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Inversely and adaptively planned interstitial brachytherapy: A single implant approach

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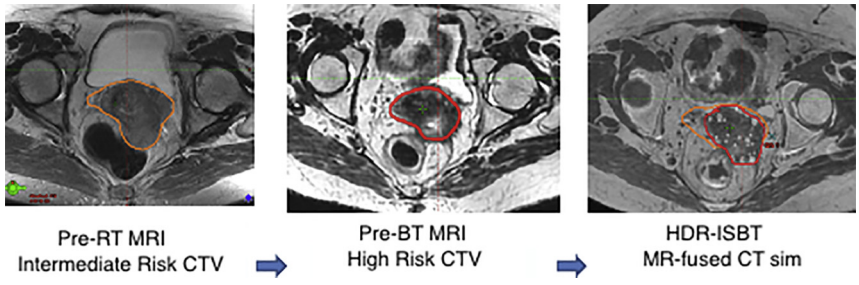
HIGHLIGHTS

- A condensed regimen of single implant interstitial brachytherapy is safe and effective.
- An inverse and adaptive planning technique for each fraction is feasible.
- One of the most locally advanced gynecologic cohorts treated with brachytherapy

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To evaluate the efficacy, feasibility and safety of image-based, inversely and adaptively planned high-dose rate interstitial brachytherapy (HDR-ISBT) to treat advanced primary or recurrent gynecologic malignancy in a single implant, three-consecutive-day regimen.

Methods. Clinical demographics and outcome data were abstracted from all patients with primary and recurrent gynecologic malignancies who received HDR-ISBT boost from 2014 to 2017. Treatment consisted of a single implant (~7 Gy × 4 fractions) of interstitial needles using the Syed-Neblett template over a three-day hospital admission. CT-based (3D) simulation with inverse and adaptive planning was utilized for each fraction. MR prior to and MR immediately after external beam therapy were fused for HDR-ISBT target delineation.

Results. Forty women with an overall median follow-up of 18 months (range: 6–54 months) received an HDR-ISBT boost. Of the 30 primary cases (83% cervix, 10% vaginal, 7% uterine), 44% had organ invasion (bladder, rectal or both) on MRI. Median coverage and dose are reported (V_{100}: 98%, HR-CTV EQD_2: 85.1 Gy, D_{90}: 92 Gy). A significant association existed between rectal doses exceeding GEC-ESTRO recommendations ($D_{2cc} < 75$ Gy) and the development of grade 3 gastrointestinal toxicity with a relative risk of 1.4 [1.1–1.8] ($p = .046$). Actuarial two-year overall survival (OS), local control (LC) and progression-free survival (PFS) were 81%, 81% and 64%, respectively.

Conclusions. A four fraction, inversely and adaptively planned, single-implant approach of image-based HDR-ISBT provides excellent coverage, minimal toxicity and effective local control in patients with advanced and recurrent disease.

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1. Introduction

Brachytherapy (BT) is a critical component of treatment in gynecologic malignancies. Despite the advent of advanced external beam modalities such as Intensity-Modulated Radiotherapy (IMRT) and Stereotactic Body Radiotherapy (SBRT), BT offers superior dose conformity, dose escalation, and normal tissue sparing [1]. Studies continue to evaluate replacement therapies for women ineligible for BT; however, when brachytherapy is omitted (an observed trend nationally), patients suffer from reduced recurrence-free and overall survival [2–6]. Intracavitary brachytherapy (ICBT) is the most common form of brachytherapy; however, there are certain indications (<8% of cases worldwide) that necessitate the use of interstitial brachytherapy (ISBT) [7–11].

Due to the relative rarity of locoregionally advanced cervical cancers that occur in developed countries, studies evaluating outcomes using ISBT with modern treatment planning techniques remain sparse [12]. Given that standard of care for locally-advanced disease (FIGO IB2 and above) is definitive chemoradiation (EBRT and BT), radiation oncologists must continue to make ISBT available [13]. Additionally, ISBT provides a unique salvage modality for locally recurrent gynecologic malignancies, which represent a significant clinical challenge to both gynecologist and radiation oncologists, and when feasible (no prior radiation, vaginal/central recurrence) may provide the best option for salvage [14,15].

Given the recent focus on mitigating the financial toxicity of healthcare in the United States, impetus exists for single implant ISBT, which further minimizes risk to patients by avoiding additional anesthesia and needle placement episodes. Our main purpose is to report our clinical experience with image-based, inversely and adaptively planned high-dose rate interstitial brachytherapy (HDR-ISBT) in patients with primary or recurrent gynecologic malignancy treated in a condensed fashion (four fractions over three days). We review the efficacy, feasibility and safety of this treatment in terms of dosimetric coverage, toxicity and tumor control.

2. Materials and methods

We conducted a retrospective, single-institution review of patients with gynecologic malignancies treated with inversely and adaptively planned, CT-based/MR-fused HDR-ISBT. All women with primary or recurrent gynecologic malignancy treated between January 1, 2014 and December 21, 2017 were identified from existing clinical rosters. Clinical demographics, dosimetric and clinical details of treatment and outcomes were abstracted for all subjects.

2.1. Treatment planning

As part of routine treatment planning, cases were discussed at multidisciplinary tumor board in collaboration with gynecology oncology, radiology, pathology as well as radiation oncology to determine optimal care based on National Comprehensive Cancer Network (NCCN) guidelines, taking into consideration standard clinical criteria including tumor size, location, Eastern Cooperative Oncology Group (ECOG) performance status and previous treatment [16]. In addition, cases referred for radiotherapy were evaluated at a brachytherapy peer-review conference consisting of multiple radiation oncologists experienced with brachytherapy. Case review for all subjects included a review of history and pertinent imaging with a final disposition to ISBT or ICBT.

2.2. EBRT dose, technique and timing

For patients with radiographic evidence of local nodal disease at presentation, we utilized intensity-modulated radiation therapy (IMRT) to a prescribed dose of 4500–5040 cGy in 25–28 fractions to the pelvis along with a simultaneously integrated boost of 5154–5589 cGy (207 cGy/fx) to the involved node(s), followed by a sequential boost of 6000–6600 cGy based on maximum dose tolerance (e.g. bowel). For patients without radiographically positive nodes, 3D conformal radiotherapy (3D-CRT) was used to a dose of 4500 cGy in 25 fractions. An MRI is obtained twice, once prior to EBRT and once immediately prior to ISBT. Generally, ISBT boost directly followed the completion of EBRT with a 56-day treatment completion goal.

2.3. HDR-ISBT implantation, simulation, contouring and delivery

As per institutional standard of care, brachytherapy was completed in a single hospital admission over three days (Fig. 1) for all subjects. On admission, each subject was brought to the operating room and placed in lithotomy position under general anesthesia. Seventeen-gauge titanium steel interstitial needles (250 mm) with trocar points (Varian Medical Systems, Palo Alto, CA) were implanted utilizing a Syed-Neblett template sutured to each subject's perineum. A tandem was used in all cases without prior hysterectomy along with an obturator. Pre-BT MR imaging as well as an exam under anesthesia were used to inform needle placement. A Foley balloon with contrast was inserted into the bladder to assist intra-operatively and for treatment planning. Transabdominal ultrasound guidance as well as fluoroscopy were used intraoperatively to assist with needle implantation. 30 cm^3 of rectal contrast (1:2 omnipaque: normal saline) was also administered. Following post-operative recovery, the patient was transferred to the clinic with peripherally-administered, patient-controlled analgesia (PCA) for CT simulation and her first treatment fraction. At the attending physician's discretion, minor adjustments to needle depth were sometimes made at time of simulation; however, no needles were added or removed outside of the operating room. Additionally, patients with small bowel near the treatment field were simulated/treated with a full bladder when it was determined it would be advantageous. PCA was available for the entirety of the inpatient stay.

A Zephyr HDR patient positioning and transfer system (Orfit Industries NV, Wijnegem, Belgium) was used to transfer the patient with minimal motion from CT simulation to the HDR treatment bunker to assure each subject was treated in the planned position. CT-based simulation and a new, adaptive plan were obtained for every fraction with fixed registration of the pre-RT and pre-BT MR. High-risk clinical target volumes (HR-CTV) based on pre-BT MR and intermediate-risk clinical target volumes (IR-CTV) based on pre-RT MR were defined per GEC-ESTRO recommendations (Fig. 2) [11]. While fixed fusion of MR/CT was performed based on position of the uterus/cervix, it is understood that because MR was done prior to needle implantation, that there may be differences in organ position due to distortion of the patient's normal anatomy (e.g. uterus). Therefore, the radiation oncologist used MR as a tool to aid contouring decision-making. All final volumes were ultimately drawn on CT.

Treatment was carried out utilizing the VariSource iX HDR Brachytherapy Afterloader (Varian Medical Systems, Palo Alto, CA) with a single, 5 mm Iridium-192 source with 5 mm dwell position spacing. Each fraction lasted between 10 and 30 min depending on source activity and number of needles. On the day of implantation, a patient received her first fraction. The next day, the patient received two additional treatments with a minimum of 6 h in between and on the following day the patient received her fourth and final treatment. The device was then removed in clinic, hemostasis was achieved, and the patient was assessed for discharge.

2.4. CT-based (volumetric) inverse and adaptive planning

Once contouring was completed, each needle was digitized and given an available active length for source dwell positions corresponding to the length of the target structure in relation to the needle. A plan was then optimized using the linear source model, TG-43 based, Nelder-Mead Simplex algorithm in the Varian BrachyVision (Varian

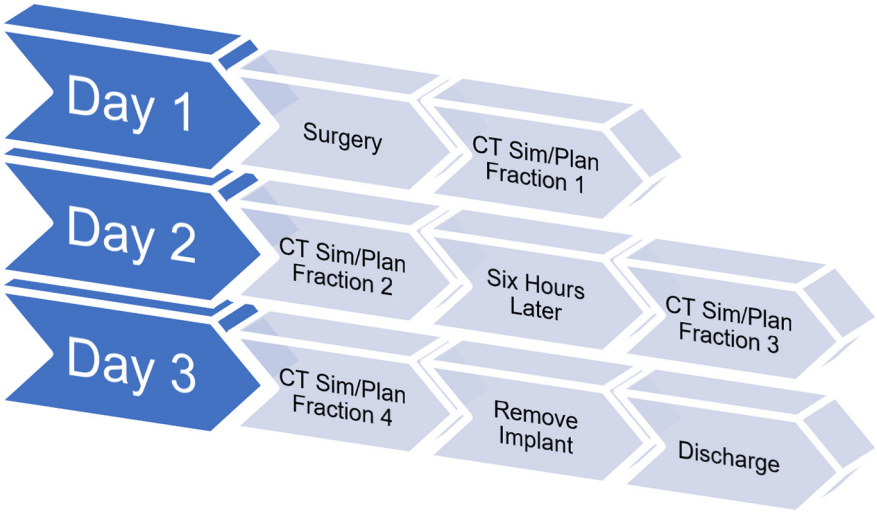

Fig. 1. Daily HDR-ISBT workflow over a three-day hospital admission.

Medical Systems, Palo Alto, CA) treatment planning system. Inverse planning followed by dose-shaping was employed for plan optimization with goals based on desired target coverage, limits to target heterogeneity, and dose tolerances to the surrounding critical structures.

EBRT doses were converted into biologically equivalent dose in 2 Gy fractions (EQD_{2Gy}) using the linear quadratic model approach for the target area as well as the rectum, bladder, urethra, bowel, and sigmoid [17]. The EQD_{2Gy} was calculated for the HDR dose given so that a total EQD_{2Gy} dose could be calculated and verified to be less than the tolerances for each structure as well as greater than an EQD_{2Gy} of a minimum of 80 Gy for the HR-CTV and an EQD_{2Gy} of a minimum of 60 Gy for the IR-CTV. When calculating EQD_{2Gy} doses, an α/β ratio of 10 was used for the target and 3 for the normal tissue late effects.

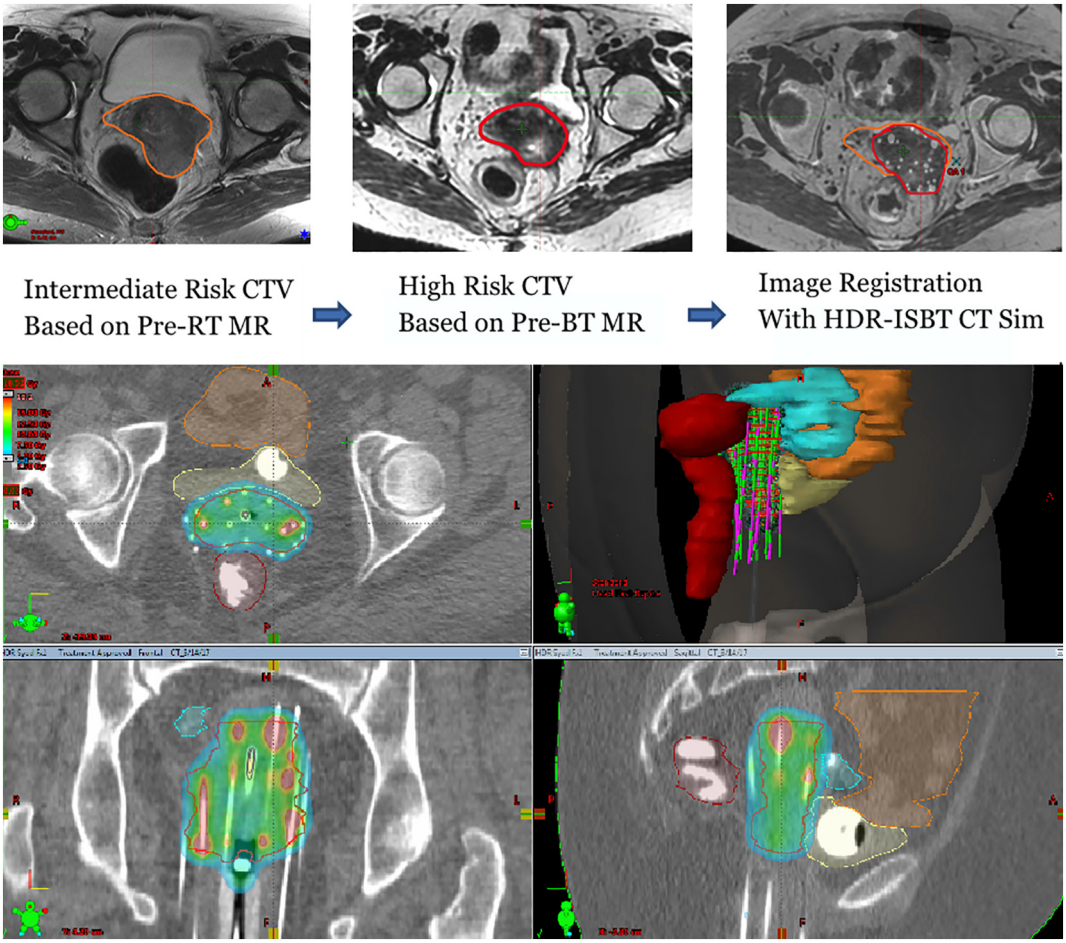

Fig. 2. Image-based treatment planning utilizing MR-fusion assisted contouring.

We utilized adaptive-planning, which allows for minor adjustments between treatments to the previously delivered plan to accommodate for anatomical changes (e.g. gas in the rectum) or needle displacement secondary to patient movement. Thus, for all subsequent fractions, the patient was re-simulated, and the new CT underwent image fusion with previous HDR fractions. At the time of each subsequent CT, the radiation oncologist assessed the position of inserted needles for shifts, both on the template marks as well as on imaging. Within the treatment planning system, the physicist brought the virtual needles over from the prior fraction with the previous dose/dwell times and manually matched them to the needles on the new CT sim for accuracy. Once the dose (dwell times for each of the needles) was copied over to the newly digitized needles, the plan was re-optimized, reviewed by the radiation oncologist and sometimes manually adjusted (utilizing dwell times/positions or dose-shaping tool) with the help of the radiation physicist.

2.5. Optimization

Objectives defined for optimization included: 95% of the target volume receiving 100% of the prescription dose, 150% of the prescription dose limited to 25% of the target volume and 200% of the prescription dose limited to 10% of the target volume. Optimization objectives for each of the pertinent normal tissues were defined as below.

In general, a biologically equivalent dose of 85–90 Gy to the HR-CTV was planned. Normal tissue objectives were D_{2cc} for each organ as follows: bladder (≤90 Gy EQD_2), rectum (≤75 Gy EQD_2), sigmoid (≤75 Gy EQD_2), bowel (≤60 Gy EQD_2) as well as an overall normal tissue constraint to reduce unnecessary dose outside the target volume. The urethra objective was based a smaller volume of 0.1 cm^3 (≤90 Gy EQD_2). For patients undergoing re-irradiation, stricter constraints were utilized (bladder < 60 Gy EQD_2 and rectum < 65 Gy EQD_2) with prescription dose based on physician discretion. Following inverse planning dose optimization, the physicist and physician occasionally made minor manual adjustments to dwell times to improve target coverage or decrease dose to surrounding normal structures (i.e. dose-shaping) at the physician's discretion.

2.6. Follow-up

Patients are followed by both radiation and gynecologic oncology every three months for two years and every six months thereafter per NCCN guidelines [16]. A PET/CT is performed three to six months after patient completes treatment with consideration of pelvic MRI in certain cases. Surveillance consists of a focused history and physical examination, annual cytology if indicated and further imaging if clinically warranted.

We primarily focused on objective endpoints to define toxicity based on the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0).

2.7. Statistical analysis

Descriptive statistics are reported as median values as a measure of central tendency as well as interquartile range (IQR) to describe non-normal quantitative variables. Kaplan-Meier models were utilized to generate curves describing local control, progression and overall survival. Associations between clinical and dosimetric factors were evaluated on a contingency matrix and univariate analyses were performed. For comparing categorical data, a Fisher's Exact test was employed. For comparing groups of data with normal distributions, a Student's *t*-test was utilized. Prism 7 (GraphPad Software, La Jolla, California USA) as well as JMP 14 (SAS Institute Inc., Cary, NC) were used for statistical analysis.

3. Results

3.1. Patient demographics

We identified 40 patients treated with HDR-ISBT at our institution within the defined study window. Median age at treatment was 49 years (range, 29–67). Demographic features of these subjects are summarized in Table 1. Thirty patients were treated for primary malignancies (25 cervical, three vaginal and two endometrial) and 10 patients were treated in the salvage setting (six endometrial, four cervical) due to vaginal cuff recurrence. Of the patients treated for recurrence, three patients had adverse histologic variants (two serous, one neuroendocrine) and three patients had prior pelvic radiation (i.e. underwent reirradiation). Median time to recurrence from primary treatment of malignancy for these subjects was 15 months (Table 2).

In patients treated for primary cervical cancer, median HR-CTV volume was 70.8 cm^3 (range, 22.6–229.1 cm^3). The International Federation of Gynecology and Obstetrics (FIGO 2009) staging breakdown was as follows: I (4%); II (36%); III (36%); IV (24%). Nodal involvement was radiographically observed in 72% of patients, of which 20% had para-aortic nodal involvement. While cystoscopy was needed for stage IV classification, bladder and rectal invasion were noted on MRI in 44% and 16% of patients, respectively. Most common indications for ISBT were parametrial extension (72%), vaginal involvement (20%) or prior hysterectomy (8%).

3.2. Treatment

With one exception, all cases received external beam radiotherapy (EBRT) to the whole pelvis (median dose: 4860 cGy). The majority (90%) received concurrent, platinum-based chemotherapy. Most patients were treated with intensity-modulated radiation therapy (IMRT) utilizing a simultaneously integrated boost as well as a sequential boost to the radiographically involved nodes and all were followed by HDR-ISBT. Median total brachytherapy dose delivered was 27 Gy (range, 20–29 Gy, 500–720 cGy/fx) for patients treated with EBRT + HDR-ISBT boost, excluding one patient treated in the recurrent setting who received HDR-ISBT alone to 40 Gy (8 Gy × 5 fractions). Three patients received <24 Gy brachytherapy dose because of either: prior history of radiation (lower prescribed dose) or because their external beam prescription dose was higher than usual (i.e. external beam nodal boost in the pelvis close to the brachytherapy target). A median

Table 1
Patient characteristics (n = 40).

Factor	Number (percent)
Age (years)	
20–39	7 (18%)
40–59	22 (55%)
>60	11 (28%)
Histology	
Squamous cell carcinoma	26 (65%)
Adenocarcinoma	11 (28%)
Adenosquamous	2 (5%)
Neuroendocrine	1 (3%)
Pre-treatment hemoglobin	
<10 g/dL	10 (25%)
10–12 g/dL	18 (45%)
>12 g/dL	12 (30%)
ECOG	
0	11 (28%)
1	20 (50%)
2	9 (23%)
Comorbidities	
Diabetic	10 (25%)
HIV+	2 (5%)
Risk factors	
Uninsured	25 (63%)
Current smoker	8 (20%)

Table 2
Clinical treatment details.

	Cervical	Vaginal	Uterine	Total
Primary HDR-ISBT cases (n)	25	3	2	30
FIGO stage (%)				
I	1 (4%)	0	0	1 (3%)
II	9 (36%)	0	0	9 (30%)
III	9 (36%)	1 (33%)	1 (50%)	11 (37%)
IV	6 (24%)	2 (67%)	1 (50%)	9 (30%)
Primary cervix cases (n = 25)				
Median tumor size (IQR)	6.6 cm (5.6–7.2)			
Median BT HR-CTV volume (IQR)	71 cm^3 (41–85)			
Adverse features (%) n				
Parametrial extension	88% [22]			
Lower vaginal involvement	32% [8]			
Pre-Tx hydronephrosis	28% [7]			
Pelvic nodes	72% [18]			
Para-aortic nodes	20% [5]			
Bladder involvement[a]	44% [11]			
Rectal involvement[a]	16% [4]			
Recurrent cases (n = 10)				
Primary cancer (%) n				
Cervix	60% [6]			
Endometrial	40% [4]			
Adverse histology (%) n				
Adenosquamous	10% [1]			
Serous	20% [2]			
Neuroendocrine	10% [1]			
Prior pelvic RT	30% [3]			
Median time to initial recurrence	15 months			

[a] By MRI or cystoscopy/colonoscopy.

of 21 needles (catheters) [IQR, 17–27] were utilized for treatment planning. Target coverage and dose are reported (V_{100}: 98%, HR-CTV EQD_2: 85.1 Gy, D_{90}: 92 Gy) along with dose volume histogram (DVH) parameters for organs at risk (OAR) in Table 3. In regard to inverse planning objectives, our goal of 200% of prescription dose limited to 10% of the target volume was attainable in approximately 60% of patients. In all cases, subsequent adaptive plans required at least minor adjustments in the form of dose-shaping from the prior fraction and were more commonly re-optimized starting with the plan from the previous fraction. Two examples of inter-fraction variation secondary to the changes in rectal anatomy are presented (Fig. 4).

3.3. Toxicity

For all cases identified (n = 40), overall median follow-up time was 18 months (6–54 months). Two subjects experienced acute complications following ISBT. The first was incidentally found to have a subclinical pulmonary embolus several days following the procedure when she underwent a CT chest for an unrelated issue. The second developed an intra-abdominal hematoma and required percutaneous drainage. This was thought to be secondary to a failure to hold daily, prophylactic enoxaparin prior to device removal. The major late toxicities (n = 7) were gastrointestinal and genitourinary in nature (Table 4). 17% of our patients developed radiation proctitis of any grade. Five patients developed grade 3 radiation proctitis (confirmed on colonoscopy) which required argon laser cauterization. One patient with a large tumor had abutment/early invasion into the rectum and following treatment had vaginal and rectal biopsies for suspicion of recurrence and as a result developed a recto-vaginal fistula. A significant association was found between rectal doses exceeding GEC-ESTRO recommendations (D_{2cc} < 75 Gy) and the development of grade 3 gastrointestinal toxicity with a relative risk of 1.4 [1.1–1.8] (p = .046). Of the patients developing grade 3 gastrointestinal toxicity the median dose (range) was 76.7 Gy (75.0–79.8 Gy). In patients with a rectal D2cc <65 Gy (n = 6) there were no GI toxicities. One of the three patients undergoing re-irradiation developed grade 3 radiation proctitis at rectal dose of 61.6 Gy and was excluded from the above dosimetric analysis.

Table 3
Dosimetric details.

		Median (IQR)
# of needles		21 (17–27)
Tumor BED (Gy_{10})		102 (99–103)
V100% HR-CTV		98% (94%–100%)
	EQD_2 (Gy)	HDR dose/fx (Gy)
Target volumes		
HR-CTV	85.1 (83.5–85.9)	6.8 (6.5–7.0)
IR-CTV	62.1 (60.8–66.9)	5.0 (4.9–5.4)
D_{90} HR-CTV	92.0 (87.4–95.8)	7.4 (7.0–7.8)
Organs at risk		
Bladder D_{2cc}	82.3 (71.9–89.0)	5.3 (4.3–5.8)
Rectum D_{2cc}	74.8 (70.7–76.9)	4.5 (4.0–4.8)
Sigmoid D_{2cc}	59.7 (57.3–67.1)	2.6 (2.1–3.6)
Bowel D_{2cc}	54.2 (51.8–58.0)	1.8 (0.9–2.1)
Urethra $D_{0.1cc}$	74.4 (60.7–84.7)	4.4 (3.1–5.5)

The only grade 3 genitourinary toxicity was a ureteral stricture which required stent placement. One patient developed urinary incontinence which was spontaneous and required pads (grade 2) while three patients developed occasional urinary stress incontinence which improved over time (grade 1).

3.4. Survival, control and progression

Actuarial rates of two-year survival (OS), local control (LC) and progression free survival were 81%, 81% and 64%, respectively (Fig. 3A). For patients treated for cervical cancer primaries (n = 25), a one-year OS of 86% decreased to 74% at two years with a LC and PFS of 75% and 59%, respectively (Fig. 3B). In our cohort of recurrent patients (n = 10), median follow up time was 28 months and two-year OS, LC and PFS were 100%, 90% and 90%, respectively (Fig. 3C). For primary cases stratified by FIGO stage, we observed a two-year LC of 100% for stage II, 70% for stage III and 62% for stage IV as well as a PFS of 100%, 45% and 33%, respectively.

Clinical and dosimetric factors such as tumor size, overall treatment time, HR-CTV volume and DVH parameters (V_{100}, D_{90}) were assessed for associations with clinical outcomes, including recurrence, progression or survival. Results of these analyses indicate that pre-treatment hemoglobin (Hgb) ≥8 g/dL was the only variable significantly associated with overall survival (p = .03). As of date at last follow up, eighteen patients had disease progression, seven had progression at the primary site alone (all within the HR-CTV), nine had distant metastasis and two patients progressed both distantly and locally. Of the local failures treated in the primary setting, all had HR-CTVs >30 cm^3 and the majority were >70 cm^3. Of the distant metastases, sites of progression were lung (n = 4), liver (n = 3), mediastinum (n = 1) and para-aortic node (n = 1). All three patients with liver metastasis had rectal involvement at time of initial treatment.

4. Discussion

We reported our experience with CT-based/MR-fused HDR-ISBT for gynecologic malignancies. To our knowledge, our cohort of patients with previously untreated primary malignancy represents one of the most locally advanced BT populations published to date and the first to utilize four fractions over three days with an inverse and adaptive planning technique for each fraction. Our institution operates within the Harris Health System, a largely publicly funded safety net health system. Women served by this system have insufficient access to preventative care and often present with advanced diseases. Thus, our cohort of patients differs from those generally included in prospective clinical trials and includes a substantial number of patients with advanced, neglected primary gynecologic malignancies, thereby strengthening our ability to analyze the efficacy, feasibility, and safety of inversely and adaptively planned HDR-ISBT. Further, due to the nature of a

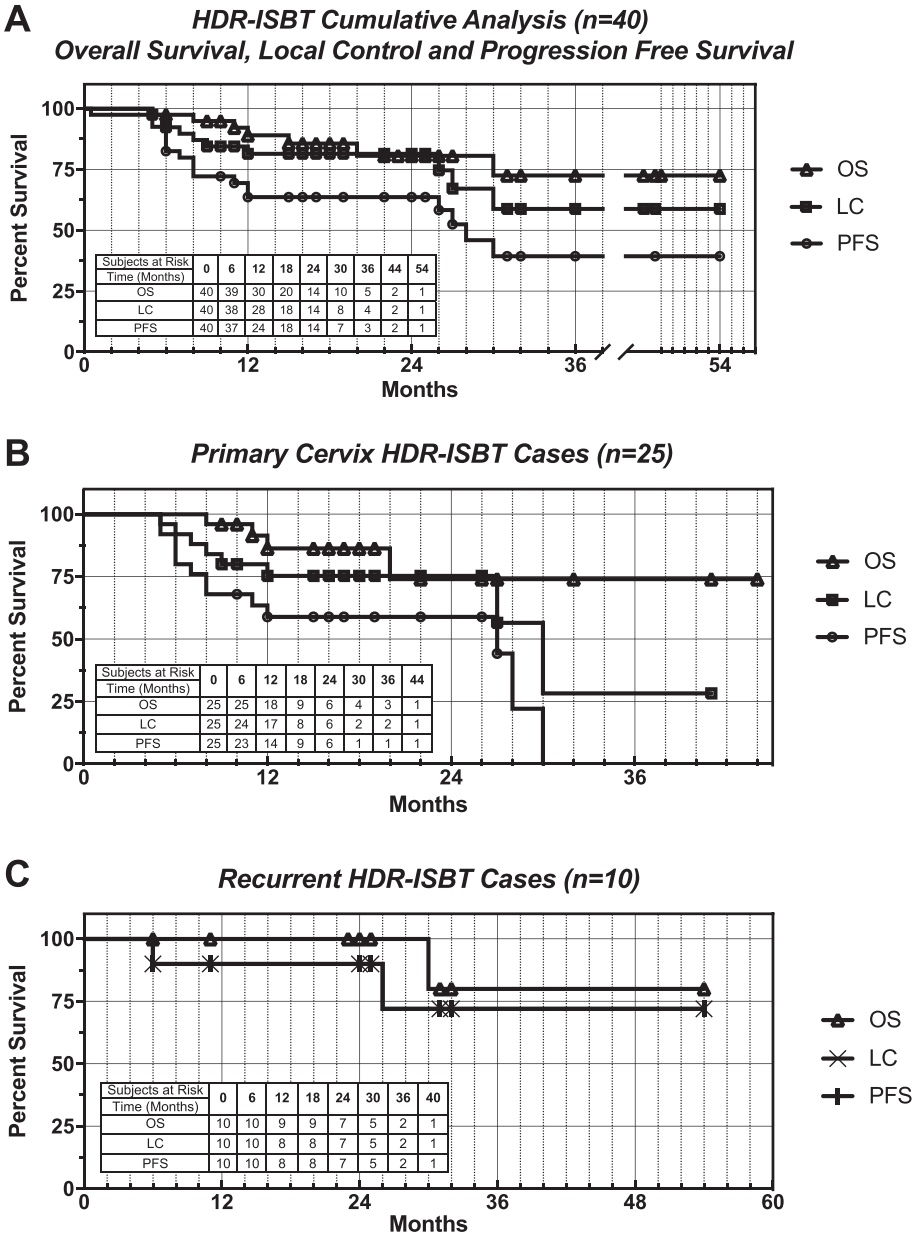

Fig. 3. Overall survival (OS), local control (LC) and progression free survival (PFS) Kaplan-Meier curves for cumulative study population, primary cervix and recurrent cases.

hospital system without financial incentive and with limited OR availability, our HDR-ISBT were all performed in a single three-day hospital admission.

MR is an invaluable tool which complements CT and physical exam and has demonstrated benefits in local control and toxicity when used for BT treatment planning [18,19]. The workload of diagnostic MR scanners at high-volume safety net centers may be at or over capacity and may not be located near the HDR bunker, making MR-guided BT impractical. Rather, we rely on CT-based plans with MR-fusion (cognitive/fixed) and the Syed-Neblett template which we have found to be reliable. We believe that MR fusion remains a viable, cost-effective alternative, when used as a guide for physician contouring, specifically given image-based plans in which treatment volumes are already significantly reduced versus classical point prescriptions. Therefore, while lack of true MR-guidance may lead to larger treatment volumes due to uncertainty, we have not found this to be of significant issue in our practice. Further, we found that the ability to limit 200% of prescribed dose to <10% of the treatment volume (achieved in ~60% of the cases) was a result of having multiple well-placed needles, especially in the inner-ring surrounding the tandem as well as the use of inverse planning objectives for overall plan heterogeneity.

Regarding our fractionation, multiple ISBT implants would be a financial and logistical barrier to care in our patient population and our experience demonstrates that a single implant is safe, effective and ideal for patient satisfaction. Other institutions have also published single admission ISBT data. Wang et al. published a similar study in which patients were treated with a single implant and achieved favorable local control and toxicity; however, they utilized five fractions [20].

Regarding planning, we recognize that over the course of hospital admission, changes exist in patient anatomy secondary to needle displacement, organ motion/deformation and physiologic changes which may lead to plan degradation as reported by Gladwish et al. [21]. Therefore, we acquire a new CT simulation scan and an adaptive plan for every fraction. In our experience with adaptive planning, all patients required at least minor modification from the prior fraction to adjust for changes in rectal anatomy as well as needle movement. For many cases, if the plan was left the same, rectal, sigmoid and even small bowel doses would exceed tolerances based on movement secondary

to gas. The benefit of adaptive planning does come at the cost of physician/physicist time as each fraction/simulation requires a replacement of all virtual needles in the planning system (in theory, they can automatically be transferred, but in practice, due to changes in patient setup, we found this to be less than accurate). Additionally, a new set of contours and a re-evaluation/re-shaping of dose/dwell time from the prior plan are required. However, given large treatment volumes and high doses per fraction, we strongly believe that these additional steps are worthwhile.

While our median OAR DVH parameters (D_{2cc}, $D_{0.1cc}$) were within GEC-ESTRO guidelines, there existed a subset of patients who required exceeding recommended rectal and/or bladder doses to achieve sufficient coverage (tumor abutted or invaded bladder or rectum). Our finding that rectal D_{2cc} > 75 Gy correlated with incidence of grade 3 gastrointestinal toxicity supports GEC-ESTRO dose constraint recommendations and affirms the same relationship found by Mazeron et al. in data analyzed from the EMBRACE study [22]. Their data also found that doses <65 Gy were associated with less frequent and less severe rectal toxicity and likely should be considered when achievable with adequate coverage. Our series again affirms this finding, as a limited number of select patients in whom a rectal D2cc <65 Gy was possible had no rectal toxicities. Overall, our coverage and dose (median V_{100} of 98%, median HR-CTV dose of 85.1 Gy and D_{90} 92 Gy) despite large, bulky tumors was excellent. However, this did come at a cost, as 17% of patients in our cohort developed some grade of radiation proctitis. All patients with symptomatic radiation proctitis at our institution underwent argon plasma coagulation (APC) (typically repeated 2–3 times) by our gastroenterology colleagues and had complete resolution of their symptoms.

BT series are difficult to compare due to the heterogeneity of populations as well as the retrospective nature of most studies. We report an overall local control of approximately 81% at two years. In terms of previously untreated cervical cancer, our two-year local control rate was 75% and somewhat inferior to the 79% found in a systematic review by Mendez et al. [23] where 60% of patients were stage IIIB or higher. However, it is important to consider that our median HR-CTV in this cohort was 71 cm^3 and a quarter of patients were FIGO stage IV secondary to bladder or rectal invasion. For comparison, patients treated in the retro EMBRACE study (multicenter cohort) were stratified according to tumor size: small (<20 cm^3), intermediate (20–30 cm^3) and large (31–70 cm^3) with a significant drop in local control for tumors >30 cm^3 as well as a dose-volume relationship suggesting a need for dose escalation (D_{98} ≥ 95 Gy) in patients with large volume disease [24]. In our study, our local recurrences in the primary setting all had tumors classified as large (>30 cm^3). Clinically, our findings suggest that organ-invasion (specifically bladder or rectum) should not preclude evaluation for aggressive management of bulky, locally advanced cervical cancer with HDR-ISBT boost, specifically with image-based treatment.

Our patients treated in the recurrent setting did exceptionally well with 90% LC and 100% OS at two-years. We attribute this to be the result of careful case selection with our gynecology oncology colleagues as well as the ability of MR to localize recurrence and establish target volumes. In the recurrent setting, this treatment modality for select cases may represent an ideal method of salvage and has been shown to be effective in other series [25,26].

Limitations of our study include the retrospective/observational design, lack of patient-reported toxicity data and sample size. Further, while we report two serious acute complications, less severe, yet important acute toxicities are likely unreported in the current series given the lack of prospectively collected data.

5. Conclusions

Our reported experience supports the use of a condensed, four-fraction regimen of inversely and adaptively planned, CT-based/MR-fused HDR-ISBT which provides safe, effective treatment and excellent tumor coverage for patients with advanced and recurrent disease. Patients with bulky tumors or rectal involvement should be specifically consented regarding the risk of radiation proctitis. Ultimately, while local control is achievable in patients with advanced disease, the rate of distant progression remains high and improvements in systemic control are needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.11.020.

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Disclosure

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