Diagnostic improvement based on image processing in low extremities inflammation scintigraphy

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Abstract. The purpose of this study is the improvement in evaluation of the inflammation extent on the scintigraphic imaging, by utilizing statistical indices (Inflammation Projection Ratio - IPR, skewness, kurtosis and Mean Pixel Value - MPV). Image analysis was performed by means of an Interactive Data Language (IDL) tool. Twelve patients were referred for a radionuclide (Tc99m- Leukoscan) scan, by a GE Healthcare gamma camera, on the suspicion of an infectious lesion in the extremities. The findings of the study are that pathological tissues have a higher IPR index (3.12 to 4.32) compared to normal tissue (~ 1). Furthermore, MPV, skewness and kurtosis differ significantly (> 5%) from normal to inflammable extremities. As a conclusion, image processing provides effective information in the structure and facilitates diagnosis semi-quantitatively.

1. Introduction
Imaging of inflammatory processes and infection is a form of tissue characterization by nuclear medicine [1, 2]. This derives from the fact that scintigraphic detection of infection and inflammation is based on functional tissue changes. Thus, it is preferred from other radiological techniques which merely rely on anatomical changes [3-5].

The agent utilized in this study is Tc99m-labeled Fab’ fragment of IMMU-MN3, which is an immunoglobulin GI murine monoclonal antibody. It can detect infection/inflammation with an accuracy that is comparable to white blood cell (WBC) scanning [6-10].

In this study, an improvement in the evaluation of the inflammation extent on the scintigraphic imaging was attempted, by determination of the index Inflammation Projection Ratio (IPR) and the intensity isocontours creation on the images. Furthermore, statistical analysis was attempted by utilizing mean pixel value (MPV), skewness, and kurtosis to create indicative indices.

2. Materials and methods
2.1. Monoclonal antibody preparation and labeling
Tc99m-Sulesomab, that is Tc99m- labeled Fab’ fragment of IMMU-MN3, was used to obtain images of both lower extremities of each patient, produce indices from the measured counts on the acquired images and make cartographies of the disease local extension by intensity isocontouring of the normal and inflamed extremities.

The Fab’ fragment is provided in a ready to label lyophilized kit from Immunomedics, (Leukoscan) [11]. Labelling was accomplished by adding approximately 1000 to 1500 MBq of Tc99m-pertechnetate in saline directly into the vial containing 1.25 mg of the monoclonal antibody Fab’ fragment. The injected material contains 0.25 mg protein labelled with 555 - 925
MBq (15 to 25 mCi) of Tc99m. It is prepared using a 5 minute, 1 step procedure with a labelling efficiency greater than 99%. Tc99m- LeukoScan has a biological half-life of 10.5 hours. The labelled antibody is injected intravenously over 30 seconds. Tc99m- Anti-Granulocyte Fab’ normally concentrates in the liver, spleen, kidneys, and bladder.

2.2. Acquiring images
Twenty-minute whole body planar images of high statistics, at 3 hours, 8 hours and 24 hours post injection of radiopharmaceutical Tc99m- Sulesomab were acquired by a GE Healthcare gamma camera connected to a GE healthcare dedicated processor Xeleris-2. Total counts of each planar extremities’ image were more than 400 kcounts. The distribution is evaluated using the information from statistics retrieved from anterior and posterior scintigrams.

2.3. Inflammation projection ratio
Three regions of interest (ROI) were drawn on each one of the spot images of the lower extremities: one that encompassed the whole pathologic area, a ROI at a corresponding area of the normal extremity and a ROI for background counts for the evaluation of the projection of the infectious area. Image analysis by normalized ROIs is used to determine pathologic area uptakes (see figure 1). From the measured counts, an index, Inflammation Projection Ratio (IPR), representing the projection of the lesion for each patient was calculated. The IPR indices, for all 12 patients, were calculated for the 3 series of data (3h, 8h, 24h). The indices represent the ratio of the counts in the pathologic area to the counts of a normal area similar to the infected tissue, after subtraction of normalized background counts, obtained from a normal soft tissue area.

![Figure 1. Typical regions of interest (ROIs) of pathological and normal extremities and a background ROI for the lower extremities (A) in the left tibia, (B) in the right tibia, (C) in the right knee, and (D) in the left foot.](image)

2.4. Inflammation intensity isocontours- image processing
Image analysis is performed by means of an Interactive Data Language (IDL) tool, which is a platform independent data analysis tool with broad range of mathematical and graphical capabilities.

Local extent of the inflammation is obtained by the intensity isocontours on the inflammation region created by IDL programming. A region of interest (ROI) is an area of an image defined for further analysis or processing. CONTOUR is a routine that enable the programmed definition of ROIs. It traces the outlines of thresholded ROIs (see figure 2) [12, 13].

Image Statistics calculated with the IDL mathematical operators are the sum, mean, standard deviation, variance of the pixel values, skewness and kurtosis of an image. Skewness, kurtosis and mean pixel value were found to be useful characteristics of the images that show not only qualitatively but in a semi-quantitative measure the extent of inflammation localization.

Skewness is defined as a measure of symmetry, or more precisely, the lack of symmetry. Skewness is zero if the data are distributed symmetrically around the mean, negative if the data are more spread out on the left of the mean, and positive if the data are more spread out on the right of the mean [14, 15]. Kurtosis is a measure of whether the data are peaked or flat relative to a normal distribution [14].
3. Results

3.1. IPR estimates

The three sets of Inflammation Projection Ratios (IPR) calculated for each patient are shown in table 1. The IPRs values, obtained by the 24h post injection Tc99m- Leukoscan images, seem to be the higher values that give a greater range for inflammation evaluation. By analyzing the data, it is shown that pathological tissues have a higher IPR index compared to normal tissues which is clearly depicted in figure 3. More specifically, the pathological IPR ranges from 3.12 to 4.32 while the IPR of the healthy tissue should be approximately 1 (or a little more owing to the inhomogeneities of the human body).

Table 1. Inflammation projection ratio (IPR) patient specific/inflammation focus.

| Patient number | IPR 3h | IPR 8h | IPR 24h | IPR aver ± SD IPR | IPR totalaver |
|----------------|--------|--------|---------|------------------|---------------|
| 1              | 4.1    | 4.2    | 4.8     | 4.37 ± 0.22      |               |
| 2              | 3.8    | 4.3    | 4.7     | 4.27 ± 0.26      |               |
| 3              | 3.5    | 4.2    | 4.5     | 4.07 ± 0.30      |               |
| 4              | 4.9    | 4.7    | 5.1     | 4.90 ± 0.12      |               |
| 5              | 4.2    | 3.9    | 4.4     | 4.17 ± 0.15      |               |
| 6              | 3.3    | 3.4    | 3.8     | 3.50 ± 0.15      | 3.72 ± 0.60   |
| 7              | 3.1    | 3.1    | 3.4     | 3.20 ± 0.10      |               |
| 8              | 3.5    | 3.3    | 3.7     | 3.50 ± 0.12      |               |
| 9              | 2.8    | 2.6    | 3.1     | 2.83 ± 0.15      |               |
| 10             | 3.3    | 3.1    | 3.9     | 3.43 ± 0.24      |               |
| 11             | 2.9    | 2.7    | 3.3     | 2.97 ± 0.18      |               |
| 12             | 3.3    | 3.5    | 3.4     | 3.40 ± 0.06      |               |

Normal patient 1 | 1.17 | 1.15 | 1.15 | 1.16 ± 0.007 | 1.11 ± 0.04 |

Normal patient 2 | 1.15 | 1.05 | 1.013 | 1.07 ± 0.04 |
3.2. Isocontours analysis

The isocontouring and statistical analysis of Tc99m- Leukoscan images accentuates the extension of inflammation region. The comparison of skewness and kurtosis of abnormal and normal part of the image gives a numerical grade of the data population of the inflammation presented by Tc99m- Leukoscan imaging (see table 2). By calculating the t-value from 'Student's' t-test (for paired samples), it is estimated that skewness and kurtosis both equal to 12, while the theoretical value for t, defining the level of significance in 5%, equals to 2.23. The calculated value outnumbers the theoretical value which means that the null hypothesis (the two populations are equal) is rejected. So, skewness and kurtosis differ from pathological to healthy tissues significantly.

Apart from skewness and kurtosis, another index evaluated is the mean pixel value (MPV). Table 3 compares the MPV of a ROI in the pathological region to the corresponding in the normal region. By calculating the p- value, it is clearly shown that this index changes significantly in case of infection.

**Table 2.** Statistical analysis of Tc99m-leukoscan images – Skewness/Kurtosis.

| Patient number | Skewness | Kurtosis-3 |
|----------------|----------|------------|
|                | Normal extrem. | Inflam. Extrem. | Normal extrem. | Inflam. Extrem. |
| 1              | -1.22     | -0.84      | 1.62          | 0.05           |
| 2              | 0.39      | 0.37       | -1.14         | -1.20          |
| 3              | -1.59     | -1.65      | 2.03          | 2.16           |
| 4              | -0.63     | -0.28      | -0.98         | -1.60          |
| 5              | -0.59     | -0.65      | -1.06         | -1.14          |
| 6              | -1.04     | -0.70      | -0.20         | -1.19          |
| 7              | -0.50     | -0.38      | -1.06         | -1.43          |
| 8              | -0.59     | -0.65      | -1.06         | -1.14          |
| 9              | -0.84     | -0.48      | -0.57         | -1.43          |
| 10             | -0.94     | -0.87      | -0.53         | -0.75          |
| 11             | -1.19     | -1.19      | -0.05         | 0.32           |
| 12             | -0.78     | -0.76      | -0.30         | -0.40          |

**Table 3.** Statistical analysis of Tc99m-leukoscan images – Mean pixel value.

| Patient number | Normal extremities | Inflammable Extremities | p- value |
|----------------|-------------------|------------------------|----------|
|                | Mean Value | SD | Mean Value | SD |                |
| 1              | 192       | 62 | 183       | 70 | <0.0001         |
| 2              | 73        | 70 | 77        | 74 | 0.0249          |
| 3              | 217       | 54 | 217       | 55 | 0.0002          |
| 4              | 162       | 91 | 147       | 101| <0.0001         |
| 5              | 190       | 61 | 173       | 81 | <0.0001         |
| 6              | 211       | 54 | 179       | 90 | <0.0001         |
| 7              | 42972     | 19445 | 40376     | 21786| 0.001           |
| 8              | 190       | 61 | 173       | 81 | <0.0001         |
| 9              | 204       | 56 | 167       | 92 | <0.0001         |
| 10             | 198       | 68 | 191       | 75 | 0.0006          |
| 11             | 202       | 63 | 195       | 66 | 0.0011          |
| 12             | 200       | 58 | 199       | 59 | 0.0024          |
4. Discussion
As far as the projection of the infectious lesion is concerned, the calculated IPR shows that Tc99m- Leukoscan presents high lesion to normal area ratio and more specific comparing to other radiopharmaceuticals [16]. This index, IPR, could also be used for quantitative analysis and for the differentiation of healthy and infected tissue or for the extraction of various functional parameters. The calculated indices IPR in combination with the processed isocontouring images, contribute to the conclusion that Tc99m- Sulesomab scintigrams are characterized by high projection ratios specific for each case and demonstrate the full extent of the inflamed area in the lower extremities, with great accuracy. IPR seems to be a reliable index to determine whether a tissue is pathological or not, although the study of more patients is necessary in order to confirm this conclusion.

Furthermore, skewness, kurtosis and mean pixel value are reliable indices in order to give a numerical grade of the data population of the inflammation presented by Tc99m- Leukoscan imaging. Skewness and kurtosis indices change radically with a slight variation in the sample population especially when the sample is small and care should be taken when using these indices.

References
[1] James S L and Davies A M 2006 Eur. J. Radiol. 58 27–40
[2] Prandini N, Lazzeri E, Rossi B, Erba P, Parisella M G, and Signore A 2006 Nucl. Med. Commun. 27 633–44
[3] Auler M A, Bagg S and Gordon L 2007 Semin. Roentgenol. 42 117–21
[4] Becker W and Meller J 2001 The Lancet Infectious diseases 1 326-33
[5] Love C and Palestro C J 2004 J. Nucl. Med. Tech. 32 47–57
[6] Becker W, Goldenberg D M and Wolf F 1994 Semin. Nucl. Med. 24 1–13
[7] Becker W et al 1996 Clin. Orth. Rel. Res. 329 263–72
[8] Pakos E E, Koumoulis H D, Fotopoulos A D and Ioannidis J P A 2007 Radiol. 245 732-41
[9] Pakos E E, Trikalinos T A, Fotopoulos A D and Ioannidis J P A 2007 Radiol. 242 101-8
[10] Vicente A G et al 2004 Clin. Nucl. Med. 29 781-5
[11] Australian Nuclear Science and Technology Organization 2002 LeukoScan Kit: Preparation of Technetium-99m Labelled LeukoScan (New Jersey: Immunomedics Inc.)
[12] IDL Tutorial 2008 ITT Visual Information Solutions: Advanced Image Processing http://www.ittvis.com/
[13] IDL 2009 ITT Visual Solutions: Image Processing v. 7.1
[14] NIST/SEMATECH e-Handbook of Statistical Methods http://www.itl.nist.gov/div898/handbook/eda/section3/eda35b.htm
[15] Motoyoshi I, Nishida S, Sharan L and Adelson E H 2007 Nature 447 206-9
[16] Lyra M, Frantzis A and Limouris G S 2001 Radiopharmaceuticals for inflammation /infection eds G S Limouris, Biersack H J and Shukla S K (MEDITERRA-Pub.) pp 118-28 http://www.medimaging.gr/tutorials/RADIATION%20DOSIMETRY%20IN%20INFECT%20Lyra%20et%20al%202001.pdf