Radiobiology of brain metastasis: applications in stereotactic radiosurgery

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✓Stereotactic radiosurgery is a neurosurgical modality in which a target lesion can be irradiated while sparing normal brain tissue. In some respects, brain metastasis is well suited for radiosurgery, as metastatic lesions tend to be small and well circumscribed and displace (but do not infiltrate) normal brain tissue, facilitating the delivery of radiation. Advances in stereotactic radiosurgical planning, such as blocking patterns and beam shaping, have allowed further targeting of discrete lesions while minimizing the effect of radiation toxicity on the central nervous system. In this paper the authors review the radiobiology of brain metastases and stereotactic radiosurgical approaches that can be used to treat these tumors safely.

KEY WORDS • brain metastases • radiobiology • radiosurgery • stereotaxy

FIRST INTRODUCED by Lars Leksell in 1951, SRS is a neurosurgical modality that combines stereotactic technique with highly focused high-energy radiation treatments, making it possible to deliver large doses of radiation to an extremely small target.^{22,34} By keeping individual doses of radiation small, normal brain parenchyma is protected while allowing a large dose of radiation to be delivered to the desired target.

In many respects, areas of brain metastasis are ideally suited for radiosurgery.²⁴ These neoplasms tend to be small, have clear margins with respect to normal brain tissue, and are spherical or spheroid in shape, permitting treatment through single or multiple fractions.⁷ Published papers on SRS for brain metastasis have shown a control rate ranging from 85 to 95%.^{1,16–19} Good local tumor control and median survival rates comparable to that of resection followed by fractionated radiotherapy have been reported following SRS.^{10,18–20,31,40} Study results have also shown that patients with one or two brain metastases treated by radiosurgery have prolonged survival periods similar to those achieved using resection.^{9,36}

In recent years, the development of hyperfractionated radiosurgery, which is thought to reduce risks of patient morbidity, as well as frameless image-guided radiosur-

gery, which allows treatment of extracranial lesions, has further increased the scope of radiosurgery in the treatment of brain and spinal metastases. As the role of radiosurgery evolves in the treatment of brain metastasis, neurosurgeons will likely continue to be gatekeepers in deciding which patients will benefit from radiosurgery, conventional radiation treatment, open surgery, or other combinations of these modalities. To understand the rationale for these decisions fully, it is important to understand the biology of brain metastasis and the factors that make a lesion amenable to radiation treatment. In this paper we review the basic concepts of radiobiology and their use in the treatment of brain metastasis.

TYPES OF IONIZING RADIATION

The biological effectiveness of x-rays, gamma rays, and protons is roughly equivalent, and each is considered to be a form of low linear energy transfer radiation. The use of protons in radiosurgery is based on the physical properties of these particles and the characteristics of dose deposition in irradiated tissues.^{32,33} Protons have a slightly higher radiobiological effectiveness than cobalt-60, which is a common source of gamma radiation. In practice, an adjustment is made for this small difference by calculating the dose for protons in cobalt Gray equivalents both in single and multiple fractions.

Abbreviations used in this paper: CNS = central nervous system; MTD = maximum tolerated dose; SRS = stereotactic radiosurgery.

Dose deposition is characterized by the Bragg peak, which is used in deciding treatment regimens that involve use of the proton beam. Qualitatively, the entrance dose for particle beams is relatively low compared with that for photons. An unaltered beam deposits more than 50% of its energy over a 2- to 3-cm narrow path at a depth in water that depends on the beam energy. The beam may be altered to spread the Bragg peak to conform to the thickness and depth of the volume to be treated. However, the entrance dose is significantly increased in this case.³

Gamma rays and x-rays are forms of electromagnetic radiation whose energy ranges from 10.0 to 10.2×10^{10} electron volts. The x-rays are produced when electrons in the outer shell of heavy atoms fall from a high to a low energy level and are thus produced extranuclearly. These x-rays may be the product of radioactivity or created by human intervention using x-ray tubes or a linear accelerator, which accelerates electrons on a heavy metal target, producing a continuous spectrum of photon energies.

Gamma rays are photons emitted by radioactive nuclei and have a narrow range of energies (10 keV–10 MeV). Gamma rays and x-rays are otherwise identical. The most common source of gamma rays used in radiotherapy is cobalt-60, which is commercially produced from cobalt-59 and undergoes beta decay with a half-life of 5.27 years. Two gamma energies are emitted—1.17 and 1.33 MeV⁴⁶—with an effective average energy of 1.21 MeV. It is the subsequent gamma emission that makes it applicable to SRS.^{32,33}

When cells are irradiated using low linear energy transfer radiation, most photons interact with water molecules by stripping an electron from a hydrogen atom, resulting in a fast electron and an ionized water molecule through scattering. The resulting fast electrons further interact with water molecules through further ionizing events, resulting in a positively charged water molecule that exhibits a short half-life before dissociating into an H^+ ion and an OH^- free hydroxyl radical. The hydroxyl radical is reactive and has sufficient energy to break chemical bonds in nearby molecules. This indirect effect of radiation through a free radical intermediary is responsible for the majority (> 70%) of radiation-induced damage. The remaining damage is attributable to the direct effect of fast electrons interacting with biologically important molecules (that is, DNA).¹²

PRINCIPLES OF RADIOBIOLOGY

Malignant tumors usually contain a proportion of hypoxic cells, which are often resistant to damage by x-rays or gamma rays.²⁵ Cell survival after a single dose of ionizing radiation is a probability function measured using the Gray unit (absorption of 1 J of radiation energy by 1 kg of tissue). Studies on tumor cell lines have shown that the apparent radiosensitivity of cultured tumor cell lines depends heavily on the culture conditions and the assays used to determine cell survival.^{26,27} In assessing cell survival, there appears to be a point at which the accumulation of sublethal insults at low doses has a cumulative effect. This may be a result of the fact that DNA is the target for cellular damage by ionizing radiation, and a double-stranded break may result in cell death. Double-stranded breaks may be a result of a single particle or the interac-

FIG. 1. Line graph demonstrating the fraction of surviving mouse lymphosarcoma cells following irradiation in vivo. The change in slope results from the response of the predominant cells present at higher radiation doses, which are hypoxic cells.

tion of two single-stranded breaks caused by separate particles occurring at close temporal and spatial distances.⁵

Typically, mammalian tumor cell survival curves obtained after a single dose of radiation have a characteristic shape, which is depicted in Fig. 1. There is generally a change in cell viability (often by a factor of 2.5–3) following radiation treatment, in which aerated cells become nonviable and the site of irradiation is dominated by hypoxic cells. From this observation, it is thus important to note that treatment of a tumor with a single large dose (tens of Gray) of radiation is often futile, as hypoxic cells are not adequately depopulated.

In spite of this, some groups have demonstrated a phenomenon known as reoxygenation, whereby tumors may reestablish their original pattern and proportion of oxygenated and hypoxic cells between sessions in which they receive fractionated doses of x-rays or gamma rays. In a fractionation regimen, therefore, each dose of radiation kills a proportion of cells and the interval between treatments allows hypoxic cells to reestablish their oxygenated state.³⁸

Another noteworthy radiobiological principle arises from experimental evidence indicating that there is a difference in shape between the dose–response relationship curve characteristic of early-responding tissues (including tumors) and that characteristic of late-responding tissues.⁴² The inference from experiments in animals, which has been confirmed in clinical practice, is that the dose–response curve for late-responding tissue diminishes more rapidly than that for early-responding tissue. In mathematical terms, if the dose–response relationship is expressed in terms of a linear quadratic equation (see Wilder and colleagues⁴²) in which cell survival (S) is $S = \exp - \alpha D - \beta D^2$ (“exp” represents exponential, “ α ” and “ β ” are constants, and “ D ” represents dose), the α/β ratio in the linear quadratic survival model shows that the dose needed to kill cells is small (< 3 Gy) for late-responding tissues and larger (> 8 Gy) for early-responding tissues.^{4,37}

The practical outcome of this difference in the shape of the dose–response curve is a marked difference in the res-

ponse to fractionation in these two types of tissues. Late-responding tissues are more sensitive to fractionation than early-responding tissues. Nevertheless, late-responding normal tissues are more likely to be spared when a fractionated treatment regimen is used than when a single acute dose is delivered for a given level of tumor damage.⁴³

Providing sufficient time between fractions allows maximal recovery from sublethal damage, which is critical because sparing normal tissue is crucial in radiosurgery. The best information on the kinetics of repair of sublethal radiation damage in the CNS is found in the work of Ang and colleagues,² who found half-times of 0.7 and 3.8 hours, respectively, for the fast and slow components of repair.

RADIATION IN THE TREATMENT OF BRAIN METASTASIS

Malignant tumors generally fall into the category of early-responding tissue containing hypoxic cells, whereas normal brain tissue consists primarily of late-responding tissues containing well-aerated cells. The efficacy of radiation treatment for brain metastasis can be greatly improved by fractionation, when compared with a single large radiation dose. Fractionation increases the cellular depopulation of a tumor for a given total radiation dose because of the phenomenon of reoxygenation. At the same time, fractionation reduces the damage to critical late-responding normal tissues, as shown by differences in the shape of the survival curve for late-responding tissues and by greater sensitivity to changes in fractionation.^{15,28} This phenomenon is in contrast to the treatment of many benign tumors and arteriovenous malformations, in which both targeted abnormal tissue and normal brain tissue consist of late-responding tissue of similar radiological types. There is little to be gained by fractionation in this situation.³⁵

A large region of metastasis can also benefit from fractionation. As larger lesions have been associated with reduced MTDs, treatment often results in less effective local control.^{6,30} Fractionated therapy has been shown to permit more aggressive irradiation without an unacceptable increase in toxicity.²³

The number of metastatic lesions has also been thought to influence the dose of radiation that can be tolerated, as cumulative targeting of multiple targets may lead to dangerous levels of radiation. However, authors of several studies have calculated this cumulative radiation to be within an acceptable range.^{44,45}

RADIOSURGICAL TREATMENT SCHEMES FOR BRAIN METASTASIS

In the treatment of brain metastasis, various radiosurgical modalities—Gamma Knife, linear accelerator, and proton beam—achieve their effects by treating a discrete tumor with a high volume of radiation.⁸ Because early-responding tissue (the tumor) has a relatively high α/β ratio, it is relatively insensitive to fractionation and a single treatment is possible. Furthermore, unlike gliomas, the vast majority of brain metastases displace normal brain tissue, rather than infiltrate it, and provide a distinct bor-

der that is useful for radiosurgical treatment.

The reason why the rules of fractionation can be violated in radiosurgery is because radiosurgery allows the surgeon to isolate the tumor from normal brain tissue spatially by prescribing a rapid dose falloff. In select cases, however, fractionated radiosurgery can be performed through external stereotactic treatment or by using an interstitial implant. Interstitial implant radiosurgery is performed by placing temporary or permanent low-dose-rate, high-activity ¹²⁵I implants around the area containing the surgically accessible lesion.¹¹ Although effective in some cases, the major disadvantage of this technique is the possibility of rapid tumor shrinkage during the irradiation period, which could result in significant damage to normal brain tissue.²¹

An alternative approach is to use fractionated external-beam radiosurgery. The fractionated external-beam technique allows for corrections to be made in the treatment regimen as the tumor shrinks, and for most patients it is easily performed during a short hospital stay. Generally speaking, the number of fractions used for the radiosurgical treatment of brain metastasis is significantly less than the 30 or more fractions associated with conventional radiotherapy. Using a small number of fractions is important because many types of brain metastasis (such as melanoma metastasis) are radioresistant and analysis has shown that they exhibit a large shoulder on the dose-survival curve). The use of a small number of fractions supports one of the potential advantages of radiosurgery (that large fractions are more effective at killing radioresistant tumors) while adding to the advantages of fractionation described earlier in this paper.

EFFECTS OF RADIATION ON NORMAL BRAIN TISSUE

Normal brain tissue can be viewed as late-responding tissue (low α/β ratio) and is thus sensitive to radiation effects in large doses; this raises the concern about radiation necrosis during radiosurgery treatment planning.⁸ Evidence in experimental animal models, including non-human primates, has shown that increasing the volume to be irradiated to encompass normal brain or spinal cord tissue lowers the threshold of neuronal injury in the region and increases the slope of the dose-response curve to radiation, effectively causing more tissue injury.¹³ The volume effects of radiation are more pronounced in areas receiving high doses of radiation than in those receiving lower doses.

Although treatment strategies, such as blocking patterns (described later in this section) and fractionation to effectuate dose delivery while sparing normal tissue, theoretically lower the risk of radiation-induced damage following radiosurgery, recent work has shown that the volume of brain tissue irradiated is correlated to the future development of radiation-induced toxicity.^{29,30} The Radiation Therapy and Oncology Group examined the MTD of single-fraction radiosurgery as a function of the total irradiated volume and established single-dose (margin) MTDs for volumes less than 4.2 cm³, from 4.2 to 14 cm³, and from 14.1 to 31 cm³. These MTDs are 24, 18, and 15 Gy, respectively. When delivered in 2-Gy fractions, the equivalent doses are 64, 90, and 156 Gy, respectively.³⁰

There is evidence that repair of radiation-induced damage in the CNS occurs, particularly with respect to damage involving the spinal cord or the optic apparatus.^{14,39} This phenomenon is most likely to be at least partially attributable to a repopulation of normal cells from surviving stem-cell populations or migration of cells from normal, nonirradiated tissues. These issues are particularly relevant in decisions of whether and when to again irradiate a region in a patient with evidence of tumor recurrence. However, most of the evidence regarding repeated irradiation of a CNS metastasis comes from an extrapolation from preclinical and retrospective clinical data and should be weighed carefully with alternatives to radiation and the risk of permanent sequelae after repeated radiosurgery.²⁹

APPROACHES TO MINIMIZE TOXICITY IN THE CNS

The best strategy to minimize radiation-induced CNS toxicity is always to minimize the dose administered to and the volume of the irradiated tissue. Careful treatment planning based on findings on modern modalities of imaging, such as computed tomography and magnetic resonance imaging, effective patient immobilization and fixation, and accurate treatment delivery all contribute to minimizing the size of the treated volumes and minimizing the dose delivered to normal structures. Dose-volume histogram analysis is also an essential element in optimizing radiosurgical treatment planning. Emerging technologies such as inverse treatment planning and intensity-modulated radiotherapy have also contributed to a reduction in the volume of normal tissue that is irradiated as well as reductions in the dose per fraction and the total dose.⁸

Development of blocking patterns is an established method of refining radiosurgery treatment, offering improved conformity and allowing the surgeon to adjust the peripheral isodose to the tumor margins. Standardized blocking patterns can significantly reduce the exposure to radiation, while increasing the conformity of the treatment plan, even for tumors with irregular margins.⁴¹

Single-dose radiosurgery may be preferable in cases in which the tumor volume is small and normal tissue tolerance is well respected. In other situations, however, in which normal structures (that is, the optic chiasm, brainstem, and spinal cord) lie adjacent to the tumor or in cases in which the tumor is large, dose fractionation may be the only method to provide safe and efficacious treatment. A specific study of cellular mechanisms of cell damage and repair following CNS irradiation is needed to improve our understanding of other ways in which we may protect the CNS from radiation-induced injury.

CONCLUSIONS

Brain metastases are well suited for radiosurgery because of their relatively small size and shape and location at the gray-white matter junction. The growth characteristics, oxygenation, and mitotic activity of metastasis in the brain are all major factors in determining the biological effectiveness of radiosurgery in treating metastatic disease. Although the incidence of radiation-induced damage

following radiosurgery is low, experimental studies have shown a relationship between both the radiosurgical dose and volume treated and the extent of damage to normal tissue. Some of these problems can be reduced by the development of blocking patterns and by dose fractionation.

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