Published in final edited form as:

Brachytherapy. 2019 ; 18(3): 277–284. doi:10.1016/j.brachy.2019.01.012.

Novel intraoperative radiotherapy (IORT) utilizing prefabricated custom three-dimensionally printed high dose rate (HDR) applicators

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Abstract

Background: Intraoperative radiotherapy (IORT) is an effective strategy for the delivery of high doses of radiotherapy to a residual tumor or resection cavity with relative sparing of nearby healthy tissues. This strategy is an important component of the multimodality management of pediatric soft tissue sarcomas, particularly in cases where patients have received prior courses of external beam radiotherapy (EBRT).

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Disclosure. The authors of the study have no commercial interests or potential conflicts of interest.

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Purpose: Tumor beds with significant topographic irregularity remain a therapeutic challenge since existing IORT technologies are typically most reliable with flat surfaces. To address this limitation, we have developed a novel strategy to create custom, prefabricated HDR-IORT applicators designed to match the shape of an anticipated surgical cavity.

Materials/Methods: Silastic applicators are constructed using three-dimensional (3D) printing and are derived from volumetric segmentation of preoperative imaging.

Results: HDR pre-planning with the applicators improves dosimetric accuracy and minimizes incremental operative time. In this report, we describe the fabrication process for the 3D printed applicators and detail our experience utilizing this strategy in two pediatric patients who underwent HDR-IORT as part of complex base of skull sarcoma resections.

Conclusions: Early experience suggests that usage of the custom applicators is feasible, versatile for a variety of clinical situations and enables the uniform delivery of high superficial doses of radiotherapy to irregularly shaped surgical cavities.

Keywords

IORT; intraoperative; 3D-printing; HDR brachytherapy; custom fabrication

Introduction

High dose rate (HDR) intraoperative radiotherapy (IORT) allows for the delivery of significant doses of radiation to a tumor bed with improved ability to minimize integral dose to adjacent healthy tissues. The advantages of IORT have been well documented: the strategy enables dose escalation and reduces the chances of treatment misses since the margins at risk are clearly exposed and the surgeon can directly observe applicator placement (1,2). IORT is particularly versatile in the re-irradiation setting and has been utilized for a variety of tumor histologies (3–5). Our group has previously demonstrated that HDR-IORT can be used safely and effectively for pediatric patients (6,7).

HDR-IORT is most suitable for patients who had gross total, or near total resections as the high dose volume is typically limited to 0.5–1 cm depth in tissue. An important technological development for IORT was the development of the flexible Harrison–Anderson–Mick (HAM) surface applicator (Mick Radio-Nuclear Instruments, Inc.-an Eckert and Ziegler, Bebig company, Mount Vernon, NY). The flexible Silastic material and variety of HAM sizes creates significant versatility and allows for very conformal treatment even on curved and deep body surfaces. The HAM applicator requires direct placement against the surgical margin for predictable dosimetry, therefore it is most suitable for cavities with smooth contours. Tumor cavities with significant topographic irregularity (e.g., base of skull or intrathoracic tumors) thus remain very difficult to treat.

To address this challenge, we have developed a novel strategy to create custom, prefabricated HDR-IORT applicators designed to match the shape of the anticipated surgical cavity. The applicators are constructed using three-dimensional (3D) printing and are derived from volumetric segmentation of preoperative imaging. This case report describes a) the feasibility of the approach b) the methods for custom HDR applicator preparation and c) our

recent experience using custom applicators for two pediatric patients who underwent HDR-IORT as part of complex base of skull resections.

Material and methods:

Applicator fabrication

For both cases, the surgeon and radiation oncologist collaborated with the head and neck neuroradiologist and post processing technologists in the Memorial Sloan Kettering Cancer Center Department of Radiology Advanced Imaging Lab using a preoperative computed tomography (CT) scan to segment the gross tumor volume expected to undergo surgical resection. This process involved delineating the tumor volume after which the anticipated surgical resection margin around the tumor was marked out. CT imaging was used for tumor delineation for its high spatial resolution. One may also register magnetic resonance imaging (MRI) to CT for segmentation, should MRI provide a more accurate tumor volume (e.g., intracranial tumors). The tumor volume and the outline of the anticipated surgical resection cavity were then exported and translated into a Computer Aided Design (CAD) file for 3D printing, and a 3D model of the tumor and the planned tumor resection was made (Objet 260 Connex, Stratasys, Rehovot, Israel). Materials available for this 3D printer are not suitable for implantation within the body cavity. To produce a semi-rigid biocompatible applicator that can be sterilized and used in the intraoperative setting, a mold (a negative imprint) of the 3D printed tumor model was made and used to cast a Silastic version of the 3D tumor model. HDR catheters were inserted into the Silastic applicator manually at a spacing of approximately 5 mm, keeping a distance 3–5 mm from the surface of the applicator, and a CT scan of the finished applicator was acquired. Figures 1A and 1B show an example (Case #1) of the 3D tumor model. One (1) applicator was made for Case #1. Because of uncertainty in extent of surgical resection two applicators were made for Case #2: a small applicator representing the tumor only, and a larger applicator representing tumor plus 5 mm margin. To ensure efficiency in the operating room, treatment plans were pre-produced for both applicators. The larger applicator was eventually used for treatment.

Treatment planning

To ensure the applicator was correctly made, the preoperative CT and the CT scan of the applicator were registered. A treatment plan was generated using the registered scans. HDR-IORT treatment plans were reviewed and approved by the radiation oncologist and independently checked by medical physics prior to surgery. Figure 1C shows a coronal cross section of the registered planning CT. Once approved, the applicator channels were labeled according to the plan and the applicator was sterilized using ethylene dioxide. Figure 1D shows the applicator in the treatment position.

Treatment delivery

HDR-IORT was performed using Iridium-192 afterloaders (GammaMedPlus, Varian Medical Systems, Charlottesville VA). Treatment was delivered in a special shielded operating room; all staff remained outside the operating room during the treatment for radiation safety purposes during which time the patient's vital signs were monitored remotely. Planned and actual treatment durations were 2563 Ci·s and 10.7 minutes, and 1971

Ci-s and 7.4 minutes for cases 1 and 2, respectively. The entire process of applicator placement, afterloader connection, HDR-IORT, safety checks, radiation surveys, and applicator removal added approximately 30 minutes of operative time.

Case #1 – parameningeal rhabdomyosarcoma

Initial presentation and diagnostic workup—The first patient was a 7-year-old boy diagnosed with intermediate risk (Stage 3, Group 3) embryonal rhabdomyosarcoma (RMS) at 5 years of age in the context of persistent right sided facial pain and refractory otalgia. Initial staging positron emission tomography (PET) and CT showed a 3.8 cm hypermetabolic right masticator space mass (Figure 2A-B) and several avid right level II cervical lymph nodes. Incisional biopsy was consistent with embryonal RMS. The mass abutted the skull base with widening of the right foramen ovale consistent with V3 nerve perineural spread. There was mild dural thickening consistent with intracranial extension. No metastatic disease was noted and cerebrospinal fluid (CSF) analysis was normal. Bone marrow biopsy was deferred. A biopsy was attempted of the cervical lymph node, but it was nondiagnostic and multidisciplinary consensus was that it was likely involved.

Initial treatment regimen and response—The patient was treated as per the Children's Oncology Group (COG) high risk RMS protocol ARST0431 with 54 weeks of vincristine, irinotecan, cyclophosphamide, doxorubicin, etoposide, ifosfamide and dactinomycin. At week 13, the patient began definitive proton beam radiotherapy (PBRT) to 36 Cobalt Gray Equivalents (CGE) to the pre-chemotherapy region followed by a cone down of 50.4 CGE to the gross disease. PBRT was delivered in conventional 1.8 CGE fractions using 3D conformal planning with 2 uniform scanning beams (Figure 2D). Acute toxicities included the expected grade 2–3 dermatitis in the treatment field and grade 1–2 mucositis of his oral cavity.

Overall the patient tolerated initial treatment well. Orbital MRI performed at the end of chemoradiotherapy revealed a small interval decrease in the size of the infratemporal mass which was stable on an interval scan three months later.

Relapse and salvage therapy—Roughly 16 months after the completion of therapy, surveillance imaging was concerning for local relapse. Orbital MRI showed an increased conglomerate of lesions measuring $4.3 \times 3.6 \times 4.0$ cm within the right masticator space with cortical thinning of the mandibular ramus concerning for direct tumor extension (Figure 2E). PET scan revealed several avid tumor foci (Figure 2F). No regional or distant disease were appreciated and incisional biopsy confirmed local recurrence.

CT sinus found a 5 cm lesion which extended cephalad into a widened right foramen ovale without further intracranial extension. There was widening of the proximal right mandibular canal filled by tumor which extended anteriorly to the last molar tooth. No tumor involvement of the right orbit, hard palate, pterygoid process or plates, pterygopalatine fossa, cavernous sinus or Meckel's cave was appreciated. A normal fat plane was observed between the lesion and the right internal carotid artery.

Multidisciplinary review recommended salvage chemotherapy as per COG protocol ARST0921. The patient received 3 neoadjuvant cycles and then underwent radical tumor resection with HDR-IORT. The infratemporal fossa was approached in two ways (right temporal craniotomy and right lower cheek approach) to enable *en bloc* resection. Surgical pathology revealed mostly viable embryonal RMS with spindle cell features and 10–20% fibrosis. Of note, all surgical margins were 1 mm negative.

Following tumor resection, tracheostomy was performed, and a nasogastric feeding tube was placed. Next, the custom Silastic applicator was positioned into the surgical defect for the delivery of HDR-IORT. Prescription dose was 800 cGy approximating the surface of the applicator medially, and at 5mm depth from the applicator surface superiorly (Figures 3C–E).

At the completion of HDR-IORT, a plastic surgeon performed a soft tissue reconstruction of the large mandibular defect using an anterolateral thigh free flap. As part of the reconstruction, the facial artery and a large side branch off the internal jugular vein was dissected and then microsurgically anastomosed to the flap arteries. Strong flap Doppler signal was appreciated.

Postoperative course and complications—The patient recovered well with excellent flap perfusion, was successfully decannulated on day 7 and discharged on day 8. MR nasopharynx after 1 month showed evolving postoperative changes with no evidence of recurrence. Chemotherapy was continued per ARST0921. Adjuvant PBRT was recommended to cover the margins felt to be most at risk, specifically the superior resection edge along the skull base and the posterior margin behind the soft tissue flap. A dose of 30.6 CGE in 17 fractions was planned using pencil beam scanning (Figures 3F–G).

The patient began adjuvant PBRT re-treatment five weeks postoperatively. Following completion of the fifth fraction of PBRT (9 CGE), the patient suffered a self-limited episode of significant, sudden onset epistaxis and oral hemorrhage. Bleeding had resolved on arrival to medical care where initial workup was notable for febrile neutropenia and 2-gram hemoglobin drop. CT angiography revealed a 0.9×0.7 cm pseudoaneurysm of the mid right facial artery located along the lateral flap edge with significant hematoma in the masticator space (Figures 3A–B). The patient underwent successful right facial artery coil embolization and remained hemodynamically stable with no subsequent bleeding.

Multidisciplinary review of the HDR-IORT dosimetry concluded that the aneurysmal area was unlikely to have received significant brachytherapy dose. While the area appears to be located within the full dose region of the HDR-IORT plan (Figures 3C and 3D), during the IORT, the lateral tissue plane which contained the facial vessels was retracted away from the applicator.

Therefore, the pre-operative imaging used for HDR planning is not representative of true lateral wall dosimetry. Furthermore, the flap anastomosis was completed after the HDR-IORT had finished. However, given that the aneurysm was within the PBRT field (Figures 3F–G), consensus was that the possible benefit of resuming PBRT given that the tumor had

been completely resected was unlikely to outweigh the risks of possible further vascular injury from higher doses of RT. Therefore, additional PBRT was terminated and he continued chemotherapy per protocol.

Routine post-treatment imaging performed one month later had no evidence of recurrence but was notable for a peripheral fluid collection along the graft margin concerning for possible abscess which was drained and treated with a two-week course of amoxicillin clavulanate and fluconazole.

At the time of this case review, the patient was clinically asymptomatic and had completed nine planned adjuvant chemotherapy cycles. Restaging imaging revealed contraction of the right postoperative bed abscess, no evidence of further aneurysm and no convincing evidence of recurrent disease.

Case #2 – radiation associated osteosarcoma

Clinical presentation and diagnostic evaluation—The second patient was a 10-year-old girl who was diagnosed at 3 years of age with a third ventricular anaplastic ependymoma. This was treated with resection followed by intensity modulated radiotherapy (IMRT) to 5940 cGy which she tolerated well. Routine surveillance brain MRI performed six years after completion of her initial treatment was notable for two new findings. First, a 1.4 cm nodular area of contrast enhancement was noted in the right cingulate gyrus concerning for recurrent ependymoma. Second, there was a 2.3 cm mass in the left ethmoid sinus with abutment of the cribriform plate and concern for possible medial rectus muscle invasion (Figures 4A-B).

PET/CT showed a metabolically active ethmoid sinus mass but no other appreciable metastases. Diagnostic chest CT and MRI spine were both negative. Endoscopic biopsy of the ethmoid sinus mass revealed a grade 2 osteosarcoma, osteoblastic type, which was felt to be treatment-associated in the context of prior radiotherapy.

Multimodal treatment and HDR-IORT—Multidisciplinary consensus recommended neoadjuvant chemotherapy per COG osteosarcoma protocol AOST0331 including four 5-week cycles of neoadjuvant cisplatin, doxorubicin, and high-dose methotrexate. It was felt that this chemotherapy regimen could also stabilize her presumed ependymoma recurrence. After 8 weeks of chemotherapy, MRI brain confirmed stability of both lesions and she was taken for surgical resection of the cingulate gyrus lesion. Gross total resection was achieved with pathology showing a spindle cell and epithelioid proliferation, consistent with meningioangiomatosis.

She then continued per COG protocol AOST0331. Restaging scans showed no evidence for residual enhancement in the right cingulate gyrus. Residual ethmoid sinus osteosarcoma measured 2.1 cm with tumor involvement of the left ethmoid sinus, midline nasal septum, inferior crista galli, planum sphenoidale and cribriform plate with elevation of the left olfactory bulb. The patient sought several surgical opinions, the consensus of which was that she would require a left orbital exenteration.

Detailed review of the imaging at our institution suggested that while tumor was bulging into the orbit, the medial rectus and orbital apex were spared and thus a more limited resection could be attempted with the goal of preservation of the eye and optic apparatus. Due to a more limited surgery, HDR-IORT was recommended given the possibility of close surgical margins and prior IMRT.

The patient subsequently underwent an anterior craniofacial resection with bifrontal craniotomy and left lateral rhinotomy with resection of the anterior skull base tumor. Intraoperatively, the surgeons noted gross disease within the left ethmoid sinus and erosion of the lamina papyracea of the left orbit but sparing of the periorbita. Superiorly, there was invasion of the cribriform plate but no obvious gross dural invasion. Within the nasal cavity, tumor crossed the midline requiring resection of the upper nasal septum but there was no invasion of the nasopharynx or sphenoid sinus.

The tumor was resected *en bloc* with pathology revealing predominantly viable high-grade osteosarcoma involving the sinus wall with negative margins. Following resection, the prefabricated HDR-IORT applicator was placed in the surgical defect against the area at risk, along the medial left orbital margin (Figure 5), and secured in place using wet laparotomy pads. A predetermined radiotherapy plan was then delivered, targeting the applicator surface to a dose of 1200 cGy. The case was then turned over to the surgical team for reconstruction/closure and placement of a lumbar drain given surgical dural defects.

On postoperative day 3, the patient developed a symptomatic CSF leak. Since then, her course has been uneventful and she was found to have good wound healing at 1-month post procedure. She has resumed adjuvant chemotherapy per AOST0331 and has not been restaged at the time of this report.

Discussion

We report the successful fabrication and utilization of 3D-print based HDR-IORT applicators and present early outcomes from two pediatric patients. Custom, patient-specific molds offer several advantages including allowance for catheter locations, orientations and dosimetric topographies that are not readily achievable with commercially available products. Our approach enables high quality, pre-implantation HDR planning, which minimizes the incremental operative time required for HDR-IORT. While current IORT techniques rely on clinical placement of the applicator and cognitive assessment of the dose distribution in the patient from standard template-like plans, this method includes image-based treatment planning. Finally, in cases where uncertainty exists about the extent of surgery, several plans and applicators can be produced to prepare for various scenarios.

In both patients, the applicator was easily positioned in the surgical cavity and fit comfortably and tightly, suggesting that segmentation of the tumor shape with a planned surgical resection margin on preoperative imaging is a reliable predictor of the actual surgical cavity contour. We utilized cognitive positioning for our applicator and both the radiation oncologist and surgeon felt there was good approximation of the applicator against the edges of the tumor cavity. While we did not employ an image guided strategy,

radiopaque fiducial markers could be embedded into the applicator and intraoperative fluoroscopy or CT scanning could be utilized for anatomic matching with respect to bone. This would provide an additional check for the applicator position and thus accuracy of the HDR treatment. However, confirmation of the applicator's goodness of fit using cross-sectional intraoperative fluoroscopy or CT may be challenging given the radiodensity of Silastic material and probable imaging artifacts created from nearby surgical metal.

3D printing is an important contemporary technological development and not surprisingly, there has been early enthusiasm for potential areas of utility within clinical radiation oncology practice. Several opportunities have been identified including fabrication of photon or electron bolus (8–13), proton beam compensators (14) and facial skin shielding blocks (15). In terms of brachytherapy applications, Jones *et al.* describe using a pre-plan technique with 3D printing to create idealized superficial HDR applicators for skin brachytherapy (16). Cunha and colleagues have reported the usage of 3D printing for gynecologic brachytherapy cylinder construction, enabling customization of cylinder size and internal catheter geometric paths (17). 3D printing has also been utilized for creation of individualized templates for needle guidance for low dose rate brachytherapy (18) and development of custom sized spherical applicators for electron-based intraoperative breast brachytherapy (19). To our knowledge, this report reflects the first description of 3D printed, catheter-based HDR-IORT applicators.

This report is principally intended to highlight feasibility however initial safety signals are important to address. Of note, patients receiving re-irradiation for head and neck cancer are a high-risk population at baseline. Systematic review of HDR brachytherapy for head and neck reirradiation suggests that rates of at least moderate complications may be 30–60% (5). At the time of manuscript preparation, consensus opinion of our team is that neither patient had unexpected wound healing complications attributable to HDR-IORT.

Patient #1 suffered a grade 4 facial artery pseudoaneurysm roughly a month after HDR-IORT and after receiving 900 CGE of adjuvant proton therapy. Pseudoaneurysms of the carotid artery and branches are a rare, dreaded consequence of head and neck surgery and radiotherapy (20). While reirradiation increases the risk of vascular injury, the literature associates pseudoaneurysm with significantly higher cumulative dose exposure (21). However, the tolerance of pediatric vasculature may be lower.

Conclusion

Creation of customized 3D printed HDR-IORT applicators is feasible and enables the uniform delivery of high superficial doses of radiotherapy to irregularly shaped tumor cavities. This strategy may be particularly attractive for high risk patients such as those with significant prior radiation exposure and/or those who are planned to undergo complex reconstructions.

Acknowledgments

Funding: This research was funded in part through the National Institute of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

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Figure 1.

Pictorial representation of Case #1 is shown: (A) 3D printed model of the tumor (pink) and skull and (B) of the tissue planned for resection (tumor [pink] and part of the mandible [white]); (C) coronal cross section of the registered CT scans of the patient and applicator used for treatment planning; (D) applicator in the treatment position with two lead shields (denoted with white arrows) adjacent to the applicator. Based on measurements, the shields reduce the dose to tissue by approximately 30 percent.

Figure 2.

Initial parameningeal rhabdomyosarcoma of the right masticator space shown on axial T1 fat saturated MRI (A) and PET (B) imaging. (C) Restaging FDG PET imaging after initial chemotherapy prior to first course of proton beam therapy. (D) Dosimetry of initial proton beam therapy delivered to dose of 36 CGE to the pre-chemotherapy region followed by a cone down of 50.4 CGE to the areas of gross disease. Recurrent disease was appreciated in axial T1 FLAIR post contrast MRI (E) and FDG PET imaging (F).

Figure 3.

CT angiography shows pseudoaneurysm of the right facial artery shown in the axial (A) and coronal (B) planes as highlighted by red arrow. Axial (C) and coronal (D) pre-planned dosimetry of the HDR-IORT where the yellow outlined structure is the applicator. (E) Legend for the dose color wash for figures C and D in Gy. Axial (F) and coronal (G) dosimetry of the adjuvant proton therapy treatment plan with cGy isodose lines denoted by the scale in figure H.

Figure 4. Volumetric reconstructions are created using the preoperative CT scan images. Figures A and B show the extent of tumor location within the ethmoid sinus. Figures C-F show representative volumetric scans created from the CT scans from which 3D prints are created.

Figure 5.

A lateral rhinotomy was carried out to expose the medial orbital wall and ethmoid sinus. Osteotomies through the nasal process of the medial maxilla are shown in (A). A frontal craniotomy was then done and osteotomies through the cribriform plate and orbital roof carried out as shown in (B). En bloc removal of the tumor was accomplished with the resultant cavity shown in (C). A preformed IORT applicator was then inserted into the surgical defect as shown in (D).