Stenting of the Portal Vein Combined with Different Numbers of Iodine-125 Seed Strands: Dosimetric Analyses

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Abstract

Background: Portal-vein stent combined with one iodine-125 (¹²⁵I) seed strand has become a new treatment for portal vein tumor thrombosis. However, dosimetric aspects of this irradiation stent have not been reported. Therefore, we aimed to undertake dosimetric analyses comparing portal-vein stents combined with different numbers of ¹²⁵I seed strands.

Methods: A water cylinder was created by a treatment-planning system to simulate a portal-vein stent. The stent was combined with one, two, or three ¹²⁵I seed strands (Groups I, II, and III, respectively). At different prescribed doses (PDs), ¹²⁵I seeds of identical activities were loaded on Groups I–III. Conformation number (CN), external volume index, and homogeneity index were calculated. Linear regression analyses were used to evaluate the obtained data.

Results: For identical ¹²⁵I seed activity, when the ¹²⁵I seed strand increased from one chain to two, D₉₀ (dose delivered to 90% of the target volume) increased by ≥184%; when it increased from two chains to three, D₉₀ increased by ≥63%. When the PD was 105 Gy and ¹²⁵I seed strands increased from one chain to two, V₁₀₀ (percentage of the target volume receiving ≥90% of the PD) increased by 158–249%; when it increased from two chains to three, V₁₀₀ increased by 7–175%. CN was correlated positively with ¹²⁵I seed activity (B = 0.479, P < 0.001) and number of ¹²⁵I seed strands (B = 0.201, P < 0.001) and was independent of PD (B = −0.002, P = 0.078).

Conclusions: A portal-vein stent combined with a single ¹²⁵I seed strand could not meet dosimetry requirements. For a stent combined with two ¹²⁵I seed strands, when the PD was 105 Gy and seed activity was 0.7 mCi, the dose distribution could satisfy dosimetry requirements. For a stent combined with three ¹²⁵I seed strands, if the PD was 105, 125, or 145 Gy, the recommended seed activities were 0.5, 0.5, and 0.6 mCi, respectively.

Key words: Brachytherapy; Computer Simulation; Hepatic Vein Thrombosis; Radiometry; Stent

Introduction

In 2012, 782,500 patients worldwide were newly diagnosed with liver cancer, and 745,500 of these patients died. Shockingly, Chinese patients accounted for 50% of the total number of deaths.[¹] Hepatocellular carcinoma (HCC) is the most common histologic subtype of primary liver cancer. The prognosis of advanced HCC remains poor, particularly if patients have portal vein tumor thrombosis (PVTT).[²]

Management options are limited and the optimal treatment for HCC patients with PVTT is controversial. In the last decade, combinations of some treatment modalities have been explored to treat HCC with PVTT, of which transarterial chemoembolization (TACE) in combination with stenting of the portal vein is very promising.[³] Percutaneous transhepatic stenting of the portal vein has been used as palliative relief from obstruction but has no therapeutic effect on thrombosis due to a tumor. The concept of endovascular brachytherapy with iridium-192 was reported first in 2007 for tumors of the vena cava.[⁴]

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Recently, malignancy-induced stenosis has been managed by implantation of a low dose-rate iodine-125 (\(^{125}\)I) seed-loaded stent.\(^{[6-8]}\) Several animal\(^{[9,10]}\) and clinical\(^{[11-14]}\) studies have also demonstrated the short-term efficacy and safety of endovascular placement of a single \(^{125}\)I seed strand and a stent combined with TACE for HCC with PVTT. However, those studies focused only on the seeds activity, number, and effectiveness of \(^{125}\)I seeds and complications of the modality; dosimetric aspects of a stent combined with \(^{125}\)I seed strand(s) have seldom been reported.

Clinical reports of treatment of vascular thrombosis have involved stent implantation combined usually with a single \(^{125}\)I seed strand. However, ensuring a conformal and uniform dose distribution within the tumor target has proved difficult. By simulation of radioactive portal-vein stents combined with different numbers of \(^{125}\)I seed strands using a treatment-planning system (TPS), we wished to: (i) analyze the characteristics of dosimetric distribution in the tumor target volume; (ii) ascertain the optimal regimen based on calculated dosimetric parameters; and (iii) provide a reference for clinical application.

**METHODS**

**Simulation of a model of radioactive stents**

Using a module within a TPS (Prowess, Concord, CA, USA) based on the American Association of Physicists in Medicine TG43 and TG43U1 reports, we created a water cylinder (1 cm × 1 cm × 10 cm) to simulate a stent in the portal vein. The diameter of the stent was 1 cm, and the length was 10 cm. Along the long axis of the cylinder, the cross-sectional image height was set to 0.5 cm, so 20 layer cross-sectional images (simulated as computed tomography scans) were formed.

**Delineation of target volume**

An image at the intermediate level was used as a benchmark. The edge of the water cylinder was outlined to simulate the inner boundary of the tumor target volume and then expanded by 0.5 cm to simulate the outside border of the tumor target area. The upper and lower reference images were also outlined and formed seven continuous images. Then, 15 images were delineated. Therefore, the gross tumor volume had a length of 7.5 cm. Delineation of the target volume is shown in Figure 1a.

**Treatment planning**

Experimentally simulated radioactive stents were combined with one, two, or three \(^{125}\)I seed strands (Groups I, II, and III, respectively). For each group, \(^{125}\)I seed(s) (model 6711) were arranged evenly on the edge of the stent [Figure 1b-1d]. Furthermore, seed(s) were loaded on each layer of the cross-section of the 15 delineated images to form the \(^{125}\)I seed strand [Figure 1b-1d]. To improve calculation accuracy, TPS grid size was set to the maximum: 128 × 128 pixels/layer.

Reports have shown that a prescribed dose (PD) of 100–160 Gy is safe and efficacious for \(^{125}\)I seed interstitial implantation for solid tumors.\(^{[15-20]}\) In addition, the PD recommended for prostate cancer is 145 Gy.\(^{[16,17]}\) Therefore, the PD (in Gy) was set at 105, 125, and 145. At different PDS, \(^{125}\)I seeds of 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 mCi (mCi is a unit of radioactivity, which is the number of decay of the nucleus per unit time. 1 mCi = 37 MBq) were loaded on Groups I, II, and III, respectively. To evaluate the dose distribution of the target volume, we recorded the dosimetric parameters of dose–volume histogram (DVH) shown in different PDS and different activities of \(^{125}\)I seeds: \(D_{90}, D_{95},\) and \(D_{100}\) (dose delivered to 80%, 90%, and 100% of the target volume, respectively); \(V_{90}, V_{95},\) and \(V_{100}\) (percentage of the target volume receiving \(\geq 90\%), \geq 100\%,\) and 150% of the PD, respectively).

**Dosimetric evaluation**

The dosimetric quality of our brachytherapy plans was evaluated according to the conformation number (CN), external volume index (EI), and homogeneity index (HI). All parameters were computed on the basis of the DVH.

The CN was defined as:\(^{[21]}\)

\[
CN = \frac{V_{T,ref}V_{T,ref}}{V_{T,ref}V_{T,ref}}
\]  

(1)

Where \(V_{T,ref}\) is the volume of the target receiving a dose equal to or greater than the PD, \(V_{T}\) is the target volume, and \(V_{T,ref}\) is the volume receiving a dose equal to or greater than the PD. The value of the CN is between 0 and 1, where “1” denotes “optimal conformation” and “0” denotes “no conformation.” A value of “0” arises if the target is missed (\(V_{T,ref} = 0\)) or if a very large volume of normal tissue receives a dose equal to or greater than the PD (\(V_{T,ref} \gg V_{T,ref}\)).

The EI was used to determine irradiation of tissues outside the target volume and was defined as:\(^{[22]}\)
If \( V_{\text{ref}} = V_{T,\text{ref}} \), an ideal value of “0” is obtained, suggesting that the dose normal tissue receives is less than the PD. The larger the EI, the greater is the volume outside the target volume receiving PD.

The HI was used to describe dose homogeneity within the target volume and was defined as:

\[
\text{HI} = \frac{V_{T,1.5\text{ref}} - V_{\text{ref}}}{V_{\text{ref}}} \times 100\%
\]  

(3)

Where \( V_{T,1.5\text{ref}} \) is the volume of the target receiving a dose ≥150% of the PD. The “ideal” HI is 100%. A larger HI suggests more uniform dose distribution within the target.

**Statistical analyses**

Statistical analyses were conducted using SPSS version 19.0 (IBM, Armonk, NY, USA). Using linear regression analyses, \( P < 0.05 \) (two-tailed) was considered statistically significant.

**RESULTS**

The two- and three-dimensional dose distributions for different activities of \(^{125}\)I seeds in Groups I, II, and III are shown in Figures 2 and 3.

**Volume-dose parameters**

The volume-dose parameters \( D_{0.7}, D_{90}, \) and \( D_{100} \) for Groups I, II, and III are listed in Table 1. The latter showed that, if using identical activities of \(^{125}\)I seeds, \( D_{100} \) (in Gy) for Groups I, II, and III changed from 15.0 to 37.7, 42.7 to 112.1, and 69.6 to 185.7, respectively. For an identical activity of \(^{125}\)I seed, when the \(^{125}\)I seed strand increased from one chain to two chains, \( D_{90} \) increased by ≥184%; when the \(^{125}\)I seed strand increased from two chains to three chains, \( D_{90} \) increased by ≥63%. For an identical activity of \(^{125}\)I seed, for Groups I, II, and III, compared with \( D_{0.7} \), \( D_{90} \) decreased by 9–20%, 12–13%, and 12–13%; compared with \( D_{90} \), \( V_{100} \) decreased by 38–42%, 39–40%, and 44–46%, respectively.

**Dose–volume parameters**

The dose–volume parameters \( V_{90}, V_{100}, \) and \( V_{150} \) at a PD (in Gy) of 105, 125, and 145 for Groups I, II, and III are shown in Figure 4. Using the definition of dose–volume parameters stated above, for an identical activity of \(^{125}\)I seed, \( V_{90}, V_{100}, \) and \( V_{150} \) will decrease with increasing PD. Curves for \( V_{90}, V_{100}, \) and \( V_{150} \) curves in Figure 4 were consistent with this concept.

For an identical activity of \(^{125}\)I seed, when the PD was 105 Gy and the \(^{125}\)I seed strand increased from one chain to two chains, \( V_{100} \) increased by 158–249%; when \(^{125}\)I seed strand increased from two chains to three chains, \( V_{100} \) increased by 7–175%. For an identical activity of \(^{125}\)I seed, when the PD was 125 Gy and the \(^{125}\)I seed strand increased from one chain to two chains, \( V_{100} \) increased by 138–251%; when \(^{125}\)I seed strand increased from two chains to three chains, \( V_{100} \) increased by 21–174%. For an identical activity of \(^{125}\)I seed, when the PD was 145 Gy and the \(^{125}\)I seed strand increased from one chain to two chains, \( V_{100} \) increased by 138–248%; when \(^{125}\)I seed strand increased from two chains to three chains, \( V_{100} \) increased by 43–169%.

**Parameters for assessment of the brachytherapy plan**

The parameters for planning assessment (the CN, EI, HI) at a PD (in Gy) of 105, 125, and 145 for Groups I, II, and III are summarized in Table 2. Using the CN, EI, and HI as dependent variables and the PD, activity of \(^{125}\)I seeds, and number of \(^{125}\)I seed strands as independent
variables, we undertook linear regression analyses of the data obtained.

The adjusted \( R^2 \) was found to be 0.767, 0.613, and 0.250 for CN, EI, and HI, respectively. The CN was positively correlated with the activity of \( ^{125} \text{I} \) seeds \((B = 0.479, P < 0.001)\) and the number of \( ^{125} \text{I} \) seed strands \((B = 0.201, P < 0.001)\) and was independent of the PD \((B = 0.002, P = 0.078)\). The EI was positively correlated with the activity of \( ^{125} \text{I} \) seeds \((B = 0.990, P < 0.001)\) and the number of \( ^{125} \text{I} \) seed strands \((B = 0.225, P < 0.001)\) and was negatively correlated with the PD \((B = -0.005, P = 0.005)\). The HI was negatively correlated with the activity of \( ^{125} \text{I} \) seeds \((B = -0.336, P < 0.001)\) and was independent of the PD \((B = 0.002, P = 0.080)\) and the number of \( ^{125} \text{I} \) seed strands \((B = -0.036, P = 0.063)\).

**Table 1: \( D_{80}, D_{90}, \text{and} \ D_{100} \) for Groups I, II, and III (Gy)**

| Seed activity (mCi/seed) | \( D_{80} \) | \( D_{90} \) | \( D_{100} \) |
|--------------------------|-------------|-------------|-------------|
|                          | I II III    | I II III    | I II III    |
| 0.3                      | 16.4 48.8 80.0 | 15.0 42.7 69.6 | 9.0 26.0 38.0 |
| 0.4                      | 23.0 64.8 105.6 | 18.3 56.6 92.4 | 11.0 34.0 51.0 |
| 0.5                      | 27.4 80.7 131.2 | 23.7 70.5 115.2 | 14.0 42.0 64.0 |
| 0.6                      | 33.9 96.7 158.9 | 28.9 84.4 138.1 | 17.0 51.0 76.0 |
| 0.7                      | 38.4 112.7 184.5 | 32.2 98.2 162.3 | 20.0 59.0 89.0 |
| 0.8                      | 44.9 128.7 210.2 | 37.7 112.1 185.7 | 22.0 68.0 101.0 |

\( D_{80}, D_{90}, \text{and} \ D_{100} \) refer to the dose delivered to 80%, 90%, and 100% of the target volume, respectively; I, II, and III refer to a portal-vein stent combined with one, two, or three \( ^{125} \text{I} \) seed strands, respectively. 1 mCi = 37 MBq. \( ^{125} \text{I} \): Iodine-125.

**Discussion**

With increasingly detailed studies of intraluminal implantation of \( ^{125} \text{I} \) seed-loaded stents,\(^{23}\) stenting of the portal vein combined with implantation of \( ^{125} \text{I} \) seed strands has become a new treatment of HCC with PVTT. In clinical application of this technology, most researchers have used the formula: obstruction length (mm)/4.5 + 4 to calculate the required number of \( ^{125} \text{I} \) seeds. However, the dose distribution in the tumor target has been reported rarely.\(^{13,14,24}\) Luo *et al.*\(^{14}\) adopted the formula shown above to calculate the required number of \( ^{125} \text{I} \) seeds and, according to the software used to calculate distribution of the \( ^{125} \text{I} \) radiation field, the mean radiation dose of PVTT was 142.1 ± 39.9 Gy. Sun *et al.*\(^{24}\) chose 0.6 mCi/seed for the implantation of \( ^{125} \text{I} \) seed strands. The number of \( ^{125} \text{I} \) seeds for their patients was calculated.
using the formula: obstruction length (cm)/0.5 + 2. Finally, the mean dose absorbed 1 cm from the source axis within 60 days was 40–50 Gy. The activity of $^{125}$I seeds in the study by Chuan-Xing et al.\cite{12} was 0.6–0.8 mCi, and the matched peripheral dose calculated by the TPS was 110–150 Gy.

Review of the literature shows that the calculation methods for dose distribution of $^{125}$I seed strands are different; range of target radiation dose is very broad; radiation dose of normal tissues around the target volume is rarely described; assessment of the brachytherapy plan is absent. Therefore, comparison of clinical efficacy among different studies also becomes difficult. This is also the reason why we choose the criteria for prostate cancer to conduct our study.

Dose distribution is the most direct and important factor influencing the outcome of brachytherapy.\cite{23} A change in radiation dose affects local control of the tumor significantly.\cite{24} The American Brachytherapy Society recommends three steps for the assessment of the quality of implantation of $^{125}$I seeds:\cite{25} (i) review distribution of the isodose to offer the most direct assessment of dose coverage; (ii) generate a DVH to obtain volumetric parameters; (iii) determine the CN and HI to evaluate the dosimetric quality of the brachytherapy plan (which may be of value in assessment of the future clinical outcomes).

Figures 2 and 3 show that, when stenting of the portal vein was combined with implantation of a single $^{125}$I seed strand and activity of the $^{125}$I seed was 0.3–0.8 mCi, reference isodose curves/surfaces could not completely “wrap” the target volume around the stent. Hence, the target volume (which is not covered by the reference dose) forms a low-dose area, which is likely to cause local recurrence or metastasis of the tumor, leading to stent restenosis and occlusion.

The British Columbia Cancer Agency recommends $D_{90}>90\%$ PD and $V_{100}>85\%$ for brachytherapy of prostate cancer.\cite{26} In the present study, when the PD (in Gy) was 105, 125, and 145 and the corresponding seed activity (in mCi) was $\geq0.5$, $\geq0.5$, and $\geq0.6$, respectively, $D_{90}$ and $V_{100}$ of Group III could meet the requirements mentioned above. When the PD was 105 Gy and seed activity was 0.7 mCi, $D_{90}$ and $V_{100}$ of Group II were 98.2 Gy and 85.4%; when seed activity was 0.8 mCi, the data
were 112.1 Gy and 93.4%, respectively. For irradiated stents in Group I, $D_{90}$ and $V_{100}$ could not achieve the requirements mentioned above. When the PD was 105 Gy and seed activity was 0.8 mCi, $D_{90}$ and $V_{100}$ were the largest, and the maximum was 44.9 Gy (43% PD) and 30.1%, respectively.

Image-guided interstitial brachytherapy using $^{125}$I seeds can fully accommodate the contours of the tumor volume, as well as achieve highly accurate conformity and rapid fall-off of dose. A CN $>$0.6 has been recommended for "conformal radiotherapy." Table 2 shows that, when the PD (in Gy) was 105, 125, and 145 and the corresponding seed activity (in mCi) was 0.4 and 0.5, 0.5 and 0.6, and 0.6 and 0.7, respectively, the CN of Group III was $>$0.6. When the PD was 105 and 125 Gy and the corresponding seed activity was 0.7 and 0.8 mCi, respectively, the CN of Group II was 0.61 and 0.60, respectively. The CN of Group I was $<$0.6. When the PD was 105 Gy and seed activity was 0.8 mCi, the maximum CN was 0.22. Due to the inverse-square law and the law of exponential decay, it is difficult for $^{125}$I seed brachytherapy to ensure the uniformity of dose distribution in the target volume. Therefore, the CN and EI should be more important for the evaluation of brachytherapy plan. In our study, as the activity of $^{125}$I seeds and the number of $^{125}$I seed strands increased, the CN and EI also increased. Hence, increases in the activity of $^{125}$I seeds and number of $^{125}$I seed strands do not always result in a better brachytherapy plan.

A stent combined with a single $^{125}$I seed strand in Group I led to difficulties in meeting the requirements for dosimetry. When the PD was 105 Gy and activity of $^{125}$I seeds was 0.7 mCi, the dose distribution of Group II satisfied the dosimetry requirements of our study. For a portal-vein stent combined with three $^{125}$I seed strands, when the PD (in Gy) was 105, 125, and 145 and the corresponding activity of $^{125}$I seeds (in mCi) was 0.5, 0.5 and 0.6, and 0.6 and 0.7, respectively, the dosimetry could be met. For stents in Group III, when the PD was 125 Gy and activity of $^{125}$I seeds increased from 0.5 mCi to 0.6 mCi, $D_{90}$ increased by 20%, $V_{100}$ increased by 12%, the CN decreased by 4%, the EI increased by 107%, and the HI decreased by 28%. Therefore, a seed activity of 0.5 mCi could be a rational choice. Similarly, when the PD was 145 Gy and activity of $^{125}$I seeds increased from 0.6 mCi to 0.7 mCi, $D_{90}$ increased by 18%, $V_{100}$ increased by 9%, the CN decreased by 7%, the EI increased by 91%, and the HI decreased by 25%. Hence, a seed activity of 0.6 mCi could be the best choice.

The present study was in strict accordance with the assessment steps of brachytherapy dosimetry recommended by the American Brachytherapy Society. We explored the dosimetric characteristics of portal-vein stenting combined with different numbers of $^{125}$I seed strands. In the real world, the tumor target would change in the morphology, shape, and size after the stent expansion in the occluded portal vein. Thus, the dosimetry distribution may be different from the water cylinder, so our basic research could only provide a theoretical basis for rational, safe, and effective clinical application. Nevertheless, the clinical experience of brachytherapy using $^{125}$I seeds for luminal tumors is very limited. The PD, activity of $^{125}$I seeds, and criteria for evaluation of dosimetry parameters are mainly those chosen for prostate cancer, which may have led to some bias in our results. In addition, this work is a treatment planning study, the relative position of adjacent critical structures (mainly liver, kidneys, stomach, and small intestine) to target volume, the relative position between the critical structures, and the volume of the critical structures are difficult to determine in our study. Thus, we did

Table 2: The CN, EI, HI at a PD of 105, 125, and 145 Gy for Groups I, II and III

| PD (Gy) | Seed activity (mCi/per seed) | CN | EI (%) | HI (%) |
|---------|-----------------------------|-----|--------|--------|
|         |                             | I   | II     | III    |
| I       | 0.3                         | 0.06| 0.16   | 0.44   | 1.1  | 2.8  | 8.4  | 42.5 | 51.1 | 58.1 |
| 125     | 0.5                         | 0.05| 0.11   | 0.32   | 0.4  | 2.3  | 5.6  | 35.7 | 46.6 | 59.1 |
| 145     | 0.4                         | 0.04| 0.10   | 0.23   | 0.3  | 1.3  | 3.5  | 37.8 | 45.8 | 57.7 |
| 105     | 0.09                        | 0.09| 0.31   | 0.66   | 2.1  | 5.8  | 18.0 | 45.0 | 59.4 | 48.5 |
| 125     | 0.07                        | 0.07| 0.21   | 0.53   | 1.3  | 3.6  | 10.7 | 44.6 | 53.8 | 54.7 |
| 145     | 0.06                        | 0.06| 0.16   | 0.41   | 1.3  | 2.5  | 8.3  | 42.3 | 52.0 | 59.5 |
| 105     | 0.05                        | 0.14| 0.45   | 0.65   | 2.1  | 12.1 | 43.6 | 48.4 | 57.2 | 34.5 |
| 125     | 0.11                        | 0.11| 0.34   | 0.67   | 1.2  | 7.0  | 22.1 | 45.0 | 58.0 | 46.9 |
| 145     | 0.09                        | 0.09| 0.25   | 0.59   | 1.0  | 4.0  | 13.4 | 46.9 | 55.6 | 52.7 |
| 105     | 0.06                        | 0.17| 0.56   | 0.54   | 4.5  | 21.4 | 80.2 | 46.4 | 49.9 | 18.5 |
| 125     | 0.14                        | 0.14| 0.46   | 0.64   | 3.1  | 11.6 | 45.8 | 48.4 | 56.8 | 33.9 |
| 145     | 0.11                        | 0.11| 0.37   | 0.68   | 1.7  | 7.4  | 24.5 | 44.1 | 58.4 | 44.8 |
| 105     | 0.07                        | 0.19| 0.61   | 0.45   | 8.2  | 34.6 | 119.8| 42.9 | 42.7 | 8.4 |
| 125     | 0.17                        | 0.17| 0.54   | 0.56   | 3.9  | 20.7 | 75.7 | 46.3 | 50.9 | 20.2 |
| 145     | 0.14                        | 0.14| 0.46   | 0.63   | 3.0  | 12.3 | 46.8 | 47.5 | 56.7 | 33.4 |
| 105     | 0.8                         | 0.22| 0.59   | 0.38   | 11.9 | 54.2 | 160.4| 41.5 | 34.5 | 3.6 |
| 125     | 0.19                        | 0.19| 0.60   | 0.48   | 7.1  | 30.6 | 107.9| 44.0 | 44.8 | 10.4 |
| 145     | 0.16                        | 0.16| 0.54   | 0.56   | 4.3  | 19.0 | 72.4 | 46.2 | 51.3 | 21.6 |

I, II, and III refer to a portal-vein stent combined with one, two, or three $^{125}$I seed strands, respectively. CN: Conformation number; EI: External volume index; HI: Homogeneity index; PD: Prescribed dose; $^{125}$I: Iodine-125.
not take into account the doses to adjacent critical structures. Furthermore, portal-vein stents combined with two or three 125I seed strands were simulated by a particular TPS, and its clinical feasibility and safety requires verification.

In conclusion, it was difficult for a portal-vein stent combined with a single 125I seed strand to meet the requirements for clinical dosimetry. For a stent combined with two 125I seed strands, when the PD was 105 Gy and the activity of 125I seeds was 0.7 mCi, the dose distribution could satisfy the dosimetry requirements of our study. For a stent combined with three 125I seed strands, if the PD was 105, 125, or 145 Gy, the recommended seed activities were 0.5, 0.5, and 0.6 mCi, respectively.

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Conflicts of interest
There are no conflicts of interest.

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