

Bioevaluation of ^{125}I Ocu-Prosta seeds for application in prostate cancer brachytherapy

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Background & objectives: In recent years, brachytherapy involving permanent radioactive seed implantation has emerged as an effective modality for the management of cancer of prostate. ^{125}I -Ocu-Prosta seeds were indigenously developed and studies were carried out to assess the safety of the indigenously developed ^{125}I -Ocu-Prosta seeds for treatment of prostate cancer.

Methods: Animal experiments were performed to assess the likelihood of *in vivo* release of ^{125}I from radioactive seeds and migration of seeds implanted in the prostate gland of the rabbit. *In vivo* release of ^{125}I activity was monitored by serial blood sampling from the auricular vein and subsequent measurement of ^{125}I activity. Serial computed tomography (CT) scans were done at regular intervals till 6 months post implant to assess the physical migration of the seeds.

Results: The laser welded seeds maintained their hermeticity and prevented the *in vivo* release of ^{125}I activity into the blood as no radioactivity was detected during follow up blood measurements. Our study showed that the miniature ^{125}I seeds were clearly resolved in CT images. Seeds remained within the prostate gland during the entire study period. Moreover, the seed displacement was minimal even within the prostate gland.

Interpretation & conclusions: Our findings have demonstrated that indigenously developed ^{125}I -Ocu-Prosta seeds may be suitable for application in treatment of prostate cancer.

Key words ^{125}I seeds - permanent implant brachytherapy - prostate cancer

Prostate cancer is the most prevalent form of malignancy in the male population in the West. Transperineal interstitial permanent prostate brachytherapy has emerged as a promising and viable treatment option for patients with clinically localized and early stage prostate cancers. It is a simple

outpatient procedure with low morbidity and high dose conformity. There are several reports in literature suggesting that the biochemical disease control obtained by brachytherapy with ^{125}I seeds is similar to radical prostatectomy and external beam radiation therapy (EBRT)⁴. This modality of treatment allows

delivery of a highly localized radiation dose that is not achievable by conventional external beam radiation therapy. Interstitial brachytherapy for prostate cancer is convenient, cost-effective, and offers minimal morbidity in appropriately selected patients and does not compromise the patient's quality of life. Candidates with low risk prostate cancer [pre-treatment prostate specific antigen (PSA) <10 ng/ml, Gleason score (GS) <7, prostate volume, <60 ml and stage T1-T2a] are considered ideal for interstitial brachytherapy⁵. The three radioactive isotopes currently used for making radioactive seeds are ¹²⁵I (Iodine-125), ¹⁰³Pd (Palladium-103) and ¹³⁷Cs (caesium-137). In order to cater to the need of ageing population and to tap the therapeutic potential of permanent radioactive seed implantation, ¹²⁵I Ocu-Prosta seeds were developed as per the reported procedure⁶⁻⁸. During therapy, the radioactive seeds come in direct contact with the body fluids and in case of leakage of activity from the seeds, deposition of activity into the thyroid gland and other non target tissues is observed⁹. Hence, bioevaluation of the seeds was found essential to ensure integrity of seeds and safety during therapy. The verification of the seed migration after implantation is also vital to ensure desired post-implant dosimetry. Following implantation, these ¹²⁵I seeds will remain in prostate tissue permanently, the probability of dispersion of radioactivity from the radioactive seed as well as its physical migration is a concern which needs to be addressed. Therefore, in the present study, a thorough biosafety evaluation of the indigenously prepared seeds implanted in the prostate gland of a healthy rabbit was undertaken at Radiopharmaceuticals division, BARC, Mumbai during 2010-2011.

Material & Methods

Silver wires of 0.5 mm (ϕ) with guaranteed purity were purchased from Silver Plaza, Mumbai. Titanium capsules of 0.8 mm (OD) x 4.75 mm (l) were fabricated by Titan Industries Limited, India. ¹²⁵I as Na¹²⁵I for seed preparation was procured from Bhabha Atomic Research Centre, India. A 50W Nd: YAG laser welding system M/s Quanta Systems, Italy, was used for welding the sources. Well type ion chamber (Sun Nuclear Corporation, Melbourne, FL, USA) calibrated for standard ¹²⁵I source of similar dimension was used for radioactive measurement. MICK applicator was obtained from M/s Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA. Computed tomography (CT) scans were carried out using Siemens, SOMATOM, sensation version 4 machineTM, USA.

Preparation of ¹²⁵I seeds: The source core consisted of a palladium coated silver wire [3 mm (l) x 0.5mm (ϕ)] in which ¹²⁵I was incorporated as per the reported procedure^{7,8}. These source cores were encapsulated in titanium capsules of 4.75 mm (l) x 0.8 mm (OD) using a 50 W, Nd:YAG laser welding system. The ¹²⁵I seed is a radioactive sealed source, in which the source core is positioned inside the titanium capsule, welded at one extremity. The source strength of ¹²⁵I seed for prostate implants is usually between 11.1-29.6 MBq per seed. Each ¹²⁵I seed was subjected to checks such as visual inspection, activity measurement, leak test, immersion test, swipe test, *etc.* according to the standard procedure⁷.

Bioevaluation studies: The animal study was carried out in accordance with the institutional animal ethics committee of BARC, Mumbai. The bioevaluation studies were carried out in a healthy male New Zealand rabbit as an experimental model. The study involved surgical intervention followed by repeated exposure to X rays. Due to relatively small size of rabbit prostate, two radioactive seeds containing 13.7MBq ¹²⁵I per seed were implanted in prostate gland of the rabbit (weight 2.5 kg) by surgical intervention.

In vivo release of ¹²⁵I activity was studied by withdrawing blood from the animal and measurement of ¹²⁵I activity in the blood in a NaI (TI) gamma scintillation counter from ECIL, India. Marginal auricular vein was used for serial blood sampling because of the ease of repeated sampling. Sampling was started after post-operative recovery of the animal on 2nd day after implantation.

The migration of the seeds from the implanted site to other tissues was monitored by serial CT scans at periodic intervals for six months study period. A thermoplastic mould (OrfitTM) was used to immobilize the animal and maintain reproducibility during serial CT scans. Radio opaque fiducial markers were placed on the orfit using laser guidance. These markers were later used to precisely calculate the distance of the seeds; however, variability of the position of the fiducial markers was observed due to the breathing movements which lead to erroneous results while measuring the seed distance, later a fixed bony landmark (tip of the pubic arch) was used to measure the seed distance. The migration (displacement) of the seeds from original site of implantation in the serial scans was calculated with respect to the baseline scan (*e.g.*, if lateral distance from tip of pubic arch is x cm in the baseline scan and in subsequent scan it is x₂ cm, then the lateral

displacement is considered to be $x-x_2$ cm). The vertical and anterior-posterior (A-P) displacements were also calculated in a similar way. The seed displacement was considered to be negative if it was less than the baseline scan and was considered positive if it was greater than the baseline scan.

The rabbit was administered with anaesthetics (Ketamine 50 mg/kg and Xylaxine 10 mg/kg) before the scan. A whole body CT scan of 2.5 mm slice thickness was performed and was later reconstructed into 1 mm slice thickness. After 6 months, seeds were recovered from prostate gland of rabbit and activity estimated. The seeds were examined for their integrity as well as structural appearance.

Results

Quality control of seeds: ¹²⁵I seeds were prepared and subjected to strict quality control assessment as per the guidelines¹⁰. Results of surface contamination test and leak test conducted on the seeds revealed that the radioactivity levels were well below 185 Bq. The uniformity in the distribution of ¹²⁵I activity in the seed was examined by autoradiography.

Two ¹²⁵I Ocu-Prosta seeds were implanted in the prostate gland of the rabbit. The animal was monitored for any intraoperative or post surgical complications and was given prophylactic antibiotics. In the post-operative period, the rabbit had mild to moderate loose motion for two days, which could be attributed to the effect of anaesthesia and antibiotics administered after surgery. However, the loose motions resolved spontaneously without any intervention.

In vivo studies: Blood (1 ml) was drawn from the marginal auricular vein of the rabbit ear on 2nd and 15th day after implantation and subsequently at monthly intervals up to a period of six months. The results are summarized in Table I.

It was seen from the result that the measured activity was close to background counts. The blood tests did not detect any radioactivity during the follow up period, which indicated that the laser welded seeds maintained their hermeticity and prevented the *in vivo* release of ¹²⁵I into the blood.

Seed migration: Initially, ultrasonography of ¹²⁵I Ocu-Prosta seeds was carried out to visualize the seeds after implantation in the prostate phantom. However, due to nonavailability of ultrasound probe for rabbit, tracking of seeds was carried out by CT imaging. Single photon

Table I. Blood activity measured in NaI (T1) gamma scintillation counter

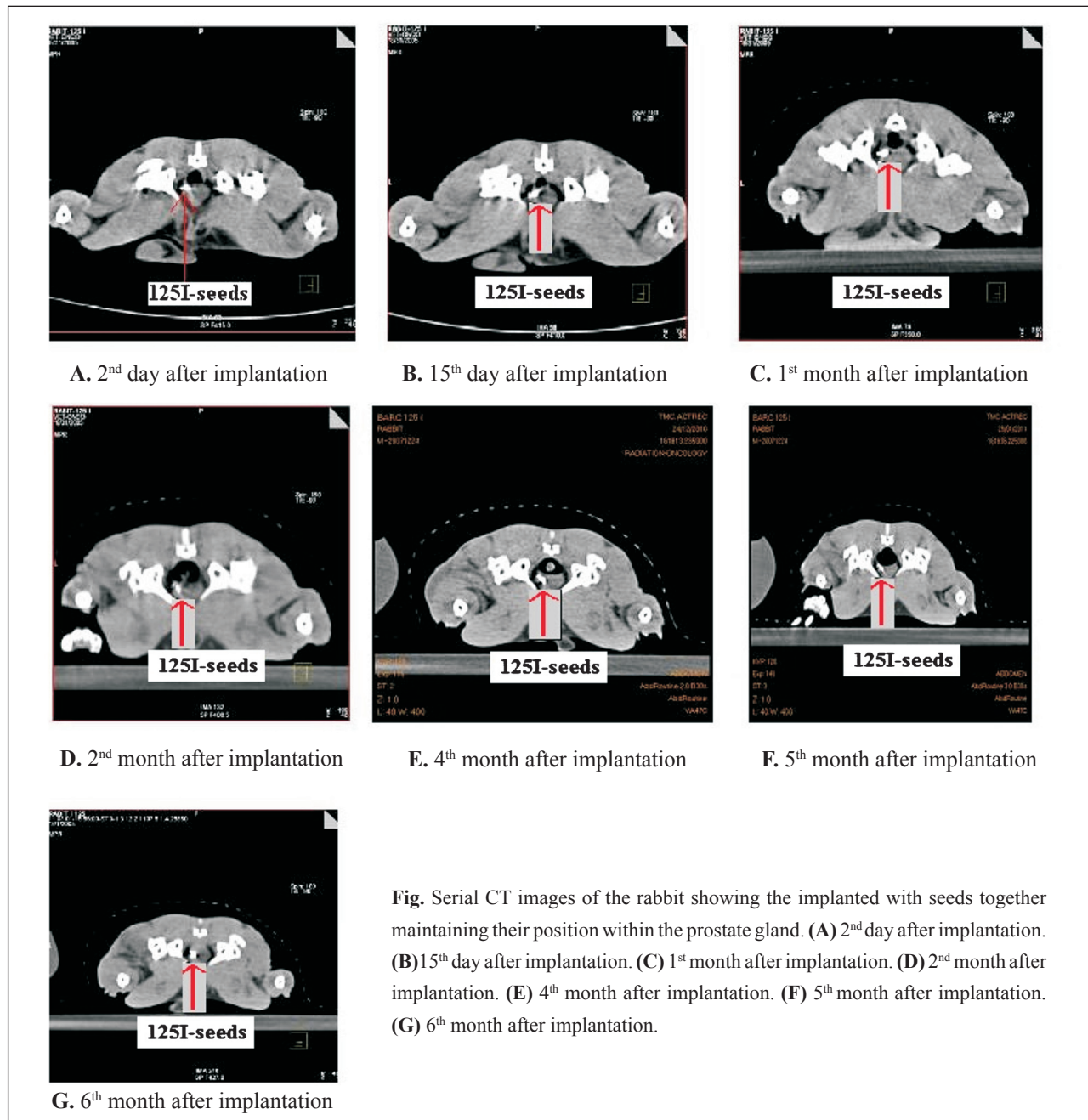
Days after implantation	Counts in blood/30 sec*	Background counts/30 sec*
2	93±7	92±6
15	87±10	87±11
30	107±9	101±10
42	106±10	107±17
66	67±6	73±7
94	92±6	94±5
119	105±7	104±6
149	82±5	80±6
177	96±5	90±6

Values are mean ± SD (n=3 observations)

emission computed tomography (SPECT) of ¹²⁵I seeds after permanent brachytherapy for prostate cancer has also been reported¹¹. However, due to unavailability of appropriate scintigraphy machine for rabbit imaging at our institute, we conducted the seed migration study using CT scan. Moreover, with CT imaging the seed position can be related with known anatomical and soft tissue landmarks.

Both the seeds were observed in the prostate gland during the entire period of the study (6 months). Serial CT images are shown in the Figure (A-G). The exact position of the seeds was calculated from an anatomical bony landmark (tip of pubic arch). Table II shows the distance/position of seeds from the bone (tip of pubic arch). Tables II and III give the distance of the seeds from the pubic arch and their displacements in all the three dimensions with respect to baseline CT scan. Our observations showed that the maximum distance of the seeds was in the anterior-posterior (A-P) direction or Z-dimension with a mean of 1.17 cm (range: 0.93-1.32 cm; SD ± 0.168) and minimum in superior-posterior direction (Y-dimension) with a mean distance of 0.15 cm from the pubic arch (range: 0 - 0.3; SD ± 0.11). The mean lateral displacement (X), mean vertical displacement (Z), and the mean longitudinal displacement (Y) were only 0.025, -0.173 and 0.067 cm, respectively (Table III).

Physical integrity of the encapsulated seed: The seeds after recovery were examined visually for integrity and were found to be intact with no visual damage. The seeds were subjected to leakage test in which the recovered ¹²⁵I seeds were placed in boiling water for about 2 min. Non-appearance of bubbles from the sealed sources indicated retention of hermetic characteristics. Further,



these were subjected to swipe test by swiping the sources using alcohol immersed cotton wool and checking the radioactive content in a NaI(Tl) scintillation counter. Radioactivity in the immersed cotton wool was less than 185 Bq (5nCi) which indicated secured encapsulation. The radioactivity associated with seed was estimated to be ~444KBq (12 μ Ci) after 10 months that accounted for the decay loss and no release of activity.

Discussion

Safety and quality of the encapsulated ¹²⁵I seed is the prime consideration for the therapeutic use. The safety features of radioactive sources depends on the radioisotope used, process of making source core, capsule material used, capsule design and encapsulation technique.

Table II. Seed migration data

CT scan no.	Fiducial markers (Scan no.)*	Seeds (scan no.)	Pubic arch (scan no.)	Lateral distance 'X' (cm)	Longitudinal distance 'Y' (cm)	Vertical distance 'Z' (cm)
Baseline	361	411	412	0.40	0.1	1.32
2	308	358	359	0.46	0.1	1.30
3	912	962	965	0.54	0.3	1.29
4	349.5	400.5	400.5	0.54	0.0	1.06
5	310	364	365	0.28	0.1	1
6	355	402	405	0.32	0.3	0.93
7	375	427	429	0.41	0.2	1.30
Mean distance	-	-	-	0.42	0.15	1.17
SD	-	-	-	±0.10	±0.113	±0.168
Range	-	-	-	0.28-0.54	0.0-0.3	0.93-1.32

*Scan section where all the 3 fiducial markers appear in one plane
The distances measured from the centre of the seed to the tip of the pubic arch

The three commonly used isotopes used in permanent radioactive seed implantation are ¹²⁵I, ¹⁰³Pd and ¹³⁷Cs. ¹²⁵I has a half-life of 60 days with an average energy of 28 KeV, ¹⁰³Pd has a half-life of 17 days with an average energy of 21 KeV and ¹³⁷Cs has a half-life of 9.7 days with energy of 29 KeV. The photon energies of these isotopes are nearly identical as the penetration distance in the human tissue for these radioisotopes is only 1.7 cm, which allows for localizing the energy inside the tumour instead of irradiating the surrounding

organs. The primary difference between these is the rate at which these decay¹²⁻¹⁶. Although there appears to be no significant difference in the choice of one radionuclide over another, the lack of large scale production process for ¹⁰³Pd and ¹³⁷Cs limits their application. Moreover, the logistics and cost considerations of these isotopes do not permit their wide use. On the other hand, ¹²⁵I with its relatively longer half-life coupled with well-established production of ¹²⁵I in several GBq quantities in the research reactor is a cost effective isotope. Prior to the deployment of ¹²⁵I seeds for clinical prostate brachytherapy, it is important to study the migration probability (within and outside the prostate) as well as *in vivo* release of ¹²⁵I activity from the seed.

Table III. Seed displacement with respect to baseline CT scan

Scan no.	Lateral displacement 'X' (cm)	Longitudinal displacement 'Y' (cm)	Vertical displacement 'Z' (cm)
2	0.06	0.0	0.02
3	0.14	0.2	0.03
4	0.14	-0.1	0.26
5	-0.12	0	-0.32
6	-0.08	0.2	-0.39
7	0.01	0.1	0.02
Mean	0.025	0.067	-0.173
SD	± 0.109	± 0.121	± 0.169
Median	0.035	0.05	-0.145
Range	-0.12-0.14	-0.1-0.2	-0.39-0

Radioactive seeds should be placed within the treatment volume in a predetermined array and held in that array throughout the therapeutic life of the sources, for propitious therapeutic outcome. In prostate brachytherapy, seeds can detach from their deposited sites and move locally in the pelvis or migrate to distant sites including the pulmonary and cardiac regions. The prostatic capsule has a rich venous plexus with vessels large enough to accommodate seeds. Seeds placed extraprostatically have access to this plexus and often migrate away from their intended position via venous circulation. Through the venous pathway, seeds can migrate through the inferior vena cava and into the other part of the body^{17,18}. For therapeutic efficacy, the seed

should ideally remain within the prostate. Undesirable consequences of seed migration include inadequate dose coverage and dosimetry within the tumour and the possible morbidity due to tissue irradiation effects at the site of migration.

In our animal study, ^{125}I Ocu-Prosta seeds were easily tracked by CT imaging during follow up of the rabbit implanted with seeds in the prostate. Physical migration of the seed was minimal and was within the prostate gland. None of the seeds implanted migrated to any distant organ such as the lung or the heart although there are some reports in humans where seed migration has been noted at distant sites especially in lungs where the reported incidence of seed migration is between 0.7-55 per cent of patients¹⁹. The laser welded seeds maintained their hermeticity and prevented the *in vivo* release of ^{125}I activity into the blood.

In conclusion, successful preclinical evaluation of indigenously developed ^{125}I Ocu-Prosta seeds was done and seeds were found to be suitable for clinical application. The potential to translate these findings from rabbit to human prostate is promising.

References

- Koukourakis G, Kelekis N, Armonis V, Kouloulis V. Brachytherapy for prostate cancer: a systematic review. *Adv Urol* 2009; 327945.
- Yoshioka Y. Current status and perspectives of brachytherapy for prostate cancer. *Int J Clin Oncol* 2009; 14 : 31-6.
- Langley SE, Laing RW. Iodine seed prostate brachytherapy: an alternative first-line choice for early prostate cancer. *Prostate Cancer Dis* 2004; 7 : 201-7.
- Hinnen KA, van Vulpen M. Predictors in the outcome of ^{125}I brachytherapy as monotherapy for prostate cancer. *Expert Rev Anticancer Ther* 2011; 11 : 115-23.
- Sahgal A, Roach M 3rd. Permanent prostate seed brachytherapy: a current perspective on the evolution of the technique and its application. *Nat Clin Pract Urol* 2007; 4 : 658-70.
- Mathew C, Majali MA, Balakrishnan SA. A novel approach for the adsorption of ^{125}I on silver wire as matrix for brachytherapy source for the treatment of eye and prostate cancer. *Appl Radiat Isot* 2002; 57 : 359-67.
- Saxena SK, Shanta A, Rajurkar NS, Majali MA. Studies on the production and quality assurance of miniature ^{125}I radioactive sources suitable for treatment of ocular and prostate cancers. *Appl Radiat Isot* 2006; 64 : 441-7.
- Saxena SK, Sharma SD, Dash A, Venkatesh M. Development of a new design ^{125}I -brachytherapy seed for its application in the treatment of eye and prostate cancer. *Appl Radiat Isot* 2009; 67 : 1421-5.
- Chen QS, Blair HF. Thyroid uptake of iodine-125 after prostate permanent brachytherapy. *J Urol* 2004; 172 : 1827-9.
- AERB Safety Standard No. AERB / SS3 (Rev 1). *Testing and classification of sealed radioactive sources*. Mumbai: Atomic Energy Regulatory Board, Government of India; 2001.
- Kono Y, Kubota K, Mitsumoto T, Tanaka A, Ishibashi A, Kobayashi K, *et al.* Scintigraphic detection of ^{125}I seeds after permanent brachytherapy for prostate cancer. *J Nucl Med* 2008; 49 : 541-5.
- Wallner K, Merrick G, True L, Sutlief S, Cavanagh W, Butler W. ^{125}I versus ^{103}Pd for low-risk prostate cancer: preliminary PSA outcomes from a prospective randomized multicenter trial. *Int J Radiat Oncol Biol Phys* 2003; 57 : 1297-303.
- Nath R, Roberts K, Ng M, Peschel R, Chen Z. Correlation of medical dosimetry quality indicators to the local tumor control in patients with prostate cancer treated with iodine-125 interstitial implants. *Med Phys* 1998; 25 : 2293-307.
- Stock RG, Stone NN, Lo YC, Malhado N, Kao J, deWyngaert JK. Postimplant dosimetry for ^{125}I prostate implants: definitions and factors affecting outcome. *Int J Radiat Oncol Biol Phys* 2000; 48 : 899-906.
- Anderson LL, Moni JV, Harrison LB. A nomograph for permanent implants of palladium-103 seeds. *Int J Radiat Oncol Biol Phys* 1993; 27 : 129-35.
- Wallner K, Merrick G, True L, Cavanagh W, Simpson C, Butler W. ^{125}I versus ^{103}Pd for low-risk prostate cancer: morbidity outcomes from a prospective randomized multicenter trial. *Cancer J* 2002; 8 : 67-73.
- Nag S, Beyer D, Friedland J, Grimm P, Nath R. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999; 44 : 789-99.
- Eshleman JS, Davis BJ, Pisansky TM, Wilson TM, Haddock MG, King BF, *et al.* Radioactive seed migration to the chest after transperineal interstitial prostate brachytherapy: extraprostatic seed placement correlates with migration. *Int J Radiat Oncol Biol Phys* 2004; 59 : 419-25.
- Nakano M, Uno H, Gotoh T, Kubota Y, Ishihara S, Deguchi T, *et al.* Migration of prostate brachytherapy seeds to the vertebral venous plexus. *Brachytherapy* 2006; 5 : 127-30.

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