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Neutron stimulated emission computed tomography applied to the assessment of calcium deposition due to the presence of microcalcifications associated with breast cancer

Tomografia computadorizada de emissão estimulada por nêutrons aplicada para avaliar a deposição de cálcio devido à presença de microcalcificações associadas ao câncer de mama

Rodrigo S. S. Viana[1] and Hélio Yoriyaz[1]

[1] Instituto de Pesquisas Energéticas e Nucleares, Comissão Nacional de Energia Nuclear (IPEN/CNEN), São Paulo (SP), Brazil.

Abstract

In this paper we presented an application of the Neutron Stimulated Emission Computed Tomography (NSECT), which uses a thin beam of fast neutrons to stimulate stable nuclei in a sample, emitting characteristic gamma radiation. The photon energy is unique and it is used to identify the emitting nuclei. This technique was applied for evaluating the calcium isotopic composition changing due to the development of breast microcalcifications. A particular situation was simulated in which clustered microcalcifications were modeled with diameters less than 1.40 mm. In this case, neutron beam breast spectroscopy was successful in detecting the counting changes in the photon emission spectra for energies, which are characteristics of ^{40}Ca isotope in a low deposited dose rate.

Keywords: NSECT, microcalcifications, breast cancer, spectroscopy, diagnosis.

Resumo

Neste trabalho, apresentou-se a aplicação da tomografia computadorizada de emissão estimulada por nêutrons (TCEN), que usa um feixe de nêutrons rápidos para estimular os núcleos estáveis em uma amostra, emitindo radiação gama característica. A energia do fóton é única e é utilizada para identificar os núcleos emissores. Esta técnica foi aplicada para avaliar a mudança da composição isotópica de cálcio devido ao desenvolvimento de microcalcificações mamárias. Uma situação em particular foi simulada, na qual microcalcificações agrupadas foram modeladas com diâmetros inferiores a 1,40 mm. Neste caso, a espectroscopia da mama do feixe de nêutrons obteve sucesso ao detectar as mudanças da contagem nos espectros de emissão de fótons para energias, que são características do isótopo de ^{40}Ca em uma razão de baixa taxa de dose depositada.

Palavras-chave: TCEN, microcalcificações, câncer de mama, espectroscopia, diagnóstico.

Introduction

Breast cancer is the second most common cancer worldwide and the leading cause of death among women in Brazil. According to estimates for 2010, it is expected approximately 49,000 new diagnosed cases[1].

One of the main signs of breast cancer at an early diagnosis is the development of microcalcifications. Because of calcium radiological properties, microcalcifications are associated with nonpalpable lesions that can be visualized on mammography, which makes it the primary mode of breast cancer diagnosis[2]. The importance of detecting microcalcification formations in their early stages is a well-known fact and, according to the literature, the survival rate of patients who developed breast cancer is inversely proportional to the lesion size. Regardless of prognosis,

Corresponding author: Rodrigo Sartorelo Salemi Viana – Instituto de Pesquisas Energéticas e Nucleares – IPEN – Avenida Lineu Prestes, 2.242, Cidade Universitária, P.O. Box 11049, São Paulo (SP), Brazil – CEP 05508-000 – E-mail: rodrigossviana@gmail.com

women with invasive breast tumors with a diameter of 10 mm or even smaller die due to complications at diagnosis[3]. However, in early stages, those microcalcifications are very small, which become difficult to be detected by mammography.

The presence of isolated breast microcalcifications is not a decisive factor in the diagnosis of breast cancer, but it is one of the first signs of metabolism disorder. In addition, the morphological changes caused by microcalcifications and visible on mammography screening occurs later on physiological changes due to increased calcium deposition.

In recent years, a new technique for *in vivo* spectrographic imaging of stable isotopes was presented as Neutron Stimulated Emission Computed Tomography (NSECT)[4]. In this technique, which uses multiple projections, a fast neutron beam interacts with the stable isotopes of the irradiated tissue through inelastic scatterings, making them jump into an excited state. When they return to their ground state, they emit photons, which energies are intrinsic to the emitting nuclei. The emitted gamma energy spectra can be used for two purposes: to reconstruct the target tissue image and; to determine the tissue elemental composition. Considering a clinical application, the spectroscopy of elements distribution in the body may be used in the study of the tissues metabolism. As the development of calcium deposits in the form of microcalcifications alter the abundance of this element in the breast, this spectrographic technique may be used to evaluate the calcium isotopic composition changing due to the development of microcalcifications.

In the present work, the energy spectrum data obtained from the simulated spectroscopy of a healthy breast have been compared to those obtained from the simulated spectroscopy of a breast model with inserted microcalcifications and different diameters. Simulations have been done using the Monte Carlo code MCNP5. From these comparisons, it was possible to establish a relationship between the microcalcification sizes and the calcium emission photopeak intensities. A particular situation represented by clustered microcalcifications has also been analyzed. In this approach, a mammography unit was simulated in order to relate the variation of calcium isotopic composition with the spatial distribution of microcalcifications.

Methodology

Monte Carlo code MCNP5

The Monte Carlo method can be described as a statistical one, which uses a sequence of random numbers to perform a simulation. In terms of radiation transport, the stochastic process can be seen as a family of particles moving randomly in each individual collision as they travel through matter. The average behavior of these particles is described in terms of macroscopic quantities, such as flux or particle density. The expected value of these quantities corresponds to the deterministic solution of the Boltzman equation. Specific quantities, such as deposited energy or dose, are derived from these quantities.

The MCNP code is a well-known and widely used Monte Carlo code for neutron, photon, and electron transport simulations[5]. The first MCNP version was released in the mid-1970s for neutron and photon transport, and it was enhanced over the years to include generalized sources and tallies, electron physics and coupled electron-photon calculations, macrobody geometry, statistical convergence tests and other features. The present work used the last MCNP released version, which is the 5th. The MCNP5 particle transport simulation requires an input file (inp), which allows the user to specify all the information about geometry modeling, source specifications, material compositions, and specific quantities to be estimated (tallies).

Simulations

The simulated breast was modeled as a half of an ellipsoid placed in the x-y plane. The breast composition was taken from the literature[6]. Microcalcifications assume two distinct chemical compositions: calcium oxalate ($CaC_2O_4.2H_2O$) and hydroxyapatite ($Ca_{10}(PO_4).6H_2O$). Some morphological characteristics revealed that benign tumors have microcalcifications predominantly composed by calcium oxalate, while microcalcifications composed by hydroxyapatite can be associated with both benign and malignant tumors[2]. The microcalcifications simulated in this paper were modeled considering these two chemical compositions.

The NSECT is a spectrographic technique and the analysis of any sample is understood by both the spatial distribution of stable isotopes and the photon emission spectrum, which characterizes the isotopic composition of irradiated medium. However, the approach proposed in this paper uses only the spectroscopic analysis of tissues under investigation.

First, the photon emission spectrum of the healthy breast was obtained and used as a reference assuming the existence of a normal[6] calcium concentration. Subsequently, the breast was modeled with the inclusion of microcalcifications with different diameters (1-14 mm) and using both chemical compositions already described. The resultant spectra obtained from the simulations were compared with the reference spectrum, with the aim of establishing a relationship between the diameters of the microcalcifications and the calcium emission photopeak intensities. Since the background is a common factor in all obtained spectra, it was not necessary to adopt any suppression or background extraction procedure.

Two hyper-pure germanium (HPGe) detectors were modeled as cylinders of 5.32 g/cm^3 density, with 12 cm diameter and 15 cm height. The detectors were separated 90° from each other and both forms 45° with the neutron beam axis. The neutron source was modeled in MCNP5 as a monoenergetic energy beam of 7 MeV and with a square section of 1 cm^2. 5x10^8 incident neutrons have been simulated and photons, whose emission was stimulated by

inelastic scattering of fast neutron beam, were recorded on the surface of the detectors using the F2 superficial flux tally. This tally estimates the average particle scalar flux on a user-specified surface and it was associated with the E*n* card that allows separating the counting photons according to energy bins of interest. Using this MCNP5 tally resource, it was possible to build the energy spectrum of the scattered photons arriving in the detectors. The configuration adopted of the spectrometric system is shown in Figure 1.

Since 1913, when the first description of microcalcifications in a mammography was reported, many studies were conducted to characterize and classify the types of microcalcifications[7]. Because microcalcifications are radiopaque structures, some researches show the importance of monitoring the development of calcifications mainly in the early diagnosis through mammography screening. Additionally, as hydroxyapatite can be found in both malignant and benign tumors, other parameters associated with microcalcifications should be evaluated, such as shape, composition, quantity, and distribution. However, the probability of malignancy is proportional to the number of calcifications[8]. Based on this fact, in order to simulate a more realistic case, using the spectrometric system setup showed in Figure 1, randomized clustered hydroxyapatite microcalcifications with different diameters (0.15-1.40 mm) have been modeled for analysis. The spectrum obtained was compared with the reference spectrum of the healthy breast.

As already described, mammography is the primary mode of diagnosis of breast cancer and currently it is in constant technological development. To confirm the change in the calcium abundance, due to clustered microcalcifications development, a mammography unit was modeled considering a 23 keV photon beam focusing on a molybdenum target at a distance of 15 cm from the rhodium filter 25 μm thick and 45 cm from the compressor plate. A 10 cm compression thick and a decrease in breast volume by 10% were considered. Using the resources available in MCNP5, the mammography screening was simulated using the flux image radiograph (FIR) tally, which property reproduces a radiographic image of the photon flux that goes through a user-specified image grid.

In any diagnostic techniques with ionizing radiation, the absorbed dose in patients during the procedure requires special attention, and all intrinsic parameters to the diagnosis should ensure that the ALARA principle be satisfied. Therefore, the absorbed dose rate on neutron spectroscopy of the breast, with clustered microcalcifications, was estimated and compared with the allowed limits for the average glandular dose for mammography.

Results and Discussion

Simulations were performed on a Linux environment at Ubuntu operating system on a 2.67 GHz Intel® Core™ i7 and 6 GB RAM desktop, in an average CPU time of five days. All results presented in this section were obtained considering a maximum standard deviation of 3%.

As described in the methodology section, in the first approach, the emission spectrum of the healthy breast and the spectrum of the breast with the inclusion of microcalcifications of different diameters have been simulated. Comparing both calculated spectra, it was possible to observe the change of the breast isotopic composition in function of breast calcium concentration. Figure 2 shows the behavior of the normalized counts by emission spectrum of the healthy breast for different photopeak energies characteristics of ^{40}Ca isotope, due to the increase in the microcalcifications diameter.

The first feature that can be observed is the difference in the range of normalized counts relative to differences in the microcalcification compositions. This behavior is justified by the number of calcium atoms in hydroxyapatite and calcium oxalate molecules, which has a ratio of 10-1. According to the literature, the recognition of lesion malignancy by invasive methods is determined by physical, chemical, and morphological characteristics of the lesion sample, and the most used noninvasive procedure is the analysis of mammographic findings. However, noninvasive methods like mammography for diagnosis of breast cancer are limited to a minimum detectable size of the microcalcification itself. As an example, we can mention the use of high-frequency ultrasound[9].

With the obtained spectra, it is possible to verify the sensitivity of the presented spectrometric technique to distinguish the composition of microcalcifications as a function of the amplitude of the normalized counts once calcium oxalate microcalcifications are strictly associated with benign tumors. Another favorable factor for the diagnosis is associated with the possibility of evaluating 2 mm diameter microcalcifications and even smaller.

The second approach proposed is to model a breast with clustered microcalcifications and obtain spectroscopy and mammography to verify the change in the isotopic composition of calcium through the presence of microcalcifications. To achieve this purpose, 16 hydroxyapatite

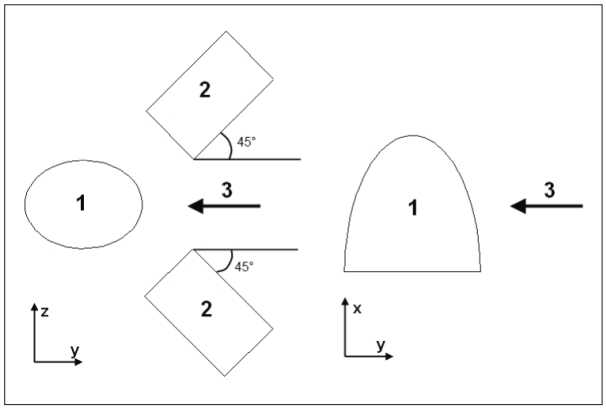

Figure 1. The MCNP5 spectrometric system setup: Breast (1); HPGe detectors (2), and neutron beam (3).

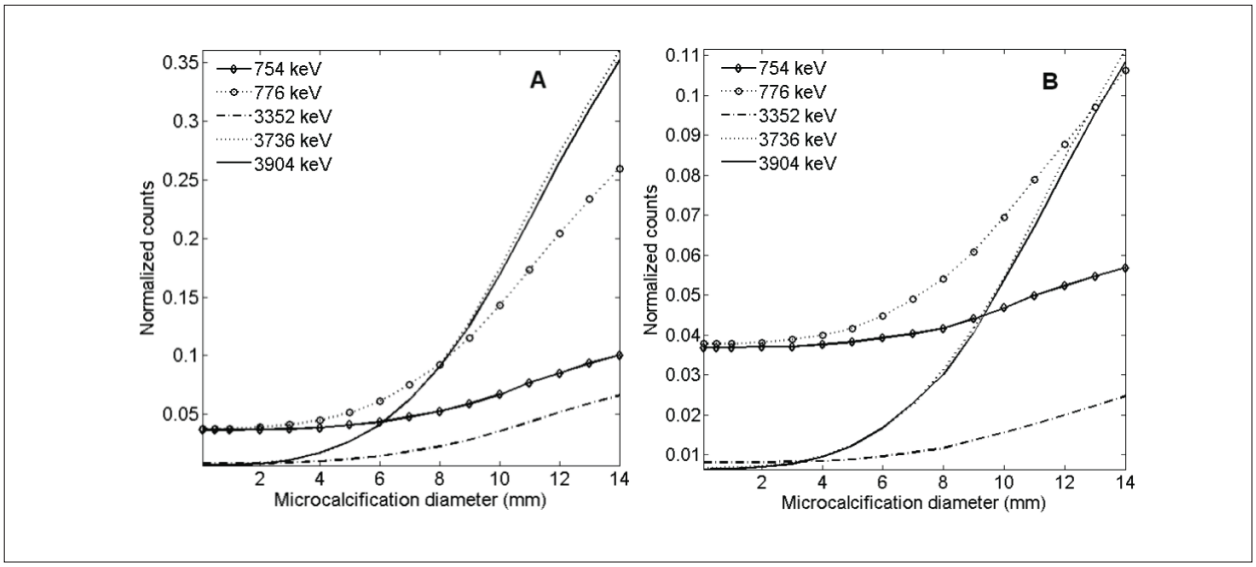

Figure 2. Change of normalized counts in accordance with the increase in diameter of microcalcifications of different chemical compositions: hydroxyapatite (A) and calcium oxalate (B).

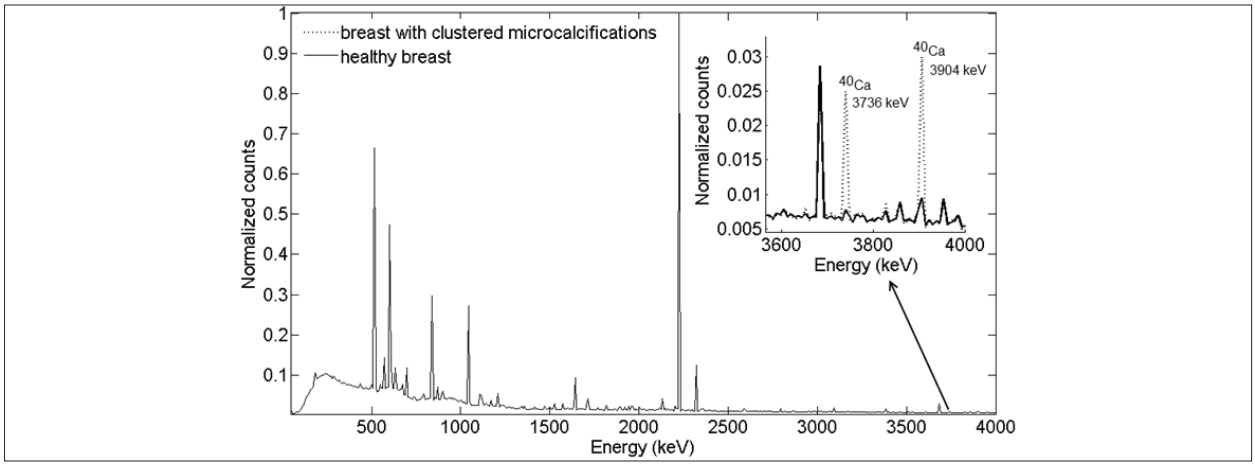

Figure 3. Photon emission spectra of the healthy breast and the one with clustered microcalcifications.

microcalcifications with diameters ranging from 0.15 to 1.40 mm were simulated. Figure 3 shows the energy spectrum of the healthy breast and breast with clustered microcalcifications in a range from 50 to 4,000 keV with the detail of the energy range of interest.

Even for clustered microcalcifications with diameters smaller than 1.40 mm, it is possible to observe the increased calcium isotopic composition, altering the normalized counts of the emission spectrum for the 3,736 keV and 3,904 keV energies. In a clinical application, this result confirms the ability of NSECT spectroscopy mode in detecting the change of calcium abundance due to the development of microcalcifications or even other conditions that would be associated with the disorder in the calcium production.

Using the same microcalcifications arrangement, the mammography screening was performed using the MCNP5 FIR tally to simulate the radiographic image of the photon on a high-resolution matrix array over a 16 x 16 cm field, with 0.1 mm resolution discrimination per pixel. Figure 4 shows the radiographic image obtained, it is possible to visualize some clustered radiopaque structures. In a hypothetical clinical case, this image could represent the first indication of breast physiology disorder.

Neutron radiation dose

Using the resources available in MCNP5, the average energy deposited by each 7 MeV neutron that interacts in breast was estimated to be 2.92 MeV. As the results provided by MCNP5 are normalized by the number of simulated particles, to obtain the absolute absorbed dose is necessary to assume that the neutron source intensity is known. For the calculation purpose, the standard intensity of an Am-Be sealed natural source, with the intensity of 10^7 neutrons emitted per second on a single projection, was adopted. Assuming that the fast neutron beam has

been simulated with this intensity, the absorbed dose rate obtained in the breast spectroscopy is 0.0074 mGy/s.

According to the American College of Radiology[10], the tolerated limit for the breast average glandular dose is 3 mGy in a single exposure. Whereas the exposure times are low, the absorbed dose rate in mammography could be superior to that of neutron spectroscopy.

Conclusion

It was demonstrated the ability of NSECT spectroscopy mode in detecting the change in calcium deposition due to the development of hydroxyapatite and calcium oxalate microcalcifications. The results obtained, where microcalcifications with different diameters were inserted on the healthy breast, revealed the change of the breast isotopic composition in function of the increasing calcium abundance through normalized counts of photopeak energies of this element.

In a clustered microcalcifications situation, even when considering microcalcifications with diameters less than 1.40 mm, the breast spectroscopy was able to detect the isotopic composition changing, and this task was achieved under a low deposited dose rate if compared to the average glandular dose limit for mammography.

Considering a compromise between deposited dose and the counting efficiency of the detectors, the factors that could have prevented the application of NSECT spectroscopy mode on breast isotopic composition analysis are exposure time and neutron source intensity.

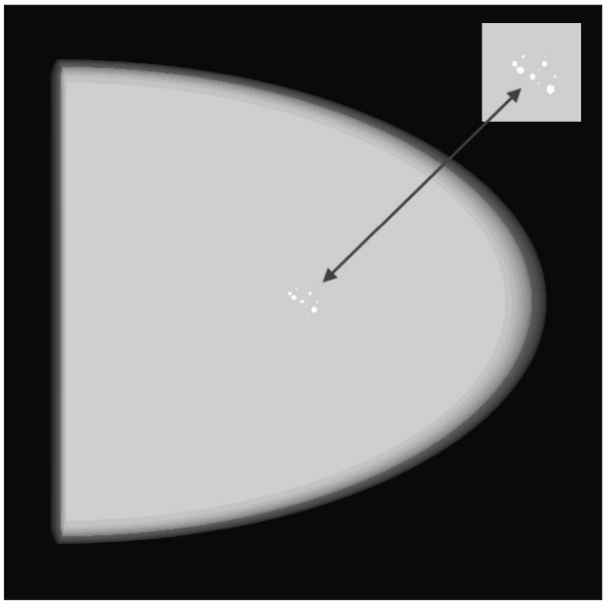

Figure 4. Mammography screening performed with 0.1 mm resolution discrimination per pixel of breast with clustered microcalcifications.

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