J Neurooncol (2010) 98:155–162
DOI 10.1007/s11060-010-0226-5

TOPIC REVIEW

Is radiosurgery a neuromodulation therapy?

A 2009 Fabrikant Award Lecture

Jean Régis · Romain Carron · Michael Park

Received: 1 May 2010 / Accepted: 6 May 2010 / Published online: 29 May 2010

Abstract Radiosurgery is commonly considered to be effective through a destructive physical mechanism on neural tissue. Since its invention by Leksell in the 1950s, clinical and experimental experience of radiosurgery has demonstrated that for classical indications, for example arteriovenous malformations and benign tumors, radiosurgery is effective because of its specific histological effects of thrombotic endothelial proliferation and apoptosis, not simple coagulative necrosis. In functional neurosurgery, the strategy is either to target a small volume of normal tissue (i.e., ventrointermediate nucleus, capsulotomy, trigeminal neuralgia, etc.) with a high dose (80–140 Gy at maximum) or to target a large volume of tissue (i.e., 5–9 cc in epilepsy radiosurgery) with a moderate dose (17–24 Gy at the marginal isodose). These procedures have been proposed, technically performed, and evaluated on the basis of the hypothesis that their mechanism of action is purely destructive. However, modern neurophysiological, radiological and histological studies are leading us to question this assumption. Tissue destruction is turning out to be either absent or minimal and in almost all cases insufficient to explain the clinical effects obtained. Therefore, one possibility is that radiosurgery is inducing changes in the functioning of the neural tissue, by inducing remodeling of the glial environment, and is leading to the modulation of function while preserving basic processing. Thus, most radiosurgery procedures may induce the desired biological effect without requiring the histological destructive effect for completion of the therapeutic objective. Therefore the concept of "lesional" radiosurgery may be incorrect and a completely hidden world of neuromodulatory effects may remain to be discovered.

Keywords Apoptosis · Gamma knife · Glia · Plasticity · Radiosurgery · Subnecrotic

J. Régis · R. Carron · M. Park
Department of Stereotactic and Functional Neurosurgery, Timone University Hospital, APM, Marseille, France

J. Régis · R. Carron · M. Park
INSERM U751, Université de la Méditerranée, Marseille, France

J. Régis (✉)
Service de Neurochirurgie Fonctionnelle et Stéréotaxique, C.H.U. La Timone, 264 rue Saint Pierre, 13385 Marseille CEDEX 05, France
e-mail: jregis@ap-hm.fr

Introduction

From the beginning, neurosurgery has been a specialty field dealing with the "ablation, removal or reduction" of structural conditions affecting neurological function [3]. Perhaps one of the first attempts at therapeutic neuromodulation was the use of electrical fish by the ancient Egyptians in 500 BC for pain management. However, only recently has the idea of restoration of function through modulation of neuronal function or restoration of damaged neurological circuitry been given consideration, thus marking a significant milestone in the intellectual and therapeutic course of neurosurgery [3]. Twenty years ago concepts of neuromodulation, gene therapy, and cellular grafting were being introduced to our field [30, 55]. Electrical stimulation, direct installation of substances in the central nervous system (CNS), and grafting are now regarded as the main avenues for technical development in neuromodulation. However, radiosurgery has always been

considered as a purely ablative treatment. This article explores some of the documented and theoretical mechanisms involved in the responses of neural tissues to radiosurgery from the perspective of an experienced user.

Lesional versus non-lesional effect

Radiosurgery, in the mind of its inventor Lars Leksell, was clearly intended to mimic the lesional effects of a surgeon's knife, hence the name "Gamma Knife" given to the first completed instrument. The high doses initially selected for the thalamotomies [55] or capsulotomies [7] or benign tumors [33, 60] were rapidly identified as being unnecessarily toxic. The first vestibular schwannoma treated with the Gamma Knife in Stockholm by Leksell and Meyerson on June 16, 1969 was treated with 35 Gy at the periphery [33]! Gradually, neurosurgeons in Karolinska came to appreciate that it was possible to provide very long-term tumor control for benign tumors using much lower doses. In 1992, we were taught by George Noren [33] to treat these tumors with 11–13 Gy at the margin, a lower dose than originally recommended but only implemented in Stockholm from April, 1989. This dose reduction policy resulted in a dramatic decrease in facial palsy rate from 27% to less than 1%, and an increase in hearing preservation to 80% with no loss of tumor control [10, 49, 53]. With this new regimen of lower doses for benign tumors, the predominant mechanism of action was presumed to be cell death mediated by DNA breakage in the populations of cells which were entering mitosis [2, 22, 25].

The objective of arteriovenous malformation (AVM) radiosurgery is to create thrombosis of the nidus thus preventing further hemorrhage. This clinical effect is obtained because of a histological change marked by endothelial proliferative thrombosis [56, 65]. This is typically a biological effect specifically induced by radiosurgery without simple destruction of vascular tissue but rather a proliferative response within the arterial wall of the vessels to radiation injury. This histological and clinical evidence consequently led Steiner [57] to propose a modification to Leksell's historical definition of radiosurgery as follows: "radiosurgery is the 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 this target volume, …". Furthermore, the much lower rate of hemorrhage after AVM radiosurgery (compared with embolization) may have something to with modulation of another specific biological effect, namely a decrease in the angiogenic response to injury with a reduction of the expression of the vascular endothelial growth factor [1].

A differential biologic effect

When an AVM, located in a highly functional area, is associated with focal seizure disorder, the probability of curing this epilepsy after radiosurgery is approximately 85% [9, 13, 18, 24, 56]. Interestingly, seizure cessation in these patients frequently occurs before the AVM occlusion, or even despite a failure of radiosurgery to occlude the nidus and in the absence of any neurologic deficit specific to the function of the surrounding brain Thus, the biological changes leading to the cessation of the epileptogenic activity in the brain adjacent to the AVM are independent of the occlusion of the AVM and are not dependent on radiographic or histologic evidence of a destructive effect in tissue removed at surgery. Such destructive changes would have been expected to lead to a functional deficit, with or without AVM obliteration [41, 42, 47, 48]. This common clinical experience in AVM radiosurgery demonstrates well the capability of radiosurgery to eliminate epileptic activity from previously epileptogenic cortex while preserving its underlying normal function (Fig. 1). This kind of observation led us to hypothesize the existence of some kind of differential biological effect of radiosurgery in tissues, namely that low-dose radiosurgery applied to normal neuronal tissue, relying on subtle but specific biological changes, may affect some processes while sparing others, producing the desired clinical effect [43]. In 1994, we published the very first paper demonstrating that the existence of such a differential effect was manifest at the biochemical level [43]. In rats, targeting of the striatum with radiosurgery was shown to lower the level of the enzyme choline acetyl-transferase while not affecting the levels of glutamate decarboxylase. Conversely, the levels of the excitatory amino acids were reduced and the non-excitatory amino acids (particularly gamma aminobutyric acid) were stable [43]. However, the clinically safe and efficient implementation of radiosurgery to effect some form of neuromodulation still requires further basic science work to enable better understanding of the effect of dose, volume, target topography, and dose distribution homogeneity on the modulation of specific biological systems [43, 48]. At the cellular level, it is well-known that non-cycling cells, for example neurons, exposed to moderate amounts of energy with radiosurgery are quite resistant with a low level of cell loss. On the other hand, cycling cells, such supporting glial and endothelial cells, can be severely injured by radiosurgery and are part of the radiation-induced biological cascade [63] with an important rate of cell loss. Lunsford [20] has described a delayed astrogliosis reaction and cell loss occurring in the field of radiosurgery in animal models. Interestingly, this death of glial cells has reportedly been seen to induce

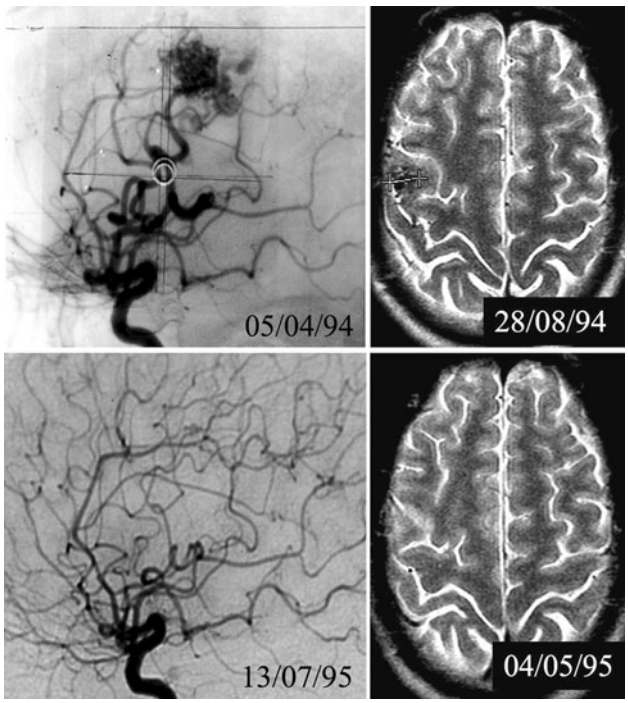

Fig. 1 M1 AVM radiosurgery. Radiosurgery produces obliteration of the AVM and the cessation of seizures, while preserving the underlying function. Both effects rely on a nondestructive mechanism

migration of progenitor cells from the subependymal matrix germinal zones (personal communication Kihlstrom 1998). These progenitors arise within the target volume of radiosurgery and differentiate into mature glial cells with a phenotype clearly different from those of the destroyed glia. Yang et al. [66] have shown that in 71 rats receiving a maximum dose of 100 Gy and then sacrificed at intervals between 3 h and 90 days after Gamma Knife radiosurgery (GKR), vascular changes with endothelial hyperplasia and vessel wall thickening, and associated hyperplasia and hypertrophy of astrocytes, are seen as early as 3 h. At later time points, between 3 and 24 h, proliferation of astrocytes is observed. Three days after GKR, an initial peak of astrocytic proliferation adjacent to the corpus callosum can be seen. From 14 to 30 days after GKR, peak proliferation is seen within the target site and at distant sites within the adjacent cortices and hippocampus. No necrosis is reported before day 30, but at day 90, a 4 mm-diameter necrotic lesion with glial scar at the periphery is visible.

Kurita et al. in 2002 studied radiation-induced apoptosis of oligodendrocytes in the adult rat brain, relying on the counting of TUNEL-positive cells with apoptotic morphology (GFAP−, CNP+). 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. These changes are dose, time, and

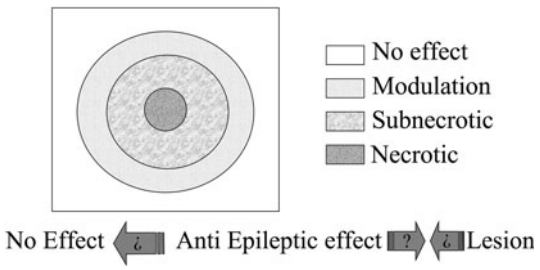

Fig. 2 The cocade theory

location-dependant, because more intense changes are seen in the external capsule than in the genus of the corpus callosum, the internal capsule, and the cerebellum [32].

The "*cocade*" theory (Fig. 2) is an original concept that we proposed some years ago summarizing the effect of a radiosurgery dose on normal brain by artificially separating it into four concentric zones [48]. When dose and volume are sufficient, the central zone shows evidence of histologic necrosis. Around this "necrotic core" is the "subnecrotic area" where cellular death is observed without coagulative necrosis. The subnecrotic area is typically the area where cellular differential effects of radiosurgery are observed with a considerable wash-out of glial cells and very few non-cycling cells (neurons) dying. Outside of the "subnecrotic area" is the "neuromodulatory area". More subtle changes are visible without significant increase in cell death. Inflammatory compounds produced in the subnecrotic area are likely to account for a significant part of the changes observed in this area. Outside this "neuromodulatory area", no effect is observed.

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 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 affecting the neuromodulatory area and necrotic core affecting the subnecrotic area). Thus the relative extent of each zone is not only dependent on the dose delivered to it 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 revealed 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, and signs of cellular edema (ischemia) with no change of the fractional isotropy maps associated with myelin sheath splitting and periaxonal space enlargement (Naoyuki Miyasaka, personal communication, 2002). Magnetic resonance imaging (MRI)

changes may sometimes be misleading [26]. Typically, the extent of the white matter changes are more related to an increase in extracellular fluid rather than 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, but those fiber tracts within the brainstem, which receive similar energies, are absolutely not modified on follow-up imaging studies (Fig. 3). Obviously, these distant changes are because of 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 the 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. Sheehan et al. [39] showed, for a group of patients with brain metastases, that those patients treated in the morning were doing substantially better than those treated in the afternoon. Does this suggest that some sort of cellular circadian rhythm affects the response of tumor and normal tissues to radiosurgery?

The genetic profile of the individual is certainly crucial. In thalamotomies, the treatment is completely standard in terms of the volume of the target, location, and dose. Although the tissue reaction to radiosurgery is reportedly very focal in some series [19, 67], up to 10% of the patients can have a much larger radiographic reaction, as seen on MR imaging, and these imaging changes may be associated with hemiparesis, usually transient. Kondziolka et al. [21, 23] have demonstrated the radio-protective effect of the 21-aminosteroid U-74389G in an experimental study in rats. They report that this drug reduces the cytokine expression normally seen after radiation injury and which may be over-expressed in patients having a greater reaction to radiosurgery seen clinically.

Main functional radiosurgery indications: a review

Ventrointermediate nucleus (VIM) thalamotomies are classically performed using a maximum dose of 130–140 Gy inducing a small area of necrosis after several months, well seen on the 12 months follow-up MRI (Fig. 4). This is one of the infrequent indications for radiosurgery where the intended effect is to mimic the histologically destructive effect produced by thermocoagulation. However, Ohye et al. [34], in 2000, proposed that the clinical effect on tremor was not only the result of the necrotic lesion. Their main argument was that the size of the lesion induced by radiosurgery was too small to account for the clinical effect seen (and it is interesting to note that the limit of the MR lesion corresponds in our experience to the volume of the 90 Gy isodose line). Some experimental observations [68] support this hypothesis but further studies are still necessary in order to better understand the nature and respective role of non-lesional and lesional mechanisms in VIM radiosurgery. Terao et al. [59], in 2008, reported that the somatotopic distribution of kinaesthetic cells was modified by GKR of the VIM, raising the possibility that the specific properties of the neurons are changed in response to GKR.

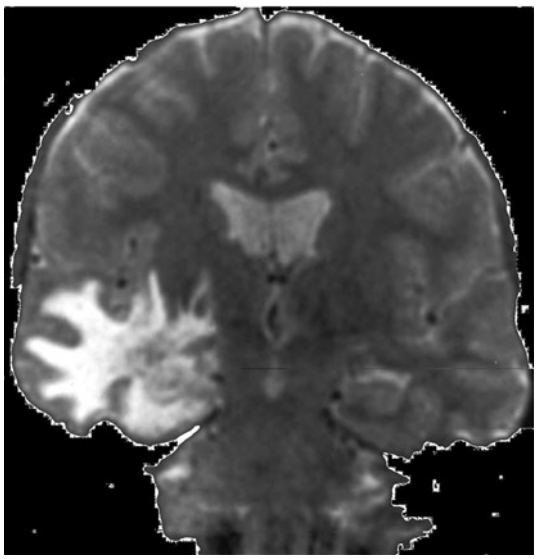

Fig. 3 White matter high T2 signal after MTLE GKS interpreted as a regional indirect response to irradiation

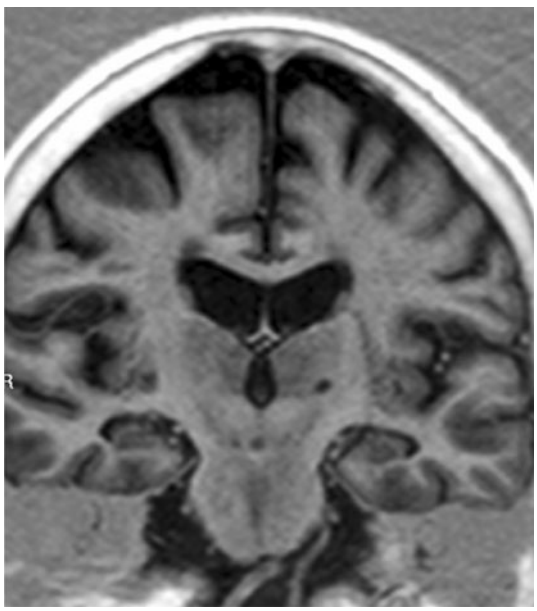

Fig. 4 VIM GKS thalamotomy. Note the precise tiny lesion produced one year after radiosurgery

Curative epilepsy surgery until the 1990s was limited to open microsurgery in which the abnormal epileptogenic tissue was physically removed. Stimulation techniques (vagus nerve stimulation or deep brain stimulation) and disconnection surgery (callosotomies or subpial transection) are palliative techniques usually reserved for very severe cases of drug-resistant epilepsies in which there is no hope left for a curative resective procedure [54]. The first cases of temporal lobe epilepsy treated with GKR, in Marseille in 1993 [42, 44], 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, 50] and long-term follow-up [6]. Other groups are attempting to confirm GKRs potential as a new, non-invasive treatment for MTLE in comparison with standard open temporal lobe surgery (personal communication, Nicholas Barbaro, USA). The impressive MRI findings observed approximately one year after radiosurgery led us initially to speculate a that necrotic lesional effect was responsible for the clinical effect [45]. However, medium-term disappearance of these MRI findings, leaving the medial structures of the temporal lobe either similar to, or only slightly more atrophic than, the preoperative status, suggests a more subtle neuromodulating effect of radiosurgery than initially thought (Fig. 5), and shows much more limited volume of the temporal lobe being involved compared with the effect of microsurgery (MS) [50]. 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 the targeting of the anterior parahippocampal cortex and, especially, the perirhinal and entorhinal cortex [12]. These findings are perfectly consistent with those of Wieser and Yasargil [64] in their series of microsurgical amygdalohippocampectomies. Perirhinal and entorhinal cortex are of a major importance in memory processing [5]. Globally, it is estimated that 40% of patients with MTLE operated microsurgically on the dominant side have a significant postoperative short-term verbal memory deficit [37, 58]. Clussman et al. [8] showed in their large Bonn series of 285 patients that this deficit was slightly more common (43.4 instead of 30.9%) when an anterior temporal lobectomy was performed instead of an amygdalohippocampectomy. Our first prospective trial of GKR for MTLE found that in 65% of those who had dominant temporal lobe treatment there was no evidence of any neuropsychological deficit [6, 50]. Since that time, our subsequent experience has confirmed this observation. Nowadays we consider this memory-sparing benefit of GKR as the major advantage of radiosurgery over MS in patients with dominant temporal lobe MTLE. Thus, the MTLE patients selected for GKR instead of MS are today are those who may suffer more and longer if an additional memory deficit is produced, namely young patients with a high level of functioning, socially adapted, working, concerned by the risk of MS and time off from work, presenting with risk factors for verbal memory loss in case of resection (no atrophy, dominant side, few neuropsychological deficits before surgery) [14]. This group of patients are more often highly functioning with a sufficient IQ enabling them to understand well the peculiarities and nuances of radiosurgery. In addition they frequently do not have the more severe epilepsies, which affords them the luxury of waiting. The San Diego group has observed in patients tested during

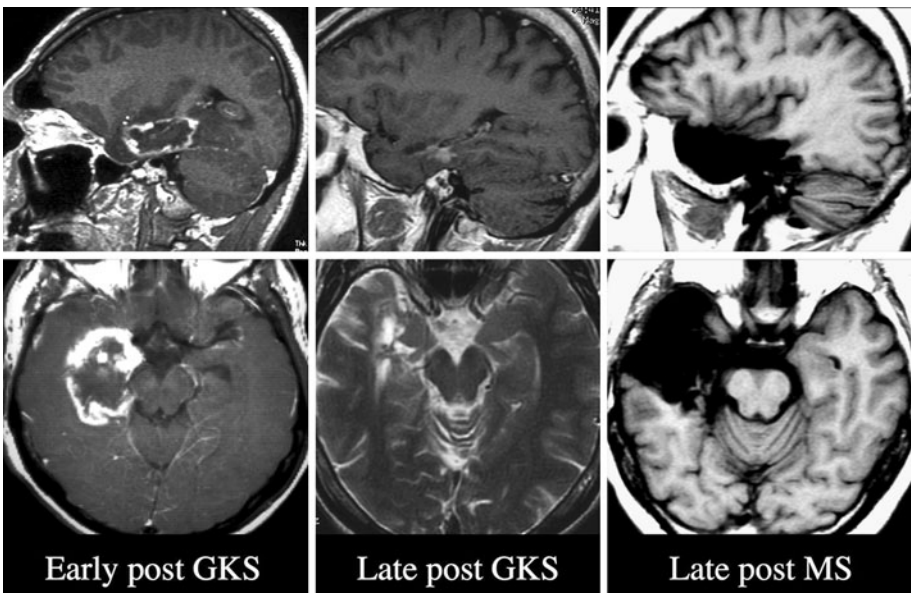

Fig. 5 Radiological differences after gamma knife radiosurgery (GKR) and microsurgery (MS) for MTLE

the "acute phase" (when the acute MRI signs are still present) a neuropsychological worsening in some patients [29], but this group has not reported the long-term results of their neuropsychological testing after resolution of the acute MRI signs. We have observed the same verbal memory sparing in our long-term MTLE patients treated on the dominant side. This same observation has recently been confirmed by the multi-centered Phase 1–2 trial in the USA [4]. The mechanism of this functional preservation is still a matter of speculation. It may be that at this dose regimen we are not lesional at all. It may also be that the cell loss is selective, affecting the glial environment primarily. Perhaps we are inducing some neuronal and astrocytic damage but the process is so slow and delayed that the brain has sufficient time to reorganize functionally. Maesawa et al. [27, 28], in elegant work, have tested, in an a rat kainic acid model of epilepsy, both the efficacy of radiosurgery and the sparing of the memory. The control group (not treated) continued to have seizures whereas 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 between 5 and 11 weeks after GKR. The Morris water maze test was used for spatial memory testing and spatial memory was highly abnormal in the control group, but the radiosurgically treated 30 Gy group had a normal spatial memory [27, 28].

Jenrow et al. [17] have reported in epileptic rats (kindling model) that the selective reduction of densities in the dentate granular cell layer and the medial CA3 pyramidal cell layer was prevented or reversed by the irradiation at 25 Gy but not at 18 Gy. These experimental studies tended to support the dose effect we have found in man [40]. Several magnetic resonance spectroscopy studies are showing, at around 12 months (usual delay for clinical and radiological major changes), a strong reduction of choline, creatine, and *N*-acetylaspartate with elevation of the lactate, pointing to lack of normal oxidative metabolism (ischemia) [11, 15, 36, 38, 61, 62]. Dr Jason Sheehan and his group report that for epileptic rats irradiated with 40 Gy to the medial temporal lobe, immunohistochemical findings suggest that at least one subtype of hippocampal interneurons are selectively vulnerable to GKR. Neuronal cells seem to have undergone a phenotypic shift with regard to calbindin and GAD-67 expression (K. Lee, personal communication, 2009). Thus, this work suggests a selective vulnerability of some neuronal subtypes to our proposed "neuromodulative" effect.

Hypothalamic hamartoma radiosurgery for epilepsy control is an even more convincing example of the functional, non-lesional effect in GKR. As an international referral center for this rare pathology, we have treated more than 80 patients. Theoretically, the question of epileptogenic zone (EZ) definition is straightforward. The hamartoma itself, usually quite well delineated on a high resolution MRI, is supposed to be the EZ [31, 51] and defines the limits of the target, thus making the targeting simpler than for MTLE. After the first multi-centered retrospective trial [46], we have organized a prospective trial [52]. In these case series, the vast majority of the patients do not show any radiographic changes on their follow-up MRI. More than 50% of the patients are seizure-free and a large portion of the patients have had a significant reduction in their seizure frequency and associated significant improvement of their quality of life. Interestingly, the psychiatric [52] and neuropsychological symptoms are also improving dramatically or resolving completely, in a larger percentage of the patients, even in those with no complete seizure cessation. This effect on the co-morbidities usually occurs before the effect on seizure control and in the absence of any changes in the MRI. The clinical observation of profound therapeutic effect with absolutely no histological necrosis induced by radiosurgery is encouraging and is again indicative of a neuromodulatory effect of radiosurgery on the surrounding brain [51].

Conclusion

The CNS is known not to be capable of meaningful regeneration of lost neurons or axons and dendritic connections after injury. Thus a lesion in the brain may result in permanent and severe loss of neurological function. Classically, the CNS regenerative process fails, in our opinion, for at least three reasons:

1 neurons are highly susceptible to death after CNS injury;
2 the CNS extracellular matrix contains multiple inhibitory factors making growth impossible; and
3 the intrinsic growth capacity of post-mitotic neurons are constitutively reduced by factors that inhibit CNS regeneration and its potential strategies to overcome those obstacles [16].

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 suggested. Their intracellular machinery may be able to adapt in response to changes in their environment and some sort of retained developmental state may have an amazing ability to correct internal errors, battling the effects of such mistakes as mutations or misfolded proteins [35]. Our hypothesis is that radiosurgery, under certain conditions, relying on non-necrotizing dose conditions, may induce an important turnover of the glial environment of neurons, enabling functional connections

the opportunity to reset, reorganize, and overcome errors disturbing their functional capability. Thus, let us create "Glial Chaos" in the system!

References

1. Akakin A, Ozkan A, Akgun E, Koc DY, Konya D, Pamir MN, Kilic T (2010) Endovascular treatment increases but gamma knife radiosurgery decreases angiogenic activity of arteriovenous malformations: an in vivo experimental study using a rat cornea model. Neurosurgery 66:121–129 (discussion 129–130)
2. Anniko M, Arndt J, Noren G (1981) The human acoustic neurinoma in organ culture. II. Tissue changes after gamma irradiation. Acta Otolaryngol (Stockh) 91:223–235
3. Apuzzo ML (2009) A new beginning: neurorestoration. Neurosurgery 64:1
4. Barbaro NM, Quigg M, Broshek DK, Ward MM, Lamborn KR, Laxer KD, Larson DA, Dillon W, Verhey L, Garcia P, Steiner L, Heck C, Kondziolka D, Beach R, Olivero W, Witt TC, Salanova V, Goodman R (2009) A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. Ann Neurol 65:167–175
5. Bartolomei F, Barbeau E, Gavaret M, Guye M, McGonigal A, Regis J, Chauvel P (2004) Cortical stimulation study of the role of rhinal cortex in deja vu and reminiscence of memories. Neurology 63:858–864
6. Bartolomei F, Hayashi M, Tamura M, Rey M, Fischer C, Chauvel P, Regis J (2008) Long-term efficacy of gamma knife radiosurgery in mesial temporal lobe epilepsy. Neurology 70:1658–1663
7. Cecconi JP, Lopes AC, Duran FL, Santos LC, Hoexter MQ, Gentil AF, Canteras MM, Castro CC, Noren G, Greenberg BD, Rauch SL, Busatto GF, Miguel EC (2008) Gamma ventral capsulotomy for treatment of resistant obsessive-compulsive disorder: a structural MRI pilot prospective study. Neurosci Lett 447:138–142
8. Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, Haun D, Elger CE (2002) Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg 97:1131–1141
9. Eisenschenk S, Gilmore RL, Friedman WA, Henchey RA (1998) The effect of LINAC stereotactic radiosurgery on epilepsy associated with arteriovenous malformations. Stereotact Funct Neurosurg 71:51–61
10. Flickinger JC, Kondziolka D, Lunsford LD (1996) Dose and diameter relationships for facial, trigeminal and acoustic neuropathies following acoustic neuroma radiosurgery. Radiother Oncol 41:215–219
11. Hajek M, Dezortova M, Liscak R, Vymazal J, Vladyka V (2003) ^{1}H MR spectroscopy of mesial temporal lobe epilepsies treated with gamma knife. Eur Radiol 13:994–1000
12. Hayashi M, Bartolomei F, Rey M, Farnarier P, Chauvel P, Regis J (2002) MR changes after gamma knife radiosurgery for mesial temporal lobe epilepsy: an evidence for the efficacy of subnecrotic doses. In: Kondziolka D (ed) Radiosurgery. Karger, Basel, pp 192–202
13. Heikkinen ER, Konnov B, Melnikow L (1989) Relief of epilepsy by radiosurgery of cerebral arteriovenous malformations. Stereotact Funct Neurosurg 53:157–166
14. Helmstaedter C, Reuber M, Elger CC (2002) Interaction of cognitive aging and memory deficits related to epilepsy surgery. Ann Neurol 52:89–94
15. Hoggard N, Wilkinson ID, Griffiths PD, Vaughan P, Kemeny AA, Rowe JG (2008) The clinical course after stereotactic radiosurgical amygdalohippocampectomy with neuroradiological correlates. Neurosurgery 62:336–344 (discussion 344–336)
16. Jacobs WB, Fehlings MG (2003) The molecular basis of neural regeneration. Neurosurgery 53:943–948 (discussion 948–950)
17. Jenrow KA, Ratkewicz AE, Lemke NW, Kadiyala M, Zalinski DN, Burdette DE, Elisevich KV (2004) Effects of kindling and irradiation on neuronal density in the rat dentate gyrus. Neurosci Lett 371:45–50
18. Kida Y, Kobayashi T, Tanaka T, Mori Y, Hasegawa T, Kondoh T (2000) Seizure control after radiosurgery on cerebral arteriovenous malformations. J Clin Neurosci 7:6–9
19. Kondziolka D (2002) Gamma knife thalamotomy for disabling tremor. Arch Neurol 59:1660 (author reply 1662–1664)
20. Kondziolka D, Linskey L, Lunsford LD (1993) Animal models in radiosurgery. In: Alexander E III, Loeffler JS, Lunsford LD (eds) Stereotactic radiosurgery. McGraw Hill, New York, pp 51–64
21. Kondziolka D, Mori Y, Martinez A, McLaughlin M, Flickinger J, Lunsford L (1999) Beneficial effects of the radioprotectant 21-aminosteroid U-74389G in a radiosurgery rat malignant glioma model. Int J Radiat Oncol Biol Phys 44:179–184
22. Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC (2007) Radiobiology of radiosurgery. Prog Neurol Surg 20:16–27
23. Kondziolka D, Somaza S, Martinez A, Jacobsohn J, Maitz A, Lunsford L, Flickinger J (1997) Radioprotective effects of the 21-aminosteroid U-74389G for stereotactic radiosurgery. Neurosurgery 41:203–208
24. Kurita H, Kawamoto S, Suzuki I, Sasaki T, Tago M, Terahara A, Kirino T (1998) Control of epilepsy associated with cerebral arteriovenous malformations after radiosurgery. J Neurol Neurosurg Psychiatry 65:648–655
25. Linskey ME, Martinez AJ, Kondziolka D, Flickinger JC, Maitz AH, Whiteside T, Lunsford LD (1993) The radiobiology of human acoustic schwannoma xenografts after stereotactic radiosurgery evaluated in the subrenal capsule of athymic mice. J Neurosurg 78:645–653
26. Lunsford L, Kondziolka D, Maitz A, Flickinger J (1998) Black holes, white dwarfs and supernovas: imaging after radiosurgery. Stereotact Funct Neurosurg 70(Suppl 1):2–10
27. Maesawa S, Kondziolka D, Balzer J, Fellows W, Dixon E, Lunsford LD (1999) The behavioral and electroencephalographic effects of stereotactic radiosurgery for the treatment of epilepsy evaluated in the rat kainic acid model. Stereotact Funct Neurosurg 73:115
28. Maesawa S, Kondziolka D, Dixon C, Balzer J, Fellows W, Lunsford L (2000) Subnecrotic stereotactic radiosurgery controlling epilepsy produced by kainic acid injection in rats. J Neurosurg 93:1033–1040
29. McDonald CR, Norman MA, Tecoma E, Alksne J, Iragui V (2004) Neuropsychological change following gamma knife surgery in patients with left temporal lobe epilepsy: a review of three cases. Epilepsy Behav 5:949–957
30. Mezey E, Chandross KJ, Harta G, Maki RA, McKercher SR (2000) Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. Science 290:1779–1782
31. Munari C, Kahane P, Francione S, Hoffmann D, Tassi L, Cusmai R, Vigevano F, Pasquier B, Betti OO (1995) Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). Electroencephalogr Clin Neurophysiol 95:154–160
32. Nagayama K, Kurita H, Nakamura M, Kusuda J, Tonari A, Takayama M, Fujioka Y, Shiokawa Y (2005) Radiation-induced apoptosis of oligodendrocytes in the adult rat optic chiasm. Neurol Res 27:346–350
33. Noren G (2004) Gamma knife radiosurgery of acoustic neurinomas. A historic perspective. Neurochirurgie 50:253–256

34. Ohye C, Shibazaki T, Ishihara J, Zhang J (2000) Evaluation of gamma thalamotomy for parkinsonian and other tremors: survival of neurons adjacent to the thalamic lesion after gamma thalamotomy. J Neurosurg 93(Suppl 3):120–127
35. Oltvai ZN, Barabasi AL (2002) Systems biology. Life's complexity pyramid. Science 298:763–764
36. Omary RA, Berr SS, Kamiryo T, Lanzino G, Kassell NF, Lee KS, Lopes MB, Hillman BJ (1995) 1995 AUR Memorial Award. Gamma knife irradiation-induced changes in the normal rat brain studied with 1H magnetic resonance spectroscopy and imaging. Acad Radiol 2:1043–1051
37. Pilcher WH, Roberto DW, Flanigin HF, Crandall PH, Wieser HG, Ojemann GA, Peacock WJ (1993) Complications of epilepsy surgery. In: Engel J (ed) Surgical treatment of epilepsies. Raven Press, New York, pp 565–581
38. Rabinov JD, Cheng LL, Lee PL, Brisman JL, Loeffler JS, Cole AJ, Cosgrove GR, Bussiere MR, Chaves T, Gonzalez RG (2006) MR spectroscopic changes in the rat hippocampus following proton radiosurgery. Stereotact Funct Neurosurg 84:147–154
39. Rahn D, Dibyendu K, Schlesinger D, Steiner L, Sheehan J, O'Quigley J, Rich T (2010) Gamma knife radiosurgery for brain metastasis of non small cell lung cancer: is there a difference in outcome between morning and afternoon treatment? Cancer (in press)
46. Regis J, Levivier MM (2003) Radiosurgery for intractable epilepsy. Tech Neurosurg 9:191–203
49. Regis J, Roberts D (1999) Gamma Knife radiosurgery relative to microsurgery: epilepsy. Stereotact Funct Neurosurg 72(Suppl 1): 11–21
47. Regis J, Peragut JC, Rey M, Samson Y, Levrier O, Porcheron D, Regis H, Sedan R (1994) First selective amygdalohippocampic radiosurgery for mesial temporal lobe epilepsy. Stereotact Funct Neurosurg 64:191–201
45. Regis J, Kerkerian-Legoff L, Rey M, Viale M, Porcheron D, Nieoullon A, Peragut J-C (1996) First biochemical evidence of differential functional effects following gamma knife surgery. Stereotact Funct Neurosurg 66:29–38
43. Regis J, Bartolomei F, Rey M, Genton P, Dravet C, Semah F, Gastaut J, Chauvel P, Peragut J (1999) Gamma knife surgery for mesial temporal lobe epilepsy. Epilepsia 40:1551–1556
52. Regis J, Semah F, Bryan R, Levrier O, Rey M, Samson Y, Peragut J (1999) Early and delayed MR and PET changes after selective temporomesial radiosurgery in mesial temporal lobe epilepsy. AJNR Am J Neuroradiol 20:213–216
40. Regis J, Bartolomei F, de Toffol B, Genton P, Kobayashi T, Mori Y, Takakura K, Hori T, Inoue H, Schrottner O, Pendl G, Wolf A, Arita K, Chauvel P (2000) Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Neurosurgery 47:1343–1351 (discussion 1342–1351)
42. Regis J, Bartolomei F, Hayashi M, Roberts D, Chauvel P, Peragut JC (2000) The role of gamma knife surgery in the treatment of severe epilepsies. Epileptic Disord 2:113–122
41. Regis J, Bartolomei F, Hayashi M, Chauvel P (2002) Gamma Knife surgery, a neuromodulation therapy in epilepsy surgery!. Acta Neurochir Suppl 84:37–47
44. Regis J, Delsanti C, Roche PH, Thomassin JM, Pellet W (2004) Functional outcomes of radiosurgical treatment of vestibular schwannomas: 1000 successive cases and review of the literature. Neurochirurgie 50:301–311
48. Regis J, Rey M, Bartolomei F, Vladyka V, Liscak R, Schrottner O, Pendl G (2004) Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia 45:504–515
50. Regis J, Scavarda D, Tamura M, Nagayi M, Villeneuve N, Bartolomei F, Brue T, Dafonseca D, Chauvel P (2006) Epilepsy related to hypothalamic hamartomas: surgical management with special reference to gamma knife surgery. Childs Nerv Syst 22:881–895
51. Regis J, Scavarda D, Tamura M, Villeneuve N, Bartolomei F, Brue T, Morange I, Dafonseca D, Chauvel P (2007) Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Semin Pediatr Neurol 14:73–79
53. Regis J, Tamura M, Delsanti C, Roche PH, Pellet W, Thomassin JM (2008) Hearing preservation in patients with unilateral vestibular schwannoma after gamma knife surgery. Prog Neurol Surg 21: 142–151
54. Schramm J, Clusmann H (2008) The surgery of epilepsy. Neurosurgery 62(Suppl 2):463–481 (discussion 481)
55. Steiner L, Forster D, Leksell L (1980) Gammathalamotomy in intractable pain. Acta Neurochir (Wien) 52:173–184
56. Steiner L, Lindquist C, Adler J, Torner J, Alves W, Steiner M (1992) Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg 77:1–8
57. Steiner L, Lindquist C, Steiner M (1992) Radiosurgery. Adv Tech Stand Neurosurg 19:19–102
58. Stroup E, Langfitt J, Berg M, McDermott M, Pilcher W, Como P (2003) Predicting verbal memory decline following anterior temporal lobectomy (ATL). Neurology 60:1266–1273
59. Terao T, Yokochi F, Taniguchi M, Kawasaki T, Okiyama R, Hamada I, Nishikawa N, Izawa N, Shin M, Kumada S, Takahashi H (2008) Microelectrode findings and topographic reorganisation of kinaesthetic cells after gamma knife thalamotomy. Acta Neurochir (Wien) 150:823–827 (discussion 827)
60. Thoren M, Rahn T, Hall K, Backlund EO (1978) Treatment of pituitary dependent Cushing's syndrome with closed stereotactic radiosurgery by means of 60Co gamma radiation. Acta Endocrinol (Cph) 88:7–17
61. Tokumaru O, Kitano T, Takei H, Ogata K, Kawazato H, Yasuda A, Nisimaru N, Yokoi I (2006) Effects of gamma ray irradiation on energy metabolism in the rat brain: a 31P nuclear magnetic resonance spectroscopy study. J Neurosurg 105(Suppl):202–207
62. Toyran N, Zorlu F, Severcan F (2005) Effect of stereotactic radiosurgery on lipids and proteins of normal and hypoperfused rat brain homogenates: a Fourier transform infrared spectroscopy study. Int J Radiat Biol 81:911–918
63. Van Der Kogel AJ (1991) Central nervous system radiation injury in small animal models. In: Gutin PH, Leibel SA, Sheline GE (eds) Radiation injury to the nervous system. Raven Press, New York, pp 91–112
64. Wieser HG, Siegel AM, Yasargil GM (1990) The Zurich amygdalo-hippocampectomy series: a short up-date. Acta Neurochir Suppl (Wien) 50:122–127
65. Yamamoto M, Jimbo M, Lindquist C (1992) Radiation-induced edema after radiosurgery for pontine arteriovenous malformation. A case report and detection by magnetic resonance imaging. Surg Neurol 37:15–21
66. Yang T, Wu SL, Liang JC, Rao ZR, Ju G (2000) Time-dependent astroglial changes after gamma knife radiosurgery in the rat forebrain. Neurosurgery 47:407–415 (discussion 406–415)
67. Young RF, Jacques S, Mark R, Kopyov O, Copcutt B, Posewitz A, Li F (2000) Gamma knife thalamotomy for treatment of tremor: long-term results. J Neurosurg 93(Suppl 3):128–135
68. Zerris VA, Zheng Z, Noren G, Sungarian A, Friehs GM (2002) Radiation and regeneration: behavioral improvement and GDNF expression after gamma knife radiosurgery in the 6-OHDA rodent model of hemi-parkinsonism. Acta Neurochir Suppl 84:99–105