Radiosurgery as Neuromodulation Therapy!

Jean Régis

Abstract Radiosurgery is commonly considered to be effective through a destructive physical mechanism acting on neural tissue. However, the results of modern neurophysiological, radiological, and histological studies are providing a basis on which to question this assumption. There are now multiple pieces of evidence pointing to a nonlesional mechanism of the radiosurgical action. It appears that tissue destruction is absent or minimal and in almost all cases insufficient to explain the clinical effects produced. There is a real possibility that radiosurgery induces changes in the functioning of neural tissue by differential effects on various neuronal populations and remodeling the glial environment, leading to modulation of function while preserving basic processing. Hence, the majority of radiosurgical procedures induce the desired biological effect without histological destruction of tissue. These findings may result in a major paradigm shift in the treatment of functional brain disorders.

Keywords Apoptosis • Gamma Knife Radiosurgery • Glia • Plasticity • Subnecrotic dose

Introduction

Radiosurgery was clearly intended to be an instrument for use in functional neurosurgery. The first disorders treated were trigeminal neuralgia and Parkinson disease. Radiosurgery is commonly considered to exert its effects through a destructive physical mechanism that acts on neural tissue. Increasing evidence, however, suggests a more subtle mechanism of action especially relevant for functional neurosurgical indications.

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Radiosurgery, always considered a purely ablative treatment, today relies on a *nonlesional mechanism of action*. In the mind of its creator Lars Leksell, radiosurgery was clearly intended to mimic the lesional effects of a surgeon's knife, hence he gave the name "Gamma Knife" for the first such instrument. The high doses initially selected for thalamotomy [50], capsulotomy [7], and benign tumors [29, 56] were rapidly identified as being unnecessarily toxic. With functional neurosurgery, the strategy is to target a small volume of normal tissue (e.g., ventralis intermedius nucleus (VIM) thalamotomy, capsulotomy, trigeminal neuralgia) with a high dose (80–140 Gy maximum) or a large volume of tissue (e.g., 5–9 cm^3 for epilepsy) with a moderate dose (17–24 Gy at the marginal isodose).

The dose reduction policy for vestibular schwannomas resulted in a dramatic decrease in the incidence of facial palsy, from 27 % to <1 %, and an increase in hearing preservation to 80 % with no loss of tumor control [10, 39, 49]. With this new regimen of lower doses for benign tumors, the predominant mechanism of action was presumed to be *apoptosis* (cell death mediated by DNA breakage in the populations of cells that were entering mitosis) [2, 20, 23]. The goal of radiosurgery to treat arteriovenous malformations (AVMs) is to create thrombosis of the nidus to prevent further hemorrhage. This clinical effect is caused by a histological change marked by *endothelial proliferative thrombosis* [52, 59]. This is typically a biological effect specifically induced by radiosurgery without any frank destruction of vascular tissue but, rather, a proliferative response within the arterial wall of the vessels to radiation injury. Consequently, radiosurgery has been redefined as "a neurosurgical procedure where narrow ionizing beams, given in a single high dose fraction, are used either to destroy a predetermined target volume or to induce a desired biological effect in the target volume" [53]. Furthermore, the lower incidence of hemorrhage after AVM radiosurgery (compared to embolization) may have something to do with modulation of another specific biological effect—a *decrease in the angiogenic response to injury* with reduced expression of vascular endothelial growth factor [1].

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Hypothalamic hamartoma radiosurgery for *epilepsy control* is an even more convincing example of the functional, nonlesional effect [3, 34, 40, 47]. More than 50 % of our 79 patients who underwent radiosurgery (50 with >3 years of follow-up) are seizure-free, and a large portion of the others report a significant reduction in seizure frequency, and they welcomed the associated significantly improved quality of life [34, 47]. The vast majority of the patients show no radiographic changes on their follow-up magnetic resonance imaging (MRI) studies. Interestingly, the psychiatric [47] and neuropsychological symptoms are also improving dramatically or resolving completely in a large percentage of patients, even in those without complete seizure cessation. The clinical observation of profound therapeutic antiepileptic effect with no histological necrosis induced by radiosurgery is encouraging and speaks again to some neuromodulatory effect of radiosurgery [46].

Differential Biologic Effect

A differential biologic effect is induced by radiosurgery under certain conditions. When an AVM located in a highly functional area is associated with focal seizure disorder, the probability of curing this epilepsy after radiosurgery is roughly 85 % [9, 12, 16, 22, 51]. Interestingly, seizure cessation in these patients frequently occurs before the AVM occlusion or even despite failure of radiosurgery to occlude the nidus and in the absence of any neurological deficit specific to the function of the surrounding brain. Thus, the biological changes leading to cessation of epileptogenic activity in the brain adjacent to the AVM are independent of the occlusion of the AVM and are not dependent on radiographic or histological evidence of a destructive effect on tissue. Such destructive changes would have been expected to lead to a functional deficit, with or without AVM obliteration [16, 35, 36, 43, 45]. This common clinical experience with AVM demonstrates the capability of radiosurgery to eliminate epileptic activity from a previously epileptogenic cortex while preserving its underlying normal function. This kind of observation led us to hypothesize the existence of some kind of differential biological effect of radiosurgery on tissue: that low-dose radiosurgery applied to normal neuronal tissue, relying on subtle but specific biological changes, may affect some processes while sparing others, thereby producing the desired clinical effect [41]. In 1996, we published the first article to demonstrate the existence of such a differential effect manifested at the biochemical level [41]. In rats, targeting the striatum with radiosurgery was shown to lower the level of the enzyme choline acetyltransferase while not affecting the levels of glutamate decarboxylase. Conversely, the levels of the excitatory amino acids were reduced, and the nonexcitatory amino acids (particularly γ-aminobutyric acid) were stable [41]. However, clinically safe and efficient implementation of radiosurgery to effect some form of neuromodulation requires further basic science work to provide better understanding of the influence of dose, volume, target topography, and dose distribution homogeneity on the modulation of specific biological systems [35, 41].

Specific Glial Tissue Changes Induced by Radiosurgery

At the cellular level, it is well-known that noncycling cells (e.g., neurons) exposed to moderate amount of energy with radiosurgery are quite resistant, with a low level of cell loss. On the other hand, cycling cells (e..g., supporting glial and endothelial cells) can be severely injured by radiosurgery and are part of the radiation-induced biological cascade [57], with a significant rate of cell loss. Lunsford's group described a delayed astrogliosis reaction and cell loss in the field of radiosurgery of animal models [18]. Interestingly, such glial cell death has been reported to induce migration of progenitor cells from subependymal matrix germinal zones (Lars Kihlstrom, 1998, personal communication). These progenitors, arising within the radiosurgical target volume, are differentiated into mature glial cells with a phenotype clearly different from those of the destroyed glia [60]. In 2005, Nagayama et al. studied radiation-induced apoptosis of oligodendrocytes in the adult rat brain. They reported rapid apoptotic depletion of the oligodendrocytes (maximum after 8 h) and a significant decrease in cell density in the white matter 24 h after irradiation [28].

"Cockade" Model

The "cockade" model is an original concept that we proposed some years ago summarizing the regional effect of a radiosurgery dose on normal brain by artificially separating it into four concentric zones [35, 38]. When sufficient dose/volume parameters are used, a "necrotic core" central zone (histological necrosis) is surrounded by a "subnecrotic area" where cellular death is observed without coagulative necrosis. This subnecrotic area is typically the area where cellular differential effects of radiosurgery are observed, with considerable wash-out of glial cells and only a few noncycling cells (neurons) dying. Outside the "subnecrotic area" is the "neuromodulatory area," where more subtle changes are visible without a significant increase in cell deaths. Inflammatory compounds produced in the subnecrotic area are likely to account for a significant portion of the changes observed in

this area. No effect is observed outside this neuromodulatory area. Messengers, proteins, and small molecules are likely to play a major role in mediating the cellular changes seen in the tissues in and around the area of the radiosurgery. Changes observed in subnecrotic or neuromodulatory areas may be the sum of the area's direct and indirect local radiation effects and those induced from neighboring areas (subnecrotic area influencing the neuromodulatory area and necrotic core influencing the subnecrotic area). Thus, the relative extent of each zone is not only dependent on the dose delivered to each zone but also on the volume of treatment, the histological and biochemical nature of the targeted brain tissue, and finally the genetics of the patient.

White matter and capillaries are classically more sensitive to the effects of radiation. Diffusion-weighted imaging has shown signs of vasogenic edema in the subcortical white matter, with a decrease of fractional isotropy associated with dissociation of the neuronal fibers by extracellular water. Also, there are signs of cellular edema (ischemia) with no change of the fractional anisotropy maps associated with myelin sheath splitting and periaxonal space enlargement (Naoyuki Miyasaka, 2002, personal communication). MRI changes are sometimes misleading [24]. Typically, the extent of white matter abnormalities are related more to an increase in extracellular fluid than to the locally delivered dose affecting the role of secondary messengers. For example, in medial temporal lobe epilepsy (MTLE), the major white matter changes extend far from the target laterally, following association fiber tracts. The fiber tracts within the brain stem, however, which receive similar energy, are not modified on follow-up imaging studies. Obviously, these distant changes are caused by propagation of inflammatory small molecules through the white matter tracts and are not induced directly by ionizing radiation—not dissimilar to the diffuse white matter changes sometimes observed after treatment of small midline meningiomas. Not surprisingly, when these inflammatory mechanisms are considered, the time course of the observed biological effects in tissue can be explained.

Rahn et al. studied results of radiosurgery for brain metastases and demonstrated that the patients treated in the morning did substantially better than those treated in the afternoon [33], suggesting that some sort of cellular circadian rhythm affects the response of tumor and normal tissues to irradiation. The genetic profile of the individual is crucial. For thalamotomy, the treatment is standard in terms of the volume of the target, location, and dose. Although the tissue reaction to radiosurgery is reportedly focal in some series [17, 61], up to 10 % of the patients have a larger reaction, seen on MRI. These imaging changes may be associated with hemiparesis, usually transient. Kondziolka et al. demonstrated the radioprotective effect of the 21-aminosteroid U-74389G in an experimental study in rats [19, 21]. They reported that this drug reduces the cytokine expression normally seen after radiation injury and can be overexpressed in patients who exhibit a clinically obvious reaction to radiosurgery.

Changes of Specific Properties of Neurons as Response to Radiosurgery

VIM thalamotomy is classically performed using a maximum dose of 130–140 Gy, which induces a small area of necrosis after several months that is well seen on the 12-month follow-up MRI. This is one of the infrequent indications for radiosurgery, where the intended effect is to mimic the histologically destructive effect produced by thermocoagulation. However, in 2000, Ohye et al. proposed that the clinical effect on tremor was not only the result of the necrotic lesion [30]. Their main argument was that the size of the lesion induced by radiosurgery was too small to account for the clinical effect seen. (It is interesting to note that the limit of the lesion seen on MRI corresponds, in our experience, to the volume of the 90 Gy isodose line.) Some experimental observations [62] support this hypothesis, but more studies are still necessary to better understand the nature and respective role of nonlesional and lesional mechanisms in VIM radiosurgery. In 2008, Terao et al. reported that the somatotopic distribution of kinesthetic cells was modified by Gamma Knife surgery (GKS) of the VIM, raising the possibility that the specific properties of the neurons are changed in response to irradiation [55].

Selective vulnerability of certain neuronal subtypes has been suggested to contribute to our proposed "neuromodulative" effect by some experimental works. Jenrow et al. reported in epileptic rats (kindling model) that the selective reduction of densities in the dentate granular cell layer and medial CA3 pyramidal cell layer was prevented or reversed by irradiation at 25 Gy but not at 18 Gy [15]. This is consistent with the dose effect we have found in humans [42]. From a histological standpoint, Lee et al. reported on epileptic rats irradiated with 40 Gy to the medial temporal lobe. Their immunohistochemical findings suggested that at least one subtype of hippocampal interneurons are selectively vulnerable to GKS. The neuronal cells appeared to have undergone a phenotypic shift with respect to calbindin and GAD-67 expression (K. Lee, 2009, personal communication).

Central Nervous System Regenerative Process

The central nervous system (CNS) regenerative process fails because (among other reasons) extracellular inhibitory factors make it nonpermissive to growth [14]. Thus, a radical change in the phenotype of the glial environment may allow a functional readjustment phenomenon. Neurons may have a

more impressive capacity for adjusting than previously thought [31]. Our hypothesis is that under certain conditions radiosurgery, relying on nonnecrotizing dose parameters, induces an important turnover of the glial environment of neurons, allowing functional connections the opportunity to reset, reorganize, and overcome errors disturbing their functional capability [38]. If supported by further experimental evidence, this hypothesis may open new perspectives for radiosurgery as a neuromodulation therapy in functional neurosurgery.

MTLE Model

The MTLE model illustrates the clinical feasibility of a neuromodulatory radiosurgical approach. Until the 1990s, curative epilepsy surgery was limited to open microsurgery, with which abnormal epileptogenic tissue was physically removed. The first cases of temporal lobe epilepsy treated with GKS in Marseille in 1993 [37, 43] were encouraging, with short-term results demonstrating the safety and efficacy of this approach. Seizure control rates were similar to those of resective surgery, and these early results are now confirmed to be durable responses on medium [4, 44] and long-term [6] follow-up. The impressive MRI findings observed roughly 1 year after radiosurgery led us initially to speculate that a necrotic lesional effect was responsible for the clinical result [48]. However, medium-term disappearance of these MRI findings leaves the medial structures of the temporal lobe either similar to or only slightly more atrophic than that seen preoperatively. It suggests a more subtle neuromodulating effect of radiosurgery than initially thought and indicates that a more limited volume of the temporal lobe is involved compared to the effect of microsurgery [44]. Further studies correlating the efficacy of the quality of the coverage of each structure of the medial temporal lobe area on seizure outcome have demonstrated the importance of targeting the anterior parahippocampal cortex and especially the perirhinal and entorhinal cortex [11]. This is consistent with the Wieser and Yasargil series of microsurgical amygdalohippocampectomies [58]. The perirhinal and entorhinal cortex plays a major role in memory processing [5]. Overall, it is estimated that 40 % of the patients with MTLE operated on microsurgically on the dominant side have a significant postoperative short-term verbal memory deficit [8, 32, 54]. Our first prospective trial of GKS for MTLE found that in 65 % of those who underwent dominant temporal lobe treatment there was no evidence of any neuropsychological deficit [6, 44]. Our subsequent experience has confirmed this observation [6]. Today, we consider this memory-sparing benefit as the major advantage of radiosurgery over microneurosurgery in patients with dominant temporal lobe MTLE. Thus, the MTLE patients currently selected for GKS are those who might suffer more and longer if additional memory deficit is produced—that is, young patients with a high level of functioning who are socially adapted, working, concerned by the risk of microsurgery and the time off from work, and presenting with risk factors for verbal memory loss in case of resection (no atrophy, dominant side, few neuropsychological deficits before surgery) [13]. This group of patients is often highly functioning with a sufficient intelligence to allow them to understand the peculiarities and nuances of radiosurgery. In addition, they frequently do not have severe epilepsy, which affords them the luxury of waiting.

The San Diego group has observed neuropsychological worsening in some patients tested during the "acute phase" (when the acute MRI signs are still present) [27]. The group has not reported the long-term results of their neuropsychological testing after resolution of the acute MRI signs. We have seen the same verbal memory sparing in our long-term MTLE patients treated on the dominant side [6]. The observation was recently confirmed by a multicenter Phase I–II trial in the United States [4]. The mechanism of this functional preservation is still a matter of speculation. It may be that the dose regimen we use is simply not lesional. It also may be that the cell loss is selective, primarily affecting the glial environment. Perhaps we are inducing a certain degree of neuronal and astrocytic damage, but the process is so slow and delayed that the brain has sufficient time to reorganize functionally. Maesawa et al., in an elegant study, tested in a rat kainic acid model of epilepsy both the efficacy of radiosurgery and memory sparing [25, 26]. The control group (not treated) continued to seize, whereas the rats treated with 30 Gy (maximum dose) had a reduction in their seizure frequency. The group treated with 60 Gy (maximum) had cessation of seizure activity 5–11 weeks after GKS. The Morris water maze test was used for spatial memory testing and showed that spatial memory was highly abnormal in the control group, whereas the radiosurgically treated 30 Gy group had normal spatial memory [25, 26].

Conclusion

Functional radiosurgical procedures using the Gamma Knife have been proposed, technically performed, and evaluated based on the hypothesis that their mechanism of action was purely destructive. However, modern neurophysiological, radiological, and histological studies have led us to question this assumption. It seems that tissue destruction is either absent or minimal and in almost all cases insufficient to explain the clinical effects obtained. One possibility to explain these effects is that radiosurgery induces changes in

the functioning of neural tissue by inducing differential effects on different neuronal populations or by remodeling the glial environment, leading to modulation of function while preserving basic processing. Thus, the majority of radiosurgery procedures may induce the desired biological effect without requiring a histological destructive effect to meet the therapeutic goal. Thus, the concept of "lesional" radiosurgery may be incorrect, and a hidden world of neuromodulatory effects may remain to be discovered [38]. It may require a major paradigm shift in functional neurosurgery.

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