Scintigraphic Detection of ^{125}I Seeds After Permanent Brachytherapy for Prostate Cancer

Yuzuru Kono¹, Kazuo Kubota¹, Takuya Mitsumoto¹, Akitomo Tanaka¹, Akihiko Ishibashi¹, Kazumi Kobayashi², Kimiteru Ito¹, Jun Itami², Mikio Kanemura³, and Shigeru Minowada³

¹Division of Nuclear Medicine, International Medical Center of Japan, Tokyo, Japan; ²Department of Radiology, International Medical Center of Japan, Tokyo, Japan; and ³Department of Urology, International Medical Center of Japan, Tokyo, Japan

The purpose of this investigation was to monitor the localization and migration of ^{125}I seeds after permanent brachytherapy for prostate cancer using a new scintigraphic technique that may overcome the drawbacks of conventional x-ray methods.

Methods: ^{125}I seeds emit γ -rays with an average energy peak of 28 keV. We used a γ -camera equipped with low-energy high-resolution collimators that were tuned to an energy level of 35 keV with a 70% window width. Sixteen patients with prostate cancer were examined after ^{125}I seed insertion. The number of seeds remaining in the prostate was confirmed using pelvic CT for postoperative dose planning; however, seeds that had migrated outside the prostate could not be detected. Furthermore, the migrated seeds were not completely traceable using chest or abdominal radiography. Thus, we adopted a scintigraphic technique to perform this task. The evaluation of radiography and scintigraphy findings was masked, and the rates of migrated seed detection were statistically examined using the McNemar test. To localize the migrated seeds, we fused the scintigraphic images of the migrated seeds and the patients' contours. **Results:** Scintigraphy was successfully used to detect 20 migrated seeds of a total of 1,182 implanted seeds, whereas radiography was successfully used to detect 7. The sensitivity of the scintigraphy results was 20 of 20 (100%), whereas that of the radiography results was 7 of 20 (35%). Seed migration was detected in 11 of 16 patients (69%) using scintigraphy, whereas seed migration was detected in only 4 patients (25%) using radiography; this difference was statistically significant ($P = 0.016$). **Conclusion:** Scintigraphy is more effective for detecting seed migration and monitoring the localization of ^{125}I seeds than radiography. The precise anatomic location of migrated seeds can be pinpointed using fusion images. Scintigraphy may become a standard procedure for monitoring seed migration during ^{125}I brachytherapy in patients with prostate cancer.

Key Words: prostate cancer; brachytherapy; ^{125}I seed; seed migration; fusion imaging

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For correspondence or reprints contact: Kazuo Kubota, MD, PhD, Division of Nuclear Medicine, International Medical Center of Japan, 1-21-1, Toyama, Shinjuku-ku, Tokyo, 162-8655 Japan.

E-mail: kkubota@imcj.hosp.go.jp

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Radioactive seed implantation for the treatment of early-stage prostate cancer has continued to gain popularity over the past 2 decades. Seeds containing the radionuclide ^{125}I are the most commonly used for permanent-implant prostate brachytherapy. In accordance with the recommendations of the American Brachytherapy Society, patients with low-risk prostate cancers may be treated effectively with brachytherapy alone.

A unique property of implanted ^{125}I seeds for brachytherapy is the possibility of radioactive seed migration away from the prostate gland during dose delivery. The periprostatic venous plexus flanks the prostate gland laterally and anteriorly and theoretically serves as a ready access for radioactive seed emboli. This venous complex drains into the iliac vessels, then into the inferior vena cava, and eventually into the right side of the heart and to the lungs (1). Migration potentially could alter the implant dosimetry and produce unwanted seed-related sequelae. Pulmonary and pelvic embolizations of radioactive seeds are frequently observed phenomena. The incidence of seed migration to the lung during follow-up is 72.5%, and the incidence of chest migration ranges from 0.7% to 55% (2,3). Four case reports of seed migration to the heart have also been made (4–7), one of which was associated with acute myocardial infarction (7).

TABLE 1
Physical Characteristics of ^{125}I Seeds (OncoSeed, Model 6711; Amersham)

Physical parameter	Characteristic
Principal radionuclide	^{125}I
Radionuclide purity	>99.9% for ^{125}I or <0.005% for ^{126}I
Half-life of ^{125}I	59.43 d
Types of radiation	x-Ray and γ -photon
Energy levels	
x-Ray/ γ -photon	27.4 keV
x-Ray	31.4 keV
γ -Photon	35.5 keV
Fluorescent x-rays from titanium capsule	22.1 and 25.2 keV

FIGURE 1. Energy spectrum obtained from ^{125}I seeds. Multichannel analyzer detected 5 energy peaks in spectrum of ^{125}I seeds: 27.4 keV (x-ray/ γ -photon), 31.4 keV (x-ray), 35.5 keV (γ -photon), and 22.1 and 25.2 keV (fluorescent x-rays from the titanium capsule), as shown in Table 1.

A conventional technique for detecting migrated seeds is postoperative diagnostic radiography for radioopaque foreign bodies. Because of their small size, however, migrated seeds can be difficult to detect, especially when they are in the lung base or in areas overlapped by bones. Furthermore, seeds in motion in the intracardiac region may not be visible on radiographs (6). Here, we evaluated the use of scintigraphy for the monitoring of implanted ^{125}I seeds and the detection of migrated seeds that were not identified on postoperative radiography.

FIGURE 2. Anterior scintigraphy of pelvis without seed migration (patient 1 in Table 2, 78-y-old man 1 d after operation). Number of implanted seeds was 94.

MATERIALS AND METHODS

Only 1 type of ^{125}I seed (OncoSeed, model 6711; Amersham) has been approved in Japan. This seed consists of radioactive ^{125}I chemically combined with silver in a titanium capsule. Each seed measures 4.57 by 0.98 mm. Though the seed manufacturers have provided the physical characteristics of the seeds (Table 1) (8), we measured their energy spectra using a multichannel analyzer (Fig. 1).

We attached a γ -camera (e.cam; Siemens) with a low-energy, high-resolution collimator tuned to an energy level of 35 keV with a 70% window width to cover all 3 photopeaks (27.4, 31.4, and 35.5 keV) emitted by the ^{125}I seeds. We then conducted experimental imaging studies on the seeds in a water medium (9) to validate the proper acquisition procedure. With regard to localizing migrated seeds, we composed a fusion image of the migrated seed and the patient's contour with the help of fusion software. To obtain the contour image, we had the patients lie on a flood-source phantom filled with a $^{99\text{m}}\text{Tc}$ medium for 1 min.

We examined 16 patients with prostate cancer between October 2006 and February 2007; all had undergone iodine-seed brachy-

TABLE 2
Clinical Data of Patients

No.	Day*	Age (y)	PSA	Gleason score	Pretherapy type	Implanted seeds		No./location of migrated seeds detected by...	
						n	Dose (MBq)	Radiography	Scintigraphy
1	1	78	21.3	3 + 4	—	94	1,438.2	N	N
2	1	82	13.95	3 + 3	Hormone therapy	69	1,055.7	N	B1
3	1	64	6.4	3 + 3	Hormone therapy	86	1,315.8	N	N
4	29	71	12.7	3 + 3	Hormone therapy	59	902.7	N	N
5	1	72	8.87	3 + 3	—	84	1,285.2	B3	B3
6	1	81	23.18	3 + 4	Hormone therapy	74	1,132.2	N	L1
7	1	73	4.7	3 + 3	—	81	1,239.3	N	N
8	1	66	9.92	6	Hormone therapy	81	1,239.3	N	P1
9	1	73	9.74	3 + 4	Hormone therapy	70	1,071.0	N	P1, B1
10	1	62	4.8	3 + 4	Hormone therapy	68	1,040.4	P2	P3
11	1	73	11	3 + 4	Hormone therapy	57	872.1	N	P1
12	8	68	12.9	6	Hormone therapy	46	703.8	P1	P3
13	1	60	6.3	3 + 3	—	80	1,224.0	N	P2
14	1	67	15.2	3 + 3	—	74	1,132.2	P1	P1
15	1	75	19.39	3 + 3	External radiation therapy	74	1,132.2	N	N
16	1	72	4.65	4 + 3	Hormone therapy	85	1,300.5	N	B2
Total no. of seeds						1,182		7	20

*Examination day after brachytherapy.

PSA = prostate-specific antigen level at time of diagnosis (ng/mL); B1 = 1 in bladder; B2 = 2 in bladder; B3 = 3 in bladder; L1 = 1 in lungs; N = no migration; P1 = 1 in pelvis; P2 = 2 in pelvis.

FIGURE 3. Chest radiography showing migrated seed (patient 6 in Table 2, 81-y-old man with 1 migrated seed in right lung 1 d after operation): posterior anterior view (A) and lateral view (B). Number of implanted seeds was 81.

therapy and had agreed to the γ -camera imaging protocol. After completing the brachytherapy on the day of operation, we took pelvic radiographs (anterior–posterior and lateral projections) and performed fluoroscopic checks to monitor any migrated seeds. A pelvic CT scan was also performed to evaluate the implanted dosimetry. On the following day, which corresponded to the day of discharge, posterior–anterior and lateral chest, abdominal, and pelvic radiographs were taken as part of a routine procedure to monitor migration. Each patient was estimated to have received

about 52.6 mGy of irradiation during the entire radiographic monitoring procedure. Next, the scintigraphic examinations were performed in a nuclear medicine room. All patients lay supine during the examination, and we obtained chest and abdominal static images (Fig. 2). Theoretically, the number of migrated seeds should be the difference between the number of implanted seeds and the number of seeds identified in the prostate using pelvic CT scans. However, pelvic CT performed to calculate the dose distribution does not include the whole pelvis and cannot determine the actual locations of seeds that have migrated outside the prostate. All radiography and scintigraphy results were evaluated in a masked manner. The efficiency of migrated seed detection was statistically examined using an exact McNemar test and Stata, version 9 (StataCorp).

The study protocol was reviewed and approved by the internal review board of the International Medical Center of Japan. Written informed consent was obtained from all subjects.

RESULTS

The patients' ages ranged from 62 to 82 y, with an average of 71 y. Fourteen patients were studied on day 1 after brachytherapy. One patient was studied on day 8 after brachytherapy, and one on day 29; pelvic CT was added on the same timing for these patients. The total number of implanted seeds ranged from 46 to 94, with an average of 74. Their radioactivities at the time of insertion varied from 703.8 to 1,438.2 MBq, with an average of 1,132.2 MBq. The patients' prostate-specific antigen levels ranged from 4.65 to 23.18 ng/mL, with an average of 11.56 ng/mL (Table 2).

The total number of implanted seeds in this study was 1,182, and 1,162 of these seeds were identified in the patients' prostates using pelvic CT scans. Thus, the total number of migrated seeds in this study was 20. Scintigraphy successfully detected all 20 of these migrated seeds, whereas radiography detected only 7. In a masked study of 16 patients, the radiographic examinations failed to show 1 radioopaque seed in the chest (Figs. 3 and 4) and 12 radioopaque seeds in

FIGURE 4. Chest scintigraphy showing migrated seed (patient 6 in Table 2, 81-y-old man with 1 migrated seed in right lung 1 d after operation): anterior view (A) and lateral view (B). Contours of patient are indicated by dotted line. Hot spots show migrated seed.

TABLE 3

Numbers of Migrated Seeds Detected Using Scintigraphy and Radiography

Radiography	Scintigraphy		
	Positive	Negative	Total
Positive	7	0	7
Negative	13	1,162	1,175
Total	20	1,162	1,182

the pelvic cavity. The sensitivity of the scintigraphy examinations was 20 of 20 (100%), whereas that of the radiography examinations was 7 of 20 (35%). If we assume that the results of the scintigraphy examinations are accurate, the positive predictive value of the radiography examinations was 7 of 7 (100%), the negative predictive value was 1,162 of 1,175 (99%), the sensitivity was 7 of 20 (35%), and the specificity was 1,162 of 1,162 (100%) (Table 3).

Using scintigraphy and radiography, we detected seed migration in 11 (69%) and 4 (25%) of the 16 patients, respectively. This difference was statistically significant ($P = 0.016$). With regard to detectability, scintigraphy had a 100% (11/11) sensitivity and 100% (5/5) specificity, whereas radiography had a 36% (4/11) sensitivity and 100% (5/5) specificity, producing a negative predictive value of 5 of 12 (42%) (Table 4).

DISCUSSION

Scintigraphy detected the migrated seeds with 100% sensitivity, whereas radiography had a sensitivity of only 36%. One seed in the chest and 12 seeds in the pelvis were missed using radiography (Figs. 3 and 4). Figure 3 illustrates how difficult it is to locate a migrated seed from a tangential viewpoint on a radiograph. In addition, some patients may have undergone a barium enema before receiving brachytherapy (Fig. 5), whereas others may have had metal surgical clips in their bodies, both of which make it more difficult for radiologists to locate migrated seeds using radiography. Furthermore, the opacity of the ribs and vertebral bones may hide migrated seeds in the lungs. Although radiographic examination is a standard technique used by many centers, it is not always useful for detecting migrated seeds, as shown in this report.

In most cases, the migrated seeds embolize a peripheral pulmonary artery and further migration is unlikely. However,

TABLE 4

Numbers of Patients with Migrated Seeds Detected Using Scintigraphy and Radiography

Radiography	Scintigraphy		
	Positive	Negative	Total
Positive	4	0	4
Negative	7	5	12
Total	11	5	16

FIGURE 5. Brachytherapy after barium enema, with migrated seeds in pelvis (patient 16 in Table 2, 72-y-old man with 2 migrated seeds in bladder 1 d after operation). Anterior scintigraphy of pelvis clearly shows 2 migrated seeds in bladder (A), but they are difficult to identify on anterior-posterior radiography of pelvis (B). Number of implanted seeds was 85.

4 cases of seed migration to the heart have been reported; in 1 of these cases, the seed migrated to the right coronary artery and was associated with an acute myocardial infarction. Another serious concern is the presence of an abnormal pathway between the right and left cardiac ventricles. If a seed migrates across an existing cardiac shunt, the seed could enter the left ventricular flow. Iatrogenic irradiation of normal tissue may result in endothelial damage. Davis et al. suggested that the metallic capsule might stimulate the formation of a fibrous sheath (4). The incidence of ventricular septal defect is 2 per 1,000 live births, and such defects are

FIGURE 6. Fused scintigraphy and contour image (72-y-old man with 1 migrated seed in right lung): scintigraphy of migrated seed (A), transmission image of patient's contour by flood-source phantom filled with ^{99m}Tc medium (B), and fusion image (C). Patient was not included in Table 2 because he was operated and examined after February 2007. This example nicely illustrates utility of fusion imaging to localize migrated seed.

found in 10% of adults with congenital cardiac malformations (10). Assuming that a proper history is taken during the consultation, patients with known septal defects are unlikely to undergo brachytherapy.

Most local seed loss occurs within 28 d of implantation, and additional seed loss beyond 60 d is extremely rare (11). However, the seed embolization rate may be higher than that reported in previous studies based on radiographic findings. The γ -camera has 7.4-mm system resolution (full width at half maximum); in contrast, the size of a seed is 0.98×4.57 mm, smaller than the resolution. A seed emits γ -rays with an average energy peak of 28 keV, which is clearly detected by the γ -camera even after attenuation through the patient, as shown in this study. Performing whole-body scans to detect small radioactive objects is a common task in nuclear medicine. Also, scintigraphic detection may be a cost-effective and patient-friendly (no additional irradiation) method for monitoring seed location. Furthermore, the precise anatomic location of the migrated seeds can be pinpointed using fusion images (Fig. 6). If the detection rate of migration is dramatically improved, we can search for possible factors associated with seed migration, potentially improving the seed implantation technique and helping the quality control of brachytherapy. This study was preliminary, and further large-scale studies involving larger numbers of subjects and other types of brachytherapy seeds are needed.

CONCLUSION

Scintigraphy is more sensitive than conventional radiography for the detection of migrated seeds after brachytherapy. Scintigraphy might become a standard procedure for the monitoring of seed localization after permanent brachytherapy.

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