

Quantitative Analysis of 3-Dimensional Volumetry and Histogram of Thyroid Gland on Neck Computed Tomography for Patients with Hashimoto's Thyroiditis

하시모토 갑상선염의 경부 전산화단층촬영에서 갑상선의 3차원 용적과 히스토그램에 대한 정량적 분석

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Purpose: To analyze three-dimensional (3D) volume and histogram of thyroid gland on neck computed tomography (CT) for patients with Hashimoto's thyroiditis.

Materials and Methods: A total of 121 subjects who underwent neck CT between March 2013 and February 2014 were included in this study. These subjects were divided into the following two groups: 1) control group ($n = 76$); 2) Hashimoto's thyroiditis group ($n = 45$). Non-enhanced and contrast-enhanced CT images were obtained. On contrast-enhanced images, the 3D volume of thyroid gland was semi-automatically calculated. On CT histogram, attenuation number, mean, median, standard deviation (SD), and coefficient of variation (CV) of thyroid gland were calculated. These values were compared between the two groups.

Results: Total 3D volume of thyroid gland was $14.9 \pm 4.8 \text{ cm}^3$ in the control group, which was significantly ($p = 0.002$) lower than that ($19.2 \pm 8 \text{ cm}^3$) in the Hashimoto's thyroiditis group. On CT histogram, the mean, median, SD, and CV of thyroid gland on non-enhanced images were 95.8, 99.3, 21.7, and 0.226, respectively, in the control group and 72.2, 72.6, 19.6, and 0.28 in the Hashimoto's thyroiditis group ($p < 0.05$). Histogram parameters on contrast-enhanced images were not significantly ($p > 0.05$) different. Median at cut-off value of 83 revealed the largest Az value (Az: 0.905; 95% confidence interval: 0.837–0.951; sensitivity: 84.4%; specificity: 85.5%).

Conclusion: The Hashimoto's thyroiditis group had larger volume but lower CT attenuation number with more prominent parenchymal heterogeneity of thyroid gland than the control group.

Index terms

Hashimoto's Disease
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INTRODUCTION

Volumetric measurement of thyroid gland has been applied in various imaging modalities to diagnose thyroid diseases, such as goiter, nodule, thyroiditis, and Graves' disease (1, 2). Shu et al. (3) have suggested that spiral computed tomography (CT) is an

easy, accurate, reliable, reproducible modality to predict the volume of thyroid. Recently, three-dimensional (3D) CT volumetry has been introduced to measure the volume of thyroid (3). Iterative and semi-automated segmentation can be applied in a multi-modal workstation to more accurately measure the volume of thyroid using 3D CT volumetry.

A few studies have reported the measurement of CT attenuation number in the thyroid gland (4-6). Neck CT can indicate decreased CT attenuation number of the thyroid gland in patients with chronic thyroiditis or Graves' disease (5). Iida et al. (4) have suggested that CT attenuation number has a linear relationship with iodine concentration in the thyroid gland *in vivo*. In previous studies, the CT attenuation number has been calculated on selective two-dimensional (2D) images which only represent part of the thyroid gland (4, 5). The CT attenuation number has also been investigated for the evaluation of treatment responses or lesion heterogeneity in other organs (7). To our best knowledge, few studies have focused on the CT attenuation number for the entire thyroid gland using histograms.

Neck CT has been commonly used to determine surgical planning for various thyroid diseases, detect anatomical morphology of the thyroid gland, and determine metastatic cervical lymphadenopathy for thyroid malignancies (8, 9). Most neck CT scans have been used to evaluate the anatomical structures of the thyroid gland. However, quantitative analysis based on reconstructed images diseases have been sparsely performed for patients with thyroiditis. The objective of this study was to analyze the volume of thyroid using 3D CT volumetry and to determine the CT attenuation number using histogram of the entire thyroid gland for patients with Hashimoto's thyroiditis.

MATERIALS AND METHODS

Patient Population

This retrospective study was approved by the Institutional Re-

view Board of our institution. Informed consent for the use of data was waived. Between March 2013 and February 2014, a total of 312 neck CT scans were performed for thyroid diseases in our institution (Fig. 1). Inclusion criteria were: 1) those who underwent thyroid function tests and autoimmune antibody profiles in our institution within 3 months at the time of CT examinations, 2) those who had any thyroid diseases, including thyroid nodules less than 1 cm in a diameter, and 3) those who had optimal image quality of CT examinations for analysis in which the thyroid gland was fully covered in the scans without being affected by beam-hardening artifacts from contrast media or clavicles. Exclusion criteria were: 1) those who underwent neither thyroid function test nor autoimmune antibody profile, 2) those who had thyroid nodules larger than 1 cm in diameter, 3) those who had suboptimal image quality of CT examinations due to inadequate scan range or beam-hardening artifacts, and 4) those who had hyperthyroidism refractory to anti-thyroid drug therapy or radioactive iodine ablation at the time of CT examinations.

Of the 312 cases, 191 were excluded due to insufficient results of laboratory tests ($n = 107$), thyroid nodules larger than 1 cm in diameter ($n = 56$), suboptimal image quality of CT examinations ($n = 19$), and hyperthyroidism ($n = 9$). Finally, 121 cases (mean age: 48.5 years; range: 24 to 77 years; male:female = 10:111) were enrolled in this study. Final diagnoses were papillary microcarcinoma ($n = 103$), follicular carcinoma ($n = 3$), follicular adenoma ($n = 6$), nodular hyperplasia ($n = 7$), and chronic thyroiditis ($n = 2$). These cases were divided into: 1) control group ($n = 76$) who had normal range in thyroid function test with negative re-

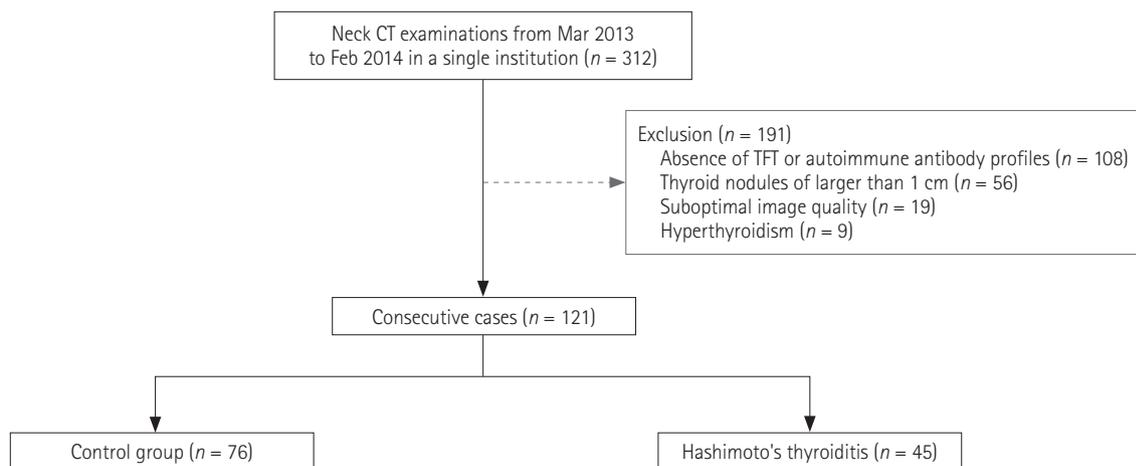


Fig. 1. Flow chart of the population. CT = computed tomography, TFT = thyroid function test

sults in autoimmune antibody profiles, and 2) Hashimoto's thyroiditis group ($n = 45$) who had elevated level of thyroid stimulating hormone (TSH) with positive results in either anti-thyroid peroxidase autoantibody (TPO Ab) or anti-thyroglobulin autoantibody (TG Ab). Laboratory evaluations were performed for serum levels of TSH, free thyroxine (fT4), TG Ab, and TPO Ab using automated immunoassay system according to the manufacturer's instructions. TSH and fT4 were measured using Modular analytics E170 with electrochemiluminescence immunoassay technique (Roche Diagnostics International Ltd., Basel, Switzerland). TG Ab and TPO Ab were measured using Architect i2000 system with chemiluminescence microparticle immunoassay technique (Abbott Laboratories, Lake Forest, IL, USA).

CT Acquisition

All CT images were obtained at Department of Radiology of our institution. Neck CT examinations were performed with multidetector CT scanners (Aquilion One: Toshiba Medical System Corporation, Tokyo, Japan; Discovery CT750 HD: GE Healthcare, Milwaukee, WI, USA). Scout view was scanned in a lateral projection. Both non-enhanced and contrast-enhanced images including the neck and superior mediastinum were obtained. Acquisition parameters of Aquilion One were: 120 kV, 180 mA, rotation time of 0.5 seconds, pitch of 0.625, field of view at 35 cm, detector collimation at 64×0.5 mm, matrix size at 512×512 pixel, slice thickness at 1 mm, and slice increment at 1 mm. The acquisition parameters for Discovery CT750 HD were: field of view at 30 cm, slice thickness at 1.25 mm, and slice increment at 1.25 mm. Other parameters were almost the same as those used for Aquilion One. Contrast-enhanced images were obtained at 40 seconds after intravenous injection of contrast media (350 mg of non-ionized iodine per milliliter, Scanlux; Sanochemia Pharmazeutika AG, Leitha, Austria) at 3 mL/sec.

Image Analysis

All imaging studies were performed by a fellowship-completed academic radiologist with 3-year experience in head and neck imaging who was blinded to clinical and laboratory data. Raw data were reconstructed into images with slice thickness of 1 mm for Aquilion One and 1.25 mm for Discovery CT750 HD without overlaps and transferred to a workstation (Aquarius iNtuition Viewer; TeraRecon, San Mateo, CA, USA). For 3D CT volume-

try of the thyroid gland, the volume-rendered image of the thyroid gland was semi-automatically obtained using contrast-enhanced images in the workstation. First, 'region growing' mode was applied to select the entire thyroid gland to include the isthmus and pyramidal lobe as much as possible. Second, the contour of the thyroid gland was manually corrected using 3D tools on reconstructed axial images. Third, 'select tool' was applied to isolate the thyroid gland automatically from its surrounding structures. Thyroid volume was calculated automatically in cubic centimeters and displayed on 3D volume-rendered images based on isolated thyroid gland.

To obtain histograms of the entire thyroid gland, raw data were reconstructed by the workstation using non-enhanced and contrast-enhanced images. First, 'centerline of flow' mode was applied to 3D volume-rendered images for an isolated thyroid gland. The center line was manually adjusted to include the level of the upper pole to the level of the lower pole of the thyroid gland. Second, contour of the thyroid gland was semi-automatically corrected on axial sections. Air density of adjacent airway, calcification (including microcalcification and macrocalcification), and surrounding normal vessels were excluded. Third, 'plaque analysis' mode was applied to quantify various attenuations of the selected thyroid gland. Histogram results for the following parameters were automatically obtained: mean, median, standard deviation (SD), and coefficient of variation (CV) of CT attenuation number in the entire thyroid gland. The CV of CT attenuation number was calculated using the following formula: $CV = SD_{\text{thyroid}} / \text{mean}_{\text{thyroid}}$, where SD_{thyroid} was the SD of the mean attenuation in thyroid gland and $\text{mean}_{\text{thyroid}}$ was the mean attenuation of the thyroid gland.

Statistical Analysis

All statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Demographic findings between the two groups were analyzed by chi-squared test for gender and by independent t test for age. Differences in thyroid volume and histogram parameters between the two groups were analyzed by independent t test. Data were expressed as mean \pm SD. A p value less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to determine the cut off value of 3D volume and to obtain the most accurate histogram parameter with the larg-

est area under the ROC curve (Az) value to differentiate Hashimoto's thyroiditis from the control group.

RESULTS

The control group had 76 cases (male:female = 9:67; mean age: 49.7 years, range: 29 to 77 years). The Hashimoto's thyroiditis group had 45 cases (male:female = 1:44; mean age: 46.5 years, range: 24 to 69 years). The gender and age between the two groups were not significantly ($p = 0.137$ and $p = 0.105$, respectively) different. In 3D CT volumetry, the total volume of the thyroid gland was $14.9 \pm 4.8 \text{ cm}^3$ in the control group, which was significantly ($p = 0.002$) lower than that ($19.2 \pm 8 \text{ cm}^3$) in the Hashimoto's thyroiditis group (Fig. 2). In ROC curve analysis of

3D volumetry, the cut-off value of thyroid volume for differentiating Hashimoto's thyroiditis from the control group was 13.7 cm^3 [Az: 0.642, 95% confidence interval (CI): 0.55–0.727; sensitivity: 82.2%; specificity: 42.1%].

The mean, median, SD, and CV of histogram in thyroid gland on nonenhanced images were 95.8, 99.3, 21.7, 0.226 in control group and 72.2, 72.6, 19.6, 0.280 in Hashimoto's thyroiditis, retrospectively (Fig. 3). The values of mean, median and CV were significantly different between two groups ($p < 0.004$). However, the value of SD was not significantly different between two groups ($p = 0.052$). Histogram parameters on contrast-enhanced images were not significantly different between groups (mean, median, SD, CV: 181.5, 192.7, 40.5, 0.223 in control group and 178.3, 187.9, 39.1, 0.219 in Hashimoto's thyroiditis, $p > 0.05$). In

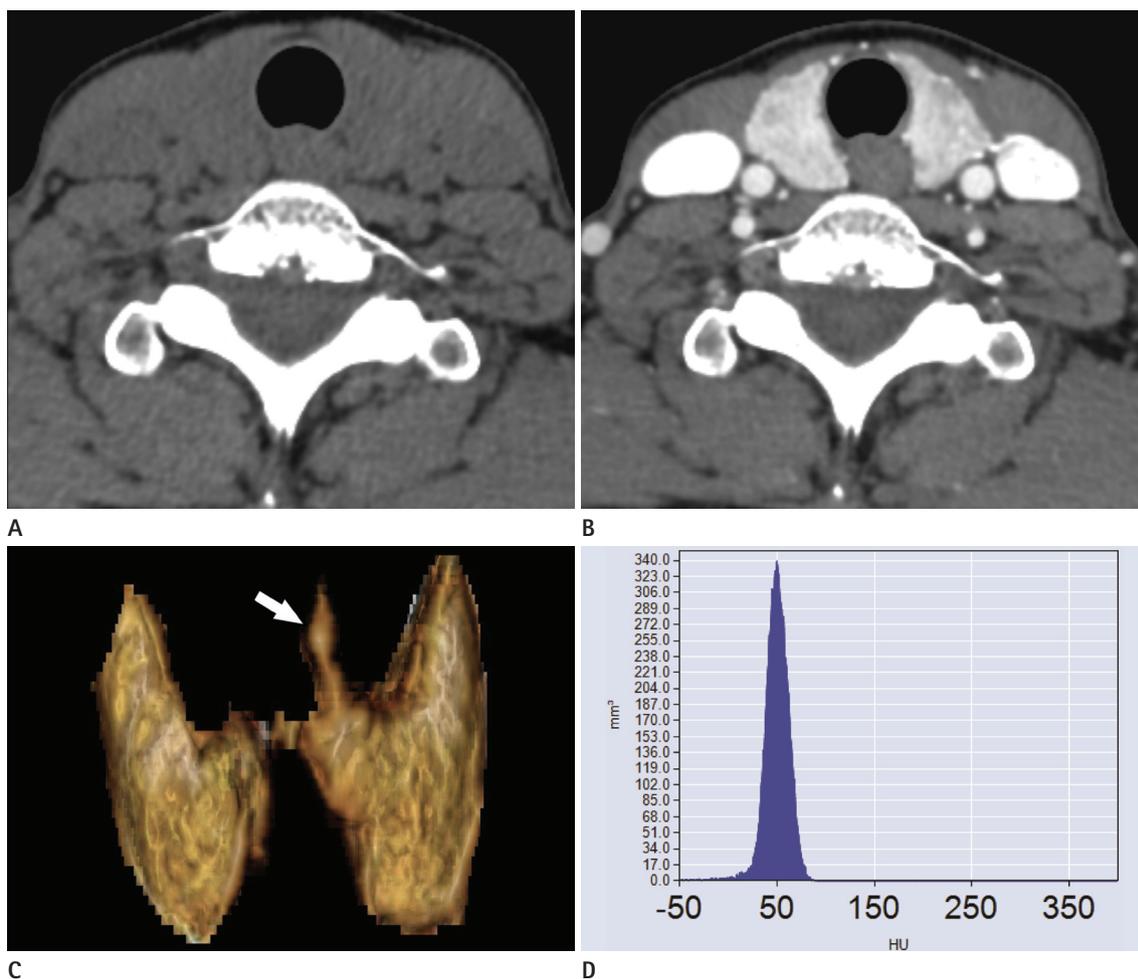


Fig. 2. A 54-year-old female with Hashimoto's thyroiditis. Thyroid gland revealing heterogeneously low attenuation in nonenhanced CT image (A) and heterogeneously well enhancement in contrast-enhanced CT image (B). On 3D CT volumetry (C), the actual shape of thyroid gland is revealed, including pyramidal lobe (arrow) and total volume of 17.1 cm^3 . Histogram (D) reveals the distribution of CT attenuation number in the entire thyroid gland, with mean of 49.6, median of 50, standard deviation of 13.34, and coefficient of variation at 0.27. CT = computed tomography, HU = Hounsfield unit, 3D = three-dimensional

ROC curve to compare histogram parameters obtained by non-enhanced images, median value as cut off value of 83 revealed the largest Az value for differentiating Hashimoto's thyroiditis from control group (Az: 0.905, 95% CI: 0.837–0.951; sensitivity: 84.4%, specificity: 85.5%) (Fig. 4).

DISCUSSION

In this study, 3D CT volumetry revealed that the thyroid volume in the Hashimoto's thyroiditis group was significantly larger than that in the control group. The size of thyroid gland has been reported to be larger in patients with diffuse thyroid diseases (including Hashimoto's thyroiditis and non-Hashimoto chronic thyroiditis) than that of normal thyroid gland (10). In patients with Hashimoto's thyroiditis, lymphoid cellular infiltration and fibrosis destructing follicular structures might result in

goitrous change in the thyroid gland (11). Further study with a larger population is needed to validate our result.

On histograms of non-enhanced CT images, lower mean and median values of CT attenuation number in the Hashimoto's thyroiditis group might represent a lower level of iodine concentration than that in the control group. A higher value of CV in the Hashimoto's thyroiditis group represented more prominent parenchymal heterogeneity of the thyroid gland. Median value of CT attenuation number in non-enhanced CT images was the most accurate parameter for differentiating Hashimoto's thyroiditis. Non-enhanced CT images might play an important role in evaluating CT findings of Hashimoto's thyroiditis because it could reflect the concentration and the distribution of endogenous iodine in the thyroid gland.

Accurate measurement of thyroid volume is required to diagnose various thyroid diseases and evaluate the outcome of treat-

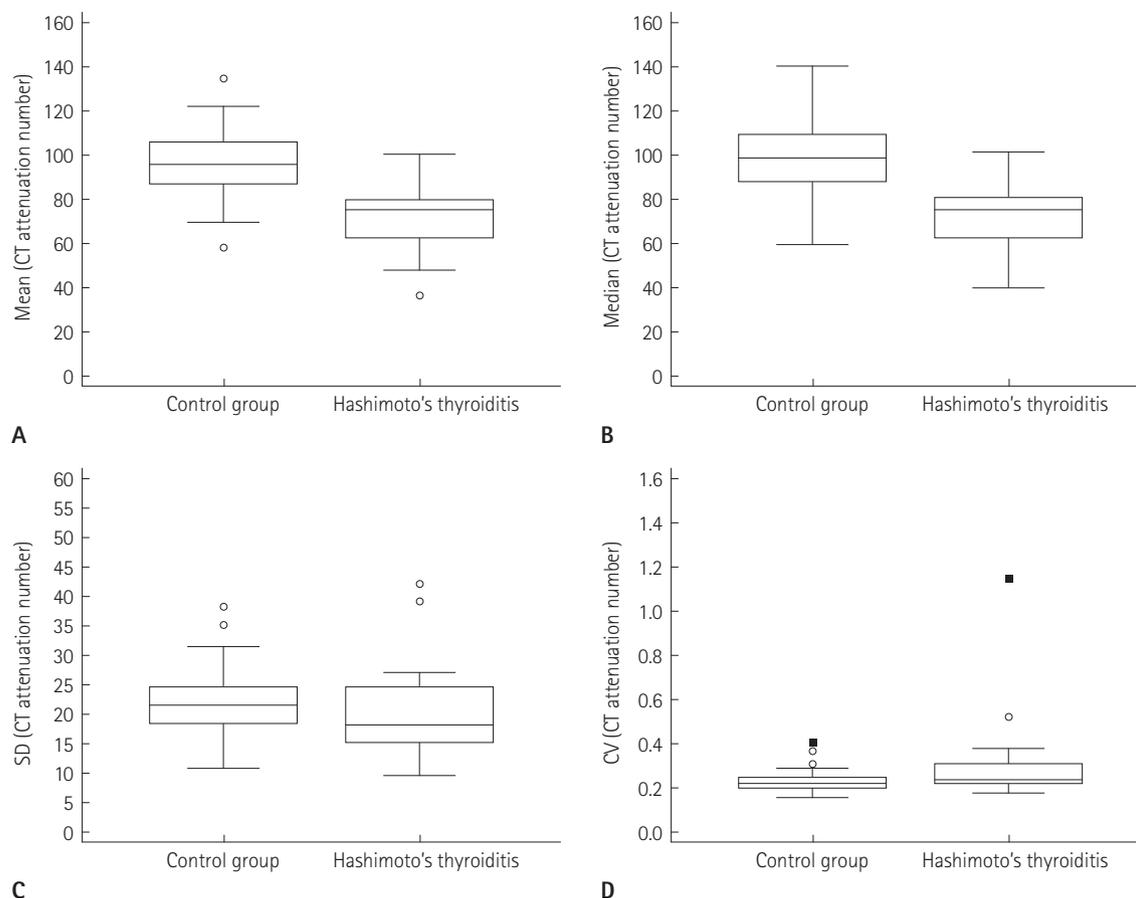


Fig. 3. Box plots showing histogram parameters of CT attenuation number on nonenhanced CT images between the two groups, including mean (A), median (B), standard deviation (C), and coefficient of variation (D). Each box stretches from the 25th percentile at lower edge to the 75th percentile at upper edge. The median is shown as a line across the box. CT = computed tomography, CV = coefficient of variation, SD = standard deviation

ments (1). Thyroid volume can be estimated by palpation, isotope scintigraphy, ultrasonography (US), and CT (12). However, results from the palpation and isotope scintigraphy are unreliable. US estimation has become an acceptable method for measuring the volume of thyroid. However, volume estimation using ellipsoid model on US can be inaccurate because thyroid gland has irregular geometry (13-15). Brunn et al. (16) have reported that deviations in the actual shape of the thyroid gland using an ellipsoid model resulted in an error rate of up to 30%. CT has been widely used as a reliable method to estimate the volume of thyroid because it is available in most medical centers. In addition, neck CT allows complete evaluation of the thyroid gland because it covers both the neck and the thorax. Furthermore, CT volumetry is highly accurate for the thyroid gland (13). Recently, 3D CT volumetry has been commercially available to estimate the thyroid volume based on the surface of the thyroid gland using semi-automated segmentation. It has higher accuracy than 2D CT volumetry using manual segmentation (3). However, CT volumetry has the following potential disadvantages: 1) It causes radiation exposure which limits its use for younger patients, 2) It has higher costs in some countries, 3) It

has side effects due to contrast media, such as nausea, vomiting, or allergic reactions. Although it has radiation hazard, 3D CT volumetry is by far the most accurate method for measuring the volume of thyroid.

Iodine produces a high CT attenuation number because it has a high electron density. Iodine is an essential material for thyroid hormone. It is captured by thyroid follicular cells and stored in colloid pools. The thyroid gland contains a quarter of iodide in the body. Accordingly, a normal thyroid gland will have a high CT attenuation number (4, 17). Iida et al. (4) have reported that the CT attenuation number of the thyroid gland has a linear relationship with iodine concentration of thyroid tissue *in vivo*. They have suggested that measuring CT attenuation number of the thyroid gland is useful to detect early stage of thyroid disease and determine its severity. It is well known that the iodine concentration in the thyroid gland is lower in patients with chronic thyroiditis than in control subjects because inflammatory cell infiltration and cellular proliferation can replace the normal follicular structure of the thyroid gland (18). Therefore, thyroid CT attenuation number is lower in patients with chronic thyroiditis than that in control subjects (19).

In previous studies, CT attenuation number was measured in manual operator-defined region of interest (ROI) on a 2D plane (5, 17, 19). Because the ROI was fixed in a round or rectangle shape, the real contour of the thyroid gland couldn't be investigated. However, in the present study, histograms were analyzed based on the 3D rendered image of the entire thyroid gland, including the isthmus and pyramidal lobes because 3D CT volumetry is regarded as the most accurate method to estimate the concentration of iodine in the thyroid gland on CT.

Several researchers have suggested that CV is an accurate quantitative score for liver texture because it reflects homogeneity or heterogeneity of hepatic parenchyma (20). A smaller value of CV has been considered to represent normal liver whereas a larger value of CV has been used to represent possible cirrhotic liver with various degrees of parenchymal fibrosis causing complex hepatic texture (20, 21). In the present study, the value of CV was larger in the Hashimoto's thyroiditis group than that in the control group. A larger CV value in Hashimoto's thyroiditis can reflect more prominent parenchymal heterogeneity of the thyroid gland because chronic thyroiditis can result in inflammatory cell infiltration and stromal fibrosis that can replace normal

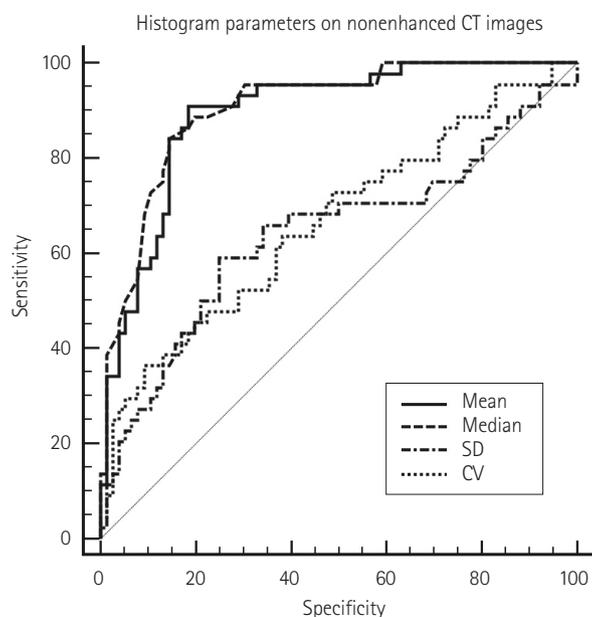


Fig. 4. ROC curve of histogram parameters on non-enhanced CT images, including mean (Az: 0.896, 95% CI: 0.827–0.944, sensitivity: 91.1%, specificity: 81.6%), median (Az: 0.905, 95% CI: 0.837–0.951, sensitivity: 84.4%, specificity: 85.5%), SD (Az: 0.641, 95% CI: 0.548–0.726, sensitivity: 59.1%, specificity: 75%), and CV (Az: 0.664, 95% CI: 0.572–0.747, sensitivity: 36.4%, specificity: 90.8%). CT = computed tomography, CV = coefficient of variation, SD = standard deviation

follicular structures.

There are several limitations of the present study. First, normal variation of thyroid volume was not considered according to patient's gender or age. This might result in error in the comparison of thyroid volume between the two groups. However, this limitation might be minimal because the gender and age between the two groups were not statistically different in this study. Second, many cases had coexisting nodular diseases such as papillary microcarcinoma or benign nodule. These nodular thyroid diseases could produce errors in the measurement of thyroid volume or the thyroid CT attenuation number. Third, intra-observer and inter-observer variability were not considered in measuring thyroid volume or histogram parameters. Fourth, the clinical usefulness of CT volumetry and histogram of thyroid gland in patients with Hashimoto's thyroiditis was not defined in the present study. Further evaluation will be needed for the clinical application of CT volumetry and histogram.

In conclusion, the Hashimoto's thyroiditis group had larger thyroid volume and larger CV value but lower CT attenuation number than the control group. Median value based on non-enhanced CT images was found to be the most accurate histogram parameter. Non-enhanced CT images were found to be more useful than contrast-enhanced CT images to evaluate Hashimoto's thyroiditis on neck CT.

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하시모토 갑상선염의 경부 전산화단층촬영에서 갑상선의 3차원 용적과 히스토그램에 대한 정량적 분석

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목적: 하시모토 갑상선염을 가진 환자에서 시행한 경부 CT를 통해 갑상선의 3차원 용적과 히스토그램을 정량적으로 분석하는 것이다.

대상과 방법: 경부 CT를 촬영한 121명을 대상으로, 대조군(76명)과 하시모토 갑상선염(45명)으로 분류하였다. CT는 조영증강 전과 후의 영상을 얻었다. 갑상선의 3차원 용적은 조영증강 후 영상에서 반자동적으로 계산했다. 히스토그램의 매개변수는 평균값, 중앙값, 표준편차, 변동계수였다. 각 집단에서 갑상선의 3차원 용적과 히스토그램의 매개변수를 측정 및 비교하였다.

결과: 갑상선의 전체 용적은 대조군에서 $14.9 \pm 4.8 \text{ cm}^3$ 였으며 하시모토 갑상선염에서 $19.2 \pm 8 \text{ cm}^3$ 였다($p < 0.01$). 조영증강 전 영상에서 획득한 히스토그램의 평균값, 중앙값, 표준편차와 변동계수는 대조군에서 95.8, 99.3, 21.7, 0.226이었고, 하시모토 갑상선염에서 72.2, 72.6, 19.6, 0.280이었다($p < 0.05$). 조영증강 후 영상에서 히스토그램의 각 매개변수는 통계적으로 유의하지 않았다($p > 0.05$). 하시모토 갑상선염을 감별하는 데 있어서, 중앙값(cut-off value: 83)이 가장 정확한 매개변수였다(Az: 0.905, 95% confidence interval: 0.837~0.951, sensitivity: 84.4%, specificity: 85.5%).

결론: 하시모토 갑상선염은 CT에서 대조군보다 더 큰 갑상선용적, 낮은 음영과 불균질성을 보인다.

인제대학교 의과대학 해운대백병원 ¹영상의학과, ²내분비내과, ³서남대학교 의과대학 명지병원 영상의학과, ⁴성균관대학교 의과대학 서울삼성병원 영상의학과