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Teaching Case

Initial clinical experience using a novel Pd-103 surface applicator for the treatment of retroperitoneal and abdominal wall malignancies

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Introduction

Definitive surgical resection is an integral component of curative intent management for localized soft tissue sarcoma, and margin status is a strong predictor for recurrence. Because of the large size and intimate association of retroperitoneal soft tissue sarcoma with vital normal structures at presentation, microscopically positive margins are common after curative intent interventions.[1] This reality has driven clinical interest in the incorporation of radiation therapy (RT) in the intraoperative context, and several series have demonstrated promising rates of local control using intraoperative electron beam RT (IOERT).[2-4] Similar principles may apply to the radical treatment of abdominal malignancies with soft tissue invasion. IOERT has been used for the treatment of locally advanced and recurrent colon cancer with promising rates of local control.[5]

Recently, an innovative, unidirectional, Pd-103 low-dose-rate brachytherapy device, CivaSheet (CivaTech, Durham, NC), has been developed for clinical use as an intraoperative RT (IORT) alternative. Here we present our initial clinical experience with the first 2 cases using this new IORT technology to boost the tumor bed after preoperative RT, including device implantation at time of tumor resection and evaluation of its positional stability with postimplant computed tomography (CT) studies.

Description of the CivaSheet IORT applicator

CivaSheet is a Food and Drug Administration–approved, unidirectional planar brachytherapy permanent implant device. It consists of a flexible, bioabsorbable membrane embedded with unidirectional radioactive sources called CivaDots. The CivaDots are positioned on a matrix with a separation of 8 mm center to center (Fig 1). Each CivaDot is a disk-like Pd-103 source with a gold plate on 1 side that is encapsulated in a proprietary polymer material. The gold plate virtually eliminates radiation dose to 1 side of the source. It also serves as a radiopaque marker on CT imaging studies. The CivaDots can be modeled in a treatment planning system (TPS) using a 2-dimensional line source model,[6] as recommended in the updates of American Association of Physicists in Medicine Task Group 43 report.[7] The CivaSheet comes in sizes of 5×5, 5×10, and 5×15 cm^2 and can be cut to custom sizes to fit implant needs during surgery.

Conflicts of interest: None.

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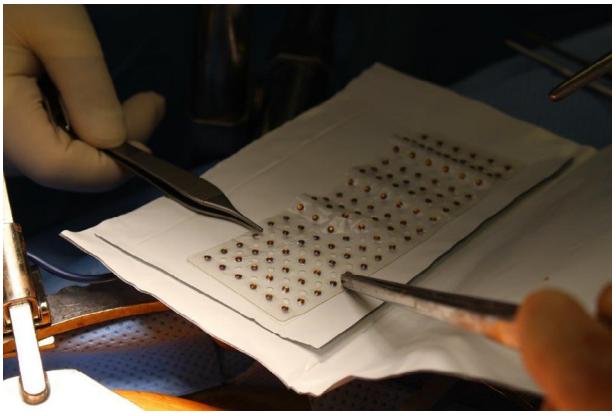

Figure 1 Photograph of a 5 cm × 15 cm CivaSheet with the shielded (gold) side facing up.

Description of the cases

Case 1

Patient 1 is a 38-year-old woman who was initially diagnosed with a retroperitoneal sarcoma after presenting with abdominal pain and swelling in 2013. She underwent R1 resection for a right-sided, $32 \times 23 \times 9$ cm^3, well-differentiated liposarcoma in February 2013, then a re-excision for gross local recurrence, with extension to the left retroperitoneum in December 2014. She developed a second recurrence along the anterior margin of the left psoas muscle in November 2015. At that time, she received neoadjuvant intensity modulated RT to a dose of 49.91 Gy in 23 fractions. Given the high risk for positive posterior margin along the psoas muscle, she was planned for IORT using the CivaSheet.

Case 2

Patient 2 is a 71-year-old woman with a history of localized gastric signet ring adenocarcinoma. She received total gastrectomy with Roux-en-Y reconstruction followed by adjuvant chemotherapy RT (50.4 Gy in 28 fractions with 5-FU/leucovorin) in 2013. She developed metastatic progression of her gastric cancer with involvement of the left abdominal wall and small bowel. This was resected in 2014. She had no evidence of disease until 2016, at which time she presented with a solitary focus of recurrence along the staple line. The patient then received neoadjuvant external beam radiation to a dose of 45 Gy in 25 fractions to the left abdominal wall nodule, which was followed by a surgical resection of the tumor and CivaSheet IORT boost.

In both cases, informed consent that permitted photographing the procedure for medical, scientific, or educational purposes, without revealing patient identity, was signed by the patients.

Preimplant CT-based planning

CT images were acquired with 2-mm slice thickness for each patient. A planning target volume (PTV) was delineated jointly by the managing surgeon and radiation oncologist. Specifically, the PTV was drawn as a 5mm-thick surface area that corresponds to the estimated region with high risk of recurrence after surgery. The BrachyVision module of the Eclipse (version 11) TPS (Varian Medical Systems, Palo Alto, CA) was used to generate a plan in which the dimension of CivaSheet (number of CivaDots) and the source strength was determined to prescribe 25 Gy (biologically effective dose in 2 Gy fractions [EQD_2] = 21.0 Gy) to at least 90% of the PTV for patient 1 (actual coverage $V_{25Gy} = 98\%$), and 29 Gy ($EQD_2 = 24.3$ Gy) to at least 90% of the PTV for patient 2 (actual coverage $V_{29Gy} = 91\%$). The EQD_2 was calculated with tissue repair half time of 1 hour.[8]

Intraoperative brachytherapy implant

On the day of procedure for each patient, the bulk tumor was surgically resected first. A high-risk tumor bed as estimated from preoperative planning then was identified and confirmed by both the surgeon and the radiation oncologist as the target for implantation. For patient 1, a 5 cm × 15 cm CivaSheet (108 CivaDots, 0.8 U per dot, or 0.5 mCi per dot) was implanted on the left psoas muscle, with the hot side facing the tumor bed and the gold shielded side facing the inside of the abdominal cavity to protect the left kidney and bowel from radiation. For patient 2, the CivaSheet was first cut to 5 cm × 9 cm (66 CivaDots, 0.6 U per dot, or 0.4 mCi per dot) to fit the dimension of the tumor bed on the anterior side of the left iliac bone; it was then implanted with the hot side facing the tumor bed and the shielded side facing the inside of the pelvic cavity. Figure 2 shows the implanted CivaSheet for patient 1. After the CivaSheet was sutured in place, gel foams were placed over the device on the gold side to further separate the CivaSheet

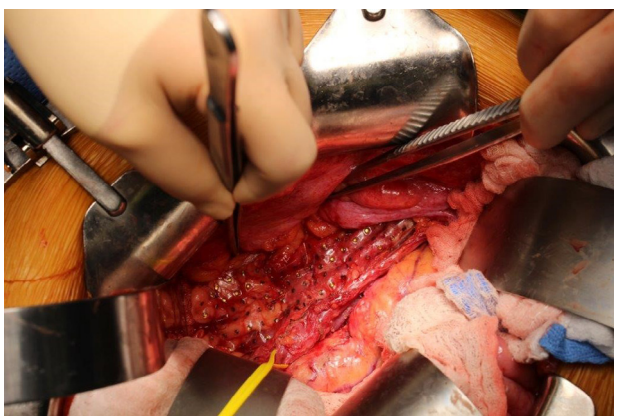

Figure 2 CivaSheet implanted to the tumor bed of patient 1.

and bowels that could drop down after surgery. Both patients recovered from the surgery within a week and were subsequently discharged with no acute complications.

Postimplantation CT study

Both patients underwent 2 post-implant CT studies to evaluate the geometrical and dosimetric stability of the implanted CivaSheet. Patient 1 had a CT study at 16 (48% dose delivered) and 86 days (97% dose delivered) after the implant. Patient 2 had a CT study at 8 (28% dose delivered) and 58 days (94% dose delivered) after the implant. In each CT scan, the CivaSheet remained in the implanted region. All CivaDots were identified and reconstructed in the TPS. Figures 3 and 4 show the preimplant estimation of the high-risk PTV; the implanted CivaDots on CT scans at different follow-up time points for patients 1 and 2, respectively. A slight trend of CivaDot clustering was observed on the CT scan performed 86 days after implant in patient 1; the bioabsorbable membrane starts to deform and disintegrate after 6 to 8 weeks, according to the manufacturer. For further dosimetric evaluation, a PTV was drawn by the radiation oncologist on each of the postimplant CT scans; a dose-volume histogram was reconstructed based on the updated CivaDot positions. The PTV D_{90} was 25.5 Gy (102% of prescription) and 29 Gy (116% of prescription) for the 2 postimplant studies for patient 1 and 26 Gy (90% of prescription) and 28 Gy (97% of prescription) for patient 2.

Both patients tolerated IORT without any signs of acute or late toxicity. There have been no signs of gastrointestinal, genitourinary, or musculoskeletal/soft tissue toxicities. Three months after treatment, both patients have no evidence of disease at the treated sites. Patient 1 did have a questionable fatty abnormality adjacent to the contralateral kidney (outside the field) in CT images before radiation to the retroperitoneal liposarcoma. Given its small size and its proximity to the contralateral kidney, we decided to observe the fatty abnormality while her retroperitoneal sarcoma received preoperative radiation followed by resection and CivaSheet brachytherapy. This small fatty tumor in the contralateral retroperitoneal space did grow 6 months after resection of her retroperitoneal sarcoma and was later proved to be liposarcoma.

Discussion

Gastrointestinal toxicity is a major concern during intraoperative and postoperative RT for retroperitoneal patients who received preoperative external beam RT, especially in the upper abdominal region.[9-11] This is addressed mainly by the unidirectional radiation profile of the CivaSheet device. Because of the strong attenuation of the gold plate, the anisotropy function of the product decreases from 0.83 at 85° to 0.15 at 95° (towards the side of the CivaDot) and approaches a minimum value of 0.03 at 180° (towards the back of the CivaDot). The gel foams placed against the gold side of the implanted CivaSheet further protects the bowel from radiation dose.

CivaSheet has a few advantages compared with its alternative (IOERT) in this clinical setting. In addition to the previously mentioned unidirectional dose profile, the sheets can be easily cut to any size and shape at the time of implant. The sheet is also malleable and can conform to curved

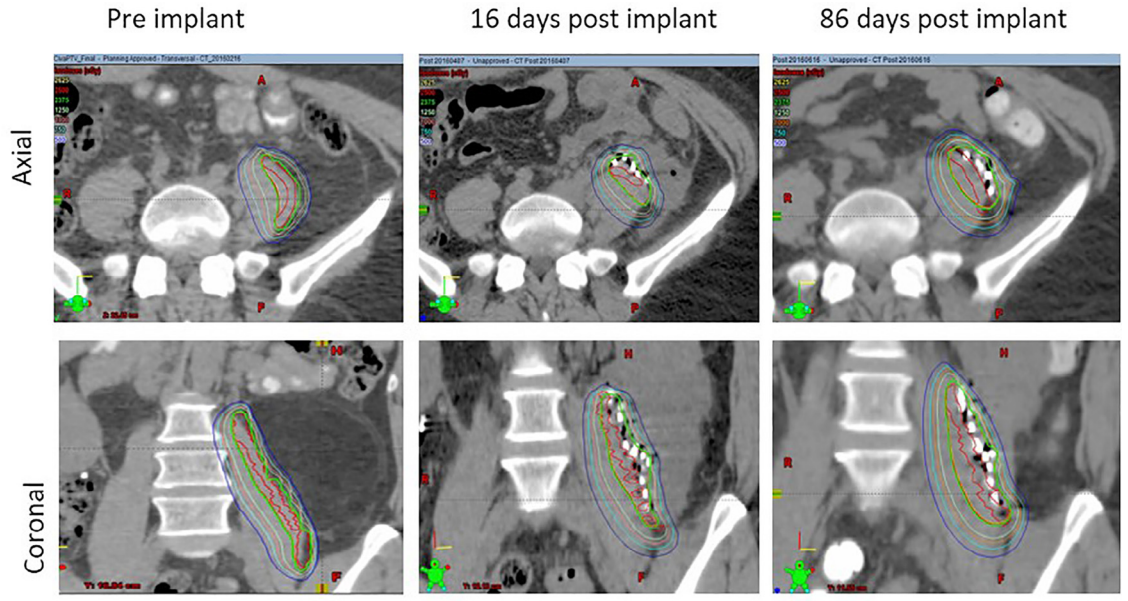

Figure 3 Pre- and postimplant computed tomography studies for patient 1. The isodoses shown are 5.0 Gy (blue), 7.5 Gy (cyan), 10.0 Gy (pink), 12.5 Gy (light green), 23.75 Gy (green), 25.0 Gy (red), and 26.25 Gy (yellow).

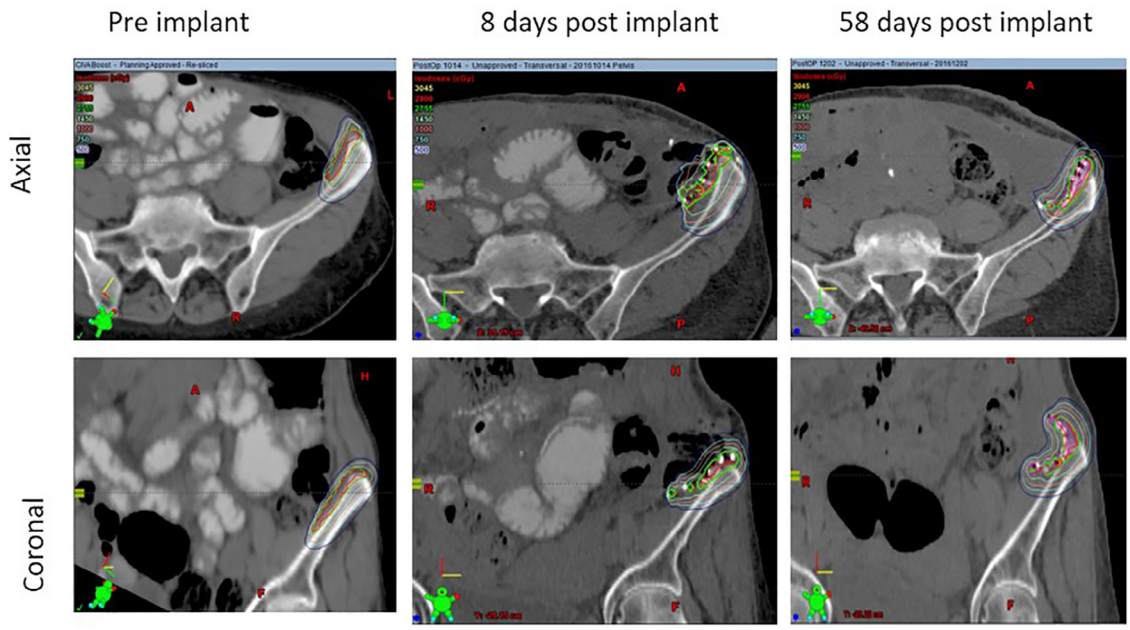

Figure 4 Pre- and postimplant computed tomography studies for patient 2. The isodoses shown are 5.0 Gy (blue), 7.5 Gy (cyan), 10.0 Gy (pink), 14.5 Gy (light green), 27.55 Gy (green), 29.0 Gy (red), and 30.45 Gy (yellow).

surfaces. Both characteristics give the physician more flexibility to treat tumor beds with irregular shape and surface curvature compared with electron beam cylindrical applicators. Another advantage of CivaSheet is the choice of radio isotope (Pd-103), which has a much lower average photon energy (20 keV), compared with typical energy of electron beam (>4 MeV). The very sharp dose falloff of the low energy photons makes CivaSheet an ideal option to treat disease within 5 mm from its surface. If deeper-situated disease is targeted, however, electron beam has the advantage of deeper penetration. In addition, CivaSheet does not require the costly installation of an intraoperative linear accelerator and therefore is a more cost-effective option, especially for centers that do not have a very high volume of such cases.

The main purpose of the gold plate is to create a "unidirectional" source. A collateral benefit is to provide radiopacity and therefore the ability to identify the CivaDots on CT imaging. The diameter and thickness of the Pd-103 portion itself is on the order of 0.5 and 0.1 mm, which is smaller than typical CT high-contrast resolution limit (1 mm). The diameter and thickness of gold plate are on the order of 2 and 0.05 mm, respectively; therefore, an imaging system needs to have resolution of better than 2 mm to resolve the location of the dot and a resolution of better than 0.05 mm to resolve the shape (and therefore the orientation) of the dot. The former is achievable with current technology, but the latter is not.

During IORT procedures, the CivaSheet's active side remained facing away from the physician because the exposure toward the back of the sheet is about 10 times less than toward the front. Tweezers were used to keep physicians' hands at least 10 cm away from the sheet. The estimated hand dose is <0.2 mSv for a 10-minute implant procedure of a 10×15 cm sheet of 0.5 mCi per CivaDot. Both the surgeon and the radiation oncologist wore finger radiation badges during the procedures; all badge readings were below minimum detectable level.

Our initial experience shows that the CivaSheet maintains its geometrical integrity in large part through at least the first 2 months after the implant, at which point >90% of the radiation dose is delivered. CT-based dosimetric evaluation with the reconstructed CivaDots location shows good target coverage throughout the delivery period. One potential deficiency of the dosimetry evaluation is that, although the location of each individual CivaDot can be clearly identified, the orientation of the dot cannot be identified on the CT image, mainly because of the limited resolution and metal artifact caused by the gold plate. The CivaDot orientation is therefore inferred from the fact that all dots are embedded in a membrane that is sutured to the tumor bed and because the postimplant CT scan shows the shape of the CivaSheet being maintained. It was also noticed that surgical clips could be mistakenly identified as CivaDots; therefore, it is recommended that the number of surgical clips placed during the procedure be minimized.

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