2009 International Nuclear Atlantic Conference - INAC 2009
Rio de Janeiro,RJ, Brazil, September27 to October 2, 2009
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: 978-85-99141-03-8

CERAMIC AND POLYMERIC DEVICES FOR BREAST BRACHYTHERAPY – MAMOGRAPHIC AND CT RESPONSE

Luciana B. Nogueira and Tarcísio P. R. Campos

Programa de Pós-Graduação em Ciências e Técnicas Nucleares, Departamento de Engenharia Nuclear
Universidade Federal de Minas Gerais
Av. Antônio Carlos, 6627
CEP: 31270901, Belo Horizonte, MG
campos@nuclear.ufmg.br

ABSTRACT

The present research investigates the radiological visibility of ceramic and polymeric devices implanted in breast phantom (*in vitro*) for future applications in brachytherapy treatments. The main research goal is to investigate the viability of monitoring ceramic and polymeric devices, *in vitro* based on simple methods of radiological diagnostic, maintaining the easiest access to the population, represented by the conventional X-ray and mammography. The methodology involves the processing of ceramic devices constituted by bioglasses of Sm, SmBa, Ho, HoBa and the production of polymeric devices, such as polymeric membranes incorporating Ho e HoBa. Contrast agent of Barium was introduced in the syntheses of those devices to improve the radiological visibility in breast equivalent-tissue (TE) phantom. The breast phantom is constituted of glandular, adipose and skin TE, reproducing a 5 cm compressed real breast. In the compressed breast phantom, all types of ceramic and polymeric devices were implanted side by side. Radiological images were generated through X-ray equipments, mammography and computerized tomography (TC), for the samples implanted in the compressed breast phantom. The results show that SmBa and HoBa seeds on breast phantom presented suitable radiological visibility, on all the radiological diagnostic methods. However, the X-rays radiological visibility of Sm seeds without contrast was discreet. On mammography and TC images, it was not possible to identify those seeds, because the same ones were degraded after two months immersed in the glandular TE, after placed on the phantom. The Ho seeds were identified on all radiological diagnostic images, although non contrast agent in its constitution was added. However, the holmium polymeric membranes in direct contact with TE did not show X-ray radiological visibility. However, the polymeric membranes of HoBa in the same conditions presented efficient X-rays radiological response. For mammography and TC methods, all membranes, with or without contrast, could be identified on the images. In all the radiological investigation, the implanted devices present enough response for visual clinical identification. However, the radiological gray-level density varied according to the method chosen. As conclusion, X-rays and mammography radiological diagnostic methods can be used to monitor implants on compressed breast, identifying the ceramic and polymeric devices in quantity and position on the implants.

1. INTRODUCTION

A radiological image of clinical good quality allows clearly visibility of the anatomical structures of the human body together with the subject of medical interest, in relation to a respective image modality. The tissues of the human body have distinct radiological responses when investigated by diferent techniques of radiodiagnostic image. This response is differentiated according to the radiological modality, such as : X rays, mammography, computed tomography (CT), ultrasound, scintigraphy and MRI. The images also show different responses in the gray of scale, according to the presence substances of metal, calcium, liquid, fat and air [1, 2].

The brachytherapy is a radiotherapy procedure in which the radioactive device is placed into or close to the neoplasic region. This method shows high deposition of dose to the tissue, due to the small distance between tissue and the radioactive source, and low dose of radiation to healthy tissue surrounding to the tumor. For this treatment are used radioactive devices of small size and various shapes, and it is possible irradiate reduced target volumes with high dose [3].

In order to identify the brachytherapy devices into the human body, such as radioactive ceramics seeds implanted in tissue, some radiology techniques promote both the visibility of the tissue, as the seeds implanted. Therefore, it is necessary to examine the properties of these devices subject to various exposure factors used in the radiological procedures according to the methods of images [2].

Biodegradable and biocompatible ceramics seeds have been investigated by the research group NRI / PCTN – *Nucleo de Radiações Ionizantes* of the Graduate Nuclear and Science Program at Federal University of Minas Gerais [4, 5, 6, 7, 8, 9]. The sol-gel processing, applied to the production of the seeds is a ceramic or bioglass synthesis in lower temperatures than those applied on traditional ceramic method. This process has been used to manufacture a new generation of radioactive bioactive glasses [10, 11, 12].

The PVA polymer (polyvinyl alcohol) is used since 1930 in textile and paper industries. More recently, it has found application on membranes for enzymes immobilization and other pharmaceutical apparatus as controlled drug delivery, ophthalmic solutions. It has been considered safe for oral administration, and it has found application on coating dietary supplements and capsules of pharmaceutical products. The methods of synthesis these devices involves dilution and drying processing [13, 14].

Ceramic seeds made of radioactive Sm-153 and Ho-166, as well as polimeric thin-foils of Ho-166 or Sm-153 may control tumors in situ. The Sm-153 and Ho-166 suffer beta decayment following gama-rays emittion with half-life of 46.8 hours and 1.11 days, respectively. For Sm-153, the major gamma rays emittion are of 103 keV e 69 keV. The main beta emittion are of 808 keV (%), 705 keV (%) and 635 keV (%), at endpoint energy. The Sm- 153 emits X-rays of 40.5 keV and 41.5 keV. For Ho-166, the main beta emittion is 1.85 MeV (%). The gamma rays emittion of Ho-166 are 0.08 MeV [15]. Barium is a suitabel nuclide for contrast. It can be incorporated on the seeds and on the foils for improving contrast. Barium may be include after activation of the powders. However it may be activated together with Sm and Ho devices, due to its lower absorbed neutron cross section and its lower half-life. However, on the present study it has been used as a model. Later, new others contrast elements can be investigated.

The goal of this study is to propose a method of monitoring implants made of polymeric and ceramic devices in humans, suitable for brachytherapy treatments of tumors *in situ*, through low cost conventional X-ray. Those radiological methods are of easy access to the population. Radiological studies have been developed on the research group NRI/PCTN [16].

2. MATERIALS AND METHODOS

2.1 Synthesis of samarium and holmium ceramics seeds

In order to synthetize the ceramics seed with three-basic-elements or four-basic-elements such as: [Si: Ca: Ho], [Si: Ca: Ho:Ba] and [Si: Ca: Sm], [Si: Ca: Sm: Ba], the following chemical compounds was used: tetraetilortosilicato ($C_8H_{20}O_4Si$), hydrate calcium nitrate ($Ca(NO_3)_2.4H_2O$), deionized and distilled water, 2N nitric acid solution (HNO_3), barium nitrate $Ba(NO_3)_2$, holmium III nitrate ($Ho(NO_3)_3$) and hydrated samarium nitrate ($Sm (NO_3)_3.6H_2O$). In the preparation of each sample, the compounds were diluted and homogenized, then poured into molds on vacuum. For the synthesis of the ceramics seed, sol-gel processing was followed. According to previous protocol [4, 5] the steps of gelation, aging, drying and heat treatment were followed. Finally the seeds were cooled in ambient temperature and saved in appropriate recipient.

2.2 Synthesis of polymeric membranes

In order to process the polymeric membranes of [PVA: Ho], [PVA:HoBa] and [PVA: HoBa] in which Ba has been incorporated by $BaSO_4$, the following compounds were used: polyvinyl alcohol (PVA), deionized and distilled water, [Si:Ca:Ho] bioglass powder with controlled granulometry, [Si:Ca:Ho] bioglass powder bioglasses also with controlled granulometry together with barium sulphate ($BaSO_4$) on powder.

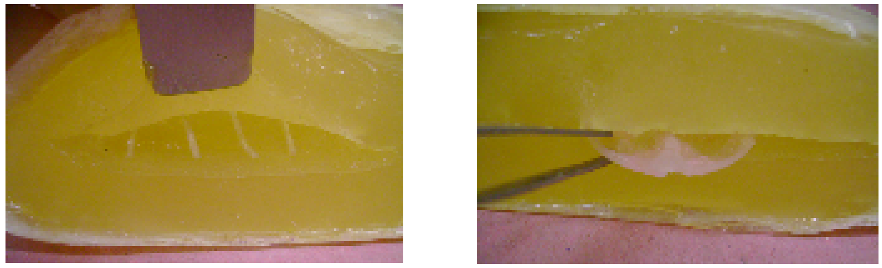
The following mixture was prepared: the distilled and deionizing water was heated at 100 °C. In a heater with magnetic stirrer, PVA powder was added slowly until the solution becomes homogeneous. The same procedure was done with the Ho bioglass powder, [Si:Ca:Ho] bioglass and $BaSO_4$ powders. The mixture was poured into silicon molds with diameter of 20 mm, where the mixture rest for 24 h at ambient temperature and submitted to pour vacuum to bobble elimination. The dry occurred in oven after 2 hours at 60 °C. The polymeric membranes were stored in appropriate recipient for future use.

2.3 Mounting ceramic seeds in thin silicon tubes

The ceramics seeds were mounted in translucent silicon tubes of 0.6 mm of external diameter and various lengths. The silicon tube was cutted for placing the ceramic seeds. These were filled with five ceramics seeds with 0.2 to 0.3 mm diameter and 1.6 mm length, separated with polymeric spacers of 0.04 mm in diameter and 3.0 mm length. These tubes were mounted with ceramics seeds made of [Si: Ca: Ho: Ba], [Si: Ca: Ho], [Si: Ca: Sm: Ba] and [Si: Ca: Sm].

2.4 Device implants on phantom of equivalent tissue (TE)

The silicon tubes of ceramic seeds and the polymeric membranes were implanted in the glandular tissue of a compressed breast phantom. The glandular equivalent tissue was cutted with a scalpel blade number 15 at the half-thickness. The devices were placed inside with helping of a tweezers. The cut was made in the longitudinal length, in the middle of synthetic glandular tissue, in which the devices were packed inside, as shown in Fig.1 (A) and (B).



A B

Figure 1 – (A) the implants of silicon tubes with ceramics seeds and (B) polymeric membranes into the synthetic glandular tissue.

2.5 X-ray image generation of the devices on the breast phantom

The image generation was performed using a conventional X-ray equipment MT-200 with maximum current and voltage of 600 kV and 120 mA respectively. The conventional equipment was chosen to take image on the breast phantom due to the X-ray hardness of the spectrum produced. Such hard spectrum may generate lower dose on the breast and being useful to figure out the position and orientation of the seeds. One shall be taken in mind that the goal is not to identify micro calcification accomplished only by mammography but monitoring macroaggregates of 0.3 x 1.6 mm dimension.

The compressed breast phantom was placed parallel the radiological 18 X 24 cm film, whose central beam was focused perpendicular to the central region of the same. For the image generation used a 1.00 m DFOFI.

2.6 Mammography image generation to the devices on a breast phantom

Mammography was taken of a compressed breast phantom in order to verify the visibility of the implanted devices and to evaluate the radiological response of the equivalent-tissues of the phantom. For the generation of the images, mammography equipment (Graph-Mamo) manufactured by VMI, semi-automatic, was used. Two incidences were taken for this protocol. The first incidence simulating a skull-flow exam of the breast, using exposure factors of 22 kV and 136 mAs, with a compression of the breast phantom of 0.37 cm. The second incidence was performed to magnify the area of the devices implantation, with exposure factors of 29 kV and 67 mAs, with compression of the breast phantom of 0.30 cm. The processing radiographic images were performed by automatic mammographic processing according to manufacturer's instructions.

2.7 Computed tomography (CT) image generation of the devices on the breast phantom

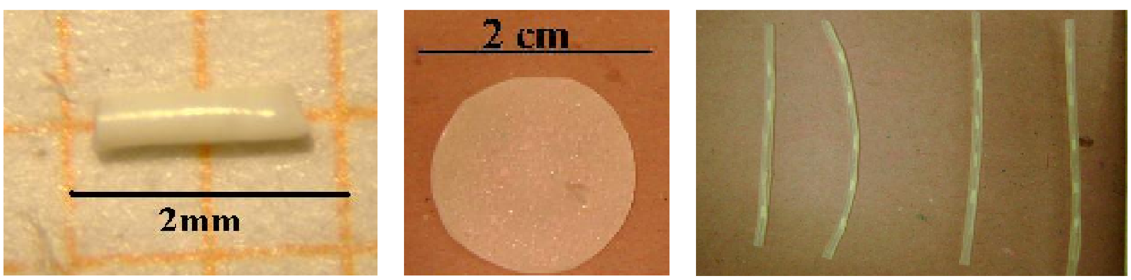
The generation of CT images of the polymer and ceramic devices implanted in the breast phantom was performed in an equipament multislice of Siemens with six channels of detectors. The protocol used on the image generation was based on a routine of the thorax, using thinner cuts than it is usual for this routine. The first exam was performed in the acquisition of axial cuts, then was the reconstruction of coronal and sagittal cuts. The thickness of each cut was 0.8 mm. The distance among sections ranged from 0.6 to 1.0 mm between acquisitions axial, sagittal and coronal acquired. The exposure factors used were 130 kV and 100 mAs with of scanning time of 40 seconds. The radiographic processing of the cuts generated was performed by the generation data software of the equipment. From the data obtained in the scan, the images were processed, generated and reconstructed.

3. RESULTS

3.1 Macroscopic devices visibility

A ceramics device is shown in Fig.2 (A) illustrating the shape and aspect of the [Si:Ca:Ho] ceramic seed on 80X optical stereoscope. The produced polymeric PVA membranes with [Si:Ca:Ho], identified by PVA:HoBa, has Ba incorporated as $BaSO_4$ and Ho incorporated as aggregate powders made of sol-gel. A sample of PVA:HoBa is shown in Fig. 2 (B).

The mounting of silicon tubes with ceramic seeds, spaced by nylon tubes, resulted on thin tubes of 3.0 cm length. The seed encapsulation on polymeric tubes allowed easy ceramics seeds placement on the glandular implant, as well as better visibility in radiological image. The four tubes of mounted seeds, previous the implant, are shown in Fig. 2 (C).



A B C

Figure 2 – (A) Ceramics seeds of [Si: Ca: Ho], (B) polymeric membrane of PVA: HoBa with $BaSO_4$ incorporated and (C) Four translucent silicon tubes with five ceramic seeds, spaced with nylon tubes, made of [Si: Ca: Ho: Ba], [Si: Ca: Ho], [Si: Ca: Sm: Ba] and [Si: Ca: Sm] respectively.

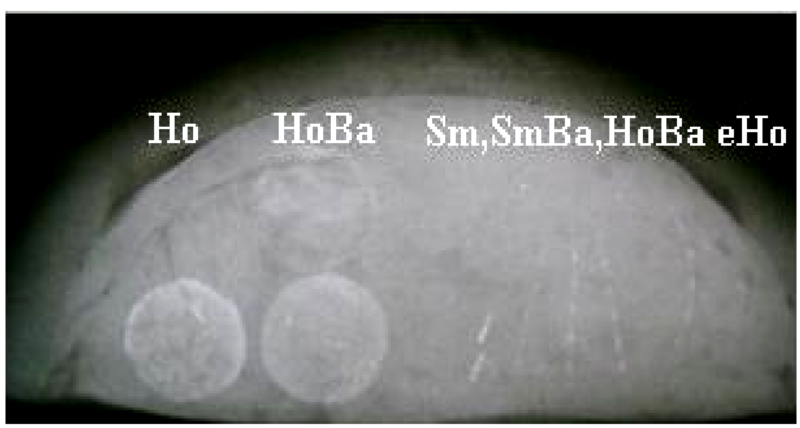
The Sm and Ho composition in its respective ceramic seeds was investigated by NAA (Neutron Activation Analysis) and spectrometry, identifying 18.0% of Sm and 20% of holmium. These data represent the weight percentage of Sm and Ho compounds found in each seed. Those values were equivalent to those defined by stoichiometry [17].

3.2 Visibility of polymer and ceramic devices on the X-ray image of the breast phantom

The images generated by conventional X-ray equipment showed radiological visibility required to identify the polymer and ceramic devices into the glandular equivalent tissue on the breast phantom. Fig.3 (A) and (B) shown images made without and with antidiffuser grade with 1.0 m DFOFI.

A

Figure 3 – (A) Conventional X-ray image of the breast phantom with the polymer and ceramic devices placed inside without the antidiffuser grade.



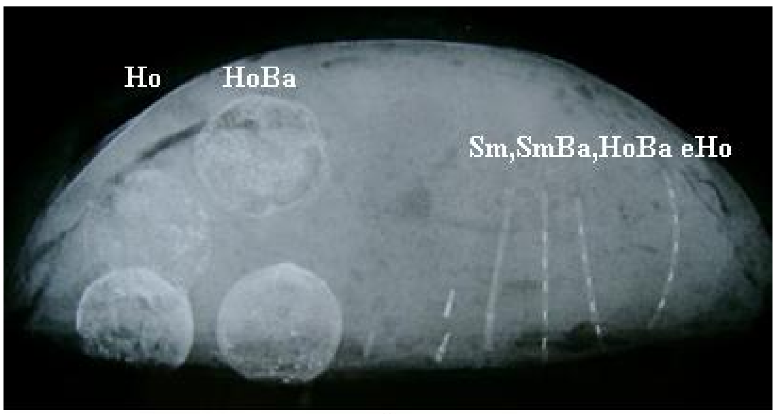
B

Figure 3 – (B) Conventional X-ray image of the breast phantom with the polymer and ceramic devices placed inside with the antidiffuser grade.

The image taken with antidiffuser grade provides better radiological visibility of the devices on the TE breast phantom. However, it is possible to note that the radiological contrast between polymer and ceramic device on the breast phantom is the same on the two images.

3.3 Visibility of polymer and ceramic devices, and breast phantom by mammography image

The images generated by mammography, showed more accurate radiological visibility than the images made by conventional X-ray equipament. It is because this method of image is very sensitive to identify microcalcification. The mammographic images have the same polymer and ceramic devices implanted in the breast phantom, which were identified by conventional X-ray equipment. The two images generated by the incendence skull-flow and magnification, provide high-quality images with suitable radiological visibility of both devices, as the TE of the breast phantom, as shown in Fig.4.



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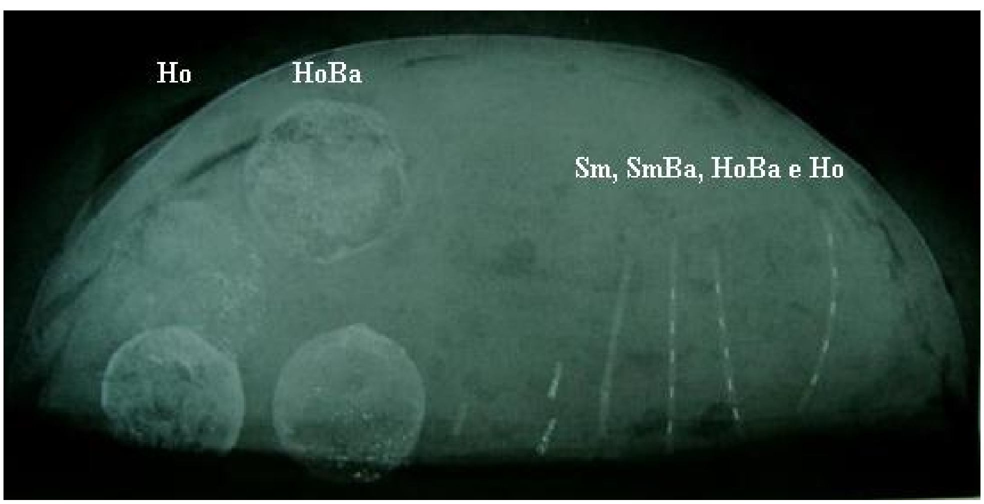


B

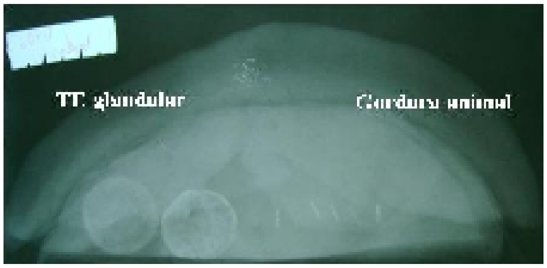
Figure 4- (A) Mammographic image of breast phantom and (B) mammographic image with an incidence magnification of breast phantom, with the polymer and ceramic devices implants.

Figure 4 (B) shows the magnification of the breast phantom. The image provides a better detail of polymer and ceramic devices, expanding significantly the structures, without losing the sharpness of same. Evaluating the images, it is clearly noticed the five ceramic seeds spaced within the SmBa, HoBa and Ho segment line. The ceramics seeds of Sm were not identified because it had degraded within a period of two months under the glandular TE. This period of time corresponds to the time that had occurred the implant until the mammography. In this case, it is observed a silicone tube empty with few fragments of the seed. Adding contrast agent, Ba:Sm seeds were observed intacted. The agent Ba increases the time of degradation of the same. For the Ho and Ho:Ba seeds, Ba slightly increases the radiological visibility, shown non sign of degradation of same.
The mammography has resulted in visualization of the four membranes. It is noted that Ho's membrane in direct contact with TE degrades and loses radiological visibility. While, the other membrane of Ho, involved with plastic, remain visible radiologically. In turn, both the membranes of PVA:HoBa and PVA: HoBa with $BaSO_4$ in direct contact with the tissue were also visible radiologically, because of the contrast agent. So, the Ba also helped in the radiological visibility by mamography of polymer and ceramic devices implanted.

The radiological response of the TE of the compressed breast phantom was investigated. The mammographic images showed the radiopacity of glandular TE, compared to the radiotransparency of the adipose TE, as shown in Fig. 5. Then, the developed compressed breast phantom shows to be a simulator of the human mammary structure.

Figure 5- Image focused on the demonstration the radiological response of the adipose TE and glandular TE.

The radiological equivalence of adipose TE can be proven by conventional X-ray image, in which the glandular TE on the breast phantom has been covered half with glandular TE and other half with animal adipose. The result of the image has the same radiological response between the two components. This result demonstrates the perfect radiological equivalence, as Fig. 6.



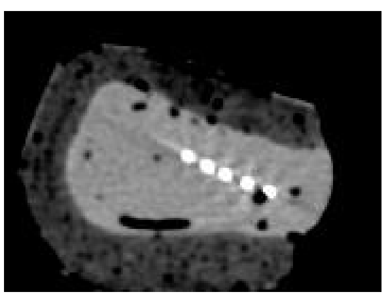
A

B

Figure 6 – (A) X-ray image of breast phantom covered with adipose TE and animal adipose (B) X-ray image focused on demonstration between adipose TE and animal adipose.

3.4 Visibility of polymer and ceramic devices on the breast phantom by computed tomography (CT) image

The images generated by CT showed radiological contrast between the implanted devices and the phantom breast. The images generated of the compressed breast phantom in sagittal sections allowed to identify the presence of ceramics seed wires and the polymeric membranes, as shown in Fig.7.



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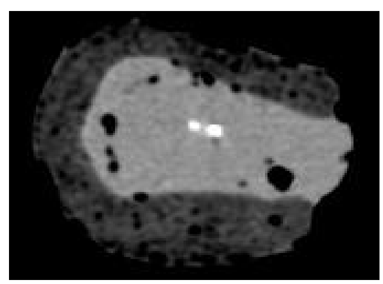

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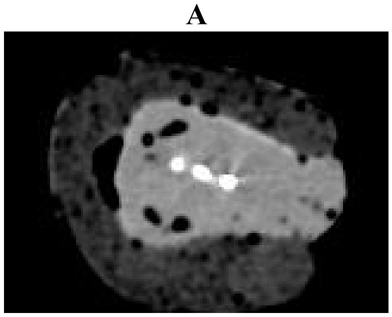

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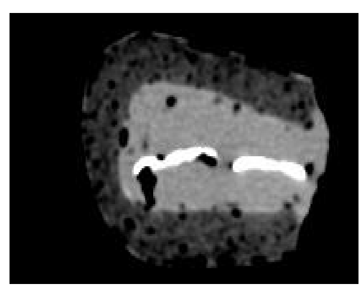
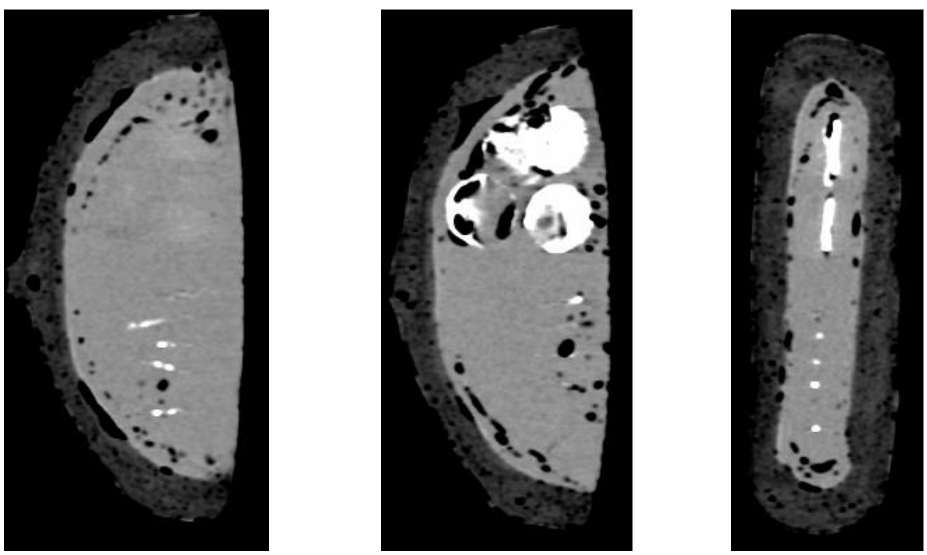


D

Figure 7 – Tomography image in sagittal cut of breast phantom showing (A) five seed of Sm:Ba, (B) two seeds of Ho:Ba, (C) three seed of Ho and (D) two polymeric membranes.

On Figure 7 (A) there is five Sm:Ba seeds implanted, while in (B) and (C) is only possible to visualize respectively, two Ho:Ba seeds and three Ho seeds implanted. This is due to the position of the wire in the implant and the direction of the cut held, since the wires mounted with the seeds were not aligned with the cut. However, through of cuts, it possible to visualize the start and end of the wire of the same. The Sm seeds mounted in silicone wire were not visualized, because it already was in advanced process of degradation. Although of the seeds are not made of metal but of ceramic material, is noted in the images the presence of small artifacts kind rays leaving the same, however well reduced. The presence of barium increased considerably the high absorption of the material and consequently the possible generation of artefact rays. Figure 7 (D) visualized the presence of two membranes implanted, a PVA:HoBa and other PVA:HoBa with $BaSO_4$, and the other two membranes consisting of PVA:Ho, showing no artifacts in the images.

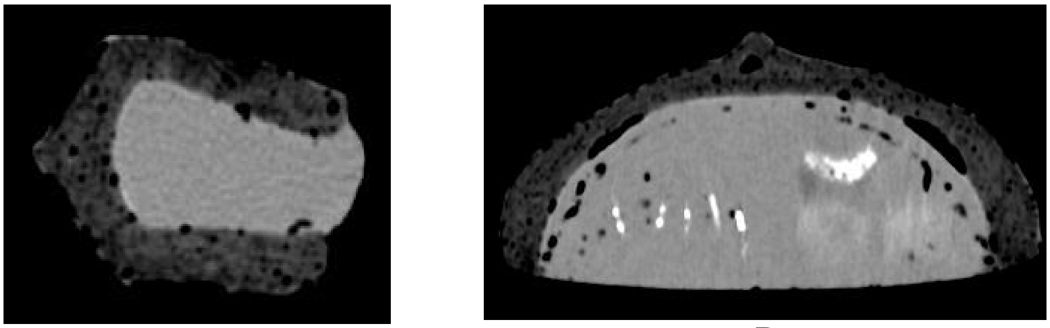
The Fig. 8 shows the acquisition of axial sections and reconstruction in coronal ones. It is observed in Figures 8 (A) and (B), respectively, the cross-section did not coincide with the plane of the ceramic seed wires, thus only part of the segments can visible. However, for the polymeric membranes, observed a better result, viewing almost all size of the same, because the cut was well located. Figure 8 (C) in coronal position, points of the ceramics seeds and the two polymeric membranes can be visualized. The CT allowed the study of implanted polymer and ceramic devices by generated images in a broader view.



A B C

Figure 8 – Tomography image in axial section of the breast phantom showing (A) four wires with the ceramic seeds, (B) four polymeric membranes and (C) points of the wires with the ceramic seeds and the polymeric membranes.

Fig. 9 (A) and (B) is to assess the composition of the TE of breast phantom, through the selection of axial and sagittal cross section in the middle of the same. The radiological anatomy of the phantom is depicted showing the papilla, the radiopacity of the glandular TE and radio transparency of adipose TE. As previously mentioned, the presence of air within the same depredates the image, with areas of high radiological density.



A **B**

Figure 9 – Tomography image in sagittal cut of the breast phantom showing (A) com glandular TE response and (B) adipose and glandular TE.

CT images are composed of color pixels in scale of gray level, which one represented by a numerical values equivalent to Hounsfield unit (HU), for example: -1000 for air, 0 for water and + 1000 to the cortical bone. The HU values for the phantom are presented in Table 1, in comparison to the HU corresponding tissues of the human body. It is found that the value for adipose TE is in according to the range of variation estimated for the corresponding tissue on the human body. However, the glandular tissue shows little variation in its range. Observe that the values of maximum and minimum reported in the literature should be better investigated. Also, several regions of the glandular TE shall be evaluated later. However, it is confirmed the equivalence by CT radiological response of the compressed breast phantom with a real breast.

Table 1. CT radiological responses reproduced by the Housfield number.

	N° de Hounsfield (H.U) / SD	Maximum	Minimum
Adipose TE	-100,1 / 16,9	-100[a]	-10[a]
Glandular TE	76,8 / 12,1	60[b]	40[b]
Seeds	1248,2 / 143,8	______________	______________

Source: a [17], b [18].

4. CONCLUSIONS

As conclusion, it is possible monitoring implants of small ceramic and polymer devices through simple method of radiological diagnostic, such as conventional X-ray and mammography which is easily accessible to all Brazilian population. This observation is limited to the conditions found in breast implants, neck implants, or parts up to 12 cm thickness, experimented on this research. The extension of this observation to anatomical parts with greater thickness shall be further evaluated. This monitoring will demonstrate the position, orientation and the degradation stage of the polymer and ceramic devices implanted. Implants in small animals are in progress. It will show the *in vivo* radiological visibility of polymer and ceramic devices in development. Those implants shall be applied for controling tumors *in situ* mainly in initial stage.

ACKNOWLEDGMENTS

The authors acknowledge the CNPq, process n. 550661/2007-7 and n. 471173/2007-0 by financial aid and the help of scholarship. The authors also thank the CNEN for the help of scholarship.

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