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## Report of the First Patient Treated for Pelvic Sarcoma With a Directional 103Pd Brachytherapy Device.

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## Teaching Case

# Report of the First Patient Treated for Pelvic Sarcoma With a Directional $^{103}\text{Pd}$ Brachytherapy Device



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## Introduction

Sarcomas are rare malignant tumors of mesenchymal origin with 80% originating from soft tissue.<sup>1</sup> The majority of soft tissue sarcomas occur in the extremities; nevertheless, 10% to 15% occur in the retroperitoneum or pelvis and are usually advanced at time of diagnosis.<sup>2</sup> Oncologic resection with or without perioperative radiation therapy has become the cornerstone for successful treatment.<sup>3-5</sup> The goal of surgery is complete resection

with negative margins (R0 resection). When not possible, either preoperative or postoperative radiation therapy is recommended.<sup>6-9</sup> Technical challenges related to anatomic complexities and large tumor size at diagnosis of most pelvic and retroperitoneal sarcomas often lead to microscopically positive margins (R1 resection) associated with high risk of local recurrence.<sup>2,10-13</sup> Delivering adequate doses of radiation in the postoperative setting represents a significant treatment challenge, especially in soft tissue sarcomas located in the abdomen, retroperitoneum, or pelvic regions.<sup>14</sup> In these cases, local control with preoperative and intraoperative radiation therapy (IORT) are important considerations.<sup>7,8,15</sup>

CivaSheet (CivaTech Oncology Inc, Durham, NC) is a Food and Drug Administration–approved bioabsorbable planar mesh device for IORT low-dose-rate (LDR) brachytherapy using shielded palladium-103 ( $^{103}\text{Pd}$ ). This novel device allows directional and customizable radiation therapy, significantly reducing radiation doses to organs at risk (OARs) with the use of 50  $\mu$  gold shield backing (Fig 1A). The directional brachytherapy device is

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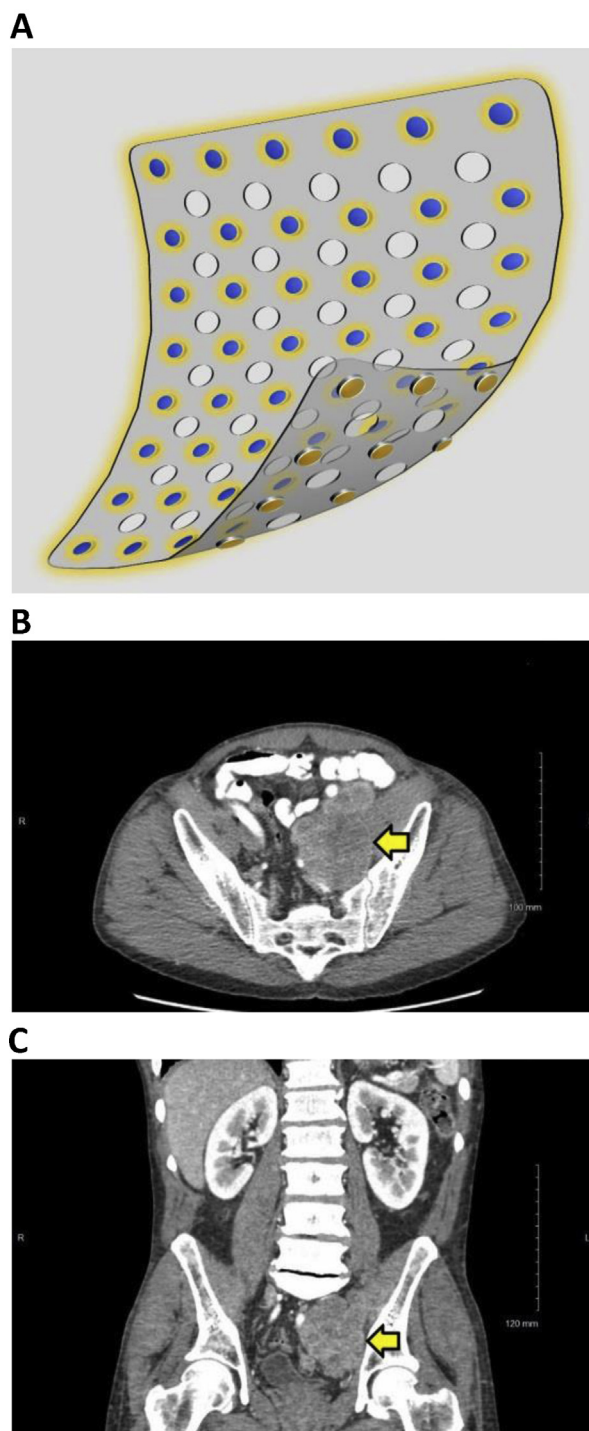
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manufactured with specified source strengths according to prescribed doses. The device size and orientation can be customized in the operating room to conform to the surgical bed. Sufficient dosimetry data and calibration standards are now available.<sup>16-19</sup>

The present report describes this treatment approach and 3-year oncologic outcome of a patient with locally advanced leiomyosarcoma in the pelvic sidewall who underwent neoadjuvant pelvic intensity modulated radiation therapy (IMRT) and had a high risk for a positive margin after resection. The patient was deemed suitable for IORT<sup>20</sup> and, among available technologies in our institution, LDR brachytherapy with a directional brachytherapy device was considered superior to other techniques and devices. Unlike the brachy mesh, CivaSheet requires no additional surgical manipulation of the omentum or other spacers to keep bowel away from unshielded seeds given its directionality. Alternative IORT options include intraoperative electron beam irradiation and placement of HDR brachytherapy catheters were not available.

## Materials and Methods

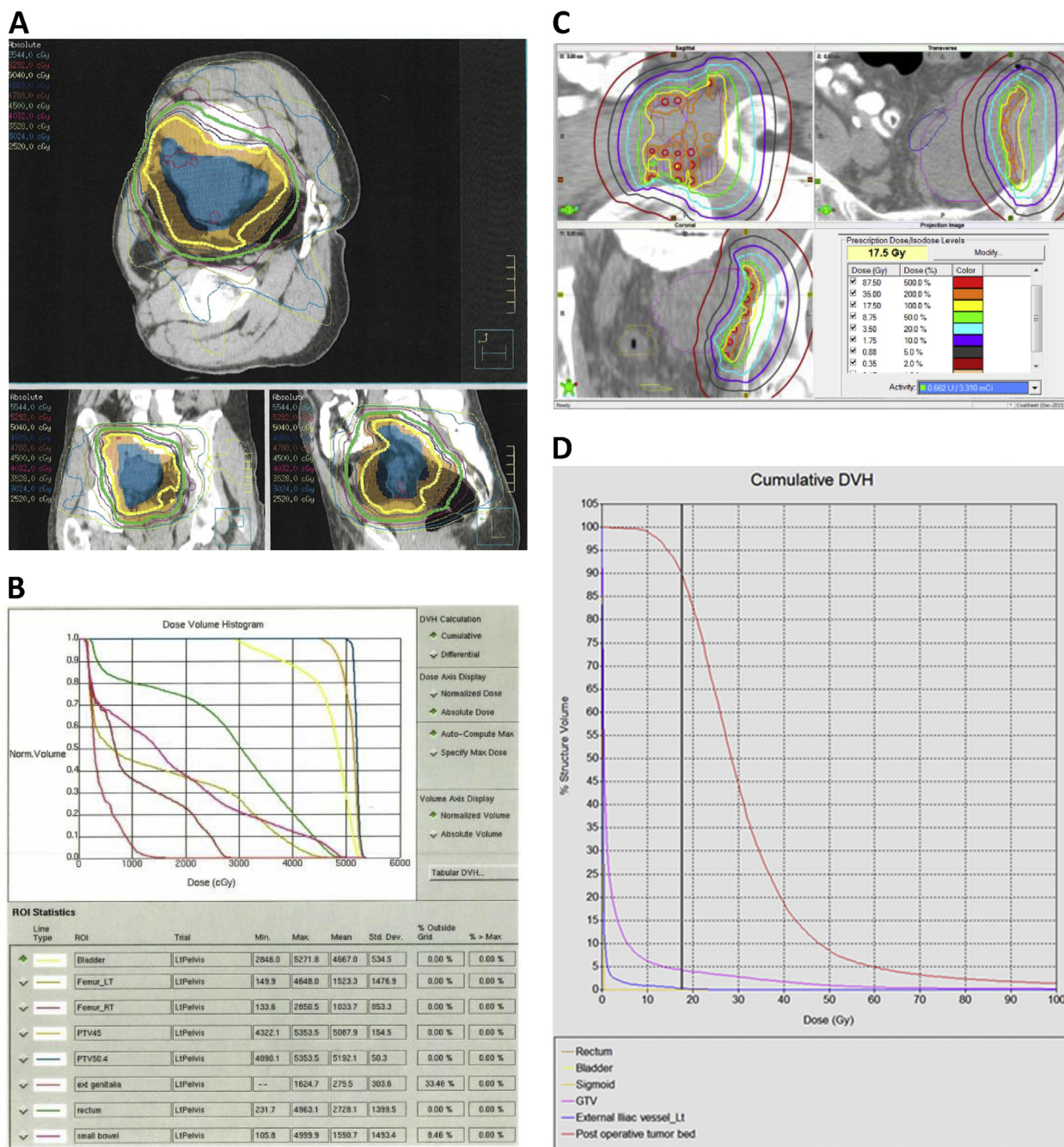
The patient is a 65-year-old black male with an incidental finding of a left pelvic sidewall mass. During July 2014, computed tomographic (CT) scan of the abdomen and pelvis revealed a left pelvic mass measuring  $3.5 \times 4.4 \times 5.1$  cm. The patient deferred management. In September 2015, the patient presented with hematuria, lower abdominal pain, and left flank pain radiating to the left groin. CT scan of the chest, abdomen, and pelvis, and magnetic resonance imaging of the pelvis showed an enlarging lobular, solid, and enhancing necrotic mass involving the left pelvic musculature. The mass measured  $8.1 \times 6.4 \times 7.2$  cm with complete encasement on angiography of the left common iliac vein and medial displacement of the common iliac artery, with no evidence of distant metastasis (Fig 1B and 1C). Ultrasound-guided core biopsy revealed a leiomyosarcoma, French Federation of Comprehensive Cancer Centers (Umicancer; formerly FNCLCC) grade 2. As discussed in multidisciplinary tumor board given American Joint Committee on Cancer (seventh edition) clinical stage IIB (T2bN0M0), tumor grade, and iliac vein encasement, the patient was recommended preoperative pelvic radiation therapy with IMRT, surgical resection with reconstruction, and an intraoperative LDR brachytherapy boost. The patient was prescribed 50.4 Gy in 28 fractions to the pelvic mass using IMRT (equivalent dose [EQD2] = 49.6). The preoperative plan was delivered in 2 phases. The initial phase with 45 Gy in 25 fractions was delivered to PTV1, created by expanding the GTV by 2 cm (anatomic constraint) plus 0.5 cm (geometric expansion). A reduced field was delivered to PTV2 with an additional 5.4 Gy in 3 fractions, created by expanding the GTV by



**Figure 1** (A) Schematic representation of the CivaSheet, a flexible brachytherapy device containing  $^{103}\text{Pd}$  sources (in blue) and gold shield backing for directionality (in golden). Computed tomographic imaging with oral and intravenous contrast in the (B) coronal and (C) axial views, before the patient received any treatment. Arrows pointing to left pelvic sidewall tumor.

0.5 cm (anatomic constraint) plus 0.5 cm (geometric expansion). The patient was then prescribed a 27.8 Gy intraoperative boost (physical dose with an EQD2 = 17.5 Gy) using the CivaSheet given concerns for



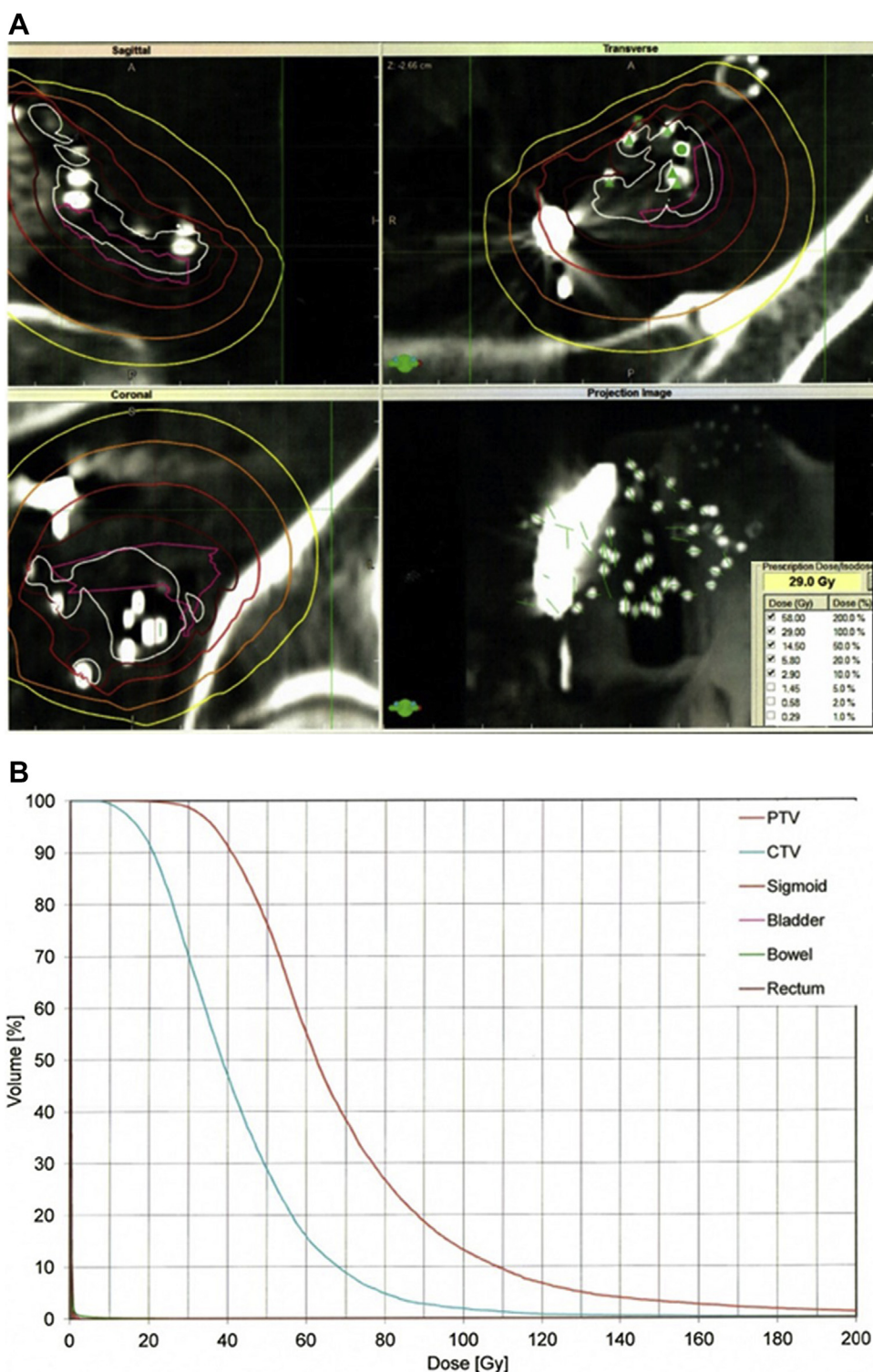


**Figure 2** Computed tomography-based preimplant dosimetry. (A) Intensity modulated radiation therapy isodose distribution and (B) dose-volume histograms. (C) Low-dose-rate brachytherapy boost isodose distribution in the anticipated area of positive margins before resection and (D) dose-volume histograms, where the reference line corresponds to the 17.5 Gy equivalent dose goal, which provided 90% volumetric coverage of the target.

microscopic residual disease in the tumor bed (Fig 2). Summation plan constraints were the following: small bowel maximal dose <52 Gy, bladder maximal dose <65 Gy, rectum V<sub>50</sub> <50%, and femoral heads V<sub>50</sub> <5%.

After completing pelvic IMRT without significant acute toxicities, the patient underwent exploratory laparotomy in January 2016 with anticipated R1 resection of the left pelvic mass. Tumor extension included the

retrosacral space involving the left psoas and iliacus muscle, underlying pelvic bone, left external and internal iliac veins and artery, and left ureter. Preoperatively, the left internal iliac artery was embolized in anticipation of potential significant blood loss. The left ureter was involved in the tumor, requiring transection and subsequent ureteroneocystostomy. The left external and internal iliac vein were also grossly involved with the tumor,

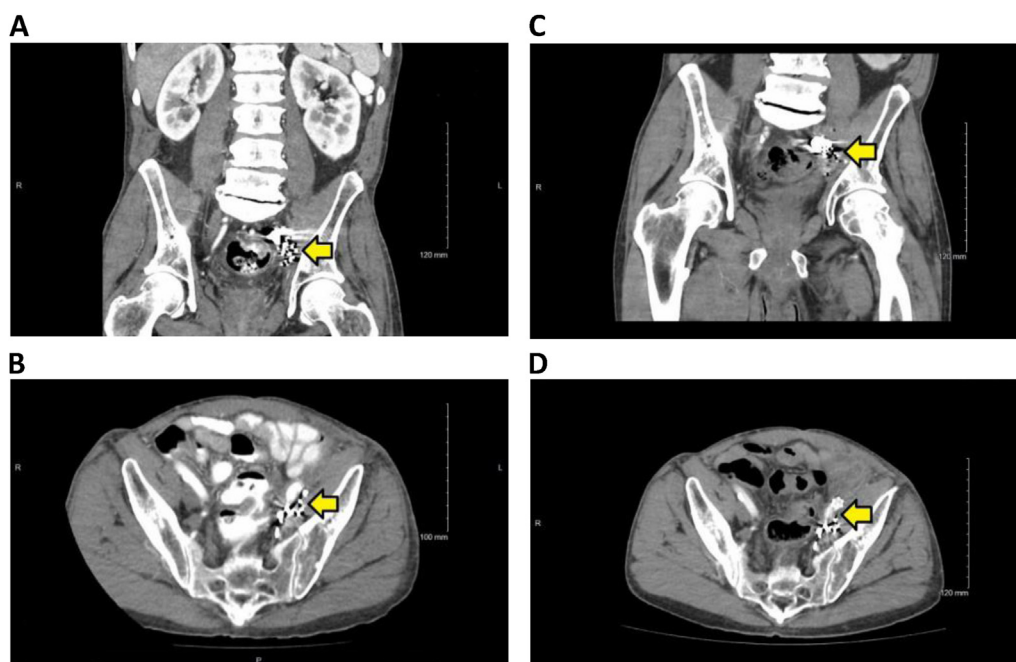


**Figure 3** Computed tomography-based postimplant dosimetry. (A) Low-dose-rate brachytherapy boost isodose distribution and (B) corresponding dose-volume histograms.

therefore the left common iliac vein was transected. The left external iliac artery was not grossly involved with the tumor but required mobilization secondary to radiation induced fibrosis. Surgical implantation of the CivaSheet was performed. The bioabsorbable sheet contained 48

seeds of  $^{103}\text{Pd}$  allowing directional irradiation of the tumor bed while sparing organs at risk, namely the bladder, rectum, and small bowel. Individual source strength on the day of implant was 1.06U with total source strength of 51U and exposure rate of 0.01 mR/h at





**Figure 4** Computed tomographic imaging with oral and intravenous contrast in the (A) coronal and (B) axial views at 28 months after resection and with intravenous contrast only in the (C) coronal and (D) axial views at 30 months after resection. No evidence of recurrence in any of the serial imaging performed. Arrows pointing to the implanted CivaSheet device.

1 m. The LDR  $^{103}\text{Pd}$  sources are positioned within a 0.8 cm rectilinear matrix (Fig 1A). Radiation dose on the shielded side of the CivaSheet ranges from a factor of 5 to 24 from 1 to 10 cm, respectively.<sup>17</sup>

Postimplant CT-based dosimetry in April 2016 confirmed adequate placement of the brachytherapy device (Fig 3A and 3B). We were pleased with agreement between the planned and expected implant dosimetry given the geometric design of the brachytherapy device. The physical dose was 27.8 Gy to a 0.5 cm depth, BED = 21.7 Gy, and EQD2 = 17.5 Gy (near the center of the desired EQD2 range). Selection of the boost dose was based upon a BED derivation of 28 Gy physical dose with  $\alpha = 0.25 \text{ Gy}^{-1}$  and  $\alpha/\beta = 8.6 \text{ Gy}$  values for rhabdomyosarcoma.<sup>21</sup> Other radiobiologic parameters were  $T_{\text{POT}} = 23$  days,<sup>22</sup> a repair half-time of 1.5 hours, and an RBE value of unity because this is a controversial topic. The tumor bed (CTV = 4.0 cm<sup>3</sup>) dosimetric coverage was 99.2%, and the total EQD2 delivered to the tumor was 67.2 Gy. All OAR constraints were met, including the bowel constraint goal with a maximum dose of 49.9 Gy from the preoperative IMRT plus 1.4 Gy from the CivaSheet implant. After 40 months of serial imaging and clinical follow-up, the patient experienced no grade 3 + late radiation therapy toxicities and no evidence of recurrent disease (Fig 4).

## Discussion

This case represents a favorable interval oncologic outcome in a patient with high-grade leiomyosarcoma of

the pelvic sidewall. He underwent preoperative IMRT, R1 surgical resection (with focally positive margins at the pelvic side-wall), and IORT boost with the CivaSheet technology. At 40 months, patient remains free from locoregional recurrence as evidenced by imaging and clinical follow-up.

Preoperative radiation therapy is preferred because it limits toxicity to the bowel, which would unavoidably fall into the treatment field after resection of tumor. Additionally, lower prescribed dose and smaller treatment field size is associated with less late radiation therapy-associated toxicities. In this present case, preoperative radiation therapy with IMRT was followed by an intraoperative boost to achieve significantly higher doses to the tumor while sparing OARs, which would have not been possible with IMRT exclusively. Given the small bowel constraint of a maximal dose <52 Gy, boost using IMRT or post-operative doses of 60 to 66 Gy would have exceeded the dose tolerance, and thus requirement for conformal brachytherapy boost.

Preoperative radiation therapy with IORT offers unique advantages for select patients with abdominal, retroperitoneal, or pelvic sarcomas.<sup>7,8</sup> However, IORT is dependent on institutional practice and resources and may not be widely available.<sup>23</sup> CivaSheet expands IORT capabilities in a resource independent manner. In the case presented herein, using preoperative IMRT and CivaSheet was associated with durable local control and significant reduction in doses to OARs including bowel, rectum, and bladder.<sup>17,24</sup>

Results from the use of CivaSheet may be comparable to published contemporary analysis of retroperitoneal soft tissue sarcoma resection and perioperative radiation therapy with 3-year local recurrence of approximately 5% to 15%.<sup>25,26</sup> Limitations to this study are attributed to results from a single patient with a modest follow-up; however, this report and a growing cohort of 66 patients who have now undergone CivaSheet IORT (personal communication, December 2018) support this treatment paradigm. Malignancies previously treated with this device include breast, colorectal, lung, pancreatic, sarcoma, head and neck, chest wall, thoracic, abdominal, pelvic, gynecologic, prostatic, and axillary malignancies, in both definitive and salvage settings. To our knowledge, this is the first report of a patient undergoing CivaSheet treatment for leiomyosarcoma of the pelvic sidewall.

Advantages include directional irradiation attributed to gold shielding on 1 side of the <sup>103</sup>Pd source and customization of its size and shape. Moreover, the directional nature of this device helps increase the therapeutic ratio by avoiding unnecessary irradiation of OARs. The bio-absorbability, flexibility, and easy identification on CT imaging allow this device to treat tumors in irregularly shaped cavities, such as the pelvic sidewall and retroperitoneum. The device seems to be a safe option in select patients requiring preoperative radiation therapy with addition of a boost. In this patient, we favored boost delivery via IORT (as opposed to IMRT) because this focused approach allowed sparing of OARs. Additionally, positioning of the device demarcates the area that received boost and serves as an anatomic reference for surveillance of local tumor recurrence. CivaSheet requires coordination among multidisciplinary teams while understanding the novelty of this device for directional brachytherapy treatment planning.

Favorable results and considerable range of potential applications have driven ongoing and future research. The [ClinicalTrials.gov](https://www.clinicaltrials.gov) website lists 4 phase 1 and 2 studies evaluating the CivaSheet device. These trials include 3 currently accruing: 2 for pancreatic cancer (NCT02843945 and NCT03109041) and 1 for prostate cancer (NCT03657108). Additionally, 2 trials are active but not accruing yet: 1 for abdomino-pelvic solid tumors (NCT02902107) and 1 for lung cancer (NCT03290534).

## Conclusions

In this patient with a pelvic soft tissue sarcoma, preoperative radiation therapy followed by intraoperative LDR brachytherapy using the CivaSheet offers durable local control. This favorable interval outcome occurred despite a focally positive microscopic margin while concomitantly sparing toxicity to critical pelvic OARs. Additional ongoing studies may guide patient selection for this promising brachytherapy technology.

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