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Clinical Outcomes of Intensity Modulated Proton Therapy (IMPT) Re-Irradiation for Gynecologic Malignancies

Running Title: **IMPT Re-Irradiation Gyn Malignancies**

Ariel E. Pollock, MD[1], Hunter Risher[2], Melanie Berger, MD[2], Dana M. Roque, MD[3], Gautam Rao, MD[3], Elizabeth M. Nichols, MD[4,5], Pranshu Mohindra, MD[4,5]

[1]Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD

[2]University of Maryland School of Medicine, Baltimore, MD

[3]Division of Gynecology Oncology, University of Maryland School of Medicine, Baltimore, MD

[4]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD

[5]Maryland Proton Treatment Center, Baltimore, MD

Corresponding author(s): Pranshu Mohindra MD, MBBS, MMM

22 S. Greene St., Rm GGJ35

Baltimore, MD 21201

Phone : (410) 328-9155

Fax : (410) 328-5279

Email: pranshumohindra@gmail.com

ORCID: 0000-0002-4873-7496

Ariel E. Pollock, MD

22 S. Greene St.

Baltimore, MD 21201

Phone : (410) 328-6080

Fax : (410) 328-5279

Email : ariel.pollock@umm.edu

ORCID : 0000-0001-8838-3365

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Abstract

Purpose: Pelvic re-irradiation (re-RT) for patients with gynecologic cancers remains a challenge due to toxicity concerns. Given the dosimetric advantages of proton therapy, we aimed to assess oncologic and toxicity outcomes of patients with re-RT to the pelvis/abdomen with intensity modulated proton therapy (IMPT) for gynecologic cancers.

Methods and Materials: We performed a retrospective analysis of all gynecologic cancer patients treated at a single institution between 2015-2021 with IMPT re-RT. Patients were included for analysis if the IMPT plan had at least partial overlap with the treated volume of a prior radiation (RT) treatment.

Results: A total of 29 patients were included for analysis, with 30 total courses of re-RT. The majority of patients had previously been treated with conventional fractionation to a median dose of 49.2 Gy (30-61.6 Gy). With a median follow up of 23 months, 1-year local control was 83.5%

and overall survival was 65.7%. Three patients (10%) developed acute and late grade 3 toxicity. 1-year freedom from late grade 3+ toxicity was 96.3%.

Conclusions: This is the first complete analysis of clinical outcomes for re-RT with IMPT for gynecologic malignancies. We demonstrate excellent local control and acceptable acute and late toxicity. IMPT should strongly be considered for treatments requiring re-RT for gynecologic malignancies.

Introduction

The management of de novo gynecologic malignancies varies by stage and disease site however will often include radiation (RT) in the form of external beam radiation therapy (EBRT) and/or brachytherapy. While patients with early-stage disease have favorable outcomes, patients with locally advanced disease are at higher risk of locoregional and distant recurrence. Distant failures have historically been managed with systemic treatments, with an emerging role for metastasis-directed ablative therapy, particularly in the setting of oligorecurrent disease[1]. Management of patients with locoregional recurrences is particularly challenging especially for gynecologic cancer patients who had history of prior abdomino-pelvic RT. Local failures are often associated with pain, bleeding, lymphedema, or fistula. Curative surgical therapy requires pelvic exenteration, which can cause significant detriment in quality of life and often deters patients from proceeding with treatment[2,3]. Stereotactic body radiation therapy (SBRT) and high-dose rate brachytherapy (HDR) are the most common modalities used for gynecologic re-irradiation (re-RT) as the dose fall-off allows sparing of critical organs at risk (OAR), however these modalities can be limited by the size and anatomical location of the recurrence.

Additionally, brachytherapy monotherapy is unable to deliver a curative dose to gross disease, resulting in suboptimal local control[4].

Proton beam therapy (PBT), and in particular intensity-modulated proton therapy (IMPT) offers advantages due to its unique physical properties and characteristic Bragg-peak, which allows for better sparing of OARs. Unlike with SBRT or brachytherapy, there are not tumor size or location limitations with IMPT and it is more likely that curative dose may be prescribed. The use of re-RT with IMPT has been studied in patients with rectal cancer, with promising outcomes[5]. There are limited data on the clinical use of re-RT with IMPT for patients with recurrent gynecologic cancers. We present the first complete analysis of re-RT in gynecological cancer patients using IMPT.

Materials and Methods

Patient Selection

An IRB-approved (HP-00084437) retrospective analysis was completed of patients with either recurrent gynecologic cancer or de novo gynecologic cancer treated with IMPT in a field of prior abdomino-pelvic RT at a single institution between 2015 and 2021. Patient, tumor, and treatment characteristics were collected.

Treatment Planning

The majority of patients underwent computed tomography (CT) simulation in the supine position with vac-lock immobilization. Most were also scanned with both a comfortably full and empty bladder for volume generation, but treated with a comfortably full bladder. Post-hysterectomy patients had Q-tip placed at vaginal cuff for target delineation. Use of intravenous and/or oral contrast or planning magnetic resonance (MRI) scan were performed at the discretion

of the treating physician. All contours were generated on a non-contrast and full bladder scan when appropriate. Gross tumor volume (GTV) and clinical target volume (CTV) varied for individual cases. IMPT plans were created in either the Eclipse treatment planning system (TPS) (Varian Medical Systems, CA), or Raystation TPS (RaySearch Laboratories, Stockholm, Sweden). Plans were robustly optimized to ensure adequate target coverage in 13 unique scenarios, accounting for 0.5cm change in 6 cardinal directions as well as 3.5% range uncertainty. As treatment planning evolved over time, in order to account for density change associated with change in bowel position or filling, two special density-override (DO) scans were generated. Loops of bowel were considered to have the density of air in one scan and the density of muscle in the other. Robust optimization was performed on these two DO scans in additional to the nominal, "un-processed" scan as above. Quality assurance CT images were obtained at least once during treatment, with schedule and frequency up to the discretion of the treating provider. Prior RT plan reports and DICOM data were reviewed when available. Patients received HDR brachytherapy after re-RT or concurrent hyperthermia with re-RT as clinically indicated and per treating physician. The re-RT dose was at the discretion of the treating physician, typically accounting for location and volume of target, proximity to critical OARs, time since prior RT, prior RT dose, feasibility of hyperfractionation for reRT plan for brachytherapy, overall treatment intent and patient performance status. For patients receiving re-RT with IMPT alone, with conventional fractionation or hyperfractionation, target dose was generally planned for 50-60 Gy, while target IMPT re-RT dose was 30-45 Gy for those planned for brachytherapy boost. EQD2 (alpha/beta 10) was calculated using RT and brachy doses when available. Hyperthermia included either superficial hyperthermia (1 patient with inguinal nodal recurrence) or locoregional hyperthermia (2 patients). Hyperthermia was administered twice weekly typically within 1 hour of completion of EBRT, with a goal of achieving therapeutic temperature

of 40°C for 45-60 minutes. Superficial hyperthermia was administered via the BSD500 and locoregional hyperthermia was administered via the BSD2000 hyperthermia unit.

Toxicity Assessment

Patients were evaluated weekly during RT and every several months after completion of RT. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Statistical Analysis

Efficacy outcomes including local control (LC), freedom from progression (FFP), and overall survival (OS) were estimated using the Kaplan-Meier (KM) method. These were calculated from date of RT completion. Patients underwent regular examination and serial imaging (CT, PET-CT and/or MRI) as clinically appropriate for response assessment. Patients who did not experience progression were censored at time of last follow up. All statistical analysis was performed using SPSS version 28.

Results

A total of 29 patients received a course of re-RT while 1 patient received two courses of re-RT during the study period. Median follow up was estimated to be 23 months (95% CI 17.1-28.9 months) by the inverse Kaplan-Meier method. Patient and disease characteristics are summarized in Table 1. Median age at time of re-RT was 65 years (range, 34-95 years) and median time between courses of RT was 24 months (range, 7-468 months). Twenty-five patients were treated for recurrent gynecologic cancers while the remaining 4 patients had de novo gynecologic cancer with prior pelvic RT for Hodgkin's lymphoma (1 patient) and anal cancer (3 patients). Most patients (n=15, 52%) were treated for recurrent endometrial cancer.

All patients had at least partial overlap between RT fields, defined by overlap of the 50% isodose lines (IDL), and 15 patients (52%) had complete target overlap. Most patients (n=24, 80%) had prior RT plan reports available for review while prior RT DICOM data sets were available for only 11 patients (37%). For the 6 patients who did not have prior RT reports available for review, description of target volumes in outside records confirmed RT field overlap. Fourteen patients (48%) had brachytherapy during their prior course of RT. Prior RT and re-RT treatment characteristics are outlined in Table 2, with additional parameters stratified by target overlap versus at least 50% IDL overlap in supplemental table 1. Median prior RT dose was 45.0 Gy (range, 30-59.4 Gy; Interquartile range (IQR) 5.4 Gy), with a median EQD2 (alpha/beta 10) 49.6 Gy (range, 32.5-76.6 Gy; IQR 15.4 Gy) and median prior RT BED10 54.2 Gy (range, 39-72.1 Gy; IQR 6.37 Gy). Patients were previously treated with conventional fractionation (n=24, 83%), 2 patients (7%) with prior SBRT or hypofractionation, 3 patients (10%) with brachytherapy alone, and 1 patient (3%) with prior palliative RT.

Median re-RT dose was 49.2 Gy (range, 30-61.6 Gy; IQR 11 Gy), with a median EQD2 (alpha/beta 10) 49.8 Gy (range, 33.6-62 Gy; IQR 10.1 Gy) and median BED10 59.7 Gy (range, 40.3-79.3 Gy; IQR 12.1 Gy). For those who did not receive brachytherapy at time of re-RT, median sum of prior RT and re-RT EQD2 dose (alpha/beta 10) was 102.7 Gy (71.6-135.6 Gy; IQR 14.9 Gy). At time of re-RT, the majority of patients were treated with conventional fractionation (n=20, 67%), while 8 patients (26%) were treated with BID hyperfractionation and 2 patients (7%) were treated with IMPT-SBRT. At time of re-RT, 6 patients (20%) received brachytherapy boost; 2 patients treated with multi-channel cylinder, 3 patients with interstitial template-based, and 1 patient with tandem and ring. For the 6 patients that did receive brachytherapy at time of re-RT, median sum of prior RT and re-RT EQD2 dose (alpha/beta 10)

was 123.7 Gy (71.4-143.2 Gy; IQR 12.3 Gy). IMPT RT treatment plan parameters are outlined in Table 3.

The majority of the patients were simulated in the supine position (n=26, 87%) as described earlier. Most patients did not receive elective nodal irradiation (n=19, 63%) however median CTV size was 387.8 cc (range, 10.1-3353.1 cc). The median GTV size was 79.3 cc (range, 7.6-955.6 cc). The majority of the plans included at least 3 beams without a range shifter, using multi-field optimization. Ten patients required a re-plan based on scheduled QACT and 1 patient required 2 replans during their treatment course.

Treatment compliance was very good with 83% of patients completing all planned treatments. Five patients (17%) had an interruption of more than 1 day in their re-RT course with median time of 5 days. One patient had a 6 day interruption due to need for replanning, 1 patient was unable to tolerate time on the table leading to 3 days of incomplete treatments, and 3 patients missed for non-compliance/other reasons. Three patients (10%) had early termination of their RT course, all by 1 fraction only, due to proton machine down time/other. One patient (3%) terminated their RT course at fraction 51 of planned 58 fractions due to skin toxicity.

Treatment was well tolerated, with only three patients (10%) with acute grade 3 toxicity, including 1 patient with grade 3 anemia and grade 3 diarrhea, 1 patient with grade 3 anemia, and 1 patients with grade 3 radiation dermatitis. There were no acute grade 4 or grade 5 toxicities (Table 4). Three patients (10%) had late grade 3 toxicity events, as in Table 3. Events included grade 3 rectal hemorrhage, grade 3 vulvar necrosis, and grade 3 sacral ulcer; there were no late grade 4 or 5 toxicity events (Table 5). 1-year freedom from late grade 3+ toxicity was 96.3% (95% CI 89.3-100%) and 2-year freedom from late grade 3+ toxicity was 82.5% (95% CI 64.7-100%) (Figure 1). By both univariate and multivariate Cox proportional hazards model, there

were not any significant predictors for late grade 3+ toxicity. There was no difference in acute or late toxicity between the group of patients who had target overlap versus the group with at least 50% IDL overlap. There were no secondary malignancies diagnosed during the follow-up period.

The 1-year local control, locoregional control and distant control were 83.5% (95% CI 68.6-98.4%), 65.7% (95% CI 47.5-83.9%), and 65.2% (95% CI 46.4-84.0%) respectively (Figure 2). Median freedom from local progression was not reached, while median freedom from locoregional progression and from distant progression were 31 months (95% CI 18.4-43.6 months) and 29 months (95% CI 18.2-39.8 months) respectively. The 1-year overall survival and 1-year progression free survival were 65.7% (95% CI 48.5-82.9%) and 38.2% (95% CI 20.6-55.8%) respectively (Figure 2). On univariate analysis, RT interruption was significantly associated with progression free survival (hazard ratio [HR]: 8.7; 95% CI 2.4-31; $p<0.001$) and overall survival (HR: 3.9; 95% CI 1.2-13.1; $p=0.027$), but not with local control, locoregional control or distant control. On univariate analysis, there were no additional variables associated with local control, locoregional control, distant control, progression free survival, or overall survival. Target overlap was not associated with any of these oncologic endpoints. Treatment for the 18 patients who progressed or recurred after re-RT included systemic therapy (n=11, 61%), palliative RT (n=1, 6%), no treatment/unknown (n=6, 33%). Systemic therapy included chemotherapy, aromatase inhibitor, immunotherapy, PARP inhibitor, and targeted therapy on a clinical trial.

Discussion

We present a series of 29 patients who underwent 30 courses of re-RT with IMPT for de novo or recurrent gynecologic malignancy in the setting of prior abdomino-pelvic RT. This is the largest series of patients treated with re-RT with IMPT for gynecologic cancer and the first full

report of analysis with IMPT. The existing data for re-RT with proton therapy includes two case reports and an abstract on the Proton Collaborative Group (PCG) registry experience that has not been published as a full report. One case report describes a a 58-year old woman who had been treated 27 years earlier for cervical cancer with 39.6 Gy to the whole pelvis, 16 Gy parametrial boost and 40 Gy LDR intracavitary implant. She subsequently developed squamous cell carcinoma of the vagina and was treated with IMPT re-RT. Re-RT dose was not documented in the report[6]. Another example includes an 80-year old woman who had previously been treated for early stage endometrial cancer with 45 Gy to the pelvis and 15 Gy in 3 fractions vaginal cuff brachytherapy, who 11 years later developed a primary vaginal squamous cell carcinoma and is treated with IMPT 39 Gy in 13 fractions with a complete radiologic response at 1 year[7]. Finally, an abstract on the PCG experience included a total of 83 patients treated with proton therapy, 25.3% of whom were reirradiated with proton therapy using a mix of passive scatter and IMPT techniques, with only 4 of these re-RT patients having grade 3-4 adverse events[8].

While the published literature lacks any series for re-RT with IMPT for gynecologic cancers, there are data suggesting the feasibility and efficacy of pelvic re-RT with proton therapy for rectal cancer. Koroulakis et al published the largest series of 28 patients treated for either de novo or recurrent rectal cancer with re-RT to a median dose of 44 Gy BID after a prior median 54 Gy. Treatment was fairly well tolerated with an estimated 13.3% late grade 3+ toxicity at 1 year, including 1 patent who developed a late grade 5 toxicity at 26 months post re-RT. Another series by Moningi et al. included 15 patients who received a median dose of 39 Gy BID after prior median 50.4 Gy. They reported only 1 acute grade 3 and 2 late grade 3 events[9]. A prospective study by Berman et al[10]. included 7 patients treated for recurrent rectal cancer and treated with a median re-RT dose of 61.2 Gy and median total sum dose of 109.8 Gy. With a

median follow up of 19.4 months, they reported 3 grade 3 events, all of which resolved, and 6 patients with initial PET response. There are however many differences between re-RT for gynecologic cancer and rectal cancer. The majority of patients with a recurrent rectal cancer would have been initially treated with neoadjuvant chemoradiation followed by total mesorectal excision, and in the recurrent setting may also be treated in the neoadjuvant setting. As a result, a large portion of the bowel and surrounding tissue that had been irradiated would have been resected prior to the course of reirradiation. On the other hand, the treatment paradigm for gynecologic malignancies tends to be definitive chemoradiation or adjuvant chemoradiation after total hysterectomy, leaving the previously irradiated bowel and surrounding tissue still in the reirradiation field. In our series, 86% of patients were treated for recurrent gynecologic cancer, while 14% had prior in-field RT for either Hodgkin lymphoma or anal cancer. In both settings, patients were treated definitively without surgery to a similar total dose as a typical gynecological cancer.

In the setting of any reirradiation, there are expected heterogeneity related to time since prior RT, prior RT dose, overall treatment intent and patient performance status. Additionally, in gynecologic cancers, factors to consider include previous use of or current plan for brachytherapy, likely day to day positional variability in critical OARs like small bowel and degree of overlap of re-RT volume with rectum/bladder. Noting the safety reported in prior rectal cancer re-RT series, we typically target a cumulative small bowel Dmax of 80-90 Gy and cumulative rectum Dmax of 90-100 Gy, while allowing higher doses in favorable settings of longer time to re-RT, smaller volume of overlap with small bowel and mobile loop of small bowel. There are limited recommendations for OAR constraints in the setting of re-RT, with some practices allowing the constraint to be 50% more in the re-RT setting than in in the de novo

setting[11]. Currently, our practice for patients receiving re-RT with IMPT alone is a target dose or 50-60 Gy with conventional or hyperfractionation, while an IMPT dose or 30-45Gy for those planned for brachytherapy boost. Further, we add superficial, deep, or interstitial hyperthermia as feasible, especially for patients at the lower end of the dose spectrum wherein we feel limited in being able to deliver high doses. Superficial hyperthermia is useful for patients with inguinal or vulvar recurrence. Deep hyperthermia is typically feasible for low pelvic tumors wherein a thermometer can be placed in rectum or bladder, whereas interstitial hyperthermia is used for patients planned for interstitial brachytherapy.

Despite the technical difficulties of re-RT in the pelvis and abdomen, in this series we demonstrate safety of re-RT IMPT with a low rate of acute and late toxicity. While not reported in this analysis, previous reports of IMPT in gynecological malignancies have demonstrated significant reduction in excess irradiation of bowel, marrow and bladder.[12,13] Three patients completed their treatment course 1 fraction early, for reasons unrelated to toxicity, while only 1 patient's course was terminated early due to skin toxicity. This rate is similar to that seen in the rectal re-RT series where 3 of 28 patients did not complete treatment, with only 1 due to toxicity[5]. A total of 2 patients developed acute grade 3 toxicity including anemia which was likely related to concurrent chemotherapy, and three patients developed late grade 3 toxicity events. Although a different patient population, these rates of acute and late grade 3 toxicities are comparable to those seen in re-RT for rectal cancer as discussed earlier. There were no acute or late grade 4/5 events in our series. Given the small patient population and low rate of adverse events, we are unable to correlate toxicity with reirradiation dose. Additionally, less than half of patient had prior DICOM images available at time of re-RT, making it challenging to assume the cumulative dose to OARs, including the D2cc for patients who received brachytherapy.

A remarkable outcome from this analysis of re-RT with IMPT is the excellent local control and overall survival seen in an otherwise high-risk patient population with very limited treatment options and significant quality of life implication from progressive local disease. This may be in part due to the large proportion of endometrial cancer patients, which tend to behave more favorably in de novo settings. However, in the recurrent settings, outcomes for these patients can still be challenging. Our patient population and the prior treatments they received is reflective of the gynecologic cancer patient at large and demonstrates that recurrences are varied with respect to histology, anatomic location, size, and how they had previously been treated.

At this time, for patients with recurrences in a previously irradiated field, options include brachytherapy, photon SBRT, or palliative photon EBRT. A literature review of re-RT series included 18-114 patients treated with brachytherapy with a median follow up of 1-4.7 years and a local control ranging from 44% to 77% at different time points[14]. Many of these patients received EBRT prior to brachytherapy. The same review includes SBRT studies with a range of 5-85 patients, a median follow up of 11-24 months and a local control anywhere between 51% and 82.5% at various time points. For recurrent endometrial cancer, local control after HDR ranges between 53-66% with minimal grade 3 toxicities. For cervical cancer, local control ranges between 44-51.3% with 16.6-25% grade 3+ toxicity. There is a large range in the local control likely due to range in size of disease and dose that was able to be prescribed to the GTV/CTV/HRCTV. In our series, there was similarly a large range in the volume of gross disease and microscopic/elective disease being treated. Median GTV was 79.3 cc, ranging up to 955.6cc. This volume of disease would be inappropriate for SBRT therefore making IMPT a promising treatment modality. Additionally for the 37% of patients who received elective nodal irradiation for their high risk of pelvic or para-aortic microscopic disease, it would have been

challenging to offer re-RT with another treatment modality. Prior re-RT series with EBRT, brachytherapy, or SBRT have demonstrated 1-year local control ranging from 51%-71.5% and 1-year overall survival ranging between 46% and 82%[14]; of note several of the patients in these series had not been previously irradiated. During the follow up period in our series, median freedom from local progression was not reached. We have promising results with 1-year local control of 83.5% and 1-year overall survival of 65.7%.

Due to the limited data on this topic, there is a lack of consensus recommendations on treatment options with re-RT. The American Brachytherapy Society (ABS) attempted to provide working group recommendations for re-RT for gynecologic cancers, however ultimately noting that there is inadequate evidence to provide consensus recommendations for re-RT and noting that emerging treatment options may include proton or carbon ions[14]. Limitations to this study are related to its retrospective nature, small sample size, and limited follow up.

Conclusion

We present the first complete series of patients treated with IMPT re-RT for gynecologic cancer, offering a promising alternative to brachytherapy or SBRT. We demonstrate good local control and overall survival despite the high risk patient population, with acceptable toxicity profile. Given that a future prospective trial in re-RT settings is expectedly challenging due to the typical heterogeneous patient population and wide range of prior treatments rendered for patients with recurrent gynecologic malignancies, based on the results of our analysis we propose that IMPT re-RT should strongly be considered for patients with recurrent gynecologic cancers. As more patients are treated with IMPT re-RT, it will be important to establish a relationship between re-RT dose and local control and toxicity outcomes.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Figure Captions

Figure 1. Freedom from late grade 3+ toxicity

A. Freedom from late grade 3+ toxicity measured from end of re-RT

Figure 2. Oncologic Outcomes

A. Freedom from local progression measured from end of re-RT B. Freedom from locoregional progression measured from end of re-RT C. Progression free survival measured from end of re-RT D. Overall survival measured from end of re-RT

Table 1. Patient and Disease Characteristics

Characteristics	**n=29 (%)**
Age, y, median (range)	65 (34-95)
Race	
White	17 (59)
Black	9 (31)
Other	3 (10)
Follow-up, mo, median (range)	17 (1-34)
Time between RT courses, mo, median (range)	24 (7-468)
Recurrent or de novo cancer	
Recurrent gyn cancer	25 (86)
De novo gyn cancer	4 (14)
Disease Site	

Endometrial	15 (52)
Cervical	7 (24)
Other (vaginal, vulvar, ovarian)	7 (24)

Table 2. Prior RT and reRT Treatment Characteristics

Characteristics	**n=30 (%)**
Prior RT dose, Gy, median (range)	45.0 (30 – 59.4)
Prior RT fractionation	
Conventional	24 (83)
SBRT/hypofractionation	2 (7)
Brachytherapy alone	3 (10)
Palliative EBRT	1 (3)
ReRT dose, Gy, median (range)	49.2 (30 – 61.6)
ReRT IMPT fractionation	
Conventional	20 (67)
Hyperfractionation	8 (26)
IMPT-SBRT	2 (7)
ReRT Setting	
Definitive RT	27 (90)
Adjuvant RT	3 (10)
Brachytherapy boost at ReRT	
Yes	6 (20)
No	24 (80)
Concurrent hyperthermia at ReRT	
Yes	3 (10)
No	27 (90)
Concurrent chemotherapy at ReRT	
Yes	13 (43)
No	17 (57)
Brachytherapy boost at ReRT	
Yes	6 (20)
No	24 (80)
Brachytherapy Modality	
Cylinder	2 (33)
Tandem & Ring	1 (17)
Interstitial Template	3 (50)

Table 3. RT Planning Parameters

RT plan parameter	**n=30 (%)**
CT simulation position	
Supine	26 (87)

Prone	4 (13)
GTV volume, cc, median (range)	79.3 (7.64-955.59)
CTV volume, cc, median (range)	387.83 (10.12-3353.1)
Elective nodal coverage	
Yes	11 (37)
No	19 (63)
ReRT Field	
Pelvic field only	22 (73)
Pelvic + para-aortic	5 (17)
Para-aortic field only	3 (10)
Optimization	
Single-field	9 (30)
Multi-field	17 (57)
Mixed	4 (13)
Number of beams	
2	11 (37)
3	12 (40)
4	5 (17)
5	2 (6)
Range Shifter	
None	22 (74)
2cm	1 (3)
3cm	2 (6)
5cm	5 (17)
Beam arrangements	
Laterals only	4 (14)
Anteriorly arranged beams	5 (17)
Posteriorly arranged beams	9 (30)
Laterals and only posteriorly arranged beams	3 (10)
Laterals and only anteriorly arranged beams	1 (3)
Laterals and both anterior/posterior beams	2 (6)
Anterior and posterior beams without laterals	6 (20)

Table 4. Acute and Late toxicities graded by Common Terminology Criteria for Adverse Events, version 5.0

	Acute Toxicities		**Late Toxicities**	
Grade	**2, n (%)**	**3, n (%)**	**2, n (%)**	**2, n (%)**
Genitourinary	1 (3)	0	2 (7)	0
Gastrointestinal	2 (7)	1 (3)	3 (10)	1 (3)
Hematologic	2 (7)	2 (7)	0	0
Skin	5 (17)	1 (3)	0	2 (7)

There were no acute or late grade 4 or 5 toxicities.

Acute toxicity: During treatment or within 3 months

Late toxicity: After 3 months

Figure 1. Freedom from late grade 3+ toxicity

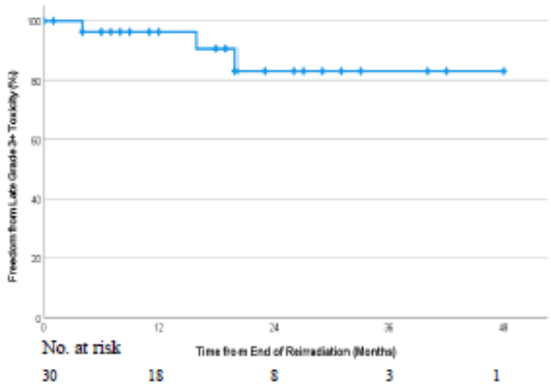

Figure 1. Freedom from late grade 3+ toxicity measured from end of re-RT

Figure 2. Oncologic Outcomes

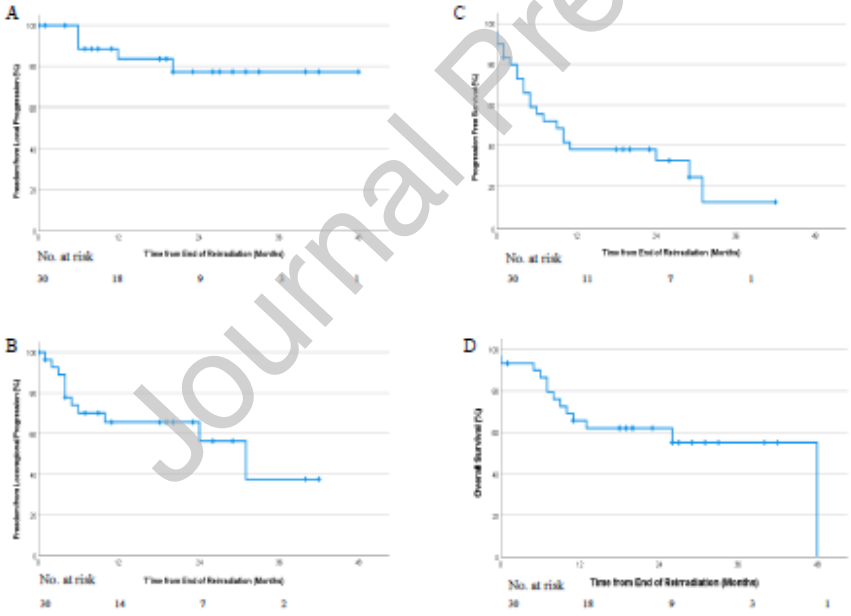

Figure 2: A. Freedom from local progression measured from end of re-RT B. Freedom from locoregional progression measured from end of re-RT C. Progression free survival measured from end of re-RT D. Overall survival measured from end of re-RT