Helical tomotherapy simultaneous integrated boost provides a dosimetric advantage in the treatment of primary intracranial tumors

Joseph M Baisden¹, Jason Sheehan², Andrew G Reish³, Alyson F McIntosh¹, Ke Sheng⁴, Paul W Read¹, Stanley H Benedict¹, James M Larner⁴

¹Department of Radiation Oncology, University of Virginia, Charlottesville, VA, USA, ²Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA, ³Medical School, University of Virginia, Charlottesville, VA, USA

Objective: The research quantitatively evaluates the dosimetric advantage of a helical tomotherapy (HT) intensity-modulated radiation therapy simultaneous integrated boost (SIB) compared to a conventional HT sequential (SEQ) boost for primary intracranial tumors.

Methods: Hypothetical lesions (planning target volumes or PTVs) were contoured within computed tomography scans from normal controls. A dose of 50 Gy was prescribed to the larger PTV1, while the boost PTV2 received a total of 60 Gy. HT SEQ and HT SIB plans were generated and compared. We evaluated the mean brain dose, the volume of normal brain receiving 45 Gy (V45), the volume of normal brain receiving 5 Gy (V5), and the integral dose. In addition, patients who were treated with the HT SEQ technique were replanned with the HT SIB technique and compared.

Results: The average reduction in mean brain dose with the HT SIB plan compared to the composite HT SEQ plan was 11.0% [standard error (SE): 0.5]. The reductions in brains V45 and V5 were 43.7% (SE: 2.3) and 3.9% (SE: 0.6), respectively. The reduction in the integral dose was 11.0% (SE: 0.5). When comparing the SIB plan to the first 50 Gy only of the SEQ plan, there was only a 2.5% increase in the mean brain dose and a 2.9% increase in brain V45. This increase was dependent on the relative volumes of PTV2 and PTV1. These results were confirmed for the patient plans compared.

Conclusions: Treating primary brain tumors with the HT SIB technique provides significant sparing of normal brain parenchyma compared to a conventional HT SEQ boost.

Keywords: Brain sparing, Radiation-induced encephalopathy, Simultaneous integrated boost, Tomotherapy

Introduction

Primary brain tumors have an incidence of 6.6 per 100 000, and this translates into 20 000 new cases per year in the United States.¹ A significant percentage of these patients receive radiation therapy, which is frequently delivered with an intensity-modulated technique in order to decrease the dose to normal brain and the associated likelihood of radiation-induced neurocognitive decline. Although the mechanism of radiation-induced central nervous system toxicity is not well defined, the likelihood of adverse central nervous system effects from brain radiation is related to total dose, dose per fraction, and the volume of normal brain irradiated.²⁻⁴

Conventional radiation treatment schedules for primary brain tumors often involve the treatment of an initial volume followed by a sequential (SEQ) boost. These two treatments combined into one constitute a simultaneous integrated boost (SIB). Previous research has evaluated the feasibility of an SIB with helical tomotherapy (HT SIB) in the treatment of metastatic brain lesions.⁵,⁶ These studies have shown that SIB by HT is able to deliver a homogeneous brain dose and a fairly conformal dose to the metastasis with surgical precision. In addition, SIB offers other advantages compared to SEQ treatment. First, SIB delivers a higher biologically equivalent dose to the cancer cells which may result in an advantage with regard to tumor control.⁷,⁸ In addition, there is a theoretical dosimetric gain by using the SIB compared to SEQ treatment. In the ideal inverse optimization, a step function-shaped dose is delivered to the boost volume without spillage to the surrounding tissue. However, this is not achievable in reality due to the lack of a 'negative
dose’, which essentially undoes the dose delivered to non-target tissue. However, the SIB technique can create an effective ‘negative dose’ by reducing the dose delivered to the initial target volume by an amount that will match the dose delivered in the boost volume. Therefore, we hypothesized that SIB would result in a more conformal dose distribution than an SEQ treatment plan. In this research, we investigated the ability of HT SIB to spare normal brain parenchyma compared to conventional HT SEQ techniques for treatment of primary brain tumors.

Materials and Methods
Computed tomography scans of patients in the supine position with an aquaplast immobilization mask were simulated for treatment planning. Normal tissues were contoured using AcQsim software (Philips Medical Systems North America, Bothell, WA, USA). Hypothetical planning target volumes (PTVs) consisting of cylindrical structures of similar diameter and height were placed at the central portion of the brain. For every hypothetical lesion, two PTVs were created. PTV1 corresponded to the initial larger treatment volume of a traditional SEQ plan, based on the peritumoral edema in the case of a typical high-grade glioma. The boost volume, or PTV2 volume, corresponded to the contrast-enhanced tumor plus a margin. Multiple sizes of PTVs were evaluated (i.e. varied combinations of PTV1 and PTV2 were employed).

Planning was performed using HI-Art Helical Tomotherapy inverse planning software (Middleton, WI, USA). SEQ plans were created by preparing two separate doses: 50 Gy to PTV1 and 10 Gy to PTV2. Composite dosimetry was performed using proprietary HT software. For the evaluation of the SIB in the treatment of primary brain tumors, a dose of 50 Gy was prescribed to PTV1 and a dose of 60 Gy to PTV2. Both the SEQ and SIB plans were optimized with similar constraints on normal tissue to minimize any potential planning bias. A total of 42 comparisons between the two techniques were analyzed.

Several dosimetric parameters were analyzed for plan comparisons, including the mean and median dose to the brain as well as the volume of brain receiving 45 Gy (V45) and the volume of brain receiving 5 Gy (V5). The mean dose was also evaluated. Analysis of the dose to the normal brain was performed using structures corresponding to the entire brain minus the PTV1 and PTV2. The volume for determining the integral dose was defined as the external contour of the head with no internal structures subtracted. Analysis and graphing of these data were performed using the Microsoft Excel Data Analysis Pak (Microsoft, Seattle, WA, USA) and SPSS (SPSS, Inc., Chicago, IL, USA). MatLab (Mathwork, Natick, MA, USA) was used in the generation of color scale images demonstrating differences in delivered dose.

To further confirm the results, three patients treated for glioblastomas who had previously received HT SEQ treatment for primary brain tumors were replanned using the HT SIB technique for comparison. In the HT SEQ plans that were delivered, all patients received a combined total dose of 60 Gy in 30 fractions. HT SIB planning used similar dosimetric constraints to the corresponding patient’s HT SEQ plan in order to achieve a valid comparison.
Results
Differences observed in simulated dose plans
A representative comparison of the two types of plans is included in Fig. 1. Panel A demonstrates that the dose volume histogram line for the normal brain is shifted to the left for the HT SIB plan, indicating that the normal brain is spared at all doses compared to the HT SEQ plan. The color wash (panel B) demonstrates the absolute difference in dose delivered between the two plans for one axial slice. Note that the greatest sparing with the HT SIB plan compared to the HT SEQ plan occurs just outside PTV2 and PTV1 in the surrounding normal brain tissue at high doses.

Figure 2 compares the SIB plans to the composite SEQ plans using several standard dosimetric end-points and illustrates significant sparing of normal tissues in favor of the SIB technique. Compared to SEQ, treatment via SIB resulted in decreases in the mean and median brain doses of 11.0% [standard error (SE): 0.5%] and 11.9% (SE: 0.5%), respectively. The mean decrease in the V45 for the SIB technique was 43.7% (SE: 2.3%), and in the V5, the reduction was 3.9% (SE: 0.6%). These results indicate a greater percentage of sparing at higher doses, which is also shown in Fig. 1B. The mean decrease in the integral dose was 11.0% (SE: 0.5%).

Given the significant sparing observed with HT SIB (Figs. 1 and 2) treatment, we calculated the magnitude of the dose increase to normal brain during delivery of 60 Gy using an SIB technique compared to 50 Gy with HT and no boost. Figure 3 demonstrates that delivering 60 Gy with the SIB technique increases normal brain doses relatively minimally compared to only the first 50 Gy of the SEQ technique. The mean, V45, and integral brain dose increases were 2.5% (SE: 0.5), 2.9% (SE: 0.5), and 4.5% (SE: 0.8), respectively. Thus, a 10-Gy boost can be delivered to a primary brain tumor using the SIB technique with only a very minor increase in dose to normal brain tissue.

In order to determine whether these increases were dependent upon the relative volumes of PTV2 and PTV1, we generated a scatter plot including the data points of the 22 comparisons made on PTV2/PTV1 ratios ranging from 0.2 to 0.8 (Fig. 4). A linear regression analysis of these data points was plotted as a best-fit line; this showed an acceptable goodness of fit ($R^2=0.831$ for the mean dose and $R^2=0.81$ for the integral dose). Thus, for clinical situations wherein the PTV2/PTV1 ratio is equal to 0.5 or less, the increases in mean brain dose and integral dose approach clinical insignificance provided that the 5% integral dose difference is used as a threshold.

Differences observed in three glioblastoma patients
To determine whether the results from Figs. 1 and 2 which were based on hypothetical lesions accurately reflect the results seen in patients with primary brain tumors, we analyzed dosimetric data for three glioblastoma patients who received HT SEQ treatments and were later replanned using the HT SIB technique for comparison (Table 1). In these three patients, the SIB plans spared the normal brain in a manner similar to the simulated results above, with the highest decrease observed for brain V45. Mean brain dose sparing ranged from 11 to 14%. Median brain dose sparing ranged from 9 to 14%. Median brain dose sparing ranged from 9 to 21%. Mean brain V45 sparing ranged from 48 to 86%. Integral dose sparing ranged from 4 to 12%. No sparing of the brain V5 was observed. PTV coverage with both planning techniques met the criteria that 95% of the volume received the prescription doses of 50 and 60 Gy for PTV2 and PTV1, respectively. PTV1 doses are 5% higher between the HT SEQ composite and HT SIB plans. PTV2 is more inhomogeneous with the SIB plans compared to SEQ plans. However, as the
measured integral dose decreases in the SIB treatment compared to SEQ, the overall dosimetric gain in normal brain outweighs the additional dose delivered to the PTV.

Discussion

Prior reports have indicated that the use of an intensity-modulated radiation therapy integrated boost provides dosimetric advantages compared to an SEQ boost, including shorter treatment time, potential radiobiological gains, and normal tissue sparing. Our HT-based data for primary brain tumor patients are consistent with these reports. The clinical significance of this dose sparing is unknown, but the reduction in unwanted high dose spillage could potentially reduce the risk of radiation-induced edema and/or necrosis. The reduction in low dose spillage to the entire brain, coupled with the reduction in high dose spillage, may decrease the chance of late cognitive deficits. In addition, the SIB technique has the advantage that more of the total dose is placed in the boost volume, since the PTV2 maximum dose is higher with the SIB than with the SEQ technique. This increase in the maximum dose reflects an increase in dose inhomogeneity in both the PTV1 and PTV2 with the HT SIB technique, which may increase the likelihood of tumor control while only minimally increasing the risk for normal tissue.

As hypothesized, the conformality was improved with SIB compared to SEQ treatment. The improvement can be understood from the principle of inverse treatment optimization. The more degrees of freedom the optimization has, the more likely a clinician is to reach the global optimum. In the case of SEQ, the optimization is performed in two smaller subspaces that do not communicate with each other. Therefore, the solution is inferior to the SIB, which is able to optimize in a larger, combined solution space. An intuitive example of this is the aforementioned negative dose. In order to deliver a perfectly conformal boost dose, no dose spillage would occur to the surrounding normal brain tissue. Theoretically, a ‘negative dose’ could be delivered to the normal tissue to offset the dose spillage from the boost treatment. However, since the ‘negative dose’ cannot actually be delivered, the boost plan in SEQ has to incorporate a higher dose spillage compared to the SIB plan, in which the boost can actually deliver a ‘negative dose’ by subtracting dose from the radiation dose to the PTV1. To obtain such a theoretical advantage, an inverse optimization routine has to be able to explore the solution space thoroughly. HT, with its ability to optimize radiation using 2πi degrees and tens of thousands of beamlets, appears to be able to convert the theoretical advantage into practical gains. With the SIB plan, the software is able to

Table 1 Normal tissue doses seen using the simultaneous integrated boost (SIB) technique compared to the composite plan from the sequential (SEQ) technique

<table>
<thead>
<tr>
<th>SIB versus SEQ composite</th>
<th>Absolute change (Gy)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean brain dose</td>
<td>1</td>
<td>-2.88</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-2.97</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-4.7</td>
</tr>
<tr>
<td>Brain V45</td>
<td>1</td>
<td>-5.9</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-5.2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-22.5</td>
</tr>
<tr>
<td>Brain V5</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>+0.9</td>
</tr>
<tr>
<td>Integral dose</td>
<td>1</td>
<td>-0.78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-1.16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-3.01</td>
</tr>
</tbody>
</table>

*Negative values indicate a decrease in dose with the SIB technique compared to the composite SEQ plan.
account for the dose delivered to both PTV1 and PTV2 and integrate this data into a single plan, resulting in improved dosimetry. Conversely, the SEQ technique does not integrate the information from the two data sets into a composite plan; therefore, the result is a significant decrease in conformity, resulting in inferior dosimetry.

Conclusions

In summary, using the HT SIB technique provides a reduction in the radiation dose to the normal brain compared to using an SEQ technique. Although the clinical benefits of the use of the SIB technique are unknown, it has the potential to decrease the likelihood of adverse neurocognitive effects, particularly in patients with good performance status and life expectancies.

References