Leakage test evaluation used for qualification of iodine-125 seeds sealing*

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Abstract. Brachytherapy is one of the possible treatments with ionizing radiation available for prostate cancer, in which small seeds containing iodine-125 radioisotope are implanted directly into the prostate. The seed consists of a sealed titanium tube containing a central silver wire with adsorbed iodine-125. The tube sealing is made with titanium at the ends, using plasma arc-welding (PAW) or laser process. This sealing must be leakage-resistant and free of cracks, therefore avoiding iodine-125 to deposit in the silver wire to escape and spread into the human body. To ensure that this problem is not occurring, rigorous leakage tests in accordance with the standard ISO-9978 should be applied. The aim of this study is to determine, implement and evaluate the leakage test to be used in the iodine-125 seeds production, in order to qualify the sealing procedure. The standard ISO-9978 presents a list of tests to be carried out according to the type of source. The preferential methods for brachytherapy sources are soaking and helium. To assess the seeds leakage, the method of immersion test at room temperature was applied. The seeds are considered leakage-free if the detected activity does not exceed 185 Bq (5 nCi). An iodine standard was prepared and its value determined in a sodium iodide detector. A liquid scintillation counter was calibrated with the standard for seed leakage tests. Forty-eight seeds were plasma arc-welded for these tests.

Key words: leakage test • iodine-125 seeds • prostate cancer • brachytherapy • titanium tube • standard ISO-9978

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Introduction

The use of permanent implants of iodine-125 seeds as a treatment of prostate cancer has increased with the introduction of new products and technological advances. The seed implants provide a less aggressive type of therapy than surgical procedures. A certain amount of seed is implanted in the patient using a fine needle through the skin to the prostate. A large dose of radiation is released only in the prostate where the tumor is, not affecting healthy organs nearby. The technique of brachytherapy requires an application that varies between 80 and 120 seeds [4].

As the occurrence of collateral effects is lower, 85% of patients up to 70 years old, remain sexually active after implantation. Also urinary incontinence rarely affects them [1]. The advantages of implants with radioactive seeds are the preservation of healthy tissues and organs near the prostate, the low rate of impotence and incontinence compared to conventional treatments, such as radical prostatectomy and external beam radiation

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[7, 8]. For most patients, seeds implantation is a low impact procedure and not a surgery. The patient can return to normal activity within one to three days, with little or no pain.

The seeds are implanted during a non-surgical procedure. Small seeds are injected directly into the prostate, between the rectum and scrotum, using a fine needle through the skin [2, 11]. A large dose of radiation is released only in the tumor, as iodine-125 radiation has a low average energy (29 keV) that is slightly penetrating, thus preserving the surrounding tissue [6, 9].

The seed consists of a sealed tube of titanium (biocompatible material to human tissue) measuring 0.8 mm external diameter and 4.5 mm in length, containing a silver wire with iodine-125 adsorbed. The sealing of the titanium tube is made, at both ends, by welding process using electric arc or laser. Taking into account plasma arc-welding this sealing should be watertight, free from cracks, avoiding the iodine-125 deposited in a silver wire to escape and spread through the human body [3].

To ensure that this is not occurring, rigorous quality control (QC) leakage tests should be applied according to the standard procedures ISO-9978: "Radiation protection – sealed radioactive sources – leakage test methods". Several procedures are described in the ISO-9978 standard and choice must be done using the Table "Selection of leakage test methods related to manufacturing technology" [5].

Methodology

Materials

For the leakage tests of the seeds according to the standard ISO-9978: "Radiation protection – sealed radioactive sources – leakage test methods", forty-eight seeds were sealed by plasma arc-welding, using tubes of commercially pure titanium, grade 2 (CP Titanium GR2), manufactured by the company Accellent Endoscopy, outside diameter ranging from 0.790 to 0.808 mm and wall thickness ranging from 0.043 to 0.058 mm and initial length from 6.90 to 6.97 mm. Inside the tubes silver wires with adsorbed iodine-131 were used. The PAW machine was made by Secheron Soudure S.A., model Plasmafix 50E, DC Voltage, maximum welding current and pilot arc current of 50 A and 5 A, respectively [3].

It was used iodine-131, that is produced in the Nuclear Research Reactor IEA-R1 (5 MW) at Institute for Nuclear and Energy Research (IPEN-CNEN/SP, São Paulo, Brazil) and has the same chemical behavior of iodine-125. The radioisotope iodine-131 has a half-life of 8 days and energy of its main gamma rays are: 80.2 keV (2.62%), 284.3 keV (6.06%), 364.5 keV (81.2%), 636.4 keV (7.27%) [10]. A liquid scintillation counter, brand Packard/Canberra, model Tri-Carb 1600 TR was used to determine the pattern of iodine-131 and to carry out the leakage tests of the seeds.

Methods

The pattern aims to determine the region of the spectrum where is located the peak of iodine-131 and quantified in counts per minute (cpm), the maximum activity allowed in the liquid, where the seeds had been washed after sealing. According to the standard ISO-9978, the maximum activity allowed in the sample liquid after washing is 185 Bq (5 nCi).

A sample of iodine-131 produced in the IEA-R1 (5 MW) at IPEN-CNEN/SP was released in the chemical form of sodium iodide, with an activity of 10.36 MBq (0.28 mCi) in a volume of 1 mL. This sample was diluted in 200 mL of water purified by an ion exchange system of the brand Milli-Q, model Academic, resulting in pattern P1, with a specific activity of 51.8 kBq/mL (1.4 μCi/mL).

A sample of 1 mL was removed from the pattern P1 and added to 99 mL of Milli-Q water, resulting in the pattern P2, with a specific activity of 518 Bq/mL (14 nCi/mL). A sample of 350 μL was removed from the pattern P2 and it was obtained the pattern P3 with a medium value of 181.8 ± 4.8 Bq or 4.91 ± 0.13 nCi, measured in a dose calibrator type sodium iodide brand Capintec, model CRC 15W. This pattern P3 was used for determining the reference value in counts per minute (cpm) in the scintillation liquid equipment.

As the value of the activity to be measured is small, less than 185 Bq (5 nCi), two types of containers were tested, one of boron-silicate glass (Pyrex) and one of polyethylene, for counting the pattern P3, Milli-Q water background (BG) and titanium BG samples. The efficiency of the liquid scintillation counter for the pattern P3 was calculated, in the glass-boron silicate and polyethylene (Eq. 1).

$$\text{Efficiency}\frac{\text{cpm}}{\text{dpm}}100\% \tag{1}$$

where: dpm is the activity of P3 in disintegration per minute [10]. As the value obtained in cpm is relative to the pattern P3 181.8 ± 4.8 Bq, the value in cpm for 185 Bq (5 nCi) was proportionally calculated.

The leakage test was chosen as the orientation provided in the guide of the standard ISO-9978 that allowed the choice of tests to be performed according to the control and type of source. The sources for brachytherapy are classified as type A3 and the preferred tests are immersion (5.1) and helium (6.1). The immersion test, at room temperature (5.1), was chosen using an ultrasound to check the seeds leakage [5].

Forty-eight plasma arc-welded seeds, with a medium activity of 851 kBq (23 μCi) per seed, were used to test the leakage of immersion. On the other hand, quality control following the ISO-9978 standard procedure, each of the seeds was immersed separately, in a vial containing a mixture of 8 mL distilled water and 2 mL of extran detergent. The vials were placed on the equipment, cleaned by ultrasound for a period of 1 h and left for another 24 h at room temperature. After this time, the seeds were removed and, to the remaining liquid, 10 mL of scintillator solution (trade name Insta-Gel) was added. Then, the activity of the radioactive solution was measured with a liquid scintillation counter. This procedure was repeated, except for the mixture of distilled water and detergent, which was replaced by 10 mL of distilled water only.

Table 1. Pattern P3 measures in dose calibrator type sodium iodide

Measures	Rating (Bq)	Rating (nCi)
1	182.0 ± 4.8	4.92 ± 0.13
2	180.1 ± 4.7	4.87 ± 0.13
3	186.9 ± 4.8	5.05 ± 0.13
4	180.2 ± 4.7	4.87 ± 0.13
5	179.7 ± 4.7	4.86 ± 0.13

Results

In Table 1, the medium activity value of the pattern P3 was calculated and the following results were obtained 181.8 ± 4.7 Bq or 4.9 ± 0.13 nCi. In Table 2, the medium value of the counting for the pattern P3, Milli-Q water background (BG) and titanium BG were evaluated and the following results were obtained:

– Pattern P3 in boron-silicate glass = 6,184.3 cpm;
– Pattern P3 in polyethylene = 6,274.8 cpm;
– Milli-Q water BG in boron-silicate glass = 48.1 cpm;
– Milli-Q water BG in polyethylene = 50.4 cpm;
– Titanium BG in boron-silicate glass = 50.1 cpm and
– Titanium BG in polyethylene = 50.6 cpm.

The value obtained with the container of polyethylene was used because it presented better efficiency, 57.5% (Eq. 1) with the liquid scintillation counter. As the value obtained in cpm matches the pattern P3, it was calculated proportionally to the amount 185 Bq (5 nCi) and the following results were obtained:

– 181.8 Bq (4.9 nCi) = 6,274.8 cpm and
– 185.0 Bq (5.0 nCi) = 6,385.2 cpm.

Out of safety, 6,350 cpm was taken as the maximum value allowed for iodine-131, contained in the liquid scintillator. After the first cleaning, as showed in Table 3 and in Fig. 1, a large variation in the values of the radioactivity counts of the remaining liquid occurred, since they were below the limit of 6,350 cpm, except for the seeds no. 33 and no. 44. The range indicates the need for a greater number of cleaning procedures.

In Table 4, the values obtained in leakage tests, after the second cleaning, may be seen. After the second cleaning, it can be observed in Fig. 1 that the values of the counts of the remaining liquid seeds were much

Table 2. Pattern and background (BG) measures in the liquid scintillation counter, in boron-silicate glass and polyethylene containers (cpm)

Boron-silicate pattern P3	Polyethylene pattern P3	Boron-silicate Milli-Q water (BG)	Milli-Q water (BG) polyethylene	Titanium BG boron-silicate	Titanium BG polyethylene
6,158.3	6,294.0	51.8	51.8	49.2	50.0
6,227.3	6,355.3	46.2	49.6	47.6	48.2
6,203.6	6,322.9	46.2	51.8	53.2	54.8
6,180.9	6,118.7	54.8	50.0	50.2	50.4
6,148.3	6,276.1	46.4	50.6	48.2	51.4
6,187.1	6,281.6	43.2	48.8	52.0	48.8

Table 3. Leakage test of the forty-eight seeds (1st cleaning)

Seed	Liquid remainder (cpm)	Seed	Liquid remainder (cpm)
1	213.2	26	785.4
2	1,284.8	27	1,136.6
3	521.8	28	1,174.0
4	654.8	29	815.0
5	709.6	30	1,435.0
6	685.4	31	872.2
7	984.6	32	4,399.8
8	1,037.6	33	6,530.0
9	806.4	34	2,039.8
10	518.0	35	2,524.8
11	455.2	36	737.4
12	655.8	37	1,837.6
13	498.0	38	726.8
14	699.2	39	1,315.4
15	1,221.4	40	1,346.6
16	990.6	41	2,234.6
17	1,272.2	42	1,776.2
18	1,527.0	43	1,419.2
19	2,373.8	44	10,258.4
20	5,790.8	45	3,145.4
21	2,359.0	46	1,332.2
22	671.0	47	2,304.6
23	1,291.0	48	1,722.4
24	3,026.8	Milli-Q water (BG)	47.6
25	2,465.8	Titanium BG	50.2

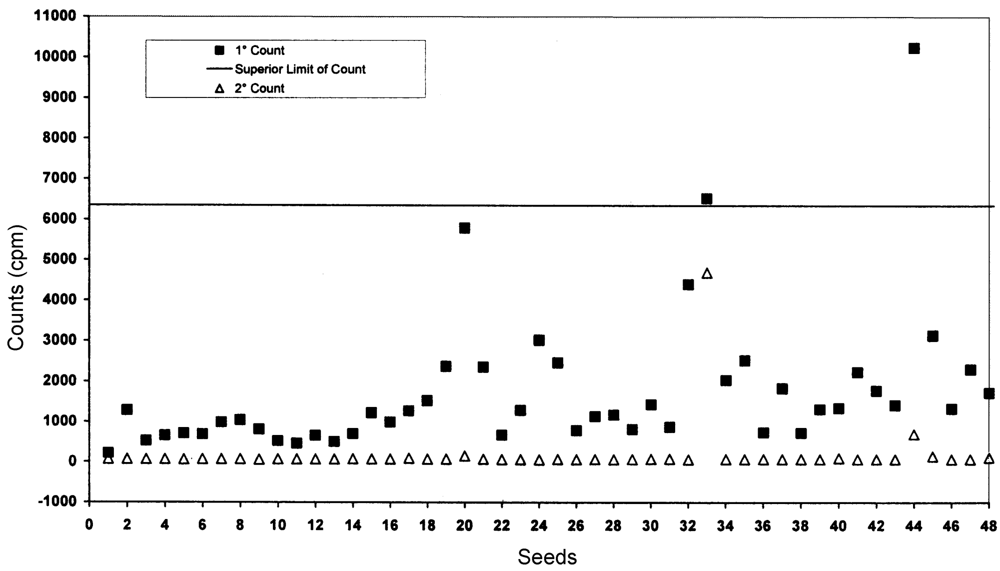

Fig. 1. Iodine-131 activity in water after leakage test (1st and 2nd cleanings).

lower than 6,350 cpm, including the values of seeds no. 33 and no. 44. Some values were close to the Milli-Q water background (BG).

With the counting of the liquid still remaining high, seed no. 33 and other five seeds that were close to a value above 100 cpm were separated and submitted to a further leakage test, as shown in Table 5. In Fig. 2, the counts values of the remaining liquid after the third leakage test were below the limit of 6,350 cpm. However, the count value of the liquid of the seed no. 33 increased drastically and exceeded the limit determined by the standard ISO-9978, confirming a leak.

Conclusions

The container of polyethylene was used because it presented better efficiency (57.5%) with the liquid scintillation counter. After the first forty-eight plasma arc-welded seeds cleaning, a large variation in the values of the radioactivity counts of the remaining liquid occurred, since they were below the maximum value allowed for iodine-131 of 6,350 cpm (184 Bq), except for the seeds no. 33 and no. 44. However, after the second cleaning the values of the liquid scintillation counts were much lower than 6,350 cpm, including the values of

Table 4. Leakage test of the forty-eight seeds (2nd cleaning)

Seed	Liquid remainder (cpm)	Seed	Liquid remainder (cpm)
1	70.0	26	59.4
2	69.2	27	66.0
3	65.0	28	59.6
4	63.4	29	66.6
5	60.0	30	73.8
6	68.6	31	76.0
7	68.2	32	59.4
8	69.2	33	4,687.8
9	58.6	34	67.4
10	66.6	35	67.8
11	63.4	36	68.2
12	66.4	37	70.6
13	63.6	38	70.6
14	73.4	39	66.4
15	69.4	40	95.4
16	71.0	41	67.0
17	89.8	42	64.2
18	67.2	43	64.0
19	71.0	44	695.0
20	146.8	45	138.8
21	69.2	46	65.6
22	62.6	47	69.0
23	61.4	48	106.2
24	58.2	Milli-Q water BG	62.0
25	63.8	Titanium BG	47.8

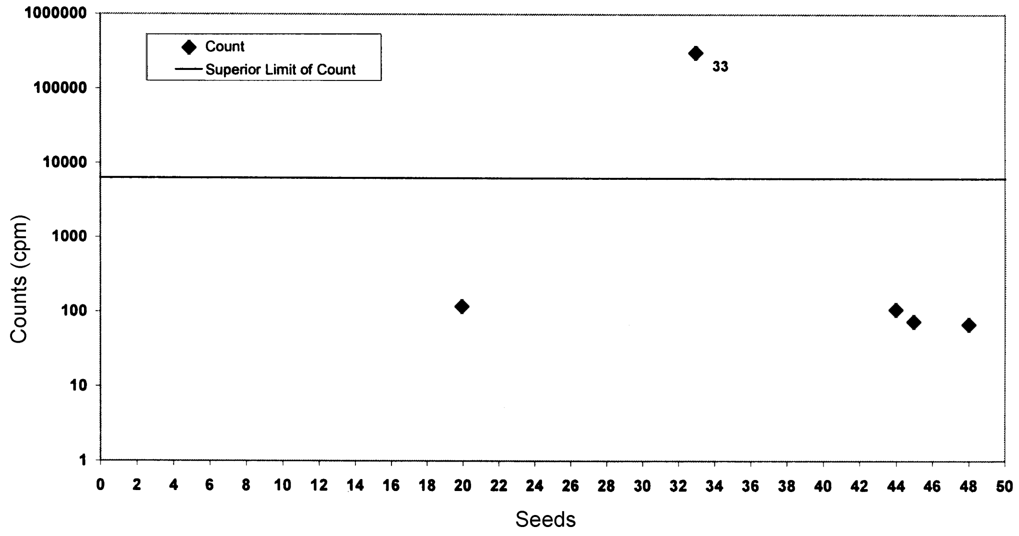

Fig. 2. Iodine-131 activity in water after leakage test (3rd cleaning).

Table 5. Leakage test of the five seeds (3rd cleaning)

Seed	Liquid remainder (cpm)
20	116.4
33	309,920.0
44	107.6
45	72.2
48	67.0
Milli-Q water BG	52.2
Titanium BG	49.7

seeds no. 33 and no. 44. Some values of the radioactivity were close to the Milli-Q water background (BG).

The seed no. 33 and other five seeds that were close to a value above 100 cpm were separated. The counts values of the remaining liquid after the third leakage test were below 6,350 cpm. However, the count value of the remaining liquid of the seed no. 33 increased drastically and exceeded the limit of 6,350 cpm determined by the standard ISO-9978, confirming a leak.

The procedure used to verify the leakage of the forty--eight plasma arc-welded seeds proved to be efficient in relation to approval criteria described in the standard for immersion tests. It could be determined the need to apply this quality control method, at least three times, for each batch of iodine-125 seeds production.

The procedure used in this work should be part of the qualification tests for sealing procedures to be used in the production of iodine-125 brachytherapy seeds encapsulated by plasma arc-welding (PAW) or even laser beam welding (LBW). Other procedures of immersion test, described by standard ISO-9978 are recommended to determine which one presents better efficiency.

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References

1. Blasko JC, Grimm PD, Rade H (1993) Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Rad Oncol 3;4:240–249
2. Butler WM (2000) Review of modern prostate brachytherapy. In: Proc of the World Congress on Medical Physics and Biomedical Engineering, 23–28 July 2000, Chicago
3. Feler A (2006) Development of plasma arc welding process for iodine-125 seed production. Master of science degree, Institute for Nuclear and Energy Research (IPEN), São Paulo, Brazil
4. Gray JR (1998) Prostate brachytherapy: a new treatment option for prostate cancer patients. HCA Healthcare Corp, Columbia. https://www.medtropolis.com/health-contents.asp?page=”/htc/prostate/CRS/index, accessed 4 July 2009
5. ISO (1992) ISO-9978: Radiation protection – sealed radioactive sources – leakage test methods. International Standard Organization
6. Meigooni AS (2000) Dosimetric characterization of low energy brachytherapy sources: measurements. In: Proc of the World Congress on Medical Physics and Biomedical Engineering, 23–28 July 2000, Chicago
7. Meigooni AS, Gearheart DM, Sowards K (2000) Experimental determination of dosimetric characteristics of best I-125 brachytherapy source. Med Phys 27;9:2168–2173
8. Pollack A, Zagars GK, Rosen II (1999) Prostate cancer treatment with radiotherapy: maturing methods that minimize morbidity. Semin Oncol MD, Anderson Cancer Center 26;2:150–161
9. Rostelato MECM, Rela PR, Gasiglia HT, Lepki V, Feher A (2000) Iodine-125 seeds production for brachytherapy use. In: Proc of the World Congress on Medical Physics and Biomedical Engineering, 23–28 July, 2000, Chicago
10. Rostelato MECM (2005) Study and development of a new methodology for iodine-125 brachytherapy seed production. PhD degree, Institute for Nuclear and Energy Research (IPEN), São Paulo, Brazil
11. Strum SB, Schulz MC (1996) Brachytherapy: implantation of prostate cancer with radioactive isotope – analysis of the Seattle experimence: May 1996 update. http://www.prostatepointers.org/seadpods/brachy07.htm/, accessed 4 July 2009