Verification of dose distribution in high dose-rate brachytherapy for cervical cancer using a normoxic N-vinylpyrrolidone polymer gel dosimeter

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(Received 11 April 2022; revised 14 July 2022; editorial decision 10 August 2022)

ABSTRACT

The polymer gel dosimeter has been proposed for use as a 3D dosimeter for complex dose distribution measurement of high dose-rate (HDR) brachytherapy. However, various shapes of catheter/applicator for sealed radioactive source transport used in clinical cases must be placed in the gel sample. The absorbed dose readout for the magnetic resonance (MR)-based polymer gel dosimeters requires calibration data for the dose-transverse relaxation rate ($R_2$) response. In this study, we evaluated in detail the dose uncertainty and dose resolution of three calibration methods, the multisample and distance method using the Ir-192 source and the linear accelerator (linac) method using 6MV X-rays. The use of Ir-192 sources increases dose uncertainty with steep dose gradients. We clarified that the uniformly irradiated gel sample improved the signal-to-noise ratio (SNR) due to the large slice thickness of MR images and could acquire an accurate calibration curve using the linac method. The curved tandem and ovoid applicator used for intracavitary irradiation of HDR brachytherapy for cervical cancer were reproduced with a glass tube to verify the dose distribution. The results of comparison with the treatment planning system (TPS) calculation by gamma analysis on the 3%/2 mm criterion were in good agreement with a gamma pass rate of 90%. In addition, the prescription dose could be evaluated accurately. We conclude that it is easy to place catheter/applicator in the polymer gel dosimeters, making them a useful tool for verifying the 3D dose distribution of HDR brachytherapy with accurate calibration methods.

Keywords: high dose-rate brachytherapy; Iridium-192; polymer gel dosimeter; quality assurance (QA)

INTRODUCTION

High dose-rate (HDR) brachytherapy is performed using the remote after-loading system (RALS) to transport a sealed radioactive source directly inside or near a tumor. The steep dose distribution according to the distance from the source makes it possible to irradiate tumors with a high dose of radiation while protecting normal tissue. With the development of imaging technologies, image-guided brachytherapy (IGBT) with computed tomography or magnetic resonance imaging (MRI) has become widely used. IGBT enables complex source transport with treatment plans that consider the geometrical relationship between target and normal tissues [1,2]. However, HDR brachytherapy does not perform detailed dose distribution verification, such as intensity-modulated radiotherapy (IMRT), stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) [3]. A quality assurance (QA) program for the treatment equipment is required to correctly execute HDR brachytherapy [4–6]. Furthermore, as with external beam...
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It is necessary to verify the dose distribution for each patient plan. Generally, ionization chamber dosimeters and films are used for dose distribution verification, but they are limited to point or two-dimensional dose distribution measurements. HDR brachytherapy requires catheter/applicator of various shapes to be placed in the body to transport the source. One source is transported into multiple positions into the catheter/applicator, considering the geometrical positional relationship with the tumor and normal tissue. Therefore, to verify a complicated dose distribution of HDR brachytherapy, 3D dose distribution verification is indispensable. In the dose distribution measurement of IMRT, an array detector arranged in a cylindrical shape or a plurality of planes is used as a quasi-3D detector. However, HDR brachytherapy with steep dose gradients does not provide sufficient dose data due to compositional and sequence spacing replacement issues.

Polymer gel dosimeters are attracting attention as a tool for measuring 3D dose distribution [7–10]. The polymer gel dosimeter is a chemical dosimeter that utilizes the polymerization reaction of water radicals and vinyl monomers in the gel matrix due to irradiation. Dose distribution measurements with a polymer gel dosimeter for sealed radioactive source have been attempted. De Deene et al. and Papagiannis et al. investigated the applicability of dose distribution measurements near an iridium-192 (Ir-192) source using polymer gel dosimetry [11, 12]. Additionally, Kipours and Watanabe et al. conducted dose distribution measurements simulating HDR interstitial brachytherapy for prostate cancer [13,14]. Magnetic resonance (MR) scans are commonly used to provide dose data of polymer gel dosimeters and calculate the transverse relaxation rate ($R_2$), which is the reciprocal of the transverse relaxation time ($T_2$) that correlates with the absorbed dose. Polymer gel dosimeters are used for relative dose measurements, and calibration curves are obtained by measuring $R_2$ for known absorbed doses. The 3D dose distribution of the main phantom to be analyzed is then obtained using the calibration curve.

However, the use of polymer gel dosimeters in clinical facilities is limited due to the lack of reliability of measured doses, and the requirement of the MR scan for dose data [15–18]. The uncertain calibration curve reduces the measurement accuracy of the 3D dose distribution of the polymer gel dosimeter. The uncertainty of the polymer gel dosimeter depends on the chemical reaction characteristics, the dose–response to radiation and the MR scan parameters. $R_2$ noise is...
Fig. 2. Dose distribution measurement of a treatment plan simulating HDR intraluminal brachytherapy for cervical cancer. (a) Schematic layout of a cylindrical glass container (ϕ125 mm × 120 mm) to which a tandem and egg-shaped applicator reproduced with a glass tube are fixed. (b) A flexible catheter with a diameter of 2 mm connected to RALS was inserted into the glass tube to transport the source. (c) The source positions (red points) of the tandem and the ovoid applicators were 6 points and 4 points, respectively. The prescribed dose was 6 Gy, which corresponds to point A (red cross, X = ± 20 mm, Y = 20 mm).

the most important cause of dose uncertainty. The causes of polymer gel dosimetry errors using dose readout by MRI are well understood. Using the optimized MR scan protocol, the uncertainty of the absolute dose that can be obtained has been demonstrated to be within 5% for a voxel size of 5 mm³ [19]. Reliable dosimetry with polymer gel dosimeters requires an improved calibration method [20–22]. The calibration method of HDR brachytherapy generally employs a technique in which the dose–response is acquired by using dose attenuation corresponding to the distance from the source [14, 23]. However, this technique causes uncertainty in the dose–response due to the steep dose gradient near the source. Moreover, the dose uncertainty of the calibration method for HDR brachytherapy has not been evaluated in detail.

There is another problem with the use of polymer gel dosimeters for dose distribution measurements in HDR brachytherapy. Procedures, such as catheter/applicator of various shapes insertion, are required to transport the source into the polymer gel dosimeter. It is difficult to place them inside a commonly used solid phantom or array detector. Polymer gel dosimeters are liquid before gelling, can be shaped freely, allowing easy placement of the catheter/applicator. However, there is a problem in that oxygen is mixed in the gel by this process; therefore, oxygen inhibition makes it difficult to measure the dose distribution of polymer gel dosimeters near the source [11]. There are few evaluations where the catheter/applicator is placed inside the polymer gel and the source positions are three-dimensionally complex.

In this study, we propose a calibration method for polymer gel dosimeters in clinical facilities to realize the dose distribution verification of HDR brachytherapy. For the acquisition of the calibration curve, we compared methods using Ir-192 source and a linear accelerator (linac). The dose uncertainty and dose resolution of each
calibration curve were evaluated. Furthermore, we verified the 3D dose distribution of the HDR intracavitary brachytherapy plan for cervical cancer and clarified its usefulness.

MATERIALS AND METHODS

Gel preparation

This study utilized a normoxic N-vinylpyrrolidone-based polymer gel (VIPET) gel dosimeter [24,25]. The composition of the VIPET gel was 4 wt% N-vinylpyrrolidone (NVP, Wako Pure Chemicals, Japan), 4 wt% N,N′-methylene-bis-acrylamide (Bis, Wako Pure Chemicals, Japan), 7 wt% gelatin (G2500, Sigma–Aldrich, UK), 85 wt% of ultra-pure water (Purelab Flex UV, Elga LabWater, UK) and 5 mM tetrais (hydroxymethyl) phosphonium chloride (THPC, 80% in water; Tokyo Kasei Kogyo Co., Ltd., Japan). VIPET gel was filled in a glass vial (ϕ40 mm × 100 mm) to evaluate the dose–response. The prepared gel sample was stored for 24 h in a darkroom at 23°C until irradiation.

Irradiations

The gel samples were irradiated with 380 keV gamma rays of average energy emitted from the Ir-192 source and 6 MV X-rays from a linac. The gel samples were placed in a water-equivalent phantom (Solid Water Phantom; Gammax, USA) to satisfy the backscattering condition (Fig. 1). A RALS, microSelectron HDR V3, Elekta Brachytherapy, Netherlands) equipped with an Ir-192 source or a linac (TrueBeam, Varian Medical Systems, Palo Alto, CA, USA) was used. A flexible catheter (ProGuide Sharp Needle, Elekta Brachytherapy, Netherlands) with a diameter of 2 mm was placed to transport the Ir-192 source into the VIPET gel. The Ir-192 source was stopped at one point, and irradiated with 0, 2, 10, 20, 30 and 40 Gy at 10 mm from the center of the source as the reference point using six samples (Fig. 1a). The absorbed dose was based on the calculation of the treatment planning system (TPS, Oncentra, Elekta Brachytherapy, Netherlands), calculated with a grid size of 1 mm. When a linear accelerator was used, three areas of one sample were irradiated with 0, 2, 10 Gy for one sample and 20, 30, 40 Gy for the second sample, respectively (Fig. 1b).

Evaluation of calibration curve

Irradiated gel samples were stored in the darkroom at 23°C for 24 h and MR scanned. \( R_2 \) was calculated from images acquired by a 1.5 T MRI scanner (SIGNA HDxt, GE, USA) using a quadrature head coil. The scanning parameters were applied as follows: spin-echo sequence, repetition time = 4000 ms, echo times (TE) = 10 and 250 ms, field of view (FOV) = 256 mm × 256 mm, matrix size = 256 × 256. The value of \( R_2 \) based on point \((i, j)\) was calculated as follows:

\[
R_2 (i, j) = \frac{1}{T_2 (i, j)} = \frac{1}{T E_2 - T E_1} \ln \left[ \frac{S_1 (i, j)}{S_2 (i, j)} \right]
\]
is the coverage factor for the confidence interval
is a conversion factor, and
and
is the offset of the absorbed dose. The dose uncertainty of the polymer gel dosimeter depends on the dose conversion and the \( R_2 \) value. The relative dose uncertainty of pixels in \( R_2 \) maps with values of \( R_2 \pm \sigma_{R_2} \) can be calculated as follows [26]:

\[
\frac{\sigma_D}{D} = \sqrt{\left( \frac{R_2 \sigma_{D}}{D} \right)^2 + \left( \frac{\alpha \sigma_{R_2}}{D} \right)^2 + \left( \frac{\sigma_D}{D} \right)^2}
\]

where \( \sigma_{D} \) and \( \sigma_{D_0} \) are the standard deviations of \( \alpha \) and \( D_0 \), respectively. The dose resolution \( D_\alpha^p \) of the polymer gel dosimeter was related to the dose uncertainty as follows [27]:

\[
D_\alpha^p = k_p \cdot 2^{\frac{p}{2}} \cdot \sigma_D
\]

where \( k_p \) is the coverage factor for the confidence interval \( p \). In this study, \( k_p = 1.96 \), and the confidence level of 95\% \( (D_\alpha^{95\%}) \) was calculated. The calibration methods \( \sigma_D/D \) and \( D_\alpha^{95\%} \) were evaluated in the linear dose–response region, respectively.

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A cylindrical glass container (φ125 mm × 120 mm) was filled with VIPET gel for dose distribution measurements in a treatment plan simulating the HDR intracavitary brachytherapy for cervical cancer. The tandem and ovoid applicators were reproduced in a 5 mm diameter glass tube and placed in a gel sample to prevent the inhibition of radical polymerization reactions by oxygen (Fig. 2). Glass containers are often used to prevent oxygen from reacting with the gel [28,29]. The tip of the glass tube was closed to prevent access to the gel and the outside. Additionally, a flexible catheter (ProGuide Sharp Needle, Elekta Brachytherapy, Netherlands) with a diameter of 2 mm connected to RALS was inserted into the glass tube to transport the source. The source positions of the tandem and the left and right ovoid applicators were 6 and 4 points, respectively. The prescribed dose was 6 Gy, which corresponds to point A used in clinical cases. The origin was the source position on the most RALS side of the tandem applicator, the left and right ovoid applicator directions were the X-axis, and the tandem long-axis direction was the Y-axis. The coordinates of the two points A were \( X = \pm 20 \text{ mm} \) and \( Y = 20 \text{ mm} \). The dwell time of the tandem and ovoid applicator for the Ir-192 source strength (32.798 mGy m\(^2\) h\(^{-1}\)) was 39.7 s and 29.8 s, respectively.

The dose distribution was evaluated by the XY plane passing through the left and right points A and the YZ plane orthogonal to it. The MR slice thickness was 2 mm. The measured dose distributions were compared to the TPS calculation using a gamma analysis with 3%/2 mm criterion by the gamma analysis software program Simple IMRT Analysis (Triangle Products, Japan) [30]. The threshold was set...
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Fig. 5. (a) Dose uncertainty and (b) dose resolution for VIPET gel dosimeters of multi-sample and distance methods using the Ir-192 source, and the linac method (slice thickness 2 mm and 5 mm). The dose resolution is a 95% confidence level calculated with a coverage factor of 1.96.

to 10% of the maximum dose (50 Gy). We also compared the X- and Z-axis dose profiles and A-point doses. Dose calculation by TPS followed the protocol of the American Association of Physicists in Medicine publication Task Group No. 43 with a grid size of 1 mm [31,32]. The geometric positions of the dose distributions of the VIPET and TPS were matched relative to the tandem and ovoid applicators.

RESULTS

Dose–response

Figure 3 shows a photograph and R2 map of a VIPET sample for calibration irradiated with an Ir-192 source and 6 MV X-rays. White turbidity according to the absorbed dose was visually confirmed radially from one point of the source position of the Ir-192 source. The catheter position can be identified as a low-signal pixel position on the R2 map (Fig. 3a). In the VIPET sample irradiated with 6 MV X-rays, the difference in cloudiness in the three regions could be clearly distinguished for each dose. The dose–response from the Ir-192 source and 6 MV X-rays showed a linear correlation (R2 > 0.991) between the dose and R2 in the dose range of 0–30 Gy (Fig. 4). Results that saturate at values > 30 Gy were obtained, as evidenced by several previous studies of VIPET dosimetric assessments [14,25]. The dose responses of the multi-sample method using the Ir-192 source and the 6 MV X-rays at a slice thickness of 2 mm were 0.073 ± 0.001 s−1 Gy−1 and 0.0721 ± 0.0004 s−1 Gy−1, respectively, which were in good agreement. The dose–response of the VIPET dosimeter was consistent with the Ir-192 source and 6 MV X-rays, with no energy dependence observed. The standard deviation was increased by the distance method using the Ir-192 source. The coefficient of variation in the distance and linac methods was 2.6% and 0.6%, respectively.

Dose uncertainty and dose resolution

Figure 5 shows the dose uncertainty and dose resolution of the Ir-192 source (multi-sample method, distance method) and 6 MV X-rays (linac method, slice thickness 2 mm, 5 mm). The dose uncertainty at 10 Gy in the multi-sample, distance, and linac methods with a slice thickness of 2 mm were 4.1%, 7.6% and 1.8%, respectively. The dose resolution at the 95% confidence level was ≤0.7 Gy for the linac method, while it was ≥1.0 Gy for the multi-sample and distance methods using the Ir-192 source. The dose resolution of the distance method was the highest. The dose resolution of the linac method at a slice thickness of 5 mm was about half that of 2 mm.

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Figure 6 shows the irradiated VIPET sample photograph and the R2 map of the XY and YZ planes passing through point A. To prevent chemical artifacts due to air inside the glass tube (applicator), the inside of the glass tube was filled with water during the MR scan. The R2 maps were dose-converted using a calibration curve obtained with a slice thickness of 5 mm for the linac method with the lowest dose uncertainty. It was confirmed that R2 increased corresponding to six points of the source position of the tandem applicator. The dose distribution measured by the VIPET sample is shown in Fig. 7, along with the TPS calculation. The gamma pass rates of the XY and YZ
Fig. 6. (a) Photograph of the irradiated VIPET gel dosimeter with a tandem/ovoid applicator made of the glass tube to simulate HDR intracavitary brachytherapy for cervical cancer. (b) The $R_2$ map of the XY and YZ planes passing through point A.

planes compared to the TPS on the 3%/2 mm criterion were 90.2% and 90.6%, respectively, which were in good agreement. However, the high dose range with a steep dose gradient near the source position did not match. In this study, the dose was converted by a calibration curve that was linearly approximated to 30 Gy obtained by the linac method. Therefore, the failing areas at values $>30$ Gy near the source positions were due to dose conversion errors. The X- and Z-axis dose profiles were in satisfactory agreement with TPS (Fig. 8). In the low-dose region of $\leq 5$ Gy, the dose error occurred because of the influence of noise in the MR image. The doses of point A on both sides of the X-axis profile were 5.8 Gy and 5.9 Gy for 6.0 Gy, respectively.

**DISCUSSION**

In this study, to verify the dose distribution of HDR brachytherapy using a VIPET gel dosimeter, we examined a calibration method using an Ir-192 source and 6 MV X-rays from linac. We evaluated two methods using the Ir-192 source, the multi-sample and distance methods. Furthermore, when 6 MV X-rays were used, the MR images of slices with a thickness of 2 mm and 5 mm were compared. The dose–response of the VIPET gel dosimeter to the Ir-192 source and 6 MV X-rays was consistent. When using the Ir-192 source, the multi-sample method was better than the distance method. The linac method was found to decrease dose uncertainty and provide higher dose resolution compared to that in the multi-sample and distance methods. In addition, the linac method improved the dose uncertainty as the slice thickness increased. We discuss this result in terms of the effect of volume, dose-rate dependence and energy dependence on the dose–response of polymer gel dosimeters for HDR brachytherapy using Ir-192 sources.

The dose uncertainty of the distance method was increased compared to that in the multi-sample and linac methods due to the steep dose gradient. For calibration curve acquisition, there is a dose difference of up to 33% at a resolution of 1 mm in the range of 6–18 mm at the center of the Ir-192 source, and the volume effect becomes a problem [11]. To obtain an accurate calibration curve, it is ideal to obtain it in a region where the dose gradient is gentle, but to assess the change in dose, a large sample is required. Kozicki et al. reported software that can process some important dosimetric data using polymer gel dosimeters [23]. Their proposed HDR brachytherapy calibration method was associated with distance and dose or $R_2$, similar to the distance method in this study. They point out the problem of dose-rate dependence in the Ir-192 source, suggesting the need for further investigation. However, our previous study confirmed that the VIPET
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Fig. 7. Comparison of the dose distributions in the XY and YZ planes between the VIPET gel dosimeter and the TPS calculations. (a) Percentages of the isodose contours for the VIPET gel dosimeters (dotted lines) and those calculated by the TPS (solid lines). (b) Results of gamma analysis with the 3%/2 mm criterion.

gel dosimeter was 1.5–25.4 Gy·min\(^{-1}\) and was dose-rate independent [14].

De Deene et al. showed that polyacrylamide gel dosimeters have no energy dependence in 6 MV and 25 MV X-rays [33]. In this study, the dose–response of the Ir-192 source (average gamma-ray energy 380 keV), which has a wider energy range, and the 6MV X-rays were in agreement. The slight difference in the dose response of the distance method compared to other methods is due to the dose uncertainty associated with the volume effect and not the energy dependence. We demonstrated that the dose–response of the VIPET gel dosimeter is energy-independent. The advantage of using high-energy X-rays is that the gel sample can be uniformly irradiated over a wide area. Therefore, MR image acquisition can set a large slice thickness and improve the signal-to-noise ratio (SNR) in the same scan time. Furthermore, the scanning time can be shortened. To encourage its use in more clinical facilities, it is essential to not only demonstrate high accuracy measurements but also shorten the working time. An accurate calibration method is indispensable for verifying the 3D dose distribution of polymer gel dosimeters. We conclude that high-energy X-rays from the linac method can be used for the calibration curve used in the dose conversion required for dose distribution measurement for HDR brachytherapy.

We simulated the clinical plan for cervical cancer, which is a typical HDR brachytherapy, and verified the dose distribution. VIPET gel dosimeters showed a linear correlation to doses in the range of 0–30 Gy. This dose range covers the dose normally provided in the treatment of cervical cancer. The International Commission on Radiation Units Measurements recommends a 2% relative dose accuracy in low dose gradients or 2 mm spatial accuracy in regions with high dose gradients [34]. Van Dyk et al. defined the dose accuracy of brachytherapy as 3% dose accuracy at distances of 0.5 cm or more at any point for any source [35]. The gamma pass rates of the XY and YZ planes compared to the TPS on the 3%/2 mm criterion were 90.2% and 90.6%, respectively. The dose distribution measured by VIPET was in good agreement with the TPS calculation, except for the high-dose area near the source position. It is expected to pass a small DTA (2 mm) even in high-dose areas with steep dose gradients. The failing area near the source position was caused by a dose conversion error owing to the limitation of the dose range (<30 Gy). It is expected that the gamma analysis results in the high-dose range will be improved by performing the dose conversion curve evaluation with a higher-order-term fitting function. However, De Deene et al. reported that in the high-dose region near the source, the monomers may be depleted and fresh monomers may flow in from the surroundings [11]. In this study, as the diffused monomer caused an error in the dose distribution measurement, the evaluation was limited to 30 Gy. Future research will focus on accurate basic characteristics and dose distribution measurement of VIPET dosimeters in the high-dose region. Furthermore, the dose at point A calculated
Fig. 8. Comparison of the dose profiles in the X and Z axes between the VIPET gel dosimeter and the TPS calculations. The doses of point A on both sides of the X-axis profile were 5.8 Gy and 5.9 Gy, respectively. The noise in the MR image increased the dose uncertainty in the low dose region (<5 Gy).

...by the linac method was −3.3% for 6.0 Gy. The results of this study show that it is possible to assess reference points for clinical planning, although dose uncertainty may need to be further decreased.

In previous studies, there was a report of dose distribution measurement using a simple plan in a polymer gel dosimeter, but there no evaluations have incorporated placement of a curved catheter/applicator and a three-dimensionally complicated source. Tachibana et al. conducted a simple plan in which the source was transported using a straight single catheter for the End-to-End (E2E) test that required clarification of the cause of the error [36]. They have shown the usefulness of polymer gel dosimeters as a QA tool for HDR brachytherapy. A comprehensive dose distribution verification simulating the clinical situation of HDR brachytherapy should include 3D geometric information of an intricately placed catheter/applicator. In this study, we succeeded in measuring the dose distribution by reproducing a catheter/applicator with an inexpensive glass tube in a gel sample. Polymer gel dosimeters have been reported to change the linearity of the dose response with oxygen concentration in the low-dose region (<10 Gy) [11]. However, in the dose distribution verification of the cervical cancer plan by the calibration curve in the linac method without the use of the glass tube, the absorbed dose at point A (6 Gy) was almost the same as that in the TPS calculation. We believe that it was possible to prevent oxygen contamination by placing the glass tube in the gel, which did not affect the dose uncertainty.

It should be noted that the procedure in this study is not an evaluation using an applicator used in an actual clinical facility. We believe that the safety mechanism using the check cable installed in RALS can solve this problem when checking the connection of the catheter actually used and the source of transportation error, such as relics in the catheter. The dose distribution measurement method using the polymer gel dosimeter in this study can be expected as a measurement tool for verifying the 3D dose distribution based on the source position and dwell time in transportation.

CONCLUSION
The polymer gel dosimeter can be used as a 3D dosimeter for complex dose distribution measurements in HDR brachytherapy. However, various shapes of catheter/applicator for sealed Ir-192 radioactive source transport used in clinical cases should be placed in the gel sample. It must also be converted to an absorbed dose by an accurate calibration method. When using an Ir-192 source, dose uncertainty increases due to the steep dose gradient resulting from the inverse square of the distance from the source. In this study, it was clarified that the gel sample uniformly irradiated for the linac improves the SNR due to the large slice thickness, shortens the MR scan time, and can acquire an accurate calibration curve. The dose distribution simulating the intracavitary irradiation of HDR brachytherapy for cervical cancer was in good agreement with the TPS calculation, and the prescribed dose could be evaluated accurately. We conclude that polymer gel dosimeters allow for the placement of the catheter/applicator required for HDR brachytherapy dose distribution measurements and are a useful tool for verifying TPS-calculated dose distribution in the clinical plan. In future work, we plan to reproduce the various catheter/applicator used in the indications for HDR brachytherapy and to verify the dose distribution at the source position, which is arranged three-dimensionally.

ACKNOWLEDGMENTS
We are grateful to the laboratory members and students of Kitasato university for the collaboration of this work.
CONFICT OF INTEREST
The authors have no conflicts of interest to disclose.

FUNDING
This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number [JP18K07769 and JP22K07645].

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