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ORIGINAL ARTICLE

Patterns of failure for glioblastoma multiforme following concurrent radiation and temozolomide

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Abstract

Purpose: To analyse patterns of failure in patients with glioblastoma multiforme treated with concurrent radiation and temozolomide.
Materials and Methods: A retrospective review of patients treated with concurrent radiation and temozolomide was performed. Twenty patients treated at the University of Alabama at Birmingham, with biopsy-proven disease, documented disease progression after treatment, and adequate radiation dosimetry and imaging records were included in the study. Patients generally received 46 Gy to the primary tumour and surrounding oedema plus 1 cm, and 60 Gy to the enhancing tumour plus 1 cm. MRIs documenting failure after therapy were fused to the original treatment plans. Contours of post-treatment tumour volumes were generated from MRIs showing tumour failure and were overlaid onto the original isodose curves. The recurrent tumours were classified as in-field, marginal or regional. Recurrences were also evaluated for distant failure.
Results: Of the 20 documented failures, all patients had some component of failure at the primary site. Eighteen patients (90%) failed in-field, 2 patients (10%) had marginal failures, and no regional failures occurred. Four patients (20%) had a component of distant failure in which an independent satellite lesion was located completely outside of the 95% isodose curve.
Conclusions: Radiation concurrent with temozolomide appears to be associated with a moderate risk of distant brain failure in addition to the high rate of local failure. The risk of distant failure was consistent with that observed with radiation alone, suggesting that temozolomide does not act to reduce distant brain failure but to improve local control.

Key words: failure; glioblastoma; pattern; radiation; temozolomide.

Introduction

More than half of the 21 800 cases of primary brain tumours diagnosed annually in the US are glioblastoma multiforme (GBM), a locally aggressive primary histology with long-term survival less than 5% among patients treated with standard therapy.[1] Among untreated patients, local progression leads to death in approximately 4–5 months.[2] The pattern of failure for GBM after radiation therapy has been studied previously and indicates that almost all tumours fail in or adjacent to high-radiation dose regions, even after irradiation to 90 Gy.[3–11] This pattern of in-field and marginal failure has been observed, despite autopsy series suggesting that GBM is disseminated within the brain.[6,12] Previous studies comparing partial and whole-brain irradiation in the setting of radiosensitising chemotherapy showed no survival benefit from whole-brain irradiation and established partial-brain irradiation as the standard therapy.[13] Pre-clinical studies have demonstrated that the addition of temozolomide to radiation can potentiate cell killing in glioma cell lines.[14] This potentiation of cell killing has been applied in clinical settings, demonstrably increasing the overall survival of patients with GBM treated with radiation and concurrent then adjuvant temozolomide.[15] We hypothesise that temozolomide concurrent with radiation may alter historical patterns of failure for GBM by improving local control. Subsequently, this improved local control would be followed by both a relative and an absolute increase in distant brain failure. A secondary objective of the analysis was to confirm the treatment margins utilised for 3D treatment planning in the New Approaches to Brain Tumor Therapy (NABTT) CNS consortium for patients with GBM receiving radiation and temozolomide. These margins are smaller than those utilised in some other US and international trials such as the Radiation Therapy Oncology Group (RTOG) protocols 0525 and 0825 and European Organization for Research and Treatment of Cancer (EORTC) protocols 26981 and 26052.

Materials and methods

Selection of patients

This retrospective study was approved by the University of Alabama at Birmingham (UAB) institutional review board. All patients with glioblastoma multiforme treated at the University of Alabama, Birmingham between April 2000 and June 2005 were retrospectively assessed. Patients included in the review had biopsy-proven GBM and suffered documented progression of disease after treatment with radiation and concurrent temozolomide. Adequate imaging prior to treatment, radiation dosimetry records and radiographic assessment at failure were available for all patients included in the review.

Therapy

All patients were treated at UAB according to the NABTT guidelines for radiation oncology. The most recent version of these guidelines is shown in Table 1. The prescribed dose varied minimally and generally was 46 Gy to an initial planning target volume (PTV) encompassing the primary tumour and surrounding oedema on post-operative T2 MRI images plus a margin of 1.0 cm. A boost volume (PTV2) defined as the residual T1 contrast-enhancing tumour plus resection cavity with a 1.0 cm margin was prescribed an additional 14 Gy. Therefore, the total dose to the boost volume was 60 Gy in daily fractions of 2 Gy. The dose-reference point was the International Commission on Radiation Units (ICRU) reference point, usually the isocentre located in the centre of the boost volume. Radiotherapy plans were optimized so the 95% isodose line encompassed the PTV completely.

Table 1. NABTT guidelines for target definition

Target Volume	Definition
GTV1	T1 enhancing and non-enhancing tumour volume (T2 or FLAIR)
GTV2	T1 enhancing tumour volume
CTV1;2	GTV plus a margin of 5 mm
PTV1;2	CTV plus a margin of 3–5 mm

Note: GTV volume is based on postoperative day 0–1 MRI. GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, planning target volume; NABTT, New Approaches to Brain Tumor Therapy.

Chemotherapy consisting of daily temozolamide at 75 mg/m^2 was administered concurrently with radiation in all cases. Additional temozolomide followed as adjuvant therapy in 17 of the 20 cases, delivered at a dose of 150–200 mg/m^2 on each of the first 5 days of every 28-day cycle for six cycles.

Patients typically were followed at intervals of 1 month post radiation, then every 2 months thereafter with serial MRI scans. Typical imaging included pre- and post-contrast T1, T2 and FLAIR sequences. Newer techniques including perfusion, diffusion and MR spectroscopy were not part of the routine follow up in these patients. Because of the possibility of post-radiation imaging changes or pseudoprogression, an imaging or clinical change developing after radiation in the absence of recurrent tumour, in-field imaging changes and clinical changes at the first follow-up scan were managed conservatively with observation or a trial of steroids. Patients outside this time frame or refractory to steroid therapy were generally considered to have progressive disease. Patients with progressive disease were treated at the discretion of the treating physician.

Analysis

Progressive changes on MRI at the primary site within 2–4 months of irradiation and concurrent temozolomide were conservatively considered to represent pseudoprogression.[16,17] Later, follow-up MRIs showing progressive changes were conservatively considered to represent recurrence of disease rather than radiation necrosis; in these cases, biopsy was considered at the UAB Central Nervous System (CNS) multidisciplinary tumour board. For this investigation, MRI scans documenting failure after concurrent temozolomide and radiation were fused to the original treatment planning CT scans electronically using the ECLIPSE treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). The recurrent tumour volumes were generated by contouring the contrast-enhancing abnormalities on the MRIs before they were fused with the isodose curves of the treatment delivered. The dose–volume histograms of the recurrent tumours were analysed to determine the amount of recurrent tumour present within the 95% isodose line of the completed treatment. The recurrent tumours were classified as 'in-field' if ≥80% of the T1-enhancing tumour volume was covered by the 95% isodose line, 'marginal' if ≥20 but ≤80% of the tumour volume was

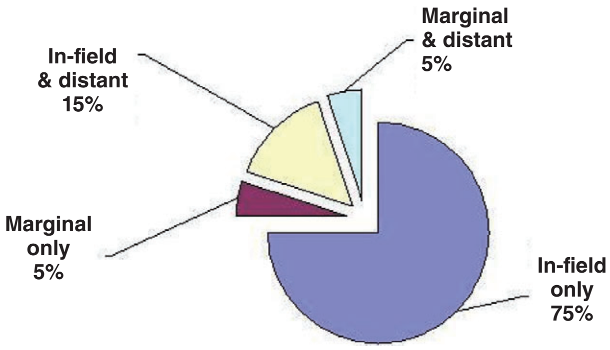

Fig. 1. Patterns of failure.

within the 95% isodose line, or 'regional' if ≤20% of the tumour volume was located within the 95% isodose line. Satellite lesions completely outside the 95% isodose line were considered distant brain failures.

Results

Twenty cases of recurrent GBM initially treated with concurrent temozolomide and radiation between April 2000 and June 2005 with adequate imaging at time of failure and sufficient data for reconstruction of radiation dose distributions were identified. Nineteen of the 20 patients received 60 Gy of radiation in 30 fractions, and one patient received 59.4 Gy in 33 fractions. All patients received concurrent temozolomide, and all but three patients also were treated with adjuvant temozolomide. The average time to disease recurrence from completion of radiation documented by MRI was 187 days (range 117–663 days). The median survival from completion of radiation was 304 days with two patients surviving over 5 years.

The spatial distribution of failures relative to the treated volume is summarized in Figure 1. Of the 20 documented failures, three patients (15%) had recurrence confirmed via biopsy. All patients had some component of failure at the primary site, whether in-field or marginal, and 15 patients (75%) failed in the high-dose volume alone. Only two patients (10%) failed at the margin alone. No regional failures were observed. Distant brain failure occurred in four patients (20%) and appeared as satellite lesions completely outside the 95% isodose line. Examples of distant failure are shown in Figures 2 and 3. The distant brain failures portrayed are not only dosimetrically separate, but also are anatomically quite distant; examples from two patients include failure in a different lobe of the brain and in the contralateral hemisphere.

Discussion

In our retrospective study, standard doses of radiation were delivered with partial-brain volumes and concomitant then adjuvant temozolomide. We observed that all patients had a component of local failure, and 20% of patients had a component of distant failure completely outside of the 95% isodose line. The median survival of patients in our study was 304 days. Although this is lower than the median survival of 445 days reported by Stupp[18] in patients treated with temozolomide and radiation, our patient population included only patients with documented failure and excluded patients with long-term disease control.

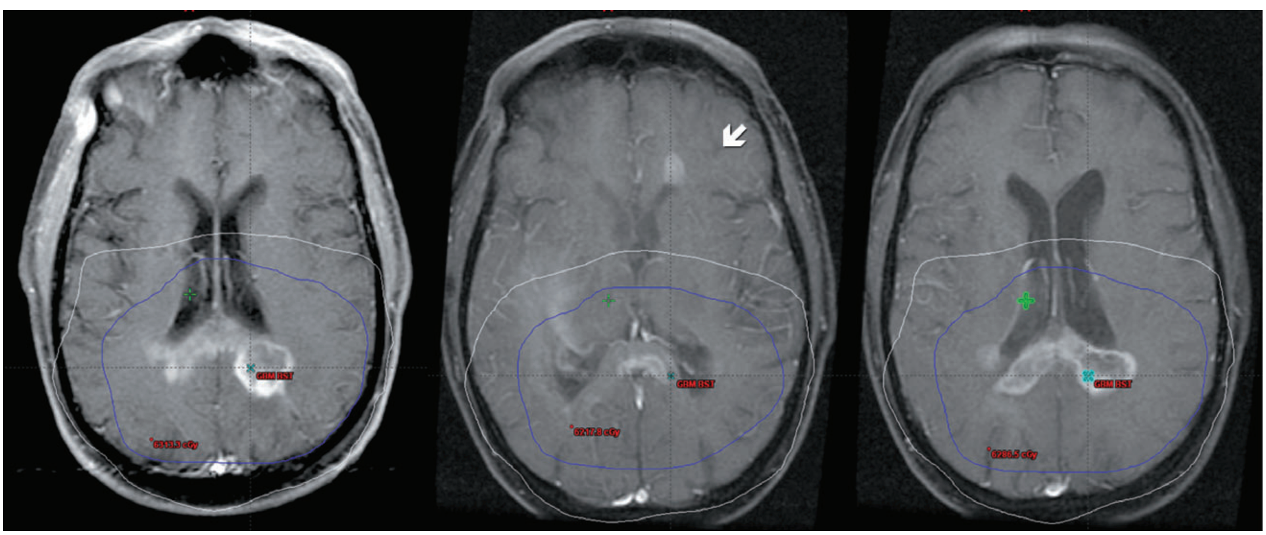

Fig. 2. At left, the pretreatment GBM posterior to the lateral ventricles is evident. After treatment with concurrent radiation and temozolomide, failure occurred locally at the primary site (seen in the right frame) and distantly anterior to the left ventrical (arrow, shown in the centre frame). Note that the distant periventricular lesion is outside the 50% isodose line.

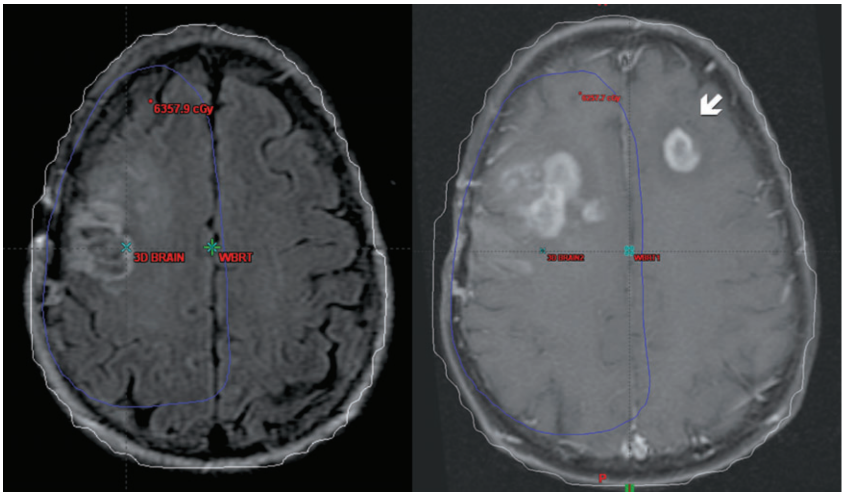

Fig. 3. Left: FLAIR image showing pretreatment disease. Right: post-contrast T1-image after concurrent radiation and temozolomide demonstrating failure in the contralateral hemisphere (arrow, shown in the right frame) between the 50% and 90% isodose lines.

Other institutions have examined the pattern of failure following radiation or chemoradiation for GBM. A report by Aydin documented recurrence patterns for 46 gliomas, 80% of which were high-grade, that were treated with radiation alone to 59.4 Gy.[4] Seventy-three per cent of failures in this study were within 2 cm of the primary tumour, and 93% lay within 3 cm. Individual locations of the primary tumour and recurrences are documented in the report; unlike our current study with concurrent and (usually) adjuvant chemotherapy, no satellite lesions or contralateral hemispheric lesions were observed after radiation alone in this German series. In Aydin's report, distance between the original and recurrent site was directly proportional to the time to recurrence.

A study by Lee reported failures among 36 patients with high-grade gliomas treated with radiation alone to 70–80 Gy using 3D-conformal technique.[19] Whereas 89% of patients experienced central or in-field failures, only one patient (3%) clearly failed outside of the high-dose region. A follow-up publication by Chan examined patients at the University of Michigan treated to a dose of 90 Gy without chemotherapy.[3] Of the 34 patients with observed intracranial failure, 91% were central or in-field, and all other patients' failures were marginal. Again, no distant failures were observed in this series of radiation alone.

Another published study of the patterns of failure of GBM after radiation and concurrent temozolomide was published by Brandes.[20] In this study, 95 patients were treated with radiation, concurrent and adjuvant temozolomide. The radiation in these patients was 60 Gy delivered to the T1 and T2 lesions on MRI with a 2- to 3-cm margin for the Clinical Target Volume (CTV). There was no field reduction during treatment. These treatment volumes are considerably larger than those used in our study. Despite the difference in target volumes, Brandes reported 21.5% of recurrences outside the radiation field, and a 6.3% of recurrences at the margin of the radiation field.[20]

One possible weakness of our study was the difficulty in distinguishing progression from pseudoprogression. By definition, pseudoprogression is worsening imaging findings not due to tumour growth and may be concomitant with unchanged or worsening clinical findings. The mechanism of pseudoprogression is unknown but could be related to inflammation, radiation necrosis or a breakdown of the blood–brain barrier.[16,17] While pseudoprogression is a possible explanation of our findings, the authors believe that this is unlikely because our clinical practice and retrospective analysis considered transient changes to be pseudoprogression. Additionally, 20% of our patients were observed to have distant lesions (completely outside the 95% isodose line) and some of these lay completely outside of the 50% isodose line (Fig. 2); inflammation, radiation necrosis and breakdown of the blood–brain barrier (the proposed causes of pseudoprogression) would be quite unlikely at less than half of the prescribed dose. Although another possible explanation for our findings is simply our smaller sample size, the authors do not believe this to be the case because our findings are consistent with those reported by others.[20]

Another goal of our study was to confirm the treatment margins utilised by the NABTT CNS consortium for patients with GBM receiving radiation and temozolomide. Our practice has used treatment fields consistent with NABTT guidelines (Gross Tumor Volume (GTV) to CTV margin of 0.5 cm), and they are notably smaller than those used by the RTOG and EORTC (GTV to CTV margin of 2–3 cm). Despite these smaller volumes, our observed patterns of failure are consistent with other published series.[20]

We suggest that temozolomide acts primarily as a radiation sensitizer to increase the efficacy of conformal radiotherapy at the primary site; its action on microscopic disease throughout the brain is substantially less. Therefore, increased survival consequent to improved control of the primary lesion permits occult brain disease to become manifest. Notwithstanding, the predominant location of failure in our study remains in-field, and our series does not suggest that a change in treatment volumes is warranted. Further studies of novel therapeutics in concert with radiation therapy should include analyses of the patterns of failure.

Conclusions

Radiation concurrent with temozolomide appears to be associated with a moderate risk of distant brain failure in addition to a high rate of local failure. This risk of distant brain failure appears to be greater than that observed with radiation alone, suggesting that temozolomide acts primarily as a radiation sensitizer within the target volume rather than as an independently cytotoxic agent among malignant cells disseminated throughout the brain parenchyma. Although these data do not support changing the standard radiation target volumes for treating GBM, they do suggest that the patterns of failure after concurrent and adjuvant temozolomide should be studied prospectively, especially if novel radiation sensitizers are added to this regimen.

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