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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Clinical Significance of Gross Invasion of Strap Muscles in Patients With 1- to 4-cm-Sized Papillary Thyroid Carcinoma Undergoing Lobectomy

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ABSTRACT

Background. Given the emerging evidence supporting the lack of prognostic significance of gross extrathyroidal extension invading only strap muscles (strap-gETE), this study investigated whether lobectomy is feasible for patients with strap-gETE.

Methods. A retrospective cohort study was conducted with 636 patients who had 1- to 4-cm-sized papillary thyroid carcinoma (PTC) treated with thyroid lobectomy. Patients with gross invasion of perithyroidal organs other than strap muscles or synchronous distant metastasis were excluded from the study. Disease-free survival (DFS) was compared according to the presence of strap-gETE.

Results. Strap-gETE was present in 50 patients (7.9%), with the remaining 586 patients (92.1%) showing no evidence of gETE. During the median follow-up period of 7.4 years, 6% of the patients with strap-gETE and 5.1% of the patients without gETE experienced structural persistent/recurrent disease ($p = 0.99$). No differences in DFS were observed between the two groups (hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.38–4.08; $p = 0.720$). After adjustment for five major risk factors (age, gender, tumor size, multifocality, and cervical lymph node metastasis status) in the multivariate analysis, the presence of strap-gETE did not exhibit an independent role in the development of structural persistent/recurrent disease (HR 1.05; 95% CI 0.24–4.53, $p = 0.950$).

Conclusions. Strap-gETE did not increase the risk of structural persistent/recurrent disease for the patients who underwent lobectomy for 1- to 4-cm-sized PTC. The study data support the limited role of strap-gETE in clinical outcomes and may broaden the indications for lobectomy for patients with PTCs.

The prognostic significance of extrathyroidal extension (ETE) in differentiated thyroid carcinoma (DTC) has changed considerably during recent decades. Until the fifth edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system was published in 199[1,7] all tumors with ETE were classified as T4 disease without distinguishing minimal ETE (mETE) from gross ETE (gETE). However, it was doubtful whether mETE resulted in the same adverse clinical outcomes as gETE.

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With growing evidence that mETE exhibits less prognostic importance than gETE,[2,3] the sixth edition of the AJCC TNM staging system published in 2002 adopted this distinction in classifying the T stage for the first time. In the sixth-edition staging system, mETE was downstaged to T3, whereas gETE remained as T4 disease.[4] Notably, T4 also was categorized further into T4a and T4b according to the organs in which the gross invasion was present, with T4b disease representing more extensive unresectable invasion.

This classification of the degree of ETE encountered another major change in the newest, eighth edition of the AJCC TNM staging system published in 2017.[5] The mETE no longer determines the T stage because little evidence exists to support mETE as an independent marker of recurrence or survival.[6–8] Instead, the emphasis has shifted toward the gETE. In particular, gETE to the anterior or posterior direction was distinguished for the first time, as follows: T3b disease (gETE involving only the strap muscles [strap-gETE]), T4a disease (gETE invading subcutaneous soft tissues, larynx, trachea, esophagus, or the RLN), and T4b disease (gETE invading prevertebral fascia or encasing the carotid artery or mediastinal vessels).

The fact that strap-gETE is considered an independent staging variable for defining T3b disease deserves special attention. The clinical impact of strap-gETE on survival outcomes has not been thoroughly assessed due to very limited data availability.[3,9,10] However, recently published studies assessing the long-term prognosis of patients with DTC and strap-gETE have reported that strap-gETE alone does not increase the risk of either recurrence or survival.[11–13] Given the growing evidence supporting the lack of strap-gETE impact on clinical outcomes, the question whether lobectomy is feasible for patients with strap-gETE may be worth investigating.

Currently, the 2015 American Thyroid Association (ATA) guidelines allow lobectomy for 1- to 4-cm-sized DTCs when they are "low risk" clinically (i.e., N0 and with no ETE).[14] In fact, the ATA risk stratification system categorizes gETE as a high-risk factor, but the evidence supporting this categorization did not focus on strap-gETE separately but rather on T4a disease.[3,8,15] Therefore, it is unclear whether strap-gETE increases the risk of recurrence and whether it should be classified as one of the high-risk factors.

To the best of our knowledge, no previous studies have evaluated the feasibility of lobectomy for patients with strap-gETE. To fill this research gap, we investigated the difference in disease-free survival (DFS) between patients who underwent lobectomy with strap-gETE and those treated without strap-gETE, with the aim of determining whether strap-gETE exhibits independent prognostic influence on structural persistent/recurrent disease.

METHODS

Study Design and Patients

This retrospective cohort study included patients with PTC who underwent thyroid lobectomy for tumors 1–4 cm in size from 1998 to 2010 at Asan Medical Center, Seoul, Korea. Routine preoperative neck ultrasonography (US) was performed for all patients undergoing lobectomy, and indeterminate or suspicious thyroid nodules in the contralateral lobe, when present, were evaluated by fine-needle aspiration cytology before surgery, as previously reported.[16]

During the study period, 4793 patients underwent thyroid surgery for 1- to 4-cm-sized PTCs. The study excluded 4121 of these patients who underwent total thyroidectomy (TT) and 36 patients who underwent planned completion thyroidectomy within 1 year after their initial lobectomies. Patients without gETE and those with strap-gETE were included, but those with gETE invading perithyroidal organs other than strap muscles (T4) or with synchronous distant metastasis were excluded because lobectomy was not considered for these patients. Ultimately, the current study enrolled 636 patients who underwent lobectomy. Data collection and subsequent analysis were approved by the Institutional Review Board of Asan Medical Center.

Identification of gETE and Classification of Patients

The preoperative neck US, operation records, and pathology reports for all the patients were reviewed to assess the extent of ETE. The patients with no gETE and those with mETE were classified as "no gETE," and those with gETE invading only strap muscles were classified as "strap-gETE." In the classification, 586 patients fell into the no-gETE group and 50 patients into the strap-gETE group.

Surgical Strategy

During the study period, TT was recommended as initial surgery based on earlier ATA guidelines, but for those who refused TT, lobectomy was performed after they were given sufficient information regarding the potential risks and benefits of lobectomy. In the Asan Medical Center, routine ipsilateral central compartment node dissection is performed even for clinically lymph node (LN)-negative patients.[17]

Primary Outcome

The primary outcome of the study was structural persistent/recurrent disease, defined as the appearance of

metastatic lesions after initial treatment, confirmed by cytologic or histopathologic examination, and/or the appearance of distant metastatic lesions on imaging, as reported previously.[18] Neck US was performed within the first 6–12 months after the initial lobectomy and routinely repeated at 12- to 24-month intervals. If indeterminate or suspicious thyroid nodules were found in the contralateral lobe or LNs, fine-needle aspiration cytology was used to confirm structural recurrence. Additional diagnostic imaging, such as neck or chest computed tomography, magnetic resonance imaging, or whole-body fluoro-deoxyglucose-positron emission tomography, was performed to detect recurrence or distant metastasis in some patients. The interval between initial surgery and detection of structural persistent/recurrent disease (DFS) was compared according to the presence of strap-gETE. Death was not considered an event for DFS.

Statistical Analysis

Data analysis used R version 3.4.0 and the R libraries survival, car, survminer, and Cairo (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). Continuous variables were presented as medians with interquartile ranges (IQRs) or as means with standard deviations (SDs) and analyzed using the Mann–Whitney *U* test and Student's *t* test, respectively. Categorical variables were presented as numbers with percentages and analyzed using Pearson's χ^2 test. Using the Kaplan–Meier method, DFS curves were plotted, and the log-rank test was used to determine significance. Variables associated with structural persistent/recurrent disease were evaluated by Cox proportional hazard models. Differences in *p* values less than 0.05 were regarded as significant.

RESULTS

Baseline Clinicopathologic Characteristics

Table 1 summarizes the baseline characteristics of the 636 study patients according to the presence of strap-gETE. The patients with strap-gETE presented with a significantly older age (mean, 49.9 years) than the patients without gETE (mean, 45 years) ($p = 0.001$). Otherwise, no differences were found in terms of gender, tumor size, multifocality, or cervical LN metastasis.

DFS According to the Presence of Strap-gETE

During the median follow-up period of 7.4 years (interquartile range [IQR], 5.0–10.8 years), 6% of the patients with strap-gETE ($n = 3$) experienced structural persistent/recurrent disease. This rate was similar to the 5.1% rate for the patients with no gETE ($n = 30$; $p = 0.99$).

Figure 1 shows the DFS according to the presence of strap-gETE. The 5-year DFS rate was 95.3% for the patients with strap-gETE and 95.4% for the patients without gETE. The two groups did not differ significantly in terms of DFS (hazard ratio [HR], 1.24; 95% confidence interval [CI], 0.38–4.08; $p = 0.720$).

Table S1 summarizes the patterns of structural persistent/recurrent disease in both groups of patients. The most common site of structural persistence/recurrence was the contralateral lobe followed by lateral cervical LNs in both groups. Two patients in the strap-gETE group and eight patients in the no-gETE group experienced structural persistent/recurrent disease in both the contralateral lobe and lateral cervical LNs.

Prognostic Impact of Strap-gETE on Structural Persistent/Recurrent Disease

The impact of strap-gETE on structural persistent/recurrent disease in the patients who underwent lobectomy was evaluated via uni- and multi-variate analyses adjusted for major clinicopathologic factors such as age, gender, tumor size, multifocality, and cervical LN metastasis state. No increased risk of structural persistent/recurrent disease was associated with strap-gETE in either the uni- or the multivariate analysis (HR 1.05; 95% CI 0.24–4.53; $p = 0.950$ in the multivariate analysis; Table 2).

DISCUSSION

Currently, the major trend in managing thyroid cancers is moving toward "less is more": less surgery for micro-PTCs, a less extensive surgical approach for 1- to 4-cm-sized PTCs, less use of radioactive iodine and lower doses when indicated, less thyrotropin suppression, and fewer stimulated tests in long-term follow-up evaluation.[14,19,20] In accordance with this trend, our study may broaden the indications for lobectomy for patients with PTC by providing evidence that lobectomy can be performed for PTCs using strap-gETE without increasing the risk for structural persistent/recurrent disease.

In the current study of patients who underwent lobectomy for 1- to 4-cm-sized PTC, no differences in DFS were observed between those with strap-gETE and their counterparts. Moreover, after adjustment for five major clinicopathologic risk factors, strap-gETE did not exhibit a poor prognostic impact on structural persistent/recurrent disease.

TABLE 1 Baseline characteristics of study patients according to the presence of strap-gETE

	Total (n = 636) n (%)	No gETE (n = 586) n (%)	strap-gETE (n = 50) n (%)	p Value
Mean age (years)	45.4 ± 11.3	45.0 ± 11.4	49.9 ± 8.9	0.001
≥ 55	134 (21.1)	117 (20.0)	17 (34.0)	0.031
Gender (female)	502 (78.9)	457 (78.0)	45 (90.0)	0.066
Median primary tumor size: cm (IQR)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.1–1.5)	0.460
Range (cm)	1.0–3.9	1.0–3.9	1.0–2.4	
Multifocality (yes)	60 (9.4)	53 (9.0)	7 (14.0)	0.153
Cervical LN metastasis				0.118
N0	403 (63.4)	378 (64.5)	25 (50.0)	
N1a	233 (36.6)	208 (35.5)	25 (50.0)	
CCND (yes)	586 (92.1)	536 (91.5)	50 (100)	0.178
Prophylactic	574 (90.2)	525 (89.6)	49 (98)	
Therapeutic	12 (1.9)	11 (1.9)	1 (2)	
Follow-up period: years (IQR)	7.4 (5.0–10.8)	7.6 (5.1–10.9)	7.0 (5.0–8.5)	

CCND central compartment neck dissection, *IQR* interquartile range, *LN* lymph node, *strap-gETE* gross extrathyroidal extension only in strap muscles

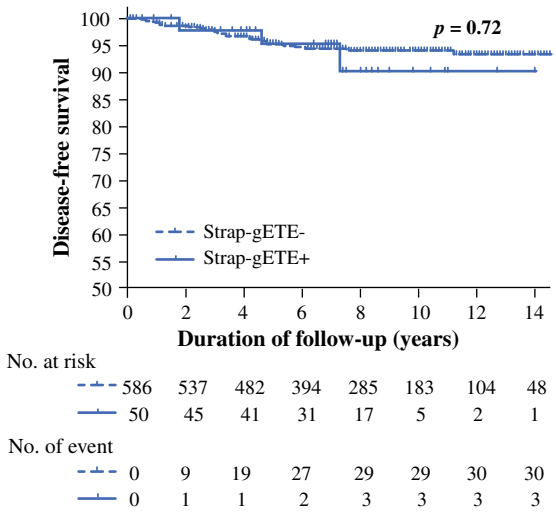

FIG. 1 Disease-free survival (DFS) curve according to the presence of gross strap muscles invasion (strap-gETE)

Lobectomy certainly has advantages over TT in terms of fewer postoperative complication risks (e.g., bleeding, hypoparathyroidism, and recurrent laryngeal nerve injury) and less need for life-long thyroid hormone replacement.[21–23] Considering these benefits, we suggest that lobectomy can be performed for patients with strap-gETE.

The eighth edition of the AJCC staging system categorizes strap-gETE solely as T3b disease regardless of tumor size,[5] but the significance of strap-gETE still remains uncertain with respect to its impact on clinical outcomes. In fact, we recently published a retrospective study regarding this issue.[13] We evaluated disease-specific survival (DSS) according to the presence of strap-gETE and observed that patients who had DTC size 4 cm or smaller with strap-gETE showed a better DSS than patients with T3a disease (HR 0.19; 95% CI 0.05–0.72; p = 0.014) and did not differ from patients with T2 disease (HR 0.81; 95% CI 0.24–2.77;

TABLE 2 Impact of strap-gETE on structural persistent/recurrent disease

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age ≥ 55 years	0.75 (0.29–1.94)	0.553	0.80 (0.31–2.12)	0.661
Gender (male)	0.82 (0.34–1.97)	0.651	0.74 (0.30–1.85)	0.523
Tumor size (per 1-cm increase)	1.25 (0.90–1.74)	0.189	1.39 (1.00–1.95)	0.049
Multifocality	1.50 (0.58–3.89)	0.407	1.47 (0.56–3.88)	0.432
Cervical LN metastasis	1.89 (0.9–3.71)	0.062	2.21 (1.06–4.62)	0.034
Strap-gETE	1.24 (0.38–4.08)	0.720	1.05 (0.24–4.53)	0.950

CI confidence interval, *HR* hazard ratio, *LN* lymph node, *strap-gETE* gross extrathyroidal extension only in strap muscles

$p = 0.737$). We concluded that strap-gETE has a limited impact on survival, and that emphasis should be placed on tumor size.

Our findings were consistent with those of a previous study reporting the lack of significant differences in DSS between patients with T2 and T3b disease and a trend toward a better DSS for patients with T3b than for those with T2.[24] The authors emphasized the need to reconsider the inclusion of strap-gETE as an upstaging factor for T3b.

Similarly, another recent study examined the differences in DSS and recurrence-free survival according to the extent of ETE and reported that strap-gETE neither affects DSS (HR 1.49; 95% CI 0.61–3.63; $p = 0.385$) nor is an independent predictor of recurrence (HR 1.09; 95% CI 0.71–1.69; $p = 0.685$).[11] A similar retrospective study showed no significant effect of strap-gETE on either DFS (HR 1.42; 95% CI 0.49–3.28; $p = 0.471$ in the multivariate analysis) or overall survival (HR 0.92; 95% CI 0.15–2.95; $p = 0.907$ in the univariate analysis).[12]

In contrast, however, no studies to date have proven a definite survival disadvantage due to strap-gETE. This lack of solid evidence regarding the prognostic significance of strap-gETE for clinical outcomes led us to investigate further whether lobectomy is feasible for patients with strap-gETE. In fact, in the two aforementioned studies,[11,12] only 4 of 3174 patients and 1 of 2084 patients with strap-gETE who respectively underwent lobectomy were included. Our study included 50 patients with this condition and clearly showed that lobectomy is feasible for PTCs 1–4 cm in size, even when gETE is present in strap muscles. We believe that the advance in surgical skills and the high likelihood of successful resection of the invasion to strap muscles may explain the reasons why strap-gETE does not result in adverse clinical outcomes.[25]

The ATA risk-stratification system used to predict disease recurrence classifies the presence of gETE as a high-risk factor, whereas it classifies mETE as an intermediate-risk factor.[14] However, the gETE is not categorized further based on the organs to which the tumor extends. According to this risk-stratification system, the presence of strap-gETE requires more extensive surgery, a higher dose of radioactive iodine for ablation, and a much lower level of target thyroid-stimulating hormone (TSH) during follow-up evaluation. However, the evidence supporting this classification is not focused on strap-gETE separately, but rather on T4a disease.[3,8,15] Based on our study, organ-specific modification in terms of gETE should be considered.

The strength of the current study was that the results demonstrated the availability of lobectomy for patients who had 1- to 4-cm-sized PTCs with strap-gETE, which to the best of our knowledge has not been investigated previously. Suggesting the possibility of performing less extensive surgery for these patients is in accordance with the current trend of downstaging the management of PTCs. However, a limitation of this study was its retrospective nature. The patients with strap-gETE were older than those without gETE, and this may have caused selection bias. Nevertheless, age was included as a variable for structural persistent/recurrent disease in the multivariate analysis and therefore was adjusted. Moreover, the number of patients with strap-gETE was 50, and although this is a higher number than in previous studies, the impact of strap-gETE should be assessed by future studies with a larger cohort.

In conclusion, lobectomy can be performed for 1- to 4-cm-sized PTCs with strap-gETE without increasing the risk of structural persistent/recurrent disease. The presence of strap-gETE does not play an independent role in the development of structural persistent/recurrent disease in these patients. Our data support the limited role of strap-gETE in clinical outcomes and suggest the feasibility of lobectomy for patients with strap-gETE.

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CONFLICT OF INTEREST There are no conflicts of interest.

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