Possible Overcoming of Tumor Hypoxia with Adaptive Hypofractionated Radiosurgery of Large Brain Metastases: A Biological Modeling Study

Lijun Ma, Chia-Lin Tseng, and Arjun Sahgal

Abstract *Objective:* The present biological modeling study evaluated possible application of adaptive hypofractionated stereotactic radiosurgery (HSRS), which involves escalation of the prescription dose according to the gradual decrease in the tumor volume between treatment sessions separated by 2- to 3-week intervals, in the management of large brain metastases.

Methods: To investigate the effects of dose escalation during three-stage adaptive HSRS, a generalized biologically effective dose (gBED) model was applied. Accounting for both a nonuniform dose distribution inside the target and tumor hypoxia was implemented, and normal brain radiation dose distributions were assessed.

Results: In comparison with conventional three-stage HSRS (with an identical prescription dose of 10 Gy at each treatment session), adaptive HSRS resulted in a 30–40% increase in gBED. This effect was especially prominent in late-responding targets (with α/β ratios from 3 to 10 Gy) and in neoplasms containing a high percentage of hypoxic cells. Despite dose escalation in the target, irradiation of the adjacent normal brain tissue was kept within safe limits at a level similar to that applied in conventional three-stage HSRS.

Conclusion: Adaptive HSRS theoretically results in significant enhancement of gBED in the target and may possibly overcome resistance to irradiation, which is caused by tumor hypoxia. These advantages may translate into higher treatment efficacy in cases of large brain metastases.

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Introduction

Single-session stereotactic radiosurgery (SRS) is highly effective in management of small (<2 cm in diameter) brain metastases (BM), whose local control rates are approaching 70–80% [1–4]. However, in cases of large tumors (>2–3 cm in diameter), the effectiveness of such treatment is steadily decreasing [3, 5–9]. Ideally, higher radiation doses should be delivered to larger neoplasms to counteract the greater burden of pathological tissue for effective achievement of local growth control. However, an increase in the irradiated tumor volume results in a corresponding increase in the irradiated volume of adjacent normal brain tissue, whose tolerance is determined by the total prescription dose and dose per fraction. Thus, for avoidance of radiation-induced injury, the prescription dose delivered during single-session SRS should be limited. The Radiation Therapy Oncology Group (RTOG) 90-05 study showed that for maintenance of acceptable toxicity rates during such treatment, brain tumors with maximum diameters of ≤2, 2.1–3, and 3.1–4 cm should receive the maximum prescription doses of 24, 18, and 15 Gy, respectively [7]. A decrease in the prescription dose in turn results in worse local control. Moreover, large malignant neoplasms are typically characterized by prominent tissue hypoxia, which further limits the therapeutic effects of irradiation.

To increase the biologically effective dose (BED) delivered to large targets while respecting normal brain tissue tolerance, the concept of hypofractionated stereotactic radiosurgery (HSRS) has been developed. Usually, it is based on delivery of a total prescription dose of 24–30 Gy, separated into 3–5 equal, consecutive or closely scheduled

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daily fractions [6]. An extreme variation of HSRS, also known as staged SRS, involves longer intervals between treatment sessions (e.g., 2–3 weeks). During such treatment, the tumor may demonstrate prominent shrinkage [5], which requires radiosurgical replanning before each stage of irradiation. Taking this fact into consideration, we have hypothesized that in such cases, the prescription dose may be escalated according to the observed decrease in the target volume while maintaining identical normal brain tissue dose distributions within safe limits (the concept of adaptive HSRS). The rationale for such a treatment strategy is based on attainment of a nonuniform dose distribution within the target, which could possibly overcome resistance to irradiation, caused by tumor hypoxia [10]. The present biological modeling study specifically investigated to what extent the prescription dose could be escalated, considering the variable distributions of the central target dose hot spots and the levels of hypoxia within the neoplasm, and whether dose escalation may theoretically provide any significant advantages over conventional HSRS for large BM.

Materials and Methods

To investigate the effects of dose escalation during adaptive HSRS of large BM and the theoretical impact of tumor hypoxia on the response to such treatment, a previously described model of generalized BED (gBED) [11] was applied. The concept and formulation of gBED for modeling of nonuniform dose distributions during SRS and stereotactic body radiation therapy (SBRT) have been reported by our group previously [11, 12]. One of the most important features is that the composite gBED for the entire treatment course during HSRS represents the sum of the gBED values of all treatment sessions, which is similar to the standard BED formula for irradiation with uniform doses during conventional fractionated radiotherapy [11].

The total survival probability (S) of a target volume receiving a nonuniform dose is expressed as:

$$s = \sum_i v_i S\left(D_i\right) \tag{1}$$

where v_i is the ith fractional volume receiving a uniform fractional dose (D_i) (i.e., (v_i, D_i) forms the ith bin of the differential dose–volume histogram for the volume of interest (VOI)). According to the standard linear–quadratic (LQ) model:

$$S_i = \exp\left(-\alpha BED_i\right) \tag{2}$$

where BED_i corresponds to the ith fractional volume. Therefore, gBED may be defined as the dose that would produce an identical total S value for the whole target volume as:

$$S = e^{-\alpha \cdot gBED} = \sum_i v_i S_i = \sum_i v_i e^{-\alpha \cdot BED_i} \tag{3}$$

Assuming that the α/β ratio for a given target is constant, Eq. (3) may be further solved as:

$$gBED = -1/\alpha \times \log\left(\sum_i v_i e^{-\alpha \cdot BED_i}\right) \tag{4}$$

where $BED_i = ND_i\,[1 + G_i D_i / (\alpha / \beta)]$; correspondingly, N is the total number of treatment sessions (fractions) and G_i is the dose rate correction factor, whose formulation has been described by our group before [13].

Dose Escalation in the Target and Control for Irradiation of Normal Brain Tissue

In the present study for determination of the appropriate prescription dose, a general dose falloff formula [14, 15] was used. The interrelationships between the normal brain volume (V) surrounding the target and the delivered marginal isodose (D) are generally described as:

$$V/V_t = CI \cdot \left(D/D_t\right)^{\gamma} \tag{5}$$

where V_t is the target volume, D_t is the prescription dose, CI is the conformity index, and γ is an empirical fitting parameter with an approximate value of -1.5, which is accepted for most radiosurgical modalities, including a linear accelerator (LINAC) and Leksell Gamma Knife Perfexion™ (Elekta AB; Stockholm, Sweden).

As follows from Eq. (5), for any relative decrease in the target volume (V_t) by Δ at the time of the 2nd, 3rd, … Nth treatment session (fraction), in order to maintain the identical dose–volume relationship of the original treatment plan, the corresponding relative increase in the prescription dose (D_t) would be computed as $(1 - \Delta)^{1/\gamma}$. For example, if a dose of 10 Gy was delivered at the first treatment session, and after a 2-week interval, the target volume decreased by 25% (i.e., it constituted 75% of the original volume), then the corresponding escalated prescription dose, still maintaining the

same peripheral isodose distribution as that applied at the time of initial treatment, would be:

$$10\times\left(1-0.25\right)^{-1/1.5}=12\,\text{Gy}.$$

Likewise, any further decrease in the target volume at the time of subsequent treatment sessions could also be accounted for in a similar fashion for adaptive dose escalation based on the actual target volume.

Accounting for Tumor Hypoxia

For evaluation of and accounting for tumor hypoxia, the hypoxia reduction factor (HRF) suggested by Carlson et al. [16] was utilized. If HRF_i for the ith fractional volume was applied, then, without losing the generality of all of the derivations, BED_i in Eq. (4) would be rendered as:

$$BED_i = ND_i \,/\, HRF_i\left[1+G_iD_i\,/\left(HRF_i\alpha\,/\,\beta\right)\right] \qquad (6)$$

Since the exact HRF_i distribution within the target during treatment was unknown, all corresponding voxels were randomly sampled with the assumption that the total hypoxic cell concentration does not exceed a fixed percentage of the total target volume (e.g., 30%, 50%, 70%, or 80%) and that any hypoxic voxel possesses a high HRF_i value of 2.0–2.8. Of note, HRF depends on oxygenation but reaches 2.8 for maximum anoxic conditions.

Comparative Analysis

For comparative analysis, the gBED enhancement ratio was defined as the ratio of gBED in the tested treatment plan for three-stage adaptive HSRS (with prescription dose escalation at each stage according to the reduction in the tumor volume) to gBED in the treatment plan of three-stage conventional HSRS (with an identical prescription dose of 10 Gy at all stages).

Results

A simulation of adaptive HSRS for a large BM of unknown origin is illustrated in Fig. 1. The actual treatment was done with three-stage HSRS (total prescription dose 30 Gy), and the treatment sessions were separated by 2- to 3-week intervals. The initial tumor volume was 20 cc and was reduced to 11 cc by the time of the third treatment session. On the basis of the dose escalation concept described above, the prescription doses for adaptive HSRS should be 10, 12, and 15 Gy for the first, second, and third treatment sessions, respectively. This would result in normal brain dose distributions identical to that at the initial treatment session (e.g., an 8 Gy isodose volume of 21.2 cc).

During adaptive HSRS, the dose distributions within the target (also known as central target dose hot spots) differed at each replanned treatment session. However, despite such variations in dose patterns, the gBED enhancement ratio showed similar characteristics (Fig. 2). It demonstrated minimal variability during modeling of adaptive HSRS in 200 independent samples with randomly distributed hypoxic voxels; the maximum standard deviation of the values was ≤4% and mainly depended on the correspondence of hypoxic voxels to dose hot spots within the target. At the same time, the gBED enhancement ratio showed dependence on the α/β ratio and the percentage of hypoxic cells within the target volume; it demonstrated the highest values if the α/β ratio was within 3–10 Gy (i.e., in late-responding targets) and in modeled cases with a higher percentage of hypoxic cells. For example, for a target with an α/β ratio of 5 Gy, application of adaptive HSRS escalated the total gBED value by 38.1 ± 1.2% in the case of fully oxygenated tissue (0% hypoxic voxels) and by 46.7 ± 3.5% in the case of highly hypoxic tissue (80% hypoxic voxels randomly distributed within the target).

Discussion

Different strategies have been developed for delivery of sufficiently high prescription doses to large BM for improvement of their local control after SRS. For example, Minniti et al. [6] applied HSRS (three daily fractions of 9 Gy each) in tumors with a median volume of 12.5 cc. Comparison of such treatment with single-session SRS for relatively smaller neoplasms (median volume 8.8 cc) revealed that HSRS was accompanied by a halved incidence of adverse radiation effects (ARE) (9% versus 18%, $P = 0.01$) and better local tumor control rates (91% versus 77%, $P = 0.01$) [6]. Higuchi et al. [5] successfully used three-stage SRS for management of BM with a volume >10 cc (mean volume 17.6 cc, which was much larger than that in the aforementioned series reported by Minniti et al. [6]). The total prescription dose was 30 Gy (10 Gy at each stage), and the treatment sessions were separated by 2-week intervals. The vast majority (>90%) of tumors in this series ($N = 43$) demonstrated prom-

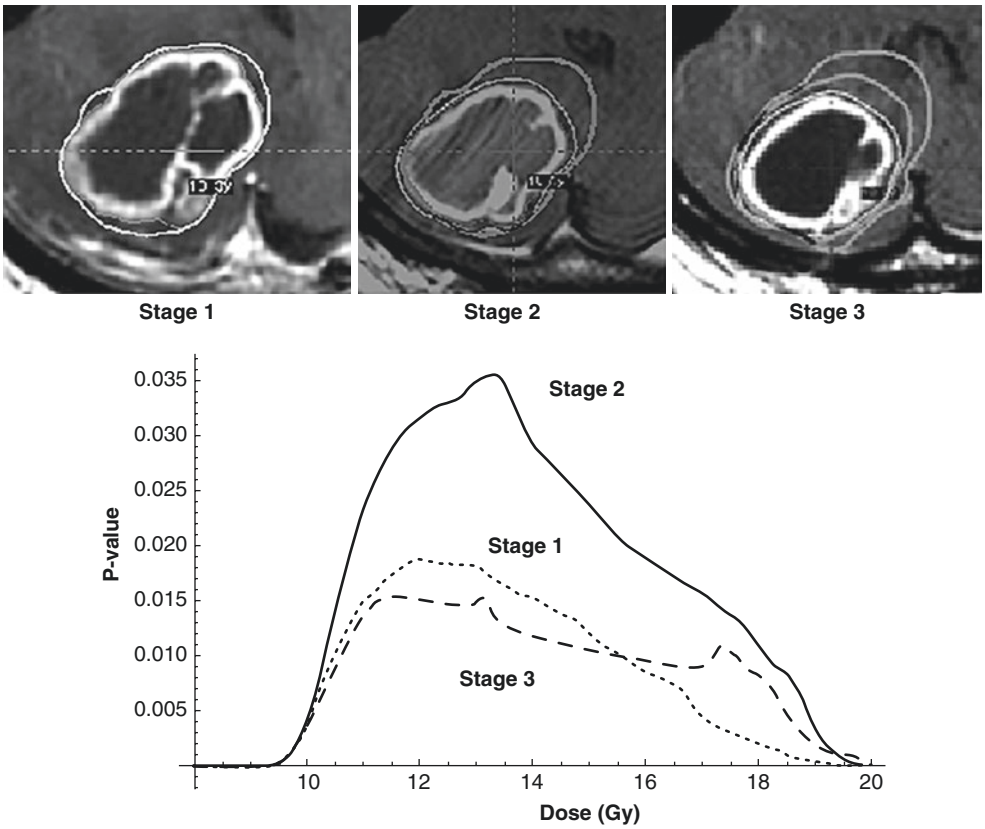

Fig. 1 Simulated three-stage treatment of a large brain metastasis of unknown origin, according to the concept of adaptive hypofractionated radiosurgery. Prescription isodose lines for each treatment session are shown on postcontrast T1-weighted magnetic resonance imaging (*top*), demonstrating a gradual reduction in the tumor volume. The differential dose–volume curves (*bottom*) suggest dissimilar variations in the probability density function of the dose distributions within the target volume for each replanned treatment session

inent shrinkage during treatment and, at the time of the second and third stages, their mean volume had decreased by 18.8% and 39.8%, respectively. ARE were noted in 9% of cases, and the 1-year local tumor control rate was 76%. [5].

Our group has developed a novel concept of adaptive HSRS for large intracranial neoplasms, which can be accomplished by means of any radiosurgical modality and involves creation of a new treatment plan at each stage of irradiation (separated by 2- to 3-week intervals), delivery of a ≥10 Gy prescription dose per treatment session, and dose escalation according to the gradual decrease in the tumor volume. This results in highly nonuniform dose distributions within the target, which, as was suggested by Ruggieri et al. [10], may be effective for overcoming resistance to irradiation caused by tissue hypoxia.

The present study was directed at theoretical evaluation of adaptive HSRS for large BM, accounting for both a nonuniform dose distribution inside the target and the effects of tumor hypoxia. The latter was controlled by modeling with different hypoxic cell concentrations within the target volume. The results indicated that adaptive HSRS may indeed be notably advantageous, providing a 30–40% increase in gBED in comparison with conventional HSRS (which delivers identical prescription doses at all stages), and this may potentially translate into better local tumor control. The effect was especially prominent in late-responding targets with α/β ratios from 3 to 10 Gy and in neoplasms containing a high percentage of hypoxic cells. At the same time, despite dose escalation in the target, irradiation of adjacent normal brain tissue during adaptive HSRS was kept identical at the different treatment sessions, similarly to conventional three-stage HSRS (10 Gy per treatment session), and this corresponded well to safe limits. Such promising findings, along with inherent neuronal tissue repair mechanisms during sufficiently long time intervals between treatment sessions, may suggest that adaptive HSRS does not carry an increased risk of ARE.

There is no doubt that despite such beneficial results obtained in this theoretical study, the exact characteristics of adaptive HSRS with regard to its efficacy and safety may be established only in clinical investigations, preferably performed in a prospective and controlled fashion. In addition, there are several issues that require further clarification (e.g., the most appropriate number of treatment stages and the optimal time intervals between them). Moreover, while solid data suggest that application of the standard LQ formula is sufficiently appropriate for analysis of large-dose treatment [17, 18], this is still debatable and may be considered as a drawback of the presented predictive model. Nevertheless, since not

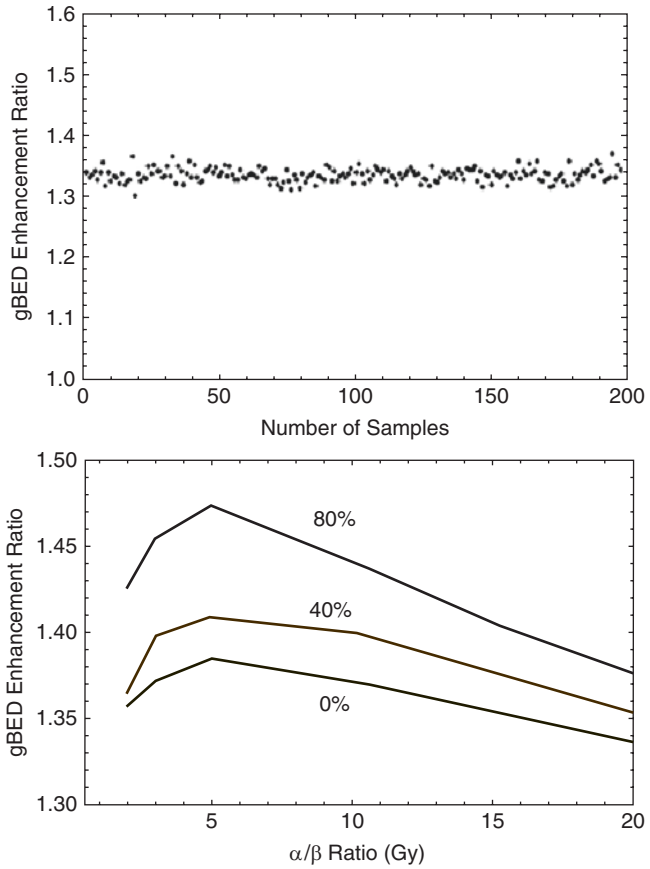

Fig. 2 Generalized biologically effective dose (gBED) enhancement ratio for adaptive hypofractionated radiosurgery in targets with a random distribution of hypoxic voxels. There is minimal variability in the values with regard to nonuniform dose distributions within the target volume during modeling in 200 independent samples (*top*) but a clear dependence (*bottom*) on the α/β ratio and the percentage of hypoxic cells (0%, 40%, and 80% as shown herein)

absolute gBED values but relative gBED enhancement ratios were computed from comparison of isodose distributions in treatment plans for adaptive and conventional HSRS, the reported results are sufficiently robust and the observed increase in total gBED (by approximately 30–40%) with the tested treatment strategy is accurate and compelling.

Conclusion

The suggested concept of adaptive HSRS based on escalation of the prescription dose according to the decrease in the tumor volume between treatment sessions theoretically results in significant enhancement of gBED in the target while maintaining delivery of a safe dose to adjacent normal brain tissue. Such a novel strategy may potentially overcome resistance to irradiation, which is caused by tumor hypoxia. These advantages may significantly increase treatment effectiveness during management of large BM; thus, further clinical evaluations of adaptive HSRS are warranted.

Conflict of Interest Drs. Ma and Sahgal have previously received educational honoraria and travel support from Elekta AB. Dr. Sahgal has received research grants from Elekta AB and has served on the medical advisory board of Varian Medical Systems.

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