Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 3, pp. 721–727, 1999

0360-3016/99/$–see front matter

ELSEVIER

PII S0360-3016(99)00170-4

CLINICAL INVESTIGATION **Palliative Care**

HIGH-DOSE SPATIALLY-FRACTIONATED RADIATION (GRID): A NEW PARADIGM IN THE MANAGEMENT OF ADVANCED CANCERS

MOHAMMED MOHIUDDIN, M.D., MIHOKO FUJITA, M.D., PH.D., WILLIAM F. REGINE, M.D., ALI S. MEGOONI, PH.D., GOEFFREY S. IBBOTT, PH.D., AND MANSOOR M. AHMED, PH.D.

Department of Radiation Medicine, University of Kentucky, College of Medicine, Lexington, KY

Purpose: With the advent of megavoltage radiation, the concept of spatially-fractionated (SFR) radiation has been abandoned for the last several decades; yet, historically, it has been proven to be safe and effective in delivering large cumulative doses (> 100 Gy) of radiation in the treatment of cancer. SFR radiation has been adapted to megavoltage beams using a specially constructed grid. This study evaluates the toxicity and effectiveness of this approach in treatment of advanced and bulky cancers.

Methods and Materials: From January 1995 through March 1998, 71 patients with advanced bulky tumors (tumor sizes > 8 cm) were treated with SFR high-dose external beam megavoltage radiation using a GRID technique. Sixteen patients received GRID treatments to multiple sites and a total of 87 sites were irradiated. A 50:50 GRID (open to closed area) was utilized, and a single dose of 1,000–2,000 cGy (median 1,500 cGy) to D_{max} was delivered utilizing 6 MV photons. Sixty-three patients received high-dose GRID therapy for palliation (pain, mass, bleeding, or dyspnea). In 8 patients, GRID therapy was given as part of a definitive treatment combined with conventionally-fractionated external beam irradiation (dose range 5,000–7,000 cGy) followed by subsequent surgery. Forty-seven patients were treated with GRID radiation followed by additional fractionated external beam irradiation, and 14 patients were treated with GRID alone. Thirty-one treatments were delivered to the abdomen and pelvis, 30 to the head and neck region, 15 to the thorax, and 11 to the extremities.

Results: For palliative treatments, a 78% response rate was observed for pain, including a complete response (CR) of 19.5%, and a partial response (PR) of 58.5% in these large bulky tumors. A 72.5% response rate was observed for mass effect (CR 14.6%, PR 52.9%). The response rate observed for bleeding was 100% (50% CR, 50% PR) and for dyspnea, a 60% PR rate only. A relatively higher response rate (CR 23.3%, PR 60%) was observed in patients who received GRID treatment in the head and neck area. No grade 3 late skin, subcutaneous, mucosal, GI, or CNS complications were observed in any patient in spite of these high doses. In the 8 patients who received GRID treatment for definitive treatment, a clinical CR was observed in 5 patients (62.5%) and a pathological complete response was confirmed in the operative specimen in 4 patients (50%).

Conclusion: The efficacy and safety of using a large fraction of SFR radiation was confirmed by this study and substantiates our earlier results. In selected patients with bulky tumors (> 8 cm), SFR radiation can be combined with fractionated external beam irradiation to yield improved local control of disease, both for palliation and selective definitive treatment, especially where conventional treatment alone has a limited chance of success.

Spatially-fractionated radiation, GRID radiation, Advanced cancer, Palliation.

INTRODUCTION

Treatment of large and bulky malignant tumors remains a challenge for oncologists. As tumor size increases, the ability of conventional external beam radiation to eradicate the tumor decreases. The limitation of normal tissue tolerance with increasing volume of tissue irradiated restricts the escalation of total radiation dose with conventional external beam therapy. Altered fractionation such as hyperfractionation or accelerated fractionation has been utilized in an effort to increase the dose to the tumor to enhance local tumor control. However, for advanced and bulky tumors (> 8 cm), local tumor control still remains dismal, even with altered dose/time fractionation approaches (3, 4). "Spatially fractionated" radiation (GRID therapy) is an adaptation of a concept in radiation therapy used in the past to deliver high cumulative doses of radiation to overcome the limitation of normal tissue tolerance. In the 1950s, this technique was routinely used with orthovoltage radiation to treat deeply seated tumors avoid prohibitive skin and subcutaneous tissue toxicity (7–9).

In the Department of Radiation Medicine at the University of Kentucky, a modified spatially-fractionated tech-

Reprint requests to: Mohammed Mohiuddin, M.D., Department of Radiation Medicine, University of Kentucky, Rose Street, Lexington, KY 40536-0084. Tel: (606) 323-6486; Fax: (606) 257-4931; E-mail: mohmohi@pop.uky.edu

This study was presented at the 39th ASTRO meeting, October 1997, Orlando, FL.

Accepted for publication 28 April 1999.

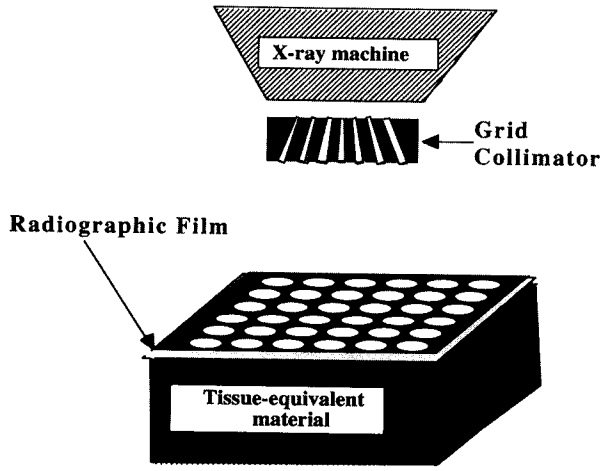

Fig. 1. Schematic diagram of the grid.

nique for use with megavoltage radiation has been utilized to treat advanced tumors (> 8 cm). This study analyzed the results of treatments in patients receiving spatially fractionated "GRID" radiation.

METHODS AND MATERIALS

From January 1995 through March 1998, 71 patients with advanced tumors (tumor size > 8 cm) were treated with SFR high-dose external beam irradiation using a GRID technique.

The GRID block was constructed from a 7-cm-thick, low-melting alloy (Cerroband) with divergent holes to produce a spatially-fractionated radiation field at the treatment area (Fig. 1). This block was mounted on a lucite tray to fit into the block tray holder of a Varian 2100C/D linear accelerator (Clinac 2100C/D, Varian Oncology Systems, Palo Alto, CA). The grid block contained 256 holes in a 16 × 16-cm square matrix to provide 50% open and 50% blocked areas. The holes through the block project 1-cm FWHM (full-width-half-maximum) beams at the isocenter of the machine with 1.8 cm center-to-center spacing. Various field sizes up to a maximum of 20 × 20 cm at the level of the isocenter can be treated with this block.

Dosimetric characteristics of the grid irradiation field were determined by measuring the relative dose distribution in a plane perpendicular to the beam (i.e., beam profile) and also along the beam direction (i.e., percent depth dose). Beam profiles of 6 MV X-rays were measured along two orthogonal directions (i.e., cross-plane and in-plane) in a tissue equivalent material (Solid Water, Radiation Measurements Inc., Middleton, WI) using Kodak radiographic film (Kodak X-Omat V Film, Eastman Kodak Co., Rochester, NY). These measurements were performed at a depth of 5 cm for field sizes of 5 × 5 cm, 10 × 10 cm, and 20 × 20 cm. For these measurements, 10 cm of backscattering material was used to provide full-scattering conditions. The beam profiles for 6-MV X-rays along two orthogonal directions are shown in Fig. 2. This figure indicates that the dose under the blocked regions of the grid was about 25–30% of the dose at the center of the grid holes. Moreover, the variations of the FWHM of the absorbed dose under each grid hole were insignificant (within 0.2 mm). The differences between in-plane and cross-plane profiles are due to the pattern of grid holes. The small peaks in the in-plane profile represents the area between two grid holes.

Absolute doses were measured at the center of the grid holes and in the blocked areas of the grid. These measurements were performed at the depth of maximum dose (D_{max}) using a thermoluminescence dosimeter (LiF TLD-100, Harshaw Chemical Co., now Solon Technologies, So-

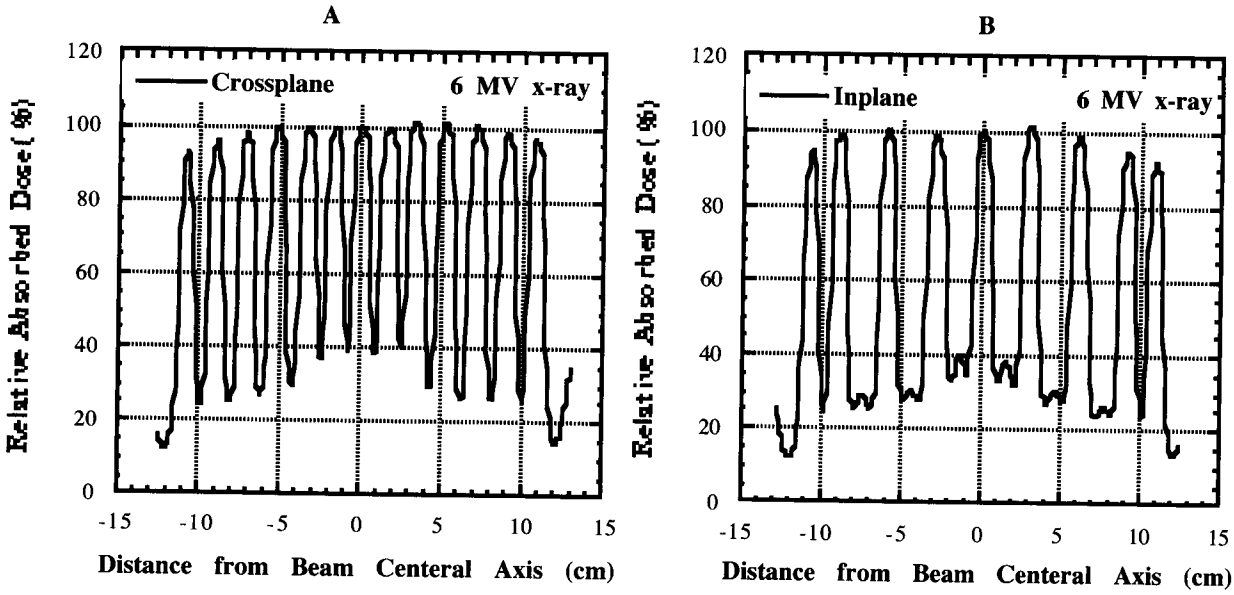

Fig. 2. Cross plane (A) and in plane (B) dose profiles with SFR radiation.

lon, OH) in a solid water phantom. The irradiated TLDs were read using a Harshaw TLD reader (Atlas 2000A-B), and responses were converted to dose following the procedures described by Meigooni *et al.* (10). Each measurement consisted of at least four TLDs at each region. After reading the TLDs, they were annealed using the procedure recommended by Cameron *et al.* (1). The results of the TLD measurements for 6 MV and 18 MV indicate a ratio of 0.983 and 0.896, respectively, between the dose at the center of the grid hole and the dose in the open field. However, the dose in the blocked region of the grid was 25% and 44% of the dose in the center of the grid hole for 6-MV and 18-MV X-rays, respectively, which is in agreement with the film dosimetry.

Of the 71 patients who received GRID treatment in this study, 40 were male and 31 were female. Sixteen patients received GRID treatments to multiple sites, for a total of 87 irradiated sites. Sixty-three patients received high-dose GRID therapy for palliation with or without regular fractionated irradiation. The most frequent complaints were pain and mass effect. Some patients complained of multiple symptoms.

Sites for GRID treatment are shown in Table 1. The total dose delivered by GRID was 1,500 cGy (68 treatment sites). Patients who had received prior radiation to the treatment site (8) were given 1,000–1,200 cGy, and patients with unusually large tumors (11) received 2,000 cGy. After the completion of GRID treatments, the responses to GRID treatments were evaluated and classified into complete response, partial response, and no response. Patients with advanced end-stage cancer who died during treatment, or within 1 month of treatment were considered inevaluable for response (7), but were included for toxicity assessment.

In 8 patients, GRID therapy was given as part of definitive treatment combined with conventionally-fractionated external beam irradiation with follow-up surgery. For patients who underwent surgery, pathological specimens were reviewed to determine the residual extent of the tumor.

Table 1. Spatially fractionated radiation: Distribution of patients by site

Site	No. of patients
Lung	18
Head & neck	17
Gastrointestinal	4
Sarcomas	10
Genitourinary Tract	5
Gynecologic	8
Skin	11
Miscellaneous:	
Melanoma	3
Breast	3
Thyroid	2
Unknown	4
Liver	2
Total	87

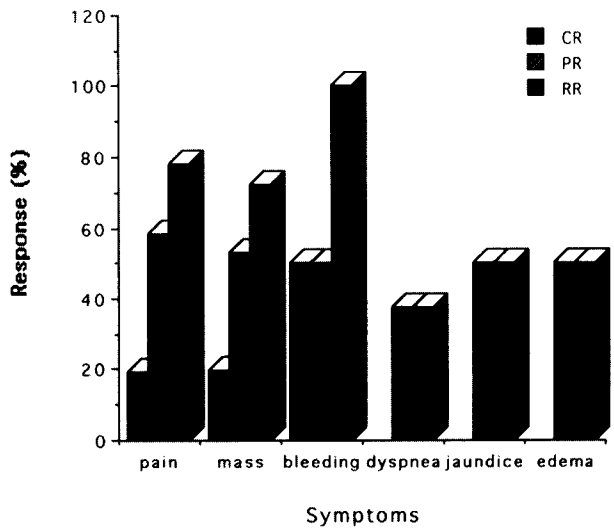

Fig. 3. Symptomatic response following SFR (grid) radiation. CR = complete response; PR = partial response; RR (response rate) = CR + PR.

RESULTS

All patients in this study were monitored closely to assess normal tissue morbidity and to observe treatment response. Follow-up ranged from 3 to 42 months (median follow-up 7 months).

Analysis of all evaluable patients revealed an overall response rate (CR + PR) of 75.7%. Complete response was observed in 16% of all treatments. For palliative treatment, a 78% response rate (CR + PR) was observed for pain, including a complete response of 19.5% and a partial response of 58.5% in these bulky tumors (Fig. 3). A 72.5% response rate was observed for mass effect, including a complete response of 14% and a partial response of 52.9%. The response rates for bleeding and dyspnea were 100% and 60%, respectively. Figure 4 shows the response rates at the different treatment sites. In the head and neck area, the response rate was relatively higher compared to other sites, including a complete response of 23.3% and partial response of 70%. Examples of patient responses are shown in Figs. 4 and 5.

The therapeutic response was analyzed according to GRID doses, and is shown in Table 2. An overall response of 94% was achieved with doses > 1,500 cGy, while grid doses < 1,500 cGy achieved a response rate of 62% (p = 0.002). Response was also analyzed by concurrent external beam radiation dose. An overall response was observed in 86% of patients treated with GRID therapy alone without external beam radiation (0% CR and 86% PR). Ninety-two percent of patients (62 of 66) treated with GRID therapy and concurrent external therapy responded, and the complete response was higher for patients treated with external beam radiation dose of 4,000 cGy or greater, as compared to lower doses (24% vs. 8%, p = 0.06) (Table 2).

Analysis of therapeutic response according to histology revealed that squamous cell carcinoma and adenocarcinoma

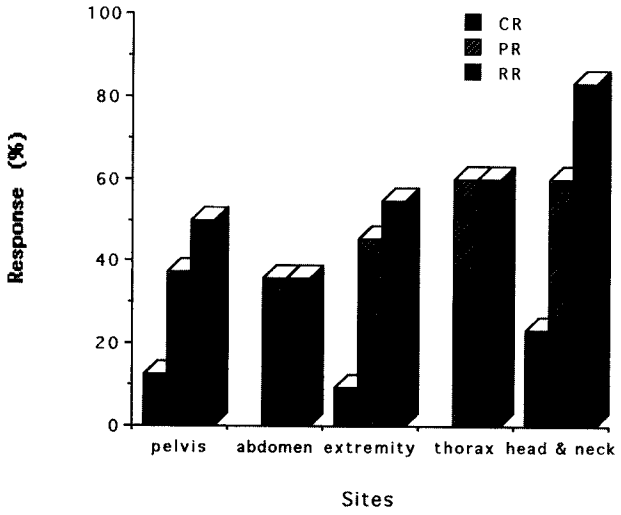

Fig. 4. Response by treatment site following SFR (grid) radiation. CR = complete response; PR = partial response; RR (response rate) = CR + PR.

had an overall response rate of 94%. Treatment for sarcoma resulted in overall response rate of 83%, while for melanoma, an overall response rate of 50% was observed (Table 3). However, complete responses were higher in squamous cancers (29%) as compared to adenocarcinomas (0%) and sarcoma (11%).

With the exception of one patient, there was no significant acute morbidity, in spite of the large single dose delivered. This patient with advanced cancer of the pharynx developed rapid tumor lysis following SFR radiation, resulting in a carotid blowout and death. Another patient received 2,000 cGy to the oral cavity and developed moderate acute mucositis (grade 3). The patient recovered from this without significant late effect. Mild erythema of the skin was observed transiently in some patients (grade 2), but did not result in skin breakdown. Nausea, vomiting, or diarrhea were not observed in patients receiving such high single dose fractions to the abdomen and pelvis. None of the patients developed severe late complications (grade 3) in the skin, subcutaneous, mucosal, gastrointestinal, or central nervous system.

In 8 patients, GRID therapy was given as a part of definitive treatment combined with conventionally fractionated external beam irradiation with or without subsequent surgery. In Table 4, the site of primary tumor, site of irradation, dose of GRID treatment, and external beam dose are shown for patients who received GRID therapy as part of definitive treatment. Three patients had head and neck primary tumors. In these 8 patients, clinical complete response was observed in 5 patients (62.5%) and pathological complete response was confirmed in the operative specimen in 4 patients (50%). One patient who had a huge (14 cm) Merkel cell tumor in the neck obtained a clinical complete response.

DISCUSSION

Current approaches to optimizing radiation therapy in the treatment of most tumors are dominated by dose/time fractionation studies. "Spatially-fractionated" radiation as opposed to dose/time fractionation has received little attention over the last several decades. In the early part of the twentieth century, roentgen therapy with 100–400-kVp X-rays was the only available means of delivering radiation treatments. Poor depth dose distribution and lack of skin sparing limited the use of orthovoltage radiation in the treatments of deeply situated tumors. In 1909, Kohler in Germany described radiation through a "perforated screen" with regularly-spaced blocked areas through a metallic screen or

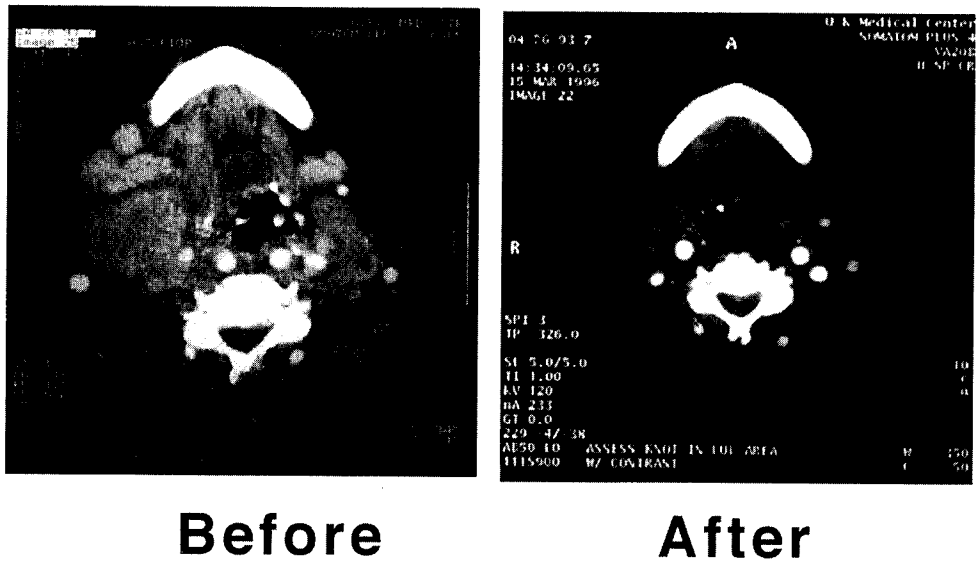

Fig. 5. Neck nodes from primary squamous cell cancer of the oropharynx. (A) Before and (B) after 1,500 cGy SFR (grid) and 6,000 cGy external beam radiation.

Table 2. Spatially fractionated radiation: Response rate by radiation dose

	No. of pts.	Complete response	Partial response	Total response	No response	Not evaluable
SF Grid Dose						
< 1500 cGy	8	1/8 (12%)	4/8 (50%)	5/8 (62%)	3/8 (38%)	0
≥ 1500 cGy	79	12/72 (17%)	56/72 (68%)	68/72 (94%)	4/72 (6%)	7
External Beam Dose						
0 cGy	17	0/14 (0%)	12/14 (86%)	12/14 (86%)	2/14 (14%)	3
< 4000 cGy	25	3/23 (13%)	18/23 (78%)	21/23 (91%)	2/23 (9%)	2
≥ 4000 cGy	45	10/43 (24%)	30/43 (70%)	40/43 (94%)	3/43 (6%)	4
		13/80 (16%)	60/80 (75%)	73/80 (91%)	7/80 (9%)	7

sieve, creating an effect similar to treatment with multiple small pencil beams (6). Subsequently, Liberson in the United States used this technique for the successful treatment of deeply seated tumors (7). This GRID technique allowed delivery of high doses of radiation in clusters of small areas without producing prohibitive normal tissue damage to skin and subcutaneous tissues. The side and back scatter properties of low-energy X-rays in tissues were exploited to obtain relatively homogenous doses of radiation in deeply located tumors. Results of clinical experience with GRID therapy indicate that the small volumes of skin and subcutaneous tissue can safely tolerate radiation doses in the range of 12,000–20,000 cGy, and differential doses of 6,000–7,000 cGy could be delivered to deep tumors (5). The development of megavoltage radiation with its potential for skin sparing and better depth dose distribution made the use of "spatially fractionated" (GRID) therapy obsolete as a means for improving depth dose delivery.

An adaptation of the principle of "spatial fractionation" using a specially constructed GRID for megavoltage radiation was previously described (11, 12). The results of GRID treatment from Thomas Jefferson University Hospital for palliation in 72 patients showed an excellent palliative response of 91%, with a complete response of 27%. A higher response rate of 100% was reported with a GRID dose of > 1,500 cGy. A higher complete palliative response rate was also observed with the combination of GRID radiation and conventional external beam radiation of 4,000 cGy or greater (12). Our study confirmed these previous findings in data collected in 87 GRID treatments in 71 additional patients from the University of Kentucky. From the previous study analyzing therapeutic response according to histology, a higher response rate was observed for sarcoma (94%) and squamous cell carcinoma (92%) (9). In this study, a higher response rate, especially of complete response, was observed in squamous cell carcinoma (29%) compared to sarcoma (11%). However, 8 of 14 patients with sarcoma in our study presented with disseminated Stage IV disease with huge tumor burden (> 20 cm), and 7 patients died within 3 months after GRID treatments. These factors might have influenced the poor response rate for sarcomas in our study.

The dose distribution from SFR grid radiation mimics that obtained with interstitial brachytherapy especially with modern high-dose rate (HDR) units. Small core areas (1–1.5 cm) of a high dose are surrounded by a transition zones of lower dose gradients, except that instead of utilizing 6–10 sources with HDR, the SFR grid is made up of up to 256 separate nonconfluent pencil beams. The SFR grid was used to deliver a single fraction of radiation to purposefully maintain the discrete inhomogeneity of dose distribution that is the singular advantage of brachytherapy in delivering a safe and higher integral dose to tissues. Our experience in this large cohort of patients treated to different sites in the body, including sensitive tissues of the abdomen and lung, indicates that this approach is well tolerated, both in terms of acute effects and that it produces no significant long-term complications. Clinical experience with open-field radiation would indicate that such doses (> 1,500 cGy) would not only produce significant acute morbidity, but also substantial late toxicity by itself (15). In contrast, SFR grid doses of > 1,500 cGy have been utilized in conjunction with definitive doses of conventionally-fractionated radiation without adding to the morbidity or detracting from the tolerance of normal tissues. Based on this experience, SFR grid radiation offers an opportunity for radiation dose esca-

Table 3. Spatially fractionated radiation: Response rate by histology

	No. of pts.	Complete response	Partial response	Total response	No response	Not evaluable
Sarcoma	19	2/18 (11%)	13/18 (68%)	15/18 (83%)	3/18 (17%)	1
Squamous Ca	36	10/35 (29%)	23/35 (66%)	33/35 (94%)	2/35 (6%)	1
AdenoCa	22	0/18 (0%)	17/18 (94%)	17/18 (94%)	1/18 (6%)	4
Melanoma	2	0/2 (0%)	1/2 (50%)	1/2 (50%)	1/2 (50%)	0
Others	8	1/7 (14%)	6/7 (86%)	7/7 (100%)	—	1
		13/80 (16%)	60/80 (75%)	73/80 (91%)	7/80 (9%)	7

Table 4. Spatially fractionated radiation: Definitive treatment H & N cancer

No.	Name	Primary site	Treatment site	Size	Grid dose	External RT dose	Clinical response	Pathological response
1	RT	Tonsil	Neck	8 × 6 cm	1500	6000	**CR**	**CR**
2	ZM	Skin	Skull	20 × 22 cm	1500	6400	PR	NE
3	JT	Parotid	Neck	9.5 × 7 cm	1500	5600	PR	**CR**
4	AA	Tonsil	Neck	8 × 4 cm	1500	6000	**CR**	**CR**
5	HA	Unknown	Neck	18 × 14 cm	1800	5800	**CR**	NE
6	WS	Merkell Cell	Neck	16 × 10 cm	1000	4640	**CR**	NE
7	CG	Skin	Face	8 × 8 cm	1500	5600	PR	NE
8	BW	Gingiva	Neck	8 × 4 cm	1500	5940	**CR**	**CR**

CR = Complete Response, RP = Partial Response (<50%), NE = Not Evaluated.

lation that hitherto was not available with conventional dose-time fractionation. This is particularly necessary in the treatment of advanced bulky (> 8 cm) cancers, where the large size of the lesion limits radiocurability and promotes intrinsic radiation resistance (3, 4).

The potential radiobiological advantage of the SFR grid radiation goes beyond the protection of normal tissue damage, and lies in its ability to significantly eradicate a large volume of tumor cells before initiating conventional-fractionated radiation. At a single dose fraction of 1,500 cGy to the open field core regions of the grid, several logs of tumor cells, both oxygenated and hypoxic, are likely to be killed, thereby allowing for better reoxygenation when irradiated by subsequent conventional radiation. In addition, new data suggest that high doses of radiation to tumor cells also results in the production of substantial cytokines that have a bystander affect in killing adjacent nonirradiated cells or partially irradiated cells under the closed areas of the grid (2, 13, 14). Preliminary data suggest that in these patients treated with SFR radiation, this effect is likely mediated through TNF-α (personal unpublished data).

Our present data, based on the experience at the University of Kentucky, confirmed the efficacy and safety of using a high-dose single fraction of spatially-fractionated radiation (SFRR) in this patient population. No significant acute morbidity was observed, and none of the patients developed late untoward effects in skin, subcutaneous, mucosal, gastrointestinal, or central nervous systems.

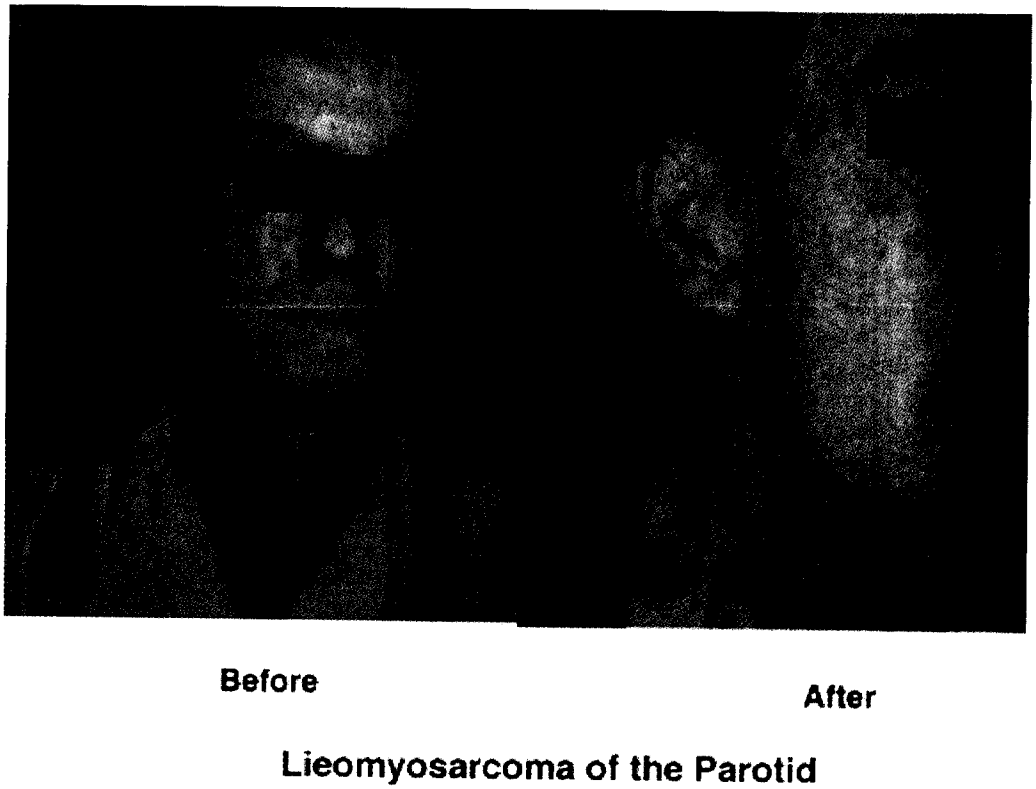

Fig. 6. Leiomyosarcoma of the parotid. (A) Before and (B) after 1,500 cGy SFR (grid) and 6,000 cGy external beam radiation (pathologically-confirmed complete response).

GRID treatment was used as a part of definitive treatment in 8 patients who presented with large tumors. We observed a clinical complete response in 62.5% of patients, and a pathological complete response was confirmed in 50% of patients. These data suggest that GRID treatment can be safely combined with full-dose conventionally-fractionated radiation to achieve significant dose escalation to improve local control. SFR radiation combined with conventional fractionated irradiation also does not compromise subsequent surgery or healing of tissues thereafter.

In summary, "spatially-fractionated radiation," adapted to megavoltage photon beams, gives us a new dimension in the radiotheraputic management of cancers, and an option to improve local control for massive and bulky tumors. This novel approach for combining spatial fractionation with tradiational dose/time fractionation should be investigated in the treatment of resistant cancers.

REFERENCES

1. Cameron JR, DeWard L, Wagner J, *et al.* Non-linearity of thermoluminescence as a function of dose for LiF (TLD-100). Vienna: International Atomic Energy, 1967.
2. Goodwin EH, Lehnert BE. Is radiation-induced inflammation responsible for bystander effects? Proceedings of the Forty-Sixth Annual Meeting of the Radiation Research Society, April 1998. p. 67.
3. Dubben H-H, Thames HD, Beck-Bornholdt, H-P. Tumor volume: A basic and specific response predictor in radiotherapy. *Radiother Oncol* 1998;47:167–174.
4. Johnson CR, Kandelwal SR, Schmidt-Ullrich RK, *et al.* The influence of quantitative tumor volume measurements on local control in advanced head and neck cancer using concomitant boost accelerated superfractionated irradiation. *Int J Radiat Oncol Biol Phys* 1995;32:635–641.
5. Jolles B. The study of connective tissue reaction to radiation. The sieve or chess method. *Br J Cancer* 1949;3:27–31.
6. Kohler H. Zur Roentiefentherapie mit Massendosen. *MMW* 1909;56:2314–2316.
7. Liberson F. The value of a multi-perforated screen in deep X-ray therapy. *Radiology* 1933;20:186–195.
8. Mark H. A new approach to the roentogen therapy of cancer with the use of a GRID. *J Mt Sinai Hosp* 1950;17:46–48.
9. Marks H. Clinical experience with irradiation through a GRID. *Radiology* 1952;58:338–342.
10. Meigooni AS, Meli JA, Nath R. Influence of the variation of energy spectra with depth on dosimetry of 192 Ir using LiF TLD. *Phys Med Biol* 1988;33:1159–1170.
11. Mohiuddin M, Curtis DL, Grizos WT, *et al.* Palliative treatment of advanced cancer using multiple nonconfluent pencil beam radiation: A pilot study. *Cancer* 1990;66:114–118.
12. Mohiuddin M, Stevens JH, Reiff JE, *et al.* Spatially fractionated (GRID) radiation for palliative treatment of advanced cancer. *Radiat Oncol Invest* 1996;4:41–47.
13. Prise KM, Michael BD, Folkard M, *et al.* Applications of microbeams in spatial studies of cellular radiation response. Proceedings of the Forty-Sixth Annual Meeting of the Radiation Research Society, April 1998. p. 67.
14. Seymour CB, Mothersill C. Low doses of gamma radiation cause release from epithelial cells of a cytotoxic factor capable of killing unexposed cells. Proceedings of the Forty-Sixth Annual Meeting of the Radiation Research Society, April 1998. p. 67.
15. Spanos WJ, Wasserman T, Meoz R, *et al.* Palliation of advanced pelvic malignant disease with large fraction pelvic radiation and misonidazole: Final report of RTOG Phase I/II study. *Int J Radiat Oncol Biol Phys* 1987;13:1479–1482.