Malignant astrocytomas: focal tumor recurrence after focal external beam radiation therapy

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Hochberg and Pruitt have reported glioblastomas recurring within 2 cm of the primary site in 90% of patients after whole-brain radiation therapy. They suggested that computerized tomography (CT) scan accuracy would permit smaller radiation fields. A treatment protocol with smaller-field focal brain irradiation following surgical resection is reported. The first 4500 cGy of radiation is focused to within a 3-cm margin around the tumor, with a 1500-cGy boost within a 1.5-cm margin. Forty-two patients with grade III or IV astrocytoma, treated with focal brain radiation therapy were reviewed retrospectively to assess patterns of tumor recurrence. Thirty patients received intra-arterial bromodeoxyuridine (BUdR) radiosensitization with focal brain radiation therapy, and 12 patients underwent conventional focal brain radiation therapy. Tumor margin was defined on preoperative and recurrence CT scans as the contrast-enhanced area; these were traced on acetate templates and compared with each other and with the actual scans.

In all 42 patients, the lesion recurred within a 2-cm margin of the original tumor. Four patients had two recurrent areas: the second area was within the 2-cm margin in two, and outside this margin in two. These results are similar to those of Hochberg and Pruitt. It is suggested that focal irradiation is now the optimal treatment for malignant astrocytoma. Since recurrences continue to be within the irradiated volumes, it appears that higher focal doses of radiation are appropriate for clinical treatment trials of malignant astrocytomas.

KEY WORDS • astrocytoma • tumor recurrence • malignant tumor • radiation therapy

The therapy for high-grade astrocytomas includes surgery, radiation, and chemotherapy. Before computerized tomography (CT) became available, imaging techniques could not determine tumor volume accurately. Therefore, whole-brain radiation therapy was necessary to assure treatment of the total tumor volume. In 1980, Hochberg and Pruitt published data on patients with grade III and IV astrocytomas treated with whole-brain radiation therapy with or without chemotherapy, followed sequentially with CT scanning to determine the extent and localization of tumor recurrence. Ninety percent of recurrences were located within 2 cm of the original tumor margin, with the other 10% outside the 2-cm margin but detectable by CT scanning. Based on these observations, they suggested that focal irradiation might be appropriate.

At the University of Michigan, three-dimensional treatment planning has been used since 1985 in an attempt to spare normal brain during irradiation. This has emphasized the consistent delivery of radiation to three-dimensionally defined volumes of brain parenchyma using multiple cross-firing fields outside the traditional axial orientations. The current retrospective study was designed to evaluate whether the significant decreases in treatment volume achieved through the use of focal brain radiation therapy would result in patterns of tumor recurrence differing from those seen following whole-brain radiation therapy. To our knowledge, the current study is the first English language report of such a study.

Clinical Material and Methods

We retrospectively studied 42 patients with pathologically verified grade III or IV astrocytoma who underwent CT-planned focal brain radiation therapy and subsequently developed recurrent disease. Ten patients had grade III and 32 grade IV astrocytomas. Their mean age at diagnosis was 51 years. Patients were included in
the study if both preoperative and recurrent CT scans were available for review. The average preoperative Karnofsky Performance Status score of the 23 patients operated on at the University of Michigan was 73 (range 50 to 100). Thirty of the 42 patients (19 men and 11 women) were enrolled in an intra-arterial bromodeoxyuridine (BUDR) radiosensitization protocol; these patients received continuous BUDR infusion via an implanted carotid artery pump system, beginning 2 weeks prior to and continuing throughout the focal brain radiation therapy. Of the remaining 12 patients, nine (three men and six women) received only focal brain radiation therapy and no chemotherapy before recurrence and three patients (one man and two women) received focal brain radiation therapy and subsequent chemotherapy (carmustine (BCNU) and/or procarbazine) before relapse.

Initial diagnostic imaging was performed with the patient in the supine position with and without intravenous injection of iodinated contrast material. For radiation treatment, patients underwent CT with 5.0-mm slice spacing and iodinated intravenous contrast enhancement.* Magnetic tape output from the CT scanner served to input the image data directly to the computerized treatment-planning system. Recurrence scans were performed in a manner similar to the diagnostic scans, and were obtained every 6 weeks for the first 3 months after the completion of radiation therapy, then at 3-month intervals for the subsequent 9 months, and every 6 months thereafter. If clinical deterioration occurred, a scan was performed at that time.

Three-dimensional tumor volume was derived from the treatment-planning CT scan. Coronal and sagittal reconstructions were frequently performed with three-dimensional surface reconstruction techniques to allow appreciation of the volumes relative to the critical structures of the eyes, optic chiasm, and brain stem. Beam orientations were chosen so as to treat the specified volumes reliably, and were not restricted to the transaxial plane (Fig. 1). Target volumes with 3.0-cm and 1.5-cm margins surrounding the CT contrast-enhanced edge were generated by the treatment-planning software in all three dimensions. Focal brain radiation therapy dosage was defined as 4500 cGy within a 3-cm margin followed by a 1500-cGy boost within a 1.5-cm margin surrounding the initial tumor (the volume of contrast enhancement). Radiation was delivered in conventional fractions of 180 to 200 cGy daily, five times per week.

All CT scans were assigned a number and grouped randomly prior to review. The tumor volume was defined as the area of enhancement after administration of intravenous contrast material. Recurrence was defined as an increase in contrast-enhancing tumor volume on any CT scan when compared to the postoperative pre-irradiation contrast-enhanced tumor volume. Recurrence was determined to be within 2 cm of the original preoperative volume if any area of contrast-enhanced tumor was located within 2 cm of the original area of contrast enhancement, whether or not part of the recurrence extended outside the 2-cm margin. The extent of the tumor was traced with a 0.25-mm pen onto 0.005-mm acetate films; most tracings were obtained from University of Michigan standard x 1.5 CT scans and the remainder were prepared from smaller outside films and enlarged to the x 1.5 standard. No

* CT scanner, Model 9800, manufactured by General Electric Co, Milwaukee, Wisconsin.

FIG. 1. Anterosuperior (vertex) views of a patient with a right frontal grade IV astrocytoma. Left: Computerized tomography (CT)-derived reconstruction of the cranium (mesh), surface of the brain (gray area), and contrast-edge-defined tumor (white area). Right: Similar CT-derived reconstruction of the cranium (mesh), surface of the brain (gray area), and volume of brain enclosed within the 90% isodose line (white area). Limitation of the irradiated brain volume was accomplished through the use of multiple non-coplanar fields of high-energy radiation.
Astrocytoma: focal recurrence after focal irradiation

Fig. 2. Contrast-enhanced computerized tomography (CT) scans of postoperative preirradiation tumor volume (upper left) and recurrence (upper right) with acetate templates drawn from preirradiation (lower left) and recurrence (lower right) scans. Isodose distributions of focal brain irradiation are shown in each CT scan of a patient with a glioblastoma multiforme. Doses are in Gy (45 Gy = 4500 rads) and represent delivered doses within the acceptable range of ± 5% of the prescribed dose at the isocenter. The outer isodose depicts the volume of brain receiving the initial 45 Gy irradiation prior to the boost treatment resulting in a total of 57 Gy delivered to the inner isodose volume.

scans were reduced. The acetate templates were compared to one another and to the actual CT scans. Areas of recurrence were noted with respect to overlap of the templates and CT scans, and to their relationship to the 2-cm margin around the original tumor area (Fig. 2).

Results

In all patients the lesions recurred either inside the original tumor margin or within 2 cm of it. Two patients had two separate recurrences, one within 2 cm of and one more than 2 cm from the original tumor volume. In these two patients, the second recurrences were 3 and 4 cm distant from the original tumor volume, the latter in the opposite frontal lobe. Tumors in two other patients recurred at two sites within the 2-cm margin. All four patients with multiple recurrences had received BUdR radiosensitization and focal brain radiation therapy. Similarly, in all but one of the 42 patients, tumors recurred within the 1500-cGy radiation boost margin of 1.5 cm. The tumor in the remaining patient recurred within the 2-cm margin. In 67% of the patients (28 cases) the entire recurrence fell within the 2-cm margin; the remaining 33% had tumor recurrence both inside and outside the margin. In all cases with recurrence, the majority of the tumor fell inside the 2-cm margin and in the original tumor bed.

The median time to recurrence in the 42 patients was 8 months (range 2 to 30 months). In the focal brain radiation therapy and concurrent intraarterial BUdR radiosensitization group, median time to recurrence was 9 months (range 2 to 30 months); in the focal brain radiation therapy group without chemotherapy, median time to recurrence was 6 months (range 2 to 12 months); and in the group that received focal brain radiation therapy and subsequent chemotherapy, median time to recurrence was 9 months (range 4 to 21 months).

Discussion

Radiation therapy remains the most effective modality for delaying progression of the high-grade malignant astrocytomas, demonstrating a dose-response relationship established by the Brain Tumor Study Group. Whole-brain external beam radiation therapy or whole-brain irradiation with focal boost has been reported to extend patient survival time when compared to surgical resection alone. However, despite advances in neurosurgical techniques facilitating more complete resection and radiation dose escalation to the 6000-cGy level, recurrences overwhelmingly continue to be local and within the irradiated field, leading to speculation that a population of radioresistant cells exists. At many institutions, irradiation of astrocytomas has traditionally involved the use of bilateral, opposed fields of treatment due to the uncertainty of cellular margins and inability to orient external beams in reproducible and verifiable nonaxial directions.

The enhanced capabilities of CT and magnetic resonance (MR) imaging now provide an opportunity for image reconstruction in all three dimensions, enabling the delineation of tumor from surrounding brain and other dose-limiting structures with greater certainty. Image reconstruction and correlation software, in conjunction with three-dimensional dose-calculation algorithms, now exist that are capable of picturing both the tumor and the surrounding tissues from any angle, as well as projecting composite radiation doses realized by the use of converging multiple fields.

Whole-Brain Irradiation

The optimal area of brain surrounding a tumor to be included in the irradiation remains unknown. In 1980, Hochberg and Pruitt published data on patients with grade III and IV astrocytomas treated with whole-brain irradiation with or without chemotherapy using serial CT scans to assess the tumor site and the extent of tumor recurrence. Eighty percent of recurrences were within 2 cm of the original tumor margin, 10% had residual disease at the primary site but also a component
extending beyond the 2-cm margin, and another 10% demonstrated disease recurrence exclusively outside the 2-cm margin. In 83% of their patients, the gross and microscopic extent of the tumor was detected by CT. More recent studies employing whole-brain irradiation with a focal boost to the tumor area have confirmed these results.\textsuperscript{22}

**Focal Field Irradiation**

Recently, Daumas-Duport, \textit{et al.},\textsuperscript{2} correlated CT- and MR image-computed volumes with stereotactic biopsies and found that the tumor extent on biopsy was encompassed by the T\textsubscript{2}-weighted high-signal image abnormality to a greater extent in high-grade than in low-grade malignancies. Aided by this increased resolution of tumor imaging, the University of Michigan has advocated focal field irradiation in order to decrease radiation toxicity to normal tissues. However, patterns of tumor failure following this method of irradiation have not been reported. In our study, 100% of patients had one area of recurrence within 2 cm of the initial volume of contrast enhancement. This is a higher percentage than found in previous studies using whole-brain irradiation with or without a focal boost. This may be partially accounted for by our method of tracing the entire tumor extent seen on CT scanning whereas, in their study, Wallner, \textit{et al.},\textsuperscript{21} used a single CT slice defining the maximum tumor area. In addition, Wallner, \textit{et al.}, operationally defined local recurrence as recurrent volume completely within the 1- or 2-cm margin around the original tumor volume. We considered disease to be a local recurrence at the original site if any of the tumor was within 2 cm of the original tumor margin, whether or not it extended outside this margin. This is the definition used by Hochberg and Pruitt.\textsuperscript{14} If any tumor is left at the margin after subtotal resection, it could extend in any direction from the original tumor bed. This pattern was seen in the study by Bashir, \textit{et al.},\textsuperscript{1} of glioblastoma recurrence following 4500 cGy whole-brain irradiation with a 1500-cGy boost to the tumor bed, which showed 95.2% of recurrences within, or within and extending from, the original tumor area.

**Local Recurrence**

In the present study, 67% of the patients had their total recurrence within the 2-cm margin. Tumors in the remaining 33% extended outside the margin; however, the majority of the tumor in these patients was within the original tumor volume. Wallner, \textit{et al.},\textsuperscript{21} found that 78% of their patients' tumors recurred within the 2-cm margin, using a single two-dimensional CT maximum tumor-slice area. Our slightly lower percentage may be explained by our use of multiple slices covering the total tumor volume, enabling us to identify extension outside the tumor area in three dimensions. We interpret our findings and those of Wallner, \textit{et al.}, to indicate that malignant gliomas recur locally and extend from recurrence or regrowth in the original tumor volume into the 2-cm margin, then into previously uninvolved areas which, in the great majority of cases, are still within the 4500-cGy 3.0-cm irradiated volume. A recent study by Halperin, \textit{et al.},\textsuperscript{13} comparing antemortem CT scans with postmortem pathologic examination, suggests a need for larger fields. In their study of 11 untreated or minimally irradiated patients with glioblastoma multiforme, only two cases would have been covered by a radiation treatment field including the tumor and a 1-cm margin and six cases would have been covered by an area including tumor plus edema and a 1-cm margin. However, in view of our results, we feel justified in continuing to recommend a field size with the first 4500 cGy directed within a 3-cm margin around the enhancing tumor, with an additional boost to a 1.5-cm margin.

**Study Limitations**

A potential limitation in the present study was variation in the observers' interpretation of tumor volumes. We attempted to avoid this by having one person perform all the tracings in a consistent pattern. All scans were studied randomly by number instead of name, so initial and recurrence scans from individual patients were not traced sequentially, except as a result of random groupings.

Our study group included patients enrolled in a halogenated radiosensitizer study with focal brain radiation therapy, as well as patients with focal brain radiation therapy with and without chemotherapy. Our study was not designed to compare these groups with respect to tumor recurrence; however, we noted no difference in recurrence patterns among any of these patient groups. Four patients in the BUdR group had two areas of recurrence. This agrees with data presented in past series where between 4% and 8.6% of patients exhibited multiple areas of recurrence.\textsuperscript{3,4,14}

In summary, in our focal brain radiation therapy protocol with static conformally designed focal fields, the vast majority of malignant astrocytomas recur locally. We believe that focal external beam irradiation should be used instead of whole-brain therapy to decrease potential toxicity to normal brain tissue. When focal brain radiation therapy is compared to whole-brain radiation therapy no difference is seen in the pattern of recurrence. An increase of focal brain radiation therapy dose is indicated to ameliorate local tumor control in Phase II trials for malignant astrocytomas. This is currently being studied at the University of Michigan.

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**References**

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