Radiosurgical options in neuro-oncology: a review on current tenets and future opportunities. Part II: adjuvant radiobiological tools

Mario Ganau1,2, Roberto Israel Foroni1, Massimo Gerosa1, Giuseppe Kenneth Ricciardi3, Michele Longhi1, Antonio Nicolato1

1Department of Neuroscience, University Hospital, AOUI, Verona - Italy
2Department of Biomedical Engineering, University of Cagliari, Cagliari - Italy
3Department of Pathology and Diagnosis, University Hospital, AOUI, Verona - Italy

ABSTRACT

Stereotactic radiosurgery (SRS) is currently a well-established, minimally invasive treatment for many primary and secondary tumors, especially deep-sited lesions for which traditional neurosurgical procedures were poorly satisfactory or not effective at all. The initial evolution of SRS was cautious, relying on more than 30 years of experimental and clinical work that preceded its introduction into the worldwide medical community. This path enabled a brilliant present, and the continuous pace of technological advancement holds promise for a brighter future. Part II of this review article will cover the impact of multimodal adjuvant technologies on SRS, and their input to the crucial role played by neurosurgeons, radiation oncologists and medical physicists in the management and care of fragile neuro-oncological patients.

Keywords: Stereotactic radiosurgery, 3D-imaging, Radioenhancers, Radioprotective agents

Introduction

Stereotactic radiosurgery (SRS) is an accepted method of treatment for single and multiple intracranial brain lesions with submillimeter accuracy; this characteristic led SRS to be considered not only as a potential adjuvant to surgical treatment but in some cases also as a valuable alternative option, especially given its clinical efficacy with acceptable morbidity (very low rates of early and late side effects). The aim of Part II of this review is to discuss the impact of multimodal adjuvant technologies on SRS and their input to the crucial role played by neurosurgeons, radiation oncologists and medical physicists in the management and care of fragile neuro-oncological patients, in order to better understand the path ahead of us.

Study design

The pace of advancement in clinical practice and the encouraging results obtained so far with SRS treatments of various primary and secondary brain tumors may be reason-ably expected to keep growing only if the rate of discoveries, coming from some of the main investigative trials currently in progress, will provide us with new biological insights. As explained in Part I of this review, over the past decade the advantages of optimized SRS treatments have been thoroughly studied and tested by comparing conventional single-dose with fractionated schedules in patients harboring brain tumors (1). Some of these lesions show innate mechanisms of radioresistance while other neoplastic subgroups, especially the most aggressive ones, accelerate the production of clonogenic cells during irradiation. Hence, unraveling the specific nuances of each of these lesions, especially through innovative proteomic and genomic platforms, is proving to be helpful in understanding the molecular pathways responsible for their growth and recurrence (2). Moreover, these investigations are providing new data to optimize patient selection, treatment plans, dose levels, and dose contours to achieve optimal therapeutic results. It is now well known that prescription doses matter both in terms of therapeutic efficacy and side effects: whereas low radiation doses (<20 Gy) delivered as a single fraction only induce fibrinoid necrosis of vessel walls, hyaline degeneration and possibly thrombosis, higher doses (>25 Gy) may bring about white matter changes leading to demyelination or myelomalacia, as well as neuronal shrinking and astrocitosis. Therefore, the recently achieved better understanding of the radiation-induced modification of a tumor’s biological behavior will enhance the cure rates and offer a more tailored alternative to current treatments. We here report the theoretical basis and related laboratory evidence suggesting why further improvements of current
neuro-oncological protocols will make the shift from bench to bedside very soon.

**Biological insights and significance for SRS**

**High-grade and low-grade gliomas**

The scientific contribution of several clinical trials to better define the radiobiological parameters of high-grade gliomas (HGGs) recently led to several attempts to create tumor control probability models aimed at achieving significant improvements of the current radiosurgical protocols. By designing a solid analytical/graphical method to match the clinical data pertaining to a total of 559 patients harboring HGGs, researchers were recently able to describe the amount of surviving cells in the tissue exposed to radiation and therefore to estimate the intrinsic tumor radiosensitivity (α), the repair capability (b), and the repopulation doubling time (3). Moreover, it was possible to calculate the number of clonogens and the kickoff time for accelerated proliferation, confirming a high α/b ratio for HGGs. The authors were also able to predict those lesions with high intrinsic radiosensitivity or characterized by a long kickoff time for accelerated repopulation, and those with less moderate [AUTHORS: Should this be “more moderate”?]

Moreover, useful data came from the current glioma stem cell theory, which suggests that gliomas, independent of their histological grade, may originate from neural stem cell populations resulting from genetic alterations that accumulate with tumor progression. HGGs can develop either de novo with no prior evidence of a previous low-grade lesion or through malignant progression from a low-grade glioma. These 2 pathological subgroups constitute distinct disease entities that evolve through different genetic pathways and consequently affect patients at different ages (4). Many glioma development hypotheses have been proposed and investigated; those most widely endorsed shed light on cancer stem cells and their key role in the mechanism underlying resistance to anticancer treatment. In this regard the most studied feature of glioma stem cells is their positivity for CD133, a transmembrane cell-surface protein. CD133+ cells usually appear in clusters close to tumor blood vessels and are occasionally seen in pseudopalisade formations delineating necrosis (5). These cells can survive radiation and chemotherapy and thereby contribute to treatment failure in de novo HGGs. Experimental data show that the Ki67 indices of CD133+ glioma cells are significantly increased in recurrent HGGs after irradiation as compared with those in primary tumors (6). Their propensity to change their phenotype to a proliferative state during development of recurrence after radiation suggests a switch in proliferation that is not temporary but rather a constitutive event of tumor regrowth. Hypotheses regarding the activation of the PI3K/Akt pathway in stem cells residing in the above-mentioned perivascular niches have also been raised (6). Overall, these insights indicate a window of opportunity for antiangiogenic therapies: targeting the tumor microvasculature to disrupt stem cell maintenance could be a promising approach to increase the efficacy of primary, adjuvant or salvage SRS.

**Metastases**

Due to the partial response of brain metastases to standard treatment options and the restricted therapeutic indications (i.e., patients with a poor performance status are not candidates for cytotoxic chemotherapy, surgery or SRS), there is a strong clinical rationale for the use of targeted therapies meant to widen the inclusion criteria (7). Many molecular pathways are currently under investigation; for instance, laboratory evidence suggests that the altered expression of epidermal growth factor receptor (EGFR) is pivotal for tumor progression in patients with brain metastases, as elucidated especially in those from lung cancer (8). Thus, EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, might raise new therapeutic hopes by providing a high likelihood of response in patients with irradiation-resistant brain metastases (9). Based on results from single-arm phase II trials showing high response rates in patients with EGFR mutation or in populations where this genotype is expected (while not confirming these data in the context of documented wild-type EGFR in disease metastatic to the brain), a growing consensus is currently reflected in the attitude to selectively recommend upfront therapy with EGFR TKIs in asymptomatic patients harboring activating EGFR mutations (10).

**Meningiomas**

Because of the anatomical constraints imposed by the cranial base and by venous sinuses, and because of the relentless tendency to recur shown by malignant tumors of meningeal origin, SRS not only has an important role in their primary treatment but also in tackling residual or recurrent disease after surgical resection or radiotherapy. Currently, SRS can be useful in achieving effective palliation of these tumors but does not ensure definitive cure. In the recurrent setting after exhaustion of all treatment options including conventional radiation therapy or SRS, no effective therapies are known for aggressive meningiomas, which represent a therapeutic challenge. Nevertheless, evidence of upregulation of proangiogenic molecules, dysregulation of some signaling pathways such as the platelet-derived growth factor (PDGF), and epigenetic modifications associated with the formation and/or progression of meningiomas has frequently been found; novel compounds might therefore offer hope for better disease control in the future (11, 12). Indeed, promising *in vitro* studies and limited clinical experiences with antiangiogenic drugs and molecular inhibitors of PDGF signaling cascades indicate that clinical trials to draw definite conclusions about the efficacy of these approaches concomitant with SRS are warranted (13).

**Pseudoprogression after SRS**

Finally, better molecular insights from radiation-induced apoptosis, which is a common pathway for any of the above-mentioned subgroups and is known to trigger cytolysis with...
### Results

As shown above, the biological response of tumor subgroups and the surrounding brain parenchyma precedes their radiographic response, upon which the effectiveness of SRS treatment is calculated. Noteworthy, many of the current data from clinical trials and SRS series will probably be redefined in the next decade due to the tremendous pace of technological progress in terms of pre- and posttreatment imaging. 3D anatomofunctional imaging will presumably provide a better definition either of the target “core” (i.e., octreotide-positive meningiomas) or the neoplastic peripheral borders (i.e., any aggressive brain malignancy). Moreover, management strategies for “oversized” or “critically located” tumors will continue to move towards multistaged treatments, so that neurosurgeons will no longer aim at single-session eradication of the lesion; rather, they will aim at gross total excision or size-staged SRS of the tumor to spare critical brain structures from surgical manipulation or excess radiation. To this extent, dosimetry programs will be designed to the specific needs of each single patient to meet the goal of stopping tumor progression while preserving more and more neurological functions. All these issues, prominently directed towards the identification of the best possible SRS schedule for neuro-oncological patients, will be discussed more in depth in the following section of this review.

### Multimodality imaging for SRS

As we just said, treatment planning aims to achieve the most accurate definition of the lesion’s boundaries and the surrounding brain region in order to maximize the dose to the target while sparing the latter structures. It is therefore mandatory to define the borders of the lesion and the nature of surrounding edema, to delineate the course of cranial nerves in the vicinity of skull base tumors, and to identify white fiber tracts close to the lesion. All these objectives are currently within our grasp through fusion of multimodality imaging such as multislice computer tomography (CT), high-field structural magnetic resonance imaging (MRI), 3D rotational angiography (DSA), diffusion tensor imaging (DTI), and metabolic positron emission tomography (PET). Such preoperative information facilitates choosing the optimal approach and conformational treatment planning.

### Optimization of MRI contrast media

In any SRS treatment, good results rely on the optimization of imaging protocols. In this respect the ever increasing knowledge of brain tumor biology is facilitating the selection of the appropriate gadolinium-based contrast agent (GBCA), which is of paramount importance for accurate lesion imaging. GBCAs differ in their safety, tolerability, and efficacy because of their diverse physicochemical properties; gadobutrol and gadobenate dimeglumine, due to their high T1-relaxivity, demonstrate superior efficacy for imaging metastatic lesions. They are therefore more likely to enhance confidence for SRS treatment planning compared with other GBCAs such as gadodiamide, gadoteridol or gadoversetamide. All GBCAs, regardless of their physicochemical characteristics, are associated with low rates of qualitatively similar adverse events in clinical studies; nevertheless, gadobutrol seems the

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**TABLE I - Biological and molecular responses to SRS**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Molecular pathway</th>
<th>Biological response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early phase response</strong></td>
<td>(2-72 hours time frame)</td>
<td></td>
</tr>
<tr>
<td>Prabhakarpandian et al, 2001 (15)</td>
<td>Expression of ICAM-1</td>
<td>Induction of inflammatory reaction involving the migration of polymorphonuclear leukocytes and other blood formed elements into the irradiated area</td>
</tr>
<tr>
<td>Gaber et al, 2003 (16)</td>
<td>Expression of ICAM-1</td>
<td></td>
</tr>
<tr>
<td>Sharp et al, 2003 (17)</td>
<td>Expression of ICAM-1, ECAMs, and E-selectin</td>
<td></td>
</tr>
<tr>
<td><strong>Late phase response</strong></td>
<td>(1-6 months time frame)</td>
<td></td>
</tr>
<tr>
<td>Hong et al, 1995 (18)</td>
<td>Increased mRNA levels of TNFα and IL1</td>
<td>Activation of tumor-associated macrophages, induction of cell adhesion, acute and chronic release of inflammatory cytokines, and cell death in the irradiated area</td>
</tr>
<tr>
<td>Chiang et al, 1997 (19)</td>
<td>Increased mRNA levels of TNFα</td>
<td></td>
</tr>
<tr>
<td>Daigle et al, 2001 (20)</td>
<td>Increased mRNA levels of TNFα</td>
<td></td>
</tr>
<tr>
<td>Tsai et al, 2007 (21)</td>
<td>Increased levels of iNOS</td>
<td></td>
</tr>
<tr>
<td>Wang et al, 2013 (22)</td>
<td>Expression of HIF-1</td>
<td></td>
</tr>
</tbody>
</table>

ECAM = endothelial adhesion molecule; HIF = hypoxia-inducible factor; ICAM = intracellular adhesion molecule; IL = interleukin; iNOS = inducible nitric oxide synthase; mRNA = messenger ribonucleic acid; TNF = tumor necrosis factor
safest choice since it provides higher macrocyclic stability, which is useful for reducing side effects related to the release of free gadolinium into human serum (23).

**DTI tractography**

Preoperative motor tractography data have been loaded onto the intraoperative neuronavigation platform to guide surgical procedures as well as SRS treatments for a while. In SRS this protocol has been adopted mostly for arteriovenous malformations (AVMs) close to the corticospinal tract, but the accuracy of 3T MRI nowadays enables acquisition and fusion of almost any kind of white matter tract into SRS treatment plans for lesions adjacent to or involving those neural structures (24). This possibility is allowing more and more treating physicians to avoid unnecessary irradiation of functional structures such as the corticospinal or optic tract while maintaining an effective prescription dose to the target. As a result, the rate of long-term side effects is expected to drop dramatically in many of the forthcoming SRS clinical series.

**3D Rotational angiography**

This neuroradiological tool was initially introduced into SRS planning only for the treatment of AVMs; given its potential to better define surrounding vascular structures (e.g., in the skull base or in case of parasagittal meningiomas) its wider application has been proposed also in neuro-oncology whenever it is mandatory to reduce the risk of symptomatic edema arising from possible radiation-induced venous occlusive complications. Indeed, 3D rotational angiography provides significant help in volumetric estimations, extraction of arterial feeders and the origins of draining veins, and identification of venous anomalies. [AUTHORS: Changes OK?] Initial successful confirmation of this approach comes from the reduced irradiation of veins in close proximity to the target lesion, which may be at risk of radiation-induced occlusion, obtained in the clinical setting without any alteration of other SRS treatment parameters including conformity, homogeneity, and target coverage (25).

**PET scan**

In selected patients the incorporation of PET scanning may yield additional information. For instance, whenever single-dose or hypofractionated SRS is chosen for the treatment of recurrent brain lesions already treated with primary or adjuvant SRS, PET should be advocated in order to help distinguish active tumor from postoperative changes or radiation necrosis (26, 27). Interesting insights are coming from the use of $^{11}$C-MET PET and $^{18}$F-FDG PET in the pre-treatment study of recurrent metastases and HGGs (28, 29). Accordingly, these radiotracers should be the ones of choice in the evaluation of any pseudoprogressing lesion because of their sensitivity for lesion identification and characterization. Specifically in case of gliomas, $^{11}$C-MET PET seems the easier technique to interpret, irrespective of the histological grade, because of the lesser interobserver variability and the more straightforward localization of $^{11}$C-MET within the tumor (26).

**Image fusion protocols**

One of the greatest advances in neuroradiology is the technique of image fusion, which is literally the process of superimposing multiple imaging modality sets to define a specific target. With regard to stereotactic treatment plans for neuro-oncological cases the main advantage provided by this technique is the better definition of the critical structures (bone, vessels or cranial nerves) surrounding the target. As for any SRS treatment the first step is the acquisition of the target: this can be achieved with a single stereotactic imaging modality (CT or MRI) with the use of a stereotactic head frame (for framed SRS) or a mask system (for frameless SRS). Upon acquisition of the background image and delineation of the target, many additional imaging sets, including other MRI sequences (such as DTI) or DSA or PET scans, can be superimposed to highlight the tumor’s relationship with adjacent cortical tracts and vascular vessels or its own metabolic activity.

Image fusion can take advantage of the specific pros of each imaging modality while minimizing its cons: fusing CT and MRI scans for instance would annul the poorer imaging resolution of the former while overcoming the geometric distortion of the latter. Noteworthily, improvements in neuroradiology and laboratory simulations for surgery/SRS are partly overcoming the risk of error introduced by inaccuracies of the fusion process, as well as the risk of image distortion along the entire fusion workflow process. Such approaches from experimental settings for virtual surgery can be easily translated to neuro-oncological scenarios: an enlightening example might be the tool for classification analysis and 3D reconstruction of vessels developed by our team with the aim to provide their correct and detailed reconstruction even where pathologies have caused morphological and geometrical variation in the vessels (30). The proof of concept experiments (initially run on images from the hepatic and portal systems) proved that the time required for the entire segmentation and 3D reconstruction process is compatible with clinical requirements, and provided us with an efficient tool for diagnosis and surgical planning which is now serving as the basis to implement this protocol also in SRS treatments for neurovascular disease (30).

**Radiosensitizers and radioenhancers for SRS**

Radiosensitizers and radioenhancers serve to increase the toxicity of radiation in cancer cells while limiting the damage to adjacent healthy tissue. A radiosensitizer is defined as a chemical or pharmacological agent that increases the lethal effects of radiation if administered in conjunction with radiation, while a radioenhancer is an agent that reduces the amount of radiation required to kill a given population of tumor cells (31). Radioprotective strategies, on the other hand, are meant to diminish the damage to healthy tissue surrounding the target lesion and thereby increase the therapeutic ratio (31). Initially, the emergence of some chemotherapy agents, such as temozolomide for HGGs, was mostly favored by their role as radiosensitizing agents due to a positive impact on survival when administered along with standard whole-brain radiotherapy or SRS. Accordingly, investigations of new nanoformulated strategies to selectively
address resistant glioma cells and open new opportunities for SRS are under way; for instance, expectations are now focused on hyaluronic acid nanospheres as carriers for anti-neoplastic drugs against HGGs (32). Moreover, some systemic agents are being explored as potential radiobiological tools, and additional therapeutic support is sought from novel radioprotective agents currently under investigation such as free radical scavengers and membrane stabilizers, as well as from compounds limiting the incidence of adverse radiation effects, like cyclooxygenase 2 inhibitors (31). Ongoing investigations are evaluating also other systemic agents (motexafin gadolinium, mammalian target of rapamycin inhibitors, farnesyltransferase inhibitors) that have shown promising activity in combination with standard radiotherapy (33).

Finally, in an effort to improve local tumor control and limit the toxicity to normal brain tissue, novel methods of delivering SRS, including the concomitant administration of gold nanoparticles, have been proposed. Theoretically, systemic injection of gold nanoshells can be targeted to various neoplasms, such as HGGs, metastases and meningiomas but also schwannomas, chordomas, etc. Upon their internalization by tumor cells, the efficacy of SRS could be increased by at least a factor of 2 (31, 34). Unfortunately, although the concept was first introduced in 2006 (34), we still lack a concrete animal model investigating this combined approach.

On the other hand, radioimmunotherapy, another promising strategy which uses antibodies labeled with a radionuclide to deliver cytotoxic radiation to target neoplastic cells, has already demonstrated good efficacy with acceptable toxicity (35). These premises lead us to expect that SRS will soon be totally or partially dominated by molecular, biological and oncogenetic approaches that will modify our present radiobiological knowledge and will widen the horizons of the application of radiosurgical protocols. In Table II the mechanisms of action

<table>
<thead>
<tr>
<th>Molecule and reference</th>
<th>Role</th>
<th>Stage of development</th>
<th>Reported mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromodeoxyuridine</td>
<td>RS</td>
<td>Phase III clin. trial</td>
<td>This halogenated pyrimidine incorporates into DNA of cancer cells and sensitizes them to radiation damage.</td>
</tr>
<tr>
<td>Effaproxiral</td>
<td>RE</td>
<td>Phase III clin. trial</td>
<td>This synthetic agent decreases the oxygen affinity to hemoglobin, leading to hypoxia and cell killing.</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>RP</td>
<td>Preclinical study</td>
<td>Barbiturates lead to hyperpolarization and decreased excitability of post-synaptic neurons, thus decreasing cerebral metabolic oxygen consumption.</td>
</tr>
<tr>
<td>Estramustine</td>
<td>RS</td>
<td>Preclinical study</td>
<td>This estradiol-based antimicrotubule agent selectively accumulates in glioma cells inducing their apoptosis.</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>RE</td>
<td>Phase I clin. trial</td>
<td>This electron-affinity agent leads to the generation of free radicals within tumor cells, thus enhancing radiation-induced cell killing.</td>
</tr>
<tr>
<td>GM1 gangliosides</td>
<td>RP</td>
<td>Preclinical study</td>
<td>Upon active incorporation into cell membranes they exert a neuro-protective effect directly and through the potentiation of endogenous neurotrophic factors.</td>
</tr>
<tr>
<td>Lonidamide</td>
<td>RS</td>
<td>Phase II clin. trial</td>
<td>Exerts a powerful inhibitory effect on oxygen consumption and aerobic glycolysis, leading to lactic acid accumulation in neoplastic cells.</td>
</tr>
<tr>
<td>Misonidazole</td>
<td>RE</td>
<td>Phase III clin. trial</td>
<td>Same as metronidazole. Nonetheless, as misonidazole is less lipophilic, it is thought to have a greater clearance rate.</td>
</tr>
<tr>
<td>21-aminosteroids</td>
<td>RP</td>
<td>Preclinical study</td>
<td>Free radical scavengers, also known as lazaroids. They inhibit the activation of proinflammatory cyclooxygenase pathways, thereby mitigating radiation-induced injury to healthy brain parenchyma.</td>
</tr>
<tr>
<td>Motexafin</td>
<td>RS</td>
<td>Phase II clin. trial</td>
<td>This metalloporphyrin shows selective tumor localization and acts by generating reactive oxygen species.</td>
</tr>
</tbody>
</table>

RS = radiosensitizer; RE = radioenhancer; RP = radioprotective agent.
of the most renowned radiosensitzers, radioenhancers and radioprotective agents are listed (36-45).

**Ancillary treatments for pseudoprogression after SRS**

Since the inception of radiosurgery, the management of post-SRS symptomatic radiographically regrowing lesions has become a common problem for neurosurgeons. Evidence that bevacizumab, an antiangiogenic monoclonal antibody, reduces both symptoms and reactive imaging changes in these patients provides a strong impetus to conduct a prospective randomized trial (46). According to the initial clinical data, although the necessary treatment duration and optimum dose are still unknown, any pseudoprogression after SRS that is unresponsive to corticosteroids could in the near future benefit from experimental trials.

Moreover, novel treatment options such as MRI-guided stereotactic laser-induced thermotherapy could find their place as feasible alternatives in the treatment of symptomatic regrowing metastatic lesions after SRS, as proposed by some authors (47, 48). This technique has shown some effectiveness in the symptomatic relief of edema and neurological symptoms paralleled by radiographic lesion control without any complications directly related to the thrombocoagulation procedure (47, 48).

**Conclusions**

The evolution of SRS has been essentially supported by serial advancements in terms of stereotactic imaging (high-Tesla MRI, image-fusion algorithms) and in terms of multi-isocentric targeting allowing highly conformal and selective planning (49). The latter is actually the most precise and ultimate form of intensity-modulated irradiation. By 1994 SRS units were adopting multiple isocenter techniques, switching to multiple static conformal fields to improve conformity, or switching to fractionated techniques and lower radiation doses in order to limit the radiotoxicity to normal brain tissue (49). More recently, a better understanding of brain tumor biology provided by new proteomic and genomic platforms, alongside dramatic advances in the pharmacological characterization of radioenhancers and radiosensitzers to better exploit the potentialities of SRS, have led to the steady optimization of prescription doses for SRS treatments. At present, given the continuous advancements of this neuro-oncological practice, we do not know how much further the doses will be safely lowered in the coming years.

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**Disclosures**

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