Application of analytic methodologies for image quantification in neuroendocrine tumor therapy with ^{177}Lu-DOTA

Aplicação de metodologias analíticas para quantificação de imagem na terapia de tumores neuroendócrinos com 177Lu-DOTA

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Neuroendocrine tumors have annual incidence of 1 to 2 cases per one hundred thousand inhabitants. The ^{177}Lu-DOTA-octreotate treatments in 3 or 4 cycles has been effective in controlling disease progression and, in some cases, promote tumor remission. To estimate radiation side effects in healthy organs, image quantification techniques have been broadcast for individualized patient dosimetry. In this paper, image data processing methods are presented to allowing comparisons between different image conjugate views, combined with attenuation correction and system sensitivity. Images were acquired 24, 72 and 192 h after administration of 74GBq of ^{177}Lu-DOTA using a dual-head gamma camera detection system and they were evaluated with ImageJ software. 4 female patients underwent to two cycles of treatment. The kidneys, liver and whole-body regions of interest were separately assessed by 4 techniques for counts method and 12 techniques for pixel intensity method, considering the main photopeak separately and aided by the attenuation correction map and adjacent windows to photopeak energy. The pixel intensity method was combined with mathematical correction for pixels with null value. The results obtained by the two methods were strongly correlated ($r>0.9$) ($p<0.001$). The paired t-test accepted the null hypothesis of compatibility between the two methods (with and without attenuation correction map) ($p<0.05$), but rejected it when the adjacent windows were combined. No significant tumor reduction ($p>0.05$) was found between the treatment cycles. In conclusion, the pixel intensity method is faster and allows macros, minimizing operator error, and may optimize dosimetry in tumor therapies with ^{177}Lu-DOTA-octreotate.

Keywords: neuroendocrine tumor therapy; image quantification; internal dosimetry

Os tumores neuroendócrinos têm uma incidência anual de 1 a 2 casos por cem mil habitantes. Os tratamentos 177Lu-DOTA-octreotate em 3 ou 4 ciclos tem sido eficaz no controlo da progressão da doença e, em alguns casos, promover a remissão do tumor. Para estimar os efeitos da radiação colaterais em órgãos saudáveis, técnicas de quantificação de imagens foram transmitidas para dosimetria paciente individualizado. Neste artigo, os métodos de processamento de dados de imagem são apresentados para permitir a comparação entre os pontos de vista diferentes de imagem, juntamente com conjugados de correção de atenuação e sensibilidade do sistema. As imagens foram adquiridas h 24, 72 e 192 após a administração de 74GBq de 177Lu-DOTA usando um dual-cabeça gama sistema de detecção de câmera e eles foram avaliados com o software ImageJ. 4 pacientes do sexo feminino submetido a dois ciclos de tratamento. Os rins, fígado e corpo inteiro regiões de interesse foram avaliados separadamente por 4 técnicas para o método de contagem e 12 técnicas de método de intensidade pixel, considerando-se o principal fotopico separadamente e ajudado pelo mapa correção de atenuação e janelas adjacentes ao fotopico de energia. O método de intensidade de pixel foi combinado com correção de matemática para os pixels com valor nulo. Os resultados obtidos pelos dois métodos foram fortemente correlacionados ($r> 0,9$) ($p <0,001$). O teste t pareado aceitou a hipótese nula de compatibilidade entre os dois métodos (com e sem correção de atenuação mapa) ($p <0,05$), mas a rejeitou quando as janelas adjacentes foram combinados. Nenhuma redução significativa do tumor ($p> 0,05$) foi observada entre os ciclos de tratamento. Em conclusão, o método de intensidade de pixel é mais rápido e permite macros, minimizando o erro do operador, e pode aperfeiçoar a dosimetria em terapias tumorais com 177Lu-DOTA-octreotate.

Palavras-chave: terapia de tumor neuroendócrino; quantificação imagem; dosimetria interna

1. INTRODUCTION

Neuroendocrine tumors have substantially increased in incidence and prevalence over the last 30 years [1]. Imaging and targeted radionuclide therapy requires a probe labeled with a diagnostic or therapeutic radionuclide that is injected intravenously into patients. The tracer will bind to sites with high somatostatin receptor density. ^{177}Lu-(DOTA0,Tyr3) octreotate has been used in the treatment of disseminated neuroendocrine tumors [1]. For all radionuclide peptide combinations it is of crucial importance to design the optimal therapeutic window with the tumor dose as high as possible and the normal tissue dose as low as achievable. Radiation dosimetry for the normal organs at risk – that is, kidneys and bone marrow - is essential for optimizing patient-tailored therapy [2]. ^{177}Lu biodistribution in organs and tumor can be quantified using sequential planar images for the cumulated activity estimation by integrating the time-activity curves. Elimination of ^{177}Lu over time must also to be evaluated. In addition to physical decay, the biological elimination occurs more quickly, promoting the elimination of ^{177}Lu from the body largely in the first 24 hours. In order to characterize the long-term retention, the measurements should be performed at intervals equal to multiples of the effective half-life, for example, 1, 3 and 5 times [3].

With the increasing use of radionuclide therapy and in order to administer a personalized dose to the patient, it is necessary to develop image quantification protocols to be used in routine [4]. The aim of the present study is to compare different methods of image quantification [3], to determine the organ uptake activity using a simple tool, for instance public domain open source software like ImageJ [5].

2. PATIENTS, MATERIALS AND METHODS

Patients

4 female patients underwent two cycles of treatment. They were selected by the criteria of inclusion and exclusion from the study protocol.

Gamma camera

The gamma camera used was a GE Millennium MG with low-energy and high-resolution collimator. The dual-head acquisition protocols, with diametrically opposed heads, were applied using six energy windows (^{177}Lu two principal gamma emission photopeaks (PP) with limits of 20% and adjacent peaks of 10% above and below each principal peak). According to the correction for scatter in photons based on multiple energy windows [3], the energy windows were defined for simultaneous acquisition images (Table 1).

Table 1: Energy windows (keV) for ^{177}Lu imaging acquisition protocol

Radionuclide	**Photopeak *PP* (keV)**	**Window *PP* (keV)**	**Windows *Left PP* (keV)**	**Windows Right *PP* (keV)**
^{177}Lu	112.94	101.7 – 124.3	90.4 – 101.7	124.3 – 135.6
	208.36	187.5 – 229.2	166.6 – 187.5	229.2 – 250.0

Acquisition protocol

The patient acquisitions were divided into two main stages: before and after therapeutic dose. Before the dose administration, the patient underwent an anterior image acquisition of attenuation map using the flood phantom filled with a standard source of ^{177}Lu. Anterior and posterior images were acquired 24, 72 and 192 h after administration of 7.4 GBq of ^{177}Lu-(DOTA0,Tyr3) octreotate.

Flood phantom

The flood phantom was manufactured at IRD/CNEN and made of acrylic, completely leakage with outside dimensions of 58.0 x 45.7 x 2.3 cm and internal dimensions of 41.1 x 53.4 x 1.3 cm. The volume capacity was approximately 2850 cm^3.

Standard source

The ^{177}Lu standard source was designed and certified by LNMRI/IRD/CNEN, with 85.040 MBq/g, with standard uncertainty of 0.61% (k=1). The solution mass in the vial was 5037.7 mg.

Softwares

In a personal computer with Mac OS operating system, the images were imported to the OsiriX software to specific folders according to the therapy cycle [6]. The ImageJ software was used for image post-processing [5].

Correction for scattered photons using multiple-energy windows acquisition

The planar images conjugate views method were characterized by simultaneous images acquisition of anterior and posterior. The patient transmission scan or attenuation map was performed before to activity administration of the radiopharmaceutical. A system calibration coefficient converted the count rate in the source region in absolute activity. The calibration factor was calculated for each image set, to ensure the performance of the detector system [3]. The source activity A_j was calculated according Eq. 1 [4] .

$$A_j = MG_j \cdot \frac{f_j}{C} \quad \text{(Eq.1)}$$

Where, f_j, is correction coefficient of attenuation coefficient and source thickness; C is *c*ount rate per activity unit (system calibration coefficient) and MG_j is geometric mean of anterior and posterior images.

The geometric mean (MG) of the images is obtained by Eq. 2. The counts obtained from anterior image and posterior image inverted horizontally were multiplied, divided by the patient transmission and square root was extracted.

$$MG_j = \sqrt{\frac{I_A \cdot I_P}{e^{-\mu_j t_j}}} \quad \text{(Eq.2)}$$

Where I_A is anterior image; I_P is posterior image; μ_j is the tissue attenuation coefficient and t_j is the patient thickness, which is the source. For transmission correction (Eq. 3), the denominator corresponds to the transmission through subject, so is the ratio of counts reaching the detection system without the patient (I_0), only the homogeneous source, by the counts obtained by the source located below the patient (I), Eq.3.

$$T = \frac{I}{I_0} = e^{-\mu_j t_j} \quad \text{(Eq.3)}$$

Regions of interest (ROIs)

The purpose of the ROIs in this step is to assess if the mathematical behavior obtained by the methods is reproducible regardless of the study area. Whole-body, kidneys and liver were references. ROIs were defined aided by a nuclear physician.

Each source organ was identified and individually evaluated. ROIs were drawn within the area of the radiopharmaceutical uptake and obtained the number of pixels (1 pixel = 1 "picture element"), the counts per pixel, the mean and standard deviation of scores. The count rate within each ROI was obtained by dividing the total number of counts per the time of image acquisition.

Counts and pixel intensity methods

Some processes were common to both methods: a) the images were loaded into ImageJ software, b) posterior image has a flip horizontal; c) all images were converted to 32 bits and underwent to the methodology described in MIRD 16; d) when using the adjacent windows was necessary to extract the values for these windows peaks over the data acquired using the main photopeak [3].

In the counts method, the counts were acquired to obtain activity in both anterior and posterior images. Four count techniques were used according to the acquisition method, that were: 1. the main photopeak energies; 2. the main photopeak energies and attenuation map; 3. the main photopeak and both adjacent energies windows; 4. the main photopeak and both adjacent energy windows, with an attenuation map.

In the pixel intensity method, counts were estimated in only one of the images according the organ of interest (anterior or posterior) and its value was extracted at the end of operations. The following count techniques were used according to the acquisition method: 1. the main photopeak energies (and correction for zero values); 2. the main photopeak energies and attenuation map (and correction for zero values combined with square root corrections); 3. the main photopeak and both adjacent energies windows (and correction for zero values); 4. the main photopeak and both adjacent energies windows and with attenuation map (and correction for zero values combined with square root corrections).

For all evaluation methods, it was necessary to manipulate the images before ROIs delimitation. The patient's attenuation map was created using the flood field images. Using the geometric mean of anterior and posterior images, combined with attenuation map, it was possible to obtain the organ final image (Figure 1).

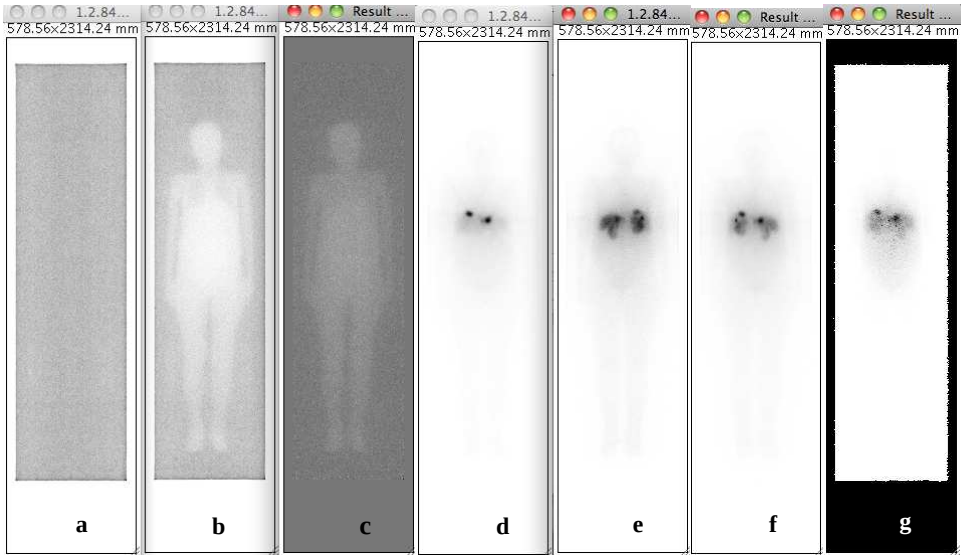

Figure 1: Evaluation methods: a) flood phantom; b)flood + patient, c) attenuation map; d) anterior image; e) posterior image; f) geometric mean image and g) final image.

Statistical analysis

The differences between count and pixel intensity methods were performed with paired t-test ($p<0.05$). The correlation between groups regarding the counts and pixel intensity of structures were performed with Pearson correlation ($p<0.05$).

3. RESULTS AND DISCUSSION

The amount of patient data comprising in the two treatment cycles (480 ROIs) was subdivided in 16 data groups. Both methods (counts and intensity) were strongly correlated ($r>0.9$) ($p<0.001$). Comparing the data for whole-body, kidneys and liver from the first cycle between acquisitions with main photopeak (MP) only, main photopeak with three windows (3W) and with both methods with and without attenuation maps (AM) linear correlation plots were obtained (Figures 2 and 3).

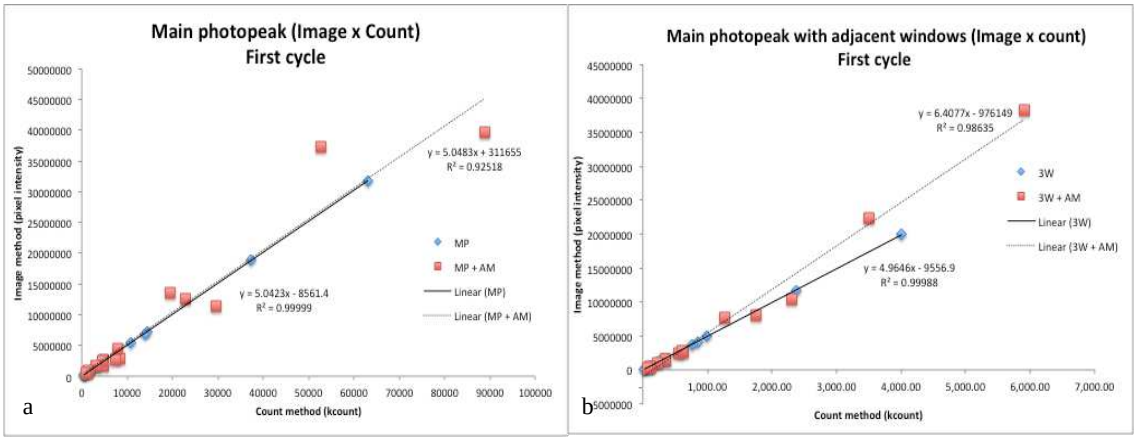

Figure 2: First therapy cycle: comparison between count and image methods over all three organs ROIs of all methods for: (a) main photopeak (MP) and main photopeak with attenuation maps (MP+AM) and (b) main photopeak with 3 adjacent windows (3W) and considering attenuation maps (3W+AM)

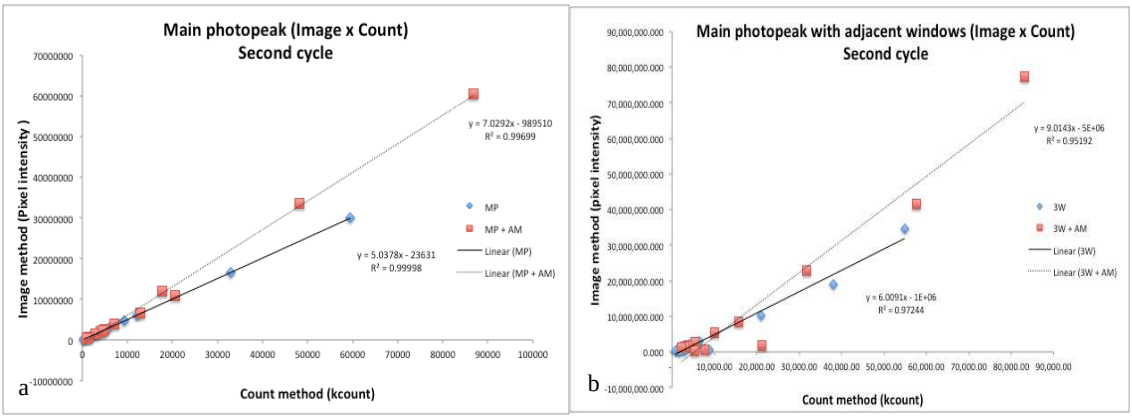

Figure 3: Second therapy cycle: comparison between count and image methods over all three organs ROIs of all methods for: (a) main photopeak (MP) and main photopeak with attenuation maps (MP+AM) and (b) main photopeak with 3 adjacent windows (3W) and considering attenuation maps (3W+AM)

The paired t-test shows compatibility between the two methods (with and without attenuation correction map) ($p<0.05$), but the methods are not equivalent when the adjacent windows were combined for scattering correction ($p>0.05$). Comparing the two treatment cycles, statistical analysis showed no significant tumor reduction in the first funding cycle ($p>0.05$). With respect to the operational usefulness, while in the count method was necessary to extract 2 to 8 ROI values to obtain a geometric mean, in the intensity pixel method only one ROI is necessary. The procedures for images manipulation before to perform quantification may be optimized with

macros that makes available at least about 50% faster, depending on the evaluator. The time spent to extract the values by counting method was higher when compared with the time taken by the pixel intensity method.

4. CONCLUSION

Aided by ImageJ software, the mathematical processes required for image post-processing have been simplified using the existing tools, without the need to develop additional tools, despite the software allow this implementation.

The results indicated that the methodology may contribute to the individualized dosimetry of neuroendocrine tumor therapies with ^{177}Lu-DOTA-octreotate. In Brazil, it is a desirable tool to optimize internal dosimetry, without the need of additional resources to the nuclear medicine professionals.

5. ACKNOWLEDGEMENTS

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1. H. R. Maecke, J.C. Reubi. “Somatostatin receptors as targets for nuclear medicine imaging an radionuclide treatment”, J Nucl Med 2011; 52:841-844.
2. M. Konijnenberg, M. Melis, R. Valkema, E. Krenning and M. De Joug. “Radiation dose distribution in human kidneys by octreotides in peptide receptor radionuclide therapy”. J Nucl Med 2007; 48:134-142.
3. J. A. Siegel et al, “MIRD Pamphlet No. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates”, J Nucl Med 1999; 40:37S-61S.
4. M. Garkavij, M. Nickel, K. Sjögreen-Gleisner, M. Ljungberg, T. Ohisson, Karin Wingardh, SE. Strand and J. Tennvall, “^{177}Lu-[DOTA0,Tyr3] Octreotate therapy in patients with disseminated neuroendocrine tumors: analysis of dosimetry with impact on future therapeutic strategy”, Cancer 2010; 116 (4 suppl):1084-92.
5. Software ImageJ” http://rsbweb.nih.gov/ij/ (accessed in 12/08/2011).
6. A. Rosset, L. Spadola, O. Ratib, “OsiriX: An open-source software for navigating in multidimensional DICOM images”, Journal of Digital Imaging, 2004, v.17, pp.205-216.