/L and sensitivity was <0.2 ug/L).

Statistical analysis

Statistical analysis was performed by chi-square or Fisher's Exact test to compare categorical variables, and Mann-Whitney U or Kruskal-Wallis test was used to compare continuous variables between groups. Locoregional recurrence free survival (LRFS) was estimated using the Kaplan-Meier method and compared with log-rank test. Variables which were significant in the univariate analysis were entered into the multivariate analysis using Cox-regression analysis. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

In our cohort, the majority (81.3%) had ipsilateral neck dissection while contralateral and bilateral selective neck dissections were performed in 9 (2.4%) and 60 (16.3%) patients, respectively. All patients had a minimum of levels II-IV nodes dissected with some (60.7%) also having level V nodes dissected at the same time. The total number of LNs (i.e. central + lateral compartments) harvested was 28.3 ± 19.3. Among this cohort, 95 (25.7%) did not have concomitant pN1a. All patients received radioiodine (RAI) ablation afterwards.

Table 1 shows a comparison of clinicopathologic features, tumor stages, *ATA* risk stratification and *MACIS* score between group I and II. Age, histological variants and nodal stage were comparable between groups. Group II had significantly more males (41.0% vs. 26.1%,p=0.006), larger-sized tumors (2.8cm vs. 2.1cm,p=0.009), more extrathyroidal extension (80.0% vs. 42.1%,p<0.001), higher T stage (40.0% vs. 14.8%,p<0.001), more high-risk tumors (31.4% vs. 14.8%,p<0.001) and higher *MACIS* scores (6.4 vs. 5.4,p<0.001) than group I.

Table 2 compares the number of harvested and positive LNs as well as size of largest positive LN between the two groups. Group II also had significantly more positive central (4.6 vs. 3.1, p=0.046) and lateral LNs (10.2 vs. 4.8, p<0.001). As a result, the overall number of positive LNs retrieved was significantly greater in group II (14.8 vs. 7.8, p<0.001) and the LNR was also significantly higher in group II (55.0% vs. 31.0%, p<0.001). The mean size of largest LN was also significantly larger in group II (26.7mm vs. 10.0mm, p<0.001). In our cohort, the smallest LN with ENE was 1.0cm and the lowest LNR with ENE was 9.6%.

Table 3 compares postoperative sTg levels, adjuvant treatment, response to initial therapy and recurrences between the two groups. RAI dose, central uptake on WBS and ERT were comparable between the two groups. However, pre- and post-ablation sTg levels were significantly higher in group II than I (p<0.001). The proportion of undetectable post-ablation sTg (<0.5ug/L) was significantly lower in group II (17.1% vs. 36.4%, p<0.001). Similarly, the proportion of patients having an excellent response to therapy was significantly higher in group I (55.7% vs. 31.7%, p<0.001). The follow-up period was slightly shorter in group I than II (110.7months vs. 121.6 months, p=0.029) presumably because ENE occurred more commonly in the earlier study period.

After a mean follow-up of 113.8 ± 61.2 months, 78 patients developed LRR as their first site of recurrence and 27 patients eventually died of PTC. Among those who died, all were aged above 64 years old at diagnosis. The most common first site of recurrence was the ipsilateral lateral compartment (n=63, 80.8%) followed by bilateral lateral compartments (n=9) and contralateral lateral compartment (n=6). No patient had isolated thyroid bed or central compartment recurrence. The mean size of recurrence was 1.5 ± 1.0cm and the number of patients with recurrence <1cm was 14 (17.9%). The 5- and 10-year LRFS were significantly worse in group II than I (60.7% vs. 88.4% and 52.0 vs. 86.2, p<0.001, respectively).

Table 4 shows cox regression analyses for LRR. In the univariate analysis, younger age (p=0.026), larger tumor size (p<0.001), presence of ETE (p=0.039) and multicentricity (p=0.001), higher *T* stage (p=0.012), greater number of positive LNs (p=0.003), higher LN ratio (p<0.001), larger-sized nodal metastasis (p<0.001) and ENE (p<0.001) were significant risk factors of LRR. Given a large number of significant variables and the inter-related association between these variables, two multivariate analyses were performed. In the first model, tumor size and ETE were entered in place of *T* stage and number of positive LNs was entered in place of LNR. In this first model, younger age (p=0.004), larger-sized tumor (p=0.029), presence of multifocality (p=0.038) and presence of ENE (p=0.002) were independent factors for LRR. In the second model, *T* stage was entered in place of tumor size and ETE and LNR was entered in place of number of positive LNs. In this second model, younger age (p=0.004), presence of multifocality (p=0.043) and presence of ENE (p<0.001) were independent factors of LRR. In both model 1 and 2, when age<45 years old was entered as a categorical variable, it remained statistically significant (p<0.05). Therefore, age<45 years old, multifocality and ENE were independent factors for both models.

DISCUSSION

Our data showed that patients with microscopic ENE in their excised LNs not only had significantly larger-sized tumors (p=0.009) but also locally more advanced primary tumors (p<0.001). Despite the successful RAI ablation in over 95% of the patients (as suggested by the very low percentage of central neck uptake on WBS), patients with ENE were less likely to have an excellent response to therapy (sTg <1ng/mL) than those without microscopic ENE (31.4% vs. 55.7%, p<0.001, respectively). Furthermore, both the biochemical (sTg >10ng/mL) and structural incompleteness were significantly more common in patients with ENE (43.8% vs. 17.4%, and 18.1% vs. 9,8%, respectively). Similar findings were reported by one study where the authors found the presence of ENE diminished the chance of biochemical completeness from 49% to 21% (p=0.01) [10]. Although the exact reason for the higher biochemical incompleteness remains unclear, the most likely reason is because patients with ENE are generally at greater risk of having residual microscopic nodal disease leading to locoregional and/or distant failures [5,9]. Interestingly, our data clearly showed that of the 4 nodal characteristics (i.e. number, size of positive LNs, LNR and ENE), the presence of microscopic ENE was a single most significant determinant of LRR in patients with cN1. In fact, ENE was the only independent nodal characteristic that was significant in both multivariate models along with younger age and presence of multifocality (see Table 4). In contrast to previous studies [4,13], our data did not show the number, size of positive LNs or LNR to be independent factors for LRR. However, given the significant inter-related association between these variables and the presence of ENE (see Table 2), it is possible that the dominant effect of ENE may diminish the effect of other factors. Nevertheless, this implies that of the 4 nodal characteristics, ENE may have the greatest prognostic significance on LRR.

It is worth noting that although none of the three significant factors (i.e. age, multifocality and ENE) were included in the latest *ATA* risk stratification system, age and multifocality had certainly been incorporated in other risk stratification systems from the Latin American Thyroid Society and the European Consensus Conference, respectively [14,15]. Furthermore, a recent meta-analysis has reported that multifocality is significantly associated with an increased risk of nodal metastases and persistent / recurrent disease [16]

Given that all of our patients already underwent a complete thyroidectomy and an adequate (≥3 levels) neck dissection in the involved lateral compartment, the implications are first, relative to those without ENE, patients with ENE should be placed under a more intense surveillance for possible LRR. Although over 40% of our patients with ENE developed LRR, this appeared comparable to other similar series [9,10]. Since over 80% of LRR were found in the ipsilateral lateral compartment, special attention should be paid to this area during USG screening. Our data showed that recurrence in the contralateral lateral compartment was very uncommon (7.7%). Second, given the higher chance of residual microscopic disease (as reflected by the higher rate of biochemical and structural incompleteness), patients with ENE may benefit from a higher dose of RAI ablation in an attempt of completely ablating any residual microscopic disease. However, only a prospective study would be able to confirm this postulation.

Despite our findings, we would acknowledge certain shortcomings. First, we only evaluated the prognostic significance of microscopic ENE and since this is usually not apparent until after surgery, our study findings are unlikely to change the initial surgical strategy/plan. Nevertheless, it is conceivable that patients with macroscopic ENE would be at an even greater risk of LRR. Second, our analysis did not specifically analyze the extent of ENE or the number of nodes having ENE. Similar to the first point, those with greater extent of microscopic ENE or number of involved nodes with ENE are probably at greater risk of LRR than those with limited ENE involvement. Third, since we did not divide the entire nodal specimen into different levels, it was not possible to tell whether the site of recurrence was positive or had ENE at the first operation. This information would have enhanced our understanding on the pattern of nodal recurrence in patients with ENE. Fourth, since this was a retrospective analysis, our study was prone to selection biases. However, it would have taken a great deal amount of time and effort to conduct a similar study prospectively.

Conclusion

Patients with microscopic ENE in their excised LNs not only had significantly larger and locally more advanced primary tumors but were also less likely to have an excellent response to initial therapy (defined as sTg <1ng/mL) than those without ENE. After adjusting for other significant

primary and nodal characteristics, ENE remained an independent factor for LRR in patients with cN1.

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None

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

BHH Lang / Tony Shek / KY Wan were involved in the review of literature, acquisition of data and drafting and completing the manuscript. BHH Lang / Tony Shek / KY Wan were also involved in the review of literature and drafting the manuscript. BHH Lang / Tony Shek / KY Wan conceived the study, participated in the co-ordination and the acquisition of data and helped to draft the manuscript. All authors read and approved the final manuscript.

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FIGURE LEGEND

Figure 1. A high-power view showing the presence of tumor cells outside the capsule of a lymph node that harbored metastatic papillary thyroid carcinoma. The black arrows outline the original lymph node capsule.

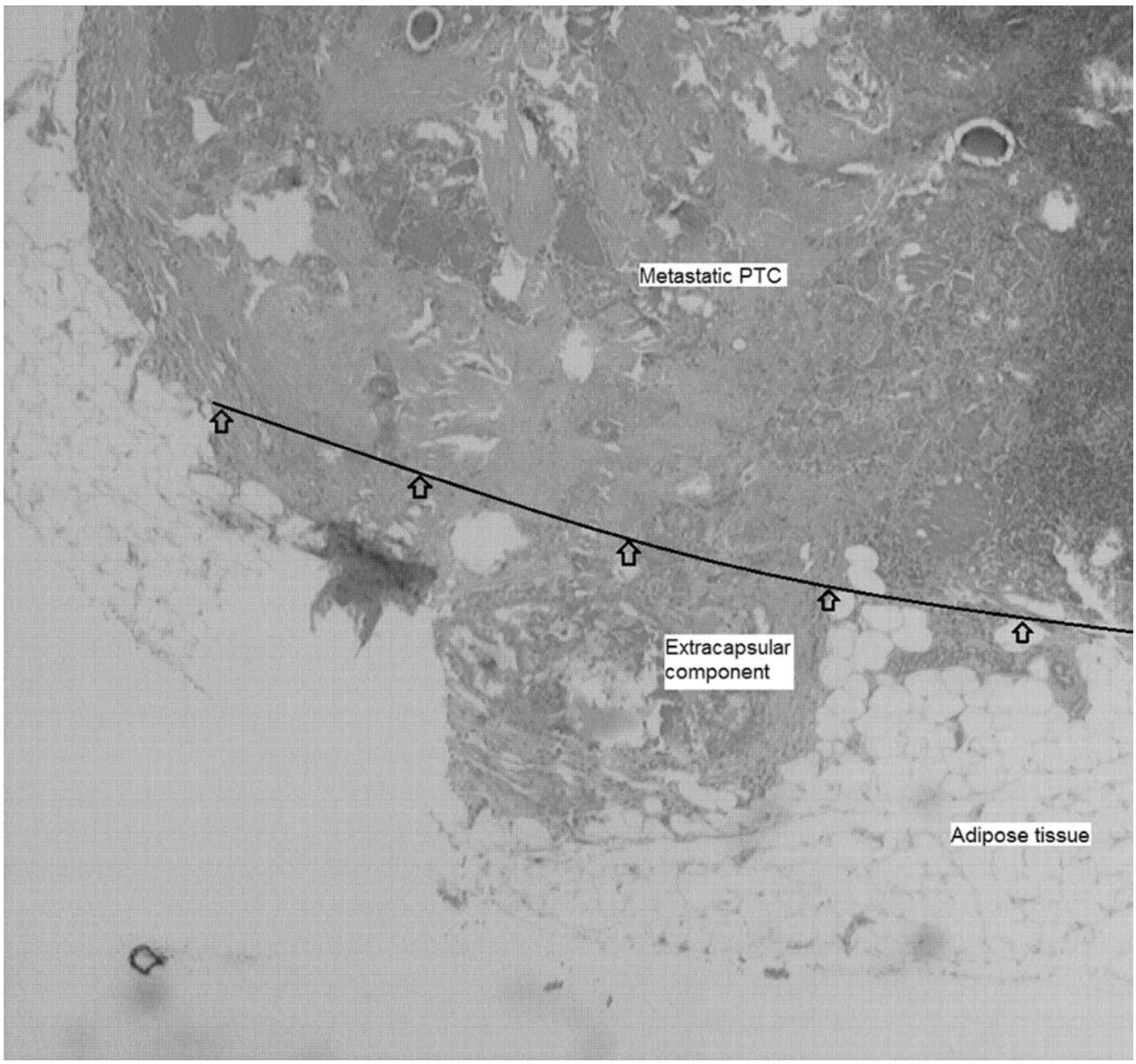

Table 1. A comparison of clinicopathological features, tumor and nodal stages, *ATA* risk stratification and *MACIS* scores between those without extra-nodal extension (ENE) (Group I) and those with ENE (Group II)

	Group I (n=264)	**Group II (n=105)**	***p*-value**
Age at operation (years)	49.35 ± 20.44	52.14 ± 20.39	0.211
Sex			**0.006**
- Male	69 (26.1)	43 (41.0)	
- Female	195 (73.9)	62 (59.0)	
Type of papillary carcinoma variants			0.241
- Classic	240 (90.9)	84 (80.0)	
- Follicular	18 (6.8)	15 (14.3)	
- Tall	3 (1.1)	0 (0.0)	
- Columnar	3 (1.1)	3 (2.9)	
Tumor size (cm)			
- Mean ± SD	2.12 ± 1.53	2.75 ± 1.92	**0.009**
- ≤ 2	156 (59.1)	54 (51.4)	0.338
- ≤ 4	81 (30.7)	36 (34.3)	
- >4	27 (10.2)	15 (14.3)	
Extrathyroidal extension			**<0.001**
- None	153 (58.0)	21 (20.0)	
- Minimal	72 (27.3)	42 (40.0)	

- Macroscopic	39 (14.8)	42 (40.0)	
Multifocality	166 (62.9)	69 (65.7)	0.671
Tumor stage*			**<0.001**
- T1	105 (39.8)	15 (14.3)	
- T2	48 (18.2)	6 (5.7)	
- T3	72 (27.3)	42 (40.0)	
- T4	39 (14.8)	42 (40.0)	
Nodal staging*			0.424
- N1b	71 (27.0)	24 (22.9)	
- N1a & N1b	193 (73.1)	81 (77.1)	
ATA initial risk stratification#			**<0.001**
- Intermediate	225 (85.2)	72 (68.6)	
- High	39 (14.8)	33 (31.4)	
MACIS score	5.44 ± 2.20	6.40 ± 2.31	**<0.001**

Categorical variables are expressed as number (percentage)

Abbreviations: ATA = American Thyroid Association; MACIS = Metastases, Age, Completeness of surgery, Invasion and Size

*Based on the 7th edition Tumor, Node and Metastasis pathological staging system

#according to the 2015 modified *ATA* risk stratification [8]

Table 2. A comparison of number of lymph nodes (LNs) harvested, number of positive LNs and size of the largest positive LN between those without extra-nodal extension (ENE) (Group I) and those with ENE (Group II)

	Group I (n=264)	**Group II (n=105)**	***p*-value**
Central compartment (level IV)			
- Total no. of LNs harvested	6.3 ± 5.8	7.5 ± 6.6	0.584
- Total no. of positive LNs	3.1 ± 2.9	4.6 ± 5.2	**0.046**
Lateral compartment (levels II-V)			
- Total no. of LNs harvested	21.2 ± 15.1	22.9 ± 16.8	0.098
- Total no. of positive LNs	4.8 ± 3.0	10.2 ± 5.6	**<0.001**
Overall (central + lateral compartments)			
- Total no. of LNs harvested	27.4 ± 17.9	30.4 ± 22.4	0.195
- Total no. of positive LNs	7.9 ± 7.2	14.8 ± 8.4	**<0.001**
- ≤ 10	204 (77.3)	36 (34.3)	
- > 10	60 (22.7)	69 (65.7)	
- LN ratio (%)+	30.98 ± 22.02	54.98 ± 25.12	**<0.001**
Mean size of largest positive LN (mm)	10.0 ± 7.4	26.7 ± 11.2	**<0.001**
- ≤ 3cm	260 (98.5)	84 (80.0)	**<0.001**
- > 3cm	4 (1.5)	21 (20.0)	

+LN ratio=(total number of positive LNs/ total number of LNs harvested) * 100

Table 3. A comparison of postoperative stimulated thyroglobulin (sTg) levels, adjuvant treatment, response to therapy after ablation and locoregional recurrence between those without extranodal extension (ENE) (Group I) and with ENE (Group II)

	Group I (n=264)	**Group II (n=105)**	***p*-value**
Postoperative stimulated Tg (sTg) (ng/mL)			
- Pre-ablation*	43.51 ± 163.92	150.57 ± 257.15	**<0.001**
- Post-ablation*	8.20 ± 20.29	40.56 ± 54.82	**<0.001**
Radioactive iodine dose (mCi)	82.70 ± 8.68	84.72 ± 72	0.082
Central neck uptake on diagnostic whole body scan	6 (2.3)	3 (2.9)	0.506
External beam radiotherapy	9 (4.5)	7 (6.7)	0.405
Response to therapy after ablation#			**<0.001**
- Excellent (*sTg <1ng/mL*)	147 (55.7)	33 (31.4)	
- Biochemical incomplete (*sTg >10ng/mL*)	46 (17.4)	46 (43.8)	
- Structural incomplete (*structural or functional evidence of disease*)	26 (9.8)	19 (18.1)	
- Indeterminate (*sTg≥1ng/mL and ≤10ng/mL*)	45 (17.0)	7 (6.7)	
Follow-up period (months)	110.68 ± 51.43	121.55 ± 50.14	**0.029**
Locoregional recurrence (LRR)	33 (12.5)	45 (42.9)	**<0.001**

Categorical variables are expressed as number (percentage)

*2-3 months and 9-12 months after surgery, respectively

#based on the 2015 ATA guidelines [8] and among those who received RAI ablation

Table 4. Cox regression analyses of locoregional recurrence

	Locoregional recurrence								
	Univariate analysis			**Multivariate analysis^**			**Multivariate analysis#**		
Variable	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**	**HR**	**95%CI**	***p*-value**
Younger age	1.013	1.002 – 1.025	**0.026**	1.025	1.009 – 1.041	**0.004**	1.024	1.007 – 1.037	**0.003**
Male sex	1.011	0.608 – 1.681	0.967						
Histological variants	1.353	0.938 – 1.950	0.105						
Larger tumor size	1.261	1.110 – 1.434	**<0.001**	1.226	1.021 – 1.417	**0.029**			
ETE	1.330	1.014 – 1.744	**0.039**	1.138	0.740 – 1.751	0.556			
Multicentricity	2.165	1.355 – 3.458	**0.001**	1.943	1.038 – 3.636	**0.038**	1.975	1.021 – 3.558	**0.043**
Higher *T* stage	1.272	1.055 – 1.534	**0.012**				1.199	0.908 – 1.584	0.200
No. of LNs harvested	0.995	0.983 – 1.007	0.426						
No. of positive LNs	1.037	1.013 – 1.062	**0.003**	1.011	0.978 – 1.046	0.514			
LNR*	1.025	1.016 – 1.034	**<0.001**				1.011	0.999 – 1.023	0.080
Size of positive LN	1.599	1.340 – 1.909	**<0.001**	1.274	0.965 – 1.683	0.088	1.211	0.922 – 1.590	0.169
Extra-nodal extension	4.404	2.807 – 6.909	**<0.001**	4.379	1.994 – 9.618	**<0.001**	4.193	2.398 – 7.332	**0.001**

ATA risk stratification	1.076	0.612 – 1.889	0.800						
RAI dose	0.990	0.961 – 1.019	0.496						
ERT	0.548	0.173 – 1.738	0.307						

Abbreviations: ETE = extrathyroidal extension; ATA = American Thyroid Association; LN = lymph node; RAI = radioactive iodine; ERT = external beam radiotherapy

^in model 1, age, primary tumor size, extrathyroidal extension, multifocality, number of positive LNs, size of largest LN and ENE were entered as co-variates. When age <45 years old was entered, the HR became 1.52 (1.002 – 2.653), *p*=0.042.

#in model 2, age, multifocality, *T* stage, LN ratio, size of largest positive LN and ENE were entered as co-variates. When age <45 years old was entered, the HR became 1.49 (1.001 – 2.551), *p*=0.049.

*LNR = (total number of positive LNs/ total number of LNs harvested) * 100