Original Article

A multicenter prospective study of lateral neck lymph node mapping in papillary thyroid cancer

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Background: Despite the high incidence of lateral neck lymph node (LN) metastasis in papillary thyroid cancer (PTC), the management of the lateral neck remains controversial. We aimed to map the draining LNs in the lateral neck using carbon nanoparticles and explore its potential in neck evaluation.

Methods: We conducted a multicenter, prospective study in PTC patients who had non-palpable yet suspicious metastatic lateral LNs on ultrasound and/or computed tomography (CT) but could not be confirmed by fine needle aspiration. Carbon nanoparticle suspension was injected peritumorally into the thyroid and modified lateral neck dissection was subsequently performed.

Results: A total of 154 patients were enrolled for analysis. And 5,070 lateral LNs were removed, of which 1,079 (21.3%) were dyed. The median of dyed LNs was 6 per case (range, 1–33). The distribution of dyed LNs in neck compartments was IV > III > IIA > IIB/V, independent of tumor size, location, multifocality or microscopic extra-thyroidal extension (ETE). Compared with undyed LNs, the probabilities of metastasis in dyed LNs were significantly increased in compartment III, IV, V, and II–V (III: 29.3% *vs.* 15.4%, P<0.001; IV: 26.3% *vs.* 14.5%, P<0.001; V: 16.7% *vs.* 3.3%, P=0.005; II–V: 26.3% *vs.* 10.0%, P<0.001). The relative risks of metastasis in dyed LNs compared with undyed LNs were 1.90, 1.82, 5.04 and 2.62 in compartment III, IV, V, and II–V, respectively.

Conclusions: It was the first prospective multicenter study to map the lateral neck LNs with carbon nanoparticles, which could help surgeons visualize the suspicious LNs during surgery. Instead of unguided LN biopsy, this method has a potential role in lateral neck assessment for indeterminate lateral LNs in PTC.

Keywords: Papillary thyroid cancer (PTC); lymphatic metastasis; neck dissection; lymph node excision (LN excision); lymph node ratio (LN ratio)

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Introduction

Papillary thyroid cancer (PTC) is one of the most common endocrine cancers, and the incidence of PTC has increased substantially worldwide over the past decades (1). PTC easily spreads along the lymphatic channels and metastasize to the cervical lymph nodes (LNs). Preventive central and lateral neck dissection showed that even for microcarcinoma with cN0, the probability of cervical LN metastasis was as high as 50–80% and the probability of lateral neck metastasis was 30–60% (2-4).

In patients with lateral neck metastasis, current guidelines recommend functional lateral neck dissection (compartment II–V); meanwhile, lateral neck dissection is not recommended in patients without evidence of lateral LN metastasis on clinical examination or imaging (5). However, preoperative neck ultrasound and computed tomography (CT) have limited sensitivities and specificities in lateral neck assessment. As reported, the sensitivities of ultrasound, CT and combination were only 51%, 62% and 66% respectively (6). A recent meta-analysis demonstrated that although CT had a higher sensitivity and ultrasound had a higher specificity in detecting lateral LNs, the overall accuracy remained low and both modalities were needed for neck evaluation (7). Although fine needle aspiration (FNA) serves as an important tool for diagnosing suspicious cervical LNs, sometimes FNA may not be feasible due to the proximity to major cervical vessels or other neck structures.

Suspicious LNs on preoperative ultrasound or CT that are not proven pathologically pose a dilemma in clinical decision making (8). Overtreatment of neck metastasis would cause unnecessary complications, while undertreatment results in cancer residue and reoperations. Therefore, accurate lateral neck evaluation is of importance in thyroid cancer surgeries. Carbon nanoparticle suspension is composed of nanosized polymeric carbon granules that would be absorbed by macrophages accumulating in LNs. It is widely used for LN tracing in multiple cancers. In thyroid cancer, the use of carbon nanoparticles leads to a more extensive central LN dissection, while improves preservation of the parathyroid glands in total thyroidectomy (9). In the current study, we aimed to find out if carbon nanoparticles could be used to map the draining LNs in the lateral neck by injecting tracer during operation and explore its potential to guide lateral neck dissection. We present this article in accordance with the TREND reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-222/rc).

Highlight box

Key findings

- We mapped the lateral neck lymph nodes (LNs) in papillary thyroid cancer (PTC) patients using carbon nanoparticle suspension, which could help surgeons visualize the indeterminate lateral LNs during surgery.

What is known and what is new?

- The management of the lateral neck remains controversial in PTC.
- The distribution of dyed LNs was consistent with the LN drainage in the lateral neck, and dyed LNs had a higher risk of metastasis.

What is the implication, and what should change now?

- This surgical procedure could help surgeons visualize suspicious lateral LNs and serve as an evaluation method in the decision making of neck dissection.

Methods

Patients

We conducted a multi-center prospective study from April 2016 to February 2020. Patients were recruited from five institutions (Fudan University Shanghai Cancer Center, Shanghai Electric Power Hospital, Jiangyuan Hospital Affiliated to Jiangsu Institute of Nuclear Medicine, Affiliated Hospital of Jiangsu University, and Xiamen Hospital of Traditional Chinese Medicine). The primary inclusion criteria were: (I) primary PTC confirmed by pathology; (II) non-palpable lateral LNs but suspicious on ultrasound and/or CT; (III) FNA of the suspicious LNs could not be performed due to the proximity to major cervical vessels or other neck structures; (IV) enough normal thyroid tissue for tracer injection; (V) patients who received lateral neck dissection (compartment IIA, IIB, III, IV and V). The exclusion criteria were: (I) prior thyroid or neck surgery; (II) thyroid cancer with macroscopic extra-thyroidal extension (ETE) on ultrasound and/or CT; (III) patients with distant metastasis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study protocol was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (approval number: 1612167-11). All participating institutions were also informed and agreed the study. All patients gave informed consent.

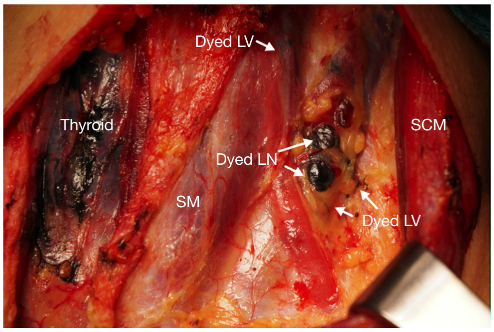

Figure 1 Dyed lymph nodes and lymph vessels in the lateral neck after tracer injection. LV, lymph vessels; LN, lymph node; SM, strip muscle; SCM, sternocleidomastoid muscle.

Procedures

Tracer injection

Carbon nanoparticles (Lai Mei Pharmaceutical Co., Chongqing, China) were used in the form of suspension (1 mL:50 mg) as previously reported (10). When the thyroid lobe was exposed, approximately 0.2 mL suspension was injected into the peri-tumoral normal thyroid tissue. The specific site and dose of the tracer injection were subject to surgeons' preferences. Cautery was used to close the needle hole to prevent the tracer from affecting the surgical vision. After tracer injection, LNs and lymph vessels in the lateral neck were dyed black (*Figure 1*).

Lateral neck dissection

All patients received modified lateral neck dissection including compartment IIA, IIB, III, IV and V. Dyed and undyed LNs were sent separately for pathology analysis. In four patients, a minority of dyed LNs were not properly classified into any specific compartment and therefore were labeled as unknown compartment.

Lobectomy and central neck dissection

Ipsilateral lobectomy, isthmic resection and central neck dissection were performed in all patients. Total thyroidectomy/subtotal thyroidectomy was performed in selected cases depending on clinical stage, recurrence risk, age, and patients' preferences. All procedures were performed by high-volume thyroid surgeons.

Statistical analysis

We categorized the lateral LNs into dyed and undyed groups according to whether the LN was blackened by the tracer macroscopically. We used Chi square test to analyze categorical variables and *t*-test to analyze continuous variables, respectively. Relative risk was reported with 95% confidence intervals (CIs). Two-sided P<0.05 was adopted to be statistically significant. All statistical analyses were conducted using IBM SPSS version 24 (Chicago, IL, USA) and GraphPad Prism version 8.2.1 (La Jolla, CA, USA).

Results

Baseline features

Five institutes enrolled a total of 174 patients, and 154 were included in the final analysis (Figure S1), including 110 (71.4%) female and 44 (28.6%) male patients. The median age of diagnosis was 36 (range, 15–69) years old. Post-operative pathology showed 151 (98.1%) cases were PTC, classical variant; one case was PTC, tall-cell variant; one case was PTC, follicular variant; and one case was PTC combined with micro-invasive follicular carcinoma. Fifty-four cancers had *BRAF* status tested, revealing 44 mutated cases, and 10 wildtype cases. Other baseline features are listed in *Table 1*.

The mapping of dyed LN in the lateral neck

A total of 5,070 lateral LNs were identified, among which 1,079 (21.3%) were dyed by carbon nanoparticles, 3,991 (78.7%) were undyed. The number of dyed LNs were 87 (9.8%), 9 (1.3%), 358 (30.0%), 582 (35.4%), 30 (5.0%), and 13 (36.1%) in compartment IIA, IIB, III, IV, V, and unknown compartment, respectively. The distribution of dyed LNs was significantly different among the compartments (P<0.001, *Figure 2A*). The medians of dyed LNs were 0, 0, 1, 2.5, 0 and 0 in compartment IIA, IIB, III, IV, V, and unknown compartment, respectively. The distribution of dyed LNs was compartment IV > III > IIA > IIB, while comparable dyed LNs were identified IIB, V and unknown compartments (*Figure 2B*). For an individual patient, the median of dyed LNs was 6 (range, 1–33).

The distribution of dyed LN is independent of clinical features

Then we focus the analysis on LNs in compartment IIA, III, and IV, and performed the analysis on per patient basis instead of per node basis. In 154 patients, 26 (16.9%), 102

Table 1 Baseline features of 154 enrolled patients

Clinical features	Value, n (%)
Tumor size (cm)	
≤1	51 (33.1)
>1, ≤2	72 (46.8)
>2	31 (20.1)
Multifocality	
No	101 (65.6)
Yes	53 (34.4)
Microscopic extra-thyroidal extension	
No	117 (76.0)
Yes	37 (24.0)
Tumor location	
Upper 1/3*	93 (60.4)
Other	61 (39.6)
Surgical procedure	
Lobectomy + CND + MND	68 (44.2)
Total/subtotal thyroidectomy + CND + MND	86 (55.8)
TNM stage (AJCC, 8th)	
Stage I	133 (86.4)
Stage II	21 (13.6)
ATA risk stratification (2015 version)	
Low risk	5 (3.2)
Intermediate risk	136 (88.3)
High risk	13 (8.4)

*, Multifocal cancers involving upper 1/3 lobe were included. CND, central neck dissection; MND, modified neck dissection; TNM, tumor node metastasis; AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association.

(66.2%) and 119 (77.3%) had dyed LNs in compartment IIA, III and IV, respectively. The distribution of dyed LNs on per case basis was compartment IV > III > IIA, consistent with that on per node basis. Subgroup analysis showed that the distribution of dyed LNs in compartment IIA, III, and IV was independent of patient sex, age, tumor size, multifocality, microscopic ETE, tumor location, *BRAF* status, TNM stage or ATA risk stratification (Table S1).

Dyed LN were more likely to metastasize

In 154 patients, one had no LN metastasis (pN0, 0.6%), five had only central neck metastasis (pN1a, 3.2%), 148 had lateral neck metastasis (pN1b, 96.1%). On per node basis, the percentages of LNs metastasis were 8.8%, 3.3%, 19.6%, 18.7%, and 4.0% in compartment IIA, IIB, III, IV and V, respectively. On per case basis, the percentage of LNs metastasis were 29.9%, 11.0%, 68.2%, 73.4% and 10.4% in compartment IIA, IIB, III, IV and V, respectively. As shown in *Table 2*, the probabilities of metastasis in dyed LNs were highest in compartment III and IV, both on per node basis and on per case basis.

Next, we analyzed the probability of metastasis of dyed versus undyed LNs on per node basis. In compartment III, IV, V, and II–V, dyed LNs had an increased risk of metastasis than undyed LNs (III: 29.3% *vs.* 15.4%, P<0.001; IV: 26.3% *vs.* 14.5%, P<0.001; V: 16.7% *vs.* 3.3%, P=0.005; II–V: 26.3% *vs.* 10.0%, P<0.001). The relative risks of metastasis in dyed LNs compared with undyed LNs were 1.90 [95% confidence interval (CI): 1.52–2.39], 1.82 (95% CI: 1.49–2.22), 5.04 (95% CI: 2.02–12.58) and 2.62 (95% CI: 2.29–3.00) in compartment III, IV, V, and II–V respectively. For compartment IIA and IIB, although higher percentages of metastasis were detected in dyed LNs, the results were not statistically significant (*Figure 3*).

Discussion

In the current study, we used carbon nanoparticles for lateral neck mapping in PTC patients with non-palpable but suspicious lateral neck LNs on imaging. Our results suggested that the distribution of dyed LNs was consistent with the LN drainage in the lateral neck. Compared with undyed LNs, dyed LNs had a higher risk of metastasis in compartment III, IV, V, and II–V, indicating the potential of this method to evaluate lateral neck intraoperatively.

In previous studies, similar surgical technique has been described in lateral LN mapping in PTC (11,12). However, Chen *et al.* used endoscopy to explore the lateral neck for LN biopsy (12), and Qian *et al.* used open surgeries (11). Consistent with the current study, they both identified compartment III–IV exhibited higher metastasis rate in dyed LN. Nevertheless, unlike their studies, we conducted the first multi-center prospective study of carbon nanoparticle-

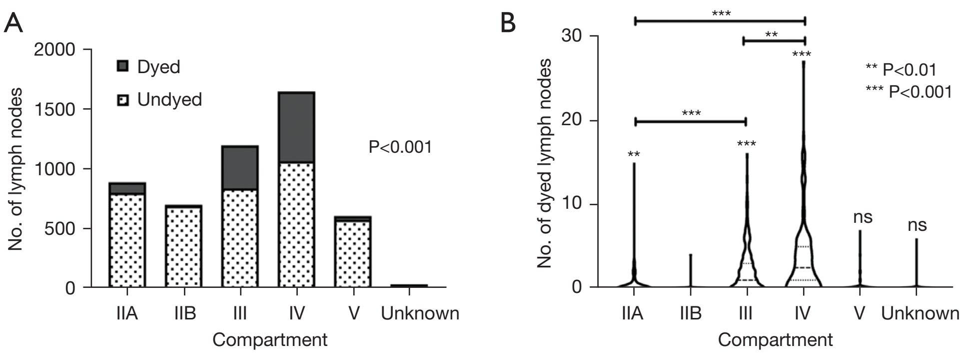

Figure 2 The distribution of dyed lateral lymph nodes according to neck compartments. (A) The total number of dyed lymph nodes were 87 (9.8%), 9 (1.3%), 358 (30.0%), 582 (35.4%), 30 (5.0%), and 13 (36.1%) in compartment IIA, IIB, III, IV, V, and unknown compartment, respectively (Chi square =586.3, P<0.001). (B) The violin plot demonstrated the distribution of dyed lymph nodes per patient. Compared with IIB, the dyed lymph nodes were significantly increased in compartment IIA (P=0.0012), III (P<0.001), and IV (P<0.001); while comparable dyed lymph nodes were identified in compartment V (P=0.07) and unknown (P=0.67). There were also more dyed lymph nodes in compartment IV than III (P=0.001) and more in III than IIA (P<0.001). ns, not significant.

Table 2 The probabilities of metastasis in dyed lymph nodes on per node and per case basis, according to lateral neck compartments

Compartments	On per node basis			On per case basis		
	Dyed LN	Metastatic LN	%	Dyed cases	Metastatic cases	%
IIA	87	11	12.6	26	10	38.5
IIB	9	1	11.1	3	1	33.3
III	358	105	29.3	102	65	63.7
IV	582	153	26.3	119	80	67.2
V	30	5	16.7	12	4	33.3
II–V*	1079	284	26.3	154	127	82.5

*, including unknown compartment. LN, lymph node.

guided lateral neck mapping and calculated the relative risks of metastasis in dyed LNs compared with undyed LNs in each neck compartment. We also performed subgroup analysis and demonstrated that he distribution of dyed LNs was independent of clinical features, suggesting lateral LN mapping could be used in patients regardless of sex, age, multifocality, microscopic ETE and tumor location.

The prognostic value of lateral LN metastasis has been discussed for decades. It is generally believed that clinical metastasis is a prognostic factor for cancer recurrence, high morbidity rates, difficult reoperations (13-15), and neck dissection improves disease-free survival in these patients (16). However, the management of non-palpable lateral LNs remains controversial. Some support that modified neck dissection or super-selective neck dissection should be performed in patients with high-risk factors to lateral LN metastasis (17-21); the others believe that prophylactic neck dissection is not reasonable, because of the indolent nature of the disease and the morbidities of neck dissection (22,23). Non-palpable LNs should be resected only if they are becoming clinically evident on follow-up (24). Lateral LN mapping or sentinel LN biopsy might serve as the third option in neck management and provide evidence in the decision-making of neck dissections.

Several previous studies reported the occult lateral sentinel LN biopsy in thyroid cancer with different tracers (25). Dzodic *et al.* reported sentinel LN biopsy in the jugulo-carotid chain in 40 patients using methylene blue dye, with the sensitivity of 77.7% (26). Chen *et al.* used carbon nanoparticles as the tracer in neck dissection of clinically

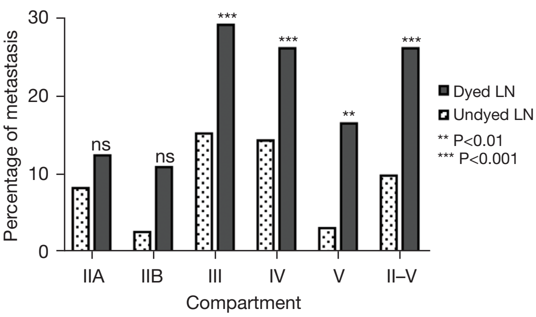

Figure 3 Dyed lymph nodes were more likely to metastasize in lateral neck compared with undyed lymph nodes. On per node basis, in compartment III, IV, V, and II–V dyed LN had a higher risk of metastasis than undyed LN (III: 29.3% *vs.* 15.4%, P<0.001; IV: 26.3% *vs.* 14.5%, P<0.001; V: 16.7% *vs.* 3.3%, P=0.005; II–V: 26.3% *vs.* 10.0%, P<0.001). P values were calculated by Pearson Chi-square test. II–V included compartment IIA, IIB, III, IV, V and unknown compartments. LN, lymph node; ns, not significant.

node-negative PTC (12). Lee *et al.* used radioisotope in the detection of occult lateral LN metastasis (27). They found sentinel LN metastasis in 31.7% patients and the clinically occult metastasis was only related to the total number of metastatic LNs in the central compartment. There was only one randomized control study to compare the local-regional recurrence of PTC in lateral sentinel LN biopsy group and control group. Investigators found that although lateral sentinel LN biopsy was able to remove occult metastasis in PTC, this procedure had no benefits on either sTg levels or on recurrence rates at a mean follow-up time of 39 months (28). However, their study populations were different from the current study, since occult metastasis was not detectable by routine methods, including preoperative ultrasound and CT (29).

In the real world, clinicians are frequently faced with indeterminate lateral LNs that are not proven metastatic but are not normal in shape in preoperative ultrasound and CT (8). We believe that these patients are better candidates for LN mapping, because indeterminate LNs are more likely to develop into pathologically proven metastasis and require re-operations. Instead of unguided lateral LN biopsy, this lateral LN mapping technique could help surgeons visualize suspicious LNs and serve as a guide for LN biopsy. If the frozen section is positive for metastasis, modified neck dissection should be performed, otherwise the patient is subject to follow-up.

Another advantage of lateral mapping in indeterminate LN is to reduce unnecessary neck dissections. The common complication of neck dissection includes skin numbness, extensive scarring, brachial plexus injury, shoulder movement disorders, phrenic nerve injury, cervical sympathetic trunk, and thoracic duct injury (23). Since PTC has a low mortality rate, the life quality of patients is even more important in the long term.

There are several limitations of our study. First of all, it was a pilot study of lateral LN mapping using nanoparticles and we did not actually perform LN biopsy in these cases. Further studies are awaited to conduct lateral LN biopsy in patients with indeterminate lateral LNs. Next, the reasonable range of neck exploration was undetermined. Extensive neck exploration might cause complications as well. Then, since the tracer had to inject into the thyroid tissue, the application of this method was confined to patients without prior thyroidectomy. Lastly, we did not compare carbon nanoparticle with other tracers used for LN mapping. Therefore, it remains unknown which tracer or the combination of tracers is the best choice for mapping LNs in PTC.

Conclusions

This was the first prospective multicenter study using carbon nanoparticles to map the draining lateral LNs in PTC intraoperatively. This surgical procedure could help surgeons visualize suspicious lateral LNs and serve as an evaluation method in the decision making of neck dissection.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-222/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-222/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-222/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (approval number: 1612167-11). All participating institutions were also informed and agreed the study. Written informed consent was obtained from each patient.

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Supplementary

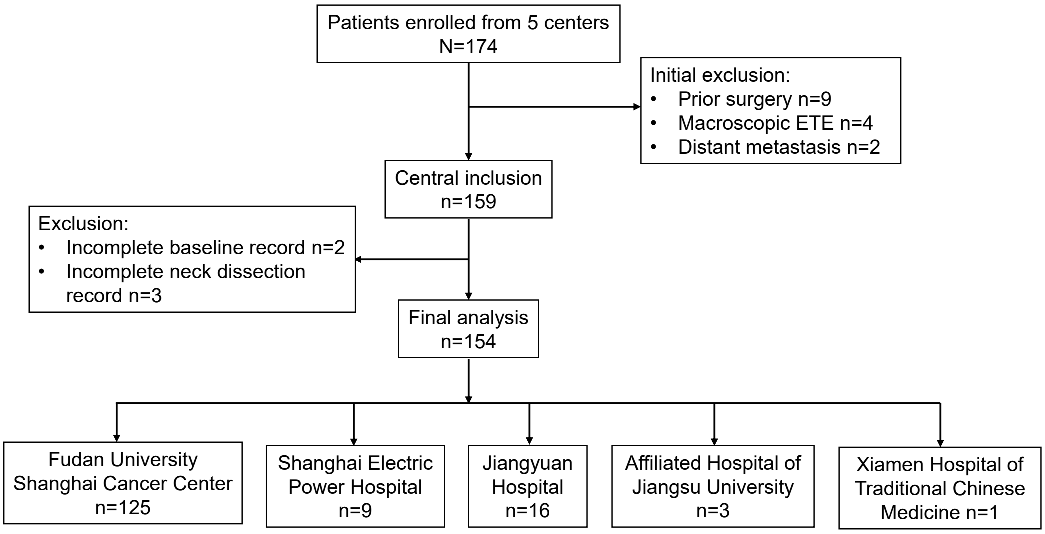

Figure S1 Flow of participants through each stage of the study. ETE, extra-thyroidal extension.

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Table S1 The distribution of dyed lymph nodes was independent of clinical features

Clinical features	Compartment IIA		Compartment III		Compartment IV	
	n (%)	P#	n (%)	P#	n (%)	P#
Sex						
Female, N=110	18 (16.4)	0.786	72 (65.5)	0.746	87 (79.1)	0.395
Male, N=44	8 (18.2)		30 (68.2)		32 (72.7)	
Age (years)						
<55	25 (18.9)	0.095	85 (64.4)	0.237	103 (78.0)	0.583
≥55	1 (4.5)		17 (77.3)		16 (72.7)	
Tumor size (cm)						
≤1, N=51	10 (19.6)	0.649	33 (64.7)	0.436	38 (74.5)	0.805
>1, ≤2, N=72	10 (13.9)		51 (70.8)		56 (77.8)	
>2, N=31	6 (19.4)		18 (58.1)		25 (80.6)	
Multifocality						
No, N=101	16 (15.8)	0.634	68 (67.3)	0.692	81 (80.2)	0.232
Yes, N=53	10 (18.9)		34 (64.2)		38 (71.7)	
Microscopic ETE						
No, N=117	18 (15.4)	0.377	80 (68.4)	0.317	94 (80.3)	0.106
Yes, N=37	8 (21.6)		22 (59.5)		25 (67.6)	
Tumor location						
Upper 1/3*, N=93	16 (17.2)	0.895	59 (63.4)	0.366	69 (74.2)	0.260
Other, N=61	10 (16.4)		43 (70.5)		50 (82.0)	
BRAF status						
Mutated, N=43	4 (9.3)	0.295	27 (62.8)	0.841	37 (86.0)	0.120
Wildtype, N=10	2 (20.0)		7 (70.0)		9 (90.0)	
Not tested, N=101	20 (19.8)		68 (67.3)		73 (72.3)	
TNM stage						
Stage I, N=133	25 (18.8)	0.111	85 (63.9)	0.125	104 (78.2)	0.492
Stage II, N=21	1 (4.8)		17 (81.0)		15 (71.4)	
ATA risk stratification						
Low risk, N=5	1 (20.0)	0.803	2 (40.0)	0.258	5 (100.0)	0.188
Intermediate risk, N=136	22 (16.2)		93 (68.4)		106 (77.9)	
High risk, N=13	3 (23.1)		7 (53.8)		8 (61.5)	

#, calculated by Pearson Chi-square test; *, multifocal cancers involving upper 1/3 lobe were included. ETE, extra-thyroidal extension; TNM, tumor node metastasis; ATA, American Thyroid Association.

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