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Source: Radiation Research, 194(6) : 724-736

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00038.1

RADIATION RESEARCH **194**, 724–736 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00038.1

Spatially Fractionated Radiation Therapy Using Lattice Radiation in Far-advanced Bulky Cervical Cancer: A Clinical and Molecular Imaging and Outcome Study

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Amendola, B. E., Perez, N. C., Mayr, N. A., Wu, X. and Amendola, M. Spatially Fractionated Radiation Therapy Using Lattice Radiation in Far-advanced Bulky Cervical Cancer: A Clinical and Molecular Imaging and Outcome Study. *Radiat. Res.* 194, 724–736 (2020).

Spatially fractionated radiation therapy (SFRT) has shown promise in generating high tumor response and local control in the treatment of various palliative and locally advanced bulky tumors. SFRT has not yet been studied systematically in cancer of the cervix. Here we report the first series of patients receiving SFRT for advanced/bulky cervical cancer. Ten patients with far-advanced bulky cervical cancer, stage IIIB–IVA (seven squamous cell and three adeno/adenosquamous carcinomas) received lattice radiation therapy (LRT), a variant of SFRT. The LRT regimen consisted of a dose of 24 Gy in three fractions, given to an average of five high-dose spheres within the gross tumor volume (GTV). The dose in the peripheral GTV was limited to 9 Gy in three fractions, using the volumetric modulated arc therapy (VMAT) technique. LRT was followed subsequently by conventionally fractionated external beam irradiation to 44.28 Gy (range: 39.60–45.00 Gy in 1.8 Gy fractions). All patients received concurrent cisplatin chemotherapy. Tumor response was assessed clinically, by morphological imaging (CT, MRI) and ^{18}FDG PET/CT. Tumor control and survival rates were estimated using Kaplan-Meier analysis. All patients had local control at a median follow-up of 16 months (1–77). The two-year disease-specific survival rate was 53.3%. All cancer deaths were due to metastatic failure with local control maintained. Among the three patients who died of disease, all had adeno- or adenosquamous carcinoma histology, and no deaths from disease occurred among the patients with squamous cell carcinoma ($P = 0.010$). There were no grade $\geq$3 short-term or long-term treatment-related complications. Intra-treatment morphological tumor regression was highly variable (mean: 54%, range: 6–91%). After therapy, the complete metabolic response was 88.9% (8/9), and one patient out of the nine patients with post-treatment PET-CT had partial response (11.1%). Our preliminary data suggest that LRT-based SFRT is well tolerated in patients with far-advanced bulky cervical cancer and results in favorable tumor responses and high local control. These observations confirm prior reports of favorable tumor control and toxicity outcomes with SFRT in other advanced/bulky malignancies. Our findings are corroborated by high molecular-imaging-based tumor response. These encouraging hypothesis-generating results require cautious interpretation and confirmation with larger patient cohorts, preferably through a multi-institutional controlled randomized clinical trial.

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INTRODUCTION

Radiation therapy options and treatment outcome in advanced cervical cancer, a disease with major worldwide prevalence, remain a profound challenge (*1*). While many improvements have been made through refinements in standard-of-care management, including more conformal external radiation options, the addition of concurrent chemotherapy to radiotherapy, and advances in brachytherapy, the outcome for far-advanced bulky tumors is frequently poor. In these patients, who often have voluminous tumors and/or severe anatomic distortions and for which radiotherapy options are limited, brachytherapy is frequently not feasible, leaving few options for dose escalation to the bulky tumor mass, and the toxicity risk to nearby dose-limiting normal tissue is high.

Spatially fractionated radiation therapy (SFRT), which applies a *non*-uniform instead of the commonly employed uniform dose pattern to the tumor, has shown promise in improving local tumor control while minimizing toxicity in various bulky advanced malignancies (*2–5*). Foundational experience with GRID-based SFRT has long demonstrated unusually drastic and rapid symptomatic responses and favorable local control in palliative treatment for bulky metastatic tumors (*2–4*). More recent experience in primary tumors of far-advanced or bulky stages showed similarly high symptom response and local control rates as well as early evidence of long-term survival in a substantial proportion of patients (*5–7*). These profound tumoricidal effects of SFRT are thought to be related to the combination of a highly inhomogeneous dose distribution with interstitial

TABLE 1
Patient Characteristics

Patient no.	Age (years)	Stage	Histology	Lymph node involvement	Surgery	Local control	Metastases	Follow-up (months)	Status
1	74	IIIB	SCC	Negative	Adjuvant hysterectomy	CR	No	77	NED
2	51	$IIIC_2$	Adeno	Pelvic + paraaortic	Adjuvant hysterectomy	CR	Bone, lymph nodes	17	DOD
3	60	$IIIC_1$	SCC	Pelvic	Adjuvant hysterectomy	CR	No	55	NED
4	61	$IIIC_1$	SCC	Pelvic	Adjuvant hysterectomy	CR	No	42	NED
5	5	IVA	SCC and adeno	Pelvic	No	PR	Liver, lung, disseminated disease	1	DOD
6	76	$IIIC_1$	SCC and adeno	Pelvic	No	CR	Abdomen, bowel, lymph nodes, neck	19	DOD
7	90	IVA	SCC	Pelvic	No	CR	No	13	DOID
8	82	IIIB	SCC	Negative	SBRT boost	CR	No	15	NED
9	59	IVA	SCC	Pelvic	Conventional radiotherapy boost	CR	No	11	NED
10	44	IVA	SCC	Pelvic	No (pending adjuvant hysterectomy)	CR	No	4	NED

Notes. All patients received lattice SFRT (24 Gy in three fractions, see Table 2) followed by EBRT. All patients had cisplatin chemotherapy (not shown in table). SCC = squamous cell carcinoma; adeno = adenocarcinoma; CR = complete response; PR = partial response; NED = alive with no evidence of disease; DOD = dead of cervical cancer; DOID = dead of intercurrent (non-cancer) disease.

high-dose-rate-brachytherapy-like dose peaks and intra-fraction modulation with nonuniform doses across both space and time (*5*). In addition, the potential inherent advantage of high-dose ablative stereotactic body radiation therapy (SBRT)-like doses in the SFRT peak dose regions are postulated to promote bystander and abscopal effects that enhance tumor response (*8, 9*).

While three large SFRT series with a total of over 150 palliatively treated patients and far-advanced primary tumors have been published (*2–5*), there is less experience in SFRT for disease-specific patient cohorts. Smaller published pilot studies in head and neck (*6, 10*), lung cancer (*11*), melanoma (*12*) and sarcoma (*13, 14*) have shown promising local control and survival outcomes that corroborate the findings of the initial multi-disease palliative and advanced-stage cohorts (*2–5*).

However, there has been no published series of SFRT outcomes in cancer of the cervix, and there is minimal experience in the literature with SFRT in this disease. We have previously shown rapid tumor response with complete pathological response of a far-advanced bulky tumor in the only published case report (to our knowledge) of SFRT in cervical cancer (*15*).

In view of the current paucity of data, the systematic evaluation of treatment regimens, tumor control and toxicity outcomes in individual malignancies is an unmet need.

Furthermore, molecular imaging, an important response assessment and outcome predictor in many malignancies, has not been studied in SFRT-treated patients. Considering the postulated biological mechanisms underpinning SFRT, functional biologic/molecular imaging before and after SFRT may hold important information for our understanding of tumor response properties in SFRT.

The purpose of this research was to study tumor control and toxicity outcomes of SFRT and report on the first cohort of cervical cancer patients to receive SFRT. Specifically, we evaluated local pelvic tumor control, regional (nodal) control, metastatic rate, disease-specific and overall survival, molecular imaging-based tumor response, and time/dose criteria, in a cohort of patients treated with a consistent regimen of SFRT combined with conventional radiation for far-advanced bulky cervical cancer.

MATERIALS AND METHODS

Patient Population

In this work, 10 consecutive patients with bulky, far-advanced stage IIIB–IVA cancer of the cervix were studied. The patients' tumors were classified as far-advanced if they were either voluminous (>7 cm diameter), had severe anatomical distortion for which brachytherapy was not feasible, or both. Patients were treated from January 2013 to April 2019 with SFRT, followed by conventionally fractionated radiation therapy. This retrospective study was approved by the Institutional Review Board. Pre-therapy evaluations and staging were performed according to International Federation of Gynecology and Obstetrics (FIGO, version 2018) guidelines and included history and physical examination, pelvic examination, cervical biopsy, complete blood count and serum chemistries, chest, abdominal and pelvic CT, MRI when clinically indicated and ^{18}FDG PET/CT. Seven patients had squamous cell carcinoma, two had adenosquamous carcinoma and one had adenocarcinoma. Six patients had stage III and four had stage IVA disease. Seven patients (7 of 10) had lymph node involvement in the pelvic nodes and another patient in both pelvic and paraaortic nodes. Patient characteristics and treatment modalities are presented in Table 1.

Patient Treatment

Lattice SFRT. Lattice radiation therapy (LRT), a variant of SFRT, was used for this patient cohort, and has been described elsewhere (*11, 15–17*). The GTV consisted of the gross cervical tumor volume, defined by examination and based on imaging from MRI and PET-CT. Two sets of images were acquired to contour the GTV with full and empty bladder to create an internal target volume (ITV). PTV was obtained from ITV with 3–5 mm expansion.

For LRT, multiple three-dimensional (3D) spherical high-dose regions (''vertices'') were created within the ITV, resulting in the vertex tumor volume (VTV) (Fig. 1). A radiation dose of 24 Gy in three fractions was prescribed to the VTV, and 9 Gy in three fractions was prescribed to the periphery of the PTV.

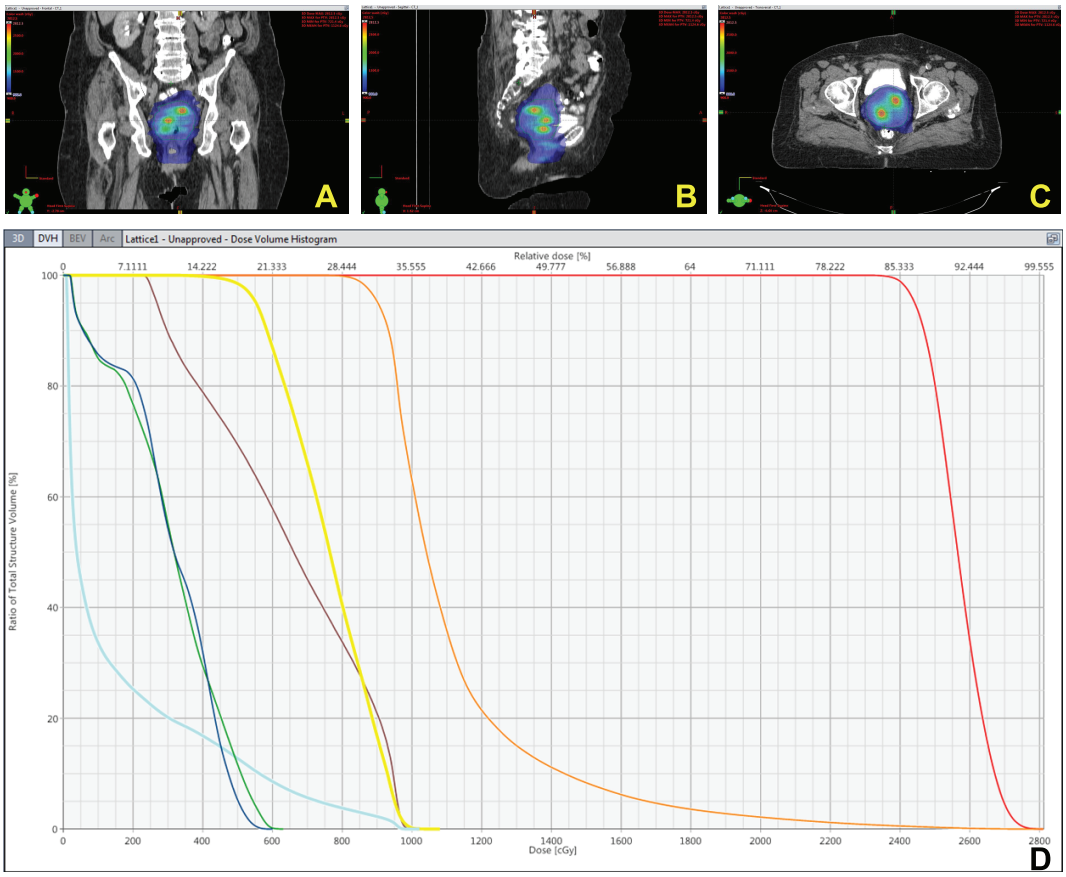

FIG. 1. LRT delivery and response in a patient with far-advanced cervical cancer. The patient is a 74-year-old woman with FIGO stage IIIB squamous cell carcinoma of the cervix without lymph node involvement with an initial tumor volume of 272.2 cm^3. Panels A–C: Coronal, sagittal and axial views of the planning CT showing the dose distribution of the LRT plan delivering 24 Gy in 3 fractions. The GTV is contoured in green, and the VTV in red. Wide dose heterogeneity is achieved within the target. The VTV received 24 Gy (yellow color wash), while the dose at the periphery of the tumor and PTV was reduced to 9 Gy (blue color wash). Panel D: The dose volume histogram for the 3 LRT fractions demonstrates that more than 95% of the VTV (red) received 24 Gy and the PTV (orange) received 9 Gy in three fractions, respectively. The V_{9Gy} of the small bowel (pale blue) is less than 50 cm^3 and the maximum small bowel dose is 10.2 Gy in three fractions (EQD2 13.06 Gy). The maximum dose to the rectum (brown) is 10.2 Gy in three fractions (EQD2 13.06 Gy). The maximum dose to the bladder (yellow) is 10.8 Gy in three fractions (EQD2 14.26 Gy). The femoral (dark blue, dark green) head received a maximum dose of 2 Gy per fraction.

The vertices were first distributed evenly throughout the GTV and further adjusted to reduce the dose at the periphery of the tumor to 9 Gy in three fractions, and to meet the normal tissue constraints (Fig. 1). The number of vertices ranged from 2 to 11 (mean: 5), based on the size and shape of the tumor and proximity of normal tissues. The proportion of the VTV, which received the vertex dose of 24 Gy, ranged from 0.6 to 2.0% (mean: 1.3%) of the total GTV. The volume of the VTV ranged from 0.8 to 4.8 cm^3 (mean: 2.3 cm^3), and the maximum dose per fraction within the VTV ranged from 8.52 Gy to 9.67 Gy (mean: 8.98 Gy). Treatment was delivered using the volumetric modulated arc therapy (VMAT) technique. Patient-specific dosimetric quality assurance was performed using the portal dosimetry system (Varian Medical Systems Inc., Palo Alto, CA) and the ArcCHECK®, a 3D dose verification device (Sun Nuclear Corp., Melbourne, FL). Details of treatment data and LRT parameters are presented in Table 2.

Conventional external beam radiation therapy. The LRT component of treatment was followed immediately, the next day, by conventionally fractionated external beam radiation therapy ($EBRT_{conv}$) using VMAT to the pelvis and tumor extensions. The mean total $EBRT_{conv}$ dose was 44.28 Gy (range: 39.60–45.00 Gy). Regional lymph nodes beyond the pelvis were included into the $EBRT_{conv}$ as indicated by the extent of involvement by PET/CT findings.

The mean total dose from the LRT and $EBRT_{conv}$ components, within the VTV, was 68.28 Gy (range: 63.60–69.00 Gy), corresponding to a mean BED of 95.45 Gy_{10}, (range: 89.93–96.30 Gy_{10}). The mean EQD2 was 79.54 Gy (range: 74.94–80.25 Gy) (Table 2). The mean total dose to the margin of the PTV was 53.28 Gy (range: 48.6–54.00 Gy), corresponding to a BED of 63.95 Gy_{10} (range: 58.43–64.80 Gy_{10}).

Normal tissue constraints. For the LRT, the maximal dose to rectum, bladder and bowel were constrained to no more than 115% of the peripheral PTV dose. The average maximal LRT dose to the rectum was 3.2 Gy per fraction (range: 2.0–3.7 Gy), i.e., 107% (range: 67–123%) of the peripheral PTV dose. The average maximal LRT dose to the bladder was 3.4 Gy per fraction (range: 2.1–4.4 Gy), i.e., 114% (range: 70–147%) of the peripheral PTV dose. For the composite dose from the LRT and $EBRT_{conv}$ components, volume constraints were implemented in accordance with RTOG 0418 (*18*) and RTOG 0921 (*19*) with the following objectives: No more than 30% of the bowel received $\geq$40 Gy; no more than 60% of the rectum

TABLE 2
SFRT Characteristics

Patient no.	No. of vertices	VTV (cm^3)	Vertex diameter (cm)	VTV/GTV ratio (%)	VTV maximum dose (Gy)	$EBRT_{conv}$ dose (Gy × fraction)	Total GTV dose (Gy)	Total VTV dose (Gy)	Vertex EQD2 (Gy)
1	6	2.29	1	0.8	9.15	25 × 1.8 Gy	54.00	69.00	80.25
2	11	4.45	1	1.1	8.52	25 × 1.8 Gy	54.00	69.00	80.25
3	2	0.80	1	1.1	8.77	24 × 1.8 Gy	52.20	67.20	78.48
4	3	1.22	1	0.6	9.23	25 × 1.8 Gy	54.00	69.00	80.25
5	3	4.83	1.5	1.4	8.57	22 × 1.8 Gy	48.60	63.60	74.94
6	4	1.45	1	1.4	9.67	25 × 1.8 Gy	54.00	69.00	80.25
7	4	1.60	1	1.9	8.69	25 × 1.8 Gy	54.00	69.00	80.25
8	2	1.18	1	1.5	9.52	25 × 1.8 Gy	54.00	69.00	80.25
9	7	3.17	1	2.0	8.82	25 × 1.8 Gy	54.00	69.00	80.25
10	6	2.63	1	1.0	8.57	25 × 1.8 Gy	54.00	69.00	80.25

Notes. All patients received a planned SFRT dose of 24 Gy in three fractions and $EBRT_{conv}$. VTV = vertex tumor volume within the GTV that received the vertex dose of 24 Gy in three fractions. $EBRT_{conv}$ = conventionally fractionated external beam radiation therapy to the whole tumor. EQD2 = equivalent dose in 2 Gy fractions for the contributions from LRT and $EBRT_{conv}$, computed using the linear-quadratic model with an α/β ratio of 10 for tumor.

received ≥40 Gy; and no more than 35% of the bladder received ≥45 Gy.

Tumor boost. Brachytherapy was not feasible in this select group of far-advanced cervical cancer patients due to residual tumor bulk and/or severe anatomic distortion. Therefore, postirradiation hysterectomy was performed in four of the 10 patients. A central tumor boost was given in two patients with conventionally fractionated radiation therapy (12.5 Gy in five fractions) and SBRT (25 Gy five fractions) after $EBRT_{conv}$. Figure 2 shows the composite dosimetry of target and critical normal tissue doses in the patient with the 12.5 Gy boost. In the remaining patients, no further radiation was given due to early development of widely disseminated disease within one month of treatment completion (one patient), inoperable candidate (one patient), patient preference (one patient) and another patient (no. 10) who was pending hysterectomy in one month at the time of this writing.

Chemotherapy. All patients received standard concurrent weekly cisplatin chemotherapy. Chemotherapy started on the first fraction of LRT on the first day of the radiation therapy course.

Follow-up and Assessments

Patients were followed by the radiation oncologist and/or gynecologic oncologist according to standard of care practice 1–3 months after treatment completion and every 3–6 months thereafter. The median follow-up time was 28.5 months (range: 4–77 months) for surviving patients and 16 months (range: 1–77 months) for the entire patient cohort, including patients who died of disease or intercurrent disease.

Treatment outcome assessments. Local (pelvic) recurrence was defined as regrowth or persistence of the tumor in the cervix based on clinical examination, biopsy or radiographic findings (as indicated). Stable local disease and partial response by imaging and/or clinical exam were not classified as local control. For disease-specific survival, death from cervical cancer, cancer-related or treatment-related complications were scored as events; and for overall survival, death from any cause was scored.

Imaging response assessment. Tumor size was measured on pre-therapy and post-therapy imaging and scored using RECIST 1.1 guidelines (*20*). Intra-treatment volumetric morphological tumor response was assessed by comparison of the 3D tumor volume on the pre-therapy CT simulation imaging and the cone beam CT imaging on the last day of $EBRT_{conv}$. Pre-therapy metabolic activity of ^{18}FDG-PET/CT was compared with post-therapy metabolic activity in the early post-therapy phase (1–4 months) and in the later post-therapy phase (>6 months) (Table 3). Metabolic tumor response in the LRT volume was scored with a modified PERCIST (positron emission tomography response criteria in solid tumors) method (*21, 22*), as detailed in Table 4. In three patients without early post-therapy PET/CT, MRI was used for early response assessment.

Statistical Analysis

The Kaplan-Meier method was employed to calculate estimates of actuarial local control, disease-specific survival and overall survival rates. Follow-up observation time was computed from the time of radiotherapy completion. Differences between patient groups were calculated using the log-rank test.

RESULTS

Patients had far-advanced, $FIGO_{(2018)}$ stage IIIB–IVA cervical cancer with either massive tumor bulk and/or extensive local tumor involvement. The mean pre-treatment tumor diameter was 7 cm (range: 5.2–9.2 cm). The mean pre-treatment tumor volume, obtained from the CT-simulation-based GTV of the cervical tumors, was 200.35 cm^3 (range: 74.1–412.4 cm^3). Tumor size and volume data are detailed in Table 3.

Tumor Response

Tumor response was assessed by clinical exam and imaging, including intra-treatment imaging assessment, and morphological and molecular imaging in the early and late post-therapy phase. A summary of imaging response outcomes is presented in Table 3.

Early molecular imaging response. Molecular response in the early post-therapy phase was available in six of the 10 patients, who had early post-therapy ^{18}FDG PET/CT at an average of 2.7 (range: 1–4) months post-therapy follow-up. PET/CT showed complete metabolic response (CMR/PERCIST in four patients (67%), and partial metabolic response (PMR) in the remaining two patients (Table 3). There were no non-responders. Three of the 10 patients had MRI instead of PET/CT in early follow-up, MRI showing complete response in two of the three. One patient declined any follow-up imaging.

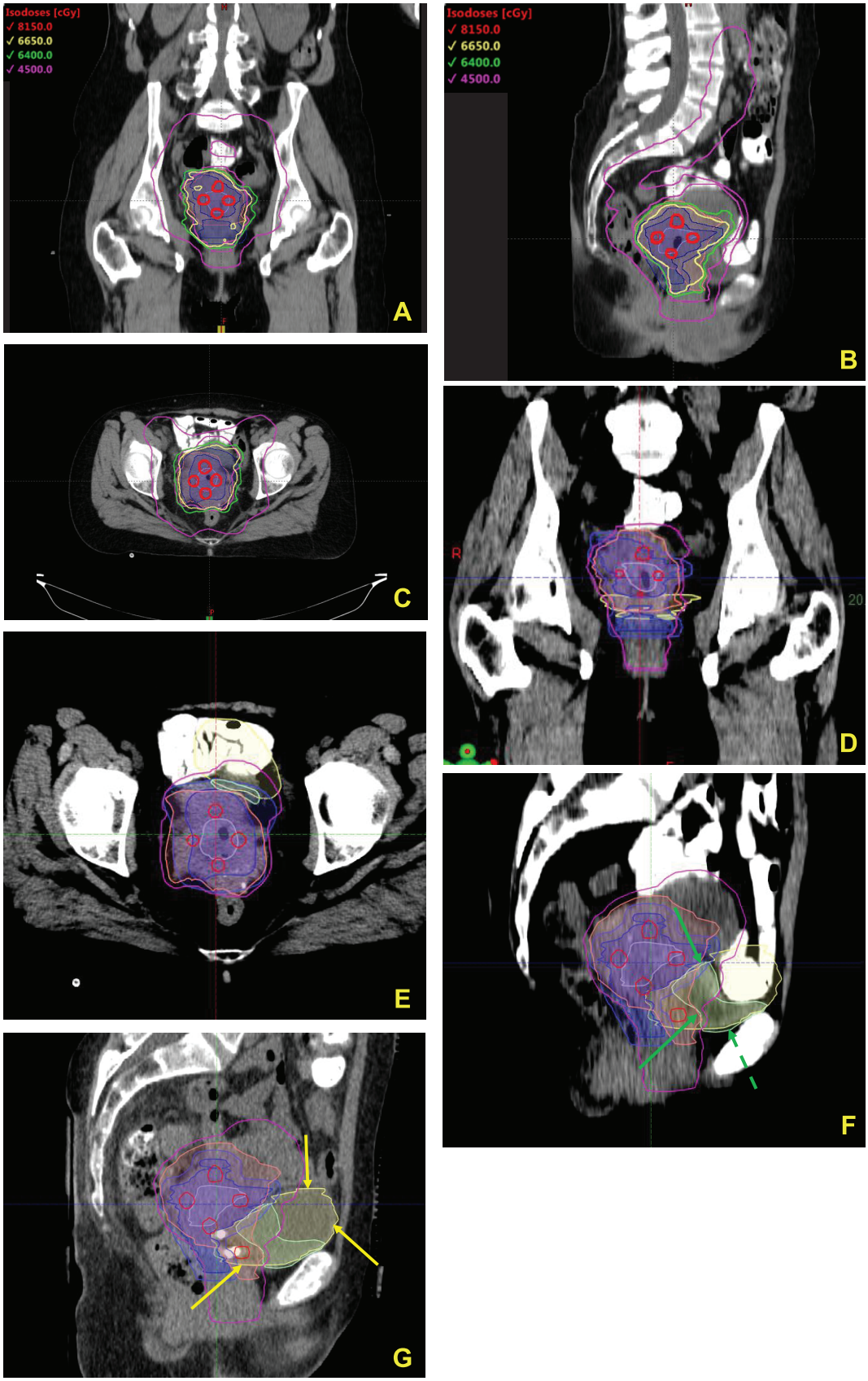

FIG. 2. Composite target and normal tissue doses. The patient is a 59-year-old woman with FIGO stage IVA squamous cell carcinoma of the cervix with extensive bladder involvement, with an initial tumor volume of 159.26 cm^3. Panels A–C: Coronal, sagittal and axial views, respectively, of the planning CT show the

Late molecular imaging response. PET/CT at the patients' most recent follow-up (considering late response given by those studies performed after 6 months of treatment completion), ranged from 10.6 months to 76 months, with a median of 17.2 months and average of 29.7 months. CMR of these most recent imaging time points was 100% (seven patients with late post-therapy imaging had CMR). The other three patients did not have late PET-CT follow-up: one did not have any study after treatment completion, another patient died one month after from progression of disease outside the pelvis and the other patient finished treatment less than 6 months ago.

Morphologic Imaging Response

The morphological imaging response rate (based on RECIST criteria) at the early post-therapy follow-up phase was high. At a median follow-up of 2.2 months (range: 0.2–4.5 months), the cervical tumor was non-detectable in 55% (five of nine patients with early post-therapy imaging), consistent with complete RECIST response. The remaining four patients had a partial response, with a mean tumor regression by 63%. Details of the RECIST-based morphological response, pre-and post-therapy tumor measurements and regression rate are presented in Table 3.

If early post-therapy imaging response was scored by both molecular and morphological response, 67% of patients had complete response (four of six with CMR; two of three with complete response) in the early <6 months post-therapy phase, and the remainder had partial response. Volumetric and molecular tumor response are shown in Figs. 3 and 4.

Intra-Treatment Volumetric Tumor Response

Volumetric 3D tumor response assessment was also performed *intra*-treatment to evaluate early tumor changes from SFRT. Volumetric response assessment was based on the CBCT on the last day of pelvic radiotherapy at a mean GTV dose of 44.28 (range: 39.6–45.00) Gy and a VTV dose of 68.28 (range: 63.60–69.00) Gy (from combined LRT and $EBRT_{conv}$ dose). Volumetric evaluation from the preirradiation CT and the cone beam CT of the last day of pelvic radiotherapy showed tumor regression by an average of 54% (range: 6–91%) at this very early time point. Intra-treatment volumetric response data are presented in Table 3.

Seven of the 10 patients required adaptive re-planning because of rapid tumor regression. At the time of adaptive re-planning tumors had regressed by an average of 43% (range: 23–83%). Adaptive planning occurred after an average of 16 (range: 11–23) total fractions (inclusive of LRT and $EBRT_{conv}$ fractions). Six of the seven patients required adaptive re-planning once and one patient twice.

Pathologic Tumor Response

Four patients underwent hysterectomy because of severe anatomical distortion preventing brachytherapy and/or suspicion of residual disease, providing pathological response data. Among the four patients with hysterectomy,

←
cumulative dose of the LRT (24 Gy in 3 fractions to the VTV, 9 Gy in 3 fractions to the PTV), $EBRT_{conv}$ (45 Gy in 25 fractions), followed by an integrated tumor boost (12.5 Gy in 5 fractions to the central/necrotic, and 10 Gy in 5 fractions to the peripheral boost volume). The corresponding images displaying the detailed target structures are shown for orientation in panels D–G. Initial target structures: PTV_p (initial PTV, pink contour) and GTV_p Conventional external color wash); target structures for the boost (mapped onto the initial planning CT): GTV_Boost_12.5Gy (light blue contour), GTV_Boost_10Gy (dark blue color wash), PTV_Boost (sky-blue contour). Panels F and G show the changes in bladder (arrows) and bowel configuration from the initial CT (panel F) to the boost CT (panel G).[2] The following composite isodose lines are shown (panels A–C): purple = 45 Gy isodose line covering the PTV-pelvis; green = 64 Gy isodose line for PTV-Boost_10Gy (dark blue color wash); yellow = 66.5 Gy for the GTV-Boost_12.5Gy (light blue contour); and red = 81.5 Gy isodose line covering the VTV. The composite DVH (panel H) represents the cumulative dose from LRT, $EBRT_{conv}$ and boost. Due to tumor volume changes and shifts between initial and boost plan,[2] the DVH of the boost to the residual tumor volume (integrated boost of 12.5 Gy to the central and 10 Gy to the peripheral residual tumor), is shown separately (panel I). To account for dose rate and fractionation effects, the EQD2 (α/β ratio = 10) for the target structures (95% PTV coverage) from all three treatment components were computed: VTV – 93.27 Gy; GTVp (initial GTV) – 60.94 Gy; PTVp (initial PTV) – 55.45 Gy; PTV Pelvis/paraaortic nodes[3] – 44.25 Gy; GTV_Boost_12.5Gy (boost/residual tumor after EBRTconv)[2] – 82.47 Gy; GTV_Boost_10Gy (boost/residual tumor after EBRTconv)[2] – 65.48 Gy; PTV (boost/ residual tumor after EBRTconv)[2] – 64.00 Gy. Dose limits to organs at risk (per RTOG 0921/0418 guidelines for pelvic radiation therapy), computed as EQD2 (α/β ratio = 3) for the LRT and $EBRT_{conv}$ component of treatment show that dose limits were achieved for bowel (30% of bowel received 37.70 Gy) and rectum (60% of bowel received 38.89 Gy). OAR limits were exceeded for the bladder (35% of bladder received 58.08 Gy) because of the patient's extensive bladder involvement with tumor (panel F, solid green arrows). The patient had complete metabolic response and no evidence of complications 11 months after treatment completion.

[2] Mapping of cumulative doses onto the initial planning CT represent approximations that do not fully account for effects from major tumor volume changes, positional shifts of the uterus and alterations in normal tissue volume and configuration, which commonly occur in cervical cancer during the treatment course. In particular, dose effects from changing bladder configuration due to a small bladder volume (from a lack of bladder control related to tumor invasion, panel F, solid green arrows, bladder contoured in light green colorwash) in the initial treatment phase, versus re-expansion of the bladder (after tumor response, panel G, yellow arrows, bladder in yellow colorwash) at the time of the boost should be interpreted with caution. Co-location of vertex doses with boost volume should also be viewed with caution as vertex doses were given only to the initial tumor volume.

[3] The lymph node volume also included the para-aortic region.

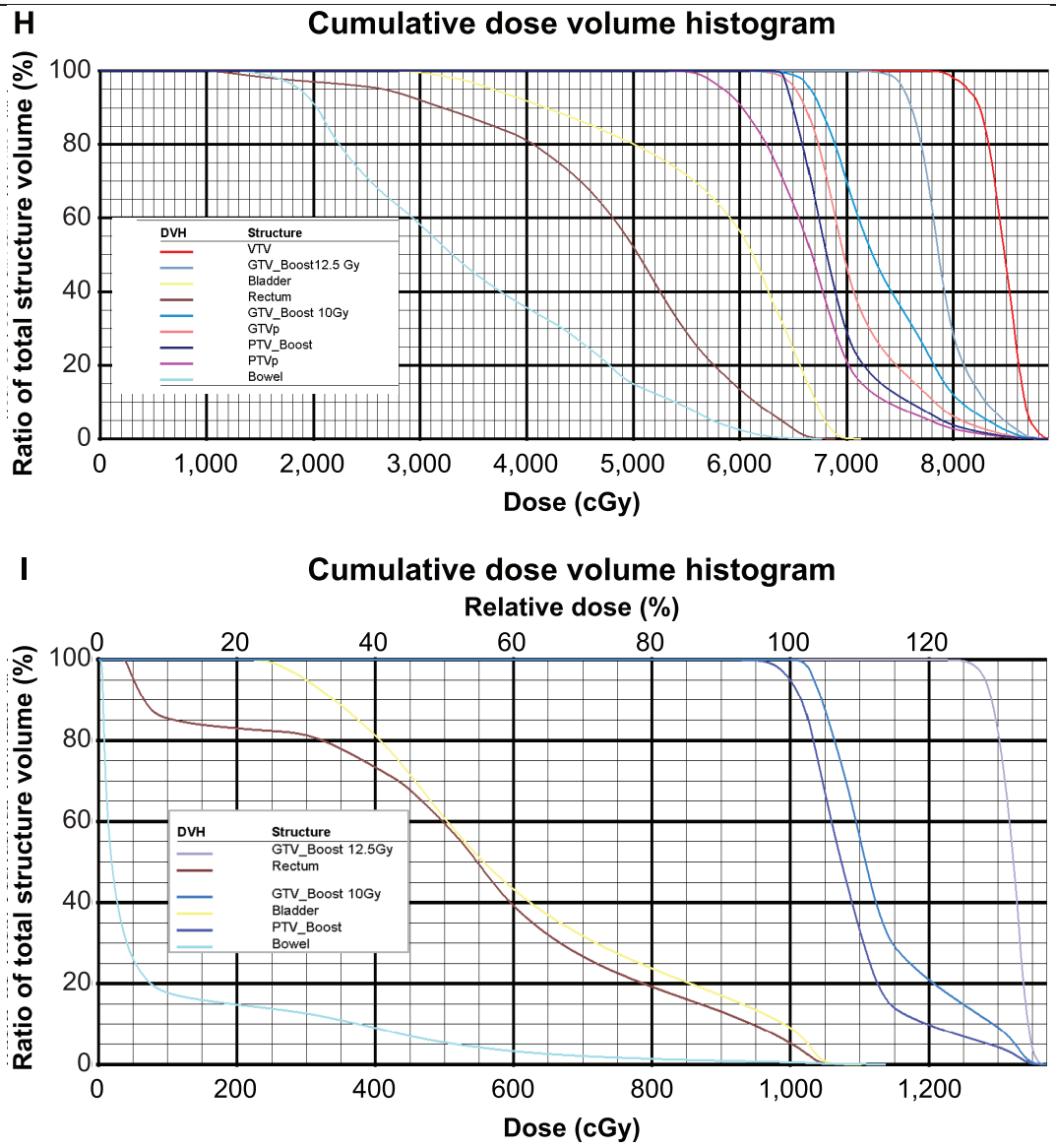

FIG. 2. Continued.

two had a pathological complete response with no residual tumor in the surgical specimen 4 and 6 months after completion of radiotherapy and were without evidence of disease 48 and 77 months after therapy. One patient with an initially 7.2-cm tumor (198.8 cm^3 GTV) and hysterectomy only one month after treatment completion, had a 2.6-cm-diameter residual squamous cell carcinoma in the surgical specimen and was alive without evidence of disease 42 months after treatment. One patient was found to have adenocarcinoma extensively involving the uterine specimen and died of metastases 17 months after treatment while maintaining local pelvic control.

Local Control

All patients, including the six with definitive radiotherapy and four with hysterectomy after radiotherapy, and regardless of the velocity intra-treatment volumetric tumor response or completeness of response in the early post-therapy phase, achieved and maintained local tumor control in the pelvis at the time of this analysis 1–77 months (median: 16 months overall; and median: 28.5 months for surviving patients) after treatment completion. Because of the high local control rate and the uniformity of our dosing regimen, correlation of dose and tumor control was not meaningfully feasible.

Disease-Specific and Overall Survival

Among the 10 patients, three developed distant metastatic disease; one of these patients also had paraaortic retroperitoneal nodal progression. All three patients succumbed to their disease. At the time of this analysis, six of the 10 patients remain alive with no evidence of disease 4–77

TABLE 3
Volumetric and Molecular Imaging Response to SFRT

	Tumor volume regression intra-treatment			RECIST		
				Early follow-up (1–4 months after treatment)		
Patient no.	GTV volume pre-treatment (cm^3)	GTV volume post-LRT + $EBRT_{conv}$ (cm^3)	GTV volume percentage regression	Tumor diameter planning CT (cm)	Tumor diameter post-treatment (cm^3)	RECIST
1	272.2	83.13	69%	8.0	0	CR
2	412.44	260.45	37%	9.2	3.6	PR
3	74.1	69.89	6%	5.2	0	CR
4	191.75	104.82	45%	7.2	0	CR
5	375.4	182.19	51%	9.0	2.0	PR
6	104.1	68.29	34%	5.8	0	CR
7	84.4	7.46	91%	5.4	–	–
8	76.96	16.00	79%	5.3	1.3	PR
9	159.26	90.00	43%	6.7	4.0	PR
10	252.85	42.36	83%	7.8	0	CR

Notes. Diameters in cm. Volumes in cm^3. SUV_{max} = maximum standardized uptake value of ^{18}FDG PET/CT; CR = complete response; PR = partial response; CMR = complete metabolic response; PMR = partial metabolic response.

[a] SUV of 0 indicates background activity, consistent with CMR.

[b–d] Three patients had MRI instead of PET/CT in the early (1–4 months) post-treatment follow-up.

[b] Patient no. 3 had MRI 2.2 months after therapy showing no residual tumor;

[c] patient no. 4 had MRI 3.6 months after therapy showing no residual tumor;

[d] patient no. 8 had MRI 0.2 months after therapy showing a 1.3 cm residual tumor, consistent with PR.

[e–f] In two patients the most recent PET/CT was less than six months after therapy.

[e] The most recent PET/CT of patient no. 5 was 1.2 months after therapy and showed an SUV_{max} of 5.5. This patient died of disseminated disease within 2 weeks of the PET/CT.

[f] The most recent PET/CT of patient no. 10 was 1.8 months after therapy and showed an SUV_{max} of 0.

months after treatment completion. One additional 90-year-old patient died of non-cancer-related cause. The actuarial (Kaplan-Meier) estimates of two-year disease-specific survival and two-year overall survival are 53.3% and 46.7%, respectively.

Among the three patients with adenocarcinoma or adenosquamous carcinoma, all died of their malignancy from distant dissemination. The actuarial two-year disease-specific survival for patients with adenocarcinoma/adenosquamous carcinoma was 0%, compared to 100% for patients with squamous cell carcinoma ($P = 0.010$). Two-year overall survival was 0% vs. 80%, respectively ($P = 0.054$).

Treatment-Related Toxicity

Treatment-related toxicity was minimal. Grade 1 diarrhea, which occurred commonly during treatment, was well controlled with low-fiber diet and oral antidiarrheals and

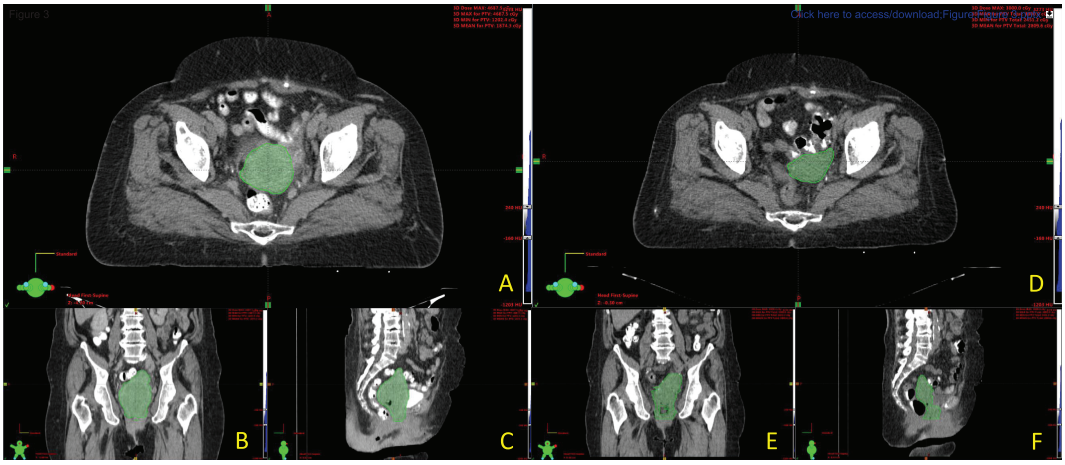

FIG. 3. Rapid intra-treatment response, same patient with bulky stage IIIB cervical cancer as in Fig. 1. Comparison of the axial, coronal and sagittal views simulation images (panels A–C) and re-simulation (panels D–F) for the purpose of adaptive re-planning after 24 Gy in 3 fractions of LRT and 18 Gy in 10 fractions of $EBRT_{conv}$ shows rapid tumor volume reduction from 272.2 cm^3 pre-therapy to 167.8 cm^3 (regression by 38%).

TABLE 3
Extended.

	PET/CT response			
	1–4 Months after treatment		>6 Months after treatment	
SUV_{max} pre-treatment	SUV_{max} early post-treatment	mPERCIST	SUV_{max} late post-treatment	mPERCIST
7.6	0[a]	CMR	0	CMR
10.3	0	CMR	0	CMR
8.1	–[b]	–	0	CMR
8.1	–[c]	–	0	CMR
9.9	5.5	PMR		–[e]
24.5	0	CMR	0	CMR
7.2	–	–		–
10.9	–[d]	–	0	CMR
16	2.3	PMR	0	CMR
27.8	0	CMR	0	–[f]

TABLE 4

Modified PERCIST guidelines (mPERCIST) for local tumor response
Complete metabolic response (CMR)
A. Decrease in FDG avidity of all tumor lesions to background and
B. No new tumor lesions in the pelvis
Partial metabolic response (PMR)
A. Decrease in FDG avidity of 30% or more from baseline measurements and
B. No new tumor lesions in the pelvis
Stable metabolic disease (SMD)
No CMR, PMR or PMD
Progressive metabolic disease (PMD)
A. Increase in FDG avidity of 30 % or more from baseline, or
B. Increase in extent of FDG avidity (enlargement of tumor) or
C. New tumor lesions[a]

[a] The classic PERCIST guideline (*21, 22*) was adapted to specifically assess the response within the GTV treated with LRT (cervical tumor and uterus), i.e., local tumor response. Thus, new tumor lesions only outside the cervix, uterus and pelvis (e.g., progression in extra-pelvic lymph nodes and distant metastatic sites without progression in the pelvis) were classified as continued CMR or PMR (as applicable) within the LRT volume. Extra-pelvic progression was scored separately.

resolved after completion of therapy. One patient, who also had bladder involvement with tumor, experienced grade 2 cystitis that improved later during therapy. No rectal toxicity was seen. There was no grade ≥3 short-term or long-term gastrointestinal, urinary, cutaneous or other toxicities.

DISCUSSION

GRID-based SFRT has been studied, initially in largely palliative patient cohorts (*2–5*) and later, increasingly in patients with advanced bulky primary tumors (*5, 6, 10, 12–14*). SFRT has shown unexpectedly high symptomatic and objective tumor responses while toxicity was unexpectedly low (*2–6, 10, 12–14*). More recently, these favorable response outcomes have also been confirmed in smaller disease-specific series with longer observation times, and these studies showed early evidence favorable of longer-term local control and survival outcomes. Such experience has been promising in head and neck cancer (*6, 10*), lung cancer (*5, 11*) and sarcoma (*13, 14*).

Our observations in this first series in cervical cancer, a malignancy also prone to excessive tumor bulk and extensive involvement, overall support the results previously seen in other advanced primary tumors and metastases (*5, 6, 10, 12–14, 23*). Our developed and consistently applied lattice radiotherapy regimen of 24 Gy in three fractions upfront, followed by standard-dose radiation therapy,

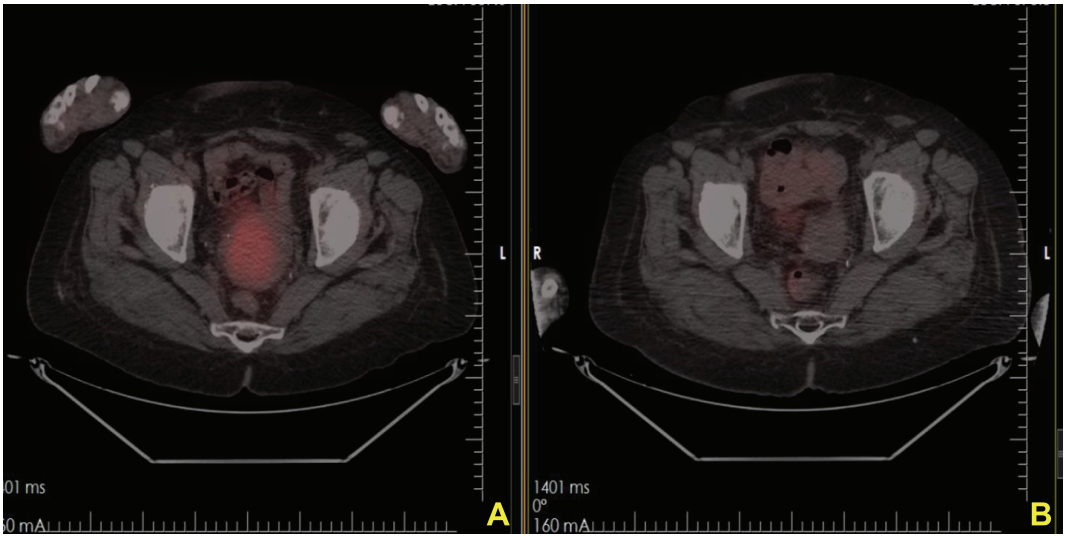

FIG. 4. Molecular tumor response, same patient with bulky stage IIIB cervical cancer as in Fig. 1. Pre-therapy PET/CT (panel A) shows metabolic uptake in the cervix with an SUV_{max} of 7.6. The 3-month post-therapy PET/CT (panel B) shows both tumor volume reduction and complete metabolic response.

enabled systematic assessment of response rate, local control and toxicity in our pilot series of cervical cancer patients.

Local Tumor Control and Survival

The observed complete response in 88.9% and partial response in 11.1% in our patients at an early time point after therapy and our two-year local tumor control rate of 100% are encouraging in view of the advanced disease stage, extensive involvement and voluminous tumor bulk in our cervical cancer patients (Table 1). While our patient numbers are too small and the data must be interpreted with caution, our results confirm the general observations of high tumor control rates seen in previous SFRT studies in other malignancies (*2–6, 10, 12–14, 23*). The findings from this first series of SFRT in cervical cancer support our previous observations in the only other published SFRT experience in this disease (*15*). In this earlier case report of a far-advanced cervical cancer patient with a voluminous 250-cm^3 tumor, we observed a similar complete clinical and pathological response to LRT.

In the absence of other data in cervical cancer, these results may be most comparable to those observed in head and neck cancer (*3, 5, 6, 10*), a disease which generally shares many tumor-biological properties with cervical cancer. In addition, the combined-modality treatment approach with platinum-based chemotherapy concurrently with radiation therapy is commonly employed for both diseases.

Response and local control rates similar to ours were reported by several investigators in head and neck cancer, particularly in squamous cell histology (*3, 5, 6, 10*). In the classic analysis of response rate by tumor site and histology in one of the largest SFRT cohorts, Mohuiddin *et al*. (*3*) observed the highest response rates of over 80% in squamous cell carcinomas in their study which included eight head and neck cancer patients. Huhn *et al*. (*6*) observed a local control rate of 86% in their group of 14 patients with advanced head and neck cancer with bulky stage N2–3 neck disease, who were treated with GRID SFRT (15 Gy in one fraction), followed by definitive conventionally fractionated (uniform) external radiation therapy. A proportion of their patients also received concurrent chemotherapy. Penagaricano *et al*. (*10*) corroborated these results in a cohort of 14 patients treated with their standardized GRID SFRT and conventionally fractionated radiotherapy regimen, and reported a local control rate of 79%. Our local control rate of 100% (88.9% complete tumor response and 11.1% partial tumor response) with a median follow-up of 16 (range: 1–77) months is consistent with the local control rates of 86% and 79%, reported by Huhn *et al*. and Penagaricano *et al*., respectively, in head and neck cancer that were observed with similar median follow-up times of 10 (range: 1–44) months (*6*) and 19 (range: 2–38) months (*10*), respectively.

Survival

While our follow-up is short and our patient numbers are limited, survival outcomes in our cohort are promising. Of our far-advanced cervical cancer patients, 60% (6 of 10) are alive with no evidence of disease at the time of this analysis. Our two-year disease-specific survival of 53.3% is consistent overall with the 2.5-year disease-specific survival of 50% reported by Huhn *et al*. (*6*) and the estimated survival of 50% (7 of 14 patients alive without disease or dead of intercurrent disease) reported by Penagaricano *et al*. (*10*) in their head and neck cancer series.

It has been previously suggested that responsiveness to SFRT may be higher in squamous cell carcinoma histologies than in adenocarcinoma (*3*). Although our numbers are too small to draw definitive conclusions, interestingly, our outcome data reflect this trend. Among our 10 patients, seven had squamous cell carcinoma and three had adenocarcinoma or adenosquamous histologies. All three patients with adeno- or adenosquamous carcinoma have died of disease, largely from distant metastases, while the two-year disease-specific survival in squamous cell carcinoma was 100% ($P = 0.010$).

Molecular Imaging Based and Volumetric Tumor Response

Our series is unique in that it includes for the first time pre-, intra- and post-therapy imaging assessment, particularly metabolic imaging in an SFRT cohort. This serial imaging allows insight into the biological response dynamics in our cervical cancer patients, both morphologically and functionally with respect to tumor glucose metabolism.

We observed a high proportion of complete (6 of 9, 67%) and partial (3 of 9) responders in the early post-therapy phase 1–4 months after treatment completion. Our metabolic and MR imaging response findings strengthen our outcome data beyond our relatively short follow-up. Both ^{18}FDG PET/CT imaging and early post-therapy MRI have been recognized as strong surrogate outcome predictors for long-term tumor control and survival in cervical cancer *(24, 25)*. Complete metabolic response in the 2–4-month post-therapy FDG-PET imaging is a strong predictor of ultimate disease-free and overall survival in cervical cancer (*25*); and tumor regression by MRI is a strong predictor of tumor control and survival (*24*). However, longer follow-up time and larger patient numbers will be needed to corroborate this finding.

We also assessed intra-treatment volumetric tumor response immediately at the end of $EBRT_{conv}$ to gain more insight into the morphological response dynamics of SFRT. While our data show profound tumor volume reduction (by mean 54%) at a mean VTV dose level of 68.28 Gy and GTV dose of 53.28 Gy, response velocity was highly variable. Despite that initial heterogeneity at this early intra-treatment time point, longer-term molecular imaging

response (Table 3) and local control rate (100%, Table 1) were high.

No correlation between the intra-treatment volumetric response dynamics and local control or complete pathological response could be established. This suggests, based on our small cohort, that very early or intra-treatment morphological response assessment, even if performed with a more accurate volumetric technique, may not be predictive of longer-term tumor control in SFRT for cervical cancer.

Only one prior study reported imaging assessments of SFRT response. Neuner *et al*. (*5*) reported post-treatment radiographic imaging response on routine post-therapy imaging in a subgroup of 40 of their 79 patients with predominately lung and head and neck cancer. The investigators found a relatively modest imaging response (overall response: 13–16%; complete response: 1–3%) although the time interval is unclear (*5*). The low-imaging-based response rate did not correlate well with their favorable clinical outcome result of symptomatic response rate; however, this study was not designed to assess longer-term local control and survival. Our PET/CT and morphological imaging results add further information on imaging-based response and tumor control outcomes in SFRT and suggest that molecular imaging is an important component of response assessment.

Toxicity

We found only mild early (acute) RTOG grade $\leq$2 and no late digestive, genitourinary tract or other toxicity from SFRT despite the abdominal/pelvic location of the treatment target and expected complication risk. These observations overall reflect those in the two head and neck cancer series (*6, 10*), and that of our lung cancer cohort (*23*). One exception is the relatively higher skin toxicity observed in the series of 14 patients, reported by Penagaricano *et al*. (*10*), all of whom received concurrent platinum-based chemotherapy. However, this was largely an early reversible toxicity. Similar to the study by Penagaricano *et al*., all of our patients were treated with concurrent cisplatin chemotherapy, starting with the SFRT portion of the treatment. The lesser toxicity seen in our patients may be related to the lower skin exposure in the treatment for cervical cancer than in the head and neck cancer patients in the study by Penagaricano *et al*., and perhaps also due to the greater ease in reducing radiation dose at the tumor periphery and thereby to nearby critical normal tissues with LRT.

The LRT Concept of SFRT

We designed the LRT dose schedule based on the GRID (*2, 3, 5, 6, 10*) and stereotactic radiotherapy experience. The vertex dose of 24 Gy emulates a commonly employed SBRT schedule of 24 Gy in three fractions (*26*). This schedule is in keeping with the 15–20 Gy single-fraction dose in GRID SFRT, as 24 Gy in three fractions corresponds to a BED of 43.2 Gy_{10}, which is within the BED range of 37.5–60.0 Gy_{10} of the classic 15–20 Gy single-fraction GRID regimens. The prescription dose of 9 Gy in three fractions to the GTV periphery was based on a commonly adopted 3 Gy fraction approach for the control of severe vaginal bleeding, which is a frequent complication of advanced cervical cancer.

Based on the large body of GRID-based SFRT literature, we placed the LRT component at the beginning of the treatment course. This sequencing has been favored for the theoretical advantage of leveraging the heterogeneous dose distribution of the SFRT to promote immunologic and bystander effects, while also rapidly reducing tumor bulk (through the high doses delivered with SFRT) and lowering doses at tumor periphery that are close to normal structures. Based on preclinical studies (*8, 27–30*), the marked dose heterogeneity of SFRT is thought to help mediate bystander and immunogenic effects that enhance tumor response. These effects are postulated to be promoted by both the high-dose (''peak dose'') regions of SFRT and the low-dose (''valley dose'') regions, which are low enough to preserve lymphatic cells, tumor microvasculature and perfusion to allow for circulation of cytokines and chemokines and/or immunogenic factors. These data lend further support to the concept of administering LRT at the beginning of the treatment course instead of at the end when high-uniform whole-tumor dose has depleted lymphatic tissue, altered vasculature and frequently produced significant fibrosis.

While we recognize that the fractionated SFRT regimen may be vulnerable to inter-fraction motion effects with potential misalignment of the vertices from fraction to fraction, we chose the three-fraction regimen to further reduce toxicity. We worked to mitigate the motion effect by a strict IGRT alignment process. However, uncertainty regarding positional reproducibility remains, and such potential motion effects will require further study.

With this SFRT regimen, our local tumor control and survival rates were overall similar to those seen with GRID SFRT (*6, 10*). Thus, our clinical outcome results lend further validation to the findings of prior studies in other cancers, i.e., that SFRT doses in the BED range of 37.5–60.0 Gy_{10} to very small volumes within bulky tumors, followed by conventional radiation, result in high response and local tumor control rates.

The biological effects of SFRT have yet to be fully understood. It has been proposed by prior experimental (*31, 32*) and clinical-translational correlation studies (*8, 9*), that heterogeneous dose distributions and spatially fractionated, highly ablative doses may promote non-target bystander and microvascular effects through the production of immune-mediating cytokines, such as tumor necrosis factor-α, and secretory sphingomyelinase and ceramide, which promote endothelial cell apoptosis. Our observed high response and local control rates in bulky far-advanced cervical cancer lend further clinical support to the concept of SFRT-induced bystander and microvascular apoptotic effects.

Limitations

As in several of the disease-specific SFRT series (*6, 10, 12–14, 23*), our patient cohort is small and post-treatment follow-up time is still relatively short. Our results require confirmation by independent cohorts of cervical cancer patients with larger patient numbers and longer follow-up. Four of our patients underwent hysterectomy, thereby preventing assessment of long-term local control based on cytotoxic (radiotherapy, chemotherapy) treatment alone in this subgroup. However, in turn, this subgroup provides a unique and important pathological assessment of SFRT effects in the early post-treatment phase, a rare clinical-pathological correlation that remains generally elusive in patients receiving definitive radiation therapy for cervical cancer.

CONCLUSION

This first series of lattice-based SFRT in far-advanced bulky cervical cancer patients shows high clinical and molecular-imaging-based tumor response, and high local tumor control. Treatment toxicity with lattice-based SFRT was minimal despite concurrent chemotherapy. Our results confirm the previously reported favorable responses to SFRT in other malignancies, and support SFRT as a promising option for challenging, bulky far-advanced cervical cancer. These preliminary hypothesis-generating results are encouraging but need to be interpreted with caution and require confirmation with larger patient cohorts, ideally with a multi-institutional prospective randomized clinical trial.

Received: January 30, 2020; accepted: July 7, 2020; published online: August 27, 2020

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