Fully Automatic Region of Interest Selection in Glomerular Filtration Rate Estimation from ^{99m}Tc -DTPA Renogram

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Abstract Glomerular filtration rate (GFR) is a common accepted standard estimation of renal function. Gamma camera-based methods for estimating renal uptake of ^{99m}Tc -diethylenetriaminepentaacetic acid (DTPA) without blood or urine sampling have been widely used. Of these, the method introduced by Gates has been the most common method. Currently, most of gamma cameras are equipped with a commercial program for GFR determination, a semi-quantitative analysis by manually drawing region of interest (ROI) over each kidney. Then, the GFR value can be computed from the scintigraphic determination of ^{99m}Tc -DTPA uptake within the kidney automatically. Delineating the kidney area is difficult when applying a fixed threshold value. Moreover, hand-drawn ROIs are tedious, time consuming, and dependent highly on operator skill. Thus, we developed a fully automatic renal ROI estimation system based on the temporal changes in intensity counts, intensity-pair distribution

image contrast enhancement method, adaptive thresholding, and morphological operations that can locate the kidney area and obtain the GFR value from a ^{99m}Tc -DTPA renogram. To evaluate the performance of the proposed approach, 30 clinical dynamic renograms were introduced. The fully automatic approach failed in one patient with very poor renal function. Four patients had a unilateral kidney, and the others had bilateral kidneys. The automatic contours from the remaining 54 kidneys were compared with the contours of manual drawing. The 54 kidneys were included for area error and boundary error analyses. There was high correlation between two physicians' manual contours and the contours obtained by our approach. For area error analysis, the mean true positive area overlap is 91%, the mean false negative is 13.4%, and the mean false positive is 9.3%. The boundary error is 1.6 pixels. The GFR calculated using this automatic computer-aided approach is reproducible and may be applied to help nuclear medicine physicians in clinical practice.

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Introduction

The glomerular filtration rate (GFR) is a significant index of renal function in health and disease [1]. Many nuclear medicine solutions for estimating GFR using ^{99m}Tc -diethylenetriaminepentaacetic (DTPA) are widely used

today. Renal clearance can be estimated from the measurement of activity in single or multiple blood samples [2–6], from the rate of removal of activity from tissue or blood [7, 8], from the rate of appearance of tracer in urine [9], and from the rate of renal tracer uptake. The most widely used gamma camera approach is a method introduced by Gates using approximately 3 mCi (111 MBq) of ^{99m}Tc -DTPA and measuring the dosage in the syringe by counting it 20 cm from the face of a gamma camera before and following injection [10–12]. The region of interest (ROI) over each kidney is manually assigned on the composite image added from 2 to 3 min following injection, and the net count for each kidney is determined in the time interval from 2 to 3 min following the tracer arrival.

Currently, most gamma cameras are equipped with a commercial ROI tool for GFR measurement. Delimitation of the kidney boundary is estimated using the single-threshold method if the shape of the kidney is well defined, or there is a manually drawn ROI if the kidney shape is irregular.

The single-threshold method is the simplest way to obtain the renal ROIs. A preliminary rectangular or elliptical ROI is placed over each kidney [13]. The maximal renal count for each kidney is defined as the maximal count within the ROI. Pixels with values exceeding about 30% of the maximal renal count are selected as renal ROI.

Tomaru et al. developed a semi-automated renal ROI method using the double-threshold technique in which the operator clicks around the center of each kidney [14]. The maximal renal count is calculated as the maximal count in a small rectangular area 5×9 pixels size. Pixels with values exceeding 60% of the maximal renal count are selected as renal central areas in a large rectangular area of 21×27 pixels. If there is continuity between two areas in a renal central area due to one pixel, the pixel is deleted to break the continuity. The area consisting of the pixels adjacent to the renal central area is determined. Pixels in this area with values exceeding 30% of the maximal renal count are selected as the renal peripheral area. Finally, the renal ROI consisting of the renal and peripheral areas is obtained. By Tomaru et al.'s approach, the double-thresholding method failed in three of 62 kidneys on the composite image obtained by the summation of dynamic images from 1- to 2-min time period, and none of them on 2- to 3-min composite image.

In addition, several manual and semi-automated methods have been proposed to decrease operator dependency in defining ROIs for the estimation of renal function, including the edge detection-based method [15–17] and the temporal information-based method [18–20]. But none

has been widely accepted as a method of choice in clinical practice.

The major reason why the manual and semi-automated methods may not have found broad applicability is the difficulty with automatically generating ROIs both in normal renal function and renal disease subjects. Because of poor contrast between the kidney and the main background (liver, spleen, heart, and great vessels), the renal contours are difficult to be detected from background radioactivity. Our new approach adopted the temporal information in “pre-processing” to eliminate the main background (liver, heart, spleen, and great vessels) radioactivity, which can increase the reliability for kidney delineation.

Segmentation of kidney delineation is quite difficult when applying the threshold methods to a composite renal scintigram [14, 18], and the hand-drawn ROI is tedious. Due to the drawbacks of the hand-drawn ROI and the semi-automated threshold methods, we attempt to develop a robust method to automatically detect kidney ROI from DTPA dynamic studies without any operator intervention in GFR estimation with high sensitivity and specificity for use in clinical applications.

As shown in Fig. 1, our approach consists of three main steps: pre-processing, image contrast enhancement, and kidney segmentation, each with a section below. The “Pre-processing” section introduces the pre-processing step. The “Image Contrast Enhancement” section provides details of image contrast enhancement based on the intensity-pair distribution. The “Image Segmentation” section deals with kidney segmentation based on an adaptive thresholding algorithm. The primitive results from 54 kidneys showing the performance of our approach and discussion are given respectively in section “Results” and “Discussion.” A “Conclusion” section summarizes this approach.

Fig. 1 Flowchart of the proposed approach

Materials

Patients and Images

In this study, 30 patients referred for renography to evaluate various renal disorders were examined (19 females and 11 males, mean age 58 years, range 18–86 years). Four patients had a unilateral kidney, and the others had bilateral kidneys. The medical ethics committee of Chang Gung Memorial Hospital approved this investigation.

Renography

To provide adequate hydration, patients were encouraged to drink 300 ml of water 30 min prior to the examination. All acquisitions were performed with the patient in the supine position. A 1-min pre-injection count of the administered dose was performed by placing the syringe 30 cm from the center of the collimator (the upper-left part of Fig. 2). After a bolus injection of ^{99m}Tc -DTPA, posterior dynamic imaging was performed for about 20 min. Fifty-seven frames of slow dynamic acquisition at a rate of one frame per 20 s (the middle part of Fig. 2) were collected after 60 1-s frames of quick dynamic acquisition. The injected dose was determined based on the body surface area and 200 MBq/m² was given. After the conclusion of the patient part of the study, a similar 1-min post-projection syringe count was performed (lower-right part of Fig. 2). The acquisition was done on a dual head gamma camera (Siemens, E-CAM) equipped with a low-energy, general-purpose collimator. Images were recorded as 128×128

matrices in Word mode with a 20% energy window around the ^{99m}Tc photon peak.

In order to get a good signal-to-noise ratio image for benefiting the kidney delineation processing, after acquisition, a composite image was created by adding slow dynamic frames from a time period. The time period of 2 to 3 min following injection was adopted by many relative studies [14, 21–23]. In our approach, the time period selection for generating a composite image was based on these studies, and the processing result can be shown in Fig. 3a.

Methods

Pre-processing

The detailed algorithms for removing background of liver, heart, spleen, and great vessels based on the temporal changes in counts of the slow dynamic renograms, Gaussian smoothing filter, Max filter, and removing the unnecessary regions by reference points are presented below.

As shown in Fig. 3a, the composite image (I^{COM}) reveals radiotracer in the liver, spleen, heart, and great vessels, as well as the kidney. This phenomenon increases the difficulty for kidney segmentation. Peak cortical uptake normally occurs 3 to 4 min after tracer administration [24], and the peak uptake of liver, spleen, and heart usually appear before 1 min after injection [25]. Between 1 and 3 min after injection, the uptakes of liver, spleen, heart, and great vessels reduce gradually, but the kidney

Fig. 2 Illustration of the dynamic renography

Fig. 3 **a** The composite image (I^{COM}). **b** The first and **c** sixth images (I^{80} , I^{180}) of the slow dynamic images. **d** The rough blood pools region (I^{RBP}). **e** The final blood pools region (I^{BP}). After removing the blood pools and applying Gaussian filter and Max filter to image I^{COM} , image I^{GM} (**f**) is obtained (the denoted symbols are mentioned in the text)

uptake is cumulative. The first and sixth images (60–80, 160–180 s) of the slow dynamic frames were selected and were denoted as I^{80} (Fig. 3b) and I^{180} (Fig. 3c). In order to remove the main background (liver, heart, spleen, and great vessels) in I^{COM} for the benefit of the kidney

delineation, we adopted I^{COM} , I^{80} , and I^{180} as the input images and then output an image containing the rough area of the main background by Algorithm 1. The processed image is denoted as I^{RBP} . The rough region of the blood pool is shown in Fig. 3d.

Algorithm 1. Locate the rough region of blood pool

Input: Images I^{80} and I^{180} .
 Variables: x = image horizontal coordinate,
 y = image vertical coordinate,
 h = image height, w = image width,
 m = mean intensity count of I^{80} .
 Output: an image containing the rough region of blood pool (I^{RBP}).
 01. **for** $y = 0: h$
 02. **for** $x = 0: w$
 03. a = the intensity count of $I^{80}(x, y)$
 04. b = the intensity count of $I^{180}(x, y)$
 05. **if** $(a-b) > (m / 4.5)$ **then**
 06. $I^{\text{RBP}}(x, y) = 255$
 07. **else**
 08. $I^{\text{RBP}}(x, y) = 0$
 09. **end if**
 10. **end for**
 11. **end for**

We then adopted a float-fill components labeling algorithm [26] to identify object regions in image I^{RBP} . The components labeling algorithm can be summarized as follows. The image is scanned until a foreground pixel is found. An unlabeled foreground is marked with a new label, and its position is pushed on a stack. While the stack is not empty, the pixels on the stack are marked with the label, and the neighbor pixels are pushed on the stack. When the stack is empty, the search continues to the next seed point for the float-fill.

After the processing above, the object regions in I^{RBP} were identified, and if the pixel number of one object was less than a pre-selected value, that object was removed. In order to eliminate some small holes in the images, morphological operations, dilation, and erosion were applied in the image. We performed dilation followed by erosion two times in the image to eliminate small holes, and the processed image was denoted as I^{BP} (Fig. 3e). If the intensity count of a pixel in I^{BP} was 255, then the intensity count of the pixel which had the same coordinates in image I^{COM} was set to 0, and the resulting image is denoted as I^{BPR} .

The major source of noise in scintigram is the random photon distribution of scattered and background radioactivity detected by the gamma camera. The noise is higher in scintigrams than other imaging modalities. Higher noise would obscure the contrast and reduce the image quality. Even though the blood pool portion of the renogram was identified and removed by previous procedure, the noise of

the remaining renogram is still high, which will obstruct the kidney segmentation processing. Therefore, we adopted a Gaussian smoothing filter to the image histogram for suppressing the noise since the Gaussian kernel used for smoothing image has become extremely popular. The Gaussian form was isotropic, zero-mean, and may be expressed by:

$$G(x, y) = \frac{1}{2\pi\sigma^2} e^{-(x^2+y^2)/2\sigma^2} \quad (1)$$

To smooth the noisy renal scintigram (I^{BPR}), we applied an approximation involving a 5×5 convolution mask with a standard deviation (σ) of 1.4.

The so-called Max filter is given by:

$$I^{\text{GM}}(x, y) = \max_{(s, t) \in S_{xy}} \{ I^{\text{BPR}}(s, t) \} \quad (2)$$

This filter is required prior the following pre-processing steps. The Max filter enhances bright values in the image by increasing its area. Similar to a dilate function; each mask (kernel) is processed for the brightest surrounding pixel. The brightest pixel then becomes the new pixel value at the center of the mask, which helps to preserve kidney boundary data. In addition, because the pepper noise has low gray values, it is reduced by this filter as a result of the maximum selection process in the sub-image area S_{xy} . In our approach, the size of the sub-image was selected with a 3×3 mask. The processed result is shown in Fig. 3f, denoted as I^{GM} .

Then, we used image I^{GM} to locate the reference points for body region and the separation point. By scanning the horizontal line from the image center in left direction, the first zero pixel was denoted as p^{lb} (labeled “a” in Fig. 3f). This approach was similarly applied to locate the first zero pixel in the right direction (p^{rb} , labeled “b” in Fig. 3f). Then, the separation point p^{sep} (labeled “c” in Fig. 3f) was obtained by:

$$p^{sep}(x) = \{ [p^{rb}(x) - p^{lb}(x)] / 2 \} + p^{lb}(x), p^{sep}(y) = p^{lb}(y) \quad (3)$$

Each horizontal line was scanned vertically from image top to reference point p^{sep} , and the first non-zero pixel was denoted as p^{str} (labeled “d” in Fig. 3f). Moving downward from the reference point p^{str} to reference point p^{sep} , the number of zero pixels between the reference point p^{lb} and p^{rb} were calculated for each row. The row which had the most zero pixels was denoted as L (Fig. 3f).

Algorithm 2 was used to eliminate the unnecessary areas in image I^{GM} and assist the kidney segmentation procedure. The processed results are shown in Fig. 5a, denoted as I^{RM} .

Algorithm 2. Remove the unnecessary regions in I^{GM}

Input: I^{GM} .
Variables: x = image horizontal coordinate,
 y = image vertical coordinate,
 h = image height, w = image width.
Output: image I^{GM} .
01. **for** $y = 0: h$
02. **for** $x = 0: w$
03. **if** $y < L(y)$ or $x < p^{lb}(x)$ or $x > p^{rb}(x)$
 or x between $[p^{seg}(x)-3, p^{seg}(x)+3]$
04. $I^{RM}(x, y) = 0$
05. **else**
06. $I^{RM}(x, y) = I^{GM}(x, y)$
07. **end if**
08. **end for**
09. **end for**

Image Contrast Enhancement

Contrast enhancement is widely used in medical image processing and as a pre-processing step in image segmentation and other image processing applications. A contrast enhancement algorithm that can enhance the contrast of a noisy renogram without noise amplification is necessary for our approach. Jen et al. proposed a straightforward approach for edge enhancement based on intensity-pair

distribution that possesses both the local and global information of the image content [27]. 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 attain an intensity mapping function, which suppresses image noise and stretches the contrast of edge areas in the output image. We adopted this algorithm to enhance the noisy renogram. The procedure of this contrast enhancement algorithm is briefly described as follows.

For a given image, each pixel is checked with its 8-connected neighbors. Due to the commutative property of intensity pairs, we only check four neighboring pixels rather than eight; and we only check the intensity difference between that pixel and its upper-left pixel, upper pixel, upper-right pixel, and left pixel. After calculating intensity differences, if the intensity difference of an intensity pair is larger than a predefined threshold level, we treat that pair as an edge pair, and a corresponding train of EF is generated. Otherwise, a train of AFE is generated. The result can be shown in the upper-left part of Fig. 4.

For a noisy renogram, as we enhance image contrast, image noise is also enhanced. If we can distinguish the intensity levels belonging to smooth regions from the intensity levels of edge regions, we can enhance edge regions but not flat regions. The concept of net expansion force (NEF) is proposed to suppress noise enhancement. The NEF is obtained by the following formula:

$$NEF[h] = EF[h] - g \times AEF[h] \quad (4)$$

where $0 \leq h \leq 255$ and g are a parameter that controls the magnitude of anti-expansion. In this approach, g was

Fig. 4 Procedure for generating the intensity mapping function

selected to be 0.1 empirically. If the NEF at h is less than zero, that value is reset to zero. The calculation result of NEF is shown in the upper-middle part of Fig. 4.

To reduce the dynamic range of the NEF, a magnitude mapping function $M(\cdot)$ is applied to constrain the expansion force to an extent such that a better enhancement result can be obtained. The magnitude mapping function is defined as:

$$Y = M(K) = K^{1/m} \quad (5)$$

where K is the NEF, Y is the adjusted NEF, and m is the behavior controlling parameter. Then, the modified NEFs are then integrated to obtain the expansion function (upper-right part of Fig. 4). This expansion function is added to the original mapping function to pull up the mapping function, as shown in the lower-right of Fig. 4. Then the adjusted mapping function is normalized to fit into the full gray level range of 0~255.

Finally, the intensity mapping function (IMF) is obtained by calculating the weighted sum of the original mapping function (OMF, slope=1) and the normalized expansion function (NMEF) and can be shown as:

$$\text{IMF} = a \times \text{NMEF} + (1 - a) \times \text{OMF} \quad (6)$$

where a is the combination parameter ($0 \leq a \leq 1$). The lower-left part of Fig. 4 shows the final intensity mapping function. Using the final intensity mapping function to modify the intensity of the kidney scintigram for contrast enhancement, the enhancement result is shown in Fig. 5b, denoted as I^{ENH} .

Image Segmentation

Yeh et al. successfully extracted a significant breast lesion from an ultrasound scan by an adaptive thresholding algorithm [28]. Since segmentation of kidney delineation is difficult when applying a fixed threshold level to a renogram. In the proposed approach, we adopted the adaptive thresholding algorithm to extract the rough kidney area from image I^{ENH} . The adaptive thresholding algorithm can be summarized as follows.

The ratio of mean gray level within the whole renogram 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 kidney area, and then the threshold level should be assigned to a lower value. Since the ratio can be served as an index to distinguish the characteristic of each ROI within the whole renogram, it can be used as a weighting factor for adjusting the threshold value.

Figure 5c shows the cumulative distribution function (CDF) of three manually drawn ROIs [black square boxes

in Fig. 5b] with the size of 8×8 indicating the kidney area (ROI 1), kidney edge (ROI 2), and background (ROI 3) regions, respectively. As shown in Fig. 5c, the rate of CDF increase for the background region is greater than that either the kidney edge or kidney area.

A threshold value is fundamental for roughly separating background, kidney edge, and kidney area three regions. 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 this approach, the threshold value was obtained by analyzing a series data from 40 patients. The training group was independent from the testing group (30 patients). For the results presented here, we determined a threshold value as the product of the gray level of 40% corresponding CDF and the weighting factor. The quantities of CDF and weighting factor are uncorrelated. In Fig. 5c, the threshold levels of the three selected ROIs are 57, 76, and 112, respectively. The pixels within the ROI below the threshold level are assigned to zero (background). The adaptive thresholding procedure is executed until the entire image is converted into a binary image. In order to obtain a completely binary image from the original one, the process arrays multiple ROIs to cover the entire image. ROIs with the size of 8×8 pixels were arrayed adjacent to each other with overlap of 56 pixels. Figure 5d shows the thresholding result (I^{SEG}).

Following the thresholding procedure, the float-fill components labeling algorithm was adopted again to identify object regions in I^{SEG} . After processing, the object regions were identified, and if the pixel number of one object was less than a pre-selected value, that object was removed from image I^{SEG} . Then, the most significant kidney region was extracted.

Morphological operations of dilation and erosion were then applied to the significant kidney area. We performed dilation followed by erosion three times on the image to eliminate small holes.

Due to the noise, it is possible that some pixels were misclassified. Image $I^{\text{ENH}}[S(x,y)]$ was involved in this stage to refine the extracted area (I^{SEG}). We computed the mean object's gray value $\text{gm}_{\text{kidney}}$ as follows:

$$\text{gm}_{\text{kidney}} = \frac{1}{N_g} \left[\sum_{\forall (x,y) \in I^{\text{SEG}}} S(x,y) \right] \quad (7)$$

where N_g represents the total number of non-zero pixels in I^{SEG} . Further, since the zero gray level pixels in image I^{SEG} may belong to the kidney area, and some non-zero pixels may belong to the non-kidney area, we dilated five times for the kidney region in I^{SEG} to obtain the outer band region of I^{BAND} in Fig. 5(e), which does not include the kidney area in image I^{SEG} . Because most of the pixels in image

Fig. 5 After removing the unnecessary regions in image I^{GM} , the image I^{RM} **a** is obtained. **b** Result of image contrast enhancement (I^{ENH}). Three ROIs representing the kidney (ROI 1), kidney edge (ROI 2), and background (ROI 3) regions, respectively. **c** CDF rising rate of background is larger than that of either the kidney edge or kidney region. **d** Adaptive thresholding result (I^{SEG}). **e** Outer band region (I^{BAND})

$I^{BAND}[B(x,y)]$ are background pixels, we calculate the mean background's gray level by following equation:

$$gm_{bkg} = \frac{1}{N_h} \left[\sum_{\forall (x,y) \in I^{BAND}} B(x,y) \right] \quad (8)$$

where N_h represents the total number of non-zero pixels in image I^{BAND} . Based on gm_{kidney} and gm_{bkg} , for the gray image I^{ENH} , we scanned all non-zero pixels in the area of $I^{SEG} \cup I^{BAND}[A(x,y)]$. If the gray level of a pixel is near gm_{kidney} , we classified it as an object pixel, otherwise, as a background pixel. The region of the refined object was

denoted as I^{REF} and can be formulated by the following expression:

$$I^{REF}(x, y) = \begin{cases} 1 & \text{if } (x, y) \in I^{SEG} \cup I^{BAND} \text{ and} \\ & |A(x, y) - gm_{kidney}| < |A(x, y) - gm_{bkg}| \\ 0 & \text{otherwise} \end{cases} \quad (9)$$

where “1” denotes the region of the final kidneys region and “0” denotes the background. Then, the dilation and erosion operations were performed after obtaining I^{REF} in order to eliminate some small holes. Figure 6c and f shows the finally segmented kidneys, where the kidney contour is plotted with a white curve on image I^{COM} .

Fig. 6 **a** ROIs of the patient (patient no. 10) with normal renal function using the single-threshold method with a 30% threshold. **b** ROIs of the same subject using the double-threshold method with 60% and 30% thresholds. **c** ROIs of the same subject using our proposed approach. **d** ROIs of the patient (patient no. 14) with renal failure function using the single-threshold method with a 30 % threshold. **e** ROIs of the same subject using the double-threshold method with 60% and 30% thresholds. **f** ROIs of the same subject using the proposed approach

Fig. 7 User interface of our program. A demonstration can be found at http://yschen.ee.yzu.edu.tw/Academic/CVLab/demo_GFR.asp

Results

In order to evaluate the proposed algorithm in this approach, we implemented a program constructed using C++ Builder 6.0 Enterprise Suite (Boarland, Austin, TX). The current system includes pre-processing, image contrast enhancement, segmentation, and morphology operations. Figure 7 shows the user interface of our program. A demonstration can be found at http://yschen.ee.yzu.edu.tw/Academic/CVLab/demo_GFR.asp.

To evaluate the accuracy of our approach, we quantitatively compared the automated delineations with the manual delineations obtained by two nuclear medicine physicians. The first determination for ROI selection evaluation is to find a parameter to be compared. Parameters derived from the boundaries, such as the perimeter or the area enclosed, may be compared or the boundaries themselves may be compared directly. The parameters derived either from the boundary or the area enclosed are usually application dependent, and often the accuracy of measuring these parameters is the functional goal of image segmentation [29]. Therefore, the manual delineation from two experienced nuclear medicine physicians was considered as the “gold standard.” The boundary error and estimation area error between two gold standard and the delineations obtained by our approach were used for further evaluation.

The boundary error is defined as the mean shortest distance between the manual contour and our approach’s delineation. We denote the manual contour boundary as $M = \{m_1, m_2, \dots, m_n\}$ and the boundary obtained by our approach as $P = \{p_1, p_2, \dots, p_n\}$, where each element of M or P is a point on the corresponding contour. We calculate the distance of every point in P from all points in M , and

define the distance to the closet point for $p_k (\forall p_k \in P)$ to the contour M as

$$d(p_k, M) = \min_h \|p_k - m_h\| \quad (10)$$

where $\| \cdot \|$ is the 2-D Euclidean distance between any two points. Then, all d values are calculated to obtain the statistics of maximum, mean, minimum values.

The area error is depicted by the three parameters including true positive (TP), false positive (FP), and false negative (FN). They are defined as follows:

$$TP(\%) = \frac{|A_m \cap A_p|}{|A_m|} \quad (11)$$

$$FP(\%) = \frac{|A_m \cup A_p - A_m|}{|A_m|} \quad (12)$$

$$FN(\%) = \frac{|A_m \cup A_p - A_p|}{|A_m|} \quad (13)$$

where A_m refers to the area of the kidney as estimated by physician’s manual ROI drawing, and A_p is the area of the kidney determined by our approach. TP describes the fraction of the total amount of pixel in A_m with which the A_p overlaps. FP denotes the amount of pixel falsely identified by our approach as a fraction of the total amount of pixel in A_m . FN indicates the fraction of pixel defined in A_m that was missed by our approach. The three parameters were used to obtain the difference between the contour obtained by our approach and the gold standard as shown in Fig. 8.

Fig. 8 Illustration of the error parameters including TP region (oblique lines), FN region (vertical lines), and FP region (horizontal lines)

Two experienced physicians were invited to manually draw the kidney boundaries in 54 kidneys, and then the results were compared with the proposed approach. Statistical analyses between detected contours by our approach and the two physicians' manual delineations are shown in Fig. 9. The symbols "A" and "B" on the lateral

axis depict the physicians order. There were 54 independent estimates of TP , FP , FN , and shortest distance in each physician's manual delineations. Table 1 shows the patient information and the evaluation results of our approach with two physicians'. There are high correlations between two physicians' manual contours and the contours obtained by our method. The mean TP area is 91%. The mean FN is 13.4% and the mean FP is 9.3%. The mean shortest distance error between two physicians' manual delineations and contours obtained by our approach is 1.6 pixels. The standard deviation and maximum value results are 0.5 and 4.5 pixels, respectively.

Discussion

GFR can be obtained from measurement of activity in single or multiple blood samples, from the rate of removal of activity from blood or tissue, from the rate of appearance of tracer in urine, and from the rate of renal tracer uptake [30]. Camera-based methods to measure GFR are simple and suitable for clinical use. Among these methods, the Gates' method [10–12] has been widely used since 1982 in nuclear medicine facility because it is very convenient and simple to estimate the GFR of any individual kidney function as well as global renal functions [31].

Fig. 9 Statistical analyses between two physicians' manual contours and detected delineations by our proposed approach are shown in: **a** TP, **b** FN, **c** FP, and **d** shortest distance estimates and their standard deviations

Table 1 Patient information and evaluation results of true positive (TP), false positive (FP), false negative (FN), and shortest distance (SD) for two physicians (P1, P2) versus our approach.

Patient no.	Age (years)	Sex	BUN (mg/dL)	Kidney side	TP (%)		FP (%)		FN (%)		SD (Pixel)	
					P 1	P 2	P 1	P 2	P 1	P 2	P 1	P 2
1	47	M	17.2	Right	82.9	96.7	1.7	11.3	17.1	4.2	1.97	1.76
				Left	87.7	90.3	0.5	7.3	12.3	28.8	1.17	1.28
2	18	F	16.8	Right	88.6	92.5	1.9	2.3	7.5	7.5	1.64	0.98
				Left	93.8	95.9	3.9	6.1	10.1	24.1	1.3	1.68
3	48	F	15.6	Right	91.4	94.7	6.6	24	5.3	5.3	1.07	1.28
				Left	93.4	98.5	1.2	24.6	9.9	1.5	0.59	1.62
4	70	F	85.7	Right	82.7	94	3.6	8.1	6	6	1.4	0.76
				Left	82.5	97.8	4.8	14.1	28.8	2.2	1.64	1.48
5	79	F	56.7	Right	0	0	0	0	0	0	0	0
				Left	88.7	87.8	5.2	29.5	11.3	12.2	1.5	2.9
6	75	F	54	Right	89.7	94.1	7.9	10	7.9	5.3	1.66	1.43
				Left	81.1	95.3	4.3	11.2	21.3	5.3	1.44	1.01
7	53	M	20.3	Right	90.6	90.9	4	19.8	9.1	9.1	1.75	1.22
				Left	88.2	91.5	9.8	26	12.1	8.5	0.31	2.24
8	86	M	21.2	Right	95.5	92.4	6.8	10	4.5	6.5	1.32	1.3
				Left	96.9	98.8	7.6	6.6	3.1	2.3	0.71	0.8
9	28	F	10.9	Right	97.9	96.3	7.7	20.3	2.1	4.6	0.71	1.74
				Left	0	0	0	0	0	0	0	0
10	59	M	19.8	Right	97.3	98.1	5.6	10	2.7	1	0.89	1.12
				Left	97.5	98.9	10.2	11.2	2.5	2	0.63	0.82
11	62	F	43.8	Right	87.2	84.8	8.2	8.9	12.8	15.2	1.39	1.71
				Left	0	0	0	0	0	0	0	0
12	53	M	20.7	Right	91.7	91.5	12.1	8	6.4	8.5	0.76	0.87
				Left	99.1	96.9	9.5	5.8	2.8	3.1	1.48	1.25
13	33	F	12.2	Right	0	0	0	0	0	0	0	0
				Left	96.9	94.6	11.3	3.8	3.1	5.4	1.07	0.99
14	78	F	140.9	Right	87.7	84.2	18.5	18.7	12.3	15.8	2.12	2.79
				Left	79.7	88.2	5.3	29.9	20.3	11.8	1.7	2.41
15	38	F	12.8	Right	90.8	90.9	19.1	18.6	9.2	9.1	0.83	0.93
				Left	91.8	97.1	9.3	2	8.2	2.9	2.15	1.45
16	81	F	112.3	Right	91.2	92.1	17.8	9.8	9.8	7.9	1.87	1.88
				Left	80	94.7	10.8	28	19	4.9	2.13	1.52
17	43	F	3.4	Right	98	94.7	10.7	5.1	4.1	11.6	1.33	1.36
				Left	94.4	85.3	18.1	1.9	3.5	8.4	0.97	0.8
18	75	F	130.4	Right	83.1	86.8	14.1	24.1	16.9	13.2	3.72	2.33
				Left	75.3	93.8	15.7	9.7	24.7	6.2	1.04	2.53
19	25	F	9.4	Right	97.2	96.6	12.3	15.3	1.4	3.4	0.77	1.06
				Left	98.4	98	20.9	19.5	3	2	1.57	1.6
20	36	M	29.1	Right	98.6	99.5	19.2	29.5	3.4	0.5	2.34	1.75
				Left	92.4	97.7	14.2	10.3	5.6	2.3	0.96	2.25
21	48	M	13.4	Right	96.4	96.3	21.6	27.3	3.2	3.1	2.11	1.62
				Left	98	98.7	12.2	15.9	2.4	1.9	0.33	1.52
22	22	M	14.6	Right	98.9	92.1	22.4	10.3	1.8	7.9	0.88	1.07
				Left	94.7	97.5	12	8.1	4.6	2.5	1.92	1.37
23	80	M	32.7	Right	87.5	89.9	20.1	25.1	8.7	10.1	1.81	2.02
				Left	99.3	97.5	15.1	15.5	4.5	2.5	1.29	1.52

Table 1 (continued)

Patient no.	Age (years)	Sex	BUN (mg/dL)	Kidney side	TP (%)		FP (%)		FN (%)		SD (Pixel)	
					P 1	P 2	P 1	P 2	P 1	P 2	P 1	P 2
24	78	M	44.2	Right	84.2	88.1	21	10.2	17.9	10.2	2.54	2.73
				Left	82.6	89.9	15.6	16.2	15.3	11.8	1.86	2.67
25	85	F	97.3	Right	83.3	87.3	17.4	17.4	16.7	13.3	2.52	2.14
				Left	73.3	86.1	21	23.8	26.7	13.3	2.28	2.46
26	56	F	18.7	Right	92.1	88.4	24.1	24.1	7.9	11.6	1.67	2.12
				Left	95.7	99.6	18.1	14.1	4.3	0.4	1.89	1.76
27	82	M	83.1	Right	82.1	84.8	23.1	12.4	21.9	9.7	2.65	2.21
				Left	80.1	91.2	17.1	15.2	15.9	14.3	1.95	1.99
28	66	F	136.7	Right	79.6	83.2	17.5	15.2	15.4	22.6	1.57	1.74
				Left	81.2	78.8	12.9	9	23.8	15.4	2.23	1.46
29	45	F	120.6	Right	81.5	86.5	16.9	17.7	20.1	10.2	1.75	2.37
				Left	77.1	87.5	19.7	18.1	21.3	15.8	2.05	2.09

BUN blood urea nitrogen

The assignment of the kidney ROIs is a critical factor for GFR estimation. With the single-threshold method, it is difficult to delineate the kidney area even in normal subject (Fig. 6a) because of poor contrast between the kidney and the background. Detectability of the kidney region depends on the fixed threshold value. If the threshold value is set lower to get slightly larger ROIs, detectability is reduced. For the same reason of poor contrast between the kidney and the background, the edge detection based method [15–17] cannot perform well to find the edge information delineating the kidney and the background. The dual-threshold method performs well in normal subjects (Fig. 6b) but poorly in the patient with renal failure function (Fig. 6e) [14]. This method adopts two morphology kernels to break the one pixel continuity between the kidney and the background, if the continuity is more than one pixel; it fails to separate the kidney and the background.

In the study by Inoue et al. [18], an operator manually placed a large rectangular ROI over each kidney, a circular ROI within the liver, and a rectangular ROI between the kidneys. According to these ROIs, semi-automated renal ROIs are located on the basis of the temporal changes in counts. Adopting the temporal information is valid to break the continuity between the kidney and the background, but it is tedious for too many manual ROI assignments. In addition, manual ROI drawing can cause artificial intra- and inter-operator variations. In this approach, we use the temporal information and a set of digital image processing techniques to avoid the drawbacks of manual ROI drawing and the threshold methods [14, 18].

For better delineation of kidney contour, we subtract 160–180 s dynamic image from 60–80 s dynamic image to eliminate unwanted background radioactivity within

the overlapping regions such as liver, spleen, heart, and great vessels. The time period selected for background and kidneys were 60–80 and 160–180 s, respectively, from the data of healthy controls [24, 25]. This raises the concern that whether the time period was suitable for other patient groups especially those with impaired renal function. From our results, all subjects showed higher count rates in the liver, spleen, heart, and great vessels regions from 60–80 s dynamic image as compared to 160–180 s image. In contrast, higher count rates at kidney region can be found from 160–180 s image as compared to 60–80 s image even in renal function impaired subjects. Although the highest kidney count rates may not take place 3 to 4 min post injection [24], the count rates differences of the main background region (liver, spleen, heart, and great vessels) and kidneys in the two images enables us to eliminate the unwanted background as shown in our results (Fig. 6d–f).

We consider that the automatic computer-aided kidney ROIs selection in GFR measurement from ^{99m}Tc -DTPA renogram promises better consistency in GFR estimation for either normal or abnormal conditions. Though our proposed approach has several adjustable parameters, which were obtained from a training group (40 patients), this approach provides another practicable direction for delineating the kidney ROIs. Method to reduce the number of adjustable parameters is a good topic for further research.

Conclusion

This study developed a process for fully automatic kidney ROI selection in GFR value estimation from

renograms. The results of kidney ROI selection from our approach correlated well with manual results from two physicians since the mean *TP* overlap between manual contours and contours obtained by the proposed approach is over 90%, and the mean shortest distance is 1.6 pixels. This program saves considerable manpower and time achieving the initial goals of fully automatic processing with high specificity and sensitivity. It provides better renal detectability, and the GRF value obtained using this approach is reproducible and acceptable in routine clinical practice. This novel approach improved ROI generation by utilizing the image information at 60–80- and 160–180-s time periods. This may be useful for the delineation of complicated organs from dynamic studies such as hepatobiliary scintigraphy.

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