ORIGINAL ARTICLE

Korean J Intern Med 2013;28:62-71
http://dx.doi.org/10.3904/kjim.2013.28.1.62

KJIM

Neck circumference correlates with tumor size and lateral lymph node metastasis in men with small papillary thyroid carcinoma

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Received: February 14, 2012
Revised : March 23, 2012
Accepted: April 18, 2012

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Background/Aims: Obesity is correlated with numerous diseases, including thyroid cancer, but the clinical significance of obesity with regard to the clinical characteristics of thyroid cancer remains unclear. Neck circumference is an index of upper-body adipose tissue distribution.

Methods: In total, 401 patients with papillary thyroid carcinoma (PTC) measuring ≤ 2 cm were included. Neck circumference was measured horizontally at the level just below the thyroid cartilage on preoperative neck computed tomographic images.

Results: Neck circumference correlated significantly with tumor size in men (p = 0.001) but not in women (p = 0.930). Body mass index (BMI) did not significantly correlate with tumor size in either sex. Neck circumference was significantly larger in men with lateral lymph node (LN) metastasis than in those without (p = 0.004). Neck circumference and BMI did not differ significantly in women according to other factors such as tumor size, multifocality, extrathyroid extension, and LN metastasis. Tumor size and the prevalence of lateral LN metastasis in men tended to increase in the middle/large neck circumference subgroup compared with those in the low neck circumference subgroup. Multivariate logistic regression analysis revealed that neck circumference (p = 0.009) was a predictor for the presence of lateral LN metastasis in men. BMI was not a predictive factor for lateral LN involvement in either sex.

Conclusions: Neck circumference, an indicator of central or visceral obesity but not BMI, may be associated with some prognostic factors in men with small PTC.

Keywords: Body mass index; Neck circumference; Obesity; Papillary thyroid carcinoma

INTRODUCTION

Primary tumor size is a major histopathological prognostic factor of differentiated thyroid carcinoma [1]. The easy and frequent application of improved diagnostic tools, such as ultrasound, has resulted in a rapid increase in the incidence of thyroid cancers worldwide [2,3]. Consequently, most thyroid cancers diagnosed in recent years tend to be small [4]. However, whether these small thyroid cancers assure a good prognosis is unclear.

Obesity is a serious global health problem and an

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pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

important underlying cause of cardiometabolic disorders, and is associated with several malignancies. A high body mass index (BMI), a practical marker of obesity, is associated with an increased risk of various malignancies, including thyroid cancer [5]. However, the relationship between obesity and thyroid malignancy has not been consistent [5-11]. In contrast, obesity is a significant prognostic factor for certain malignancies. The association between higher BMI and recurrence or aggressiveness of prostatic and breast cancers is well known [12-15]. Although a recent study failed to confirm the relationship between higher BMI and more aggressive features or worse outcome [16], the importance of obesity as a prognostic factor for thyroid cancer has not been clarified.

Neck circumference is a valid marker of obesity that correlates well with other anthropometric measurements [17]; this marker is a better indicator of central or visceral obesity [18]. Significant positive correlations have been documented between neck circumference and cardiometabolic disorder factors, such as insulin resistance, metabolic syndrome, and the risk of cardiovascular disease, even after adjusting for other anthropometric measurements [18-20]. However, the significance of neck circumference as a prognostic marker for malignancies is not known.

The purpose of this study was to verify the association between obesity and aggressiveness or poor prognosis of papillary thyroid carcinoma (PTC), particularly small tumors, which are the most prominent feature of recently diagnosed thyroid cancers. We compared the relationships between postoperative clinicopathological features and preoperative neck circumference and BMI to determine which marker is more valuable.

METHODS

Patients

A total of 504 patients underwent thyroid surgery for PTC at Pusan National University Hospital between July 2007 and December 2009. Of these, 412 with a tumor measuring ≤ 2 cm on pathology reports were included, because large tumors could affect neck circumference measurements. Patients who were incidentally diagnosed with papillary microcarcinoma during surgery for benign nodules (n = 4), those with papillary microcarcinoma along with other pathological findings such as anaplastic changes or Hürthle cell adenoma (n = 2), and those who did not undergo preoperative neck computed tomography (CT) to analyze neck circumference (n = 5) were excluded. Finally, 401 patients with PTC were available for analyses.

All thyroid surgeries were performed by three surgeons (BJL, JCL, and SGW) during the study period. Total thyroidectomy, the surgical procedure of choice for patients with PTC according to our protocol, was performed in 398 (99.3%) patients. Bilateral central-compartment neck dissection was routinely performed during total thyroidectomy in all patients, and lateral or modified neck dissection was performed in patients with clinically overt or ultrasound-detected metastatic cervical lymph nodes (LNs; n = 78, 19.5%). Preoperative assessment of lateral cervical LN metastasis included preoperative neck ultrasonography, fine-needle aspiration cytological examination, and CT. Informed consent was obtained from each participant at the time of surgery. This retrospective review protocol was approved by the Institutional Review Board of Pusan National University Hospital.

BMI and neck circumference measurements

Each patient's height and weight were measured at admission for the thyroid operation. BMI was calculated by dividing weight (in kilograms) by the height (in meters) squared. Neck circumference was measured on preoperative neck CT images. Neck CT was checked for preoperative assessment of LN involvement within 3 months prior to surgery in all patients. Neck circumference was measured with an imaging tool along a horizontal line at the level just below the thyroid cartilage [19]. BMI was categorized as follows as: BMI ≤ 18.5, 18.5 < BMI ≤ 22.9, 23.0 < BMI ≤ 24.9, and BMI > 25 kg/m^2. Neck circumference was classified into one of the following three subgroups: ≤ 25th percentile (low), > 25th percentile and ≤ 75th percentile (middle), and > 75th percentile (high).

Statistical analyses

All statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (Mariakerke, Belgium) software. Continuous data are expressed as medians and ranges. The Mann-Whitney test or the independent two-sample *t* test was used to compare continuous variables between the two subgroups. Differences between the groups were examined by analysis of variance, followed by the Bonferroni's test for normally distributed values or by the Kruskal-Wallis and Dunn's tests for nonparametric values. Pearson's chi-square test was performed to analyze categorical data, as appropriate. Pearson's correlation coefficients were used to analyze the relationships between different variables. Factors related to lateral LN metastasis were assessed by multivariate logistic regression analysis according to the "Enter" procedure. Multivariate models for lateral LN metastasis were adjusted for age, tumor size, multifocality, extrathyroid extension, BMI, and neck circumference as independent variables. Receiver operating characteristics (ROC) analysis was employed to calculate the area under the curve (AUC) for neck circumference to identify the best cut-off value for identifying lateral LN metastasis in men. Additionally, the sensitivity and specificity of this cut-off value were estimated. A p value < 0.05 derived from the two-tailed tests was considered significant.

RESULTS

Demographic and clinicopathologic characteristics

Seventy men and 331 women were included (age, 17 to 79 years; median age, 49.0 years). Median tumor size was 0.8 cm (range, 0.2 to 2.0). The pathology of six (1.5%) patients was a follicular variant (n = 5) and a diffuse sclerosing variant (n = 1). Pathological extrathyroid extension, LN metastasis, and lymphovascular invasion were identified in 51.9%, 48.1%, and 1.2% of patients, respectively. Of the 401 cohort cases, 124 (30.9%) had multifocal lesions on tissue pathology. Central LN metastasis was found in 192/201 (47.9%) patients, whereas lateral LN involvement was identified in 54/401 (13.5%) patients. One patient was initially diagnosed with a distant metastasis (lung). According to the American Joint Committee on Cancer/Union Internationale Contre le Cancer Tumor, Nodes, and Metastases classification, patient age was divided into one of the two age categories: ≤ 45 years or > 45 years. Of the patients aged ≤ 45 years (n = 116), 115 had stage I tumors and one had a distant lung metastasis. Of the patients aged > 45 years (n = 285), 89 (31.2%) had stage I disease (31.2%), 158 (55.4%) had stage III disease, and 38 (13.3%) had stage IV disease. Minimal extrathyroid extension (pT3) accounted for 97.1% (202/208) of patients with extrathyroid extension.

Neck circumference positively correlated with BMI (r = 0.681 in men, r = 0.682 in women; both p < 0.001). BMI differed significantly between men (median, 24.5; range, 17.8 to 32.0) and women (median, 22.6; range, 14.9 to 33.9; p = 0.001). Neck circumference was 6.3 cm larger in men (median, 41.3; range, 36.3 to 49.5) than that in women (median, 35.0; range, 29.2 to 50.3; p < 0.001). The prevalence of lateral LN metastasis was higher in men than in women (21.4% vs. 11.8%, p = 0.032). No significant difference in age or any other pathological factor was observed between sexes.

Neck circumference and BMI according to clinicopathological features

Neck circumference significantly correlated with tumor size in men (r = 0.375, p = 0.001) (Fig. 1), but not in women (r = 0.005, p = 0.930). The positive correlation between tumor size and neck circumference remained after adjusting for age and BMI in men (r = 0.317, p = 0.009). BMI did not significantly correlate with tumor size in either sex (r = 0.220, p = 0.067 in men; r = 0.020, p < 0.930 in women). As shown in Table 1, neck circumference and BMI differed significantly between

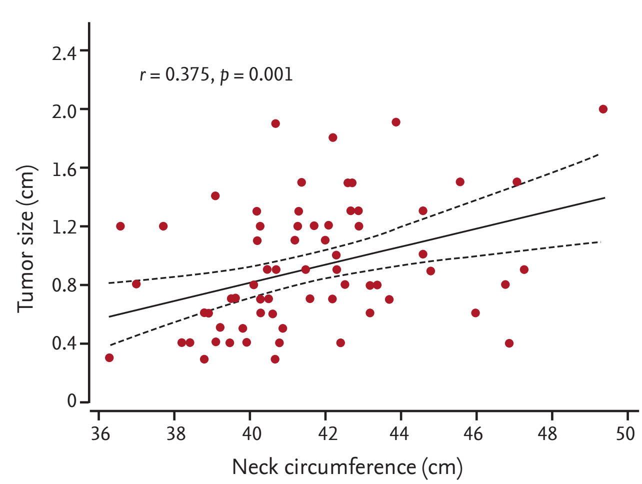

Figure 1. Correlation between tumor size and neck circumference in men.

http://dx.doi.org/10.3904/kjim.2013.28.1.62

Table 1. Relationship between anthropometric factors and tumor clinicopathological features in women (n = 331)

Variable	BMI, kg/m²	*p* value	Neck circumference, cm	*p* value
Age, yr		< 0.001		< 0.001
≤ 45	21.4 (15.8–33.9)		34.3 (30.4–43.1)	
> 45	23.2 (14.9–32.0)		35.4 (29.2–50.3)	
Tumor size, cm		0.964		0.300
≤ 1	22.7 (14.9–33.9)		34.9 (29.2–50.3)	
> 1	22.5 (16.7–32.0)		35.6 (31.0–49.8)	
Multifocality		0.831		0.775
Absence	22.5 (14.9–33.9)		35.1 (29.2–50.3)	
Presence	22.7 (15.8–31.2)		34.9 (29.8–46.5)	
Extrathyroid extension		0.779		0.779
Absence	22.5 (14.9–33.9)		34.9 (29.8–50.3)	
Presence	22.7 (17.6–31.5)		35.2 (29.2–49.8)	
Lymph node metastasis				
Absence	22.8 (14.9–31.2)		35.1 (29.8–50.3)	
Central lymph node	22.3 (17.6–33.9)	0.860[a]	34.8 (29.2–43.2)	0.400[a]
Lateral lymph node	23.7 (18.4–31.5)	0.360[b]	35.5 (30.4–46.5)	0.465[b]

Values are presented as median (range). *p* values were obtained by the independent sample *t* test.
BMI, body mass index.
[a]Absence vs. central lymph node metastasis.
[b]Absence vs. lateral lymph node metastasis.

the two age categories in women (both $p < 0.001$), but no significant difference in neck circumference or BMI was observed in women according to other factors, including tumor size, multifocality, extrathyroid extension, and LN metastasis (Table 1). Neck circumference was significantly larger in men with lateral LN metastasis than in those without ($p = 0.004$) (Table 2). However, no significant difference in BMI with regard to nodal metastasis was observed in men.

Clinicopathological features according to BMI and neck circumference

No pathological feature differed significantly among BMI categories in either sex (data not shown). Pathological factors except age did not differ significantly in women based on neck circumference (Table 3). In men, tumor size increased significantly with neck circumference (Table 4, Fig. 2A). The prevalence of lateral LN metastasis also appeared to differ between the low and middle/high neck circumference subgroups ($p = 0.033$ for trend) (Fig. 2B).

Prognostic factors for lateral LN metastasis

The multivariate logistic regression analysis showed that the presence of extrathyroid extension ($p = 0.033$) and neck circumference ($p = 0.009$) were predictors for the presence of lateral LN metastasis in men. However, neck circumference ($p = 0.688$) was not significantly associated with the presence of lateral LN metastasis in women. BMI was not a predictive factor for lateral LN involvement in either sex (Table 5).

Finally, we calculated the cut-off value for the association between neck circumference and the presence of lateral LN metastasis in men. The cut-off value for

Table 2. Relationship between anthropometric factors and tumor clinicopathological features in men (n = 70)

Variable	BMI, kg/m^2	p value	Neck circumference, cm	p value
Age, yr		0.221		0.808
≤ 45	25.4 (20.8–32.0)		41.3 (37.7–49.4)	
> 45	24.4 (17.8–27.7)		41.2 (36.3–47.3)	
Tumor size, cm		0.381		0.112
≤ 1	24.4 (18.1–32.0)		40.7 (36.3–47.3)	
> 1	25.1 (17.8–29.7)		42.0 (36.6–49.4)	
Multifocality		0.247		0.114
Absence	24.3 (17.8–29.7)		40.7 (36.3–49.4)	
Presence	24.9 (20.9–32.0)		41.9 (38.2–47.1)	
Extrathyroid extension		0.842		0.176
Absence	24.4 (17.8–32.0)		40.7 (36.3–46.9)	
Presence	24.8 (19.9–28.7)		41.7 (37.0–49.4)	
Lymph node metastasis				
Absence	24.4 (18.1–28.1)		40.6 (36.3–46.8)	
Central lymph node	24.3 (17.8–32.0)	0.686[a]	41.7 (36.6–47.1)	0.833[a]
Lateral lymph node	25.4 (19.9–27.8)	0.189[b]	42.3 (39.1–49.4)	0.004[b]

Values are presented as median (range).
The p values were obtained by the Mann-Whitney test.
BMI, body mass index.
[a]Absence vs. central lymph node metastasis.
[b]Absence vs. lateral lymph node metastasis.

Table 3. Clinicopathological factors according to the neck circumference subgroups in women

Variable	Neck circumference, cm			p value
	≤ 33.6 (n = 83)	> 33.6, ≤ 36.8 (n = 165)	> 36.8 (n = 83)	
Age, yr	47.0 (21–71)	49.0 (18–76)	54.0 (17–79)	< 0.001
Tumor size, cm	0.70 (0.2–2.0)	0.80 (0.2–2.0)	0.80 (0.2–2.0)	0.873
Extrathyroid extension	45 (54.2)	79 (47.9)	48 (57.8)	0.299
Multifocality	31 (37.3)	42 (25.5)	29 (34.9)	0.103
Lymph node metastasis				
Central lymph node	39 (47.0)	78 (47.3)	37 (44.6)	0.918
Lateral lymph node	10 (12.0)	18 (10.9)	11 (13.3)	0.861

Values are presented as median (range) for continuous variables and frequency (%) for categorical variables.

neck circumference using the ROC curve was 41.6 cm (AUC, 0.744; sensitivity, 80.0%; specificity, 67.3%; p < 0.004) (Fig. 3).

DISCUSSION

The results of this study show that increased neck circumference, but not BMI, correlated with factors

http://dx.doi.org/10.3904/kjim.2013.28.1.62

Table 4. Clinicopathological factors according to neck circumference subgroups in men

Variable	Neck circumference, cm			p value
	≤ 40.1 (n = 18)	> 40.1, ≤ 42.9 (n = 36)	> 42.9 (n = 17)	
Age, yr	46.0 (23–62)	49.0 (35–70)	46.0 (29–61)	0.255
Tumor size, cm	0.55 (0.3–1.4)	0.90 (0.3–1.9)	0.90 (0.4–2.0)	0.003
Extrathyroid extension	6 (33.3)	22 (62.9)	8 (47.1)	0.115
Multifocality	2 (11.1)	14 (40.0)	6 (35.3)	0.093
Lymph node metastasis				
Central lymph node	10 (55.6)	18 (51.4)	10 (58.8)	0.875
Lateral lymph node	1 (5.6)	8 (22.9)	6 (35.3)	0.096

Values are presented as median (range) for continuous variables and frequency (%) for categorical variables.

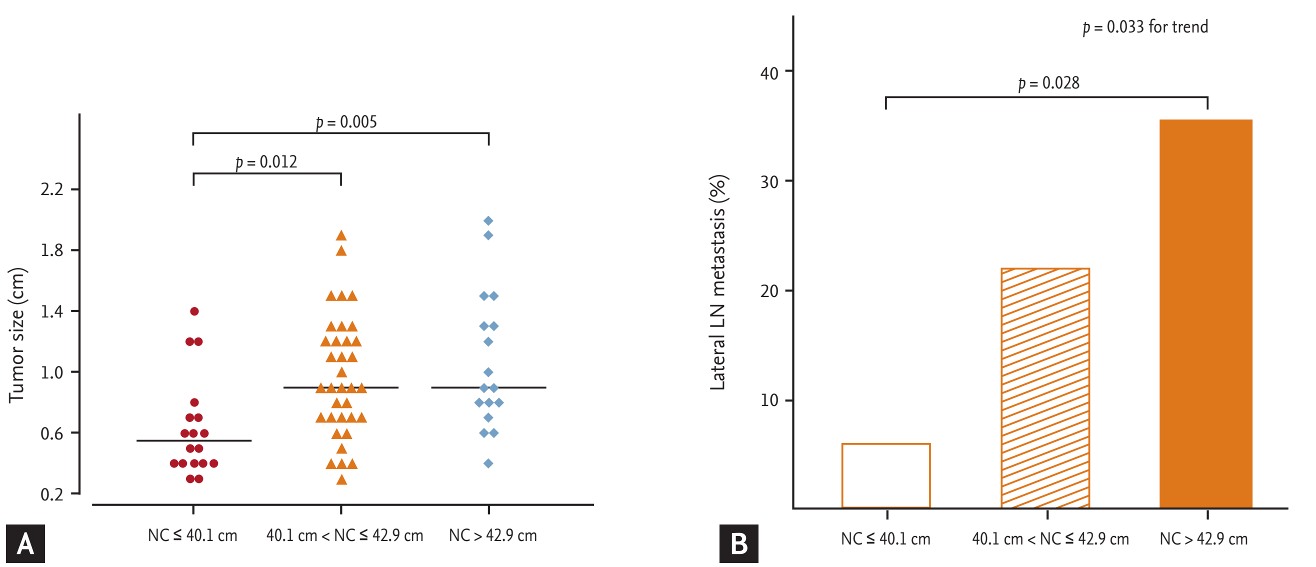

Figure 2. Tumor size (A) and the prevalence of lateral lymph node metastasis (B) according to neck circumference subgroups in men. NC, neck circumference; LN, lymph node.

indicating tumor aggressiveness, such as tumor size and lateral node metastasis, in men with small (≤ 2 cm) PTC. However, obesity measured by neck circumference or BMI was not significantly associated with tumor aggressiveness in women.

Several studies have reported that obesity measured by BMI is significantly associated with an increased incidence of thyroid cancer in women [6-8]. However, disagreement persists regarding the relationship between obesity and the incidence of thyroid cancer [9-11]. In our study, preoperative neck circumference and BMI were not associated with factors related to PTC aggressiveness, such as extrathyroid extension or nodal metastasis, in women. The relationship between neck circumference and tumor aggressiveness remained unchanged, even after stratifying by age (≤ 45 or > 45 years) and BMI (≤ 25 or > 25 kg/m^2) among women (data not shown). Some histopathological factors correlated with neck circumference in men. These results are consistent with those of previous studies of the relationship between BMI and the incidence of thyroid cancer. Oh et al. [10] demonstrated a signifi-

Table 5. Prognostic factors for lateral lymph node metastasis

Variable	Category	OR	95% CI (*p* value)
Women			
Age, yr	≤ 45 vs. > 45	0.909	0.409–2.021 (0.815)
Tumor size, cm	≤ 1 vs. > 1	2.225	1.085–4.560 (0.029)
Extrathyroid extension	Presence vs. Absence	2.672	1.181–6.047 (0.018)
Multifocality	Presence vs. Absence	1.516	0.747–3.078 (0.249)
BMI, kg/m^2	-	1.077	0.925–1.254 (0.338)
Neck circumference, cm	-	0.965	0.810–1.149 (0.688)
Men			
Age, yr	≤ 45 vs. > 45	0.982	0.165–5.859 (0.984)
Tumor size, cm	≤1 vs. > 1	2.454	0.591–10.184 (0.216)
Extrathyroid extension	Presence vs. Absence	7.659	1.184–49.563 (0.033)
Multifocality	Presence vs. Absence	1.452	0.351–6.007 (0.607)
BMI, kg/m^2	-	0.842	0.565–1.255 (0.399)
Neck circumference, cm	-	1.688	1.138–2.504 (0.009)

OR, odds ratio; CI, confidence interval; BMI, body mass index.

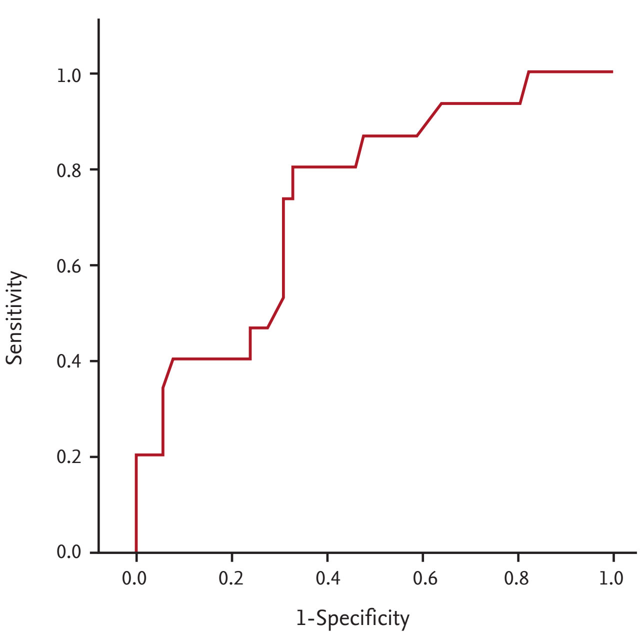

Figure 3. Receiver operating characteristic curve for the association between neck circumference and lateral lymph node metastasis in men. The cut-off value of neck circumference for identifying lateral lymph node metastasis was 41.6 cm, with a sensitivity of 80.0% and a specificity of 67.3% ($p < 0.004$).

cant positive linear trend between BMI and the incidence of PTC in Korean men. In a meta-analysis of prospective observational studies, a five-point increase in BMI was strongly associated with the incidence of thyroid cancer in men, although a weaker positive association was found in women [5].

A previous clinicopathological cohort study demonstrated an unexpected inverse relationship between BMI and nodal metastasis/tumor invasion [16]. This result was not in agreement with our finding of a significant relationship between neck circumference and some histopathological factors that occurred only in men. This difference may be due to a difference in study design. Our study was conducted with a more limited study population, consisting of patients with small (≤ 2 cm) PTC. We analyzed the data according to sex, and significant differences in obesity and nodal metastasis were observed between men and women. Men had higher BMI, neck circumference, and prevalence of lateral LN metastasis than did women. In addition, the differences may be attributed to differences in race or geographic location between the two studies.

http://dx.doi.org/10.3904/kjim.2013.28.1.62

Anthropometric factors other than increased BMI, such as waist-to-hip ratio or waist circumference, might be better indicators of adiposity in terms of cancer [21,22] and cardiovascular risk [23]. Neck circumference, an index of upper-body fat distribution, closely correlates with visceral adiposity [18]. Nielsen et al. [24] suggested that neck circumference predicts disease risk more accurately than does visceral adiposity or BMI.

Adipokines, which are secreted from adipocytes, contribute to the mechanisms by which obesity influences cancer risk and progression through endocrine, paracrine, and autocrine factors [25]. Leptin, a well-known adipokine, positively correlates with BMI and body adiposity [26]. Leptin can act as a mitogen and an angiogenic factor [27]. Cheng et al. [28] demonstrated that leptin and leptin receptor expression in PTC are positively associated with indicators of cancer aggressiveness including tumor size and LN metastasis. Uddin et al. [29] suggested that leptin is associated with the downstream cell-signaling pathway in a PTC cell line. Further studies of the relationships between whole-body adiposity, intra-thyroidal adiposity, and leptin expression in cancer cells are needed to explain the relationship between neck circumference and tumor aggressiveness. In contrast, adiponectin inversely correlates with visceral adiposity. Adiponectin has an inhibitory effect on tumor growth by downregulating cell proliferation, upregulating apoptosis, and inhibiting tumor-related angiogenesis [25]. Cnop et al. [30] reported that adiponectin concentrations are higher in women than in men, which may explain sex differences in the association between adiposity and cancer development and growth.

Obesity is related to insulin resistance and hyperinsulinemia, which stimulate carcinogenesis and mitogenesis [31]. Insulin-like growth factor-1 (IGF-1) inhibits apoptosis and stimulates vascular endothelial growth factor synthesis in patients with thyroid carcinoma [32]. Because central or upper-body adiposity reflects insulin resistance and hyperinsulinemia, neck circumference, an index of upper-body or central adiposity, may be closely related to tumor growth or invasiveness based on the relationship between the insulin/IGF-1 axis and cancer growth.

The results of this study are subjected to some limitations. First, this study was not based on longitudinal observations, but was conducted with a cross-sectional design. Although neck circumference was associated with tumor size and lateral LN metastasis in men, its effect on overall prognostic factors, such as tumor recurrence and survival, are not clear. As the number of male patients was relatively small, the impact of neck circumference on thyroid cancer pathological features was difficult to determine. Additionally, we could not analyze the association between neck circumference and lymphovascular invasion or distant metastasis because of the small number of patients with such pathological findings. In the near future, we will redesign the study with an increased number of patients and include larger (> 2 cm) PTC. The waist-to-hip ratio and waist circumference will be added as prognostic markers to evaluate their relationship with PTC. Second, we measured neck circumference on preoperative CT scans. Although this technique may reduce errors when measuring neck circumference, measurement can be performed more accurately and easily with a plastic tape, along with other anthropometric measurements.

In conclusion, neck circumference, a valid marker of upper-body adipose tissue distribution, may be a prognostic factor in men with small PTC. In addition, neck circumference may be used to investigate the relationship between obesity and thyroid cancer development/growth.

KEY MESSAGE

1. Increased neck circumference, but not body mass index (BMI) correlated with tumor aggressiveness such as tumor size and lateral node metastasis, in men with small (≤ 2 cm) papillary thyroid carcinoma (PTC).
2. Obesity measured by either neck circumference or BMI was not significantly associated with tumor aggressiveness in women.
3. Neck circumference as a valid marker of upper body adipose tissue distribution may play a role as a prognostic factor in men with small PTC.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

Acknowledgments

This study was supported by a clinical research grant from Pusan National University Hospital (2011).

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