To fractionate or not to fractionate? That is the question for the radiosurgery of hypoxic tumors

Laboratory investigation

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Object. This study aimed to investigate the impact of tumor hypoxia on treatment outcome for metastases commonly treated with radiosurgery using 1 fraction of radiation and the potential gain from reoxygenation if the treatment is delivered in a few radiation fractions.

Methods. In silico metastasis-like radiosurgery targets were modeled with respect to size, density of clonogenic cells, and oxygenation. Treatment plans were produced for the targets using Leksell GammaPlan, delivering clinically relevant doses and evaluating the tumor control probability (TCP) that could be expected in each case. Fractionated schedules with 3, 4, and 5 fractions resulting in similar biological effective doses were also considered for the larger target, and TCP was determined under the assumption that local reoxygenation takes place between fractions.

Results. The results showed that well-oxygenated small- and medium-size metastases are well controlled by radiosurgery treatments delivering 20 or 22 Gy at the periphery, with TCPs ranging from 90% to 100%. If they are moderately hypoxic, the TCP could decrease to 60%. For large metastases, the TCPs from single-fraction treatments ranged from 0% to 19%, depending on tumor oxygenation. However, for fractionated treatments, the TCP for hypoxic tumors could significantly increase up to 51%, if reoxygenation occurs between fractions.

Conclusions. This study shows that hypoxia worsens the response to single-fraction radiosurgery, especially for large tumors. However, fractionated therapy for large hypoxic tumors might considerably improve the TCP and might constitute a simple way to improve the outcome of radiosurgery for patients with hypoxic tumors.

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KEY WORDS • radiosurgery • metastases • tumor hypoxia •
fractionation • stereotactic radiosurgery

DELIVERING a highly conformal dose distribution to the target while sparing the normal tissues surrounding it is one of the central principles of stereotactic radiosurgery. Nevertheless, the distribution of the dose to the tissue is determined by the physics of radiation interaction with the matter and the technological characteristics of the radiation delivery system. Consequently, the dose to the target is often dictated by the tolerance of the normal tissue. Furthermore, the inverse correlation between the volume of the target and the dose that can be delivered to it usually limits the target sizes that can be irradiated with stereotactic techniques. This correlation also leads to the paradox that larger tumors, presumably containing more cells, are treated with lower doses than are smaller tumors with fewer cells.

The success of stereotactic radiosurgery also depends on clinical and radiobiological factors. Delivering the dose in 1 fraction addresses 2 of the classic Rs of radiobiology,

repair and repopulation: delivering a single fraction will not allow time for the tumor to repair sublethal damage or to proliferate and thus to increase the target population through repopulation. Given the sizes of the doses usually delivered, redistribution will not likely influence the outcome. However, oxygenation status of the tumors to be treated will likely influence the outcome, and treatments employing 1 or very few fractions are less influenced by reoxygenation. Indeed, delivering the dose in 1 or a few fractions, as in stereotactic body radiation therapy, prevents slow reoxygenation caused by preferentially killing the well-oxygenated cells at the periphery of the tumor and thus decreasing oxygen consumption and making oxygen available to the hypoxic cells located in the core of the tumor, as described by Thomlinson and Gray.³⁶ However, short-term local reoxygenation due to opening of temporarily closed blood vessels, as initially postulated by Brown⁵ and later demonstrated by Chaplin et al.,⁹ a process independent of radiation delivery, could change cellular radiosensitivity during multifraction delivery. This study aimed to explore the impact of tumor hypoxia on the outcome of radiosurgery to treat metastases and the potential of fast

Abbreviations used in this paper: BED = biological effective dose; HF = hypoxic fraction; HI = heterogeneity index; TCP = tumor control probability.

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reoxygenation to improve the results of fractionated dose delivery for this type of treatment.

Methods

The impact of hypoxia and reoxygenation was studied with in silico tumor models with heterogeneous oxygenations. Three sizes of radiosurgery targets were assumed: 1, 2, and 3 cm in diameter. Also, 3 possible oxygenation states were assumed for the tumors (Fig. 1). They could be well oxygenated, or in the case of larger tumors, they could have a moderately hypoxic or a more hypoxic core. The oxygen distributions calculated for each region accounted for relevant distributions of intervessel distances and the physical processes of oxygen diffusion and consumption, as extensively described in previous publications.^{10,11} The density of clonogenic cells was assumed to be a uniform 10^6 cells/cm³ throughout the tumors.

For each target, a plan was made in the Leksell GammaPlan version 10.1.1 (Elekta AB) with the 50% isodose covering the target (Fig. 2). The dose prescription in each plan was target size dependent, with 22 Gy to the 50% isodose for the 1-cm target and 20 Gy and 18 Gy to the 2-cm and 3-cm targets, respectively (Fig. 3). Table 1 lists other dosimetric parameters of interest for each plan, including the gradient index,³¹ the Paddick conformity index,^{30,41} and the heterogeneity index HI:

$$HI = \frac{D_{max} - D_{min}}{D_{mean}},$$

where D_{max} is the maximum dose, D_{min} is the minimum dose, and D_{mean} is the mean dose to the target volume.

Tumor response was assessed as tumor control probability (TCP), calculated as

$$TCP = \exp \left\{ - \sum_{i=1}^{N_{vox}} N_i [SF(d_i, p_i)] \right\},$$

where N_{vox} is the number of calculation voxels in the tumor, N_i is the number of cells in voxel i , and $SF(d_i, p_i)$ is the cell survival in voxel i dependent on dose d_i and oxygen tension p_i . Cell survival was calculated with the linear quadratic model,^{7,16} using the formalism described in Toma-Dasu and Dasu.³⁸ Thus, cell survival SF_i in each voxel receiving dose d_i is described by

$$SF(d_i, p_i) = \exp \left[- \frac{\alpha}{OMF(p_i)} d_i - \frac{\beta}{OMF^2(p_i)} d_i^2 \right],$$

where α and β are the linear quadratic parameters relevant for oxic cells and $OMF(p_i)$ are oxygen tension-dependent modification factors:

$$OMF(p_i) = OER_{max} \frac{k + p_i}{k + OER_{max} p_i},$$

where OER_{max} is the maximum protection achieved in the absence of oxygen and k is a reaction constant as described by Alper and Howard-Flanders.¹ The following oxic parameters were assumed for calculation¹⁷: $\alpha = 0.35$ Gy⁻¹ and $\alpha/\beta = 10$ Gy.

Fig. 1. Sections through the central plane of tumor models used in the study, showing examples of the different oxygenation states considered. **A:** A well-oxygenated small tumor, 1 cm in diameter (0.52 cm³ volume); the HI, calculated as the percentage of values with $pO_2 < 5$ mm Hg, is 0%. **B:** A moderately hypoxic (HI = 4%) medium-size tumor, 2 cm in diameter (4.19 cm³ volume). **C:** A hypoxic (HI = 10%) large-size tumor, 3 cm in diameter (14.14 cm³ volume).

Fig. 2. Dose distributions in the central plane for each target size illustrated in Fig. 1, with the 50% isodose covering the target.

Fractionated schedules with 3, 4, and 5 fractions leading to the same biological effective doses (BEDs) to the tumor³ (i.e., for $\alpha/\beta = 10$ Gy) were also considered for the larger target (Table 2). In this case, TCP was calculated assuming that fast local reoxygenation takes place between fractions.

Results

The simulations showed that well-oxygenated small- and medium-size metastases could be very well controlled by radiosurgery treatments delivering a single fraction of 20 Gy or 22 Gy at the periphery, with TCPs ranging from 90% to 100%. However, for moderately hypoxic tumors, the TCP would decrease to 60%. In contrast, large metastases were difficult to control with single-fraction regimens, with TCPs ranging from 0% to 19%, depending on the assumed oxygenation state. Thus, it appears that hypoxia worsens the response to single-fraction radiosurgery, especially for large tumors.

With fractionated treatments for hypoxic tumors, interfraction reoxygenation resulted in significantly increased TCPs, up to 51% (Table 3). Better results are obtained for oxic and even moderately hypoxic tumors, but even large, severely hypoxic tumors could be controlled with fractionated regimens. Furthermore, for the latter the TCP increases with the number of fractions, highlighting the importance of the number of opportunities for reoxygenation to improve the possible outcome. These results therefore emphasize the importance of using pretreatment tumor oxygenation status to choose the best treatment option for radiosurgery patients.

Discussion

Tumor hypoxia is an important determinant of outcome in radiation therapy, as the absence of oxygen could render the cells resistant to radiation and could also contribute to the selection of more aggressive tumor cell phenotypes.⁴² Several proposals have been made to

Fig. 3. Dose distributions in the central plane for each target size illustrated in Fig. 1, with 22 Gy to the 50% isodose for the 1-cm target (A), 20 Gy for the 2-cm target (B), and 18 Gy for the 3-cm target (C).

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TABLE 1: Treatment plan dosimetric parameters for the targets considered in this study

Parameter	10-mm Target	20-mm Target	30-mm Target
4-mm shots	3	0	0
8-mm shots	1	3	14
16-mm shots	0	1	9
composite shots	0	0	0
grid size (mm)	0.7	1.2	1.6
coverage	99%	99%	98%
selectivity	92%	97%	97%
gradient index	3.20	2.56	2.70
Paddick conformity index	0.91	0.96	0.95
HI	0.72	0.82	0.87

counteract the hypoxic cells in conventional radiotherapy, although they have been slow to enter clinical practice.²⁹ The most recent proposals for antihypoxic strategies aiming to increase the doses to the hypoxic foci in tumors are quite promising, and several studies have been initiated to investigate their clinical potential.^{37,39,40}

Hypoxia is not usually taken into account for stereotactic radiosurgery, in part because of the large doses that could be delivered to the target while keeping irradiation of normal tissues within tolerances. Nevertheless, the results of this study show that hypoxia could negatively affect the results from single-fraction stereotactic radiosurgery, especially for larger tumors, for which normal tissue imposes limitations on the maximum dose that can be delivered to the target. Given that the options available for patients with large inoperable cranial tumors are usually limited to palliative treatments or treatments with conventional fractionations, it is worthwhile to explore whether they could benefit from stereotactic radiation treatments. The present study shows that allowing local reoxygenation of the tumors by fractionating the treatment could significantly improve the outcome for patients with large tumors by taking advantage of the favorable dose distributions that could be delivered with radiosurgery techniques.

These results were obtained under the constraint that the fractionated treatments deliver the same BEDs to the edge of the target. The corresponding effect to the normal brain decreases with increasing fractionation, as shown in the last column in Table 2, due to the lower values of α/β

TABLE 2: Fractionated schedules with 3, 4, and 5 fractions leading to the same BEDs to the tumor, BED_{10} , as 18 Gy delivered in a single fraction, and the corresponding BED to normal tissue, BED_2

Total Dose D (Gy)	Dose per Fraction d (Gy)	No. of Fractions n	BED_{10} (Gy ₁₀)	BED_2 (Gy ₂)
18.0	18.0	1	50.4	180.0
26.7	8.9	3	50.4	145.3
29.2	7.3	4	50.4	135.4
31.1	6.2	5	50.4	127.7

TABLE 3: Tumor control probabilities for a large tumor under 2 oxygenation conditions*

Total Dose D (Gy)	No. of Fractions n	TCP	
		Moderately Hypoxic (HF = 4%)	Hypoxic (HF = 10%)
18.0	1	0%	0%
26.7	3	46%	11%
29.2	4	51%	35%
31.1	5	51%	43%

* For the treatment schedules using ≥ 1 fraction, TCP was calculated assuming that local reoxygenation occurs between fractions.

for this tissue. This has 2 important implications for maximizing tumor control and minimizing complications in normal tissues: 1) fewer side effects are expected with the same effect to the tumor, which is especially important for larger targets, for which a lower dose gradient can be achieved, with a higher radiation burden on the normal tissue compared with smaller targets; and 2) further improvements in tumor response could be obtained by escalating the delivered dose within the limit of the normal tissue tolerance. Indeed, the most fractionated regimen assumed in this study was 31.1 Gy in 5 fractions; similar stereotactic regimes delivered using linear accelerators may employ 40 Gy in 5 fractions.

Our results were obtained from theoretical simulations and may therefore be influenced by the inherent limitations of the method. The simulations focused on the direct effect of radiation on the tumor cells, whereas other mechanisms may also be involved in cell death. For example, the immune system may be responsible for removing a few logs of cells.¹⁴ Although accurate numbers are not available for this process, it was partly included in our simulation by assuming a low density of clonogens per unit volume. Furthermore, tumor cells depend on the supply of nutrients through the vascular network. Tumor vasculature, although not directly associated with radiosurgery, has long been considered a possible target to increase cell death.^{12,13} A high-dose fraction in the range of 8–11 Gy may induce endothelial apoptosis of the tumor vasculature, thus indirectly increasing cell death by abolishing nutrient supply,³⁵ much like vascular targeting. This effect is in addition to direct cell death by radiation, and it could increase the TCPs above those given in Table 3, as suggested by Park et al.³² The additional effect of vasculature damage could decrease with increased fractionation, because the fractional dose is lower than the threshold for inducing vascular effects. Nevertheless, the effect of vascular damage changes the baseline TCP values for extremely hypofractionated schedules, and hypoxia could be regarded as an additional factor able to modulate response to radiation therapy. In this respect, the results of this study also agree with those of Carlson et al.,⁶ who showed that extreme hypofractionation should be avoided for hypoxic tumors because reoxygenation possibilities are severely reduced during the treatment course.

Another possibility that was not included in this simulation was that cellular density might vary with tumor

oxygenation. Severely hypoxic tumors could have fewer viable cells toward their center, as necrosis would set in. In this case, an increased dose to the center would be delivered to a sparsely populated region of the tumor. From this perspective, the models in this study and TCP results should be regarded as worst-case scenarios regarding the impact of hypoxia and improvements that could be obtained in clinical settings. Nevertheless, this study shows the significant improvements that could be obtained through fractionation even for the most unfavorable intratumor cell distributions (Table 3).

Finally, the validity of the linear quadratic model for the large doses employed in radiosurgery is an ongoing debate.^{4,18,24,34} However, the present study focused on the response of mixed cell populations containing a large hypoxic subpopulation for which the linear quadratic model is able to accurately describe the response,²⁵ so the results should be relevant for clinically used dose prescriptions to cranial targets treated with stereotactic radiosurgery.

An important question is whether predictions from theoretical simulations are compatible with clinical experience. Several analyses show that local control for single-fraction radiosurgery decreases when the dose delivered to the tumor margin decreases or when tumor size increases.^{8,19,20,27,43} Furthermore, the results reported by these analyses are compatible with the theoretical TCP results in the present study; vascular and immunologic effects are probably responsible for any differences. Chang et al.⁸ reported local control rates at 1 and 2 years, respectively, of 86% and 78% for lesions < 1 cm, and 56% and 24% for lesions > 1 cm, treated with a minimum peripheral dose of 20 Gy ($\text{BED}_{10} = 60 \text{ Gy}_{10}$). Similarly, Hasegawa et al.²⁰ reported local control rates of 84% and 77%, respectively, for tumors < 4 cm³ (~ 2 cm equivalent diameter) at 1 and 2 years after treatment with a mean marginal dose of 18.5 Gy ($\text{BED}_{10} = 52.7 \text{ Gy}_{10}$). Vogelbaum et al.⁴³ reported 1-year control rates of 85% in tumors < 2 cm treated with 24 Gy ($\text{BED}_{10} = 81.6 \text{ Gy}_{10}$), 49% in tumors of 2–3 cm treated with 18 Gy ($\text{BED}_{10} = 50.4 \text{ Gy}_{10}$), and 45% in tumors > 3 cm treated with 15 Gy ($\text{BED}_{10} = 37.5 \text{ Gy}_{10}$). More recently, Fokas et al.¹⁵ reported 73% local control at 1 year after 20 Gy in 138 patients with tumors with a median diameter of 1.5 cm.

In contrast, fractionated radiosurgery appears to lead to improved local control, especially for larger tumors, in line with results of the present study. Aoyama et al.² reported 81% local control at 1 year in 87 patients with tumors with a median equivalent diameter of 1.8 cm treated with a median dose of 35 Gy in 4 fractions ($\text{BED}_{10} = 65.6 \text{ Gy}_{10}$). Narayana et al.²⁸ reported 70% local control at 1 year after 30 Gy in 5 fractions ($\text{BED}_{10} = 48 \text{ Gy}_{10}$) in 20 patients with 1.9-cm tumors. Higuchi et al.²¹ analyzed 43 patients with tumors > 3 cm and reported 76% local control at 1 year after 30 Gy in 3 fractions ($\text{BED}_{10} = 60 \text{ Gy}_{10}$). Fokas et al.¹⁵ reported 1-year local control rates of 75% and 71% in 122 patients treated either with 35 Gy in 7 fractions ($\text{BED}_{10} = 52.5 \text{ Gy}_{10}$) for tumors of about 1.6 cm or with 40 Gy in 10 fractions ($\text{BED}_{10} = 56 \text{ Gy}_{10}$) for tumors of about 2.2 cm, respectively. Rajakesari et al.³³ reported 56% local control at 1 year in 70 patients with a median tumor diameter of 1.7 cm treated mainly with 25 Gy in 5 fractions ($\text{BED}_{10} = 37.5$

Gy_{10}). Minniti et al.²⁶ reported 1- and 2-year local control rates of 88% and 75%, respectively, for 135 patients treated with 36 Gy in 3 fractions ($\text{BED}_{10} = 79.2 \text{ Gy}_{10}$) for tumors < 2 cm and with 27 Gy in 3 fractions ($\text{BED}_{10} = 51.3 \text{ Gy}_{10}$) for tumors > 2 cm. Fractionated treatments also appear to lead to lower toxicity rates than single-fraction treatments,^{15,22,23,26} also in line with the proposals of the present study. Although only a randomized trial will show whether fractionated radiosurgery may improve the outcome of larger tumors with less toxicity, this *in silico* analysis nevertheless appears to support this hypothesis. Further theoretical and practical exploration of the potential of fractionated stereotactic radiosurgery is therefore warranted.

Conclusions

This study showed that hypoxia worsens the response to single-fraction radiosurgery, especially for large tumors. Fractionated therapy for large hypoxic tumors might considerably improve the TCP. These results therefore suggest that determining pretreatment tumor oxygenation status and considering fractionation for the patients with hypoxic tumors might improve the outcome of radiosurgery. This may be a practical and relatively simple way to individualize treatment for radiosurgery patients.

Disclosure

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