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(54) **Title**: BRACHYTHERAPY SEED, METHODOLOGY AND CALCULATING DOSE OF BRACHYTHERAPY AND METHOD OF TREATMENT

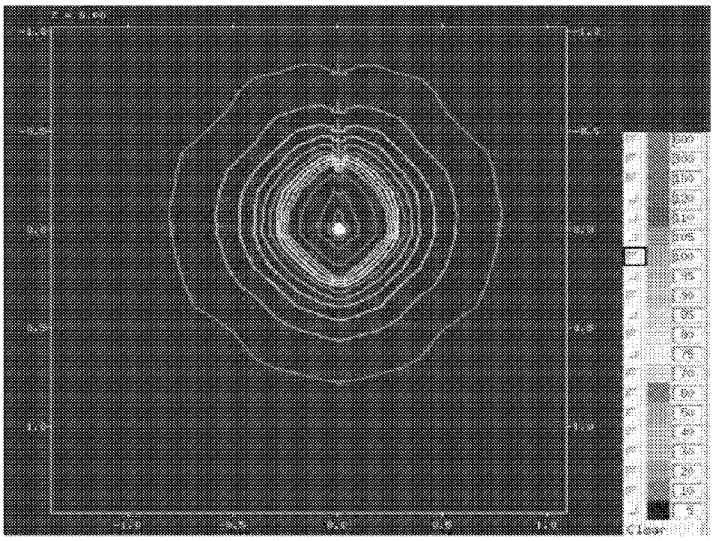

FIGURE 3

(57) **Abstract**: The invention provides for a brachytherapy seed, wherein the seed includes at least two disparate radionuclides of a chemical element, the radionuclides encapsulated to form a brachytherapy seed and wherein the combination of the disparate radionuclides of the chemical element is used to augment dosimetric parameters and radiobiological characteristics of the brachytherapy seed. The invention also provides a method of manufacturing a brachytherapy seed that includes the steps of bombarding elemental silver with high energy protons produced by a cyclotron to obtain a target of 100Pd and 103Pd; dissolving and passing the target through a column of resin beads; placing at least one resin bead having adsorbed 100Pd and 103Pd into a titanium tube that is closed at one end; inserting a radiopaque member into the titanium tube; and closing the opposite end of the titanium tube.

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Brachytherapy seed, methodology of calculating dose of brachytherapy and method of treatment.

Field of the invention

The invention is in the field of internal radiotherapy, sealed source radiotherapy, curietherapy or endocurietherapy, as a form of radiotherapy, where a radionuclide is encapsulated to form what is commonly known as a brachytherapy seed.

Background

The inventors are aware of the use of internal radiotherapy, sealed source radiotherapy, curietherapy or endocurietherapy, as a form of radiotherapy, where a radionuclide is encapsulated (brachytherapy seed) and is placed inside or next to an anatomical area requiring treatment. Brachytherapy is commonly used as a treatment for cancers such as cervical, prostate, breast and skin cancer.

The inventors are also aware that current radionuclides used in brachytherapy are often not the optimal radionuclide, due to cost considerations. In this respect ^{125}I (59 days half-life) is often used but it is known that the use of alternative (more expensive) radionuclides may result in tumour control at a much lower dose and lower mortality.

The inventor believes that a need exists for a brachytherapy seed that optimizes treatment and is more cost effective than currently available brachytherapy seeds.

Summary of the invention

Definitions for the purpose of interpreting this specification:

Dosimetry - the process or method of measuring the dosage of ionizing radiation.

Brachytherapy - a form of radiotherapy where a radiation source (a brachytherapy seed) is placed inside or next to the area requiring treatment.

According to an aspect of the invention, there is provided a brachytherapy seed, wherein the seed includes at least two disparate radionuclides of a chemical element, the radionuclides encapsulated to form a brachytherapy seed and wherein the combination of the disparate radionuclides of the chemical element is used to augment dosimetric parameters and radiobiological characteristics of the brachytherapy seed.

The half-lives of the disparate radionuclides may be different and may result in different energies and decay properties. The dosimetric characteristics of the disparate radionuclides may thus be different, and the final dose distribution and radiobiological effectiveness of the resultant radiation may thus be dependent on the combination of the dosimetric characteristics of the combination of the type of radionuclides used in the brachytherapy seed.

The ratio of the disparate radionuclides, and therefore the dosimetry of the disparate radionuclides, may differ from the time of calibration to time of use.

A ratio at the time of use may be derived from a ratio at time of calibration.

The ratio at time of use may be derived from the ratio at time of calibration by using the published half-lives of the radionuclides and the decay equation $A = A_0 e^{-\ln(2).t/t½}$

The dosimetric parameters may be determined by using mathematical modelling, wherein the disparate radionuclides may be considered separately and the theoretic dose distributions may be calculated and converted into desired parameters.

The mathematical modelling may be the Monte Carlo simulation wherein the disparate radionuclides may be considered separately and the theoretic dose distributions may be calculated and converted into the TG43 parameters[1].

The dosimetric parameters may be determined by measuring the dosimetry around an actual seed at two or more different times, the times being long enough to show material changes in the dose distribution.

The dosimetric parameters may be determined by using a linear quadratic model to determine the relative biological effective (RBE) of the dosimetry before combining the radionuclides.

Utilising the known changes in the ratios and the measured changes in the dose distribution may assist in determining the dosimetric contributions of the radionuclides.

The radionuclides may be Palladium (Pd).

The radionuclides may include ^{100}Pd and ^{103}Pd radionuclides.

^{100}Pd and ^{103}Pd radionuclides may be obtained by bombarding a natural silver target with high energy protons produced by a cyclotron.

It is to be appreciated from this specification the radionuclides may be obtained by any suitable means, including but not limited to nuclear reactors, particle accelerators and/or radionuclide generators.

The brachytherapy seed may, at the time of manufacture, include a range of 5-25% ^{100}Pd.

The brachytherapy seed may, at the time of manufacture, typically include 16% ^{100}Pd.

[1] AAPM Radiation Therapy Task Group No. 43 (Med Phys 22(2) Feb 1995: 209-234 updated Med Phys 31 (3) Mar 2004: 633 – 674)

Treatment planning software may facilitate the percentage of the ^{100}Pd at the time of implantation relative a malignancy in a patient and the physical half-lives of the ^{100}Pd and the ^{103}Pd.

The dosimetry and half-life of each radionuclide may be calculated separately.

The ^{100}Pd dosimetry may be weighted so that the doses of the ^{100}Pb is brought into line with the RBE of ^{103}Pd before the finalisation of the dosimetry.

Weighting the ^{100}Pd dosimetry may have the desired effect of resulting in a dosimetric equivalent of a pure ^{103}Pd seed.

The brachytherapy seed may include a column of resin beads.

The radionuclides may absorb onto the resin. Typically, more than 95% of the total Pd activity may absorb onto the resin.

The brachytherapy seeds may include a radiopaque substance for radiographic visualization of the brachytherapy bead.

The radiopaque substance may include any suitable material and may typically be in the form of a lead or gold bead.

The radiopaque beads may be sandwiched between the resin beads.

The resin and radiopaque beads may be encapsulated in a titanium tube.

The higher energy photons from the ^{100}Pd may have a higher penetration potential, *in situ*, than the photons of the ^{103}Pd.

The higher energy photons of the ^{100}Pd compared to the photons of the ^{103}Pd, *in situ*, may result in an improved anisotropy that may aid in allowing for alternative placement of the brachytherapy seeds.

According to another aspect of the invention, there is provided a method of manufacturing a brachytherapy seed that includes the steps of;
- bombarding elemental silver with high energy protons produced by a cyclotron to obtain a target of ^{100}Pd and ^{103}Pd;
- dissolving and passing the target through a column of resin beads, thereby adsorbing the target onto the resin beads;
- placing at least one resin bead having adsorbed ^{100}Pd and ^{103}Pd into a titanium tube that is closed at one end;
- inserting a radiopaque member into the titanium tube;
- closing the opposite end of the titanium tube.

The ends of the titanium tube may be closed by laser welding.

Example of the invention and description of drawings

The invention will now be exemplified by the following non-limiting example and drawings;

^{103}Pd with a half-life of 17 days has a distinct advantage over the more commonly used ^{125}I (59 days half-life) in that the same effect with a much lower dose and thus less morbidity can be obtained. ^{103}Pd is however much more expensive to manufacture and from a cost benefit point of view is generally excluded from use in permanent implant prostate brachytherapy. ^{103}Pd it is the only solution considered acceptable for partial breast irradiation but the cost continues to limit the use thereof.

^{103}Pd is obtained by bombarding an elemental silver target with high energy protons produced by a cyclotron which also produces ^{100}Pd. It is impossible to separate isotopes (radionuclides) from each other. In order to obtain the required ^{103}Pd purity, the target must be left to decay until the percentage ^{100}Pd is acceptably low; however in the process up to 90% of the activity is lost.

At the time of manufacture, the mixture typically comprises 16% ^{100}Pd.

The target is dissolved and passed through a column of resin beads, sifted beforehand to obtain a desired grain size resulting in the absorption of the target onto the resin beads.

Thereafter, an open end of a 4mm long, 0.8 mm diameter Titanium tube is laser welded closed; two Pd adsorbed resin beads are inserted into the tube; a lead or gold bead is inserted into the tube for X-ray visualization; two more resin beads are added to the tube and the opposing end of the tube are welded closed.

The inventor believes that the current invention has the advantages of dramatically reducing the cost of manufacture of a brachytherapy seed including ^{100}Pd.

The inventor also believes that the higher energy photons from the ^{100}Pd are more penetrating that that of ^{103}Pd and will therefore likely improve the anisotropy of the brachytherapy seed as well as allowing for a more lenient source spacing (sources can be placed further apart and small migrations will be better tolerated).

The Monte Carlo (MC) Modeling of a Brachytherapy seed is used to report on the relative absorbed dose distributions in water of a brachytherapy seed.

Benchmarked EGSnrc[1] based MC codes are used to simulate the transport of kilo-voltage photons from a model of the radioactive source located in water. In order to accomplish that the following is realized:

a) The materials constituting the source are assembled to calculate new cross-section data for electron and photon threshold energies of 1 keV. Previous data was limited to 10 keV which is, in light of the source energies, too high and is likely to introduce significant range artifacts in the dose calculation grid. Rayleigh scatter is included in said new data, and is significant to the photon energies under consideration.
b) An IDL user code is developed to enable modeling of the source, typically encapsulated. The resolution is set at 0.05 mm which is the capsule thickness. This also necessitated using smaller transport cut-off energies as described

above. (Smaller resolution can lead to negative step values in the MC transport process that can produce biased results, particularly in metals).

c) A second FORTRAN code file is developed to read the model and to convert it into a suitable format for the EGSnrc MC codes to be read. This file contains the dose calculation grid, materials and densities of the materials.

d) The energy spectra files are set up as counts per bin whilst ensuring that averaging effects do not distort the energy spectra. The energy spectra that is used in the calculation is rounded off to exclude decay modes with percentage probabilities less than 2.1 percent, as it is accepted that these percentage probabilities do not have a significant impact on the absorbed dose distributions.

e) MC simulations are carried out with the following transport parameters set, keeping in mind that most of them can be safely 'turned off' for megavoltage photon transport:

Transport parameter	**Choice**
ECUT	0.512 MeV
PCUT	0.001keV
Range rejection	Off
Boundary crossing algorithm	Exact

Transport parameter	**Choice**
Electron step algorithm	PRESTAII
Electron impact ionization	On
Spin effects	On
Bound Compton scattering	On
Rayleigh Scattering	On
Atomic relaxations	On

f) Eight simulations of one billion histories each are run, four of the simulations using energy spectrum A and four of the simulations using energy spectrum B. A FORTRAN code is utilised to sum the eight resulting dose files after the dose files for each isotope is properly weighted. Factors that are taken into account include, a) The percentage of each isotope in the combined brachytherapy source; b) the half-life of each source; and c) the fact that the brachytherapy seeds are likely to stay in the patient well after the radionuclides have decayed completely. A weighting factor to account for these factors is determined as follows:

$$w = C\int_0^\infty e^{-\lambda t}\,dt = \frac{C}{\lambda}$$

The interpretation of the dose weighting is:

Isotope A constitutes (C = 15 percent) of that for B. Its half-life ($t_{1/2}$) is much shorter than for isotope B (3.6 d vs. 16.99 d). The activity constants ($\lambda = \ln 2/t_{1/2}$) have the numerical values of 0.1925 (A) and 0.0407 for B. The weight factor for Isotope A is 15/0.1925 = 77.922 and B is 100/0.0407 = 2457.00. The dose weighting factors account for the total accumulative dose from time zero.

Aforementioned weighted dose files are added and normalized at a point in water adjacent to the capsule material. Dose distributions described herein will therefore include the cumulative relative dose after an infinite time.

Figure1 shows the geometry of the brachytherapy seed as constructed using the IDL code. Dimensions and materials are not disclosed as this is already known. The IDL-generated model of the seed contains 5 spheres of known materials encapsulated in a metal material. This model has been used in MC simulations.

The relative dose distributions are adapted and the dose in water adjacent to the capsule wall is normalized to 1000 percent. The dose inside the capsule is capped at this value in order to derive a useful isodose data.

Figure 2: Isodose distribution for the brachytherapy seed in the y = 0 plane. The Z-axis is vertical and the X-axis horizontal (left to right). The color-bar on the right shows the activated isodose values. A 50 percent case is exemplified in this example. The source orientation matches that shown in Figure 1.

The 600 Percent isodose line is located at about 1mm from the capsule wall. Adjacent to the capsule the dose was normalized to 1000 percent in water. The 30 percent isodose line reaches to about 5 mm from the center of the source along the X-axis.

The view shown in Figure 3 is in the Z = 0 plane. The isodose lines through the axis can be taken as true distances. At other angles, for example, 45 degrees from these main axes, the isodose lines forms a 'dent' which may be considered as 'slight' artifacts. The isodose lines should be circular in the xy-plane due to cylindrical symmetry of the source capsule. Round-off errors in the capsule modelling causes longer effective paths for the photons traversing the capsule, causing more attenuation which are not present in the real case. The resolution is in the order of the capsule thickness, thus at 45 degrees the effective thickness is about 1.414 times thicker compared to the modeled capsule thickness on the main axis. If the source resolution is smaller (to reduce these dent effects) the MC code will encountered step length errors which will alter the isodose data significantly. This necessitates keeping the resolution grid at 0.05 mm.

Figure 3: Isodose distribution for the brachytherapy seed in the z = 0 plane. The Y-axis goes from top to bottom (X from left to right). The color-bar on the right shows the activated isodose values. The 'dents' in the isodose lines (prominent for the 20 and 10 percent isodose lines) are due to more attenuation in the modeled capsule thickness. The left and right parts of the dose are averaged in this plane giving rise to the symmetrical shape about the Y-axis. (The 5 percent isodose line is omitted in this Figure).

Figure 4 shows the radial dose profile along the X axis for the data in Figure 1. The data is normalized to 1000 percent at about 0.4 mm from the origin in water adjacent to the capsule wall location. As expected, low energy photons, which dominate the energy components in the sources effects, would be absorbed strongly due to higher interaction cross-section coefficients. The effect is a steep dose gradient falling rapidly to about 30 percent at 5 mm from the source center. Normalize the dose in water adjacent to the capsule was necessary as photo-electric absorption in the encapsulation increased the dose to about 35 times of that in water just adjacent to the capsule metal wall.

The radial dose profile is taken along the positive X-axis to avoid capsule thickness biasing effect at 45 degrees. Table 1 shows the numerical values for the radial dose profile.

Figure 4 shows the radial dose profile normalized to 1000 percent to a point in water located adjacent to the capsule wall (0.4 mm from the zero distance position).

Table I: Radial dose profile taken from the capsulation wall at 0.04 cm to 4.1 cm

Dist (cm)	**Dose %**	**Dist (cm)**	**Dose %**	**Dist (cm)**	**Dose %**	**Dist (cm)**	**Dose %**
0.04	1000.00	1.09	4.70491	2.19	0.76853	3.29	0.240928
0.09	490.193	1.19	3.96427	2.29	0.409765	3.39	0.116955
0.19	181.845	1.29	3.4178	2.39	0.728984	3.49	0.083677
0.29	89.8542	1.39	2.7141	2.49	0.586933	3.59	0.204636
0.39	50.4976	1.49	2.22735	2.59	0.37798	3.69	0.059105
0.49	30.5062	1.59	2.18036	2.69	0.426131	3.79	0.059452
0.59	21.9893	1.69	1.52535	2.79	0.283434	3.89	0.064542
0.69	14.3114	1.79	1.13052	2.89	0.345896	3.99	0.138185
0.79	11.5428	1.89	0.900217	2.99	0.222585	4.09	0.053555

The water bath dimensions are 30 x 30 x 30 cm^2, to account for full in-phantom scatter. The voxel size of 1 mm outside the source overestimates the dose by less than 3 percent within the first 1 cm, but decreases to less than one percent thereafter. This is mainly caused by the steep dose gradient depicted in Figure 4. The voxel resolution of the source was 0.05 x 0.05 x 0.05 mm^2 which reduced biased dose errors to less than one percent. Beyond the source, the phantom resolution was 1 x 1 x 1 mm^2. The above findings were based on the work of *Taylor et al*[1]

where brachytherapy source dose distributions were simulated with the EGSnrc MC code and some isotope data have been compared with AAPM's TG43 recommendations.

The same transport parameters are used to simulate the brachytherapy source as recommended in the work of Taylor *et al.* The dose data may be slightly overestimated by 3 percent near the source. At locations beyond 1 cm this effect is well within one percent. The statistical variance within the data is below 1 percent for the outer voxels and well within this margin near the source origin. The overall uncertainty in the data is well within 3.5 percent with the overestimation of 3 percent in the dose near the source within a 1 cm boundary. Since this can be corrected for the overall uncertainty may fall below 2 percent.

Reference

[1] R.E.P Taylor and D.W.O. Rogers, "Benchmarking BrachyDose: Voxel based EGSnrc Monte Carlo calculations of TG-43 dosimetry parameters," Med. Phys. 34, 445- 457 (2007).

1. A brachytherapy seed, wherein the seed includes at least two disparate radionuclides of a chemical element, the radionuclides encapsulated to form a brachytherapy seed and wherein the combination of the disparate radionuclides of the chemical element is used to augment dosimetric parameters and radiobiological characteristics of the brachytherapy seed.

2. A brachytherapy seed as claimed in claim 1, wherein the disparate radionuclides have different half-lives, which result in different energy and decay properties.

3. A brachytherapy seed as claimed in any one of the preceding claims, wherein the dosimetric parameters of the disparate radionuclides are different, and the final dose distribution and radiobiological effectiveness of the resultant radiation being dependent on the combination of the dosimetric characteristics of the disparate radionuclides used in the brachytherapy seed.

4. A brachytherapy seed as claimed in any one of the preceding claims, wherein a ratio of the disparate radionuclides, and therefore the dosimetry of the disparate radionuclides, differs from the time of calibration to the time of use.

5. A brachytherapy seed as claimed in claim 4, wherein the ratio of the disparate radionuclides at the time of use is derived from a ratio of the disparate radionuclides at time of calibration.

6. A brachytherapy seed as claimed in any one of claims 4 to 5, wherein the ratio of the disparate radionuclides at time of use is derived from the ratio of the disparate radionuclides at time of calibration by using the published half-lives of the radionuclides and the decay equation $A = A_0 e^{-\ln(2).t/t_{1/2}}$

7. A brachytherapy seed as claimed in any one of the preceding claims, wherein the dosimetric parameters of the brachytherapy seed are determined by using mathematical modelling and wherein the disparate radionuclides are considered separately and the theoretical dose distributions are calculated and converted into desired dosimetric parameters.

8. A brachytherapy seed as claimed in claim 7, wherein the mathematical modelling is the Monte Carlo simulation, wherein the disparate radionuclides are considered separately and the theoretic dose distributions are calculated and converted into TG43 parameters[1].

9. A brachytherapy seed as claimed in any one of the preceding claims, wherein the dosimetric parameters are determined by measuring the dosimetry of an actual seed at two or more different times, the times being long enough to show material changes in the dosimetry.

10. A brachytherapy seed as claimed in any one of the preceding claims, wherein the dosimetric parameters are determined by using a linear quadratic model to

[1] AAPM Radiation Therapy Task Group No. 43 (Med Phys 22(2) Feb 1995: 209-234 updated Med Phys 31 (3) Mar 2004: 633 – 674)

e relative biological effective (RBE) of the re encapsulating the disparate radionuclides.

11. A brachytherapy seed as claimed in anyone of claims 4 to 10, wherein utilising the known changes in the ratios and the measured changes in the dose distribution may assist in determining the dosimetric contributions of the disparate radionuclides.

12. A brachytherapy seed as claimed in any one of the preceding claims, wherein the disparate radionuclides are the ^{100}Pd and the ^{103}Pd radionuclides.

13. A brachytherapy seed as claimed in claim 12, wherein the ^{100}Pd and the ^{103}Pd radionuclides are obtained by bombarding a natural silver target with high energy protons produced by a cyclotron.

14. A brachytherapy seed as claimed in any one of claims 12 to 13, wherein the brachytherapy seed, at the time of manufacture, includes a range of 5-25% ^{100}Pd.

15. A brachytherapy seed as claimed in claim 14, wherein the brachytherapy seed, at the time of manufacture, includes 16% ^{100}Pd.

16. A brachytherapy seed as claimed in any one of the preceding claims, wherein the dosimetry and half-life of each disparate radionuclide is calculated separately.

17. A brachytherapy seed as claimed in any one of claims 12 to 16, wherein the ^{100}Pd dosimetry is weighted, thereby permitting the dose of the ^{100}Pb to be brought into line with the RBE of the ^{103}Pd before the finalisation of the dosimetry.

18. A brachytherapy seed as claimed in claim 17, wherein the weighing of the ^{100}Pd dosimetry results in a dosimetric equivalent of a pure ^{103}Pd seed.

19. A brachytherapy seed as claimed in any one of the preceding claims, wherein the brachytherapy seed includes a column of resin beads, for the radionuclides to absorb thereon.

20. A brachytherapy seed as claimed in any one of the preceding claims, wherein the brachytherapy seed includes a radiopaque substance for radiographic visualization of the brachytherapy seed.

21. A brachytherapy seed as claimed in claim 20, wherein the radiopaque substance is sandwiched between the resin beads.

22. A brachytherapy seed as claimed in any one of claims 19 to 21, wherein the resin beads and the radiopaque substance are encapsulated in a titanium tube.

23. A method of manufacturing a brachytherapy seed that includes the steps of;
bombarding elemental silver with high energy protons produced by a cyclotron to obtain a target of ^{100}Pd and the ^{103}Pd;
dissolving and passing the target through a column of resin beads, thereby adsorbing the target onto the resin beads;
placing at least one resin bead having adsorbed ^{100}Pd and the ^{103}Pd into a titanium tube that is closed at one end;
inserting a radiopaque member into the titanium tube;

closing the opposite end of the titanium tube

24. A method of manufacturing a brachytherapy seed as claimed in claim 23, wherein the ends of the titanium tube may be closed by laser welding.

25. A new brachytherapy seed as claimed in claim 1.

26. A brachytherapy seed substantially as herein described and illustrated.

27. A new method of manufacturing a brachytherapy seed as claimed in claim 23.

28. A new method of manufacturing a brachytherapy seed substantially as herein described and illustrated.

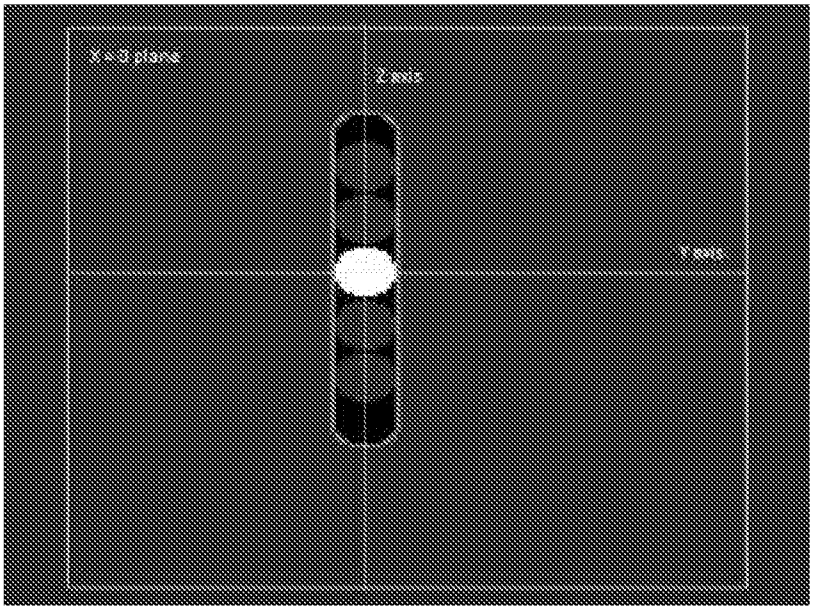

FIGURE 1

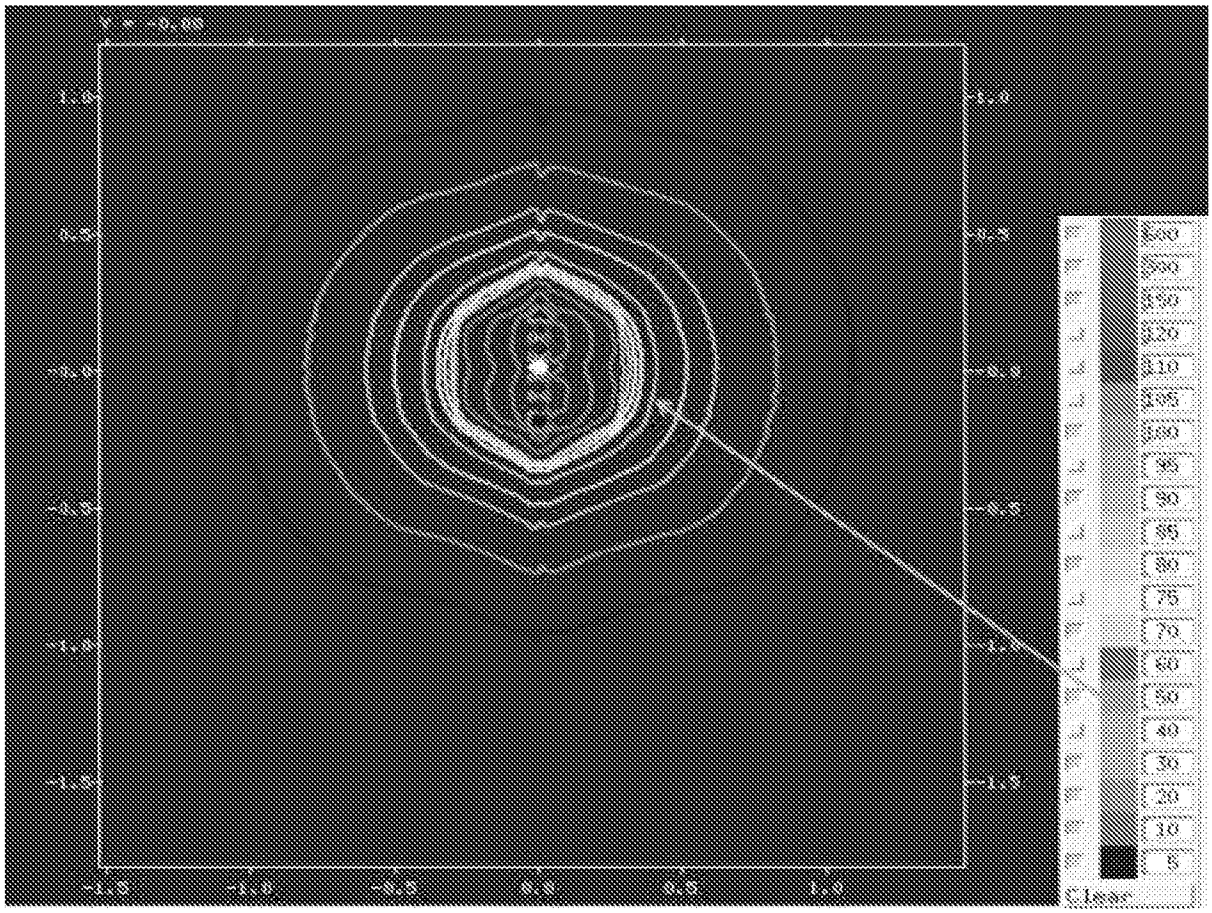
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FIGURE 2

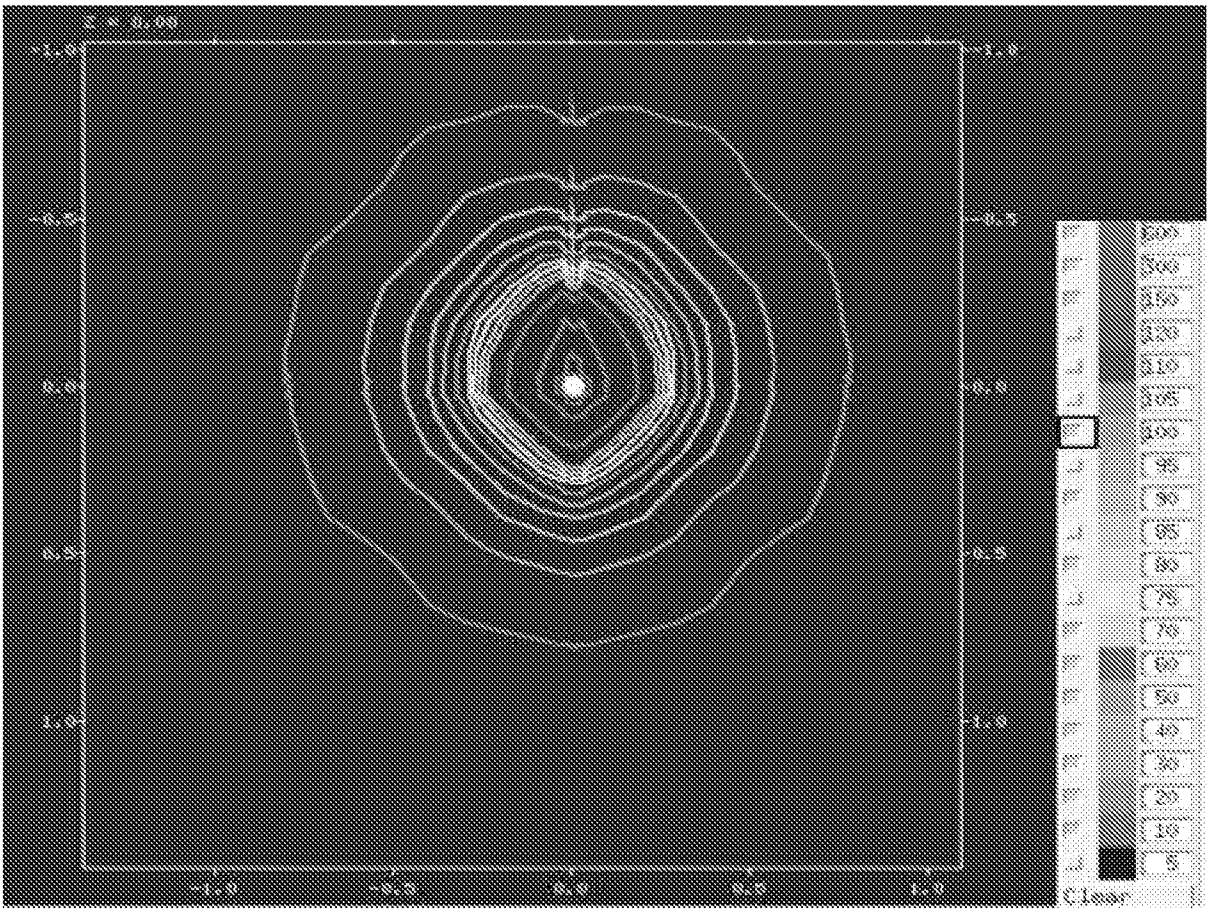

FIGURE 3

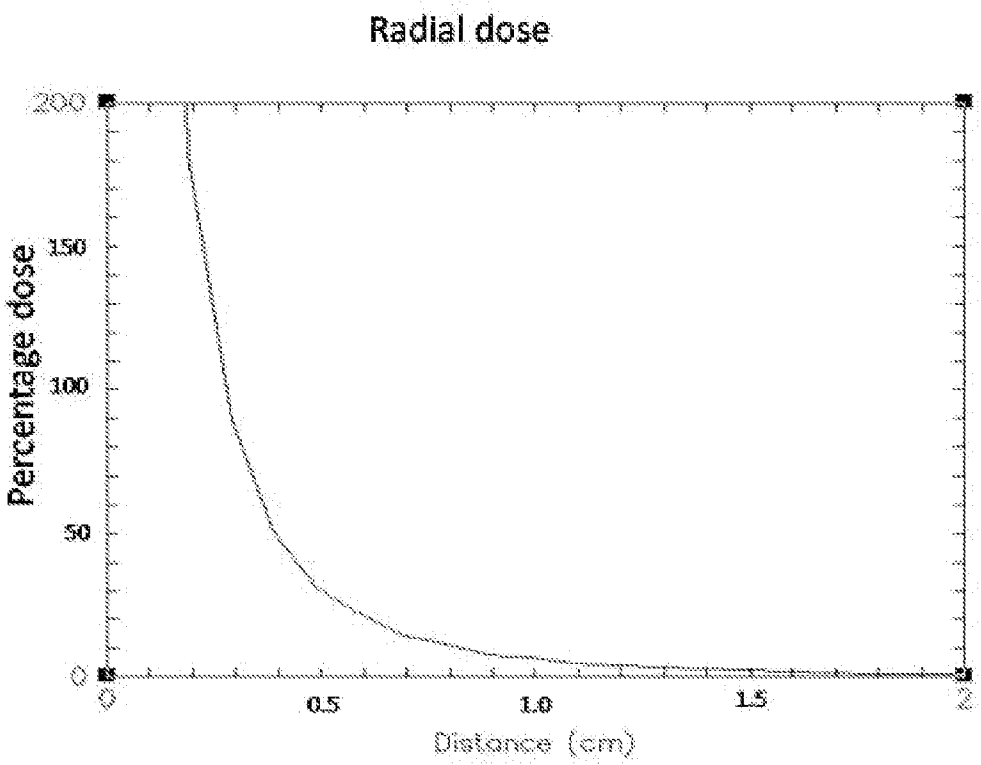
Radial dose
Percentage dose
200
150
100
50
0
0
0.5
1.0
1.5
2
Distance (cm)

FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/055151

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ***A61N 5/00*** (2006.01) ***A61K 51/00*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, EPODOC: IPC, ECLA A61N 5/-, A61K 41/-, 51/- and Keywords (brachyther+, radiother+, seed?, source?, radionuclide?, multi+, ratio, palladium, silver, cyclotron) and like terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000/029034 A1 (NYCOMED AMERSHAM PLC) 25 May 2000 See page 5, lines 19-25; page 6, lines 5-13; page 6, line 35-page 7, line 6; page 7, lines 26-30; page 8 and page 14, lines 12-21.	1-11, 16 and 19-22
X	US 2009/0247807 A1 (LUCAS et al.) 1 October 2009 See figure 1; paragraphs [0026] and [0034]-[0037].	1-11, 16 and 20
X	US 2008/0249398 A1 (HARDER et al.) 9 October 2008 See figures 4 and 5; paragraphs [0033], [0034], [0037] and [0075].	1-11, 16 and 20
X	US 5342283 A (GOOD) 30 August 1994 See figures 1 to 6; column 16, line 1-column 17, line 3; column 54, line 46-column 55, line 17; Table 1.	1-18 and 20

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2012	27 March 2012
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **OSCAR VIOLANTE** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 7959

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/055151

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0006255 A1 (SAJO et al.) 8 January 2004 See paragraph [0025].	20 and 21
A	US 6143431 A (WEBSTER) 7 November 2000 See column 1, lines 66-67.	23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/055151

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **25 to 28**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 25 and 27 do not comply with Rule 6.3(a) because the definition of the matter for which protection is sought is not in terms of the technical features of the invention. In particular, the term "new" used to define the invention is of indefinite scope

Claims 26 and 28 do not comply with Rule 6.2(a) because they rely on references to the description and drawings.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No: III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1 to 22 are directed to a brachytherapy seed. The feature of *a brachytherapy seed which includes at least two disparate radionuclides of a chemical element* is specific to this group of claims.

- Claims 23 and 24 are directed to a method of manufacturing a brachytherapy seed. The feature *of bombarding elemental silver with high energy protons to obtain a target of ^{100}Pd and ^{103}Pd, adsorbing the target onto a column of resin beads, placing at least one resin bead into a titanium tube that is closed at one end, inserting a radiopaque member into the titanium tube, and closing the opposite end of the tube*, is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB2011/055151

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	0029034	AU	10648/00				
US	2009247807	EP	1846103	WO	2006063419		
US	2008249398	WO	2008124778				
US	5342283	AU	89207/91	CA	2067804	EP	0500928
		JP	H05503303	US	6099457	US	6666811
		US	2004242953	WO	9203179		
US	2004006255	US	6761679				
US	6143431	AU	34034/99	CA	2331400	EP	1076905
		JP	2002513946	WO	9957731		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX