DEVELOPMENT AND CHARACTERISATION OF IRIDIUM-192 SEEDS FOR BRACHYTHERAPY TREATMENT OF OCULAR TUMORS

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Even ocular tumors are not amongst the cases with a high incidence, they affect the population, particularly children. The Institute of Energy and Nuclear Research (IPEN-CNEN/SP) in partnership with Escola Paulista de Medicina (UNIFESP), created a project to develop an alternative treatment for ophthalmic cancer that uses iridium-192 seeds in brachytherapy. This work aims to study and develop a seed of iridium-192 from a platinum-iridium alloy The prototype seed has a 3.0 mm long core sealed by a titanium capsule of 0.8 mm of outer diameter, 0.05 mm of wall thickness and 4.5 mm long. We developed a methodology that covered: characterisation of the material used in the core, creation of a device for neutron activation of the cores and leakage tests. The results show that this methodology is feasible. As a suggestion for future work, studies regarding metrology and dosimetry of these sources should be carried out.

1. Introduction

1.1 Cancer in Brazil and Worldwide

According to World Health Organization (WHO), cancer is a leading cause of death worldwide. Only in 2007, 7.9 million deaths were accounted (about 13% of worldwide deaths) and 12 million new cases of cancer were diagnosed [1,2]. The continued ageing and population growth will affect significantly the impact of cancer in the world. Recent studies carried out by the International Agency for Research on Cancer (IARC) estimates that in 2030 will be 26.4 million new cases diagnosed, with 17 million deaths accounted worldwide [3]. The most incidents, excluding non-melanima skin cancer, are prostate and lung cancer in males and breast and cervical cancer in females [1,2].

1.2 Ocular Tumors

Despite of ocular tumors are not amongst the cases with a high incidence, they still affect the population, particularly children [4,5]. The methods used for treatment of ophthalmic tumors are: enucleation (complete removal of the eye), teletherapy (EBRT External Beam Radiotherapy), cryotherapy, chemotherapy and brachytherapy. These forms of therapy are valid, but have limitations. Brachytherapy has been shown as an effective way for treatment since it is practible for ocular tumors [6].

1.3 Ophthalmic Brachytherapy

The ophthalmic brachytherapy is a therapy that uses radionuclides for treatment of ocular tumors. These radionuclides are arranged in anatomically designed plaques, for ophthalmic use, which are placed surgically just above the base of the tumor. These plates (Figure 1) are made of platinum or gold and may be filled with radioisotopes seeds, such as ruthenium-106, rhodium-106, iodine-125, palladium-103, gold-198, cobalt-60 and iridium-192 [7,8].

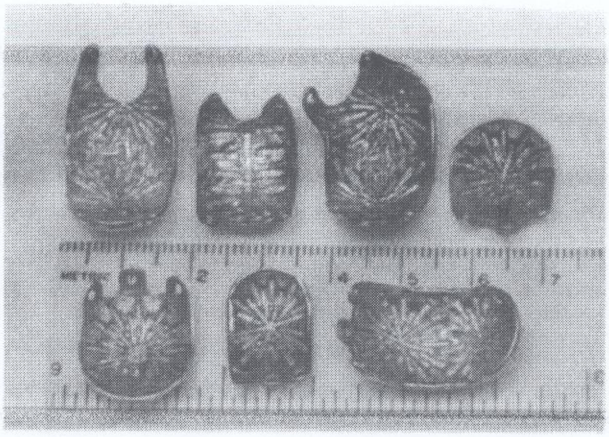

Fig 1: Ophthalmic plaques made of gold, with internal grooves to deposit radioactive seeds[7].

The selection of the most appropriate plaque for the treatment depends on size, depth, type of tumor, and particularly, the distribution of dose desired by the physician. The plaques used for the treatment of ophthalmic tumors in Brazil are imported and very expensive [25,26]. This project of Nuclear and Energy Research Institute - IPEN came up due to the need to reduce costs and provide this treatment to a larger number of patients under the national healthcare service. This work aims to develop a seed of Iridium-192 for further evaluation of its use in ophthalmic brachytherapy.

2. Methodology

The wire was purchased from the multinational company Goodfellow, which provides Ir-191 in the form of a platinum-iridium alloy, with a composition of 25% iridium and 75%, encapsulated with 100% platinum and 50cm long. The scheme of iridium-192 seeds (Figure 2), that will be used for this work, is arranged as follows: the core, (capsule of platinum-iridium alloy), 3.0 mm long, is sealed by a titanium capsule with 0.8 mm of outer diameter, 0.05 mm of wall thickness and 4.5 mm long.

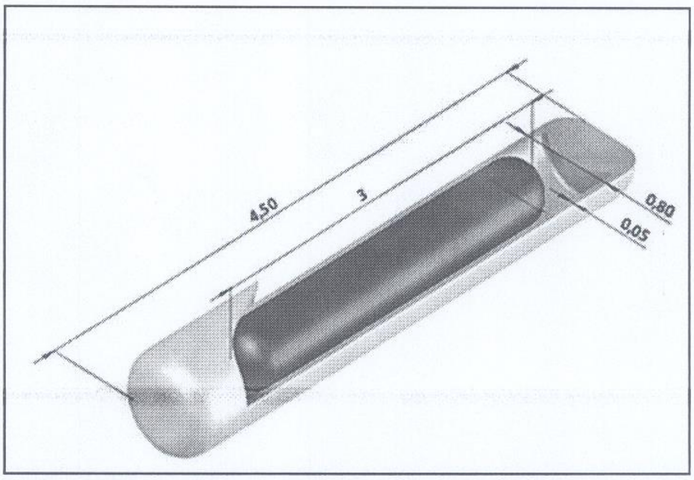

Fig 2: Dimensions of Iridium-192 seeds

2.1 Characterisation of Iridium-192 wires by Wavelength-dispersive X-ray spectroscopy (WDXRF)

The analysis of the Iridium-platinum alloy (Ir-Pt) was performed using the technique of wavelength-dispersive X-ray spectroscopy (WDXRF), in order to verify the presence of contaminants in the covering and core of the wire.

The methodology for the determination of major and minor constituents, using this technique, was divided into three steps:
1° Step:: The sample, Ir-Pt alloy (25-75) encapsulated with platinum (100%) was placed on an acrylic substrate and set to established conditions for RIX 3000 X-ray fluorescence spectrometer.
2° Step: A mass of 0.76 g of sample was dissolved in a solution of "aqua regia", in the proportion of 3 HCl: 1 HNO_3, under heating (200-250 ° C). After three days, an aliquot of 100 μL was deposited on a substrate of polypropylene (thin film for XRF, 5μ-SPEX). When the sample was already dry, it was placed on a specific sample holder for this type of test (micro X-cell - SPEX) and set to established conditions for RIX 3000 X-ray fluorescence spectrometer. This step is required to remove the encapsulation of the sample, in order to analyse the constituents of the alloy core.
3° Step: The undissolved sample (residue in aqua regia solution) was washed with MilliQ water, dried and weighed. Subsequently the sample was placed on an acrylic substrate and set to established conditions for RIX 3000 X-ray fluorescence spectrometer.
Quantitative determination was performed using using *2 theta scan* mode, available on the software of the spectrometer. It was assumed that the sample is homogeneous, has infinite thickness and has a flat surface [6].

2.2 Iridium Activation at IEA-R1

Iridium activation was achieved by leaving the sample for 4 h at the IEA-R1 reactor (IPEN), which is currently operated at a maximum power of 4.5 MW [9].
The activated isotopes of the irradiated Pt-Ir wire are the following:
I. Iridium-192, half life of 74.2 days, cross section of 910 barns, average gamma-emission energy of 370 keV and 37.3% of isotopic abundance (Ir-191) [10].
II. Iridium-194, half life of 19 hours, cross section of 112 barns, gamma-emission energies of 294 keV and 328 keV (major) and 62.7% of isotopic abundance (Ir-193) [10].
III. Platinum-197, half life of 18.3 hours, cross section of 0.7 barns, gamma-emission energies of 77.7 keV, 191.4 keV and 25.3% of isotopic abundance (Pt-196) [10].
IV. Platinum-199, half-life of 30.8 minutes, cross section of 3.7 barns, gamma-emission energies of 186 keV, 246 keV, 317 keV, 493 keV, 543 keV and 714 keV and 7.2% isotopic abundance (Pt-198) [10].
For activation of iridium cores at IEA-R1 reactor under the required conditions, the iridium-platinum wire was cut into 70 pieces, 3 mm long. Then, it was measured the length (in mm) and weight (in grams) of each core. The cutting process of the cores was made manually, and then, it was obtained length variation between 2.82 mm - 3.32 mm. The weights of these cores also varied in the range of 4.3 mg - 5.3 mg.
Core supporting devices were developed using two materials: Teflon (polytetrafluoroethylene) and Aluminum-27. The first, when activated, generates two radionuclides: carbon-14, with a half-life of 5700 years, but with a very low activity (0.0007 Bq), and fluorine-20, with a half-life of 11.07 seconds. Aluminum-27 produces sodium-24, half-life of 15 hours, through α decay, and this becomes magnesium-24 (stable) through β-decay. It also produces aluminum-28, half-life of 2.3 minutes, which undergo β^- decay, generating silicon- 28 (stable) with a half-life of 2.3 minutes [11-12].

2.2.1 Device 1

It was developed using *Teflon* (tetrafluoroethylene) cylinder, with approximately 1.8 cm of diameter. Using a pneumatic drill, 18 holes of 0.5 mm diameter and 1.5 mm was made in the tube, so each core could be placed (Figure 3). The system also has a lid (Teflon) to prevent core shifting during irradiation and an aluminum handle for manipulation of the system.

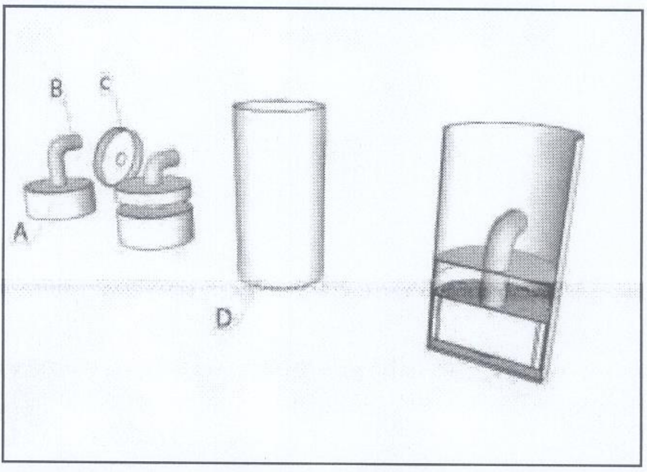

Fig 3: Diagram of the device used to support the cores. A) *Teflon*-piece used as a support of the nucleus, B) aluminum handle used to manipulate the system, C) Teflon lid used to prevent displacement of the cores, D) "rabbit" container.

2.2.2 Device 2

Device 2 was developed using a Teflon cylinder with a diameter of approximately 1.8 cm. At the center of this cylinder, a sagittal cut was made resulting in two arcs of equal measures. In these arcs surface, small cavities were created in four columns and five rows, in order to deposit the iridium cores (Figure 4). The two were bonded to each other in such way that the cores suffer no displacement during irradiation in the reactor

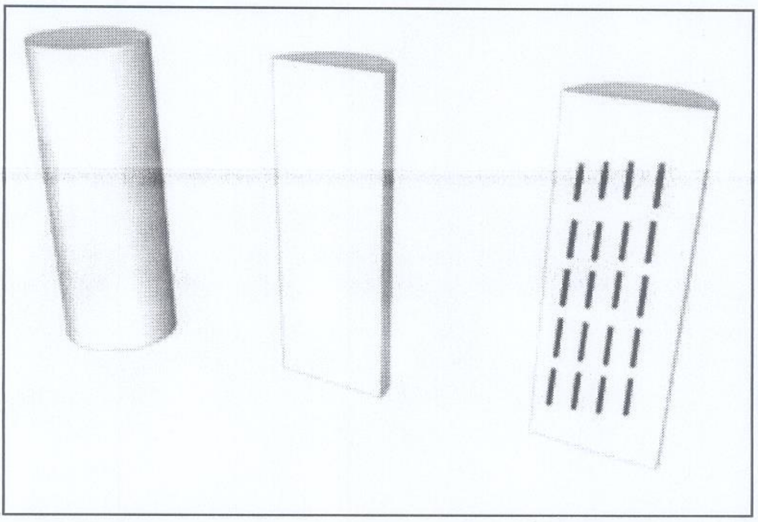

Fig 4: Schematic design of the device used to support the cores. From left to right: Teflon cylinder; sagittal cylinder; cavities arranged in a "matrix" form (rows and columns) for accommodation of the cores.

2.2.3 Device 3

It was developed using an aluminum cylinder with a diameter of approximately 1.8 cm. At the center of this cylinder a sagittal cut was made resulting in two arcs of equal measures. Cavities were created for the deposition of the iridium cores at the surface of one of the arcs (Figure 5). To ensure a fixed position of the cores inside the holder, the device was sealed with a thin aluminum sheet (0.5 mm).

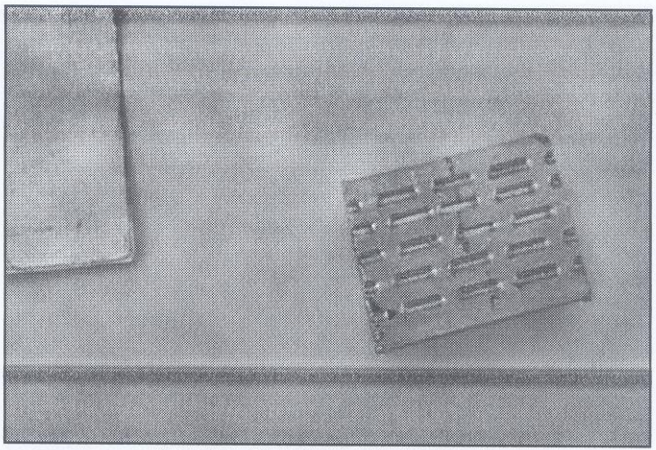

Fig 5: Scheme of device 3

2.3 Activity measurements of Iridium-192 cores

The activity of the cores was measured using a Capintec gas ionisation chamber, well type, model CRC-15R. The activity of each core was measured 3 times, and then, the average activity was calculated.

2.4 Encapsulation of the cores using laser welding

The radioactive cores were inserted into a capsule made of titanium and sealed at both ends. The capsule of titanium has a diameter of 0.5 mm, length of 5.0 mm length and must be already sealed at one end (figure 12). The equipment used was a laser welding supply company Miyachi Unitek laser welder, Model LW 15A - 2T, which operates at 15 W of power. There was also a microscope focused on the welding region to facilitate the procedure (Figure 6).

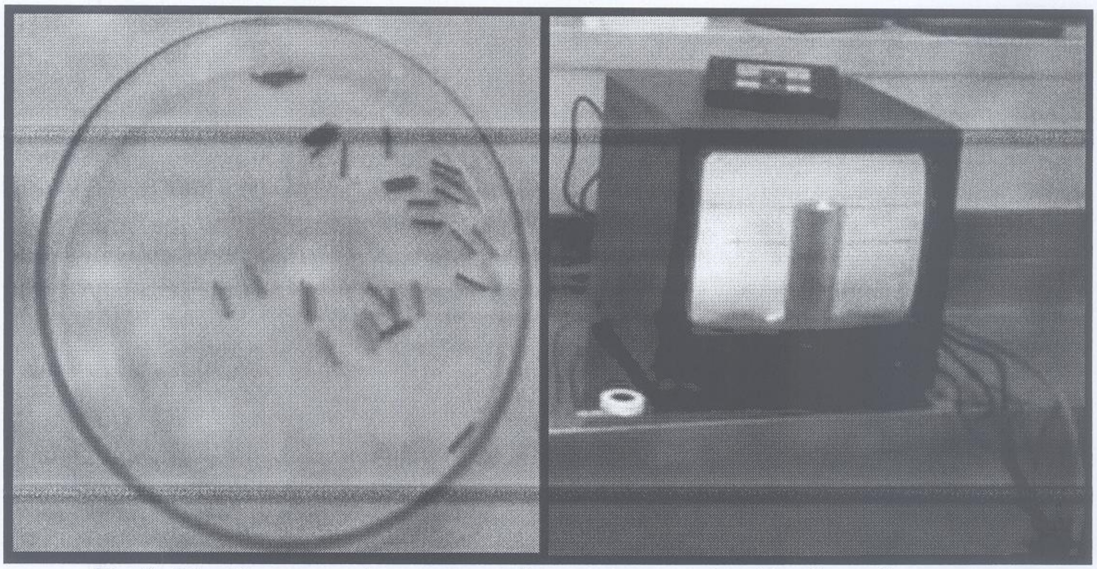

Fig 6: Titanium capsules and welding region provided by the microscope

2.5 Leakage tests in accordance with the standard *ISO-9978*

Each seed was put separately into acrylic test tubes and placed into a device coupled to an ultrasonic cleaner. In each tube, 2 mL of distilled water was added and then, the ultrasonic cleaner was turned on for 10 minutes. After that, seeds were left immersed in the tubes for 24 hours at 20 ° C (± 5 ° C). Finally, the water activity of each test tube was measured by two different radiation detectors: gas ionisation chamber and NaI(Tl) detector, both Capintec - model CRC-15W [13].

2.6 Measurement of the source activity

The activity of the source produced after the whole process was measured by a Capintec pressurized ionisation chamber, model CRC-15R.

3. Results

The wire supplied by the company Goodfellow, has a diameter of 0.25 mm and consists of a core of Ir- Pt alloy (25/75), with a coverage of 100% platinum .

Spectra obtained by wavelength-dispersive X-ray spectroscopy (WDXRF)), show that the sample consists of a layer of platinum (AM- 1) of high purity (99.9 %) and a core composed of iridium -platinum (AM- 2) in which platinum is the major component . Furthermore, we noticed that the aqua regia solution did not dissolve the core (the alloy of Ir -Pt), since in the dissolved sample (AM -3), only spectrum lines characteristic of platinum were identified (same result obtained by AM- 1.)

The difference in intensities amongst samples AM-1, AM-2 and AM-3 is due to scattering and absorption of primary X-rays, caused by the substrate and the amount of sample. In the sample AM -1 we used 0.76 g and in the AM-2, 0.08 g, both of acrylic substrate. In AM- 3, we used 100 µL of solution onto the polypropylene substrate. In Figure 7, it is possible to see that the presence of iridium occurs only in AM- 2 .

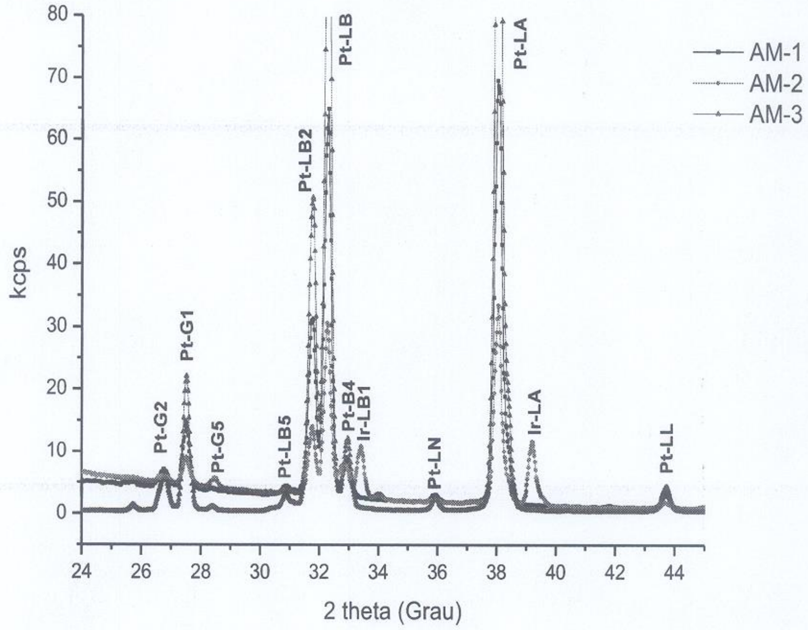

Fig 7: WDXRF Spectra of Ir-Pt alloy

Table 1 shows the results concerning wire composition obtained by WDXRF.

Tab 1 – Results obtained by WDRFX of Ir-Pt wire sample.

Element	AM-1(%)	AM-2 (%)	AM-3 (%)
Pt	99,9±0,1	76,7±0,1	99,9±0,1
Ir	***	23,3±0,1	***

*** = Not detected

The proposed core supporting devices, described above, were made by the mechanical workshop of IPEN. Table 2 shows the average activity measured for each seed core in each device.

Tab 2: Determination of core activation homogeneity obtained by the 3 devices

	Device 1	**Device 2**	**Device3**
Cores	**Average (µCi)**	**Average (µCi)**	**Average (µCi)**
1	284	221	722
2	214	270	728
3	277	246	787
4	218	245	668
5	250	258	664
6	300	242	723
7	219	241	799
8	252	245	710
9	215	265	593
10	227	265	625
11	204	217	773
12	266	213	676
13	194	223	617
14	224	243	696
15	216	247	684
16	229	240	712
17	220	243	731
18	214	227	709
19	-----	219	640
20	-----	258	705
21	-----	-----	648
22	-----	-----	750
23	-----	-----	730
24	-----	-----	777
25	-----	-----	703
Variation	35.1%	12.3%	11.4%

The variation of seeds activity measured using devices 1,2 and 3 were 35.1%, 12.3% and 11.4% respectively. After sealing, the seeds were measured again using Capintec detector, model CRC-15R, and the activity values found were almost the same. Thus, the titanium capsule does not act as a shield. The leakage test performed showed activity about 1000 times smaller than that required by ISO-9978, in which the maximum activity allowed, after washing in water, is 185 Bq (5 nCi) activity [13]. Then, it was possible to conclude that there was no leakage of radioactive material.

4. DISCUSSION AND CONCLUSIONS

Results obtained by WDFRX analysis show that the wire provided by Goodfelllow has no impurities that may compromise its use in brachytherapy.

Analysis of the activation of the cores, performed with devices 1, 2 and 3, show that activation is enhanced depending on the position of the cores during irradiation. Devices 1 and 2 were made with *Teflon* material. It was noted that the cores did not maintain their initial positions because *Teflon* does not withstand the influence of radiation, compromising its structure. However, some improvement was observed, regarding the scattering of activity measurements, comparing the cores from device 2 with those from device 1. Probably, due to the position at which the cores were arranged on the device 2, the activity results were better.

Aluminum was used to construct the device 3. As it does not change its structure when exposed to radiation, good results in terms of homogeneity and activation were observed.

We must mention the existence of various uncertainties in this process, not quantified, which may contribute to a high dispersion of values, such as uncertainties of the ionisation chamber, the neutron flux, irradiation times, core masses and length - considering that the material is activated by the number of atoms in the sample.

Sealing process of the radioactive material, performed by laser welding, showed great results. The activity measured, after the procedure of ISO-9978, was close to zero, much lower than the 185 Bq (5 nCi) required by the norm.

Future works should be carried out: Adaptation of a more precise cutting process; evaluation of all the energies emanating from the seeds of iridium-192, Monte Carlo simulations of the source produced and mechanical and thermal trials required by ISO-2919.

5. REFERENCES

1 – WORLD HEALTH ORGANIZATION (WHO). *Cancer* . Fact Sheet nº 297 – Fev-2012. Available on: <http://www.who.int/mediacentre/factsheets/fs297/en/>.

2 - INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). *World Cancer Report 2008*. Lyon: International Agency for Research on Cancer (IARC), 2008. Available on: <http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/wcr_2008.pdf>.

3 - INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). *Globocan 2008 . Fast Stats - World*. Available on: <http://globocan.iarc.fr/factsheet.asp#INCIDENCE1>.

4 - INSTITUTO NACIONAL DO CANCER .*Estimativa 2012. Incidência de Câncer no Brasil/Instituto Nacional de Câncer*. Rio de Janeiro, 2011.

5 - Instituto Nacional do Câncer. *TNM: Classificação de tumores malignos*. Rio de Janeiro. 6° ed p. 254 - 258. 2004.

6 - AMENDOLA, B.; ET AL. Analysis of treatment results in 36 children with retinoblastoma treated by scleral plaque irradiation.*Journal of Radiation*.vol. 17, p. 63–70, Jan.1989.

7 - G. LUXTON, M. A. ASTRAHAN, P. E. LIGGETT, D. L. NEBLETT, D. M. COHEN, and Z. PETROVICH.Dosimetric calculations and measurements of gold plaque ophtalmic irradiators using iridium-192 and iodine-125 seeds. *International Journal of Radiation Oncoloy - Biology- Physics*. vol. 15, no. February, p. 167–176, 1997.

8 - LEDDICOTTE, G. W. The Radiochemistry of iridium. *Nuclear Science Series*, NAS-NS 3045. 1961.

9 - REATOR IEA-R1.INSTITUTO DE PESQUISAS ENERGÉTICAS E NUCLEARES. Available on: <www.ipen.br/sitio>

10 - ROSTELATO,M. E. C. M. Preparação de fontes de irídio-192 para uso em braquiterapia. 1997. Dissertação (Mestrado)- Instituto de Pesquisas Energéticas e Nucleares, São Paulo.

11 - NUDAT 2.6.Chart of Nuclides. Available on: <http://www.nndc.bnl.gov/nudat2/chartNuc.jsp.> acesso em mar. 2013.

12 - SEEMAN-EGGEBERT,H.; PFENNIG,W.; MUNZEL, G.; KLEWE-NEBENIUS,H.Chart of Nuclides. Karlsruhe , 1981.

13 - INTERNATIONAL STANDARD ORGANIZATION. (ISO 9978) Radiation protection – sealed radioactive sources – leakage test methods.1992.