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PHYSICS CONTRIBUTION

THERAPEUTIC ADVANTAGE OF GRID IRRADIATION FOR LARGE SINGLE FRACTIONS

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Purpose: In the present work, we used model calculations of cell survival to compare the effects of single fraction high-dose grid therapy with those of uniform dose delivery on tumor and normal tissues.

Methods and Materials: The grid consisted of a hexagonal pattern of divergent holes in a Cerrobend block. A linear-quadratic model was used to find the surviving fraction of tumor and normal tissue cells after high-dose irradiation. Equivalent uniform doses were determined according to the tumor cell kill. The ratio of the normal tissue surviving fraction under grid irradiation to that obtained under equivalent uniform dose irradiation was taken as a measure of therapeutic gain.

Results: The therapeutic ratio varied from 0.80 to 13.22 for the range of cell sensitivities investigated, with single fraction doses of 10.0–20.0 Gy. Optimization studies showed no significant dependence of therapeutic gain on hole spacing.

Conclusion: With high, single-fraction doses, grid irradiation revealed a therapeutic advantage over uniform dose irradiation whenever the tumor and surrounding normal tissues cells were equally radiosensitive, or, particularly, if the tumor cells were more radioresistant than the normal cells. The therapeutic gain did not appear to be a strong function of grid design. © 2004 Elsevier Inc.

Grid therapy, Linear-quadratic model, Equivalent uniform dose.

INTRODUCTION

The advantages of grid use in large-dose radiotherapy (RT) have been well known since the era of orthovoltage irradiation (1, 2). It was found then that when small areas of the irradiated skin and subcutaneous tissues were shielded, such as with a grid, these protected areas served as centers for regrowth of the normal tissues overlying the target. The buildup of dose in the shielded regions owing to scattered photons allowed adequate dose uniformity to be achieved at the tumor depth. With the advent of megavoltage X-ray machines and their associated skin sparing, the use of grids fell away. Recently, however, megavoltage grid therapy has been reintroduced to deliver large, single fractions of radiation to patients with bulky tumors (3–7). The technique is generally used either to debulk the tumor by reducing the tumor cell population significantly before the initiation of fractionated RT or to offer palliation to patients who have already been treated to tolerance (3, 4). A goal of this therapy is to achieve the debulking and/or palliation with minimal damage to the healthy surrounding tissues. Mohiuddin *et al.* (3) demonstrated the efficacy and safety of this technique in a study of 71 patients undergoing grid RT at maximal single-fraction dose levels of 10–20 Gy.

Several mechanisms have been proposed to explain the success of grid therapy in this context (3). For patients given grid therapy followed by conventional fractionated RT, the high local cell kills after a single, high-dose fraction are expected to yield improved reoxygenation during the subsequent conventional RT. Also, a cytokine-based bystander effect leads to enhanced cell kill in regions adjacent to those receiving high single-fraction doses. In the present work, we made use of standard linear-quadratic modeling to evaluate the cell survival in regions undergoing high-dose single-fraction grid irridation at megavoltage energies and compared the effects of grid therapy with those of uniform dose delivery on tumor and normal tissues at high, single-fraction dose levels.

METHODS AND MATERIALS

The dosimetric characteristics of high-energy grids have been discussed by Mohiuddin *et al.* (3), Mitev and Suntharalingam (5), and Reiff *et al.* (6). A megavoltage grid currently in clinical use is shown in Fig. 1. The grid consists of a hexagonal

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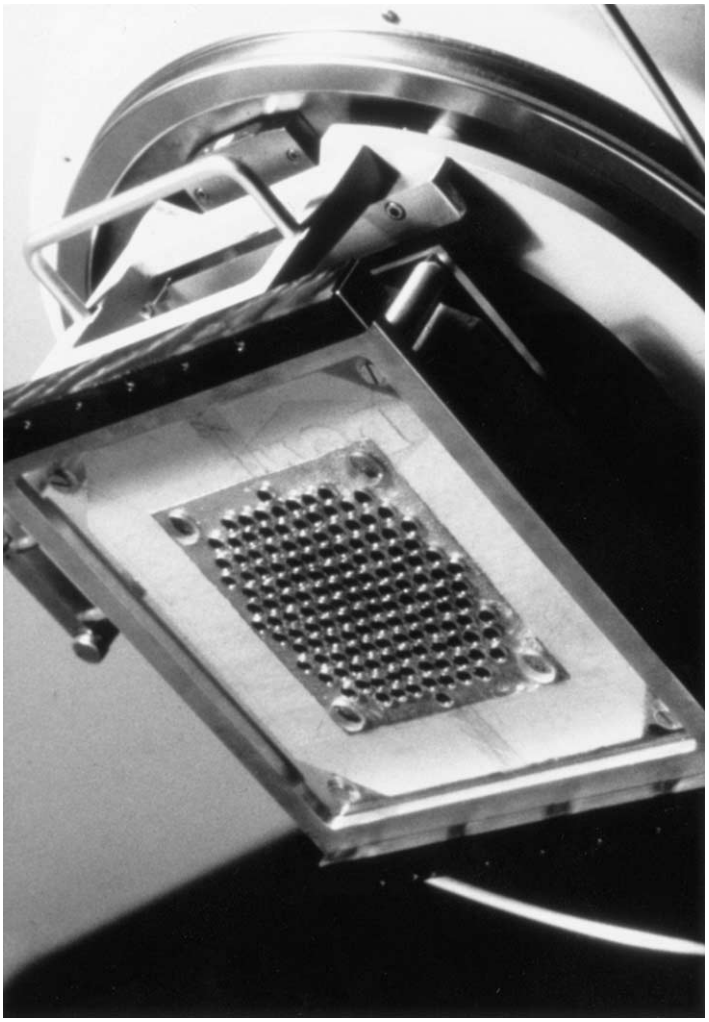

Fig. 1. Grid used clinically.

pattern of circular divergent holes in a Cerrobend block, designed to be mounted in the standard linear accelerator accessory mount. The holes have an effective diameter of 1.3 cm and a center-to-center separation of 1.8 cm when projected to isocenter. With this design, approximately one-half of the tissues in the collimated field are irradiated by unattenuated rays of the primary beam, with the other one-half falling under the Cerrobend block. Partial volume irradiation such as that achieved with the grid can be expected to affect the various cell types differently. In the linear-quadratic model of cell survival (8), the surviving fraction (SF) of cells after a single instantaneous uniform dose (D) is

$$S = \exp(-\alpha D - \beta D^2) \quad (1)$$

Typical values for the α/β ratio are 10 Gy for tumor cells and 2.5 Gy for normal tissues. These values were used in the calculations presented here. Following Niemierko (9), a cell survival of 0.5 for a dose of 2 Gy was also assumed, although a wide range of values can be found in the literature. If this value is used for both tumor and normal cells, the resulting value of α and β will be 0.289 and 0.0289, respectively, for tumor cells and 0.193 and 0.077, respectively, for normal tissues.

Figure 2 shows a dose function representing the relative dose plotted outward, at constant depth, from the central ray of an irradiated region under a grid hole. This dose hemi-profile was generated using the averaged data from profiles measured at 5 cm depth in a 6-MV photon beam. As seen from the dose function, the dose minima under the grid strips are typically at a dose level of about 25% of the dose maxima. To illustrate the effect of the grid on cell kill in a transparently simple model, we initially ignored the dose penumbra and assumed that for a 15-Gy grid radiation, one-half of the volume would be irradiated at a level of $D_1 = 15$ Gy and the other one-half at a level of $D_2 = 3.75$ Gy. Using Eq. 1, the SF for the tumor cells would be 1.98×10^{-5} at the 15-Gy level and 0.2256 at 3.75 Gy. For normal tissues, the corresponding SFs would be 1.67×10^{-9} at 15 Gy and 0.1645 at 3.75 Gy. The average SFs, assuming equal volumes irradiated at the two dose levels, are found from

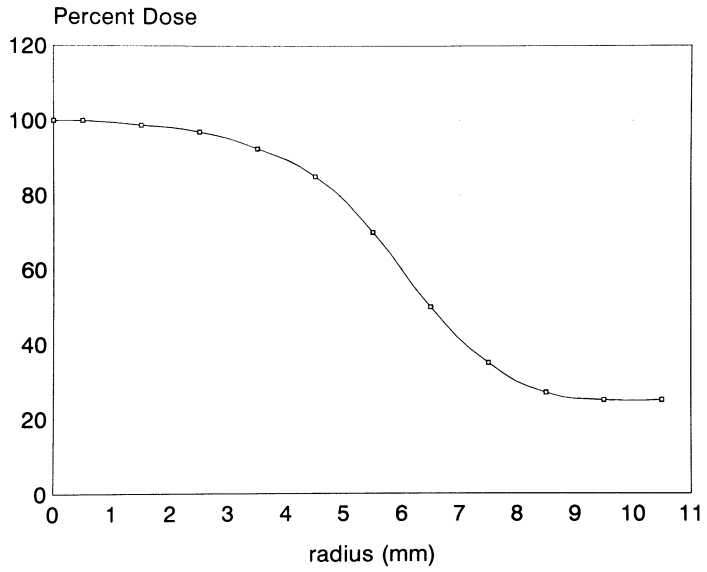

Fig. 2. Relative dose as function of distance from center of projected grid hole position at depth of maximal dose.

$$Sav = 0.5*[\exp(-\alpha D_1 + \beta D_1^2) + \exp(-\alpha D_2 - \beta D_2^2)] \quad (2)$$

This gives Sav = 0.1128 for the tumor and 0.0823 for normal tissues.

The single uniform open field dose that would result in a tumor cell SF of 0.1128 can also be found from Eq. 1. Solving the equation for the unknown D gives a tumor cell equivalent dose (D_{eq}) of 5.03 Gy. Thus, if a uniform dose of 5.03 Gy were used in place of the 15-Gy grid dose, the tumor cell kill would be the same (9). However, the normal tissue SF for a uniform dose of 5.03 Gy is

$$SF_n(5.03\ Gy) = .0540$$

This is somewhat less than the SF determined for the grid radiation. Thus, for the two irradiation schemes resulting in identical tumor cell kill, the normal tissue cell survival would be greater with the grid than with the open field.

The therapeutic advantage of grid irradiation was modeled in this study in terms of the normal tissue cell survival ratio (grid/open field ratio) for the same tumor cell survival. In the present case of a 15-Gy single dose, with the penumbra effects ignored, the therapeutic ratio is

$$TR = SF_n(15\ Gy\ grid)/SF_n(5.03\ Gy\ open) = 1.52$$

Thus, in the simplified case of a bilevel dose distribution, the use of a grid in place of an open field uniform dose to achieve a desired tumor cell kill results in a 52% increase in normal tissue cell survival (7).

In the case of megavoltage irradiation through an actual grid, the dose distribution may be dominated by physical penumbra. From measurements on film irradiated in a flat phantom (3), it was found that the dose at a given depth in the grid radiation field can be reasonably approximated by a cylindrically symmetric distribution around each local dose maximum under the hole projections. The local dose profile can then be characterized by a radial dose function centered on each local maximum (Fig. 2). The whole field dose distribution at a given depth can then be described in terms of a collection of identical field units (Fig. 3), with each unit characterized by the same radial dose function. By neglecting the variation of the dose with depth, the dose–volume histogram for a given radiation level can then be obtained

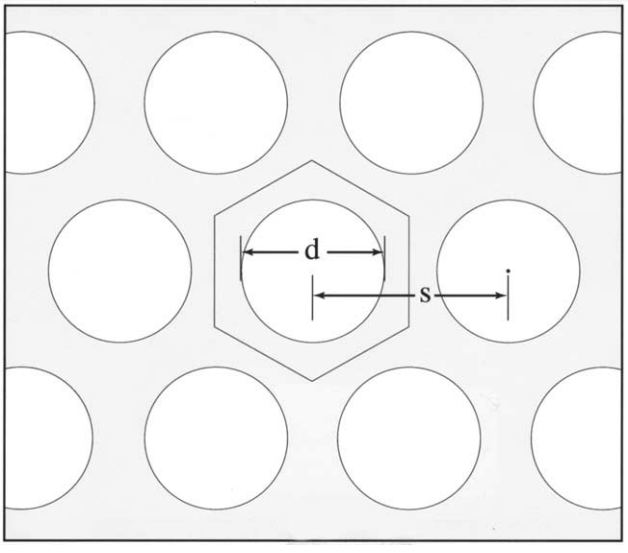

Fig. 3. Fundamental grid unit.

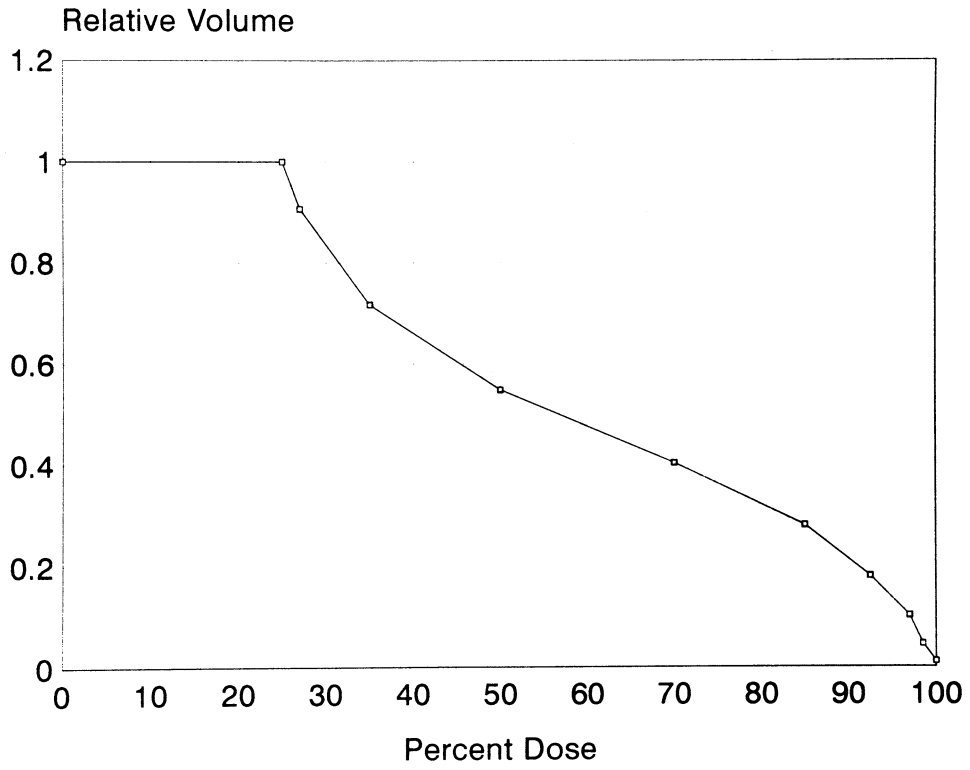

Fig. 4. Representative grid dose–volume function at fixed depth in phantom.

from that of a single unit (Fig. 4). The cell surviving fraction in tissue irradiated by such a distribution is determined from

$$SF = \Sigma\, v_i \exp(-\alpha d_i - \beta d_i^2), \quad (3)$$

where d_i is the dose delivered to the i-th volume element, and v_i is the fractional volume of that element (i.e., $\Sigma\, v_i = 1$.

The surviving fraction calculations were carried out using a differential dose–volume function (Fig. 5) derived from the dose–volume function shown in Fig. 4. Using the values of α and β given previously (for 2-Gy SFs of 0.5), with a grid radiation of 15-Gy maximal dose, the SFs would be 0.0590 for tumor cells and 0.0334 for normal tissue cells. The tumor cell equivalent uniform dose in this case would be $D_{eq} = 6.088$ Gy. If this uniform dose were applied, the resulting normal tissue cell survival would be 0.0178. As in the simplified bi-level example, a therapeutic benefit is predicted, in this case with an even greater therapeutic ratio of 1.88.

The above example assumes a cell survival of 0.5 for a 2-Gy uniform dose for both tumor and normal tissue cells. We can examine the therapeutic effect of the grid on cells of differing radiosensitivity further by varying the 2-Gy SFs. To this end, the tumor tissue 2.0-Gy SF ($SF2_t$) was assigned values from 0.3 to 0.7, with the normal tissue 2.0-Gy SF ($SF2_n$) held constant at 0.5. The resulting therapeutic ratios are shown in Table 1 for maximal grid doses of 10, 15, and 20 Gy.

To examine the effects of varying the normal tissue sensitivity, additional calculations were carried out with the tumor $SF2_t$ held constant at 0.5 and the $SF2_n$ varied from 0.3 to 0.7. The results are shown in Table 2. From these, we note that the predicted therapeutic benefit increased with the maximal dose and decreased with increasing normal tissue radioresistance, as represented by $SF2_n$.

As noted previously, the grid currently in clinical use was designed to achieve approximately equal volumes of directly irradiated and shielded tissues. Numerical studies were carried out to determine whether cell SF considerations could be used to determine an optimal grid design. For this purpose, the hole separation was varied while the hole diameter remained fixed. The resulting dose–volume histograms were estimated under the assumption that the radial dose function of Fig. 2 remained valid within the limits of each grid field unit. The dose–volume functions were then used in Eq. 3 to determine cell survival and the corresponding therapeutic ratios as a function of hole separation. It was also assumed that in varying the hole separation (and fraction of tissue under primary beam irradiation), maintaining the clinical effectiveness of the current grid on tumor cells was desired. For this purpose, as the ratio of irradiated to shielded tissue volumes was varied, the dose maximum was also varied so as to keep the tumor cell SF at a constant value. The effect of this variation on normal

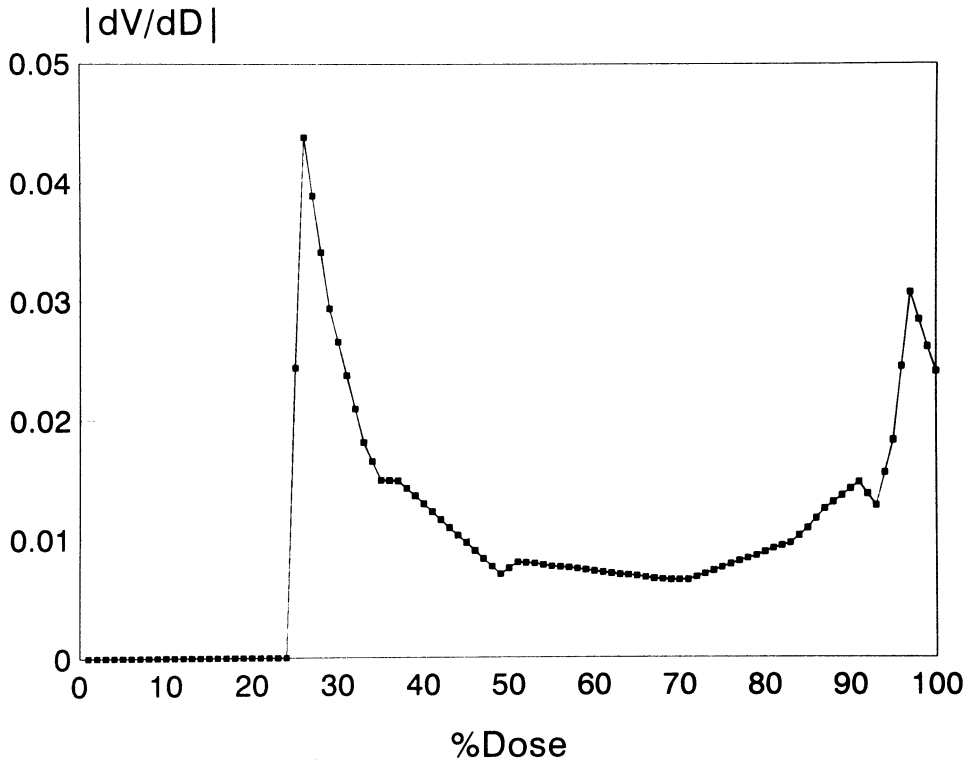

Fig. 5. Differential dose–volume function from dose–volume histograms of Fig. 4.

tissue cell survival and the therapeutic ratio was studied to investigate the possibility of optimizing the grid design.

RESULTS

For all values of $SF2_t$ examined, it is seen from Table 1 that the therapeutic benefit predicted for the grid increased with the maximal single-fraction dose. It can also be seen that the therapeutic ratio increased with increasing $SF2_t$. Because higher values of $SF2_t$ represent tumor cells more resistant to the effects of radiation, we concluded that the therapeutic benefits of grid RT will be more pronounced for more radioresistant tumor cells. We also noted that for tumor cells that are radiosensitive relative to normal tissues ($SF2_t \leq 0.3$), grid RT cannot be recommended on the basis of cell survival alone.

For variable normal tissue cell sensitivity, Table 2 also shows a positive therapeutic ratio for most of the range studied. A negative effect was seen only in the case of very radioresistant normal tissue cells. Such normal tissue resistance to high single-fraction radiation doses is not generally observed.

The results of the investigation of grid design parameters are given in Table 3, which shows the maximal dose, normalized integral dose (volume-weighted average dose, normalized integral dose $= \Sigma\ v_i\ d_i$), percentage of volume under primary beam irradiation (under the holes), and therapeutic ratio as a function of center-to-center hole separation (as projected to the isocenter). The maximal dose was varied to maintain the tumor

Table 1. Therapeutic ratios as a function of tumor 2-Gy surviving fraction, with normal tissue 2-Gy surviving fraction at 0.5

	Therapeutic ratio		
$SF2_t$	MD 10 Gy	MD 15 Gy	MD 20 Gy
0.3	0.88	0.94	1.02
0.4	1.10	1.29	1.51
0.5	1.40	1.88	2.45
0.6	1.85	3.05	4.63
0.7	2.56	5.90	11.53

Abbreviations: $SF2_t$ = tumor 2-Gy surviving fraction; MD = maximal dose.

Table 2. Therapeutic ratios as a function of the normal tissue 2-Gy surviving fraction with tumor 2-Gy surving fraction at 0.5

	Therapeutic ratio		
$SF2_n$	MD 10 Gy	MD 15 Gy	MD 20 Gy
0.3	3.37	6.96	13.22
0.4	2.02	3.27	5.00
0.5	1.40	1.88	2.44
0.6	1.06	1.23	1.41
0.7	0.80	0.89	0.92

Abbreviations: $SF2_n$ = normal tissue 2-Gy surviving fraction; MD = maximal dose.

Table 3. Maximal dose, integral dose, percentage of volume under primary beam irradiation (under the holes), and therapeutic ratio as a function of center-to-center hole separation, for a maximal dose of 15 Gy at hole separation 1.8 cm

s (cm)	D_{max} (Gy)	d_{int} (Gy)	$\%V_{irr}$	TR
1.5	9.99	7.30	72	1.81
1.6	11.50	7.86	63	1.91
1.7	13.29	8.49	56	1.93
1.8	15.0	8.97	50	1.88
1.9	16.35	9.20	31	1.78

Maximal dose was varied so as to maintain the tumor cell equivalent uniform dose constant at 6.088 Gy. Results show a broad maximum around a separation of 1.7 cm, but a variation in therapeutic ratio of only 8% for the range examined.

Abbreviations: S = (hole) separation; D_{max} = maximal dose; d_{int} = integral dose; $\%V_{irr}$ = percentage of volume under primary beam irradiation; TR = therapeutic ratio.

cell equivalent uniform dose constant at 6.088 Gy, the value obtained for a 15-Gy maximal grid dose using the current actual hole spacing of 1.8 cm at the isocenter. The results showed a broad maximum around a separation equal to 1.7 cm, but a variation in therapeutic ratio of only 8% for the range examined. The average cell kill in all cases was greater with penumbra effects included than for the bi-level idealization, even though the integral dose was somewhat smaller. Also, the inclusion of the penumbra effects led to a greater therapeutic ratio at the higher maximal dose levels.

The data of Table 3 were plotted in Fig. 6, along with the corresponding therapeutic ratios for maximal grid doses of 10 and 20 Gy. These curves all showed broad maxima for hole separations from 1.6 to 1.85 cm, but relatively little variation in the therapeutic ratio in the range studied. Because of the weak dependence of the therapeutic ratio on hole separation, the positions of the therapeutic ratio maxima may be sensitive to dose calculation accuracy and model approximations.

CONCLUSION

The results presented showed that, for a wide range of tumor tissue sensitivities, on the basis of cell survival considerations alone, single-dose partial-volume RT using a grid may have a significant therapeutic advantage over open field RT to achieve the same level of tumor cell kill. Only if the surviving fraction at 2 Gy is considerably lower for tumor cells (indicating highly radiosensitive cells) than for normal cells is this trend reversed. The combination of radiosensitive tumor cells and radioresistant normal tissues is not commonly encountered in the clinical setting. In the more interesting case of radioresistant tumor cells, the therapeutic gain from grid use appears to be significant. Highly radioresistant, hypoxic cells are often present in bulky untreated tumors, and it is in these cases in which grid use appears to be most advantageous.

Studies of grid design have shown that the calculated therapeutic ratios are not strongly dependent on the percentage of the tumor volume subjected to primary beam RT for the range

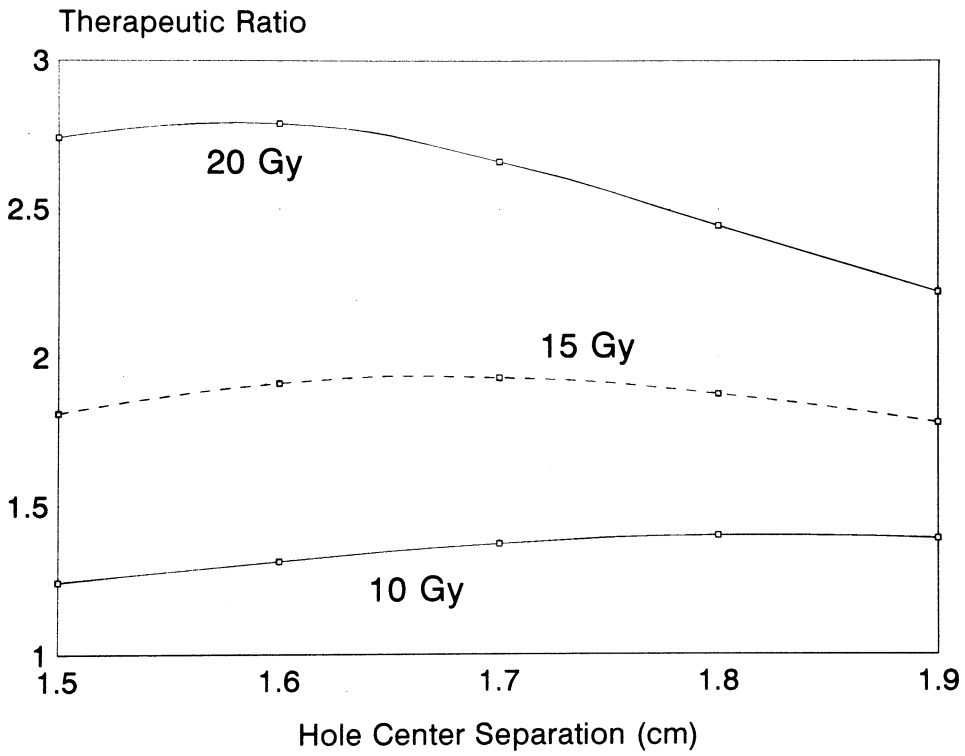

Fig. 6. Therapeutic ratio as a function of spacing between grid holes for maximal grid doses of 10, 15, and 20 Gy.

indicated in Table 3. The weak dependence of the therapeutic ratio on hole separation and the percentage of irradiated volume is confirmed by the data in Fig. 6 for grid dose maxima of 10, 15, and 20 Gy at a hole separation of 1.8 cm, covering the range of clinical experience. Thus, varying the grid design parameters did not result in a corresponding improvement in the therapeutic ratio; therefore, cell survival alone does not appear to be a dominating factor in grid optimization. Additional refinements in grid design, including studies of hole size and penumbra effects, may be carried out in the future, but are not expected to yield dramatic improvements. Grid design does not appear to be critical in achieving good therapeutic results.

The predicted improvement in normal tissue cell survival with grid irradiation is expected to act in concert with other clinical advantages traditionally associated with grid therapy to increase confidence in this modality for single high-dose RT further. The findings of the linear-quadratic model presented here could be tested by means of *in vitro* cell survival experiments using cell lines with appropriate survival characteristics. For example, the use of normal fibroblasts/epithelial cells and tumor cell lines with appropriate grid and uniform dose RT should be highly relevant to this model. Verification of the model in animal studies, particularly using tumor xenografts in nude mice, would be more difficult, because both normal and tumor cell responses need to be considered. Such studies should await the results of animal studies currently underway at our institution with the goal of clarifying the significance of bystander effects in partial-volume irradiation. These effects could significantly influence the design and interpretation of *in vivo* model verification experiments.

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