Visibility of an iron-containing fiducial marker in magnetic resonance imaging for high-precision external beam prostate radiotherapy

Osamu Tanaka1 | Hisao Komeda2 | Shigeki Hirose3 | Takuya Taniguchi1 | Kousei Ono1 | Masayuki Matsuo4

1Department of Radiation Oncology, Murakami Memorial Hospital, 3–23 Hashimoto-cho, Gifu City, Gifu, Japan
2Department of Urology, Gifu Municipal Hospital, Gifu City, Gifu, Japan
3Division of Radiation Service, Gifu Municipal Hospital, Gifu City, Gifu, Japan
4Department of Radiology, Gifu University School of Medicine, Gifu City, Gifu, Japan

Correspondence
Osamu Tanaka, Department of Radiation Oncology, Murakami Memorial Hospital, 7-1 Kashima-cho, Gifu City, Gifu 500–8513, Japan.
Email: c.bluered@gmail.com

Abstract

Introduction: Visualization of fiducial gold markers is critical for registration on computed tomography (CT) and magnetic resonance imaging (MRI) for imaging-guided radiotherapy. Although larger markers provide better visualization on MRI, they tend to generate artifacts on CT. MRI is strongly influenced by the presence of metals, such as iron, in the body. Here we compared efficacies of a 0.5% iron-containing gold marker (GM) and a traditional non-iron-containing marker.

Methods: Twenty-seven patients underwent CT/MRI fusion-based intensity-modulated radiotherapy. Markers were placed by urologists under local anesthesia. Gold Anchor (GA; diameter: 0.28 mm; length: 10 mm), an iron-containing marker, was placed on the right side of the prostate using a 22-G needle and VISICOIL (VIS; diameter: 0.35 mm; length: 10 mm), a non-iron-containing marker, was placed on the left side using a 19-G needle. T2*-weighted images MRI sequences were obtained. Two radiation oncologists and a radiation technologist evaluated and assigned scores for visual quality on a five-point scale (1, poor; 5, best visibility).

Results: Artifact generation on CT was slightly greater with GA than with VIS. The mean marker visualization scores on MRI of all three observers were significantly superior for GA than for VIS (3.5 vs 3.2, 3.9 vs 3.2, and 4.0 vs 2.9). The actual size of the spherical GA was about 2 mm in diameter, but the signal void on MRI was approximately 5 mm.

Conclusion: Although both markers were well visualized and can be recommended clinically, the results suggest that GA has some subtle advantages for quantitative visualization that could prove useful in certain situations of stereotactic body radiotherapy and intensity-modulated radiotherapy.

KEYWORDS
fiducial marker, MRI, prostate radiotherapy

1 | INTRODUCTION

High-precision radiotherapy is increasingly used for the treatment of prostate cancer. Stereotactic body radiotherapy (SBRT) and intensity-modulated radiotherapy (IMRT) commonly use fiducial gold markers (GM).1,2 Because the reproducibility of treatment is important for clinical use, it is essential to use a GM for fusing images obtained using computed tomography (CT) and magnetic resonance imaging (MRI). If a GM is not placed in the abdominal or pelvic region, such as for the liver or prostate, it can be difficult to detect such organs during radiotherapy, with the delineation of the prostate using only CT being particularly difficult.3,4 However, it is difficult to visualize a small GM on MRI.

Recently, cone-beam CT (CBCT) has been used for registration of the target organ and for planning CT. However, with this method, the borders that tumors have with the organ and soft tissues may be indistinct. It is difficult to remove scattered radiation, which increases noise in the CBCT images because a flat-panel detector is used. In addition, it takes approximately 1 min to obtain a CBCT image, and body movement during this can affect image quality.

The MRI image is greatly influenced by internal metal (such as metal clips or metallic stents). Recently, iron-containing GMs have been used
TABLE 1  Characteristic of the patients (N = 27)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years); mean (range)</td>
<td>75.6 (range: 64–82)</td>
</tr>
<tr>
<td>Race</td>
<td>all Asian</td>
</tr>
<tr>
<td>Risk (D’Amico classification)</td>
<td></td>
</tr>
<tr>
<td>low (number)</td>
<td>6</td>
</tr>
<tr>
<td>intermediate (number)</td>
<td>11</td>
</tr>
<tr>
<td>high (number)</td>
<td>10</td>
</tr>
<tr>
<td>Initial PSA (ng/ml); median (range)</td>
<td>15.3 (6.2–38.4)</td>
</tr>
<tr>
<td>Gleason score; median (range)</td>
<td>8 (7–9)</td>
</tr>
<tr>
<td>Prostate volume (cm³); median (range)</td>
<td>31.1 (18.4–41.2)</td>
</tr>
<tr>
<td>Hormonal therapy (Yes)</td>
<td>12</td>
</tr>
<tr>
<td>Chemotherapy (Yes)</td>
<td>none</td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen, Initial PSA: PSA level at the initial diagnosis

2  | MATERIALS AND METHODS

2.1 | Patients

This study was approved by our Institutional Review Board and the trial was registered in the UMIN-Clinical Trial database. The study was conducted between April 2016 and July 2016. A total of 27 patients were enrolled, with written informed consent obtained from each before enrolment. Patient characteristics are shown in Table 1.

2.2 | Gold markers

We compared a spherical GM containing 0.5% iron by volume, the Gold Anchor (GA; Naslund Medical AB, Huddinge, Sweden), with a
FIGURE 2  Visibility on plain radiography, CT and MRI. Left upper, planning CT. Right upper, plain radiograph. Left lower, T2*-2D-weighted image. Right lower; T2*3D-weighted image. Gold Anchor: 0.28 mm (white arrow); VISICOIL: 0.35 mm (patchy pattern arrow). The visualization of both markers was equally good in radiography and CT. Gold Anchor is well visualized on MRI [Colour figure can be viewed at wileyonlinelibrary.com]

commonly used non-iron-containing linear marker, the VISICOIL (VIS; RadioMed Corporation, Bartlett, TN, USA). GA is 0.28 mm in diameter and 10 mm in length. However, VIS is 0.35 mm in diameter and 10 mm in length and is most commonly linear in shape (Figures 1 and 2). GA consists of a set of linear segments inserted as linear markers (Figure 1), which were crushed so that the segments were pushed together to form an irregular shape.

The fiducial markers were placed by urologists via the transperineal approach under local anesthesia, with VIS placed on the left side of the prostate using a 19-G needle and GA on the right using a 22-G needle. Patients on anticoagulant therapy were excluded from this study. CT and MRI scans were acquired 3 weeks after insertion.

2.3  Image acquisition

2.3.1  Parameters for T2-WI

T2-weighted fast spin-echo (repetition time [TR]/echo time [TE], in ms) (4000/80); number of signals averages (NSA), four; number of phase-encoding steps (PES), 205; number of frequency-encoding steps (FES), 256 and typical spatial resolution (TSR); frequency/phase, 0.63/0.80.

2.3.2  Parameters for T2*-2D-WI

T2*-weighted gradient echo (700/18); NSA, two; PES, 205; FES, 256; and TSR; frequency/phase, 0.63/0.78.

2.3.3  Parameters for T2*3D-WI

T2*-3D-weighted gradient echo [TR/TE1/deltaTE] (37/14/7.3); NSA, two; PES, 218; FES, 272; and TSR; frequency/phase, 0.55/0.54.

2.3.4  Parameters for planning CT

Slice thickness 1.25 mm, field of view 40 cm × 40 cm, 460 mA, 120 kV.

The CT scans were obtained with an Optima CT580 (GE Medical Systems, Milwaukee, WI, USA) and the T2*WI MRI scans with an Intera 1.5 Nova (Philips Medical Systems, Eindhoven, The Netherlands). The MRI examination was performed within 20 min of completing the CT. All patients were administered butylscopolamine to stop bowel movements. The Novalis Tx system radiotherapy equipment (Varian Medical Systems, Inc., Palo Alto, CA, USA) is used in our hospital. Parameters for cone-beam CT is as follows; slice thickness, 2.5 mm; number of pixels, 384 × 384; 80 mA, 125 kV. GA. We recognized both GA and VIS in all cases clearly similarly in CBCT.
Primary outcomes of interest were the degree of artifact generation on CT and the visualization quality of GM on MRI images of the prostate.

2.4 Evaluation of the images

We estimated CT and MRI slice levels for the evaluation of artifacts and the signal void were at the same level of the image slice (Figures 2 and 3). Two radiology oncologists with 20 and 17 years of experience in external beam radiotherapy and a radiation technologist with 15 years of experience in MRI-guided radiotherapy physics evaluated the images. They categorized the results on a scale of 1–5: 1, poor; 2, rather poor; 3, neutral; 4, somewhat better; and 5, best visibility. The degree of recognition of the marker on MRI images of the prostate was scored using the same criteria. CT images with fewer artifacts were assigned a higher score. For clearest images among three sequences, the MRI sequences used were T2*2D-WI for 21 patients and T2*3D-WI for six patients. T2-WI was not used. The differences in observers’ scores between the GA and VIS were assessed by using analysis of variance (ANOVA). P-values of < 0.05 were considered as indicating significant differences. The statistical analyses were performed using BelCurve for Excel software (Social Survey Research Information Co., Ltd., Tokyo, Japan).

3 RESULTS

Table 2 summarizes the comparison of GA and VIS. There was good recognition of both markers on plain pelvic radiographs (Figure 2). The radiation technologist observed significantly more artifacts on CT with GA than with VIS. Visibility of GA was significantly superior to that of VIS on MRI, as scored by all three observers (Figures 2 and 3). Although GA was placed on the capsule of the prostate, it was well depicted on MRI (Figure 3).

4 DISCUSSION

The clinical outcomes of radiotherapy depend on the precision and reproducibility of the technique used for its delivery. When based on dynamic assessment, the dose to the prostate itself is increased whereas the dose exposure of the surrounding normal tissue is minimized. Real-time tracking can minimize the complications associated with image-guided radiotherapy because of changes in prostate position. With CT alone, the outline of the prostate tends to be indistinct and may not be well delineated. However, the outline of the prostate is clearly discernible on MRI; thus, MRI is used to overcome the uncertainty of contouring on CT. Markers are used to register the position on both CT and MRI; these are useful not only to ensure the reproducibility of radiotherapy but also for registration.

4.1 Types of markers

Various marker sizes are used around the world. In Japan, GA (0.28 mm in diameter), VIS (0.35 mm, 0.5 mm and 0.75 mm in diameter) and VISICOIL (spherical, 0.35 mm diameter) are used. Table 3 shows a summary of the characteristic of GA and VIS (and other markers). Furthermore, the prostate is a small organ, and the presence of metal may itself affect dose distribution. We developed an optimal MRI sequence method based on this observation and adopted 0.35 mm; however results from our initial experience of iron containing marker, we have use GA. It has been widely used worldwide since it was first developed in Sweden in 2012. Available data suggest that GA is associated with less artifact generation on CT compared with conventional GMs. However, it is pertinent to mention here that GA was placed spherically.

4.2 Magnetic resonance images

Because the diameter of the spherical GA which was placed using a 22-G or 25-G needle, there is a possibility that it is bigger than VIS of 0.35 mm placed linearly. The actual diameter of GA is approximately 2 mm but the diameter of the signal void on MRI was approximately 5 mm in both T2*2D-WI and T2*3D-WI sequences. If GA is positioned in a zigzag shape, the signal void on MRI is visualized better than that produced by traditional markers. Clinical trials using linearly placed GA and VIS are currently ongoing at our hospital. Regarding the diameter of the marker, the 0.5-mm diameter is popularly used. There have been no previous studies that investigated the use of GA and other markers together in the same human body, although there have been reports of their use in phantom studies. Infection and bleeding rates are lower with GA than with other traditional markers.

<table>
<thead>
<tr>
<th>TABLE 2 Comparison of the iron-containing marker Gold Anchor™ (0.28-mm diameter) and the non-iron-containing marker VISICOIL™ (0.35-mm diameter). Both markers were 10 mm in length.</th>
<th>Artifacts on CT</th>
<th>Signal voids on MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1 (RT)</td>
<td>Gold Anchor (mean ± SD)</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>Observer 2 (RO)</td>
<td>Gold Anchor (mean ± SD)</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Observer 3 (RO)</td>
<td>Gold Anchor (mean ± SD)</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>VISICOIL (mean ± SD)</td>
<td>1.8 ± 0.9</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>VISICOIL (mean ± SD)</td>
<td>1.9 ± 0.7</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>p value</td>
<td>0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>p value</td>
<td>0.46</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

RT, radiation technologist; RO, radiation oncologist; SD, standard deviation. In the evaluations of artifacts on CT, higher scores reflected less artifact generation. For signal voids on MRI, higher scores reflected superior visualization of the marker. p values were calculated using the analysis of variance (ANOVA) test.
**FIGURE 3** Gold Anchor placed on the capsule of the prostate (white arrow). Left upper, planning CT. Right upper, T2*-2D-weighted image. Left lower, T2*-3D-weighted image. Right lower, T2-weighted image. Gold Anchor is well visualized on MRI [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Comparison of Gold Anchor and VISICOIL (including other gold markers)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Gold Anchor (GA)</th>
<th>VISICOIL (and Others)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folding and expanding</td>
<td>Coiled shape</td>
<td></td>
</tr>
<tr>
<td>Diameter</td>
<td>0.28 mm and 0.40 mm</td>
<td>0.35, 0.5, 0.75, and 1.1 mm</td>
</tr>
<tr>
<td>Length</td>
<td>10 mm and 20 mm</td>
<td>10 mm and 20 mm</td>
</tr>
<tr>
<td>Iron content</td>
<td>0.5%</td>
<td>none</td>
</tr>
<tr>
<td>SHAPE</td>
<td>spherical or linear</td>
<td>linear</td>
</tr>
<tr>
<td>Migration rate</td>
<td>0.0% [We have been told by several users that they have not seen any migrations of GA, but there is no one who has reported that in a study]</td>
<td>1% (5/512) Moman et al. [18]</td>
</tr>
<tr>
<td>Infection rate, prostate per rectum implantation 22G</td>
<td>0.3% (2/668) from Castellanos et al. [16]</td>
<td>0.5%–7.7% (including other marker’s data) [16–23]</td>
</tr>
<tr>
<td>Rectal bleeding rate 22G</td>
<td>2.8% from Mista et al. [17]</td>
<td>11% from Gill et al. [19] (using pure gold of 1 mm in diameter by 5 mm in length)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.7% from Igdem et al. [20] (marker data was not found)</td>
</tr>
</tbody>
</table>

This may be because of the thinner needle used, as well as the slightly lower migration rates than other GMs because of its zigzag or spherical shape. If the prostate does not move during MR examinations, GA is recognized as signal void of 5 mm, and VIS as a void of 1 mm. However, when the prostate moves during the examination, VIS is not recognizable, although GA remains visible because of its iron content, which helps produce a larger signal void and clearly decreases the level of uncertainty. Whether the prostate moves during MR examinations depends on individual patients. The visual evaluation system was subjective, but it was nevertheless clinically appropriate. Our study
showed that the iron-containing marker greatly contributed to registration using MRI in case of the radiation treatment planning in the clinical practice, especially for SBRT and IMRT settings.

### 4.3 Limitations

This study had some limitations. Our initial intention was to blind the three observers regarding which marker was which, but this was not possible because GA was immediately apparent in several cases initially. Similarly, in CBCT, both GA and VIS were clearly recognized in all cases. Furthermore, we reported a case in which GA was placed to the liver and was clearly recognizable in CBCT. Our institution uses kilovoltage CT; we think there should be a controlled trial using megavoltage CT (MVCT), such as Tomotherapy. Yue et al. reported that, because of the relatively poor image quality of MVCTs, additional investigations may be required to confirm image quality in MVCT compared to kVCT. The quantitative measurements are difficult, because, for example, the size of signal void does not reflect the quality (signal void of both 2 and 5 mm are similarly efficient to recognize position of marker in the prostate).

### 4.4 Future of MRI-only-based radiotherapy planning

Recently, there have been tremendous developments in image modalities, such as dual-energy CT, MRI (diffusion-weighted and functional image), and 18F-FDG PET/CT. However, MRI-only-based radiotherapy remains in clinical use. Johnstone et al. reported that the MRI-only radiotherapy planning techniques could be grouped into three categories (bulk density override, atlas-based, and voxel-based), which all produce a pseudo-CT scan from MR image(s). They concluded that atlas-based and voxel-based techniques were the most suitable for integration into the clinic. In the case of GA, the signal void on MRI is easily recognized. It is convenient to replace it with pseudo-CT with the Hounsfield unit value of gold.

### 5 CONCLUSION

MRI visualization of the iron-containing marker GA was distinctly superior for image registration. The use of GA is likely to be beneficial for high-precision radiotherapy such as SBRT and IMRT in the clinical setting.

### CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

### FINANCIAL SUPPORT

None.

### ETHICAL APPROVAL

This study was approved by the Institutional Review Board.

### INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

### ORCID

Osamu Tanaka [http://orcid.org/0000-0002-7189-8407]

### REFERENCES


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