Changing perspectives in radiosurgery
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Introduction: The original idea of Lars Leksell and Borje Larson (12, 13) of delivering a single, highly collimated dose of radiation energy either to perform or to treat focal endocranial lesions, has gradually become a powerful and attractive therapeutic option for several neurosurgical disorders. However, for almost half-a-century, some major “tenets” have represented unquestionable pre-requisites for a correct indication to radiosurgery: 1. Limited target volume 2. Well-defined imaging 3. Appropriate cytology and 4. Compatible location (9, 15, 20, 30).

Newer options: During the last decade, on one side impressive advances in computerized neuroradiology - i.e. fusion algorithms, virtual, non-rigid reproduction and particularly “atamai warping”- have strongly favoured the advent of morpho-functional imaging. Detailed 3D high-Tesla anatomical mappings, using contour definition, signal intensity patterns and voxel matching (7, 19), have been integrated with a variety of functional (f-MR, DTI, MR-spectroscopy etc.) and/or molecular (PET-scan) recordings from the region of interest, thereby providing refined details of the target and of the neighbouring areas (14). On the other, the advent of robotic technology, together with newer acquisitions in terms of radiobiology, have further refined the phases of dosimetry planning. The spectrum of treatment modalities (dose- or volume-staged radiosurgery, dosimetry with inverse models, use of “hybrid” collimators etc.) has lead to increased chances for tumor daunting, while preserving normal tissues from undue damages (3, 23). The growing role of such newer acquisitions deserves some examples: 1. In GK radiosurgery, dealing with low-LET sources highly influenced by tissue oxygen levels, treatment plans may specifically exploit the radiosurgical dose inhomogeneity, creating peculiar hot spots to offset the relative hypoxic protection of the neoplastic core. 2. A particularly steep dose-gradient at the target periphery is extremely important to further enhance the higher potential of DNA repair of normal glial-neural cells (“sublethal damage”) in functionally crucial areas. 3. Similar mechanisms should be responsible also for the better protection of normal brain offered by “staged radiosurgery” (3, 23).

Several practical obstacles to radiosurgical treatments have been overcome. However some functional tenets seem to be still relevant in determining the efficacy on the target as well as the relevance of side effects.

Tenets updated: Well defined imaging: Accurate target localization is still the must for appropriately planned radiosurgery. The highlights of stereotactic imaging include optimal contrast discrimination between normal and abnormal tissue in addition to high spatial resolution, short scan time, and thin slices volume acquisition. In case of nonenhancing tumors, FLAIR sequences can be helpful in differentiating the lesion itself from the surrounding edema.

Limited target volume and appropriate cytology: It is generally accepted that - regardless of the nature of the lesion - the diameter of eligible radiosurgical targets should never exceed 30-32 mm, since any increase in lesion volume must be paralleled by a decrease in
delivered dose. This is one of the major radiosurgical constraints: a large decrease in dose for larger lesions leads to a relatively ineffective treatment or at least does not seem to improve on what might be obtained by standard fractionated radiation techniques. Failure to decrease the dose for larger volumes can lead to unacceptable risk of adverse radiation effects (ARE) on normal surrounding brain tissue, cranial nerves, etc. The concept is not an absolute hallmark, of course, tumors larger than the mentioned diameters may successfully respond to limited radiosurgical dosages provided that the oncotype belongs to the radiosensitive ones (e.g. lymphoma). And *vice versa* glioblastoma offers an eloquent example of the opposite. To this regard differential radiosensitivity thresholds or divergent $\alpha/\beta$ ratio may assume a determinant role as regards clinical results.

**Plain morphology:** Highly conformal and selective dose planning are always important in radiosurgical treatments. They become a conditioning factor when dealing with irregularly shaped targets. Multiple isocenters using narrow radiation beams, or multiple delivery angles may help creating a three dimensional dosimetry planning with excellent coverage of the target volume and steep dose fall off within a few mm from the lesion border.

**Compatible site:** The chances of causing symptomatic radiation injury to the brain from radiosurgery are deeply conditioned by the site of the lesion. Cranial nerves appear to have an extremely variable, differential radiosensitivity. Special sensory nerves (optic, cochlear) are the most sensitive- specifically the cochlear channels and the optic chiasm (5, 21), followed by somatic sensory nerves; the motor nerves are the most resistant. Although the differential radiation sensitivity of the various cerebral areas is still hard to explain, as a matter of fact some peculiar brain regions are more likely to be associated with detectable symptomatic radiation injury than others. As a consequence the ideal radiosurgical management of intracranial lesions – mimicking what had happened in microsurgery - has gradually shifted in the last decades from the compulsive search of radio-ablation, to reasonable level of shrinkage preserving the neurological function.

**Most relevant indications: newer perspectives:** Radiosurgery has become a definitive alternative to microsurgery for patients with newly diagnosed or recurrent benign tumors, especially those of the skull base, involving critical neural or vascular structures, where residual is associated with a high risk of additional deficits. Adjuvant radiosurgery is also used for incompletely removed lesions requiring tumor debulking because of incumbent mass effect. Pre-planned secondary radiosurgery is an effective strategy to deal with these residual tumors, minimizing undue neurological risks.

**HGGs and LGGs:** Malignant gliomas (HGGs) continue to represent one of the most serious clinical challenges in neuro-oncology. However, the observation that local control and median survival can be improved through the radiation dose escalation, has gradually introduced SRS in the therapeutic panel for HGGs (22, 26). Randomized trials have confirmed that SRS administered as a boost within 6 weeks from the completion of external beam irradiation may lead to a significant increase in median survival (up to 25 months versus 13 months in the radiotherapy alone arm) without an increase in treatment related toxicity (12, 13). However such experiences are still limited both in terms of number of patients and of recruiting centers. Low grade gliomas (LGGs) represent a substantially different issue (8, 28): *here oncotypes may be considered “late responding” radiobiological targets due to their relatively small proportion of cells*.
in a proliferative phase of the cell cycle. As published by the Prague Gamma Knife team using a protocol for fractionated SRS an 83% rate of partial or complete tumor regression, and an 11% of stabilization of disease was achieved at a reasonable mean FU. Progression free survival was 92% at 3 years, and 88% at 5 years (8).

**Metastases:** SRS seems an appropriate therapeutic option for patients harboring oligometastatic (1-4) brain disease. During the last decade SRS has been proposed either as a monotherapy, or as a boost with whole-brain radiotherapy (WBRT); in newly diagnosed patients, as well as a salvage therapy for progressive or recurrent intracranial disease after WBRT. Several retrospective studies have shown excellent local tumor control rates after radiosurgery (73-94%) when compared to WBRT alone (55-60%), and an increase in median survival from 3-6 months with WBRT to 7-12 months with radiosurgery, with negligible side effects. However these interesting results have been confirmed by retrospective studies rarely reaching class III evidence, whereas stratified, randomized studies are still limited (1,2,5,6,17).

**Meningiomas:** Radiosurgery offers an effective alternative to surgery for residual or recurrent meningiomas, as well as for those instances where complete resection would lead to unacceptable morbidity. Delayed tumor recurrence after surgery, as well as surgical morbidity and mortality (especially in the elderly) have increasingly emphasized the role of radiosurgery even in primary management of critically located meningiomas. Most skull base lesions, particularly meningiomas of the cavernous sinus are eloquent examples of the “therapeutic shift” of the last decade. It is also worth mentioning that in cavernous sinus meningiomas SRS has shown to be effective – e.g. in restoring ocular motility – not only by reducing the tumor volume and its mechanical compression but also via an octreotide receptor mediated effect, that seems to prevent an anticolinergic activity of those lesions even without modifying the actual tumor size (21). With these premises tumor growth control (TGC) remains high (87-82%) in large series of patients with mid-term (10 years), to long-term (20 years), follow. Indeed, a recent review published by the Gamma Knife group in Pittsburg confirms in a cohort of 972 patients, with an up to 20 year FU, an overall tumor control rate up to 97% and morbidity rate of 7.7% (11)

**Schwannomas:** Once again, long term results in large cohort of patients have established radiosurgery as an important minimally invasive alternative to microsurgery. Kondziolka et al reported a 98% tumor control rate in 5 to 10 years intervals; with a preservation of hearing capability in 60-70% of patients (10). To this regard, growing oto-radiosurgical experience has shown that the main determinant of hearing preservation is represented by adequate sparing of the cochlear channels, with a cut-off radioexposure threshold of 4-to-5 Gy (5). Due to technical improvements facial and trigeminal nerve function can now be spared in the majority of patients (> 95%).

**Pituitary adenomas:** Radiosurgical treatment of these tumors may have two major objectives: 1) oncological “dooming”, 2) endocrinological control. Critically effective dose-thresholds are different, since tumor control can be obtained using much lower dosages than those required to normalize endocrinopathy (27). As regards hypersecreting adenomas they seem to share a variable degree of radiosensitivity, from prolactinomas (the most resistant), to GH secreting (intermediate responders), to ACTH secreting (the most sensitive). In all these oncotypes hormonal medications seem to exert a mild-to-heavy radio-protective effect. Radiosurgical results are enhanced withdrawing hormonal medications at least 2 months before the treatment.
**AVMs:** The goal of radiosurgery in these patients is the complete obliteration of the AVMs nidus. **Radiosurgery causes a cascade of growth-factor (GF)-mediated histological effects on the wall of pathological vessels**—including endothelial proliferation—that eventually lead to luminal occlusion. **Normal vessels are substantially spared, probably because of the absence of such embryonal GF.** The treatment dose is chosen according to appropriate algorithms, balancing the expected obliteration rate (dose response curve) and the corresponding risk level (dose-complication curve). For small volume AVMs (<5cc) obliteration rates ranging from 70% to 95% have been documented 3 years after a single procedure. In larger AVMs (volume 5-15cc) results are less brilliant although often satisfactory, instead the corresponding complication rate are high (4, 24). Furthermore when the original radiosurgical procedure leads to an incomplete response, within the due time, a second treatment may lead to obliteration with an acceptable risk. **For all these reasons staged volume SRS has been advocated either for larger or for critically located AVMs (29).** It is still debated whether radiosurgery leads to a substantial reduction in hemorrhage risk, or not, before complete obliteration occurs. Recently Maruyama et al studied this question and concluded that chances for hemorrhage were decreasing over time. Their analysis also showed that bleeding was possible, although rare, after seemingly complete angiographic obliteration, due to residual microscopic nidus or perhaps the collapse of the frail granulation tissue of the AVM scar (18).

**Functional Neurosurgery**

**Trigeminal Neuralgia:** Over the last 15 years, trigeminal neuralgia has grown to become the most common functional indication for SRS. The aim, like for other ablative techniques, is to interfere with neurophysiological pathways of pain transmission. The procedure is well tolerated and can be offered to almost any patient. Indeed, the low incidence of complications and the theoretical possibility to repeat the treatment in case of recurrence are among the greatest advantages of this technique. The glial reaction induced by SRS should reduce the axonal crosstalk and therefore block the ephaptic transmission with a clinical decrement of pain paroxysm. To date the largest reported series confirm the high success rate after Gamma Knife treatment: up to 76% of patients achieve Grade I according to McGill analogical scale, and 65 to 88% Grade II. The reason for such a favourable results may be probably explained by: 1) an accurate selection of patients (e.g. never previously treated forms), 2) the appropriate targeting (plexus triangularis) 3) and a careful choice of maximal dose (90 Gy) to minimize side effects. Most of the patients start experiencing pain relief within 6 months from radiosurgery (median 2 months), and complete pain relief is sustained even at 3 years from the procedure in 56% of patients (16).

A second procedure may be considered only if complete pain relief had been achieved with subsequent recurrence, and in any case a reduction of the maximal dose of prescription (60-70 Gy) is mandatory in order to assure the safety of the procedure.

In the near future, further improvements in clinical results may be reasonably expected from some of the main investigative trials presently on in progress.

1. Tridimensional anatomo-functional imaging will presumably provide a better definition either of the target “core” – e.g. in secreting tumors like pituitary adenomas, or in large, octreotide positive meningiomas – or of the neoplastic peripheral borders, like in brain malignancies.
2. Management strategies for “oversized tumors” will probably routinely include either planned neoplastic debulking followed by radiosurgery on the residual mass, or “multi-staged” radiosurgical procedures, with additional protection of normal brain structures.

3. Dosimetry programs seem consistently oriented toward lower levels, once again to meet the goal of stopping tumor progression while preserving neurological functions. The introduction of novel radio-enhancers might accelerate this process.

4. Additional therapeutic support should come from newer radioprotective agents presently under investigation - e.g. free radical scavengers, membrane stabilizers, like 21-aminosteroids etc., as well as from compounds limiting the incidence of adverse radiation effects, like cyclooxygenase 2 inhibitors (10).

It is generally accepted that *mid-to-long-term future* of radiosurgical treatments will be totally or partially dominated by molecular, biological and onco-genetic approaches modifying our present radiobiological knowledge, and putatively introducing the era of gene-therapy in several radiosurgical protocols.

References


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