Original Article

Software development for hepatopulmonary shunt estimation by gamma camera method in transarterial radioembolization

ABSTRACT

Trans-arterial radioembolization (TARE) is an established treatment for inoperable hepatocellular carcinoma and liver metastases from Carcinoma of gastrointestinal tract. Radiation-induced toxicity to the lung parenchyma is the dose-limiting factor in TARE. Pretreatment hepatopulmonary shunt (HPS) is estimated by gamma camera method by transarterial administration of 370MBq ^{99m}Tc macro aggregated albumin. We have developed HPS software on XELERIS-1.123 workstation, GE medical systems, Milwaukee, USA, for accurate calculation of HPS. This software has also been tested on a higher version of XELERIS workstation, and it has been found to work well in all versions.

Keywords: Hepatopulmonary shunt, transarterial radioembolization, Y-90 microspheres

INTRODUCTION

Transarterial radioembolization (TARE) using Y-90 labeled microspheres is an established treatment modality for primary as well as secondary hepatic malignant tumor.[1-5] There are two Food and Drug Authority, USA, approved commercial ^{90}Y-microsphere products are available in the market, i.e., ^{90}Y-SIRSphere by SIRTEX, Sydney, Australia, and ^{90}Y-TheraSphere by MDS Nordion, Ottawa, Canada.[6,7] TARE requires multidisciplinary therapeutic approach, to circumvent the therapy-related complications. To minimize the TARE-related complications, mapping of microsphere distribution becomes very important along with super selective delivery of microsphere. [99m]Tc macro aggregated albumin (^{99m}Tc-MAA) is used as surrogate to map the post-therapeutic microsphere distribution in hepatic tumor, normal liver, shunt in lung, and any other abnormal distribution such as in stomach, duodenum, and gallbladder. Usually, for planning the treatment, a planar and single-photon emission computed tomography (SPECT) studies are performed on gamma camera after transarterial infusion of ^{99m}Tc-MAA in intervention radiology.[8-10] Extra hepatic uptake of tracer can be seen either in stomach,

gallbladder, and duodenum due to collateral arterial supply from hepatic artery or in lung due to arteriovenous shunt in tumour resulting to hepatopulmonary shunt (HPS).[11] Uptake in stomach and duodenum can be prevented by super selective delivery of microsphere and coiling the collateral artery which supplies to these organs.[6-8] HPS results in radiation dose to the lung and there is no way either to reduce the unwarranted exposure or prevent it. Hence, HPS is a limiting factor in therapeutic dose calculation in TARE. A radiation dose of more than 30 Gy in single setting and 50 Gy in a life time to the lung is a contraindication to carry

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out the therapeutic procedure because it causes irreversible radiation-induced injury to the lung. More than 20% HPS value requires dose modification and above 30% HPS, TARE cannot be performed.[12-15] Hence, accurate evaluation of HPS is of utmost importance to avoid complications.[9,10] HPS evaluation is performed using planar or SPECT study. We have developed software for HPS estimation using planar gamma camera imaging and evaluated it.

MATERIALS AND METHODS

Software development
HPS Software has been developed using Aladdin editor on Xeleris-1.1234 workstation, GE medical systems, Milwaukee, USA.

Software design
This Software has two main divisions, left panel [Figure 1A] and right container [Figure 1B]. The left panel contains two buttons-Main button and HPS button [Figure 1A1], and three panels – color panel, zoom panel, and text panel [Figure 1A2], right container is divided into two columns and three rows making a total of six image cells. Upper two rows (i.e., 4 image cells) of image container are used to load images, and third row is used to display results. In

first row anterior and posterior images of thorax including lung and liver of patient with Co-57 phantom (SET-1) are loaded [Figure 1B1 and 1B2] and in second row anterior and posterior images without phantom (SET-2) of the same area are loaded [Figure 1B3 and 1B4] and in third row results are displayed in Figure 1B5 and B6. Software algorithm is shown in Figure 2.

Software code
This software has various sections of code, i.e., variable declaration, image validation, main processing, and HPS calculation.

Variable declaration
In this section of code, all the variables are declared to store image, region of interest (ROI) counts and pixels.

Image validation
This part of code validates the images in runtime during the launch of the software. It only permits defined image type and format, which is validated by this section of code; otherwise, validation fails and error massage is displayed. Two sets of images in anterior and posterior projections, i.e., total four static images are validated. These images are then transferred to the main processing section.
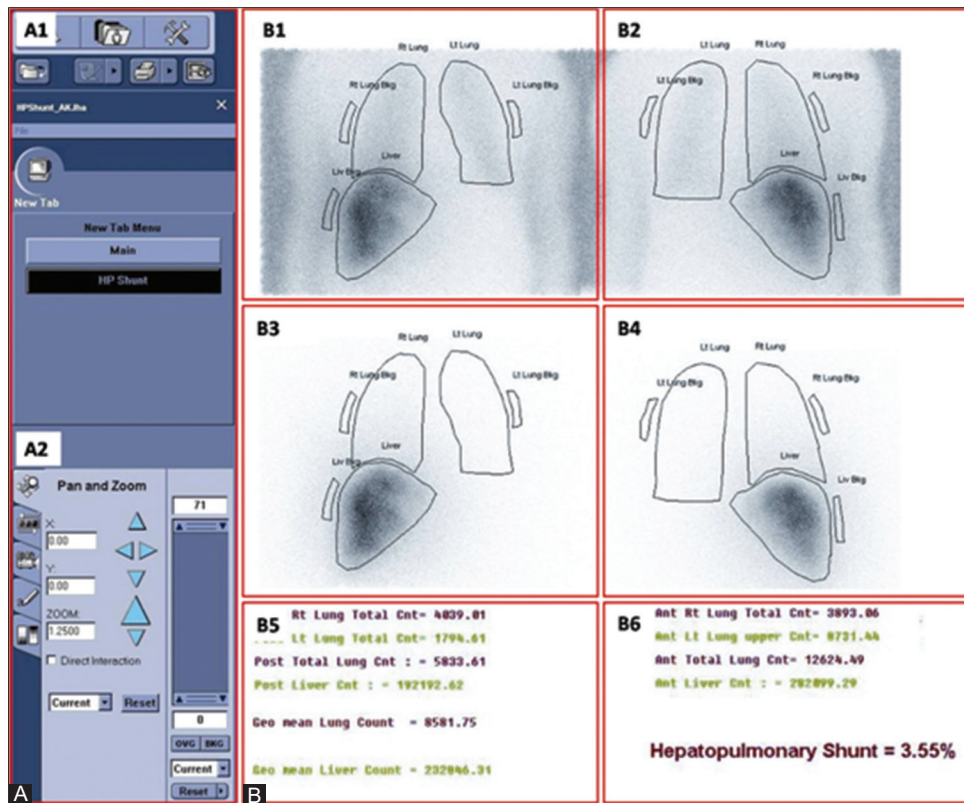

Figure 1: This is the display of the hepatopulmonary shunt software has left (A) and right (B) devision; (A1): Contains main button and hepatopulmonary shunt button. (A2): Contains zoom panel, color panel, and text panel. (B1 and B2): Contains SET-1 image in anterior and posterior view. (B3 and B4): Contains SET-2 image in anterior and posterior view. (B5 and B6): Displays background corrected region of interest counts, geo mean counts, and hepatopulmonary shunt fraction
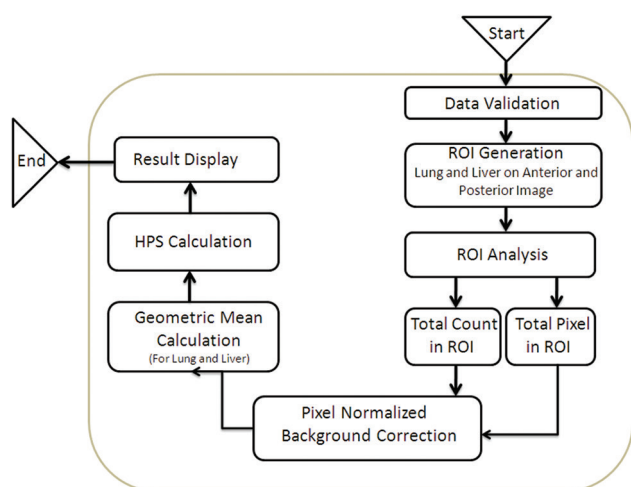
Figure 2: Software algorithm shows the entire process of hepatopulmonary shunt calculation by this software

Main processing

In this part of code, images are loaded in the software and displayed in the first two rows. Once all four images are displayed, software prompts to draw ROI on the first set of images, and the same ROIs are copied on the second set of images and ROI analysis takes place. Total ROI counts and total ROI pixels are captured and stored in the declared variable. Pixel normalized background corrected counts are obtained for right lung, left lung and liver ROIs using Equation 1 for anterior as well as posterior projections. Geometric mean count is also calculated for right lung, left lung, and liver using Equation 2.

Hepatopulmonary shunt calculation

This part of code is designed to calculate HPS using Equation 3.

Software installation

This software named HPS can be installed on all versions of Xeleris workstations using Aladdin editor with slight modifications.

$$C_{cor} = C_{roi} - \left[\frac{C_{bkg} \times P_{roi}}{P_{bkg}} \right] \qquad \text{Equation 1}$$

Where:

C_{cor} = Background corrected count
C_{roi} = Total ROI count
C_{bkg} = Total background count
P_{roi} = Total ROI pixel
P_{bkg} = Total background pixel

$$C_{geo} = \text{Sqrt} (C_{ant} \times C_{post}) \qquad \text{Equation 2}$$

Where:

C_{geo} = geometric mean count

C_{ant} = Anterior count
C_{post} = Posterior count

$$\% \text{ HPS} = \left[\frac{\left(C_{lLung} + C_{rLung} \right) \times 100}{\left(C_{liv} + C_{lLung} + C_{rLung} \right)} \right] \qquad \text{Equation 3}$$

Where:

% HPS = Hepatopulmonary shunt
C_{liv} = Total liver mean count (background corrected)
C_{lLung} = Total left lung mean count (background corrected)
C_{rLung} = Total right Lung mean count (background corrected)

Imaging

Static and SPECT imaging was performed on Infinia Hawkeye 1.123, GE medical system, Haifa, Israel, after transarterial administration of freshly prepared 370MBq ^{99m}Tc-MAA in the liver tumor. Two sets of static images in anterior and posterior projection and one set SPECT were performed including lung and liver in the same frame. Those two sets of static images-one with a Co-57 flood phantom SET-1 and another without the phantom SET-2 are acquired for 10 min each on gamma camera in anterior and posterior projection in 256 × 256 matrix and 1 zoom including lung and liver in the same field of view in identical position.

Imaging requirement for clinical use of software

Two sets of static images are required for processing on this software. Name of the images should be preset as Ant-HPS-Ph and Post-HPS-Ph for SET-1 anterior and posterior images and Ant-HPS and Post-HPS for SET-2 anterior and posterior images.

Image processing and hepatopulmonary shunt calculation by this software

All four images from two image sets are selected and opened in HPS Software on XELERIS workstation. The software opens with active main button and no image loaded in it. Once the main button is clicked both the sets of images are validated and loaded in the image cell of the first two row of image container [Figure 1]. First row contains SET-1 image and second row contains SET-2 images and third row remains empty. Software prompts to draw right lung, left lung, liver, and three respective background ROIs on both projections of SET-1 images. Once all the ROIs are drawn HPS button becomes active. HPS can be calculated by clicking HPS button on the left side panel. The background corrected left and right lung and liver counts are displayed in the 5th cell of image container and HPS fraction is displayed in the 6th cell of image container [Figure 1].

Software validation
Debugging

This software was evaluated for its robustness and accuracy in estimating HPS before routine clinical utilization of this

software. Debugging of software is performed for all the involved processes such as image validation, ROI generation, and HPS calculation.

Phantom-based validation
Phantom preparation
Two phantoms, i.e., NEMA IQ Phantom (Data Spectrum Inc., Durham, NC, USA) and Jaszczak phantom (Data Spectrum Inc., Durham, NC, USA) were used to make HPS Reference Model (HRM) phantom [Figure 3]. IQ phantom was used to mimic lung, and Jaszczak phantom was used to mimic liver in HRM phantom. HRM Phantom was filled with $^{99m}TcO_4^-$ to create model for HPS 5%, 10%, 15%, 20%, and 30% by filling up IQ and Jaszczak phantom in respective ratio as described in Table 1.

Phantom imaging
Phantom imaging was performed in the clinical parameters as described above twice in respective HPS settings in test and retest setting for 2 min per acquisition.

Clinical validation
HPS imaging data of all the patients referred to our department for HPS study were utilized for validation of this software. The study was approved by intuitional ethics committee. Software validation was performed by comparing the HPS calculated by the automated software with HPS calculated by manual method.
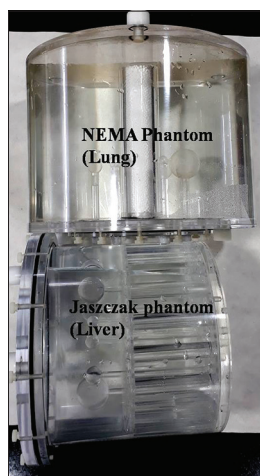

Figure 3: Hepatopulmonary shunt reference model phantom

Statistical test
Phantom study
The percentage error in HPS estimation by software was calculated for test-retest setting. Furthermore, the percentage error in HPS estimation by software with respect to the reference HPS value was calculated.

Clinical study
Average and standard deviation were calculated for HPS obtained by software and manual method as well. The correlation coefficient was calculated between HPS obtained by Software and manual method. Wilcoxon Signed-Rank Test was also performed to find the significance between the HPS calculated by this software and manual method.

RESULTS

This software passed all the debugging tests. For example, if valid image sets are not available user is prompted to select valid images. It prompts the user to draw specific ROIs on a specific image and does not allow drawing ROI on wrong image set. Automatically, ROIs are copied on SET-2 images utilized for ROI analysis. It is able to fetch ROI data such as total counts in ROI, average counts in ROI, and number of pixels in ROI for further calculation.

The HPS estimation performed in test-retest and compared [Figure 4]. The percentage error in HPS estimated by this software in test-retest setting across all the HPS level was 2.07% [Table 2]. Furthermore, the percentage error in HPS estimation in comparison with that of reference HPS across all the HPS level was 5.20% [Table 2].

A total of 36 patient's (35 males and 1 female), data were processed and HPS was calculated using this software and manual method. There was no much difference noted in HPS calculated by software HPS calculated by manual method [Table 3]. HPS of both the sets were compared, we found excellent correlation between two groups (correlation coefficient = 0.998). Wilcoxon Signed-Rank Test was performed, no significant difference at $P \leq 0.01$ was found between two sets of HPS calculated by Software and manual

Table 1: Activity in the National Electrical Manufacturers Association image quality and Jaszczak single-photon emission computed tomography phantom mimicking lung and liver, respectively

Phantom	Activity in the phantom (mCi)				
	5% HPS	10% HPS	15% HPS	20% HPS	30% HPS
NEMA IQ phantom	0.319	0.567	0.989	1.312	1.881
Jaszczak SPECT phantom	6.620	6.560	6.340	6.289	6.138
Actual HPS percentage (%)	4.82	8.64	15.60	20.86	30.65

SPECT: Single-photon emission computed tomography; HPS: Hepatopulmonary shunt; NEMA: National Electrical Manufacturers Association; IQ: Image quality

Table 2: The percentage error in hepatopulmonary shunt estimation by hepatopulmonary shunt software in comparison reference percentage with at various hepatopulmonary shunt level

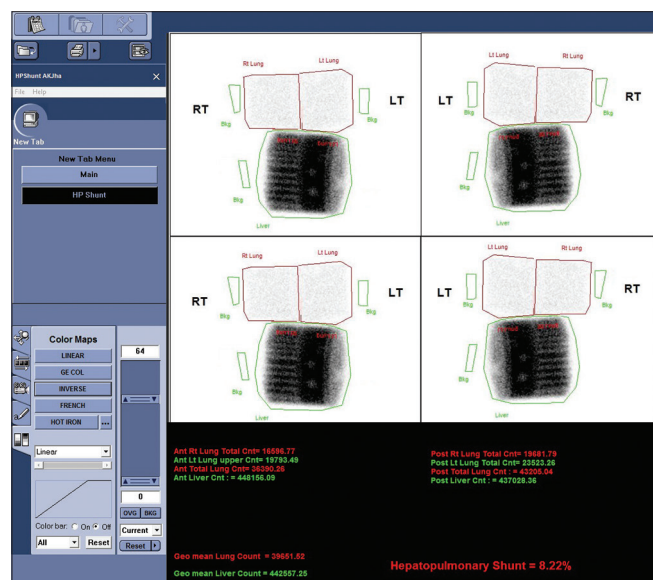|	HPS and percentage error in HPS estimation in phantom (%)				
	5% HPS	10% HPS	15% HPS	20% HPS	30% HPS
Actual HPS percentage in phantom (%)	4.82	8.64	15.60	20.86	30.65
Test	4.58	8.22	14.82	19.98	28.54
Retest	4.52	8.03	14.44	19.54	27.95
Percentage error in test-retest	1.25	2.31	2.56	2.20	2.07
Percentage error in test-reference	5.08	4.86	5.00	4.22	6.88

HPS: Hepatopulmonary shunt

Figure 4: Hepatopulmonary shunt calculated by hepatopulmonary shunt software using in-house prepared hepatopulmonary shunt phantom

method ($P = 0.15272$). The Table 4 shows the details result of Wilcoxon Signed-Rank Test.

DISCUSSION

HPS in TARE therapy is widely reported in the literature resulting in fractional accumulation of microsphere in the lung and an unwanted radiation dose to the lung. As per literature the radiation dose >30 Gy as single exposure and >50 Gy cumulative exposure to the lungs may cause irreversible damage to the lung.

Hence, radiation exposure to the lung due to HPS is one of the limiting factors to perform TARE.[12-15]

As per available literature, reduction of administered therapeutic activity of 90Y-microsphere is suggested for the patients with HPS between 20% and 30% whereas no dose modification is suggested below 20% of HPS. However, for patients with above 30% HPS, TARE is not recommended, considering radiotoxicity to the lungs.[6-7,10-15] Hence, accurate estimation of HPS is mandatory to avoid any radiation-related

Table 3: Hepatopulmonary shunt calculated by software and manual method

Serial number	Case number	HPS (%)	
		HP Shunt AKjha software	Manual method
1	Patient_1	3.4	3.42
2	Patient_2	7	6.92
3	Patient_3	3.8	3.89
4	Patient_4	8.67	8.62
5	Patient_5	3.17	3.23
6	Patient_6	3.83	3.69
7	Patient_7	12.5	11.29
8	Patient_8	15.79	16.52
9	Patient_9	4.4	4.37
10	Patient_10	2.88	3.1
11	Patient_11	6.4	6.54
12	Patient_12	12.5	12.95
13	Patient_13	9.25	9.34
14	Patient_14	3.33	3.51
15	Patient_15	3.44	3.49
16	Patient_16	4.41	4.27
17	Patient_17	3.4	3.75
18	Patient_18	3.42	3.62
19	Patient_19	3.32	3.82
20	Patient_20	10.12	10.68
21	Patient_21	8.12	8.24
22	Patient_22	4.24	4.38
23	Patient_23	7.77	7.12
24	Patient_24	12.72	13
25	Patient_25	32	31.69
25	Patient_25	17	17.29
26	Patient_26	4.7	4.32
27	Patient_27	5.5	5.49
28	Patient_28	6	6.12
29	Patient_29	16	16.12
30	Patient_30	4.4	4.65
31	Patient_31	7.68	7.21
32	Patient_32	9	9.52
33	Patient_33	5.6	5.26
Average		7.82	7.87
SD		5.89	5.89
Correlation coefficient			0.9980

SD: Standard deviation; HPS: Hepatopulmonary shunt

complication to the patient. HPS is estimated in the Nuclear Medicine Department by gamma camera imaging after

Table 4: Wilcoxon Signed-Rank test result

Parameters	Value
Significant level	$P \leq 0.01$
W	214
Mean difference	0.9
Sum of positive ranks	214
Sum of negative ranks	381
Z	−1.4276
Mean (W)	297.5
SD (W)	58.49
P	0.15272

SD: Standard deviation

transarterial administration of ^{99m}Tc-MAA in the interventional radiology department. Most of the vendors supplying gamma camera or SPECT systems are not providing software for HP Shunt calculation, hence manual calculation of HPS is the only option left with the nuclear medicine professionals. With the manual technique, drawing liver and lung ROI accurately become difficult without anatomical demarcations which may cause erroneous HPS calculations with harmful implications. A precisely drawn ROI and proper background correction technique are mandatory to calculate accurate HPS. In our HPS Software, the Co-57 flood phantom image is used for accurate organ delineation and also helps to draw precise ROI around lung, liver, and background [Figure 1].

Our software uses an established technique of pixel normalized background correction, and geometric mean techniques to obtain accurate counts from the ROIs and HP shunt formula (Equation 3) is used for HPS calculation. HPS Software prompts the operator on every stage of image processing which makes this software user-friendly and reliable for HPS estimation. This software was also tested for the robustness. Software shows excellent result with the phantom as well as clinical studies. Error in HPS estimation in test-retest was found to be as low as 2%, and for test-reference, it was around 5%. We observed good correlation between the HPS calculated by manual method and software method in clinical study. Our results with phantom study as well as clinical study show good reproducibility, reliability, and robustness of this software.

CONCLUSION

Liver-lung interface is better delineated with the incorporation of phantom image; enabling accurate ROI placement which results in robust calculation of HPS. The clinical impact is seen in large tumors which obscure the liver margins. Self-instructional nature of the software makes it user-friendly.

Clinical relevance

Accurate estimation of HPS should be done as it is a dose-limiting factor in TARE. HPS software is a precise tool to estimate HPS accurately.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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