99mTc-Sulfur colloid single photon emission computed tomography for assessment of liver function

Y Dwihapsari1*, M Evalisa2 and F Nazir3*

1Physics Department, Institut Teknologi Sepuluh Nopember (ITS), Surabaya, Indonesia 60111
2Department of Nuclear Medicine, Center for Technology of Radiation Safety & Metrology – National Nuclear Energy Agency of Indonesia (PTKMR – BATAN), Jakarta, Indonesia

yanuritadh@physics.its.ac.id, evalisafadil@gmail.com

Abstract. The assessment of liver function is essential in diagnosis and assessment of therapy of liver diseases. Single-photon emission computed tomography (SPECT) gamma camera allows the assessment of liver function and measurement of functional liver volume. Several studies reported SPECT imaging of liver using some radiotracers, such as 99mTc-GSA and 99mTc-mebrofenin. In this study, liver function was observed using 99mTc-labelled sulfur colloid SPECT imaging. 99mTc-labelled sulfur colloid was administered intravenously and scanned using SPECT in 24 volunteers. Images were then processed to obtain liver and spleen uptake. The segmented images were processed to obtain liver/spleen uptake and left lobe/right lobe uptake in the liver to assess the liver function of volunteers. The result showed that 99mTc-sulfur colloid could give description on liver function and showed significant difference between normal and abnormal volunteers.

1. Introduction
Liver disease is one of major health problem in Indonesia [1]. The understanding of disease mechanism and change of liver function due to disease is essential to observe the best optimum treatment. The assessment of liver function is important for observation of several functionality of liver such as synthetic function, obstructed biliary excretion and live cell injury. The clinical scoring system such as Child-Pugh [2] and model for end-stage liver disease (MELD) [3] scoring system were generally performed to measure liver function [4]. The result from scoring system usually does not represent biochemical produced purely in the liver. In other cases, the result is affected by other conditions or other functions which contributes to miscalculation of the exact liver functionality. Indocyanine green (ICG) clearance test [5] and galactose elimination capacity [6] are some general tests for quantitative liver function. In some cases, these techniques do not represent underlying liver disease and measure global liver function without considering regional variation.

The quantitative liver test was also performed using modalities such asComputed Tomography (CT) volumetry [7] which can give information on liver volume and showed abnormalities in the presence of malignancies. Although CT volumetry can image liver function real-time, it cannot distinguish between functional and non-functional liver tissues. The nuclear medicine instruments such as single photon emission computed tomography (SPECT) gamma camera can give information on image liver uptake of radiopharmaceutical injected and give quantitative result and its variation in different part of liver. The other advantages of SPECT gamma camera are its ability to predict...
progression of liver diseases [8] and postoperative complication in liver surgery [9]. The combination of SPECT gamma camera and CT even provide more visual information with 3-dimensional image of segmental liver function and liver functional volume [10-11].

SPECT gamma camera uses radioisotopes which are labelled using a specific labelling agent inside subjects and the emission from gamma rays is captured by gamma camera. Some previous studies used $^{123}$I and $^{131}$I radioisotopes for liver function scanning [12-13]. Due to toxicity level of $^{131}$I inside liver, $^{99m}$Tc is more widely used in the study of liver function. $^{99m}$Tc-labeled diethylene triamine penta-acetic acid ($^{99m}$Tc-DTPA) [14] for galactosyl human serum albumin (GSA) scintigraphy and $^{99m}$Tc-labeled iminodiacetic acid (IDA) [15] for hepatobiliary scintigraphy (HBS) are some examples of techniques in SPECT gamma camera to observe liver function. The other studies used $^{99m}$Tc-Mebrofenin for hepatobiliary scintigraphy and $^{99m}$Tc-sulfur colloid ($^{99m}$Tc-SC) for measurement of liver uptake [10].

The liver uptake was generally obtained by planar static imaging and liver function was assessed by SPECT imaging. Several quantitative methods had been proposed for obtaining liver function [8, 16-17]. The results, however, were varied across studies. In this study, liver function was observed using $^{99m}$Tc-SC SPECT imaging in 24 volunteers who participated in double-blinded studies by having signed informed consent. $^{99m}$Tc SC was injected intravenously to subjects and liver function was assessed by defining region-of-interest of liver and spleen. The segmented images were processed to obtain liver/spleen uptake and left/right lobe uptake of the liver.

2. Materials and Methods
The subjects of this study consisted of 24 volunteers with ages ranged from 43 to 59 years old. The volunteers previously underwent medical check to obtain several medical questions, physical examination including measurements of body weight, height, pulse, temperature, blood pressure and the size of the abdominal circumference. $^{99m}$Tc-Sulfur Colloid ($^{99m}$Tc-SC) for SPECT imaging was obtained by mixing $^{99m}$Tc and pharmaceutical cold kit substance containing sodium thiosulfate in acidic media and heated at 95-100°C for 5-10 minutes inside waterbath. The pH of mixture was set to pH 6-7 with added buffer solution. Pharmacokinetically $^{99m}$Tc-SC consisted of mixture composition of thiosulfate and acid. Gelatin was used as guard colloid and ethylene diamine tetra acetic acid (EDTA) was used to eliminate the presence of aluminium ions in the $^{99m}$Tc eluate. The particle size of this mixture varied from 0.1 - 1 μm with an average of 0.3 μm. The size to be distributed varied depending on the pharmaceutical cold kit and the preparation.

The activity of radiopharmaceutical $^{99m}$Tc-SC was counted and the background activity of radiopharmaceutical inside syringe was counted using dose calibrator. The measurement was performed in the syringe enumerated using a dose calibrator which has been subtracted from the count background before being administered intravenously on each subject. Static liver scintigraphy was performed using dual-head SPECT AnyScan-S gamma camera (Mediso, Hungary) with a low-energy high-resolution (LEHR) collimator which was positioned in the liver and spleen area in the front and back of each subject. Static planar images were taken 30 minutes after injection of radiopharmaceutical to obtain anterior, posterior, left and right lateral and oblique images of liver and spleen respectively.

SPECT imaging was performed in anterior and posterior projections with 128 x 128 matrix in a 3-degree angle of sampling with total of 60 images were produced. Images were processed using built-in Interview XP software (Mediso, Hungary). The region-of-interest (ROI) technique was performed around the left and right lobes of liver and spleen with the total field-of-view. A fraction of liver and spleen from whole-body total count was calculated to obtain liver and spleen uptake. Uptake ratio of liver/spleen and left/right lobe in the liver were processed to estimate SC distribution and obtain the liver function values of volunteers.

The correlation between injected dose and the uptake values was obtained using Pearson correlation to obtain Pearson correlation coefficient (r). The correlation coefficient (r) ranges between -1 and 1, where r = 0 indicates no correlation, while r = 1 and r = –1 show the highest positive and
negative correlation. In this experiment, the correlation was observed between injected dose and several values from SPECT scanning, such as liver uptake, spleen uptake, liver/spleen uptake and left lobe/right lobe uptake in liver.

3. Results and Discussion

The sulfur colloid labelled with $^{99m}$Tc radioactive decayed and emitted electromagnetic radiation as it was injected into the body. The radiation which had high penetrating power was partly absorbed by organs as it passed through some organs inside the body before it was detected by the detector system in SPECT gamma camera. The computer program converted the radiation profile from detector system into images which described the distribution of radioactive compound inside the body. The distribution of radioactive compound inside the body depended on several factors, such as the physiology, pathophysiology, morphology and density of organ at particular sites, functional status of organs and the level of metabolism in some tissues. The previous studies showed that colloidal particles inside $^{99m}$Tc-SC were 80% phagocytised by the Kupffer cells of the liver, 5 to 10% by the spleen and the rest by the bone marrow [11]. In case of liver pathologies, the distribution of colloid inside the body changed due to changes in morphology, functional status, pathological process and level of metabolism.

In this experiment, the body weight of 24 volunteers ranged between 49 and 78 kgs and the height ranged between 143 and 174 cm. Eleven volunteers were considered normal according to routine medical checkup before SPECT scanning and used as a control group. The administered dose ranged from 3 – 6 mCi and the doses outside the range were excluded from this study. The mean dose delivered was 3.61 ± 0.57 mCi for control group and 4.36 ± 1.12 mCi for other groups. Anterior coronal cut of the liver and spleen after SPECT image segmentation to obtain the ratio of uptake of the left/right lobe of the liver and liver/spleen were given in Figure 1. From the anterior appearance, it was shown that $^{99m}$Tc-SC was concentrated in the liver and spleen and showed the distribution and function of the endoplasmic reticulum (RES) and possible malignancies involving RES when followed by a picture of a non-smooth surface of the liver. Radiolabel taken by RES gave information on the whole liver function and showed good correlation with liver function [18].

![Figure 1](image1.png)

**Figure 1.** The coronal anterior view of liver and spleen after segmentation of an SPECT image to obtain uptake ratio of liver/spleen and left/right lobe of liver: a. normal volunteer, b. volunteer with liver cirrhosis, and c. volunteer with other pathologies.

The control group of normal volunteers were determined by shape and position of right and left lobes and considering medical check-up result before SPECT experiments. The uptake of $^{99m}$Tc-SC from 9 normal volunteers in this study was 3.85 ± 0.53 g/ml (range 2.99 - 4.58 g/ml) in liver and 0.74
± 0.22 g/ml (range 0.43 - 1.08 g/ml) in spleen, respectively. No significant correlation was found between dose injected and spleen counts ($r = -0.16$) although the significant correlation was found between dose injected and liver counts ($r = 0.48$).

The result of our experiment was consistent with result from other studies which found changes of injected dose in liver but no changes of dose in spleen in SPECT imaging [16-17]. The result showed that $^{99m}$Tc-SC radiolabel was mostly accumulated in liver. The accumulated dose in spleen could not be figured totally which might be caused by radiolabel clearance from liver which was not fully absorbed by spleen, but distributed to other organs, such as jejunum and ileum. In addition, scanning time of 30 minutes was probably not enough for radiolabel to be completely absorbed by spleen after liver clearance.

The insignificant correlation was found in uptake ratio of liver/spleen ($r = 0.11$) in normal volunteers as shown in Figure 2.a and related with the result obtained in liver and spleen. The liver/spleen ratio was related to spleen volume and this method could not be used as a comparative method among volunteers due to different volume of spleen in volunteers. However, this method might be useful as an individual method to assess disease progression [19]. The correlation between dose and uptake ratio of left lobe/right lobe in liver in normal volunteers showed significant correlation to $^{99m}$Tc-SC dose ($r = 0.81$) which showed the consistency of dose intake in liver where the uptake of right lobe was higher compared to uptake of left lobe in liver (Figure 2.b).

![Figure 2](image.jpg)

Figure 2. The correlation between injected dose and uptake of normal volunteers: a. liver/spleen uptake ratio and b. left/right lobe of liver uptake ratio.

The same procedures were performed to thirteen abnormal volunteers which consisted of 4 volunteers with liver cirrhosis and 9 volunteers with other pathologies. In volunteers with liver cirrhosis, there was highly significant correlation of liver/spleen uptake to dose injected ($r = 0.98$). The moderate significant correlation was also found in left/right lobe uptake. The results showed that liver/spleen uptake was correlated with distribution of $^{99m}$Tc-SC and could be used to assess liver function and disease progression in liver cirrhosis subjects [8, 16].

The moderate significant correlation was also found in left/right lobe uptake in liver in volunteers with other pathologies. The result was consistent with the result of normal volunteers and volunteers with liver cirrhosis where the uptake of right lobe was higher compared to uptake of left lobe in liver. The significant correlation of liver/spleen uptake, however, was not found in volunteers with other pathologies. It showed that liver/spleen uptake could not provide information on liver function in volunteers with other pathologies as found in normal volunteers. Other medical examinations were needed to obtain information on the pathologies and more accurate assessment of liver function.
4. Conclusion
The assessment using $^{99m}$Tc-sulfur colloid could give description on liver function and showed significant difference between normal and liver cirrhosis volunteers. The uptake of left/right lobe of liver was correlated with dose injection in all volunteers and showed the higher uptake of right lobe compared to left lobe in liver. The liver/spleen uptake was proven to be an important tool for assessment of liver function in liver cirrhosis volunteers.

5. References
[1] Ministry of Health Republic of Indonesia 2018 *Indonesia Health Profile 2017* Jakarta 172
[2] Nagashima I, Takada T, Okinaga K, Nagawa H 2005 *J Hepatobiliary Pancreat Surg* **12** 44
[3] Kamath PS, Kim WR 2007 *Hepatology* **45** 797
[4] Bennink RJ 2012 *Semin Nucl Med* **42** 124
[5] Paumgartner G 1975 *Schweiz Med Wochenschr.* **105** 1
[6] Redaelli CA, Dufour JF, Wagner M, et al. 2002 *Ann Surg* **235** 77
[7] Akaki S, Okumura Y, Sasai N, et al. 2003 *Ann Nucl Med* **17** 23
[8] Zuckerman E, Lobodin G, Sabo E, et al 2003 *J Hepatol* **39** 326
[9] Takeuchi S, Nakano H, Kim YK, et al 1999 *Hepatogastroenterology* **46** 1855
[10] de Graaf W et al 2010 *J Nucl Med* **51** 742
[11] Matesan MN, Bowen SR, Chapman TR, et al 2017 *Nucl Med Comm* **38** 577
[12] Du Y, Tsui BM, Frey EC 2006 *Phys Med Biol* **51** 1269
[13] Dewaraja YK, Wilderman SJ, Koral KF, Kaminski MS, Avram AM 2009 *Cancer Biother Radiopharm* **24** 417
[14] Onodera Y, Takahashi K, Togashi T, et al 2003 *Ann Nucl Med* **17** 181
[15] Loberg MD, Cooper M, Harvey E, et al 1976 *J Nucl Med* **17** 633
[16] Groshar D, Slobodin G, Zuckerman E 2002 *J Nucl Med* **43** 312
[17] Hoefs JC, Sheikh MY, Guerrero H, Milne N 2005 *Dig Dis Sci* **50** 283
[18] Hoefs JC, Wang F, Kanel G 1997 *Am J Gastroenterol* **92** 2054
[19] Hoefs JC, Wang FW, Lilien DL, Walker B, Kanel G 1999 *J Nucl Med* **40** 1745

Acknowledgments
Kementerian Riset Teknologi dan Pendidikan Tinggi (Kemenristekdikti) and Institut Teknologi Sepuluh Nopember (ITS) are highly acknowledged for support of Research Grant.