Case Report

Treatment of pediatric vaginal rhabdomyosarcoma with the use of a real-time tracked custom applicator

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ABSTRACT

PURPOSE: To describe the development, design, and implementation of a 3D printed MR-compatible pediatric vaginal multichannel brachytherapy cylinder. Safety and quality measures to ensure consistent treatment required innovative identification on MR and CT, and real-time tracking.

METHODS AND MATERIALS: A 4-year-old with vaginal botryoides rhabdomyosarcoma underwent MR-simulation with a custom 3D printed biocompatible resin cylinder with four channels to ensure dose optimization capability. A total of four identifier regions were designed into the applicator in order to utilize these for MR-visualization and real-time tracking. A biocompatible 3D printed cylinder was designed to meet dose objectives using an MR and CT compatible material. 3D slicer was required for real-time tracking during treatment.

RESULTS: Based on MR simulation, a treatment plan was created with dose differentials in the area of prior surgery versus normal vaginal tissue. Creation of a low dose CT scan on a mobile CT allowed CT visualization of the applicator for verification. Treatment was administered under the use of a real-time optical tracking with rotational and depth adjustments monitored.

CONCLUSIONS: This advanced integration of 3D printed MR and CT biocompatible material, with unique design features consistent with a multi-channel vaginal cylinder, and incorporation of real-time optical tracking ensured that no positional changes were required, allowed successful treatment with differential dosing for a post-operative pediatric vaginal rhabdomyosarcoma patient.

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1. Introduction

Vaginal botryoides rhabdomyosarcoma (RMS) presents with an intraluminal mass. Treatment includes multi-agent chemotherapy and local control with organ-preserving surgery or radiation. Radiation is currently indicated in all but group-I embryonal disease based on results of ARST0331, which demonstrated an increased risk of loco-regional failure without radiation after a complete response to chemotherapy or delayed primary excision (1). In order to minimize the late effects of radiation, brachytherapy may be considered with a vaginal cylinder (2,3). However, commercially available vaginal cylinders are difficult to utilize in pediatric cases given that standard sizes are too large and are limited in their ability to dose optimize away from critical pediatric structures including the cervix and ovaries.

Compared to single-channel vaginal cylinders (SCVCs), multi-channel vaginal cylinders (MCVCs) improve target coverage and organ at risk (OAR) sparing thanks to the increased dose modulation capacity provided by the peripheral channels (4). The ability to adequately shape the dose distribution is of paramount importance in the setting of pediatric vaginal RMS. Commercially available MCVCs come in sizes which are not acceptable for pediatric use (25–40 mm diameter) (5). To treat these pediatric patients,
others have reported on the use of custom vaginal molds (2,3). Vaginal mold applicators are patient-specific but can lack the ability to reproducibly distend the vagina and enable uniform dose to the mucosa.

The advent of image-guided gynecologic brachytherapy has been shown to improve local control and reduce toxicities (6,7). Recent studies underline the value of MR-guidance by showing that the most important source of uncertainty in the image-guided procedure is target delineation (8). Therefore, applicators considered should be MR-compatible. Additionally, due to the hypointense signal produced in MR imaging of plastic applicators, treatment planning including the registration a digital applicator model to define the dwell positions is required (9,10). Uncertainties between the planned and actual applicator position can be of greater dosimetric significance for pediatric patients. In the case of an applicator with an outer cylindrical symmetry such as the MCVC, careful steps must be taken to properly define the rotational alignment of the applicator.

In the era of personalized and precision medicine, 3D printing is starting to be adopted by the radiation oncology community (11). The need for custom, patient-specific devices coupled with novel materials which meet the United States Pharmacopeia (USP) and ISO-10993 international standards (12) for biocompatibility make 3D printing an attractive solution in a technically proficient medical specialty.

In this work, we report on the design, quality assurance and clinical use of a custom MR/CT-compatible MCVC made of an FDA-approved, biocompatible material. We also describe an in-house real-time optical tracking system used for applicator position monitoring during treatment delivery.

2. Materials and Methods

2.1. Clinical Presentation

A 4-year-old presented with a vaginal mass and discharge and was found on vaginoscopy examination under anesthesia to have a pedunculated lesion on a stalk. Ultrasound images of the vagina shows a 2.6 x 2.5 x 1.2 cm$^3$ heterogeneous hypoechoic mass appearing to extend to the vaginal introitus (Fig. 1). Surgical resection was performed with residual microscopic positive margins. She received chemotherapy with VAC/VA as per ARST1431 regimen C 8 cycles and was evaluated by the radiation oncologist (JV) to discuss vaginal brachytherapy.

2.2. Clinical development of applicator

Based on the patient’s age and vaginal size, it was determined that a standard adult vaginal cylinder would not be safe or feasible. In seeking enhanced options, 3D printing was considered with the goal to create a vaginal cylinder of appropriate dimension, length and sufficient flexibility to ensure complete coverage of the surgical resection site. A custom 3D printed brachytherapy applicator was designed (MM) and a prototype generated. This prototype was presented by 2 authors (MM, JV) along with the anticipated workflow to The Johns Hopkins Hospital Innovative Therapy Committee, which sanctions official use of non-FDA approved products. This committee evaluated the applicator and determined that clinical implementation was appropriate and authorized proceeding with treatment. Parental consent was obtained for the patient’s treatment and for publication of the content of this paper including images. The IRB acknowledged the plans to publish this case report as non-human-subjects research.

Based on consultation with the patient’s surgeon and post-operative MRI of the patient, a 14 mm diameter multichannel vaginal cylinder with four peripheral channels was designed in a CAD software (Fusion 360 Autodesk, San Rafael, CA) as shown in Fig. 2. 14 mm was deemed the largest diameter based on clinical exam. The lack of a lesion at the time of MRI simulation influenced the decision to have equally spaced peripheral channels. Four channels were the most that could fit within the 14 mm diameter cylinder while ensuring the applicator would be adequately sturdy. The applicator was designed with four small (3 mm$^3$) pockets along the outer surface which serve as MR/CT fiducials for localizing the applicator. As the applicator appears as a hypointense signal on T2-weighted MRI, the pockets were to be filled with lubricant gel, known to appear markedly hyperintense (13), and sealed with sterile tape. The applicator was 3D printed using the biocompatible Dental-LT resin (Formlabs Inc., Somerville, MA, USA). Dental LT Clear is a Class IIa CE-certified long-term (>30 days) biocompatible photopolymer resin that is typically used for intraoral applications.

![Fig. 1. Preoperative ultrasound of the vagina shows a 2.6 x 2.5 x 1.2 cm$^3$ heterogeneous hypoechoic mass appearing to extend to the vaginal introitus.](image-url)
goal was to deliver 4 Gy/fx and 3 Gy/fx to the CTV_{HR} and CTV_{IR} for 7 fractions, respectively. After completion of an approved treatment plan, using daily sedation with propofol, the applicator was inserted with an optical tracking device attached (Fig. 2). The patient was then brought into the HDR suite for treatment delivery.

The multichannel holes were made large enough to receive 2 mm diameter (6 French) rounded brachytherapy catheters. To fix the catheters in-place, the applicator was designed to use the Venezia guide tubes (Elekta Brachy, Veenendaal, The Netherlands) which have a catheter locking mechanism. To evaluate the Dental-LT resin material for brachytherapy dosimetry, $^{192}$Ir percent-depth-dose (PDD) in Dental-LT was measured with GafChromic-EBT3 (ISP, Wayne, NJ) films and compared to water using the film calibration protocol described by Devic et al. (14) and experimental setup described by Cunha et al. (15).

2.3. Daily Image Guidance

The patient was positioned on an MR-compatible transfer table (Zephyr XL; Diacor, Inc., Salt Lake City, UT) in our department’s MRI simulator and brachytherapy procedure room (16). MR-simulation and image guidance were performed using a 3D T2-weighted turbo spin-echo with variable flip-angle sequence (T2-SPACE) acquired on a 1.5-T Magnetom Espree (Siemens Medical Solutions, Malvern, PA, USA). The approximately 7-minute acquisition has echo (TE) and repetition times (TR) of 97 and 3500 ms, respectively, and produces images with voxel dimensions of 1.0 x 1.0 x 1.6 mm$^3$. The patient was then transferred to the HDR suite down the hall for treatment. Rigid image fusion to the pubic symphysis between the reference (MR-sim) and the daily image-guidance (MR or CT) was performed to evaluate applicator insertion depth and rotation.

On days when MRI was not available, applicator insertion and CT image guidance was performed in the HDR suite using a mobile CT scanner (AIRO, Brainlab Inc.). Although typical CT doses are relatively small compared to the brachytherapy treatment, we deemed it worthwhile to minimize unwanted dose given the patient’s history. A very low dose CT protocol (1.3 mGy CTDI$_{vol}$ 16-cm; helical acquisition; 9.6 mAs, 120 kVp; standard filter; 1 mm slice thickness; 256 mm FOV) was designed based on our previously reported technical assessment (17). A phantom study was performed in advance to ensure that the applicator would be visible and distinguishable from the surrounding soft tissue when imaging the patient. The 20 cm diameter Gammex-464 ACR CT accreditation phantom with bone insert (Gammex, Middleton, WI, USA) was used as a patient surrogate and the applicator was placed in the air cavity.

Fig. 2. CAD drawings of the 3D printed multichannel vaginal cylinder. Side-view and bottom-views are marked with measurements in millimeters. 3D-view shows the applicator with the ArUco marker real-time tracking jig. MR/CT-fiducial pockets along the surface of the applicator are for aligning the applicator model for planning and real-time image-guidance.

Its chemical composition is of a monomer based on acrylic esters. Finished pieces are clear and transparent with a shore hardness of 80–90 D and a flexural modulus $\geq$1300 MPa. Once printed, devices are postprocessed per protocols recommended by Formlabs involving $>$96% isopropyl alcohol and postcuring with a UV light. Given the small size of printed multichannels in this device, a small (6-French) cannula attached to a syringe was inserted into each channel to facilitate complete flushing of uncured resin using isopropyl alcohol (99% IPA), prior to UV light postcuring.

The patient was brought into the MR simulator on a Diacor table (Zephyr XL; Diacor, Inc., Salt Lake City, UT) with pediatric stirrups attached. Pediatric speculum was inserted, and examination confirmed no clinically evident residual disease. The brachytherapy applicator was inserted after injecting MR-contrast gel into four specially designed pockets embedded in the applicator resin. 3D T2-weighted imaging was performed (Fig. 1). These confirmed adequate depth and correct rotation. Contours included the defined post-operative bed evaluated in conjunction with the surgeon, defined as the high-risk clinical target volume (CTV_{HR}), and the remaining vaginal tissue was defined as the intermediate-risk target volume (CTV_{IR}). The planning
2.4. Real-Time Monitoring System

In the context of this work, real-time tracking means the continuous monitoring of the applicator’s pose in space, where the pose contains both position and orientation of the applicator with respect to the patient. We have developed a real-time optical tracking system based on the open-source computer vision (OpenCV) library using ArUco markers (18). 3D pose estimation using ArUco markers can achieve sub-millimeter and sub-degree accuracy with careful calibration (19). Our tracking system, using a single ceiling mounted camera, can detect cylinder shifts in the cephalic-caudal direction within 1.5 ± 1.0 mm. End-to-end validation of our in-house tracking system using single and dual camera setups is outside the scope of this case report and will be presented separately.

The tracking system tracks the brachytherapy applicator (Fig. 3) and using the OpenIGTLink protocol transmits the applicator transform to 3D Slicer (Slicer v4.8.0, https://www.slicer.org) (20,21). For the purposes of MCVC brachytherapy, the tracking system displays the shift and applicator rotation in the applicator frame of reference and long axis, respectively. Real-time tracking of the applicator is visualized in 3D slicer using the daily imaging (MR or CT). This is done by importing the 3D applicator model, registering the model to the image using the 4 fiducial pockets and solving the rigid transform and applying this transformation on top of the tracking transform. Applicator positioning and intrafraction monitoring are achieved in real-time with this system.

3. Results

3.1. Evaluation of Dental-LT

On CT imaging, the Dental-LT applicator is uniform in density with a mean Hounsfield unit of 115 HU. Using a standard pelvis CT scanning protocol (67 mGy CTDIvol 16-cm; 324 mAs; 120 kVp; standard filter; 1 mm slice thickness; 256 mm FOV) a contrast-to-noise ratio (CNR) of 14.0 was observed. Our custom low dose protocol had considerably more noise but enabled sufficient soft tissue to applicator discrimination with a CNR of 2.5. HU histograms for the phantom and applicator for both protocols are shown in Fig. 4.

Unnormalized PDDs in Dental-LT and liquid water are shown in Fig. 5. PDDs were within 2% of each other in the evaluated depth range. Doses higher than 6 Gy were excluded as they were beyond the red-channel film calibration.

3.2. Treatment Plan Evaluation

The MR-based treatment plan which achieved a CTVHR D90% of 98% is shown in Fig. 6. Dose-volume-histogram (DVH) metrics for the MCVC and a hypothetical SCVC with equivalent diameter for the 7-fraction treatment are listed in Table 1. For equal CTVHR D90%, SCVC achieves a 16% higher dose to the CTVHR at the expense of increasing all OAR doses by up to 29%. The total EQD2 doses for the MCVC is summarized in Table 2.
Fig. 4. Hounsfield Unit histograms for the Dental-LT applicator (light blue) and the background Solid-Water (dark blue) are shown in the plots above where the low (1.3 mGy) and high (67 mGy) dose helical CT scans are on left and right, respectively.

Fig. 5. Unnormalized percent-depth-dose using GafChromic-EBT3 film in Dental-LT (blue) and liquid water (red). Doses higher than 6 Gy were excluded as the red-channel-based film calibration was validated to 6 Gy.
3.3. Real-Time Tracking

Real-time tracking (Fig. 7) is used to assist repositioning the applicator to match simulation and to ensure that the applicator position or orientation does not change during treatment delivery. A video clip showing the entire real-time tracking workflow can be seen here: https://www.youtube.com/watch?v=3mj3AyjhYNc. Applicator to DICOM rigid registration transformations were solved with a root-mean-square error (RMSE) ranging from 0.16 to 0.64 mm for all fractions. Intrafraction positioning was found to be stable with movement within 1 mm and 1°. The tracking system reduced the number of repeat scans acquired during applicator placements.

Table 1
DVH metric comparison for plans generated for MCVC and SCVC applicators

| DVH Metric | Total dose (Gy) |
|------------|-----------------|
| MCVC       | SCVC            |
| CTVHR D95% | 27.5            |
| CTVIR D95% | 19.0            |
| Bladder D50% | 13.7         |
| Rectum D50% | 14.4           |
| Sigmoid D50% | 2.5           |
| Urethra D50% | 18.8           |
| Uterus D50% | 1.4             |
| Ovaries D50% | 1.4            |
| Cervix D50% | 3.1             |

Treatment plans were designed to deliver 4 Gy/fx to the CTVHR and up to 3 Gy/fx to the CTVIR. SCVC plan was normalized to achieve equal CTVHR D90%.

Table 2
Total EQD2 doses for the entire 7 fraction treatment using the MCVC applicator

| DVH metric | Total EQD2 |
|------------|------------|
| CTVHR D90% | 31.9 Gy10  |
| CTVIR D90% | 20.2 Gy10  |
| Bladder D50% | 13.5 Gy3  |
| Rectum D50% | 14.6 Gy3  |
| Sigmoid D50% | 1.7 Gy3   |
| Urethra D50% | 21.5 Gy3  |
| Uterus D50% | 0.9 Gy3   |
| Ovaries D50% | 0.9 Gy3   |
| Cervix D50% | 2.1 Gy3   |

α/β of 3 Gy and 10 Gy are used for OARs and targets, respectively.

4. Discussion

SCVC and MCVC brachytherapy applicators used in the treatment of endometrial and vaginal cancers are commercially available in sizes adequate for adults. Published solutions for pediatric cases include custom vaginal molds and custom SCVCs machined to a smaller diameter (2,3). Vaginal molds lack the ability to reproducibly distend the vagina enabling uniform dose to the entire vaginal (IR-CTV) mucosa. Furthermore, a case of a vagina mold tearing the vaginal opening has been reported due to the larger diameter of the impression at the apex (3). MCVCs offer two major advantages over SCVCs: (1) the peripheral channels can modulate the dose distribution and shape it to achieve high tumor conformality and OAR sparing; (2) the peripheral channels are closer to the target leading to treatment plans with comparatively lower total reference air kerma (TRAK) and therefore lower total irradiated vol-
Fig. 7. Applicator adjustment based on imaging and guided by real-time tracking. (1) Tracking based on applicator position at the time of daily imaging. (2) Rigid registration (to pubic symphysis, in white) to evaluate applicator insertion depth and rotation. (3) Tracking based on applicator position after repositioning. Blurring applied to patient for privacy.
The results of our dosimetry comparison motivated the construction of a MCVC over a SCVC (Table 1). MCVC reduced OAR doses by up to 29%. For equal CTV_{HR} coverage, SCVC CTV_{IR} was increased by 18%, however MCVC achieved a perfectly acceptable CTV_{IR} coverage of 90%. We are the first to report on a custom 3D printed MR-compatible MCVC applicator with MR-fiducial pockets and optical tracking.

We selected the Dental-LT resin due to its biocompatibility, durability and the ability to 3D print this material within our institution, and because of the need to have image-guidance with both MR and CT. To implement this applicator for clinical use conducted a validation of applicator visibility on MR and CT imaging and determined the radiation attenuation properties relative to water. Our novel applicator embedded MR-/CT-pockets filled with lubricant gel used as imaging fiducials that enable localization of the applicator in addition to its orientation which is an important degree of freedom with MCVCs.

Our tuned, very low dose CT protocol was designed in conjunction with the manufacturer to meet pediatric CT imaging standards and was adequate for assessing applicator placement in 3D while reducing the additional dose burden to the patient to a minimum. The American College of Radiology practice guidelines report suggests a limit of 25 mGy dose for children (22), our methodology resulted in significantly lower dose than threshold (~20 fold reduction). It was important to ensure that the applicator was water-equivalent due to the inability of the TG-43 dose formalism to handle material heterogeneities.

Optical tracking has been used extensively in neurosurgery (23). Tracking with low-cost open source optical tracking of augmented reality markers been shown to achieve submillimeter pose estimation (19). Granted optical tracking requires line of sight with the tracked object, it is a robust and flexible technique which can accurately localize the position and orientation of devices in a variety of environments. Due to the large dose gradients in brachytherapy small positioning errors can result in significant dosimetric errors from an 195Ir source (24). Providing an accurate localization of the applicator is therefore crucial when repositioning the applicator to match the planned position based on image-guidance immediately prior to treatment. Furthermore, real-time tracking can ensure that the applicator remains in-place and in the correct orientation (e.g., MCVC insertion depth and rotation) during treatment delivery. To ensure reproducible treatments and patient safety, we made use of our in-house real-time tracking system to accurately match daily applicator insertions to simulation and ensured stable positioning during treatment delivery.

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