Survival and Failure Patterns of High-Grade Gliomas After Three-Dimensional Conformal Radiotherapy

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Purpose: **The goal of three-dimensional (3-D) conformal radiation is to increase the dose delivered to tumor while minimizing dose to surrounding normal brain. Previously it has been shown that even escalated doses of 70 to 80 Gy have failure patterns that are predominantly local. This article describes the failure patterns and survival seen with high-grade gliomas given 90 Gy using a 3-D conformal intensity-modulated radiation technique.**

Patients and Methods: **From April 1996 to April 1999, 34 patients with supratentorial high-grade gliomas were treated to 90 Gy. For those that recurred, failure patterns were defined in terms of percentage of recurrent tumor located within the high-dose region. Recurrences with more than 95% of their volume within the high-dose region were considered central; those with 80% to 95%, 20% to 80%, and less than 20% were considered in-field, marginal, and distant, respectively.**

Results: **The median age was 55 years, and median follow-up was 11.7 months. At time of analysis, 23 (67.6%) of 34 patients had developed radiographic evidence of recurrence. The patterns of failure were 18 (78%) of 23 central, three (13%) of 23 in-field, two (9%) of 23 marginal, and zero (0%) of 23 distant. The median survival was 11.7 months, with 1-year survival of 47.1% and 2-year survival of 12.9%. No significant treatment toxicities were observed.**

Conclusion: **Despite dose escalation to 90 Gy, the predominant failure pattern in high-grade gliomas remains local. This suggests that close margins used in highly conformal treatments do not increase the risk of marginal or distant recurrences. Our results indicate that intensification of local radiotherapy with dose escalation is feasible and deserves further evaluation for high-grade gliomas.**

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THE SUCCESSFUL treatment of malignant high-grade gliomas has not been accomplished by conventional methods, which typically involve maximal surgical resection followed by adjuvant radiation therapy (RT) and chemotherapy. Whole-brain or large-field external-beam RT had been the norm before the development of computed tomography (CT), but the potential for radiation-induced toxicity to the surrounding normal brain tissue limited the achievable doses. With advancements in three-dimensional (3-D) conformal radiation, multiple field techniques have permitted increased doses to the tumor while reducing doses received by the surrounding uninvolved brain.[1,2]

One potential concern with the use of highly conformal therapy for high-grade gliomas is that the definition of the target volume(s) for the conformal planning is quite important; incorrect definition of target volumes might lead to an increase in recurrences at the edge of the target volume(s). In an ongoing dose escalation study for high-grade gliomas at our institution, it has previously been shown that treatment of patients at the 70- and 80-Gy dose levels results in failure patterns that are nearly always within the high-dose volume and that marginal failures are rare.[3] On the basis of this analysis, additional patients with supratentorial, high-grade gliomas were entered onto a protocol to receive a total dose of 90 Gy with 3-D conformal external-beam RT.

The goal of this protocol was to determine the maximum-tolerated dose of external-beam RT for high-grade astrocytomas using 3-D conformal RT, as well as to document the duration of local control, patterns of failure, and morbidity associated with these techniques. This article is a first report of the patterns of failure demonstrated in patients treated with 90 Gy of 3-D conformal RT. It involves a more rigorous analysis of failure patterns compared with historical data.

PATIENTS AND METHODS

Study Patients

This study was reviewed and approved by the University of Michigan's Institutional Review Board. From April 1996 to April 1999, 34 patients were treated with a total dose of 90 Gy postoperatively. Patients eligible for participation included those 18 years or older with pathologically proven malignant astrocytoma. For patients on the earlier dose arms of the study, any anaplastic astrocytoma or glioblastoma was eligible, but when the World Health Organization

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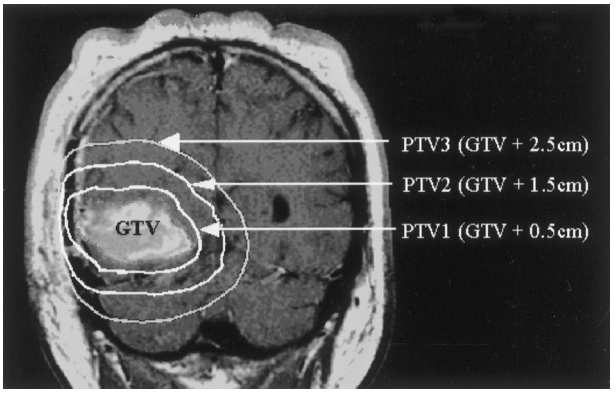

Fig 1. Protocol-defined radiation treatment volumes.

revised the pathologic grading system in 1993,[4] the study was modified to include only World Health Organization grade 4 tumors. Patients with cerebellar or brainstem lesions, those with prior cranial radiotherapy, and those whose final boost target exceeded one third of the total brain volume were ineligible.

Initial Treatment Planning and Delivery

The 3-D treatment planning methods used for the patients on this study have previously been described.[5] Briefly, all patients had a simulation using immobilization with a thermoplastic mask to ensure reproducible set-up. All patients then underwent a treatment-planning CT with images obtained at 3- to 5-mm slice intervals. In nearly all cases (32 of 34), magnetic resonance imaging (MRI) scans of the brain, obtained either for diagnostic purposes or specifically for treatment planning, were available. All imaging for treatment planning was performed postoperatively (biopsy or resection).

The available MRI scans were geometrically registered to the matching CT data sets using surface-matching techniques that have previously been described.[6-8] All imaging data were entered into the treatment planning system. Surfaces of the brain, orbits, and other nonmobile structures were contoured on each slice of the CT and/or MRI data sets. To register the new data set(s) to the baseline pretreatment CT data set, the MRI-defined surfaces were aligned with the analogous CT surfaces by using 3-D translations and rotations and confirming the registration in multiple planes of view (ie, axial, sagittal, coronal, and oblique). Verification of registration accuracy was performed with 3-D surface and multiplanar image checks.

Treatment planning was performed using an in-house 3-D planning system.[9-11] The gross tumor volumes (GTVs) were entered on each individual contrast-enhanced CT slice and/or postgadolinium MRI scan (axial/coronal planes), if available. The GTV was defined based on postoperative gadolinium-enhanced T1-weighted images (Fig 1). Surrounding edema was not included in the defined GTV. Three separate planning target volumes (PTVs) were defined. The GTV was expanded in three dimensions by 0.5 cm to make PTV1, 1.5 cm to make PTV2, and 2.5 cm to make PTV3. The PTV surfaces were then edited to limit expansions into adjacent skull and other normal structures (Fig 1).

Conformal external-beam radiation was delivered with a single plan for the entire course of treatment, giving a prescribed dose of 90 Gy (± 5%) to PTV1. PTV2 and PTV3 were treated with the same plan to lower doses according to the protocol, as described in detail by Ten Haken et al[12] (Table 1). The prescribed dose level for the annulus between PTV1 and PTV2 (called PTV2-1) was 70 Gy, which was a biologically effective dose comparable to the treatment this volume received in the earlier (70- and 80-Gy) steps of the study. The alpha/beta ratio was presumed to be 10, selected as a representative value for acute reacting tissues, such as tumor. The outer target volume PTV3 received a minimum dose of 60 Gy as part of the 90-Gy protocol step, again corrected for fractionation differences.

Table 1. Protocol-Defined PTV Margins and Prescribed Doses

Volume	Margin on GTV (cm)	Dose (Gy)	Biogray
PTV1	0.5	90 ± 5%	
PTV2	1.5	60	70
PTV3	2.5	44	60

A single segmental intensity modulation plan was used to deliver the nonuniform prescribed dose distribution to each patient. Beam arrangements were designed using beam's eye view displays of the target volumes and using segmental intensity-modulated radiation therapy (IMRT) planning tools described by Fraass et al.[13] The goal was to choose beam orientations that would comprehensively cover the PTV1, 2, and 3 target volumes with minimum doses of 85.5 Gy (95% of 90 Gy), 70 Gy, and 60 Gy while minimizing the dose to surrounding normal structures. Non-coplanar beam arrangements were used for all patients. Dose to the visual apparatus (the optic chiasm, in particular) was limited such that 50% of the structure volume could not receive more than 60 Gy. If these criteria could not be met, the patient was ineligible for this study.

No other critical structures were used for this protocol. RT began within 28 days of the patient's surgical procedure. Patients were treated using 6- to 25-MV photons. Treatment was given with conventional fractionation to the PTV1 (2 Gy per day, 5 d/wk) without any planned treatment breaks. Typically, five beam directions and a total of nine or 10 segments were used (Fig 2).

Follow-Up

Patients were seen on a weekly basis during their RT to monitor symptoms and toxicity. Follow-Up CT or MRI scans were obtained at 6 weeks, 4 months, and 10 months after the completion of radiation. Images were reviewed at a multidisciplinary tumor board to help

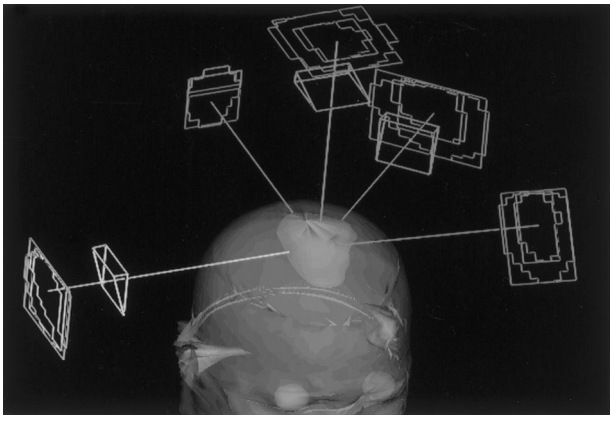

Fig 2. Example of a typical radiation treatment plan using five multisegmental beams.

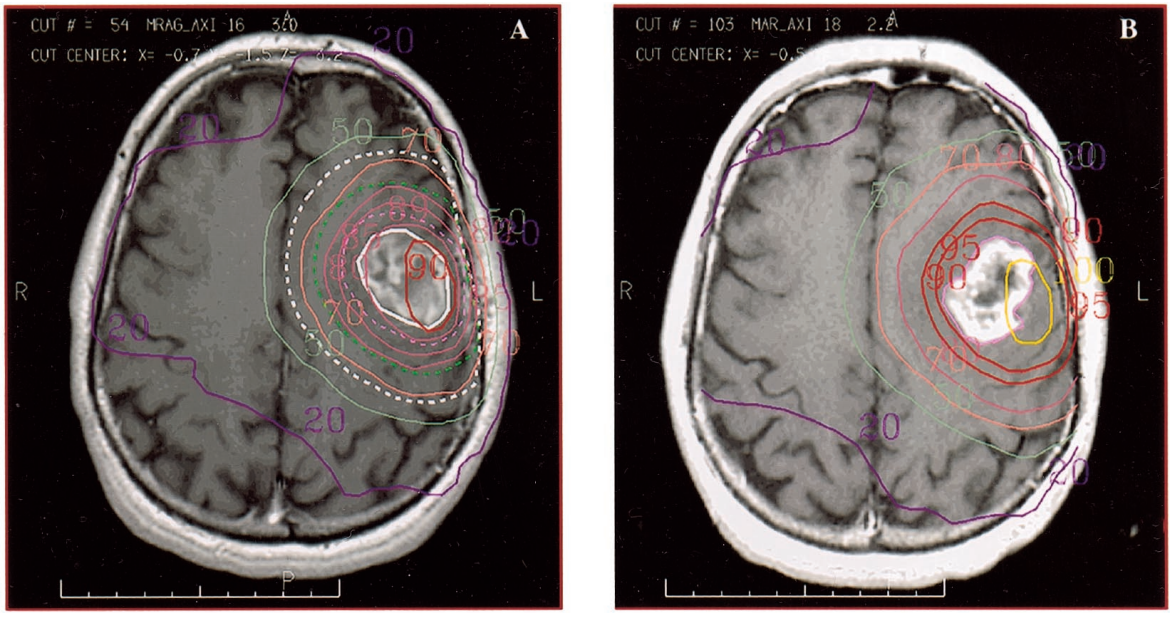

Fig 3. Example of T1, postgadolinium axial MRI scans illustrating (A) isodose distribution of an original treatment composite plan and (B) isodose distribution superimposed onto recurrent tumor volumes in the same patient.

resolve issues of tumor recurrence versus radiation necrosis. Any images suspected of indicating failure were reviewed by the radiation oncologist and neuroradiologist. Images thought to have documented radiographic evidence of tumor failure underwent further dosimetric analysis. Additional treatment for tumor failure (ie, chemotherapy, brachytherapy, and stereotactic radiosurgery) was at the discretion of the treating physician.

Survival Analysis

Duration of survival was calculated from date of study registration. The Kaplan-Meier method was used to determine actuarial survival for all patients.[14] Any survival difference between treatment dose levels was assessed using the log-rank test.

Failure Analysis

For patients who developed evidence of radiographic recurrence, images were analyzed using a previously described technique to quantify the dose that had been delivered to the volume of the recurrent lesion.[3] Failure was defined as either (1) an increase in volume of 25% or 10 cm^2 (whichever was smaller), (2) the reappearance of a lesion that had previously had a complete response, or (3) the appearance of any new lesions. All failures were documented radiographically, usually with gadolinium-enhanced MRI.

Using the image data sets obtained at the time of documented radiographic failure, the region of tumor recurrence was contoured and entered into the treatment planning system in a manner similar to the one described above for the initial tumor GTV. The failure volumes were drawn without the aid of the original treatment plan to avoid bias.

The image data set(s) obtained at failure was then registered with the original treatment planning data, using the methods already described (Fig 3). At that point, the total treatment dose received by the failure region was determined by using dose volume histograms (DVH), which illustrate the dose distribution delivered to the failure volume. For each patient, the location of the recurrent tumor volume with respect to the delivered dose distribution was quantified by using the DVH of the recurrence volume. If more than 95% of the recurrence volume was in the original high-dose field, as shown by the DVH, it was considered a central failure, while those with more than 80% to 95%, 20% to 80%, and less than 20% were designated as in-field, marginal, and distant recurrences, respectively (Table 2). Cutoffs were chosen based on the earlier analysis of the patients treated with 70 to 80 Gy.[3]

RESULTS

General Patient Characteristics (90 Gy)

The general characteristics of the 34 patients treated on the 90-Gy dose arm are listed in Table 3. The median age was 55 years, and the median length of follow-up was 11.7 months. The majority of patients underwent a subtotal resection of their tumor. At the time of analysis, 23 (67.6%) of 34 patients had experienced radiographically documented treatment failure. No significant treatment toxicities were observed.

Table 2. Recurrence Volume Categories

Category	Recurrence Volume Within High-Dose Field (%)
Central	> 95
In-field	> 80-95
Marginal	20-80
Distant	< 20

Table 3. Patient Characteristics: 90-Gy Arm (N = 34)

	No. of Patients	%
Median age at diagnosis, years	55	
Sex		
Male	20	
Female	14	
Tumor grade		
4, glioblastoma multiforme	33	
3, anaplastic astrocytoma	1	
Surgery before RT		
Gross total resection	6	18
Subtotal resection	18	53
Biopsy only	10	29
Original tumor location		
Frontal lobe	10	29
Parietal lobe	14	41
Occipital lobe	4	12
Temporal lobe	5	15
Thalamus	1	3

Survival and Recurrence Analysis (90 Gy)

The median survival time of the patients treated with 90 Gy was 11.7 months, while 1- and 2-year survival rates were 47.1% and 12.9%, respectively (Fig 4A, Table 4). DVH analyses to determine the amount of recurrent tumor volume included in the prescription isodose surface (ie, within the 95% isodose line [IDL]) demonstrated that 18 (78%) of 23 patients had central tumor recurrences, three (13%) of 23 had in-field recurrences, two (9%) of 23 had marginal recurrences, and zero (0%) of 23 had distant recurrences (Table 5). Figure 5 illustrates MRI and DVH examples of a central (Fig 5A and 5D), an in-field (Fig 5B and 5E) and a marginal (Fig 5C and 5F) recurrence, for which 100%, 83%, and 67%, respectively, of the recurrence volume was encompassed by the 95% IDL. Reclassifying the central and in-field categories into a combined category of "inside" results in 91% of recurrences falling within the 80% IDL region (Table 5). A detailed description of the DVH analyses used for the 70-Gy and 80-Gy patients has previously been published.[3]

Two patients (5.9%) had multiple recurrent lesions—one patient had three lesions (two central and one marginal) and the other had two lesions (both central). No association between multiple recurrent lesions and delivered dose was found (data not shown).

DISCUSSION

RT, with its limitations, remains the single most effective modality of treatment for high-grade gliomas after surgical resection. Before the advent of 3-D treatment planning, relatively large radiation portals were used that limited the maximum deliverable dose. However, as the use and sophistication of conformal RT have increased, brain neoplasms can now be treated to significantly higher doses while the dose to adjacent structures, such as the optic chiasm and uninvolved brain, is minimized.

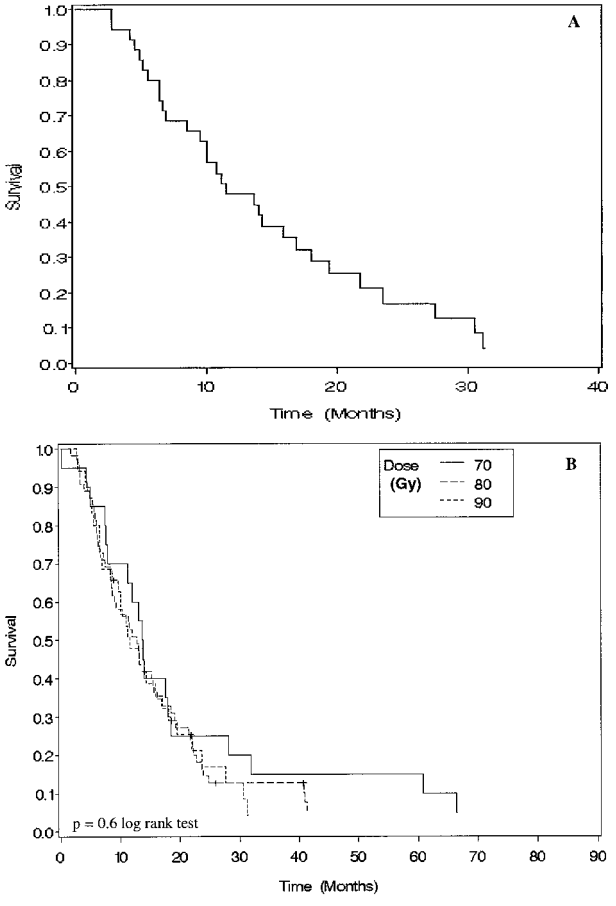

Fig 4. Kaplan-Meier survival curves (A) for patients treated with 90 Gy and (B) per treatment arm (70, 80, and 90 Gy).

To date, doses beyond 60 Gy for malignant brain neoplasms have not convincingly been shown to improve overall survival.[15] The likely reason is that local failure, despite higher doses, continues to be a major issue and the dominant cause of mortality. Higher doses for malignant gliomas have been attempted with a variety of methods, including altered fractionation,[16-18] stereotactic radiosurgery,[19] and brachytherapy.[20,21] Nieder et al[17] prospectively studied two different hyperfractionation schedules (78 Gy/1.3 Gy bid for 6 weeks and 60 Gy/1.5 Gy bid for 4 weeks) and compared them with previous patients who had received standard fractionation (60 Gy/2 Gy once a day for 6 weeks). They found no difference in survival but concluded that the shorter treatment time was not detrimental and

Table 4. Summary of Survival Analysis for All Patients and per Treatment Arm

	Median Survival		95% CI	1-Year Survival	2-Year Survival
	Months	Weeks	(weeks)	(%)	(%)
All patients	13.0	52.1	44.4-62	51.4	16
70 Gy arm (n = 20)	13.9	55.6	34-79.7	60	25
80 Gy arm (n = 55)	12.9	51.6	37.1-67.7	50.9	14.6
90 Gy arm (n = 34)	11.7	46.8	37-73.6	47.1	12.9

Abbreviation: 95% CI, 95% confidence interval.

should be considered in patients not appropriate for more aggressive regimens.[17] In contrast, the final report of Radiation Therapy Oncology Group Study 83-02, a phase I/II trial of hyperfractionated and accelerated hyperfractionated RT with carmustine for supratentorial malignant gliomas, found that glioblastoma patients receiving higher hyperfractionated doses (76.8 and 81.6 Gy/1.2 Gy bid) had longer survival times compared with patients receiving lower doses.[16] Accelerated fractionated proton/photon therapy to 90 cobalt gray equivalent was studied by Fitzek et al,[18] who showed this regimen to have a very low central recurrence rate (one of 23 patients) and an extended median survival time of 20 months.[18]

The median survival of those patients on the 90-Gy arm was 11.7 months, which was not statistically different from the median survival of those treated with 70 Gy (13.9 months) and 80 Gy (12.9 months) (Fig 4B). Survival rates of the 70-, 80-, and 90-Gy subjects were 60%, 50.9%, and 47.1% for 1 year and 25%, 14.6%, and 12.9% for 2 years, respectively (Table 4). These values are comparable to historical controls. Our analysis did not demonstrate a survival benefit with increasing escalation doses. Nevertheless, it does not seem that doses of 90 Gy result in significantly increased morbidity or mortality for the 3-D planning/delivery techniques used here. Older studies reported median survival after standard doses and fractionation to be in the range of 9 to 15 months.[22-24] Those that looked at dose escalation schemes (hyperfractionated external beam RT with or without chemotherapy, brachytherapy, or stereotactic radiosurgery) describe median survival times anywhere from 10.5 to 20.8 months.[16,18,19,25,26] It is encouraging that the techniques used in this study seem to be well tolerated clinically. However, it is clear that despite various sophisticated treatment regimens, the survival of patients with high-grade glioma remains limited. It should be noted that the current study was designed to assess the feasibility and tolerability of high-dose RT and was not primarily an efficacy trial.

Table 5. Recurrence Location Characteristics

	Frequency	
	No. of Patients	%
Recurrence location		
Central	18/23	78
In-field	3/23	13
Marginal	2/23	9
Distant	0	
Reclassified location		
Inside	21/23	91
Marginal	2/23	9
Distant	0	

The main goals of the current study were to analyze the failure pattern for patients treated with 90 Gy of highly conformal segmental IMRT plans and to evaluate whether there was evidence of marginal misses due to limited accuracy in defining target volumes or due to the use of PTV margins that were too small. Local failures have traditionally been the major site of recurrence after RT.[23,24,27,28] In 1980, Hochberg and Pruitt[29] analyzed CT data after whole-brain RT and found that more than 80% of recurrences occurred within 2 cm of the primary tumor, while only 3% of failures were outside this margin. Garden et al[24] treated 53 patients with high-grade astrocytomas (target = tumor + 3-cm margin) to a median dose of 66 Gy using CT-based treatment planning and found that the pattern of initial failure was "always at the primary site." Although Wallner et al[27] treated all of their 34 patients (25 glioblastomas, nine anaplastic astrocytomas) with whole-brain radiation of 40 to 60 Gy (74% then proceeded to a boost of 51 to 70 Gy), 25 (78%) of 32 unifocal tumors recurred within 2 cm of the initial tumor bed, as seen on CT imaging. They suggested that the addition of whole-brain radiation to localized treatment was probably not necessary given the local failure patterns observed. Hess et al[22] looked at 75 patients with malignant gliomas (63 glioblastomas, 12 anaplastic astrocytomas) given 60 to 66 Gy to a CT-localized PTV (tumor + 2 cm). Of 57 analyzable patients who experienced recurrence, they found that 49 patients (86%) developed recurrences within the treated volume (defined as within the 95% IDL), and five recurrences (9%) were partly outside the treated volume, and three (5%) were completely outside the treated volume. These results echo

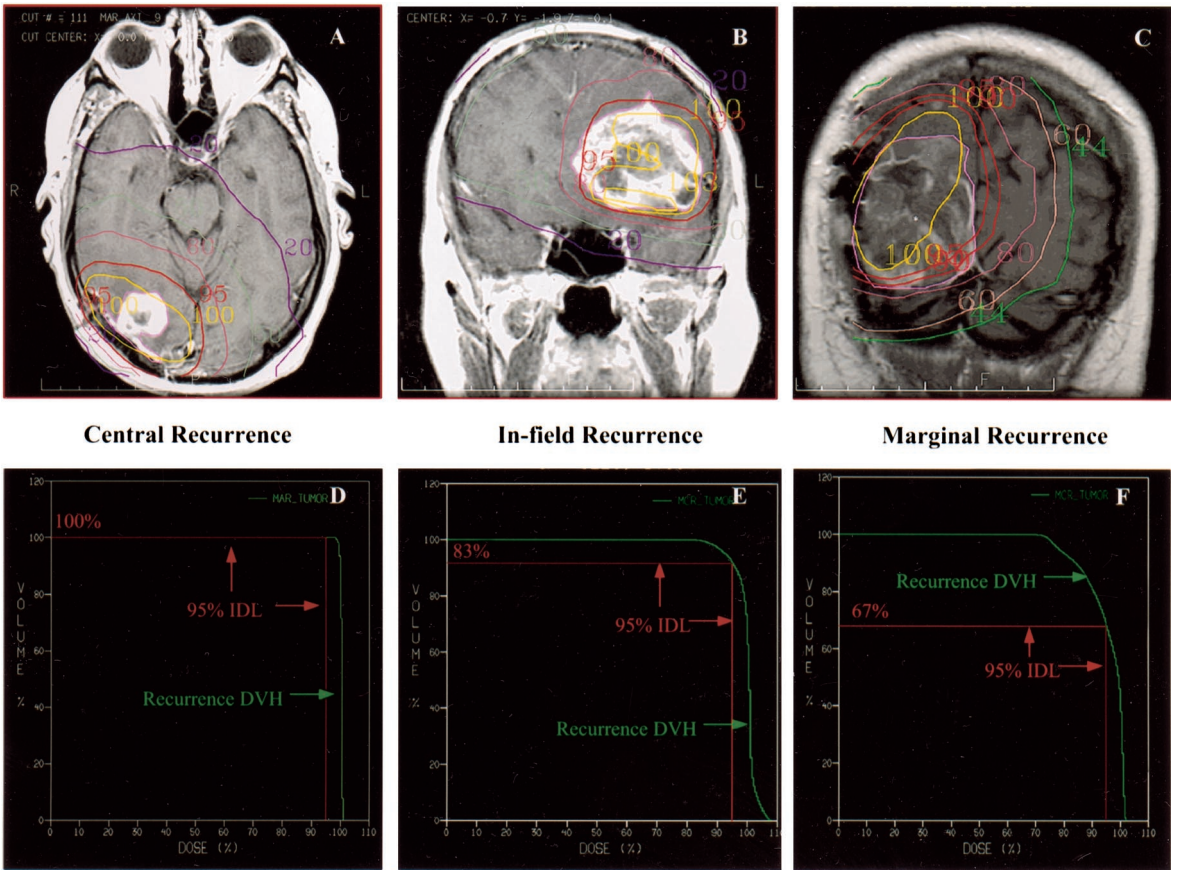

Fig 5. (A, B, C) Examples of tumor recurrences on T1-weighted MRI scans superimposed with original treatment isodose lines. (D, E, F) Corresponding DVHs demonstrating the percentage of recurrent tumor within the 95% IDL (see text).

previously described data at our institution, where 42 patients with grade 3/4 astrocytomas were treated with 60 Gy using conformal radiation techniques and all developed recurrences within 2 cm of the original tumor.[28] Lee et al[3] demonstrated that patients with high-grade gliomas treated with 70 and 80 Gy on the current dose escalation study had a predominantly local failure pattern (89% considered inside the 80% isodose surface). Results from the 90-Gy arm demonstrate that 78% of recurrences occurred within the 95% isodose surface, and a total of 91% was thought to be inside the 80% isodose surface after treatment with 90 Gy. Therefore, these results support the continued use of the current methods for defining the target volumes as well as the current distribution of lower doses to the outer PTVs compared with the core PTV, as we see no significant number of marginal or outside (outside the high-dose region) failures.

Studies looking at failure patterns in brain malignancies that have used very aggressive local radiotherapy, such as radiosurgery and interstitial implants, have demonstrated an increased proportion of failures outside the high-dose field. Mehta et al[19] treated glioblastoma patients with external-beam RT (median dose, 54 Gy/1.8-Gy fractions) plus radiosurgery (median maximum dose, 18.6 Gy). They divided the patterns of failure into central (within the high-dose region), peripheral (within 2 cm of the initial enhancing area) and distant (beyond the 2-cm margin) categories and found that there were 0% central, 79% peripheral, 17% distant, and 3% peripheral and distant failures. Likewise, Loeffler et al[21] used I-125 interstitial irradiation (median dose 50.4 Gy for primary and 54.5 Gy for recurrent disease) in 53 patients with malignant gliomas. Twenty-two patients relapsed, of whom four were considered to have local failure (< 2 cm from the implant edge), eight were considered to have marginal failure (2 to 5 cm from the edge), and 10 were considered to have distant failure (> 5 cm). These data suggest that the failure pattern for these patients may shift (from local to marginal/distant)

as the central doses are increased, although the reasons behind this phenomenon are not clear. There is no indication of this effect in patients treated with 90-Gy external-beam RT reported in the current study nor in the accelerated photon/proton-beam study described by Fitzek et al.[18] However, a Japanese study by Nakagawa et al[30] reported on a total of 38 glioblastoma patients treated with conformal postoperative radiation to doses ranging from less than 60 to 90 Gy. Unlike the present report, they found a significant increase in distant failures in the 90-Gy arm compared with the less-than-90-Gy arm (69% [nine of 13 patients] *v* 16% [three of 19 patients], respectively). It is difficult to compare these results because no definitions for local and distant failures were given. However, it should be noted that this pattern of recurrence was due to an unusually large number of patients (seven of 13) in the 90-Gy arm who relapsed with subependymal seeding. The reason for this outcome is unclear, but more aggressive surgical intervention may have contributed to the observed seeding because significantly fewer patients received only biopsy of their tumors compared with our study (2.6% *v* 29.4%). The treatment techniques were slightly different between our study and theirs (their RT consisted of a cone-down delivery method as well as a larger PTV3), but intuitively, one would predict a lower percentage of distant failures with larger treatment volumes.

Previously, there had been speculation that dose escalation could lead to a larger proportion of multifocal recurrences, given that peripheral subclinical disease would be relatively underdosed with highly conformal fields.[19,21] Although 19% of patients treated to 70 and 80 Gy developed multiple recurrent lesions,[3] the present analysis of the 90-Gy patients shows that only two (6%) of 34 patients had multifocal recurrences. From the current data, there is no indication that escalation of dose to 90 Gy (with the described target definitions and treatment techniques) will result in a larger fraction of multifocal recurrent lesions.

In the present study, no patients were found to have distant failures. This, combined with the overwhelming local failure pattern seen with limited radiation therapy, strengthens the suggestion that further dose escalation may be of benefit for patients with high-grade gliomas. Therefore, we hope to continue our study by escalating total dose or dose per fraction to the final boost volume (PTV1 = GTV + 0.5-cm margin), while keeping the outer rings at the present biogray levels (PTV3 = 60 biogray, PTV2 = 70 biogray) using automated IMRT optimization.[31] By increasing the dose per fraction, higher total doses can be delivered without extending the overall duration of treatment. In addition, the radiographic distinction between tumor recurrence and radiation necrosis can be difficult. All patients analyzed in this study were thought by a neuroradiologist and a multidisciplinary neuro-oncology tumor board to have evidence of tumor failure. However, the majority of our patients did not undergo formal pathologic confirmation. In the future, we will incorporate noninvasive functional imaging, such as positron emission tomography or single-photon emission computed tomography, in the radiographic follow-up of these patients as a means of differentiating tumor from necrosis.[32,33]

In conclusion, in this analysis of supratentorial high-grade gliomas after 90-Gy 3-D conformal RT, we find that the failure pattern remains predominantly local. The target definitions and dose distributions delivered to the different PTVs seem to be well tolerated. No normal tissue complications were clinically identified for any patient. A shift to more peripheral recurrences, suggestive of marginal misses, was not seen. Because local failures continue to be the primary cause of morbidity and mortality in these patients, further dose escalation may prove to be beneficial in this setting.

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