Technical Note: High-dose-rate interstitial brachytherapy for pelvic sidewall recurrence using intraperitoneal spacers

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Running Title:
HDR-ISBT with intraperitoneal spacers

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The author responsible for statistical analysis:
The study is an observational study, and no statistical analysis was performed; therefore, there are no authors responsible for the analysis.
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Abstract:
**Purpose:** When performing salvage radiation therapy (RT) for pelvic recurrence, it is necessary to prescribe a dose sufficient to control the tumor while taking into account the tolerable dose to normal organs (organs at risk, OARs). However, it is frequently difficult to meet this requirement following hysterectomy due to the proximity of OARs and recurrent tumors. Here, we report on a patient with recurrent uterine cervical adenocarcinoma in the pelvis who underwent a surgical spacer insertion to create space between the bowel and the recurrent tumor before salvage RT, including high-dose-rate interstitial brachytherapy (HDR-ISBT), which led to local control with no serious side effects.

**Methods and materials:** A 44-year-old Japanese woman with recurrent uterine cervical adenocarcinoma in her pelvic sidewall pelvis after radical hysterectomy underwent salvage RT. However, because the sigmoid colon migrated to the pelvic sidewall where the uterus or the ovary used to locate and adhesion of the sigmoid colon was suspected just above the recurrent tumor, a spacer was inserted into the peritoneal cavity intraoperatively first, followed by radiation including HDR-ISBT.

**Results:** The patient died of respiratory failure due to multiple lung metastases, but after salvage treatment there were no adverse events and no recurrence in the pelvic region during the 2 years and 1 month before death.

**Conclusions:** In a specific anatomical situation, such as post-hysterectomy, where the uterus was removed, and direct contact between the bowel and the recurrent tumor was observed, intraperitoneal spacers are beneficial for protecting OARs during HDR-ISBT. Otherwise, delivering tumoricidal doses to the recurrent tumor is difficult.
**Introduction:**

The management of pelvic recurrence after hysterectomy depends on whether the patient has previously received pelvic irradiation and whether the recurrence site is pelvic central or pelvic sidewall. The 2022 National Comprehensive Cancer Network (NCCN) guidelines for uterine cervical cancer recommend that patients with pelvic sidewall recurrence without a prior history of irradiation are treated primarily with surgical resection, external beam radiation therapy (EBRT), or chemotherapy. However, pelvic sidewall recurrence has a worse prognosis than central recurrence and EBRT do not provide a sufficient dosage for the recurrent tumor, making eradication difficult. On the other hand, interstitial brachytherapy (ISBT) can prescribe large doses to pelvic sidewall tumors and is a useful tool for tumor control, and this modality is effective in reducing the dose to the surrounding normal organs (organs at risk, OAR) due to its steep dose gradient. However, when OARs are in close proximity to the tumor, it is difficult to prescribe a sufficient dose to the tumor while keeping the dose to the OARs low, even with brachytherapy. Here, we report a postoperative patient with recurrent uterine cervical adenocarcinoma in the pelvis who had sigmoid colon adhesion right above the recurrent tumor and underwent brachytherapy after a laparotomy to directly insert a spacer between the tumor and the sigmoid colon, which led to adequate dose delivery with ISBT and local control with no serious side effects.

**Methods and Materials:**

A 44-year-old Japanese woman who had undergone abdominal radical hysterectomy for uterine cervical adenocarcinoma with stage IB1 based on the 2009 edition of the
International Federation of Gynecology and Obstetrics (FIGO) stage and was followed up for one year and four months without any adjuvant treatment, was diagnosed of left pelvic sidewall recurrence. The tumor size was approximately 30 x 30 x 50 mm, and to cover the entire tumor with a volume implant, needles were inserted parallelly at 5–10 mm evenly spaced intervals, necessitating the use of 14 needles for the four parallel planes. Due to the tumor's adhesion to the pelvic wall, salvage surgery was judged to be difficult, and radical radiation therapy (RT) was decided to be performed. However, there was a possibility of adhesion between the tumor and the sigmoid colon, which meant a risk that the radiation dose to the sigmoid colon would exceed its tolerable dose when a tumoricidal dose was delivered to the recurrent tumor (Figure 1). Therefore, before salvage RT, surgery to insert a spacer in the pelvic floor under direct visual guidance was performed to create space between the bowel and the recurrent tumor.

The details of the surgery are as follows: the sigmoid colon’s mesentery and the left pelvic wall, as well as the sigmoid colon’s mesentery and the left common iliac artery and vein, were found to be mildly adherent to the recurrent tumor at the time of laparotomy. Additionally, a recurrent tumor without mobility was palpable on the left side of the pelvic floor in the retroperitoneum. Next, a polypropylene mesh implant 150 mm × 150 mm in size for the treatment of intestinal hernia (Bard® Soft Mesh; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) was folded six times and stitched together with sutures (Vicryl® 3-0; Ethicon, Inc.; Johnson & Johnson, Somerville, NJ, USA), which was inserted into the pelvic floor as a spacer. After confirming that the sigmoid colon had separated from the pelvic wall, the spacer was fixed with sutures (Prolene® 3-0 stitches; Ethicon, Inc., Vicryl® 3-0; Ethicon, Inc.), and the surgery was completed (Figure 2). The subsequent CT images revealed an approximately 10 mm
thick spacer between the tumor and the adjacent sigmoid colon (Figure 3). Then, salvage radical RT was started, which consisted of a combination of external beam radiotherapy (EBRT) and high-dose-rate interstitial brachytherapy (HDR-ISBT). EBRT was performed at 50 Gy in 25 fractions with the 4-fields box irradiation technique of 0°, 90°, 180°, and 270° portals, using high-energy 15 MV X-ray photons from a linear accelerator (Figure 4). The following is a detailed description of the HDR-ISBT treatment procedure: A total of 14 interstitial needle applicators were inserted freehand and transperineally with the patients in the lithotomy position and guided by TRUS under general and epidural anesthesia. Simultaneous CT scanning was performed using a large-bore CT scanner (Aquilion® LB, Canon, Tokyo, Japan), which was capable of imaging patients lying in the lithotomy position with applicators in place without moving them, and image-guided brachytherapy planning was performed using those CT images with a slice interval of 2 mm. Dose calculation was performed by the planning system (Plato®, Nucletron, Veenendaal, the Netherlands) was used to plan the treatment, and irradiation was performed with MicroSelectron HDR™ (Nucletron, Veenendaal, the Netherlands). The clinical target volume (CTV) was defined as the gross tumor volume using CT scans taken immediately after the needle was inserted. On the surface of the CTV, reference points were marked, and a dose calculation was performed so that each point received 6 Gy per fractionation, up to a total of 24 Gy in four fractions. Dose calculation was performed by a manual graphical modification in order to completely cover the CTV with the 100% prescribed isodose line of 6 Gy while minimizing dose to OARs (Figure 5). Needle applicators were fixed and treated twice daily, every 6 hours (Figure A1). CT scanning was used to evaluate and correct for needle displacement before each morning session, and if needle displacement was greater than 5 mm, the
needles were relocated and CT scanning was performed prior to the evening session as well. The combined dose of EBRT and HDR-ISBT was calculated using the linear-quadratic dose-effect model of the equivalent dose in 2 Gy fraction (EQD2) \(^{5-7}\).

**Results:**
In this case, the minimum dose of EQD2 that covered 90% of the CTV (CTV D90%) was 94.5 Gy (\(\alpha/\beta = 10\) Gy). The doses delivered to the rectum, bladder, and sigmoid colon's most exposed 2.0 cm\(^3\) (D2cm\(^3\)) were 57.8 Gy, 60.6 Gy, and 60.1 Gy in EQD\(_2\), respectively (\(\alpha/\beta = 3\) Gy). Three weeks after the end of treatment, the tumor was no longer palpable on internal and rectal examinations, and CT scans and MR images three months later confirmed the tumor's disappearance (Figure 6). However, five months after tumor disappearance was confirmed (8 months after the end of treatment), CT scans revealed multiple lung metastases. Subsequent chemotherapy slowed tumor progression, but two years and one month after the end of the salvage HDR-ISBT, she died of respiratory failure due to multiple lung metastases without pelvic failure. Neither the radiotherapy nor the placement of the spacer caused any adverse events while the patient was still alive.

**Discussion:**
We used intraperitoneal spacers to protect her sigmoid colon for RT, especially brachytherapy. One of the characteristics of brachytherapy is its intrinsic physical property of a steep dose gradient; it delivers a high dose intensively to the tumor, and the dose rapidly decreases as the inverse square of the distance from the radiation sources.
source increases. Therefore, if there is an organ for which we want to reduce radiation
dose, we can reduce the dose by simply creating space between the organ and the
radiation source. Without the spacer, the irradiated dose to the sigmoid colon would
have been much higher. This strategy, although it requires surgery, is theoretically
reliable and has the advantage of reproducibility in creating the distance between the
recurrent tumor and the sigmoid colon at each brachytherapy session. Artificial ascites 8,
9 and hyaluronic acid gel injected into the vesicovaginal and rectovaginal spaces 10-14 are
also used as other means of dose reduction for OARs in pelvic brachytherapy. However,
these methods cannot ensure reproducibility for each treatment due to inconsistent
injection volume and position, as well as the volume of artificial ascites changing over
time because of absorption. Additionally, these methods are unable to separate the
distance between OARs and tumors that are in close proximity due to adhesion. Of
course, these methods are relatively less invasive to perform, requiring no surgery and
effective at reducing the dose of OARs, but with adequate patient understanding and
consent, intraperitoneal spacer insertion can be an extremely effective and reliable way
to accomplish this goal.

Regarding the spacer placement method, Dalwadi et al. reported a case with a pelvic
central recurrence of endometrial cancer by laparoscopic insertion of a spacer into the
peritoneal cavity just above the tumor, followed by EBRT and brachytherapy 15. They
reported that they were able to prescribe up to 79.7 Gy in EQD2 for CTV, and that the
patient achieved a complete response for more than a year without any serious adverse
events. In the current case, laparotomy was performed due to organ adhesions, but less
invasive intraperitoneal spacer placement might have been considered if possible.
The following are some limitations and future considerations; i) trying to insert spacers using laparoscopy or robotic surgery, which is less invasive than open laparotomy, ii) to perform a long-term follow-up for similar situations and investigate whether the nonabsorbable spacers, which have the risk of abdominal infection caused by residual foreign material or intestinal perforation caused by spacers’ rigidity or size associated with prolonged use, iii) to assess whether the nonabsorbable spacers can be replaced with non-surgically removable spacers under development or bioresorbable spacers such as polyglycolic acid spacers (Neskeep®, Alfresa Pharma Co., Osaka, Japan) used in carbon ion radiotherapy.

Conclusions:
Intraperitoneal spacers are beneficial not only for protecting OARs during HDR-ISBT but also for good local control.

Declarations of Interest
Hiroshi Igaki, MD, PhD received a research grant from HekaBio, CICS, and Elekta KK, received consulting fees from HekaBio, and lecture fees from Varian, Itochu, CICS, and Himedic.

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The other authors have nothing to disclose.
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Figure Captions:

Figure 1. T2-weighted magnetic resonance images (MR images) before the salvage treatment. The recurrence tumor (arrows) was adjacent to a sigmoid colon. The possibility of adhesions between the tumor and the sigmoid colon was suspected.

Figure 2. The procedure of inserting a spacer into the pelvic floor. 1) A polypropylene mesh implant 150 mm × 150 mm in size for the treatment of intestinal hernia was used. 2) After inverting the intestine, the lower portion of the abdominal cavity was examined; the sigmoid colon was mildly adherent to the retroperitoneum, but there was no direct adhesion to the tumor (red circle). 3) The mesh implant, folded six times and stitched together with sutures, was inserted into the pelvic floor as a spacer. 4) The inverted intestine was placed back on the spacer, and the operation was completed.
Figure 3. Comparison of CT images between (a) before treatment and (b) after spacer insertion. The tumor (thick arrows) was separated from the sigmoid colon (arrow heads) due to a spacer (thin arrows).
Figure 4. A dose distribution of external beam radiation therapy with the four fields box irradiation technique of 0°, 90°, 180°, and 270° portals. She was prescribed at 50 Gy in 25 fractions.
Figure 5. Brachytherapy treatment planning calculated by PLATO and shown in Oncentra® (Nucletron, Veenendaal, Netherlands). (a) The upper panel shows the dose distribution of brachytherapy. (b) The lower panel shows a 3D reconstruction of the tumor (red), the needle applicators, the sigmoid colon (blue), and the spacer (cyan).
Figure 6. Comparison of CT images between (a) before treatment and (b) two years after the salvage treatment. The tumor (thick arrow), adjacent to the sigmoid colon (arrow heads), was disappeared. The spacer (thin arrows) was a non-absorbable material and still remained in the pelvis.
Supplementary figure

Figure A1. The needle applicator secured with a button and sutures. She was irradiated with MicroSelectron HDR™ (Nucletron, Veenendaal, the Netherlands) twice daily, every 6 hours, with the patient obliged to stay in bed until the treatment was completed and the applicators were removed.