Spatially Fractionated Radiotherapy (GRID) Prior to Standard Neoadjuvant Conventionally Fractionated Radiotherapy for Bulky, High-Risk Soft Tissue and Osteosarcomas: Feasibility, Safety, and Promising Pathologic Response Rates

Authors: Snider, James W., Molitoris, Jason, Shyu, Susan, Diwanji, Tejan, Rice, Stephanie, et al.

Source: Radiation Research, 194(6) : 707-714

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00100.1

RADIATION RESEARCH **194**, 707–714 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00100.1

Spatially Fractionated Radiotherapy (GRID) Prior to Standard Neoadjuvant Conventionally Fractionated Radiotherapy for Bulky, High-Risk Soft Tissue and Osteosarcomas: Feasibility, Safety, and Promising Pathologic Response Rates

James W. Snider,[a] Jason Molitoris,[b] Susan Shyu,[b] Tejan Diwanji,[c] Stephanie Rice,[d] Emily Kowalski,[b] Cristina Decesaris,[e] Jill S. Remick,[e] Byongyong Yi,[b] Baoshe Zhang,[b] Andrea Hall,[e] Nader Hanna,[b] Vincent Y. Ng[b] and William F. Regine[b,1]

[a] *University of Alabama at Birmingham School of Medicine, Birmingham, Alabama;* [b] *University of Maryland School of Medicine, Baltimore, Maryland;* [c] *University of Miami School of Medicine, Miami, Florida;* [d] *SUNY Upstate Cancer Center, Syracuse, New York; and* [e] *University of Maryland Medical Center, Baltimore, Maryland*

Snider, J. W., Molitoris, J., Shyu, S., Diwanji, T., Rice, T., Kowalski, E., Decesaris, C., Remick, J. S., Yi, B., Zhang, B., Hall, A., Hanna, N., Ng, V. Y. and Regine, W. F. Spatially Fractionated Radiotherapy (GRID) Prior to Standard Neoadjuvant Conventionally Fractionated Radiotherapy for Bulky, High-Risk Soft Tissue and Osteosarcomas: Feasibility, Safety, and Promising Pathologic Response Rates. ***Radiat. Res.*** **194, 707–714 (2020).**

Spatially fractionated radiotherapy (GRID) has been utilized primarily in the palliative and definitive treatment of bulky tumors. Delivered in the modern era primarily with megavoltage photon therapy, this technique offers the promise of safe dose escalation with potential immunogenic, bystander and microvasculature effects that can augment a conventionally fractionated course of radiotherapy. At the University of Maryland, an institutional standard has arisen to incorporate a single fraction of GRID radiation in large (>8 cm), high-risk soft tissue and osteosarcomas prior to a standard fractionated course. Herein, we report on the excellent pathologic responses and apparent safety of this regimen in 26 consecutive patients.

INTRODUCTION

Sarcoma is a relatively rare form of malignancy, representing approximately 1% of all diagnoses in the U.S. at approximately 12,000–15,000 new cases per year (*1*). Systemic therapy, and especially chemotherapy, has proven beneficial in only limited subsets of patients and therefore, surgical resection and radiotherapy remain the consensus standard of care in most cases (*2–4*). Neoadjuvant radiotherapy has largely supplanted adjuvant approaches based on results from the randomized National Cancer Institute of Canada (NCIC) trial demonstrating equivalent oncologic outcomes with less long-term morbidity associated with the reduced radiotherapy dose and field size employed in the neoadjuvant setting (*5*).

The Radiation Therapy Oncology Group (RTOG) 0630 trial was a multi-institutional, phase II trial designed to assess the late toxicities associated with modern radiotherapy techniques for neoadjuvant treatment of extremity soft tissue sarcomas (*6*). Of the 98 patients accrued, the RTOG recently reported the toxicity outcomes from 79 eligible patients in cohort B. With image-guided radiotherapy and the reduced margin target volumes employed on this trial, major wound complications were limited to 10.5% of patients versus the 37% encountered in the NCIC trial.

Despite these encouraging results concerning toxicity, pathologic tumoral response was underwhelming, consistent with the radio-insensitive nature of high-grade soft tissue sarcoma. The pathologic complete response (pCR) rate was only 19.4% on RTOG 0630 and 27.5% on RTOG 9514, a phase II study employing interdigitated neoadjuvant chemotherapy and radiotherapy (*7, 8*). As has been the case in several historical trials and series, however, pCR clearly correlated on pooled analysis of these trials with improved disease-free and overall survival. This has led the RTOG to recommend pCR as a continuing surrogate for improved outcomes in sarcoma management to accelerate innovation in this relatively rare set of histologies.

Spatially fractionated (GRID) radiotherapy is a well-described technique for safe radiotherapy dose escalation in bulky tumors. It employs ''beamlets'' of radiotherapy that are akin to a virtual brachytherapy technique (*9*). Historically employed in the orthovoltage era to spare

[1] Address for correspondence: Maryland Proton Treatment Center, University of Maryland School of Medicine, 22 S. Greene St., Ground Floor, Gudelsky, Baltimore, MD 21201; email: wregine@umm.edu.

areas of skin between beamlets and allow for dose-escalation without severe skin reactions, it was repurposed in the megavoltage era as a boost to conventionally fractionated radiotherapy in both the definitive and palliative settings (*10–16*). It is most often delivered as a single fraction of 12 to 20 Gy prescribed to Dmax within one to three days prior to a course of conventionally fractionated radiotherapy. It can be planned using either a commercially available block or with a multileaf collimator (MLC) technique (*17*). At our institution, large sarcomas in particular have been identified as an opportunity for employment of this technique. As a result, it has become standard in our clinic to offer a single fraction of GRID to 15 Gy prior to standard, conventionally fractionated, neoadjuvant radiotherapy for patients with bulky (generally >8 cm) soft tissue sarcomas when feasible. Herein, we describe our initial experience with this technique, evaluated for safety, feasibility and pCR rates.

METHODS

On an Institutional Review Board-approved protocol, 26 patients were retrospectively reviewed, having been treated between 2005 and 2019 at the University of Maryland Medical Center (Baltimore, MD) with neoadjuvant radiotherapy employing single-fraction GRID treatment followed by definitive, surgical resection. All patients were treated at a single institution with both single-fraction GRID and conventionally fractionated therapies. All patients received a single fraction of 15 Gy GRID therapy prescribed to Dmax, while the conventionally fractionated course ranged from 45 to 50.4 Gy in 1.8–2.25 Gy/fraction. Of 24 resections performed at our institution, 20 of these were performed by the three primary sarcoma surgeons. Patient characteristics, clinical outcomes and follow-up were recorded. Formal pathologic review for this study, especially for histology subtype confirmation and necrosis/nonviability quantification, was attempted for all samples and completed in 25 cases. The one additional case was reviewed at a neighboring expert academic institution.

GRID Therapy

GRID radiotherapy was primarily delivered using an MLC technique as described by Neuner *et al*. (*17*). This approach utilizes the MLC technique in the linear accelerator treatment head to form 1 $\times$ 1 cm apertures in banks including two columns of beamlets. When multiple banks are required for a treatment, they are treated sequentially during one setup and delivery. Image guidance is mandated to ensure accurate delivery. While effort is made in planning to reduce the number of banks required, delivery can be protracted as a result of this sequential approach. Adequate immobilization devices are key, and reimaging mid-treatment has occasionally been utilized to verify intrafractional positional stability.

Energies employed ranged from 6 to 18 MV based on clinician judgment, tumoral depth and tumoral thickness. Lower energies are preferred to limit neutron production and treatment machine component activation, but when required to achieve adequate dose at depth, higher energies are utilized.

In general, the clinician delineates a GRID gross tumor volume that guides the dosimetrist in targeting the vast majority of the primary tumor while avoiding any critical organs at risk, especially with the higher entrance dose side of the distribution. This delivery technique creates streaks of dose through the gross tumor volume that fall-off distally (Fig. 1). This was delivered immediately prior (within 1–3 days generally) to initiation of conventionally fractionated radiotherapy. A break of 2–3 days was generally preferred to allow for resolution of any associated swelling effect of the large dose per fraction. The prescription dose of 15 Gy, time to initiation of fractionated radiotherapy and MLC-based technique were selected based on previous clinician and institution experiences; other methodologies including commercially available blocks and cross-fire techniques are recognized but were not utilized in this experience (*24, 25*).

Neoadjuvant Radiotherapy

The conventionally fractionated portion of the neoadjuvant radiotherapy course was delivered with a megavoltage-range linear accelerator with energies from 6 to 18 MV (n = 24) or with pencil beam scanning proton therapy (n = 2) at the University of Maryland Medical Center/Maryland Proton Treatment Center. Prescription dose ranged from 45 to 50.4 Gy based on clinician judgment, particularly with regard to surrounding organs at risk and tumoral size.

Statistical Methods

Our primary hypothesis was that the addition of a single fraction of 15 Gy GRID radiotherapy would at least match the pCR rates encountered on the RTOG 0630 trial with similar rates of major wound complication to historical techniques. The threshold set for pCR was a tumoral necrosis rate of 80% or higher based on historical data correlating this cutoff to clinical outcomes as discussed below. Due to selection criteria for this approach at our institution, we expected a cohort more enriched with particularly bulky/large, high-risk sarcomas than that enrolled on prospective trial. Due to the small size of the cohort without a direct, comparator arm, primarily descriptive statistics were employed; Kaplan-Meier analyses for locoregional control, progression-free survival, and overall survival were performed utilizing the IBM® SPSS® Statistics for Windows software suite version 25.0 Armonk, NY).

RESULTS

The cohort of 26 consecutive patients treated per this institutional standard included seven females and 19 males with a median age of 60 years (range, 34–91 years). Histologic subclassifications varied as noted in Table 1. However, the most common histologic subtypes were undifferentiated pleomorphic sarcoma (n = 7), liposarcoma (n = 4), osteosarcoma (n = 4) and myxofibrosarcoma (n = 3). Four patients with osteosarcoma and one with chondrosarcoma were included in this cohort. The majority (n = 23, 88.4%) of tumors were high grade (grade 2–3), although three patients with grade-1 tumors underwent this regimen. Primary sites also varied as shown in Table 1; however, as expected, there was a plurality of lower extremity (n = 12) lesions. The remainder were relatively evenly distributed between upper extremity (n = 3), retroperitoneal (n = 3), pelvic (n = 3) and trunk (n = 3), with the exception of a single lesion in each of the abdomen and head/neck regions. All patients were pathologically staged as ypT2a (n = 3) or ypT2b (n = 23).

Three patients had undergone resection with subsequent recurrence prior to initiation of this course of therapy. Four patients had received chemotherapy prior to this course, but

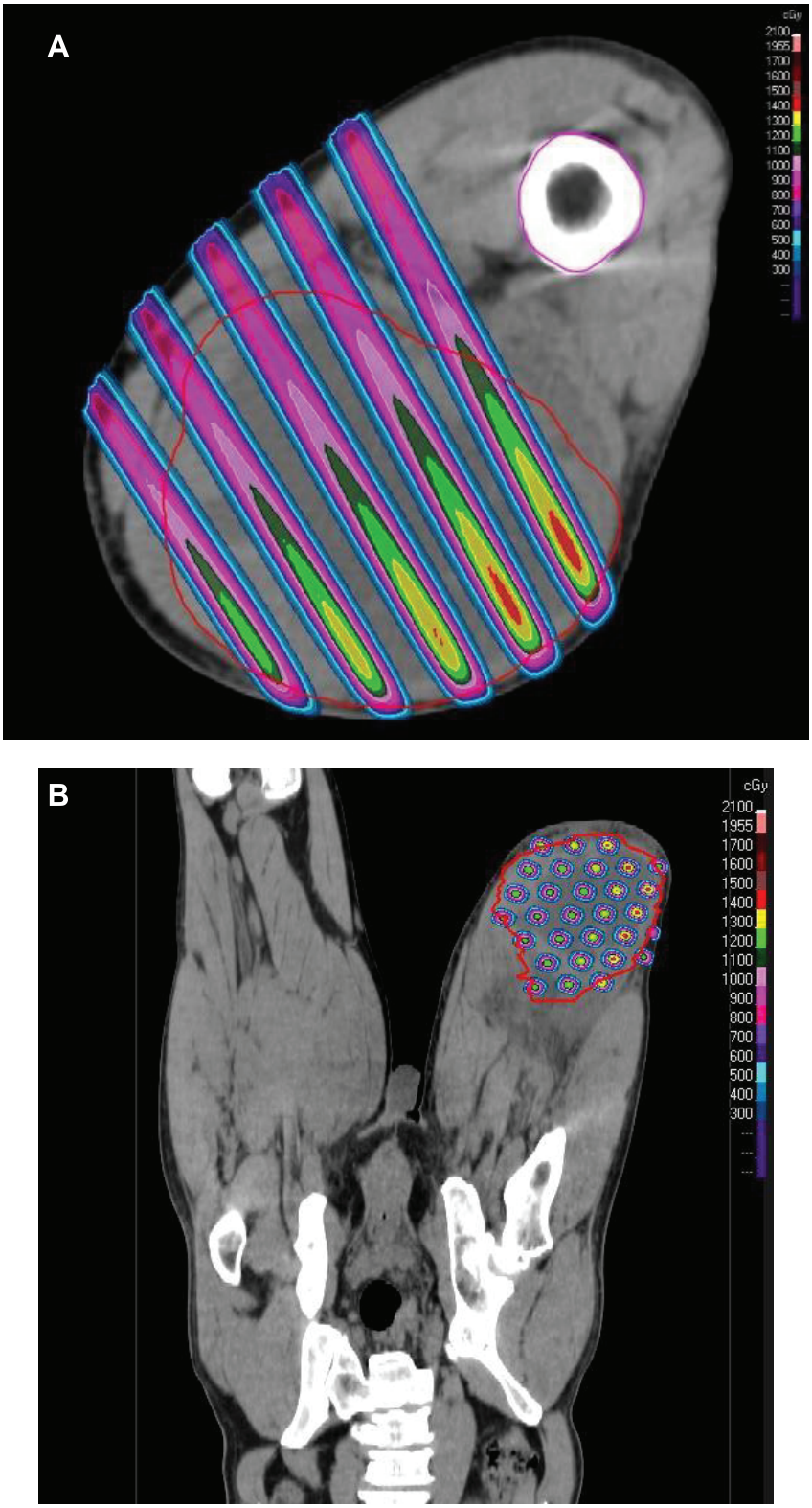

FIG. 1. Example dose distribution for a 15 Gy GRID delivery to a large thigh soft tissue sarcoma in the axial (panel A) and coronal (panel B) planes.

all of these had progressed or shown poor response prior to initiation of radiotherapy. No patients received concurrent or interdigitated chemotherapy or systemic therapy with this treatment course. Two patients received superficial thermal therapy concurrent with the fractionated portion of radiotherapy.

The average tumoral size as measured by greatest dimension between either radiographic up-front or patho-

TABLE 1

ID no.	Age	Sex	Primary site	Recurrent prior to treatment	Extremity?	Physiologic classification	Histologic grade	Pre-treatment radiographic size (cm)	Pathologic size (cm)
1	84	Male	Right thigh	No	Extremity	Undifferentiated pleomorphic	3	17×11×11	11.5×10.1×4
2	51	Male	Retroperitoneum	No	Other	Myxoid and pleomorphic	2	20×20×13	20.8×19.3×14.6
3	59	Female	Right thigh	Yes	Extremity	Atypical lipomatous tumor (well-differentiated liposarcoma)	1	14.4×4.5×5.9	12×6.5×4.5
4	64	Female	Pelvis	No	Other	Liposarcoma	1	19×9×5	15.7×10×4.2
5	59	Male	Left Calf	No	Extremity	High grade spindle cell NOS	3	15.4×6.3×5.4	16×6.5×5.5
6	48	Female	Pelvis	Yes	Other	Leiomyosarcoma	2	16×11×13	18.5×13.7×11.2
7	76	Male	Trunk-shoulder	No	Other	Myxofibrosarcoma	3	15×14.5×16.5	25.7×17.5×10.5
8	91	Male	Right calf	No	Extremity	Myxofibrosarcoma	2	4.1×5.6×9.7	8.7×7.0×5.4
9	72	Female	Retroperitoneum	No	Other	Undifferentiated pleomorphic	3	15.5×11.1×11.4	13.5×12.7×6.5
10	51	Male	Maxillary sinus	No	Other	Osteosarcoma	3	10.8×10×8	5×4.5×2.8
11	38	Male	Trunk-shoulder	No	Other	Myxofibrosarcoma	3	12×8×7.5	7.5×5.5×5.0
12	73	Female	Right Arm	No	Extremity	Leiomyosarcoma	3	10.5×7.9×7.2	11×8.5×7.4
13	75	Male	Right groin/ inguinal/ thigh	No	Extremity	Liposarcoma	3	15.5×12×10.3	15.3×9.5×8.9 cm + 5.0×3.5×1.2 cm + 9.5×6.2×1.9 cm
14	76	Male	Retroperitoneum/ Right iliac fossa	No	Other	Undifferentiated pleomorphic	3	12.5×10×9.3	8.8×8.4×7.6
15	77	Male	Abdominal	No	Other	Undifferentiated pleomorphic	2	16.3×13.7×17.1	40.0×31×22
16	58	Female	Left calf	No	Extremity	Undifferentiated pleomorphic	3	10.3×6.6×10.1 +6.5×2.7×9.8	10×9.5×6.5
17	65	Male	Left thigh	No	Extremity	Undifferentiated pleomorphic	3	16.3×10.6×8.2	18.1×11.2×10.5
18	78	Male	Right thigh	No	Extremity	Chondrosarcoma	3	12.5×12×9	12×10.2×9
19	34	Male	Right thigh	No	Extremity	Osteosarcoma	3	10×5.1×3.7	8×5.2×3.1
20	61	Male	Right thigh	No	Extremity	Osteosarcoma	3	12.8×12.7×8.6	12.5×12×11.5
21	45	Male	Right thigh	No	Extremity	Osteosarcoma	2	14×13.8×10.9	13.7×13.5×11.4
22	43	Male	Extremity-left shoulder	Yes	Extremity	Dermatofibrosarcoma	1	17.8×13.6×9.9	19.5×11.4×6.0
23	39	Female	Right thigh	No	Extremity	Liposarcoma	2	12.5×11×5.5	13.6×10.2×4.7
24	47	Male	Extremity-left shoulder	No	Extremity	Malignant peripheral nerve sheath tumor	2	8.8×5.8×8.2	8.4×7.5×6.5
25	81	Male	Pelvis	No	Other	Liposarcoma	3	12.0×7.4×13.6	11.5×5.4×2.8
26	53	Male	Chest wall	No	Other	Undifferentiated pleomorphic	3	18.1×13×10.6	13×10.5×8.5

logic staging was 15.8 cm (median, 14.2 cm; range, 8.8–40 cm) with only two lesions (8.8 cm and 9.7 cm) below 10 cm. Pre-treatment radiographic size was on average 14.2 cm (median 14.2 cm). At resection, based on the high risk, size and complex nature of these tumors, six tumors were excised with positive margins, of which none were overtly planned positive margins. No additional intraoperative or postoperative boosts were utilized. Close margins were common as noted in Table 1. A pCR was encountered in eight (32.0%) of the 25 patients for which full pathologic review was possible. The three patients with low-grade tumors had 0%, 0% and 15% necrosis, respectively. Two of the four (50.0%) patients with osteosarcoma also experienced a pCR. Finally, six (35.3%) of the 17 patients with high-grade sarcoma achieved a pCR with this regimen. Four (50.0%) of eight patients with high-grade extremity sarcomas underwent a pCR.

With a median follow-up of 2.1 years, 4 (15.4%) patients have experienced a local recurrence, including one patient who had a pCR. Nine (34.6%) have progressed (one with pCR), and seven (26.9%) have died. Actuarial two-year locoregional control, progression-free survival and overall survival were 85%, 65% and 86%, respectively. Kaplan-Meier analysis and associated curves are shown in Fig. 2.

TABLE 1
Extended.

Largest dimension (cm)	GRID dose (Gy)	Neo-adjuvant radiation dose (Gy)	Neo-adjuvant radiation dose/ fraction (Gy)	Pathologic stage	Closest pathologic margin distance (cm)	Pathologic necrosis percentages	NCIC major wound complication	Local progression after treatment	Any progression after treatment
17	15	45	1.8	ypT2b	positive	<5%	No	No	Yes
20.8	15	50.4	1.8	ypT2b	positive	<5%	No	Yes	Yes
14.4	15	50.4	1.8	ypT2b	positive	0%	No	No	No
19	15	50.4	1.8	ypT2b	positive	0%	Yes	No	No
16	15	50.4	1.8	ypT2b	negative	80%	No	No	No
18.5	15	50.4	1.8	rypT2b	positive	20%	No	No	No
25.7	15	50.4	1.8	ypT2b	0.2	90%	No	No	No
9.7	15	50.4	1.8	ypT2b	0.5	70%	Yes	No	No
15.5	15	45	1.8	ypT2b	<0.1	60%	No	No	Yes
10.8	15	49.5	1.5-2	ypT2b	<0.1	90%	No	No	No
12	15	50.4	1.8	ypT2b	0.1	60%	No	No	No
11	15	49.75	2-2.25	ypT2b	negative	95%	No	No	No
15.5	15	50.4	1.8	ypT2a	positive	ND	No	Yes	Yes
12.5	15	49.2	1.8-2	ypT2b	<0.1	50%	No	No	No
40	15	45	1.8	ypT2b	0.1	50%	No	Yes	Yes
10.3	15	50.4	1.8	ypT2a	0.7	95%	Yes	Yes	Yes
18.1	15	50.4	1.8	ypT2b	0.2	85%	No	No	No
12.5	15	50.4	1.5	ypT2b	0.9	20%	Yes	No	No
10	15	50.4	1.8	ypT2b	0.9	100%	No	No	No
12.8	15	50	2	ypT2b	0.4	50%	No	No	No
14	15	50.4	1.8	ypT2b	0.2	50%	Yes	No	No
19.5	15	50	2	ypT2b	0.6	15%	Yes	No	Yes
13.6	15	50.4	1.8	ypT2b	0.3	10%	Yes	No	No
8.8	15	50.4	1.8	ypT2a	1.5	30%	No	No	Yes
13.6	15	50.4	1.8	ypT2b	0.6	10%	Yes	No	Yes
18.1	15	50.4	1.8	ypT2b	>1.0	99%	Yes	No	No

Patients' charts were particularly screened for evidence of a major wound complication as defined by the NCIC trial. This definition includes the need for secondary operations for wound treatment, readmission to the hospital for wound care, invasive procedures for wound care, deep wound packing requirement, prolonged dressing changes necessary or repeat surgery or prolonged care for a skin graft. Nine (34.6%) of the 26 patients did have a major wound complication by this definition, including three wound dehiscence episodes, two vacuum-assisted wound drainages for persistent seromas, two debridements with vacuum drainage placements, one prolonged dressing change and one infection requiring IV antibiotics.

DISCUSSION

To our knowledge, this work represents the first significant published case series that employs only the addition of GRID to standard neoadjuvant radiotherapy in the treatment of high-risk soft tissue sarcomas. It builds on a growing experience of definitive treatments in the literature utilizing GRID for bulky cancers. The pCR rate in this small series, especially for high-grade sarcomas, well exceeded

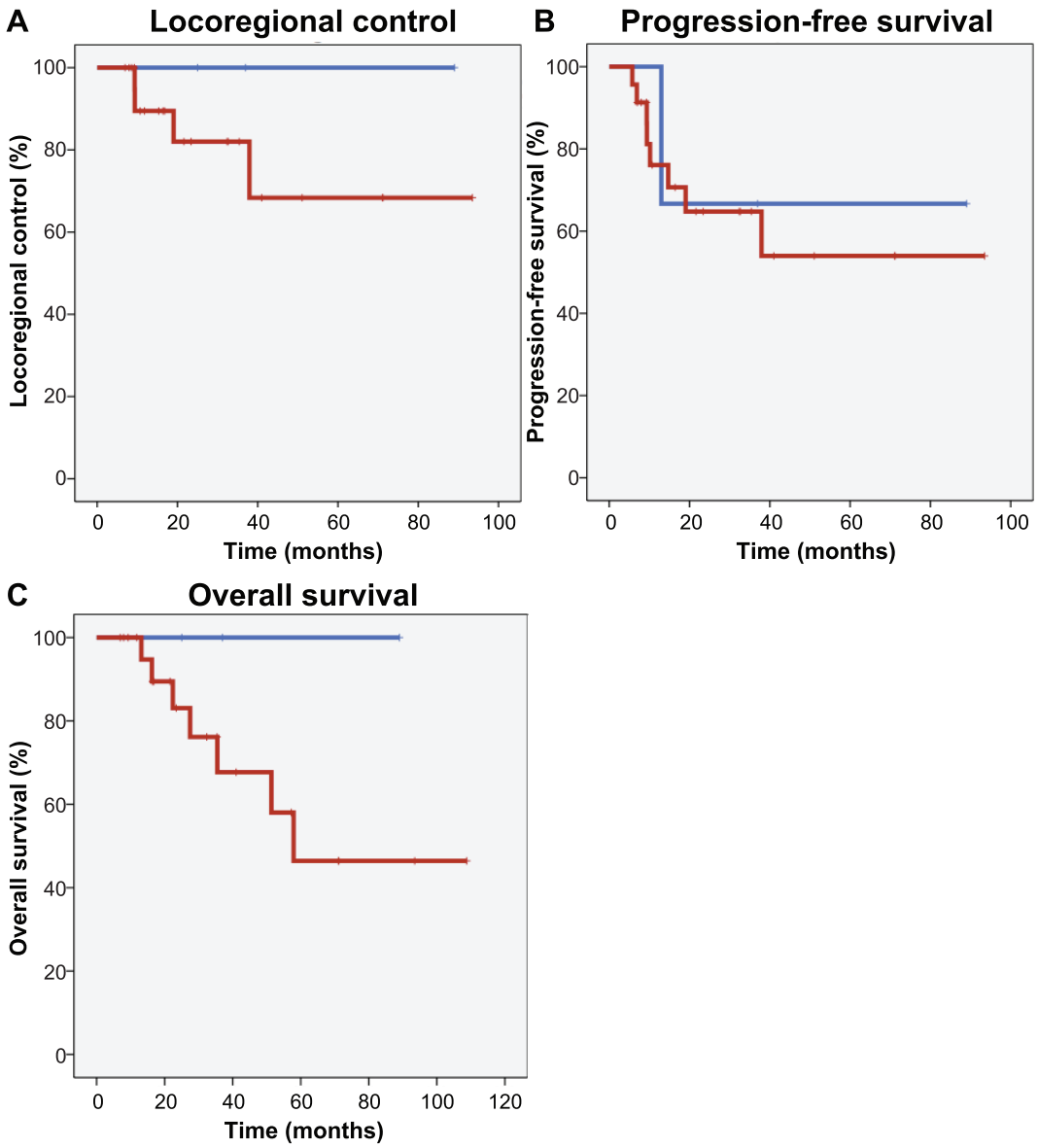

FIG. 2. Kaplan-Meier curves representing the locoregional control (panel A), progression-free survival (panel B) and overall survival (panel C) for the cohort of 26 patients stratified by tumoral grade (blue = grade 1; red = grade 2–3).

even modern prospective series encountered on the two recent RTOG trials at 19.4% and 27.5% on 0630 and 9514, respectively (*7*). For high-grade sarcomas and with a pCR threshold of 80% necrosis, GRID followed by ~50 Gy of neoadjuvant radiotherapy evidenced a pCR rate of 35.3% with 50% in extremity disease, though admittedly the number treated is small for such subset analyses. Intriguingly, low-grade tumors showed poor pathologic response, whereas included osteosarcomas responded well. As this series employed radiation alone in the neoadjuvant setting, certainly RTOG 0630 is the more direct comparator. The median tumoral size on the RTOG trial was only 10.5 cm compared to 14.2 cm in this series (*6*). Only two tumors in the current series were smaller than 10 cm. Despite a much bulkier set of tumors and including higher-risk disease sites outside of the extremities, this series achieved a numerically, substantially higher rate of pCR (*7*).

The local control in this series was consistent with historical standards and the recent RTOG trial despite, again, a bulkier, higher-risk population with a significant rate of positive/close margins (*5, 6*). Consistent with the extent of primary disease, distant metastasis and any progression occurred at a relatively high rate. However, again, pCR appeared prognostic with only one patient with pCR progressing locally and distantly. Toxicity in this series was acceptable and reasonable. The major wound complication rate was less than that experienced in the NCIC trial on which approximately two-thirds of patients had tumors less than 10 cm in greatest dimension.

Certainly, some resolvable wound dehiscences and need for vacuum assistance in wound healing are to be expected in a cohort of patients with tumors of the size of the current series. Many of the patients in this effort were treated with historical fractionated techniques, making the NCIC trial the more appropriate morbidity comparison compared to RTOG 0630, which employed modern conformal techniques with image guidance and smaller treatment margins.

The only other similar reports to our current series for sarcoma include primarily case reports of excellent clinical and pathologic responses (*18*). One other series from King Faisal Specialist Hospital and Research Centre employed 18 Gy GRID therapy followed by 50 Gy neoadjuvant radiotherapy combined with two cycles of ifosfamide and mesna, demonstrating an impressive 65% pCR (>90% necrosis) in a 14 patient series (*19*). There were no local recurrences in this series despite an initial tumoral median size of 11.5 cm. For recurrent and unresectable sarcoma, Mohiuddin *et al*. have reported the treatment of 33 patients and 40 treatment sites incorporating GRID and standard radiotherapy (four additional patients with GRID therapy alone) (*20*). Overall, they achieved a 76% response rate despite initial tumors with a median diameter of 13 cm. In patients receiving over 50 Gy fractionated radiotherapy, this improved to a 95% response rate.

GRID radiotherapy has been used in the megavoltage era in a number of disease sites and treatment settings. It has proven effective both as a short course, often for palliative purposes, as well as in the definitive treatment approach as a boost to standard fractionation. Numerous series have reflected excellent disease response or pathologic response rates in head and neck squamous cell carcinoma, melanoma and other bulky tumor types (*21–25*). There are several theorized mechanisms for the apparent benefits of GRID (*10*). First, it allows for safe dose escalation. Sarcoma has a notoriously radio-insensitive histology in which there is motivation to intensify radiotherapy, but in the neoadjuvant setting, clinicians sit squarely on the precipice of causing additional perioperative morbidity with higher doses of radiotherapy. Researchers from the University of Alabama at Birmingham, as an example, have shown tolerability of a simultaneous integrated boost to 57.5 Gy in 25 fractions to the area deemed at highest risk for recurrence. GRID offers another method for dose escalation with sparing of skin and soft tissues between beamlets which likely contributes to less perioperative and wound complications based on an improved potential for healing into the dose-escalated areas from nearby spared regions.

This echoes the original role of GRID therapy in the orthovoltage era. Bystander effects through cell–cell signaling, microvascular collapse, and immunomodulatory effects that appear unique to high- per-fraction doses of radiotherapy especially, again, with spared regions in between, have been implicated in the GRID effect (*10*). Each of these mechanisms has suggestive preclinical data support but concerted clinical trial data is desperately needed.

CONCLUSION

Single fraction GRID radiotherapy in conjunction with neoadjuvant, standard fractionation radiotherapy is feasible and tolerable in the setting of bulky, very-high-risk sarcomas. A higher than expected rate of pCR was achieved with this approach, especially in high grade tumors. Further clinical trial testing is warranted and is currently planned for a multi-institutional study.

Received: April 10, 2020; accepted: September 10, 2020; published online: October 16, 2020

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69:7–34.
2. Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Sarcoma Meta-analysis Collaboration (SMAC). Cochrane Database Syst Rev 2000; (2):CD001419.
3. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008; 113:573–81.
4. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Ganjoo KN, et al. Soft tissue sarcoma, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018; 16:536–63.
5. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002; 359:2235–41.
6. Wang D, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol 2015; 33:2231–8.
7. Wang D, Harris J, Kraybill W, Eisenberg BL, Kirsch DG, Kane JM, et al. Pathologic complete response and survival outcomes in patients with localized soft tissue sarcoma treated with neoadjuvant chemoradiotherapy or radiotherapy: Long-term update of NRG Oncology RTOG 9514 and 0630. J Clin Oncol 2017; 35:15(S):11012.
8. Kraybill WG, Harris J, Spiro IJ, Ettinger DS, DeLaney TF, Blum RH, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 2006; 24:619–25.
9. Snider JW, Francis M, Hanna N, Alexander H, Sausville E, Amin PP, et al. Use of ''virtual'' high-dose-rate (HDR) brachytherapy via spatially fractionated GRID radiation therapy (SFGRT) as part of neoadjuvant therapy in poor prognosis, bulky sarcomas. Proceedings of ASTRO, September 2014. (No. 3412). Int J Radiat Oncol Biol Phys 2014; 90:S767. (https://bit.ly/3kuoT4G)
10. Billena C, Khan AJ. A current review of spatial fractionation: Back to the future? Int J Radiat Oncol Biol Phys 2019; 104:177–87.
11. Liberson F. The value of a multi-perforated screen in deep X-ray therapy: A preliminary report on a new method of delivering multiple erythema doses without permanent injury to the skin. Radiology 1933; 20:186–95.
12. Mohiuddin M, Curtis DL, Grizos WT, Komarnicky L. Palliative

treatment of advanced cancer using multiple nonconfluent pencil beam radiation. A pilot study. Cancer 1990; 66:114–8.

13. Failla G. Irradiation through grids. Radiology 1952; 58:424–6.

14. Laissue J, Blattmann H, Slatkin D. Alban Köhler (1874–1947): Inventor of grid therapy. (Article in German). Z Med Phys 2012; 22:90–9.

15. Marks H. Clinical experience with irradiation through a grid. Radiology 1952; 58:338–42.

16. Dubben HH, Thames HD, Beck-Bornholdt HP. Tumor volume: A basic and specific response predictor in radiotherapy. Radiother Oncol 1998; 47:167–74.

17. Neuner G, Mohiuddin MM, Vander Walde N, Goloubeva O, Ha J, Yu CX, et al. High-dose spatially fractionated GRID radiation therapy (SFGRT): a comparison of treatment outcomes with Cerrobend vs. MLC SFGRT. Int J Radiat Oncol Biol Phys 2012; 82:1642–9.

18. Kaiser A, Mohiuddin MM, Jackson GL. Dramatic response from neoadjuvant, spatially fractionated GRID radiotherapy (SFGRT) for large, high-grade extremity sarcoma. J Radiat Oncol 2012; 2:103–6.

19. Mohiuddin M, Memon M, Nobah A, Ahmed Nobah, Elsebaie M, Suhaibani AAL, Shaheen RP, et al. Locally advanced high-grade extremity soft tissue sarcoma: Response with novel approach to neoadjuvant chemoradiation using induction spatially fractionated GRID radiotherapy (SFGRT). J Clin Oncol 2014; 32:15(S):10575. (https://bit.ly/3mAfVVa)

20. Mohiuddin M, Miller T, Ronjon P, Malik U. Spatially fractionated grid radiation (SFGRT): A novel approach in the management of recurrent and unresectable soft tissue sarcoma. Int J Radiat Oncol Biol Phys 2009; 75:S526.

21. Mohiuddin M, Stevens JH, Reiff JE, Huq MS, Suntharalingam N. Spatially fractionated (GRID) radiation for palliative treatment of advanced cancer. Radiat Oncol Investig 1996; 4:41–7.

22. Reiff JE, Saiful Huq M, Mohiuddin M, Suntharalingam N. Dosimetric properties of megavoltage grid therapy. Int J Radiat Biol Phys 1995; 33:937–42.

23. Kudrimoti M, Regine WF, Huhn JL, Meigooni AS, Ahmed M, Mohiuddin M. Spatially fractionated radiation therapy (SFR) in the palliation of large bulky (>8 cm) melanomas. Int J Radiat Biol Phys 2002; 54:342–3.

24. Mohiuddin M, Fujita M, Regine WF, Megooni AS, Ibbott GS, Ahmed MM. High-dose spatially-fractionated radiation (GRID): A new paradigm in the management of advanced cancers. Int J Radiat Oncol Biol Phys 1999; 45:721–7.

25. Huhn JL, Regine WF, Valentino JP, Meigooni AS, Kudrimoti M, Mohiuddin M. Spatially fractionated GRID radiation treatment of advanced neck disease associated with head and neck cancer. Technol Cancer Res Treat 2006; 5:607–12.