T2 weighted MRI in assessment of volume changes during radiotherapy of high grade gliomas

ABSTRACT

Aim: To determine whether any changes in gross tumor volume occur between pre treatment MRI and week 5 MRI in high grade gliomas treated by conformal radiotherapy.

Methods and Materials: Between july 2003-july 2005, 17 patients with WHO grades 3 and 4 malignant gliomas treated with conformal radiotherapy to a total dose of 60 Gy were included in this retrospective study. All patients had undergone T2 weighted MRI a day before treatment and then again at end of week 5 of treatment for definition of initial and boost fields respectively. Gross tumor volumes were delineated on the two MRI's of each patient and the differences were noted. Two patients with multifocal disease were excluded from the final analysis.

Results: Of the 15 patients with unifocal disease, 12/15 cases (80%) showed a reduction in tumor volumes (median 54.85 cc). Of these, 4/15(26.6%) cases (two each of grade 3 and grade 4 gliomas) had an objective reduction in GTV (>=50%) and 3/15(20%) cases (two of grade 4 and one of grade 3 gliomas) demonstrated an increase in tumor volume (median 14 cc).

Conclusions: This study has shown that a change in gross tumor volume occurred in almost all patients on week 5 MRI. The likelihood of treatment success would appear to be decreased if the tumour is not within the treatment field and hence it may be worthwhile to do a mid treatment MRI for definition of boost volumes especially in dose escalation trials employing highly conformal radiotherapy fields.

Key words: Radiotherapy, High grade gliomas, Tumor volumes

INTRODUCTION

Radiation therapy is a central modality in the treatment of glioblastoma multiforme (GBM). Integral to adequate radiation therapy delivery is the appropriate determination of tumor volume and extent at the time treatment is being delivered. As a matter of routine practice, radiation therapy treatment fields are designed based on tumor volumes evident either on pre treatment CT scans or pre-operative/immediate post-operative MRI's; another CT/MRI is generally not obtained for planning boost fields. A multi institutional trial[1] to examine how a mid-treatment MRI impacts the delineation and definition of the boost volume in GBM patients in comparison to the pre-treatment MRI scan found that GTV mid, defined as the enhancing abnormality on mid-treatment MRI's, changed 80% of the time when compared to post-operative MRI GTV's. In yet another recent study[2] that evaluated changes in tumor volume early during the course of radiotherapy (week 3) it was concluded that a routine imaging during treatment was essential for the adequate tumor coverage in the boost treatment plan, else it could potentially lead to scenarios where significant geographic miss occurs in dose escalation trials that utilize highly conformal radiotherapy techniques.

We conducted a retrospective study to determine changes in the gross tumor volumes occurring between pre treatment MRI and week 5 MRI in 17 patients of high grade gliomas treated by conformal radiotherapy at our institute.

METHODS AND MATERIALS

Seventeen patients with high grade gliomas treated with 3-D conformal radiotherapy with a median dose of 60 Gy from July’03 to July’05 were included in this retrospective study. T2 weighted
MRI had been performed in these patients a day or two before the initiation of RT and then at the end of week 5.

Patient characteristics are defined in Table 1.

All our patients had either undergone a stereotactic biopsy or subtotal resection and had evaluable disease on pretreatment MRI’s. Two patients with multifocal disease were not included in the final analysis. Five of our patients had received concurrent temozolamide as part of a clinical trial. All patients received 3-D conformal radiotherapy with MRI registration for defining boost volumes.

GTV Pre Treatment was delineated from the T2 weighted MRI performed a day prior to initiation of RT and a second GTV was outlined on a repeat MRI (T2 weighted) done at the beginning of Week 5 for defining the boost field. Treatment plan was based on 2 separate PTV’s, the first one being derived from a uniform expansion of 2 cm around GTV to a dose of 50 Gy and GTV(wk.5) taken as PTV of the boost field for treating to a total dose of 60 Gy.

**RESULTS**

Fifteen patients had unifocal disease, of which 8 patients had grade 4 gliomas and 7 had grade 3 gliomas. The changes in the GTV noted between T2 weighted pre treatment and week 5 MRI scans were as follows: 12/15 cases (80%) showed a reduction in tumor volumes (median 54.85 cc). Of these, 4/15 (26.6%) cases had an objective reduction in GTV(>=50%) and 8 cases showed a slight to moderate reduction in tumor volume at week 5 of radiotherapy. An increase in tumor volume (median 14 cc) was demonstrated by 3/15 (20%) cases.

Of grade 4 gliomas, 2/8 cases (25%) showed an objective reduction in GTV (>=50%) while 2/8 (25%) showed an increase in tumor volume (Table 2). Of grade 3 gliomas, 2/7 cases (28.6%) showed an objective reduction in GTV (>=50%), 1/7 (14%) demonstrated an increase in tumor volume (Table 3).

All patients completed their course of radiotherapy as planned.

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**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Grade 4</th>
<th>Grade 3</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Surgery</td>
<td>STR</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Biopsy</td>
<td>1</td>
</tr>
<tr>
<td>Age(years)</td>
<td>Median</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>42-70</td>
</tr>
<tr>
<td>KPS</td>
<td>Median</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>80-90</td>
</tr>
<tr>
<td>RT Dose (Gy)</td>
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<td>60</td>
</tr>
</tbody>
</table>

**Table 2: Changes in gross tumor volumes (cc) between pre treatment and week 5 MRI’s in grade 4 gliomas**

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>GTV-Pre (cc)</td>
<td>192</td>
<td>103.3</td>
<td>164.2</td>
<td>61.6</td>
<td>269.8</td>
<td>127</td>
<td>186.7</td>
<td>560.5</td>
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<tr>
<td>GTV-Wk 5 (cc)</td>
<td>142</td>
<td>62.4</td>
<td>89</td>
<td>26.4</td>
<td>144</td>
<td>141</td>
<td>195.7</td>
<td>248.63</td>
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<tr>
<td>GTV reduction (cc)</td>
<td>50</td>
<td>40.9</td>
<td>75.2</td>
<td>35.2</td>
<td>125.8</td>
<td>-</td>
<td>-</td>
<td>311.87</td>
</tr>
<tr>
<td>GTV Gained (cc)</td>
<td>14</td>
<td>9.1</td>
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<td></td>
<td></td>
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</tbody>
</table>

**Table 3: Changes in gross tumor volumes (cc) between pre treatment and week 5 MRI’s in grade 3 gliomas**

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV-Pre (cc)</td>
<td>186</td>
<td>320</td>
<td>133</td>
<td>152.5</td>
<td>57.3</td>
<td>131.8</td>
<td>672.75</td>
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<tr>
<td>GTV-Wk 5 (cc)</td>
<td>247</td>
<td>215</td>
<td>99</td>
<td>93</td>
<td>24.6</td>
<td>96.7</td>
<td>30.78</td>
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<tr>
<td>GTV reduction (cc)</td>
<td>-</td>
<td>105</td>
<td>34</td>
<td>59.5</td>
<td>32.7</td>
<td>35.1</td>
<td>641.97</td>
</tr>
<tr>
<td>GTV gained (cc)</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 1:** Comparison of Gross tumor volumes (cc) of pre treatment and week 5 MRI’s in grade 4 Malignant Gliomas

**Figure 2:** Comparison of Gross tumor volumes (cc) of pre treatment and week 5 MRI’s in grade 3 Malignant Gliomas
DISCUSSION

Long-term survival of patients with high-grade gliomas remains extremely poor. The main reason for such an outcome is local failure, or recurrence, after surgery and/or radiotherapy. GBM’s are one of the most biologically aggressive tumors with a median survival of less than one year despite the current treatment modalities which include surgery, radiotherapy and chemotherapy. Initial reports documented approximately 80% of relapses occur within a 2-cm margin from the original tumor location. The last 20 years have seen a shift away from using whole brain fields to regional fields made possible with better tumor localization associated with CT and MRI. A retrospective analysis comparing the target volumes that would have been defined by CT, T2-weighted MRI, and T1-weighted post gadolinium MRI images of the same individual and to explore the implications of the resulting volume definitions for radiotherapy indicated that the CT-defined target volume is consistently larger than that from either of the two MRI modalities. Heavily T2-weighted sequences are the most sensitive for the detection of tumor and edema extent, but the tumor focus is not well separated from surrounding edema. T1-weighted images following contrast enhancement generally provide better localization of the tumor nidus and improved diagnostic information relating to tumor grade, blood-brain barrier breakdown, hemorrhage, edema and necrosis. The contrast enhanced T1 MRI may not be a totally reliable indicator of active tumor, especially in regions where such blood-brain barrier breakdown has not occurred. Moreover, these volumes may change during the course of treatment. This was demonstrated in a well conducted multi institutional trial that employed RTOG (Radiation therapy oncology group) GBM protocol for definition of tumor margins. They found that GTV mid, defined as the enhancing abnormality on mid treatment MRI’s, changed 80% of the time when compared to post-operative MRI GTV’s. Therefore, boost radiation therapy fields designed using post-operative MRI scans alone could potentially lead to scenarios where significant geographic miss occurs. This phenomenon of geographic miss could be the result of change in the morphology of the tumor, which would be observed if the tumor demonstrated growth during treatment. In addition, several acute and sub-acute reactions after radiation therapy have been described clinically. However, acute reactions are a result of vasogenic edema of early onset and may appear during the course of radiation therapy or shortly thereafter. These manifest as a transient encephalopathy and are not associated with specific MRI or CT findings, while sub acute reactions (early delayed radiation complications) occur a few weeks to 3 months after radiation therapy.

To account for the diffuse spreading of tumor cells, we used the MRI T2 hyper intensity plus a generous safety margin of about 2 cm for the initial phase of treatment. A mid treatment contrast enhanced MRI was not affordable by most of our patients and was not done, instead the GTV on mid treatment T2 weighted scan was treated as the boost field.

A prospective trial that enrolled 21 patients of high grade gliomas treated to 70 Gy by 3D CRT demonstrated changes in gross tumor volume occurring as early as week 3 on repeat MRI imaging. Three of 12 patients of grade 4 gliomas in their study showed an increase in GTV occurring on week 3 MRI’s and all 3 cases required an increase in tumor margin of 2-3 cm to encompass the change in volumes noted. This study recommended that routine imaging during early treatment may be necessary to ensure adequate target volume coverage when highly conformal radiotherapy techniques are employed in dose escalation trials.

High quality MR imaging has made it possible to better select patients for aggressive local therapy by carefully checking for distinct tumor margins, unifocality and lack of corpus callosal involvement and reduced treatment volumes have translated into less toxicity and allowed for a 50% increase in external beam radiation doses to be safely administered using various fractionation schedules, brachytherapy, 3D-conformal radiotherapy, IMRT, or stereotactic radiotherapy. Unfortunately, no dramatic increase in survival has been obtained and local control remains elusive. However it has to be noted that none of these earlier studies or the recently concluded RTOG-98-03 dose escalation trial used repeat imaging before the boost plan. Our study was conducted on a small group of patients and a contrast enhanced MRI was not done in all patients for reasons of affordability, however a change in gross tumor volume was demonstrated in almost all patients on week 5 MRI. Whether the increase in GTV in 12 patients (median 14cc, range=9.1-61cc) would have translated into inadequate coverage was not studied and can not be commented upon.

Given the refractory nature of high grade gliomas, one can’t be certain that an adjustment of treatment volume during treatment will improve outcomes. But surely the likelihood of treatment success would appear to be decreased if the tumor is not within the treatment field.

REFERENCES