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Fully Automated Computer-Aided Volume Estimation System for Thyroid Planar Scintigraphy

Jia-Yann Huang\textsuperscript{a}, Kun-Ju Lin\textsuperscript{b, c}, Yung-Sheng Chen\textsuperscript{a}.*

\textsuperscript{a} Department of Electrical Engineering, Yuan Ze University, Chungli, Taiwan, ROC
\textsuperscript{b} Department of Nuclear Medicine, Chang Gung Memorial Hospital, Keelong, Taiwan, ROC
\textsuperscript{c} Department of Medical Physics and Imaging science, Chang Gung University, Taoyuan, Taiwan, ROC

*Correspondence author:

\begin{itemize}
\item e-mail: eeyschen@saturn.yzu.edu.tw
\item Tel: +886-3-4638800 ext 7113
\item Fax: +886-3-4639355
\item Address: 135 Yuan-Tung Road, Chung-Li 320, Taiwan, ROC
\end{itemize}
Abstract

Patient-specific dosimetry calculations are often performed for radioiodine therapy in patients with Graves’ hyperthyroidism. The radioiodine doses are typically calculated to deliver the desired amount of radiation based on gland size and radioactive iodine uptake. Thus the estimation of thyroid gland volume is of great importance for radioiodine therapy. In clinical practice, thyroid volume determinations are usually performed with ultrasonography (US) or with planar scintigraphy (PS). In traditional planar scintigraphic studies, the thyroid boundary is estimated using a fixed threshold value if the shape of the thyroid is well-defined or a manually drawn region of interest (ROI) if the thyroid shape is irregular. The thyroid volume is then calculated based on the area thus determined. Delineating the thyroid area on a planar scintigrama is not easy when applying a fixed threshold value. Moreover, hand-drawn ROIs are time consuming, tedious, and highly operator-dependent. In this study, for a PS image, a fully automated thyroid volume estimation system mainly consisting of four steps, i.e. preprocessing, image contrast enhancement, image segmentation, and automated ROI finding, was proposed to obtain the maximum height and area of each thyroid lobe, and thus calculate the thyroid volume using either Himanka-Larsson’s formula or Allen-Goodwin’s formula. A set of 40 Graves’s disease patients regarded as training set were used to determine empirically some parameters operated in the system. A set of 30 Graves’s disease patients being independent of the training set, regarded as test set for thyroid volume measurements were used for comparisons and performance analyses. In this study, the US was adopted as a standard reference. The statistical analyses were performed with bias, precision, and relative differences. The results of thyroid volume estimation from the proposed approach correlated well with those from US, and the statistical performance analyses showed good agreement between them. In comparison, our automated approach with Allen-Goodwin’s formula had not only good correlation with US ($R^2=0.99$) but also the best bias (0.8), precision ($\pm 2.32$ ml), and low
relative differences (2.2±6.1%). It is expected that this automated computer-assisted approach can help physicians in the determination of patient-specific administered activities for treatment of thyroid disease.

*Keywords:* Radioiodine therapy; Planar scintigraphy; Ultrasonography; Thyroid volume estimation; Contrast enhancement; Image segmentation; Adaptive thresholding; Morphology.
1. Introduction

Medical therapy, radioiodine therapy, and surgery are the three main methods to treat patients with Graves’ disease. Radioiodine therapy is recognized as the safest, simplest, least expensive and most convenient form of treatment for adults with uncomplicated hyperthyroidism [1-4]. Due to the radiation safety regulations, individual dosage protocols are vital in several countries [5]. The protocol usually based on estimations of thyroid volume and radioiodine uptake can be expressed in a standardized dosage formula.

\[ D = V \times \left[ \frac{100\%}{U} \right] \times C \]  

(1)

Here \( D \) represents the radioiodine therapy dosage (MBq), \( U \) is the radioiodine uptake (RAIU, \%) at 24 hours after radioiodine administration, \( C \) is a constant (usually, 3.7 MBq/g) [6, 7], and \( V \) is the thyroid volume (ml). RAIU is measured at nuclear medicine departments, whereas the thyroid volume is normally estimated by ultrasonography (US). From (1), it is obvious that the accuracy of radioiodine therapy dosage is proportional to that of thyroid volume estimation. Developing a useful method for accurately estimating thyroid volume is thus of great importance.

Magnetic resonance imaging (MRI) has excellent spatial resolution and soft-tissue contrast and can thus provide accurate estimates of thyroidal volumes. However, MRI is not readily available in all clinical settings. Ultrasonography (US), although more likely to be used in daily practice, does not provide nearly as accurate estimates of thyroidal volumes (with uncertainties of 15-20% [8-12]) and is not widely available in nuclear medicine departments [1]. Therefore, there is a need to develop a comparably accurate thyroid volume measurement method based on planar scintigraphy (PS) to avoid the dependence on other imaging techniques.
Van Isselt et al. [13] compared the accuracy of three image modalities, i.e. PS with $^{99m}$Tc injection, single-photon emission computed tomography (SPECT), and US, for the estimation of the thyroid volume in patients with Graves’ disease. These three image modalities were compared with MRI as the reference standard. For the PS study, a median filter was adopted to suppress image noise. A rectangular ROI was manually drawn. This ROI included the entire thyroid gland while excluding all non-thyroid foci of activity. Within the hand-drawn ROI, an area of $5 \times 8$ pixels with maximum count intensity was automatically calculated. Adopting a threshold of 30% of this maximum value, an isocontour was created around the thyroid gland. The thyroid area ($A$) was the number of pixels within the isocontour multiplied by the pixel size. The thyroid volume ($V$) was then calculated using the formula,

$$V = 0.33 \times A^{3/2}$$  \hspace{1cm} (2)

which was described by Himanka and Larsson [14]. Van Isselt et al. [13] reported that PS correlated poorly with MRI ($R^2 = 0.61$) and suffered from a considerable bias.

Pant et al. [1] estimated thyroid volumes in Graves’ disease by PS ($^{99m}$Tc injection) and SPECT. The results of the scintigraphic method were compared with those obtained by US. Through phantom studies, the optimum threshold level was found to be 20% of the maximum count intensity in the planar scintigram. The volume of each lobe was measured using the formula,

$$V = A \times L \times K$$ \hspace{1cm} (3)

which was described by Allen and Goodwin [15] where $V$, $A$, and $L$ denote thyroid volume, area of the frontal projection of the thyroid lobe, and height of the thyroid lobe, respectively. Pant et al. [1] used approximately the parameter $K = 0.32$ in their study and obtained the correlation coefficient ($r$) between PS and US was 0.99. However, both planar technologies, PS and US, have their limitations for accurate estimates of goitrous or irregularly shaped glands.
In traditional PS studies, the thyroid boundary was usually estimated using a fixed threshold value if the shape of the thyroid is well-defined or a manually drawn region of interest (ROI) if the thyroid shape is irregular, like Van Isselt et al.’s work [13]. Delineating the thyroid area on a PS is not easy when applying a fixed threshold value. Moreover, hand-drawn ROIs are time consuming, tedious, and highly operator-dependent. To overcome this disadvantage, the aim of this study is thus to develop a fully automated (i.e. operator-independent) PS image segmentation for the estimation of thyroid volume.

The proposed approach for segmenting the region of thyroid lobes from a PS image is based on a set of image processing techniques. Due to the pepper noise embedded and the inherent low contrast characteristic of a PS image, it will be first smoothed and then image contrast enhanced for the facility of later image segmentation. The image segmentation mainly composed of adaptive thresholding, components labeling, and a set of morphological operations is used to distinguish the PS image into background and foreground, where the foreground represents the wanted thyroid gland region. Finally, some reference points from the thyroid gland region will be located automatically in order to delineate the two thyroid lobes (left and right) for obtaining the maximum height $L$ and area $A$ of each lobe. Thus the whole thyroid volume can be calculated.

According to the result of Van Isselt et al.’s work [13], even though the bias was not negligible US had the best correlation with MRI ($R^2 = 0.97$) and the best precision. For the purpose of evaluations, in this study the thyroid volume estimated by US was taken as the reference standard for comparison with results obtained by the related PS techniques (Van Isselt et al.’s approach [13] and Pant et al.’s approach [1]) as well as the proposed fully automated approach. A high-resolution ultrasound scanner (GE, 3200) was used by one experienced radiologist to estimate the thyroid dimensions. The volume of each thyroid lobe was computed by the standard formula for ellipsoid volume [16],
\[ V = \left( \pi / 6 \right) \times a \times b \times c \]  \hspace{1cm} (4)

Where \( a, b, c \) denote the measured maximum height, width, and depth, respectively, for each lobe. The whole thyroid volume was the sum of the volumes of the two lobes.

The rest of this paper is organized as follows. In Section 2, a brief description of patients and images for the study is first introduced. Then the detailed algorithms of the proposed approach are described. The results and discussion are presented in Section 3 and Section 4, respectively. Finally, the conclusion of this study is given in Section 5.

2. Materials and methods

2.1. Patients and images

Planar scintigraphic studies were performed on 30 patients with Graves’ disease (21 female and 9 male, mean age 42 y, range 24-73 y) at 24 hours after ingestion of 3.7 MBq of \(^{131}\)I-iodide. The acquisition was done on a dual-head gamma camera (Siemens, E-CAM) with a pin-hole collimator placed on the first (i.e. anterior) detector, and all acquisitions were performed with patients in the supine position with the head tilted back. The following acquisition parameters were used: anterior view, \(256 \times 256 \times 16\) matrix, 100k counts, pinhole-to-neck distance of 6 cm, and zoom (i.e. magnification) factor of 2.16. After acquisition, the thyroid scintigram \((I^{\text{org}})\) was formed as a typical PS image as displayed in Fig. 1(a). For comparison, the thyroid volume for each patient with Graves’ disease was further estimated by US using the Eq. (4) as a reference standard, where all the estimated US data are listed in Table 1. The estimated volume of Patient No. 3 by US was far smaller than that obtained by the other methods. It could be a miswritten data due to human mistake. In this study, it still was involved in the table for some discussions.
2.2. Proposed approach

The proposed approach mainly consists of four steps to automatically obtain the maximum height and the area of each thyroid lobe. In the first step, a preprocessing including a Gaussian smoothing filter and a max filter is applied to reduce the pepper noise embedded in a PS image. The Gaussian smoothing filter was effectively applied to the computer-aided diagnosis in nuclear medicine whole body bone scan images [17]. Next in order to highlight the object of thyroid lobes, an intensity-pair distribution based method [18] is adopted for the image contrast enhancement. Then the wanted thyroid gland region is segmented from the PS image by performing an adaptive thresholding, components labeling, and a set of morphological operations. In this step, some parameters were determined empirically by visual inspection based on the study set of PS images, such as the times of erosion and dilation in morphological operations. In order to make our experiments reasonable, the 30 PS images mentioned previously were regarded as a test set, in addition we took another 40 PS images as a training set to find the appropriate values for these parameters. Finally, some reference points on the segmented thyroid gland region are located automatically based on pixel searching and used to delineate the two thyroid lobes (left and right) for obtaining the wanted maximum height and area of each lobe. Fig. 2 shows the flowchart of the proposed approach.

2.2.1. Preprocessing

Gaussian smoothing filter is usually adopted to suppress the noise in an image. Consider the Gaussian form with isotropic and zero-mean, which may be expressed by

\[ G(x, y) = \frac{1}{2\pi\sigma^2} e^{-\left(x^2+y^2\right)/2\sigma^2} \]  \hspace{1cm} (5)

According to our earlier work of whole body bone scan images in nuclear medicine [17], in this study an approximate Gaussian smoothing filter involving a 5×5 convolution mask with
a standard deviation (\( \sigma \)) of 1.4 was also adopted for smoothing the noisy PS image. The resultant image was denoted as \( I_{\text{gau}} \).

Moreover, to highlight the useful brightest pixels in PS image, which can accentuate the contour of the thyroid gland, a so-called \textit{max filter} was used and given by

\[
I_{\text{max}}(x, y) = \max_{(s, t) \in S_{xy}} \{ I_{\text{gau}}(s, t) \}
\]

(6)

where \( S_{xy} \) is the set of coordinates in a \( 3 \times 3 \) rectangular sub-image, centered at pixel \((x, y)\), \((s, t)\) is the spatial coordinates defined by \( S_{xy} \). Since pepper noise has low gray-scale values, it is reduced by this filter as a result of the maximum selection process in the sub-image area \( S_{xy} \). After the preprocessing step, a smoothed and maximized planar thyroid scintigram denoted as \( I_{\text{max}} \) can be obtained as shown in Fig. 1(b).

2.2.2. Image contrast enhancement

Contrast enhancement as a preprocessing step in image segmentation is widely used for medical image processing. For the noisy thyroid planar scintigram, a non-noise-amplifying contrast-enhancement algorithm was used. Jen et al. \[18\] proposed a straightforward approach for edge enhancement based on intensity-pair distribution that possesses both the local and global information of the image content. Based on the intensity difference in the intensity pair, either a set of expansion forces (\( EF \)) or a set of anti-expansion forces (\( AEF \)) is generated to yield an intensity mapping function, which suppresses image noise and stretches the contrast of edge areas in the output image. This method had been detailed and successfully applied for our earlier study on the glomerular filtration rate estimation from \( ^{99m}\text{Tc-DTPA} \) renogram \[19\], and was also included in this work.

To avoid over-enhancement of noisy images, an additional mapping function is combined with the original function to constrain the total expansion force and yield a normalized
expansion function. Fig. 3(a) shows the resultant planar scintigram of the thyroid processed by applying such an intensity mapping function, denoted as $I^{\text{enh}}$.

2.2.3. Image segmentation

Yeh et al. [20] successfully extracted a significant ultrasonic breast lesion by an adaptive thresholding algorithm. Since thyroid segmentation is not easy when applying a constant threshold value to a thyroid scintigram, in our current approach we adopted this algorithm to extract the rough thyroid area from image $I^{\text{enh}}$. The adaptive thresholding algorithm can be summarized as follows.

To highlight the thyroid region in the scintigram, the threshold for thyroid region segmentation must be selected adaptively. In this study, the ratio of mean gray-scale value within the whole thyroid scintigram and within a local ROI is employed to individually adjust the threshold value. If the ratio is less than 1, it means the characteristic of ROI tends to be in the thyroid area and then, the threshold level should be assigned to a lower value. Since the ratio can serve as an index to distinguish the characteristic of each ROI within the whole scintigram, it can be adopted as a weighting factor for adjusting the threshold value.

Fig. 3(b) shows the cumulative distribution function (CDF, cumulative image histogram) of three manually drawn ROIs, indicated by black square boxes in Fig. 3(a), with the size of $8 \times 8$ indicating the background (ROI 1), thyroid edge (ROI 2), and thyroid area (ROI 3) regions, respectively. As shown in Fig. 3(b), the CDF rising rate of the background region is greater than that of either the thyroid edge or thyroid area.

A threshold value is very fundamental for roughly separating background, thyroid edge, and thyroid area, respectively. Determining the appropriate threshold value is important, since variations of image noise will influence the results of thresholding if the threshold value is either too low or too high. In our current approach, the appropriate edge-defining threshold value was obtained by visually analyzing 40 PS images of a training set as mentioned in the
beginning of this section. A threshold value corresponding to the product of a gray-scale value of 35% of the CDF and a weighting factor was thus derived. The quantities of CDF and weighting factor are uncorrelated. For example, the mean gray-scale value of Fig. 3(a) is 88. For the three selected ROIs, the 35% gray-scale values of CDF and local mean gray-scale values are (20, 28), (40, 104), and (198, 150), respectively. Then, the individual weighting factors of each ROI can be obtained by the ratio of mean gray level within Fig. 3(a) and within each local ROI. Finally, the threshold levels of the three selected ROIs are obtained as 62, 34, and 116, respectively. The pixels within the ROI below the threshold level are assigned to be 0 (background). The adaptive thresholding step is executed until the entire image is converted into a binary image. In order to obtain an entire binary image from the original one, the process has to array multiple ROIs to cover the entire image. The ROIs with the size of $8 \times 8$ pixels were arrayed adjacent to each other with overlap of 56 pixels in horizontal direction. There are 7968 (249 $\times$ 32) ROIs for a thyroid scintigram with the size of $256 \times 256$ pixels, the threshold value of each ROI was then calculated by the procedure mentioned above. Fig. 3(c) shows the resultant binary image, denoted as $I^{out}$.

Following the adaptive thresholding step, we adopted a float-fill components labeling algorithm [21] to identify object regions in $I^{out}$. The components labeling algorithm is summarized as follows.

1. Let a marker be initialized ($m = 0$) and a null stack be created.

2. Do the following steps for all unmarked foreground pixels (gray-scale value $> 0$) in the image.

   2-1. If a foreground pixel is detected, then $m \leftarrow m + 1$. The pixel is marked with the $m$, and its unmarked foreground neighbors are pushed into the stack.
2-2. If the stack is not empty, then the pixel on the top of the stack is marked with the $m$ and removed from the stack; and its unmarked foreground neighbors are pushed into the stack. Repeat this step until the stack is empty.

2-3. If the stack is empty, go to step 2-1 until all foreground pixels are marked.

After performing the components labeling algorithm, the object regions were identified, if the pixel number of one object was less than a pre-selected value, that object was removed from image $I_{\text{roi}}$. And then, the most significant thyroid region ($I_{\text{roi}}$) was extracted. Fig. 4(a) shows the processing result.

In order to eliminate some small holes in a significant thyroid region, the morphological operations of dilation (expanding the shapes contained in the input image) and erosion (shrinking the shapes contained in the input image) were applied to the significant thyroid area. A small hole is usually formed with some background pixels. For filling the hole, the larger size of the hole is, the more times of dilation need, and vice versa. To maintain the original thyroid shape, the erosion with the same times should be performed after the dilation process. In our experiments, three times of dilation and erosion were suggested by empirical considerations. Thus we performed dilation followed by erosion three times on the image to eliminate small holes, and the processed image was denoted as $I_{\text{roi}}$.

Due to the noise effect, it is possible that some pixels were misclassified. Image $I_{\text{enh}}[G(x, y)]$ was involved in this stage to refine the extracted area ($I_{\text{roi}}$). We computed the mean object’s gray-scale value $g_{\text{m, thyroid}}$ as follows

$$g_{\text{m, thyroid}} = \frac{1}{N_g} \left[ \sum_{(x,y) \in I_{\text{roi}}} G(x,y) \right] \tag{7}$$

where $N_g$ represents the total number of non-zero pixels in $I_{\text{roi}}$. Further, since the zero gray level pixels in image $I_{\text{roi}}$ may belong to the thyroid area and some non-zero pixels may
belong to the non-thyroid area, we dilated five times for the thyroid region in $I^{\text{org}}$ to obtain an outer band region [$I^{\text{band}}$ in Fig. 4(b)] which does not include the thyroid area in image $I^{\text{org}}$. Since most of the pixels in image $I^{\text{band}}$ [$B(x, y)$] are background pixels, we calculate the mean background’s gray level by the following equation

$$gm_{\text{bkg}} = \frac{1}{N_{h}} \left[ \sum_{y \in \text{band}} B(x, y) \right]$$

where $N_{h}$ represents the total number of non-zero pixels in image $I^{\text{band}}$. Based on $gm_{\text{thyroid}}$ and $gm_{\text{bkg}}$, for the gray image $I^{\text{enh}}$, we scanned all non-zero pixels in the area of $I^{\text{org}} \cup I^{\text{band}}$ [$T(x, y)$]. If the gray level of a pixel is near $gm_{\text{thyroid}}$, we classify it as an object pixel, otherwise, as a background pixel. The region of the refined object was denoted as $I^{\text{refi}}$ and can be formulated by the following expression

$$I^{\text{refi}}(x, y) = \begin{cases} 1 & \text{if } (x, y) \in I^{\text{org}} \cup I^{\text{band}} \\
 & \left| T(x, y) - gm_{\text{thyroid}} \right| < \left| T(x, y) - gm_{\text{bkg}} \right| \\
0 & \text{otherwise} \end{cases}$$

where “1” denotes the region of the final thyroid region and “0” denotes the background. Then, the dilation and erosion operations were performed after obtaining $I^{\text{refi}}$ in order to eliminate some small holes, and was denoted as $I^{\text{ref}}$. Fig. 5(a) shows the processed result. Fig. 7(a) shows the final segmented thyroid gland region, where the contour of image $I^{\text{ref}}$ is plotted with a white curve on image $I^{\text{org}}$, and was denoted as $I^{\text{seg}}$.

2.2.4. Automated ROI finding

Since a thyroid lobe has an ellipse-like shape in usual, it is reasonable to find the reference points from the thyroid lobe image for suitably fitting ellipse-like shape and further computing its area. To achieve the goal of fully automated processing, the wanted reference
points, i.e. \( p^{\text{veur}} \), \( p^{\text{lur}} \), \( p^{\text{lefr}} \), \( p^{\text{ldr}} \), \( p^{\text{vedr}} \), \( p^{\text{dr}} \), \( p^{\text{rigr}} \), and \( p^{\text{rur}} \), as depicted in Fig. 5(b), were obtained for each thyroid lobe by a scanning search scheme as presented in Appendix.

Based on the ellipse-like shape, a useful ROI can be confined by four curves. Each curve was approximated by a quadratic Bézier curve \([22]\), which can be defined by

\[
B_2 = (1-t)^2 P_1 + 2t(1-t)Q + t^2 P_2
\]

(10)

There are three control points. The first two control points are the two endpoints of the curve, \( P_1 \) and \( P_2 \). The last control point is an intermediate point \( Q \), which controls the direction of the tangents of the curve at both ends. In our approach, the four control point sets \([ p^{\text{veur}}(P_1) \), \( p^{\text{lefr}}(P_2) \), and \( p^{\text{lur}}(Q) \]), \([ p^{\text{lefr}} \), \( p^{\text{vedr}} \), and \( p^{\text{ldr}} \]), \([ p^{\text{veur}} \), \( p^{\text{rigr}} \), and \( p^{\text{rur}} \]), and \([ p^{\text{rigr}} \), \( p^{\text{vedr}} \), and \( p^{\text{dr}} \]) created curve 1, curve 2, curve 3, and curve 4, respectively. In most normal cases, the shape of thyroid lobe is similar to ellipse. However, there exists a union region (the yellow color) between the two thyroid lobes as the current example, which is reddepicted in Fig. 6 for discussion. To obtain a better thyroid lobe delineation, by the use of curve 4, the overlapping effect in union region of two thyroid lobes could be reduced. After checking all non-zero pixels within the ROI confined by the four curves, the final thyroid lobe contoured in red color can be identified and the area \( A \) of thyroid lobe can be obtained by summing all the non-zero pixels within the specific ROI. From the illustration of Fig. 6, though the curves 1, 2, and 3 are not necessary for computing the area of thyroid lobe in most normal cases, they are still used in our current system to deal with the abnormal cases and get better thyroid lobe delineation. So far the maximum height \( L \) (derived in Appendix) and the area \( A \) of the right thyroid lobe have been calculated, we can use Eq. (2) or Eq. (3) to estimate the right thyroid volume. The left thyroid volume can also be obtained by the similar way. Fig. 7(c) depicts the final segmentation result for the whole thyroid grand.
3. Results

The proposed algorithms were implemented by C++ Builder 6.0 Enterprise Suite (Boarland, Austin, TX). Linear regression analysis was applied to assess the correlations between our approach and US. The difference-versus-mean method was performed for the comparison of estimates [23]. The predictive performance of the various tests was described by the bias and precision [24]. The relative difference method was used to discover the changing trend over the entire volume range. All statistical analyses were performed with MedCalc ® Version 12.6.1.0. (Ostend, Belgium). After the maximum height and area of each thyroid lobe obtained by the fully automated approach, the thyroid volume estimation could be calculated by the Himanka-Larsson’s formula [14] in Eq. (2) and Allen-Goodwin’s formula [15] in Eq. (3). Fig. 8 shows the user interface of our program. A demonstration can be found at http://yschen.ee.yzu.edu.tw/Academic/CVLab/demo_thy.asp.

To assess the performance, the results measured with US were taken as a standard reference due to its good correlation with MRI [13]. In addition to our fully automated method combining with the Himanka-Larsson’s formula [14] (denoted as D1) and Allen-Goodwin’s formula [15] (denoted as D2), two approaches presented by Van Isselt et al. [13] (denoted as B) and Pant et al [1] (denoted as C) were adopted for comparisons. This study analyzed 30 planar thyroid scintigrams. Table 1 shows the results of the thyroid volume measurements by US, Van Isselt et al.’s approach [13], Pant et al.’s method [1], and our approach. Fig. 9 shows the graphic representations of the regression analyses, whereas in Fig. 10 the bias and precision for the different approaches corresponding to US are displayed by Bland-Altman plots of difference versus mean. The numeric results are summarized in Table 2(a).

As shown in Fig. 9, Fig. 10, and Table 2, the proposed method (with D1 and D2) had the best bias (1.3 and 0.2) with US, whereas the correlations and precisions were about equal for
all approaches. However, in Table 1 we found that the given volume of Patient No. 3 by US was far smaller than that obtained by all methods. It could be a miswritten data due to human mistake. Therefore, disregard this data the same analyses as above were performed again and the numeric results are summarized in Table 2(b), in which all approaches had good correlations with US ($R^2 = 0.97$ above). Again the proposed method (with $D_1$ and $D_2$) had the best bias (1.9 and 0.8) with US. In addition, the proposed method with $D_2$ had the best precision ($\pm 2.32$ ml). As a result, the proposed approach can automatically and effectively delineate the thyroid region for the volume estimation.

To discover the changing trend over the entire volume range (11-87 ml) based on the current US estimations, the relative differences measured with US versus the four approaches, using (adopted approach - US) $\times 100$% / US, are displayed in Fig. 11. The horizontal lines of $\pm 20\%$ and $\pm 20\%$ indicating the deviations from US measurements are used for reference. Table 3 summarizes the numerical results using mean $\pm$ standard deviation (SD). Fig. 11 and Table 3 show that the proposed approach with Allen-Goodwin’s formula had the best agreement with US, where the relative differences between them were about equal over the entire volume range with $2.2\pm 6.1\%$. The proposed method with Himanka-Larsson’s formula ($5.9\pm 9.1\%$) had also a good agreement with US, compared with Van Isselt et al.’s approach ($22.9\pm 6.43\%$) and Pant et al.’s approach ($12.7\pm 6.32\%$).

4. Discussion

Radioiodine therapy is a safe and effective method of treatment for patients with Graves’ hyperthyroidism. Accurate estimation of the thyroid volume is critical for dosimetry-based prescription of the patient-specific administered activity. Three-dimensional imaging techniques such as computed tomography (CT), MRI, and positron emission tomography (PET) provide excellent delineation of the thyroid region from the surrounding tissues, either with or without contrast enhancement [25, 26]. The integration-of-areas technique has been
well standardized and verified, and its reproducibility is very good [25]. However, these imaging modalities have several drawbacks, such as limited availability, the use of iodinated contrast media, relatively high cost, and radiation exposure in the case of CT. These are obstacles to their clinical applications for thyroid volume measurements in patients with Gravies’ disease. In a clinical environment, the precision, capacity, availability, and cost of different imaging modalities often determine the physician’s choice [13].

Though ultrasonography is more likely to be used in clinical practice, it does not provide nearly an accurate estimate of thyroidal volume [8-12] and is not widely available in nuclear medicine departments [1]. Therefore, the planar scintigraphy (PS) is still often used in the nuclear medicine departments due to its inadequate radioiodine therapy dosages. Consider the treatment environment and according to the operation of Eq. (1), it is valuable to develop a reliable approach based on PS to avoid dependence on US.

According to the study of Van Isselt et al. [13] using the Himanka-Larsson’s formula [14], PS correlated poorly with MRI ($R^2 = 0.61$) and suffered from a considerable bias, whereas US had the best correlation with MRI ($R^2 = 0.97$) and the precision even though the bias was not negligible. In addition, according to the study of Pant et al. [1] using the Allen-Goodwin’s formula [15], the correlation ($R^2 = 0.99$) between PS and US could be obtained. Therefore, in our PS study, the US was adopted as a standard reference.

Compare to the image of MRI, the quality of a PS image is rather poor due to the inadequate radioiodine therapy dosages. In traditional PS studies, the thyroid boundary was usually estimated using a fixed threshold value if the shape is well-defined or a manually drawn ROI if the thyroid shape is irregular. This should be one factor affecting the accuracy of estimating thyroid volume from a PS image. In addition, delineating the thyroid contour on a PS is not easy when applying a fixed threshold value. Moreover, hand-drawn ROIs are time consuming, tedious, and highly operator-dependent. Hence to improve such a work, it is
valuable to develop a fully automated approach which is the main contribution of this paper. Though some parameters were determined empirically from a training set of PS images, the proposed approach with Allen-Goodwin’s formula had not only good correlation with US ($R^2=0.99$) but also the best bias (0.8), precision (±2.32 ml), and relative differences (2.2±6.1%), refer to the Table 2(b) and Table 3.

From the results of Table 2 and Table 3, we found that the performance of Pant et al.’s approach was better than that of Van Isselt et al.’s approach, and that of proposed method with Allen-Goodwin’s formula was better than that of proposed method with Himanka-Larsson’s formula. Note here that both Van Isselt et al.’s approach and our method with D1 adopted the same Himanka-Larsson’s formula in Eq. (2), whereas both Pant et al.’s approach and our method with D2 adopted the same Allen-Goodwin’s formula in Eq. (3). This might conclude that the estimation by Allen-Goodwin’s formula is more accurate than that by Himanka-Larsson’s formula. Furthermore, the segmentation method was also a key factor affecting the thyroid volume estimation performance. For example, the segmentation results obtained by Van Isselt et al.’s approach and Pan et al.’s were not very well, as shown in Fig. 7(b) (over-thresholding) and Fig. 7(d) (miss-segmentation), respectively. As a result, the proposed approach can automatically and effectively delineate the thyroid region for the volume estimation, and the calculation of Allen-Goodwin’s formula is more accurate than that of Himanka-Larsson’s formula.

5. Conclusion

A fully automated computer-aided thyroid volume estimation system is proposed for thyroid planar scintigraphy. The results of thyroid volume estimation from the automated measurement correlated well with those from US, and the statistical performance analyses (bias, precision, relative differences) showed satisfactory results. The main drawback of this system is the need for empirically determined parameters, such as the standard deviation and
mask size used in Gaussian smoothing filter, the percentage of CDF used in adaptive thresholding, as well as the times of erosion and dilation in morphological operations. As a future work, these considerable results encourage us to further develop a new and more efficient approach that can also be applied to SPECT images for automatically measuring thyroid volume in patients with Graves’ disease.

6. Conflict of interest statement

The authors declare that there is no conflict of interest.

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References


Appendix

Consider the image given in Fig. 5(a), in this appendix, a scanning search scheme for positioning the reference points is presented. By scanning each vertical line from the left image border to the half of image width in horizontal direction, the coordinates of the farthest-left non-zero pixel, denoted as $p^r$, were determined. In a similar way, this approach was applied to locate the furthest-right non-zero pixel, $p^l$. From the image top to bottom, by searching each horizontal line from $p^r(x)$ toward right, the coordinate of the first met non-zero pixel was regarded as the apex of the right thyroid lobe, $p^{ma}$. In a similar way, by searching each horizontal line from $p^l(x)$ toward left, the coordinate of the first met non-zero pixel was regarded as the apex of the left thyroid lobe, $p^{la}$. By scanning each vertical line between $p^{ma}(x)$ and $p^{la}(x)$, the vertical distance was calculated between the image top and the first non-zero pixel in each column. The coordinate of the non-zero pixel with maximum distance was the valley $p^v$ between $p^{ma}$ and $p^{la}$. After locating the reference points, a vertical separation line based on $p^v(x)$ was constructed to divide the thyroid gland into two parts as shown in Fig. 5(a).

We then applied the image moments algorithm to obtain the coordinates of the right lobe center. The general two-dimensional $(p+q)$th order moments of a binary image are defined as

$$m_{pq} = \sum_{x} x^p y^q$$

The coordinates of the right lobe center can be obtained by

$$x_c = \frac{m_{10}}{m_{00}}, \quad y_c = \frac{m_{01}}{m_{00}}$$
Refer to Fig. 5(b), by inspecting each line passing through the center \((x_c, y_c)\) on the right thyroid lobe, the length between antipodal points in each line was calculated and the coordinates of antipodal points of the line with the maximum length were denoted as \(p_{\text{vedr}}\) and \(p_{\text{veur}}\), respectively. The straight line formed by the two points \(p_{\text{veur}}\) and \(p_{\text{vedr}}\) was denoted as \(L^\text{long}\), and the maximum height \(L\) of the thyroid lobe was thus obtained with the length of \(L^\text{long}\).

By scanning each thyroid edge pixel at the left side of line \(L^\text{long}\), the perpendicular distance formed from \(L^\text{long}\) and each edge pixel were calculated, the edge pixel with the maximum perpendicular distance was denoted as \(p_{\text{lefr}}\). The intersection of \(L^\text{long}\) with the perpendicular line passing through \(p_{\text{lefr}}\) was denoted as \(p_{\text{intr}}\). Let \(\Delta x\) and \(\Delta y\) be the horizontal and vertical distances between \(p_{\text{lefr}}\) and \(p_{\text{intr}}\). Another five reference points \(p_{\text{rigr}}, p_{\text{lur}}, p_{\text{rur}}, p_{\text{ldr}},\) and \(p_{\text{rdr}}\) depicted in Fig. 5(b) could be then obtained respectively by

\[
\begin{align*}
    p_{\text{rigr}}(x, y) &= p_{\text{intr}}(x + \Delta x, y - \Delta y) \\
    p_{\text{lur}}(x, y) &= p_{\text{veur}}(x - \Delta x, y + \Delta y) \\
    p_{\text{rur}}(x, y) &= p_{\text{veur}}(x + \Delta x, y - \Delta y) \\
    p_{\text{ldr}}(x, y) &= p_{\text{vedr}}(x - \Delta x, y + \Delta y) \\
    p_{\text{rdr}}(x, y) &= p_{\text{vedr}}(x + \Delta x, y - \Delta y)
\end{align*}
\]
Table 1. Thyroid volume estimations in patients with Graves’ disease by ultrasonography and planar scintigraphy.

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<tr>
<th>Pat. no.</th>
<th>Volume by US (ml)</th>
<th>Volume by B (ml)</th>
<th>Volume by C (ml)</th>
<th>Volume by D1 (ml)</th>
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B: Van Isselt et al.’s approach [13]
C: Pant et al.’s approach [1]
D1: Our approach with Himanka-Larsson’s formula [14]
D2: Our approach with Allen-Goodwin’s formula [15]

*: In our investigation, the data of Patient No. 3 were strange that the volume calculated by US was far smaller than that obtained by the other methods. It could be a miswritten data due to human mistake and still listed in this table for some discussions.
Table 2. (a) Linear regression, correlation, bias, and precision analyses for thyroid volume estimations in patients with Graves’ disease by different methods applied to planar scintigraphy versus ultrasonography using the data given in Table 1. (b) shows the results disregard the data of Patient No. 3 from Table 1.

(a)

<table>
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<tr>
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<th>Volume by B</th>
<th>Volume by C</th>
<th>Volume by D1</th>
<th>Volume by D2</th>
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<tr>
<td>(L)</td>
<td>(y=1.253x+0.348)</td>
<td>(y=1.121x-0.005)</td>
<td>(y=0.964x+2.621)</td>
<td>(y=1.010x-0.213)</td>
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<tr>
<td>(R^2)</td>
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<td>0.94</td>
<td>0.96</td>
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<tr>
<td>Bias</td>
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<td>1.3</td>
<td>0.2</td>
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<td>Precision (±)</td>
<td>5.73</td>
<td>4.77</td>
<td>5.43</td>
<td>4.17</td>
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(b)

<table>
<thead>
<tr>
<th></th>
<th>Volume by B</th>
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<th>Volume by D1</th>
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<tr>
<td>(L)</td>
<td>(y=1.240x+1.334)</td>
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<tr>
<td>Bias</td>
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<tr>
<td>Precision (±)</td>
<td>4.59</td>
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L: Linear regression equation  
\(R^2\): Correlation coefficient of determination  
B: Van Isselt et al.’s approach [13]  
C: Pant et al.’s approach [1]  
D1: Our approach with Himanka-Larsson’s formula [14]  
D2: Our approach with Allen-Goodwin’s formula [15]
**Table 3.** Thyroid volume relative differences measured with US versus the four approaches by mean ± SD (%). The results are shown without the data of Patient No. 3 from Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Volume by B</th>
<th>Volume by C</th>
<th>Volume by D1</th>
<th>Volume by D2</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>22.9</td>
<td>12.7</td>
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<td>2.2</td>
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<td><strong>SD (±)</strong></td>
<td>6.43</td>
<td>6.32</td>
<td>9.1</td>
<td>6.1</td>
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</table>

**B:** Van Isselt et al.’s approach [13]

**C:** Pant et al.’s approach [1]

**D1:** Our approach with Himanka-Larsson’s formula [14]

**D2:** Our approach with Allen-Goodwin’s formula [15]
Fig. 1. Illustrations of (a) a planar thyroid scintigram ($I^{\text{org}}$), and (b) a smoothed and maximized planar thyroid scintigram ($I^{\text{max}}$).
Fig. 2. Flowchart of the proposed approach.
Fig. 3. (a) Result of image contrast enhancement ($I_{\text{enh}}$). The three ROIs represent the background (ROI 1), thyroid edge (ROI 2), and thyroid (ROI 3) regions, respectively. (b) The CDF rising rate of the background is larger than that of either the thyroid edge or thyroid region. (c) The adaptive thresholding result ($I_{\text{out}}$).
Fig. 4. After applying the float-fill components labeling algorithm to image $I_{\text{rouf}}$, (a) the rough segmented thyroid gland $I_{\text{rouf}}$ is obtained. (b) The outer band region ($I_{\text{band}}$).
Fig. 5. (a) The result after applying the thyroid gland separation step. (b) The maximum height and area of a thyroid lobe were obtained by the reference points and four Bézier curves. The denoted symbols are mentioned in the text.
Fig. 6. Illustration of four Bézier curves obtained for confining the region of a thyroid lobe. It is obvious that the use of curve 4 can reduce the overlapping effect in union region (the yellow color) of two thyroid lobes. After checking all non-zero pixels within the region confined by the four curves, the final thyroid lobe contoured in red color can be identified. Though the curves 1, 2, and 3 are not necessary for calculating the area of thyroid lobe in most normal cases, they are still used in our current system to deal with the abnormal cases and get better thyroid lobe delineation.
Fig. 7. (a) The final segmented thyroid gland region obtained by our approach, where the contour of the thyroid gland is plotted with a white curve on image $I_{\text{org}}$. (b) The segmented thyroid gland region obtained by Van Isselt et al.’s approach [13] (30% threshold level). (c) The segmented thyroid lobe regions obtained by our approach. (d) The segmented thyroid lobe regions obtained by Pant et al.’s approach [1] (20% threshold level).
**Fig. 8.** The user interface of our program. A demonstration can be found at http://yschen.ee.yzu.edu.tw/Academic/CVLab/demo_thy.asp.
Fig. 9. Linear regression analyses for thyroid volumes measured with US versus (a) Van Isselt et al.’s approach [13], (b) Pant et al.’s approach [1], (c) our approach with Himanka-Larsson’s formula [14], and (d) our approach with Allen-Goodwin’s formula [15].
Fig. 10. Bland–Altman plots of difference against mean for thyroid volume measurements with US versus (a) Van Isselt et al.’s approach [13], (b) Pant et al.’s approach [1], (c) our approach with Himanka-Larsson’s formula [14], and (d) our approach with Allen-Goodwin’s formula [15].
Fig. 11. Thyroid volume relative differences measured with US versus (a) Van Isselt et al.’s approach [13], (b) Pant et al.’s approach [1], (c) our approach with Himanka-Larsson’s formula [14], and (d) our approach with Allen-Goodwin’s formula [15]. The lines of +20% and -20% indicating the deviations from US measurements are used for reference.