Obesity Induces Different Regional Patterns of Lymph Node Involvement: Assay on 8,979 Thyroid Cancers

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Research

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Abstract

Introduction Lymph node (LN) metastasis is the first station of extra-gland metastasis of thyroid cancer. LN status can influence clinical decisions and the prognosis of patients. The aim of our study was to explore the relationship between obesity and regional patterns of LN involvement in papillary thyroid carcinoma (PTC).

Materials and methods This study retrospectively analyzed the data from 8,979 thyroid cancer patients. The rate of LN metastasis, the number of LN metastasis, the maximum diameter of positive LN, the number of LN dissections, and the LN ratios (LNR) were compared between normal-weight and obese patients.

Results LN metastasis was more common in the obese group than normal-weight patients with PTC (52.6 vs. 42.0%, $P < 0.001$). The number of LN metastasis and the maximum diameter of positive LNs were also higher in obese patients (2.41 vs. 1.79, $P < 0.001$; 2.00 vs. 1.60, $P = 0.007$, respectively). The number of lateral neck LN dissections was higher in the obese group (14.37 vs. 12.10, $P < 0.001$), there was no significant difference in the central LNs. The LNR was higher in the central LNs of obese patients (0.18 vs. 0.14, $P < 0.001$), yet there was no difference in the lateral LNs.

Conclusions Obesity was associated with poor prognoses with PTC, which was related to the LNs. There was an inverse regional difference (central and lateral LNs) between obesity and the number of LN dissections and LNR, suggesting that caution was needed when performing central neck dissection in obese patients.

Introduction

The prevalence of obesity is approximately 40% worldwide, affecting more than 2 billion adults (1). Obesity has been identified as an independent risk factor for many cancers. Some studies have reported that nearly 40% of cancers may be attributed to obesity (2), and there is strong evidence to suggest that obesity is related to cancers of the esophagus, liver, pancreas, gallbladder, ovary, thyroid, kidneys, and plasma cells (3). Although obesity has been linked to an increased risk of diabetes and coronary artery disease, the impact of obesity on the incidence rates, risk factors, morbidity, and mortality of thyroid cancer requires further exploration (4). As thyroid cancer is the most common type of endocrine tumor, understanding how body mass index (BMI) impacts this disease has vital public health implications (5). Obesity also affects the diagnostic assessment of patients negatively. Deglise *et al.* found that obese women were less likely to have undergone ultrasound (OR = 0.5) or MRI (OR = 0.3) and were at an increased risk of prolonged hospital stays (OR = 4.7) in the clinic (6).

A significant association has been established between elevated BMIs and increased papillary thyroid carcinoma (PTC) incidence rates (7). In a previous study, we identified obesity as a risk factor for thyroid cancer, specifically when tumor sizes were larger than 1 cm with multifocality and extrathyroidal extensions (8–10). However, the connection between obesity and lymph node (LN) metastasis of thyroid

cancer has not been thoroughly investigated. One of the most important prognostic factors in PTC is LN status (11). LN metastasis is the first station of extra-gland metastasis of thyroid cancer (11). Hence, LN metastasis is an excellent predictor of the prognosis of patients with thyroid cancer. LN status can influence important clinical decisions, such as therapeutic options (11). The American Thyroid Association (ATA) guidelines use the number of metastatic LNs and the maximum diameter of positive LNs as important indicators for predicting the risk of recurrence (11). Compared to patients with less than five metastatic LNs, the recurrence rates are much higher for patients with more than five metastatic LNs (19% vs. 8%) (12, 13). In terms of maximum positive LN diameter, recurrence rates are significantly higher in patients with LNs smaller than 3 cm (27% vs. 5%) (13).

In this study, we focused on the relationship between obesity and the patterns of LN involvement in PTC, with an emphasis on the number of metastatic LNs, the maximum diameter of positive LNs, the lymph node ratio (LNR), the number of dissected LNs, and the LN skip metastasis.

Materials And Methods

Setting and data collection

This study was performed using a database from the Division of Thyroid Surgery, China-Japan Union Hospital of Jilin University. The patients in this study were diagnosed with PTC at our institute between June 2008 and December 2017.

Ethics statement

This study was approved by the Health Care Ethics Committee of the China-Japan Union Hospital of Jilin University (No. 2019040806).

Participants

This study is a retrospective analysis of patients with operable PTC. All the patients eligible for this analysis received central neck node dissection. Patients were aged ≥ 18 years, pathologically-confirmed to have PTC, and normal weight or obese (according to WHO standards). The exclusion criteria included: non-PTC patients, other thyroid cancer subtypes, different types of cancer, and patients requiring reoperations (Fig. 1).

Treatments

Oncological treatment, which ranged from surgery to radioactive iodine (RAI), was standardized for all patients and in accordance with the multidisciplinary tumor board consensus. The histological subtype was assessed according to the WHO classification. According to the Chinese guidelines for diagnosis and treatment of differentiated thyroid, all patients with thyroid cancer routinely underwent prophylactic central neck dissection (CND) (14). For those LNs suggested to be malignant by ultrasonography, fine needle aspiration cytology (FNAC) was used to confirm the diagnosis. Patients with cervical lymph node metastasis were confirmed by preoperative FNAC or intraoperative frozen pathological examinations.

These patients underwent therapeutic cervical lymph node dissection. Prophylactic cervical lymph node dissection was not recommended. The upper bound of the range of CND is the lower hyoid bone, the lower bound is the superior sternum fossa, the outside is the common carotid artery, and the inside is the inside of the trachea. The lateral LN dissection minimum ranged from the IIa, III, IV, and Vb area, while other areas were treated according to the results of the FNAC.

Definitions

Body-mass index. According to the WHO-BMI standard, BMI is between $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$, which was defined as normal-weight. Obesity is defined as $\text{BMI} \geq 30 \text{ kg/m}^2$ (15). Height and weight measurements used to calculate the BMI were retrieved from electronic registration databases. BMI was calculated as weight divided by height squared. Upon the first admission, the demographics and clinical data, including height and weight, were recorded.

Pattern of metastatic LNs. The pattern of metastatic LNs included the rate of metastatic LNs, the number of metastatic LNs, the number of dissected LNs, the lymph node ratio (LNR), the maximum diameter of positive LNs, and the rate of LN skip metastasis.

Maximum diameter of positive LNs. The maximal tumor diameter of the largest metastatic LN using the concept of micro-metastases in breast cancer (16).

Lymph node ratio (LNR). LNR was defined as the number of nodes involved by the tumor divided by the total number of resected lymph nodes during the surgical treatment.

LN skip metastasis. Defined as a lateral lymph node metastasis without central lymph node involvement.

Pathological examination

Specimens removed during the operation were submitted for histological analysis to determine the presence and size of metastatic LNs. For this study, an experienced pathologist reviewed the pathological slides and measured the properties of each LN.

Outcomes and covariates

We used BMI as an index and further correlated it with the presence and pattern of LN metastases. Patients were identified as LN positive if they had a pathologic LN status of pN1a or pN1b. Based on prior studies, we included important predictors of LN status in multivariable models (17). For example, information regarding the following thyroid tumor characteristics was obtained from medical records: age, weight, height, tumor size (mm), multifocality, extrathyroidal extension, rate of metastatic LNs (%), number of metastatic LNs, number of LN dissections, LNR (%), maximum diameter of positive LNs (mm), and LN skip metastasis (%).

Statistical analysis

All data were collected using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as a percentage (frequency). Continuous variables were analyzed by the *t*-test or one-way analysis of variance (ANOVA). Categorical variables were examined using the χ^2 -test or Fischer's exact test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 22.0 software (IBM, Chicago, IL, USA).

Results

Baseline characteristics of patients

Our database included 14,795 patients with PTC, of which 8,979 patients were included in the final analysis (Fig. 1). The male-to-female ratio is 1:5. The average age is 42.52 ± 9.38 years. The average BMI is 23.26 ± 3.34 kg/m². Obesity accounted for 9.4% of patients.

Baseline characteristics of LNs

In total, 110,580 LNs were dissected, of which 16,589 LNs were metastases (15.0%). The rate of metastatic LNs was 43.0% (3858/8979). The mean number of LN metastases was 1.85 ± 3.73 . The average number of LN dissected was 12.32 ± 11.86 . The LNR was $0.14 \pm 0.23\%$, and the maximum diameter of positive LNs was 1.64 ± 3.99 mm. The rate of LN skip metastasis is 4.1% (367/8979), as shown in Table 1.

Table 1
Basic demographics and clinical data of patients included in this study.

Characteristics	Total Mean (SD) or % (n) (N = 8979)
Sex	
Male: Female	1 : 5
Mean age	42.52 (9.38)
Mean BMI (kg/m ²)	23.26 (3.34)
BMI group (WHO-BMI)	
Normal ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$)	90.6% (8133)
Obesity ($\geq 30 \text{ kg/m}^2$)	9.4% (846)
Thyroid Function	
TSH (mIU/L)	3.19 (3.56)
FT3 (pmol/L)	2.64 (1.03)
FT4 (pmol/L)	3.56 (6.87)
Pathological features	
Mean tumor size (mm)	0.80 (0.62)
Multifocality	39.2% (3524)
Extrathyroidal extension	26.2% (2352)
Rate of LN metastasis (%)	43.0% (3858)
Number of LN metastasis	1.85 (3.73)
Number of LN dissections	12.32 (11.86)
Positive rate of LNs (%)	0.14 (0.23)
Maximum diameter of positive LNs (mm)	1.64 (3.99)
Rate of LN skip metastasis (%)	4.1% (367)
Abbreviation: BMI = body mass index, TSH = thyroid stimulating hormone, FT3 = free triiodothyronine, FT4 = free thyroxine, LN = lymph node, LNR = lymph node ratio.	
* $P < 0.05$, ** $P < 0.01$	

Impact of BMI on the rate of metastatic LNs

As shown in Table 2, the rate of metastatic LNs in obese patients with PTCs was significantly higher than that of normal-weight patients (52.6 vs. 42.0%, $P < 0.001$). The rates of central metastatic LNs and lateral neck metastatic LNs were significantly higher in obese patients than normal-weight patients (47.6 vs. 38.0%, $P < 0.001$; 22.2 vs. 16.9%, $P < 0.001$). The rates of lateral neck metastatic LNs on both the left and right sides were higher than normal-weight patients (11.1 vs. 8.6%, $P = 0.015$; 13.7 vs. 9.8%, $P = 0.001$).

Table 2
Relationship between obesity and the rate of metastatic lymph nodes (LNs).

WHO-BMI		Normal % (n) N = 8133	Obesity % (n) N = 846	<i>P value</i>
Rate of total LN metastasis		42.0% (3413)	52.6% (445)	$< 0.001^{**}$
Rate of central LN metastasis		38.0% (3088)	47.6% (403)	$< 0.001^{**}$
Rate of lateral LN metastasis	Total	16.9% (1378)	22.2% (188)	$< 0.001^{**}$
	Right	9.8% (800)	13.7% (116)	0.001^{**}
	Left	8.6% (698)	11.1% (94)	0.015^*
Abbreviation: WHO = World Health Organization, BMI = body mass index, LN = lymph node.				
* $P < 0.05$, ** $P < 0.01$				

Impact of BMI on the number of metastatic LNs

As shown in Table 3, the total number of LN metastases was significantly higher in obese patients than normal-weight patients (2.41 vs. 1.79, $P < 0.001$). Among the obese patients, the number of LN metastases in the central and lateral neck regions were higher than the normal-weight patients (1.59 vs. 1.17, $P < 0.001$; 0.83 vs. 0.62, $P = 0.006$). In addition, the number of lateral neck LN metastases was higher than that of the normal-weight patients on the left side (0.40 vs. 0.27, $P = 0.018$).

Table 3
Relationship between obesity and the number of metastatic lymph nodes (LNs).

WHO-BMI		Normal Mean (SD) N = 8133	Obesity Mean (SD) N = 846	<i>P value</i>
Number of total LN metastasis		1.79 (3.67)	2.41 (4.20)	< 0.001**
Number of central LN metastasis		1.17 (2.28)	1.59 (2.72)	< 0.001**
Number of lateral LN metastasis	Total	0.62 (1.92)	0.83 (2.08)	0.006**
	Right	0.35 (1.38)	0.43 (1.39)	0.089
	Left	0.27 (1.17)	0.40 (1.43)	0.018*
Abbreviation: WHO = World Health Organization, BMI = body mass index, LNs = lymph nodes.				
* $P < 0.05$, ** $P < 0.01$				

Impact of BMI on the size of positive LNs

As shown in Fig. 2A, the maximum diameter of positive LNs in obese patients was higher than normal-weight patients (2.00 vs. 1.60 mm, $P = 0.007$). There was no significant difference in the rate of LN skip metastasis between the two groups (Fig. 2B).

Impact of BMI on the number of dissected LNs

The total number of LN dissections in the obese patients with PTC was significantly higher than the normal-weight patients (14.37 vs. 12.10, $P < 0.001$). The obese patients have a higher total number of lateral neck LN dissections (8.51 vs. 6.36, $P < 0.001$). This difference exists on the left and right sides of the neck (Table 4). However, there was no difference in the number of CNDs ($P = 0.466$).

Table 4
Relationship between obesity and the number of lymph node (LN) dissections.

WHO-BMI		Normal Mean (SD) N = 8133	Obesity Mean (SD) N = 846	P value
Number of total LN dissections		12.10 (11.69)	14.37 (13.21)	< 0.001**
Number of central LN dissections		5.74 (4.34)	5.86 (4.52)	0.466
Number of lateral LN dissections	Total	6.36 (10.13)	8.51 (11.72)	< 0.001**
	Right	3.22 (6.94)	4.22 (7.97)	< 0.001**
	Left	3.14 (7.06)	4.30 (8.33)	< 0.001**
Abbreviation: WHO = World Health Organization, BMI = body mass index, LN = lymph node.				
*P< 0.05, **P< 0.01				

Impact of BMI on the LNR

The LNR in obese patients was significantly higher than normal-weight patients (0.18 vs. 0.14, $P < 0.001$) (Table 5). While the difference was statistically significant in the central LNs (0.79 vs. 0.58, $P < 0.001$), but there was no statistically significant difference in the lateral neck LNs ($P = 0.067$) (Table 5).

Table 5
Relationship between obesity and lymph node ratio (LNR).

WHO-BMI		Normal % (n) N = 8133	Obesity % (n) N = 846	P value
Positive rate of LNs		0.14 (0.23)	0.18 (0.27)	< 0.001**
Positive rate of central LNs		0.58 (1.14)	0.79 (1.36)	< 0.001**
Positive rate of lateral cervical LNs	Total	0.03 (0.10)	0.04 (0.10)	0.067
	Right	0.02 (0.09)	0.03 (0.09)	0.106
	Left	0.02 (0.07)	0.02 (0.07)	0.157
Abbreviation: WHO = World Health Organization, BMI = body mass index, LN = lymph node, LNR = lymph node ratio.				
*P< 0.05, **P< 0.01				

Discussion

This study is a retrospective analysis of 8,979 patients with PTC, with a focus on the correlation between LN status and obesity. Obesity not only increased the rate of metastatic LNs, but also increased the number of metastatic LNs and the maximum diameter of positive LNs, which are two indicators of a poor prognosis. We analyzed two indicators that have been overlooked in previous studies, including the number of LN dissections and the LNR. These results showed opposite regional differences between obesity, the number of LN dissections, and the LNR (Fig. 3).

Effect on the rate of metastatic LNs

Previous studies on the relationship between obesity and metastatic LNs in thyroid cancer have been controversial (Table 6) (18–28). Yu *et al.* found a positive correlation between BMI and neck LN metastasis (OR = 1.58, $P = 0.02$) (24). Our previous research also yielded consistent results with those of Yu *et al.* (OR = 1.493) (8, 23, 24). One of the possible mechanisms is that serum leptin levels are higher in obese patients with PTC. *In vitro* studies have indicated that leptin promotes invasion and migration of thyroid cancer cell lines (29, 30). However, Kim, Gasior, Grani, Tresallet, and others have found that obesity is not associated with neck metastatic LNs in patients with thyroid cancer (19, 20, 26, 28). Simultaneously, Paes *et al.* found that obesity is negatively correlated with metastatic LNs (18). This finding may be due to differences in ethnicity. In the current study, we found that the rate of metastatic LNs in obese patients with PTC was significantly higher than normal-weight patients (52.6% vs. 42.0, $P < 0.001$). This effect exists in both the central and lateral neck regions (Fig. 3).

Table 6
Previous studies on the relationship between obesity and LN metastasis of thyroid cancer.

References	Date	Race	Cases (N)	BMI (kg/m ²)	Rate of obesity (%)	Correlation between BMI and LN metastasis
Paes (18)	2010	Mostly Caucasian (93%)	259	27.8	38.9% ¹	Negative correlation
Kim (19)	2013	Asian	2057	23.8	5% ¹	Non-correlation
Tresallet (20)	2014	Caucasian	1216	N/A	14.5% ¹	Non-correlation
Lee (21)	2015	Asian	1121	23.3	27% ¹	Non-correlation
Choi (22)	2015	Asian	612	23.1	2.1% ¹	Non-correlation
Kim (23)	2016	Asian	5081	N/A	5% ¹	Correlation
Yu (24)	2017	Asian	1622	N/A	24.3% ²	Correlation
Wu (25)	2017	Asian	796	25	8% ¹	Correlation
Gasior (26)	2018	Caucasian	1181	28.1	33.7% ¹	Non-correlation
Feng (27)	2019	Asian	417	23.9	6% ¹	Correlation
Grani (28)	2019	Caucasian	432	N/A	19.8% ¹	Non-correlation
¹ Defined the standard of obesity as BMI $\geq$ 27.5 kg/m ² .						
² Defined the standard of obesity as BMI $\geq$ 30.0 kg/m ² .						

Number of metastatic LNs and the sizes of positive LNs

The 2015 ATA guidelines suggest that more than five metastatic LNs yields an intermediate risk of recurrence (31). Previously, Leboulleux *et al.* found a recurrence rate of 3% with less than five metastases, while 6 to 10 metastases was associated with a recurrence rate of 7% and > 10 metastases with 21% (32). Previous studies have given minimal attention to the relationship between the number of metastatic LNs and obesity. The current study revealed a positive correlation between obesity and metastatic LNs (2.41 vs. 1.79, $P < 0.001$), which was reflected in the central and lateral neck LNs (Fig. 3).

The maximum diameter of positive LNs is another indicator of poor prognoses. The ATA guidelines classify the maximum diameter of positive LN between 0.2 and 3.0 cm as the intermediate risk of recurrence (31). In a previous study, the rate of locoregional recurrence was 5% for patients with maximum positive LN diameters smaller than 0.2 cm (12). When the maximum diameter of positive LNs

were > 3 cm, the rate of locoregional recurrence increased to 27% (13). In the current study, obese patients with PTC had larger maximum positive LN diameters (2.00 vs. 1.60, $P = 0.007$), suggesting that obesity may lead to poorer prognoses. Previous studies have primarily shown that obesity increases the rate of LN metastasis. This paper confirmed that obesity not only increases the rate of metastatic LNs, but also increases the number of metastatic LNs and the maximum diameter of positive LNs.

Number of LN dissections

Neck LNs are commonly wrapped in adipose tissue, and obese patients have more adipose tissue. Only a few studies have focused on whether the increased adipose tissue in obese patients can affect the dissection of neck LNs. This study found that obese patients had more dissectible LNs, yet this association only exists in the lateral neck area (14.37 vs. 12.10, $P < 0.001$), which seems to be more beneficial for obese patients. However, the number of CNDs is not related to obesity. There is a regional difference between the number of LN dissections and obesity (Fig. 3). One of the possible reasons is that the difficulty of intraoperative identification of LNs is reduced. LNs are often surrounded by adipose tissue, which helps the surgeon identify the LNs and minimize the burden of identification. The second reason involves inflammatory factor stimulation, as obesity can cause adipose cells to secrete inflammatory factors, such as C-reactive protein, interleukin 6 (IL-6), IL-10, and tumor necrosis factor (TNF- α). These inflammatory factors may stimulate LN hyperplasia (33).

LNR

After discovering a positive relationship between obesity and the number of lateral neck LN dissections, we speculated whether more LN dissections would yield higher positivity rates, which could contribute to the radical cure of thyroid cancer in obese patients. However, by analyzing the LNR, we found that obesity did not increase the positive rate of lateral central LNs. On the other hand, obesity was found to increase the positive rate of central LNs. Hence, there are regional differences in the LNR and the number of LN dissections.

Obese patients have difficulty in performing CNDs due to their short and thick necks. In this study, obesity was not associated with an increase in the number of CNDs, but it was associated with an increased LNR. Hence, surgeons should be cautious when performing CNDs for obese patients, as there may be more positive LNs in obese patients. If positive LNs are missed during surgery, then they will continue to cause damage in the body.

In the current study, we revealed that obesity promotes the metastasis of LNs and increases the average diameter of positive LNs. These two indicators are indicative of a poor prognosis. In addition, we considered the number of LN dissections and the LNR into the current analysis. We found a regional difference between obesity and these two indicators.

Limitations

The limitations of this study include its retrospective design, which is subject to incomplete data and potential selection bias. This paper did not analyze the relationship between obesity and LNs in various regions of the lateral neck. The number of positive nodes is often affected by the variability in nodal staging techniques, which may yield different numbers of excised nodes. Finally, this study did not analyze the disease-free survival rate or locoregional recurrence rate of patients, for which LN metastasis is a very important independent risk factor in patients with thyroid cancer after curative resection.

Conclusions

In summary, this study revealed that obesity is associated with poor prognoses in patients with PTC, which is related to the LNs. There is an inverse regional difference between obesity and the number of LN dissections and the LNR, suggesting that caution is needed when performing CNDs in obese patients. This will help ensure that all positive LNs are dissected, which will increase the overall survival of patients with PTC.

Abbreviations

PTC: papillary thyroid carcinoma

LN: lymph node

LNR: lymph node ratios

BMI: body mass index

CND: central neck dissection

Declarations

Ethics approval and consent to participate. This study was approved by the Health Care Ethics Committee of the China-Japan Union Hospital of Jilin University (No. 2019040806).

Consent for publication. Not applicable.

Availability of data and materials. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests. The authors have no potential conflict of interest to declare.

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Author information

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Authors' contributions

HS and HXG contributed equally to this paper. HS and HXG designed the research. CLL and NL collected and analyzed data. HS, GD, CLL and HXG wrote the paper. The authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of study inclusion and exclusion criteria. The figure was adapted from a previously published paper.

Figure 2

Relationship of obesity with (A) the maximum diameter of positive LN and (B) the rate of LN skip metastasis. Abbreviation: BMI=body mass index, LN=lymph node.

Figure 3

Relationship between obesity and the rules of lymph node (LN) metastasis. The part of schematic art pieces used in this figure were provided by Servier Medical art (<http://servier.com/Powerpoint-image-bank>). Servier Medical Art by Servier is licensed under a Creative Commons Attribution (CC BY) 3.0 Unported License. Abbreviation: BMI=body mass index, Lymph node ratio =LNR, LN=lymph node.