Using 2-dimensional color superb microvascular imaging vascularization index technique in the assessment of thyroid surgical bed

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Abstract

Aim: The purpose of this study was to investigate the effectiveness of the vascularization index (VI) obtained using color superb microvascular imaging (cSMI) technique in the assessment of thyroid surgical bed for remnant thyroid tissue (RTT).

Material and methods: We evaluated the thyroid surgical bed of 65 patients who had undergone total thyroidectomy (TT) due to papillary carcinoma (PC) using thyroid scintigraphy and cSMI. Color SMI was also performed for the examination of the thyroid parenchyma of 39 healthy asymptomatic participants. VI measurements were performed by manually drawing the contours of the RTT in those with remnant thyroid, the thyroid surgical bed in the patients’ group without remnant thyroid, and normal thyroid parenchyma in the control group, using the free region of interest (ROI) with 2-dimensional color SMI VI (2DcSMIVI) mode. The volume of ROI was measured and echogenicity was evaluated. The quantitative 2DcSMIVI values of the surgical bed with RTT (Group A), the surgical bed without RTT (Group B) and normal thyroid of healthy asymptomatic participants (Group C) were compared.

Results: The mean 2DcSMIVI values of Group A was significantly higher than Group B and C (p=0.001). The presence of RTT can be diagnosed with 89.1% sensitivity and 87.5% specificity when 1.75 2DcSMIVI is designated as the cut-off value.

Conclusion: The 2DcSMIVI is an effective imaging technique that can be used for the diagnosis of RTT.

Keywords: papillary thyroid carcinoma; remnant thyroid tissue; total thyroidectomy; ultrasonography

Introduction

The most common malignant tumor of the thyroid gland is papillary carcinoma (PC) [1] and the main effective treatment of thyroid PC is total thyroidectomy (TT) [2,3]. A real TT is rarely carried out as remnant thyroid tissue (RTT) remains in the surgical bed in most of the cases [4]. Post-operative RTT may be remnant cancer after an initial thyroidectomy or represent normal thyroid tissue [5]. The extent of RTT plays a significant role in PC recurrence [6]. Therefore, monitoring of these patients after surgery is essential to early detection of RTT, to achieve the improved therapeutic success of surgical results and provides early and more effective radioiodine treatment [7-9]. The RTT volume should be correctly appreciated as it is directly related to the radioiodine ablation dose [10].

The follow-up of patients with PC is traditionally carried out with thyroid scintigraphy and serum thyroglobulin (Tg) measurement. However, RTT may not concentrate iodine in scintigraphy and false-negative [11,12] or false-positive Tg levels in the early postoperative period [13]. Evaluation of the thyroid bed to investigate the presence of RTT can be particularly difficult and challenging in the early postoperative period by ultrasonog-
raphy (US) because of nonremnant benign postoperative conditions [7,14]. The distinction between RTT and benign postoperative conditions is difficult using US during the first three postoperative months and current literature suggest a waiting time for resolution of postoperative changes to investigate the presence of RTT in surgical bed [2,7,14-16].

The thyroid surgical bed consists of proliferative fibrofatty tissue that appears as a triangular hyperechogenic area compared to strap muscles at US. Remnant unresected RTT may have a similar echogenic appearance as normal thyroid tissue [14,15]. However internal vascularity is highly sensitive in predicting RTT [7,11,17]. Conventional Doppler imaging (CDI) US techniques (color and power Doppler) are used to evaluate internal vascularity in RTT [7,11,17]. However, CDI techniques are too limited to evaluate the blood flow in small microvessels [18] and insufficient to show the microvascular flow in the millimeter-sized RTT [7].

Superb microvascular imaging (SMI) was developed to overcome the limitations of CDI techniques. SMI can detect microvascular low blood flow components with details using a powerful algorithm [18]. Quantitative vascular analysis of the region of interest (ROI) can be performed using the vascularization index (VI) parameter in the cSMI examination (2-dimensional cSMI VI [2DcSMIVI]). The 2DcSMIVI reflects the proportion of vascular signals within the ROI. It is calculated by an application allowing quantification (a numerical value ranging from 0 to 100) of the vascular signals by establishing a ratio of colored pixels (vascular signals) to the total number of both colored and gray pixels within the ROI [19].

In this study, the thyroid surgical bed, RTT and normal thyroid gland vascularity were evaluated quantitatively using the 2DcSMIVI technique with objective numerical values. We aimed to investigate the utility of 2DcSMIVI in detecting the presence of RTT in the thyroid bed within the first 3 months postoperatively in patients with operated thyroid PC and to offer objective numerical data to increase the diagnostic accuracy of the US in these patients.

Materials and methods

This study was carried out between July 2019 and June 2020 after the approval by the local research ethics committee. All participants were informed about the study and written informed consent was obtained before starting their examinations.

The study population included 65 patients who had undergone TT due to PC within the last 3 months and were scheduled for radioiodine ablation therapy. Thirty-nine healthy subjects formed the control group. The control group was completely asymptomatic, the free thyroxine (fT4), thyroid-stimulating hormone (TSH) levels and thyroid B-mode US findings were normal and there was no history of thyroid disease, chronic disease or drug use. The tests were carried out with thyroid scintigraphy, B-mode US and 2DcSMIVI examinations to determine the presence of RTT. Grouping was made according to the areas where the 2DcSMIVI measurements were made. The area with evidence of RTT (right/left surgical bed or isthmus) in thyroid scintigraphy or US-2DcSMIVI examinations were classified as Group A, the thyroid surgical beds (right/left) with no evidence of RTT with these imaging techniques were classified as Group B and separately normal thyroid right and left lobe of healthy subjects were classified as Group C. If there was RTT in the isthmus localization, 2DcSMIVI measurement was performed and evaluated within group A, but measurement was not performed from the isthmus in those without RTT and the asymptomatic group. Each measurement area (ROI) was assessed separately, Group A, B, C were developed according to this ROI. Statistical analysis (age, gender, 2DcSMIVI values, echogenicity, the period since surgery, etc) was made according to the areas where the measurements were made.

The patients with newly diagnosed thyroid PC, with radioactive iodine treatment history and more than 3 months after surgery, patients who underwent TT for any other reason than PC and patients whose volume of RTT was above 2 cm³ were excluded from the study.

Thyroid scintigraphy technique

Thyroid scintigraphy was performed after intravenous administration of 185 MBq of Tc-99m pertechnetate. Anterior images were acquired using a gamma camera (E.CAM Signature, Siemens, Erlangen, Germany) equipped with a high-resolution parallel-hole collimator, with a 20 % photopeak window adjusted at 140 keV. The acquisition time for 300 k counts and 256x256 computer matrix were the parameters used during the imaging procedure.

Ultrasound and 2DcSMIVI Technique

The thyroid surgical bed of patients and thyroid glands of the control group was evaluated using the B-mode US and 2DcSMIVI examinations by a board-certified radiologist with 15 years of experience in US and 4 years of experience in cSMI. The patient group was evaluated after scintigraphy and the radiologist was blinded to the scintigraphy result. The US and 2DcSMIVI examinations of the thyroid bed - gland was performed using a high-frequency (4–14 MHz) linear array transducer (Apio 500, Canon Medical System Corporation, Tustin, CA). The participants were examined in supine position.
with the neck slightly extended. The gain, pulse repetition frequency, focal zone and wall filter were adjusted to obtain the optimal image for each participant. The examination of the thyroid bed (Group A and B) – gland (Group C) was started with the B-mode US. Each thyroid bed, RTT, in control group thyroid right and left lobe was measured in three dimensions and the volume of these was calculated by US device software using (volume of interested area = width×height×depth×10³×0.523). If there is residual thyroid tissue in more than one area (in thyroid surgical bed or isthmus) in the same patient, each area was evaluated separately. The echogenicity of ROI was analyzed and classified into four groups as marked hypoechogenic, hypoechogenic, isoechogenic or hyper-echogenic compared with the echogenicity of the strep muscles. The largest diameter of thyroid bed and RTT was also recorded.

Following the B-mode US examination, the participants underwent vascular imaging with the same US system equipped with cSMI function (150-180 Hz pulse repetition frequency), and the VI measurements were performed on cSMI images. The cSMI examination was performed on a magnified view as much as possible. During the cSMI examination, the participant was requested to breathe normally and not to swallow or move. The thyroid surgical bed, RTT and normal thyroid gland were examined in the longest transverse plane, using the cSMI for 5 seconds to measure 2DcSMIVI, following which the image was frozen. The 2DcSMIVI calculation program in the US device was activated. 2DcSMIVI measurements were performed by manually drawing the contours of the area to be measured (thyroid bed in the patients’ group without remnant thyroid, the contours of RTT, in those with remnant thyroid and normal thyroid parenchyma in the control group), using the free ROI with 2DcSMIVI mode. A 5-second image was examined backward and the highest 2DcSMIVI value calculated during this period was noted. The quantitative 2DcSMIVI value was obtained as a percentage of the number of color pixels to the total number of pixels on the examination plane within the ROI. Three 2DcSMIVI measurements were performed and the mean 2DcSMIVI value of these three measurements was calculated (fig 1). 2DcSMIVI measurement was performed twice (2DcSMI-1 and 2DcSMI-2) by the same radiologist to evaluate the intraobserver agreement. The average time was about 10 minutes for the B-mode US and 2DcSMIVI examinations.

The quantitative 2DcSMIVI values of the surgical bed in the group A, B and normal thyroid lobes in group C were compared. Also, correlation analysis between 2DcSMIVI values and the period since surgery, volume and echogenicity of RTT - bed was performed.

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS) version 22.0 (Inc., Chicago, Illinois, USA) software was used for evaluating the data. The descriptive statistics were expressed as minimum-maximum, mean, standard deviations (SD) values, frequency and percentile. Normal distribution of continuous variables was presented as mean and SD using Kolmogorov–Smirnov test. Chi-square test and analysis of variance or Students’ T-test was used to evaluate the differences between the three groups. The Pearson correlation analysis was used to evaluate the relationship between 2DcSMIVI and RTT volume, the period since the TT surgery and the echogenicity of ROI. The receiver operating characteristic

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**Fig 1.** A 29-year-old woman with operated TT due to PC, 32 days ago. B-mode US (A), cSMI (B) and 2DcSMIVI (C, D, E) images of the right thyroid surgical bed with RTT are presented. The cSMI examination shows internal vascularity in the RTT. The highest three 2DcSMIVI values of RTT in a 5-second examination are 22.3, 19.9, 24.4 respectively and the mean 2DcSMIVI value of these three measurements is 22.2.
(ROC) curve analysis was performed to evaluate the predictive abilities and determine the best cut-off value of quantitative 2DcSMIVI measurements for the surgical thyroid bed and the RTT. Sensitivity, specificity, and area under the ROC curve value were calculated by using the optimal cut-off point. The intraclass correlation coefficient was used to evaluate the intraobserver agreement for the 2DcSMIVI value. A p-value <0.05 was accepted as statistically significant.

**Results**

A total of 104 participants (79 female, mean age 45.72±13.06 years), 65 patients and 39 healthy asymptomatic were enrolled in the current study. The vascularity of 221 ROI (grouping was developed according to these ROI-measurement areas) was evaluated using 2DcSMIVI. The participants included in the study, details of the measured areas according to group classification, gender and mean age, are summarized in Table I. There was no statistically significant difference between the three groups in terms of gender (p=0.870) and age (p=0.858).

RTT was detected in 23 of 65 patients who underwent TT surgery, in 44 areas using thyroid scintigraphy and in 55 areas using the US-2DcSMIVI examination. In 42 patients who underwent TT, RTT was not observed in both scintigraphy and US examination. The mean volume of ROI, the 2DcSMIVI value of Group A, B, and C were summarized in Table II. The volume of ROI in group C was significantly higher than group A and B (p<0.001). However, no significant difference was found between Group A and B in terms of volume (p=0.453). There was no significant correlation between the 2DcSMIVI values and the volume or longest diameter of ROI, in both Group A (for volume; p=0.500, Pearson coefficient -0.093, for longest diameter; p=0.605, Pearson coefficient 0.071) and Group B (p=0.153, Pearson coefficient 0.153, for longest diameter; p=0.876, Pearson coefficient 0.017).

The mean 2DcSMIVI values of Group A were higher than Group B and C. There were statistically significant differences in 2DcSMIVI values between groups A, B, and C (p<0.001). The 2DcSMIVI values of Group A were significantly higher than Group B (p<0.001) and C (p<0.001) and the 2DcSMIVI values of Group C was significantly higher than the Group B (p<0.001), (fig 2, fig 3). The ROC curve analysis and the best cut-off value of the 2DcSMIVI value in RTT are shown in figure 4.

The average period since TT surgery was 64.47±19.69 (between 15-90) days (64.34 ± 19.44 days in Group A and 64.55 ± 19.96 in Group B, p=0.950). There was no significant correlation between the period since the TT surgery and the 2DcSMIVI values in both Group A (p=0.04, Pearson coefficient 0.278) and Group B (p=0.071, Pearson coefficient 0.194).

There was a statistically significant difference between groups A and B in terms of echogenicity. The RTT echogenicity was significantly lower than the thyroid bed without RTT (p<0.001). As the echogenicity of ROI (RTT, thyroid bed without RTT, normal thyroid parenchyma) decreased, the 2DcSMIVI values increased.

| Table I. Participants of the study and grouping of the measured area. |
|---|---|---|
| **2DcSMIVI measurements areas (ROI) and subjects** | **Localization of the ROI** | **Grouping according to the ROI** |
| 143 areas in 65 patients who underwent TT | RTT in the right thyroid bed (23) | Group A (55 ROI) |
| | RTT in the left thyroid bed (24) | (45 female, mean age 47.20±14.34 years) |
| | RTT in the isthmus (8) | Group B (88 ROI) |
| | Right thyroid bed without RTT (43) | (63 female, mean age 46.34±12.56 years) |
| | Left thyroid bed without RTT (45) | Group C (78 ROI) |
| | Right normal thyroid lobe (39) | (60 female, mean age 44.00±12.65 years) |
| | Left normal thyroid lobe (39) | |

2DcSMIVI: two-dimensional color superb microvascular imaging vascularization index; ROI: region of interest; RTT: remnant thyroid tissue; TT: total thyroidectomy

| Table II. The mean age, volume of region of interest and the 2DcSMIVI values according to the groups. |
|---|---|---|---|
| **Volume of ROI (cm3)** | **The 2DcSMIVI values** | **first measurement** | **second measurement** |
| **Group A** | 0.59±0.74 | 14.28±12.24 | 13.91±11.98 |
| **Group B** | 0.71±1.05 | 0.73±1.16 | 0.76±1.10 |
| **Group C** | 6.59±1.77 | 5.48±1.81 | 5.42±1.79 |

The results are expressed as mean±standard deviation. 2DcSMIVI: two-dimensional color superb microvascular imaging vascularization index. SD: standard deviation
The mean 2DcSMIVI values according to the echogenicity are summarized in Table III. The intraclass correlation coefficient agreement rate was 0.0997 (p<0.001) for 2DcSMIVI.

Discussion

In this study, the thyroid surgical bed was evaluated using the 2DcSMIVI technique after thyroid scintigraphy examination to investigate the presence of RTT in patients with operated thyroid PC, in the early postoperative period and we aimed to investigate the usability of 2DcSMIVI. The mean 2DcSMIVI values of RTT were found significantly higher than the surgical bed without remnant and normal thyroid gland. The result of our (p<0.001, Pearson coefficient – 0.449). The mean 2DcSMIVI values according to the echogenicity are summarized in Table III. The intraclass correlation coefficient agreement rate was 0.0997 (p<0.001) for 2DcSMIVI.

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study shows that the presence of RTT can be diagnosed using the 2DcSMIVI imaging technique with objective, quantitative numerical values with high sensitivity and specificity.

The main effective modality of thyroid PC treatment is TT [2,3]. Despite TT surgery, micro/macrosopic RTT may remain but a real TT is rarely carried out [4,20,21]. After surgery, monitoring of the thyroid surgical bed is necessary for early detection of RTT [7,8,21]. RTT may harbor remnant cancer after an initial thyroidectomy or represent normal thyroid tissue [6]. It is reported that local recurrence commonly occurs in RTT after incomplete resection of the thyroid gland [5]. Radioiodine RTT ablation is performed with I-131, a beta-emitting radionuclide [22], used to eliminate the presence of RTT, to destroy microscopic tumor disease after TT surgery [9]. The evaluation and detection of RTT using imaging techniques may provide additional information regarding the prediction of the RTT and provides early treatment, improved radioiodine treatment success results [7,23]. Since the volume of RTT affects the radioiodine ablation dose and also plays a role in deciding whether further surgery is required to complete the TT or not, it is also important to identify the volume of RTT for further treatment after surgery [10].

Radioiodine thyroid scintigraphy and the US have been widely used to estimate RTT. However, which is the ideal imaging modality for accurate RTT estimation has not been well concluded [23]. Traditionally, the follow-up of postoperative patients with thyroid PC is carried out with I-131 diagnostic whole-body scan or thyroid bed uptake measurement to evaluate the size of RTT before ablation [24]. However, using I-131 for diagnostic purposes before ablation may cause stunning which may reduce the rate of successful ablation. Thyroid scintigraphy with Tc-99m pertechnetate, on the other hand, does not induce stunning and can be used for the preablative assessment of the size of RTT. The uptake in Tc-99m pertechnetate scintigraphy and its relation with the outcome of ablation has been well established [24].

The role of the US is especially important in patients who have RTT after TT for thyroid PC particularly in patients with false-negative Tg levels, with a recurrent-remnant disease that is not I-131 avid [11,25]. In our study, RTT was detected in 23 patients and was absent in 42 patients in both scintigraphy and US examination with 2DcSMIVI technique, patient-based compatibility being high in these two examinations. However, RTT was detected in more areas in the US examination using the 2DcSMIVI technique.

The usefulness of US in detecting RTT and tumor recurrence after TT is well documented in the literature [11] and also IN international guidelines [2]. US is the current gold standard imaging technique for postoperative surveillance to detect RTT, tumor persistence-recurrence [16]. The thyroid bed can be particularly challenging to evaluate in the early postoperative period. After TT, assessment of the thyroid bed is difficult because local inflammatory response causes proliferation of fibrofatty connective tissue, hematoma, secondary edema swelling in soft tissues, granuloma, scars, etc. The distinction between RTT, residue-locoregional recurrent thyroid cancer and nonrecurrent benign lesions cannot be made based on the US features during the first three postoperative months. In current studies in the literature, before the US examination of the surgical bed, a waiting time of three months after surgery to allow for the resolution of postoperative changes is suggested [7,14-16].

Normally the surgical thyroid bed consists of fibrofatty proliferative tissue and appears typically as an inverted triangular hyperechogenic area compared to strep muscles in the US in the late postoperative period [14,15]. The postoperative thyroid bed can be observed heterogeneously in the early postoperative period [7,14-16]. Remnant unresected thyroid tissue, postoperative changes in the surgical thyroid bed, and the remnant tumor may have a similar echogenic appearance [14,15]. For these reasons, it may not be possible to distinguish the postsurgical thyroid bed, RTT and remnant tumor tissue using B-mode US [7,11]. In our study, we found the RTT echogenicity was significantly lower than the thyroid surgical bed without RTT. This finding shows that echogenicity can be used to evaluate the presence of RTT. However, as seen in Table III, RTT and the thyroid bed after surgery can have the same echogenicity. If only echogenicity is used as a criterion in the early postoperative period, it

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### Table III. The mean 2DcSMIVI values in the region of interest according to echogenicity

| Echogenicity         | Group A, n (%) | Group B, n (%) | Group C, n (%) | Mean 2DcSMIVI  |
|----------------------|----------------|----------------|----------------|----------------|
| Marked hypoechogenic | 19 (34.55)     | 2 (2.27)       | 0              | 14.04±13.31    |
| Hypoechogenic        | 26 (47.27)     | 12 (13.64)     | 0              | 10.88±12.82    |
| Isoechogenic         | 6 (10.91)      | 52 (59.09)     | 78 (100)       | 3.75±3.19      |
| Hyperechogenic       | 4 (7.27)       | 22 (25)        | 0              | 2.28±3.87      |

2DcSMIVI: two-dimensional color superb microvascular imaging vascularization index. SD: standard deviation
can be particularly difficult to investigate the presence of RTT.

A demonstration of internal vascularity using CDI techniques is very sensitive in predicting RTT [7,11]. In a study in which the thyroid bed was evaluated with the CDI technique, internal vascularity was found only in 23% of the lesions with RTT or recurrence. This study shows that CDI techniques are insufficient and too limited to show the microvascular flow present in the millimeter-sized RTT [7]. In our study, RTT was detected in 55 areas in the 2DcSMIVI examination and internal vascularity was demonstrated in all of these RTT.

The mean 2DcSMIVI values of RTT were found higher than the thyroid surgical bed without remnant and normal thyroid gland. The presence of RTT can be diagnosed with high sensitivity and specificity when 1.75 2DcSMIVI is designated as the cut-off value. There was no significant correlation between the 2DcSMIVI values and the volume, longest diameter of ROI, in both the RTT and the surgical thyroid bed. These results show that 2DcSMIVI can be used effectively to investigate the presence of millimetric RTT by showing microvascular blood flow, internal vascularity and increased vascularity in RTT compared to the adjacent surgical bed.

As the echogenicity of ROI (RTT, thyroid bed without remnant thyroid tissue, normal thyroid parenchyma) decreased, the 2DcSMIVI values increased. We found a significant negative correlation between the echogenicity of ROI and the 2DcSMIVI. B-mode US and 2DcSMIVI could be used to evaluate the presence of RTT in the surgical thyroid bed in patients with operated PC. However, since 2DcSMIVI can quantitatively show the presence of internal vascularity in RTT with an objective numerical value, we think that 2DcSMIVI is a superior examination method from the B-mode US in the investigation of the presence of RTT.

There was no significant correlation between the period since the TT surgery and the 2DcSMIVI values in both RTT and the thyroid surgical bed. This finding suggests that SMI can be used in both early and late postoperative period.

Our study has some limitations. We were not able to compare our results with other published studies because there is no previous study about the usability of 2DcSMIVI in detecting the presence of RTT in the surgical thyroid bed. We included only patients who were operated for thyroid PC to obtain a homogeneous group. The diagnosis of RTT relied on the scintigraphy, B-mode US, 2DcSMIVI. We did not perform the histopathological evaluation of the RTT and benign-malignant discrimination was not made. Patients with RTT were treated with radioiodine and were not re-evaluated with 2DcSMIVI. An experienced radiologist did all the examinations, so we could not evaluate interobserver variability. The 2DcSMIVI measurement was made in the longest transverse plane. If measurements were made in both transverse and longitudinal planes, the reliability of the 2DcSMIVI values we obtained may have been increased; however, the examination time would have increased. Vascular structures can be shown in more detail with monochrome SMI [18]. We could not use the monochrome SMI because the vascular index can not be measured using the monochrome SMI examination in current US devices. Patients who underwent TT due to PC but the period since the TT surgery was more than three months were not included in the study and the diagnostic performance of 2DcSMIVI, in detecting the presence of RTT in these patients was not evaluated. This may be the subject of future research.

In conclusion, the 2DcSMIVI is an effective imaging technique that can be used for the diagnosis of RTT, with objective, quantitative numerical values, with high sensitivity and specificity in the early postoperative period. However, further studies with a larger population are required to confirm the use of the 2DcSMIVI technique in routine clinical practice, to investigate the presence of RTT.

Conflict of interest: none

Acknowledgements: We would like to thank Funda Gökgöz Durmaz for providing help in the statistical analysis of the study.

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