The Downside of Radiosurgery, Possible Complications

O Lado Ruim da Radiocirurgia, Possíveis Complicações

Luiz Claudio Modesto Pereira
Valeria Patricia de Araujo
Thiago Henrique de Moraes Modesto

ABSTRACT

As a consequence of various last century scientific and technological advances radiotherapy and stereotactic radiosurgery (SRS) have emerged as safe and efficacious techniques for the treatment of various intracranial pathologies. Recent improvements such as in brain and tumor imaging, patient immobilization, 3D planning and radiation delivery allow it to target lesions more accurately and minimize radiation delivered to normal brain, leading to drastic improvements in terms of safety and post-therapy complication. Despite that SRS still implies in moderate to severe side effects in one fifth to one fourth of patients. Fortunately the most common SRS complications, such as edema, blood brain barrier breakdown and MRI abnormalities are self-limited and amenable to treatment. The precise pathophysiological processes of SRS complications are still under research, however multiple factors including treatment dose, modality and planning complexity, target size, shape and location are known to affect treatment results. The most reported potential SRS complications are ischemic stroke, brain or lesion hemorrhage, radiosurgery-induced neoplasms, radiation necrosis, white matter changes, cranial nerve dysfunction and cognition problems. SRS induced neurological complications may persist only in as much as 5% of patients.

Key words: Radiation; Stereotactic Radiosurgery; Brain Tumor; Brain Metastasis; Eloquent Brain Area; Complication; Side Effects; Radiation Necrosis

RESUMO

A radioterapia e a radiocirurgia estereotáxica (SRS) surgiram, em consequência a vários avanços científicos e tecnológicos do século passado, como técnicas seguras e eficazes para o tratamento de diversas patologias intracranianas. Aperfeiçoamentos recentes na obtenção de imagens cerebrais e de tumores, imobilização de pacientes, planejamento tridimensional e sistemas de aplicação de radiação permitiram maior precisão na determinação de alvos, minimizando a irradiação ao cérebro normal e levando a melhorias significativas em termos de segurança e complicações posteriores.

A pesar disto, a SRS ainda implica em efeitos colaterais moderados a severos, em um quinto a um quarto dos pacientes. Felizmente as complicações mais comuns da SRS, como edema, ruptura de barreira hematoencefálica e anormalidades em imagem da Ressonância Magnética são autolimitadas e passíveis de tratamento. Os processos fisiopatológicos precisos das complicações da SRS ainda continuam em investigação, entretanto, múltiplos fatores incluindo a dosagem, complexidade e modalidade de planejamento, localização, forma e tamanho do alvo são conhecidos por afetar os resultados do tratamento. As complicações mais relata das SRS são acidente vascular cerebral isquêmico, hemorragia cerebral ou lesional, neoplasia induzida por radiocirurgia, necrose por radiação, alterações da substância branca, disfunção de nervos cranianos e problemas da cognição. Complicações neurológicas induzidas por SRS podem persistir em cerca de 5% dos pacientes.

Palavras-chave: Radiação; Radiocirurgia estereotáxica; Tumor cerebral; Metástase cerebral; Áreas eloquentes; Complicações; Necrose

INTRODUCTION

Stereotactic Radiosurgery (SRS) has become a broadly accepted form of Central Nervous System (CNS) precise focal irradiation and has been applied for a variety of spinal and intracranial conditions such as arteriovenous malformation (AVM), primary or metastatic SNC tumors (benign or malignant), especially those for which the risk of surgery is considered unacceptable. SRS is also indicated as a prophylaxis method for selected patients at high risk of neoplastic involvement of the nervous system or as a treatment of certain neurological functional syndromes such as pain, epilepsy and movement disorders. Being a more advanced radiation method, SRS is considered to be both safer and more effective than conventional fractionated external-beam radiation therapy (CEBRT), or other modern radiation techniques such as fractionated stereotactic radiotherapy (FSRT), and intensity-modulated radiotherapy (IMRT). However, SRS has certain limitations, mostly...
due to the lesion volume or proximity to nearby important neural structures. Commonly SRS is recommended for tumors smaller than 3 cm and more than 3 mm away from the optic pathway.

To write about the downside of SRS is no easy job. An attempt to compare SRS risks to those derived from all other radiation modalities is extremely difficult, as each technique presents its particularities. SRS modalities are technically different and cannot be compared.

As technology advances both efficacy and risks increase, not necessarily in parallel manners. Sometimes advances in equipment technology enable for wider ranges of applications but simultaneously result in greater threats. Referring to a parallel in the automotive industry can make one example of such behavior. The number of motor vehicle deaths in the United States by year increased steadily from the 1920’s to 1940’s, remained stable until the 1970’s and decreased significantly in the last two decades. This fluctuation is the result of discrepancies between technology, safety standards and widespread adoption of vehicle safety culture. Initially mechanical improvements in vehicles were not accompanied by the development of better safety equipment, which lead to increase volume of casualties. Keeping up this comparison if more advanced technology necessarily implied in greater safety than the top of the line experimental self-driving cars would never crash, but they still do.

The significant technological advances of the past three decades have introduced new methods such as three-dimensional imaging of tumors and surrounding tissue, which made planning and delivery of external beam radiation possible. SRS techniques can safely deliver high doses of radiation to a precise target volume by combining multiple converging low intensity beamlets. The aggregation of radiation sources enables treatment of small three-dimensional intracranial or spinal lesions while avoiding significant damage to surrounding tissues. The multiple intersecting SRS beams produce a sharp radiation “dose falloff”. Consequently, tumorous areas receive higher dose concentration than adjacent areas. Additionally, devices such as multileaf collimators and robotic arms allowed for more efficient ways to deliver 3D energy. Nonetheless, SRS exposes the patient to a higher focal radiation dose. The risk becomes significantly higher when treating larger lesions or when near eloquent brains structures.

It is known, for instance, that larger tumors have larger normal tissue interface and less rapid SRS radiation “dose falloff”. This physical phenomenon limits the application of SRS to lesions smaller than 3 cm (occasionally 4 cm). Fractionated RT, as delivered by FSRT or IMRT, is a safer method when treating larger and irregularly or complex-shaped tumors, particularly close to critical neural structures.

Understanding the benefits of SRS’s as well as its potential consequences is fundamental. It can affect the way patients are selected, how complications are managed and how patients are counseled.

**DEFINITIONS**

**Stereotaxis** is a method of precisely locating and accessing areas in the brain (and sometimes spine).

**Stereotactically-guided irradiation** means delivering a precise and predictable radiation dose at an accurately defined intracranial target within the intracranial space (or spine), without delivering a significant proportion of dose to the surrounding neurovascular tissue.

**Stereotactic radiosurgery** (SRS) is the term for highly focused and precise radiation used to eradicate a targeted tissue. Because the radiation is precisely and narrowly focused, higher doses can be delivered during a single or few (≤5) sessions.

**SRS modalities:** SRS is currently performed with three basic modalities:

- **Heavy charged particle beam:** such as proton beam.
- **Linear accelerator or LINAC system:** High energy X-rays are used to target large tumors. This is sometimes called CyberKnife technology
- **Leksell 60Co Gamma Unit (LGU) or Gamma Knife radiosurgery (GKR):** Close to 200 beams of highly focused gamma radiation are aimed at a target region. This is used mostly for small to medium-sized brain and/or head and neck lesions.
Factors Influencing Complications

Just as we have moved on from horse drawn carriages to hybrid cars, radiation therapy has continued to develop, for the last 100 years, into an important, powerful and technological tool in the fight against CNS tumors and other neurological conditions. The use of medical radiation, for instance, has increased 6-fold in the past 30 years. Advances involved in the SRS technique, such as to precisely inactivate or eradicate defined targets, have significantly improved patient outcomes. Some might even say that SRS has significantly altered the treatment paradigm for both benign and malignant central nervous system diseases. Adding up to that even the more sophisticated modalities of SRS are still evolving. As an example Noren reported that facial weakness and facial numbness occurred in 38% and 33% of his GKR series in the mid-1970s, but that gradually decreased to less than 2% in the 1990s. Despite all experience and technology gained the tissue adjacent to a radiosurgical target still receives low or moderate dose of radiation. Complications are mostly related to location and dose of radiation to important structures.

Current treatment for brain tumors consists of a combination of different approaches, including surgery, radiotherapy, chemotherapy, and molecularly targeted agents. As a result, the effectiveness of treatment and life span of patients has increased. Despite its large utility, radiation may lead to severe and irreversible tissue damage in the CNS even years after the therapy. The improvement of postoperative survival has lead to increasing concerns regarding neurological abnormalities resulting of radiation-induced brain damage, especially cognitive deficit (usually presented months or years after treatment). This has motivated considerable research efforts to understand the response of normal brain and spinal cord to irradiation.

Investigation of radiation-induced CNS lesions has improved comprehension of its radiobiological parameters correlation as well as and the injury impact on histology and tissue function. However, the precise biochemical processes of radiation-induced CNS injury are still unknown. Initial reports of SRS safety and side effects were derived from animal models and other types of brain irradiation. More recently, models for predicting the likelihood of complications after SRS came to be based on actual clinical experience. Robbins et al. conducted a thorough investigation to reveal the mechanisms of radiation-induced neurogenesis impairment and cognitive deficits, founding an understanding of some mitigators of radiation injury and providing an approach towards developing intervention strategies. Predictive radiation-induced brain injury biomarkers are needed to properly customize treatment for each patient based on their individual needs.

There are several factors influencing the likelihood of patients developing side effects or complications from SRS. The most common described include:

A. Patient: gender (female), age and genetic susceptibility (e.g. Neurofibromatosis Type 2 (NF2)), functional impairment (low Karnofsky performance scale) and clinical comorbidities;

B. Lesion: volume of lesion and normal brain tissue treated—represented as Gross Tumor Volume (GTV), Target Volume (TV) and Planned Target Volume (PTV), target location - proximity to brainstem or visual pathway and maximum lesion diameter;

C. Irradiation: the total dose and volume of radiation delivered to the lesion and to normal surrounding brain—represented as Prescribed Dose (PD), Integral Dose within target volume (ID), Prescription Volume (PV) and Total Absorbed Energy (TAE), the Volume Of Nontarget Tissue (NTV) within the PV and the Volume of Accepted Tolerance Dose (VATD), the coverage and homogeneity of irradiation—described as Prescription Isodose Volume (PIV) (e.g. 50% or 95% isodose surface or curves), Homogeneity, and Gradient Index and Conformity Gradient Index (CGI), the fractionation schedule (1 to 5 fractions) and in certain equipment the number of isocenters;

D. Other: concurrence or sequenced chemotherapy treatment, history of previous radiation.

Among these factors, the ones related to the amount of radiation delivered to CNS nearby target structures are considered the most relevant. If we postulate that the dose plan conforms to the three-dimensional shape of the target, the major factors that will determine the amount of radiation delivered to the target...
1. Acute effects (such as acute radiation encephalopathy) that can occur during radiation up to six weeks afterwards;

2. Early-delayed effects (such as transient demyelination or blood brain barrier dysregulation) that appear up to six months after radiation;

3. Late effects (such as progressive demyelination, stem cell depletion, vascular abnormalities, sclerosing phenomena and necrosis) that develop later than six months after completion of radiation. Unlike acute and early-delayed reactions that are usually reversible, late reactions are generally irreversible.

Table 2 summarizes the reported side effects of SRS radiation. In brief, functional or constitutional manifestations can arise in the acute, subacute, or long-term setting, whereas evident neurologic side effects due to CNS radiation injury generally require at least 6 weeks to be clinically apparent. In general, the presence of early side effects is not predictive of late side effects. The most representative examples of each temporal category of complications are: the fairly uncommon acute radiation encephalopathy (presented from days to weeks following SRS), the pseudoprogression phenomenon (generally occurring within 1 to 6 months of irradiation and chemotherapy for glioblastoma multiforme) and radiation necrosis (RN), irreversibly installed at times greater than 6 months.

Scoring criteria for both early and late morbidities were published by the Radiation Therapy Outcomes Group in 2006. Summarizing the data, grades I and II represent normality, mild symptoms or lesser neurological impairment, grades III and IV represent moderate to severe dysfunction, coma or need to stay hospitalized and grade V represents any toxicity that causes death. These morbidity criteria helped to better define and score the toxicity from radiation therapy, in this case SRS therapy. This scoring system became especially useful to understand how SRS radiation risk increases when dealing with patients suffering significant clinical comorbidities (e.g. collagen vascular disease or multiple sclerosis).
Compliations by anatomiCal Region, oRgan oR tissue

SRS Induced Neoplasms and Malformations

Radiation-induced neoplasms, although more commonly observed after fractionated radiation therapy, are exceedingly rare after SRS. To avoid false diagnosis Cahan & Woodard outlined (in 1948) the following basic criteria to define radiation-induced neoplasm:

1) the tumor must not be present at the time of irradiation;
2) there must be a prolonged latency period between radiation delivery and tumor development;
3) the tumor must arise in the irradiated region;
4) the tumor must be histologically distinct from the original tumor; and
5) the patient must not have a genetic predisposition to the development of cancer.

To date, few cases reported in the world literature of SRS induced neoplasm have meet Cahan’s criteria. Based on the literature, the incidence of radiosurgery-induced neoplasm is estimated to be less than 1 per 1,000, probably represented by a cumulative risk of 64 in 100,000 person-years. The true incidence of this complication is still not known. Hopefully more accurate rates are likely to emerge after longer follow-up periods.

<table>
<thead>
<tr>
<th>Timing</th>
<th>Acute</th>
<th>Subacute</th>
<th>Long-term</th>
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<tbody>
<tr>
<td>Tumor</td>
<td>Pseudoprogression</td>
<td>Radiation necrosis, diffuse leukencephalopathy, decreased learning ability, short-term memory and problem-solving skills</td>
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<tr>
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<td>Cataract</td>
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Adapted from Hansen E, Roach M. Handbook of Evidence-Based Radiation Oncology, 2000

**LITERATURE TREND**

As SRS therapeutic effects and complications occur in a delayed fashion, some taking almost a decade to occur, thorough clinical and imaging follow-up are indispensable, ideally over a prolonged time. We performed a systematic search in PubMed, to identify papers published from 1990 to 2014 regarding SRS, SRS complications and SRS randomized controlled trials (RCT) (Figure 1). As expected the percentage of publications concerning SRS complications publications followed a Gaussian curve (inverse U shaped), while SRS RCT papers followed an exponential curve (negative). The highest publication percentage for SRS complications happened in 2001, a little more than a decade after SRS becoming widely utilized. Reports on SRS RTC, on the other hand, became more frequent since 2005, peaking in 2011. The natural interest in comparing SRS to other techniques as well as defining its role amongst the treatment options are the most probable reasons for this research trend.

**Figure 1.** Percentage of publications on SRS treatment that are either randomized controlled trials or that state on complications issues.

**COMPILATIONS BY ANATOMICAL REGION, ORGAN OR TISSUE**

**Table 2. Described Complications and Side Effects of SRS for Intracranial Pathologies**

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Vascular Effects

Numerous reports have linked radiation to the development of cerebrovascular injury including arterial stenosis/occlusion, aneurysm formation, moyamoya disease, atherosclerosis, hemodynamic changes and stroke. Radiation can cause structural and functional cerebral vasculature changes, which can occur in acute, intermediate or late manners. Most of the abnormalities happen in capillaries, especially at the endothelial cell. Early endothelial changes include capillary extracellular basement membrane abnormalities, change in endothelial cell F-actin distribution, cell retraction and cellular swelling. There is a dose-dependent increase in transendothelial flux of low molecular-weight solutes and albumin, accompanied by alterations in eicosanoid synthesis and increased secretion of growth factors and chemoattractants. These early pathological changes lead to increased permeability, which is responsible for severe cerebral edema. Latter the surviving endothelial cells undergo cytoplasmic hypertrophy and giant cell formation with increased cellular adhesiveness for neutrophils, causing endothelial proliferation and luminal narrowing. Last, the endothelial cells promote intercellular platelet deposition and platelet-fibrin thrombi may develop. These changes can ultimately lead to luminal narrowing and vessel occlusion.

Vascular complications following SRS seem to be rare and can be categorized as hemorrhage or occlusion of vessels leading to ischemia. The estimated risk of arterial occlusion is 1 to 2% while for hemorrhage can reach up to 3%.

Central Nervous System Complication

Radiation-induced CNS image changes are common, usually characterized by a bright signal on T2-weighted Magnetic Resonance Image (MRI) and occurring 3 to 15 months after treatment. Whenever associated with contrast enhancement on T1-weighted MRI, the changes may presumably represent radiation-induced injury with an associated breakdown of the blood-brain barrier. Radiation-induced CNS changes develops in approximately 30 to 47% of patients but are symptomatic in only 11% of cases. The clinical manifestations of the radiation-induced effects ranges from no symptoms to headache to signs of raised intracranial pressure, and focal neurological deficits. Progressive resolution seems to be the usual course, although in a small percentage of patients there is association with focal damage to neural tissue. Notwithstanding that a variable rate of SRS induced neurological complications (ranging from 2 to 32%) has been reported, only 3 to 5% of patients still presented neurological deficits at the time of the last follow-up. It is essential to highlight that the signal changes on MRI associated with clinical deterioration, despite being transitory in many cases, are frequently incorrectly interpreted as RN.

Increased intracranial pressure during SRS is uncommon. Whenever larger volumes of the brain are treated, especially in younger patients, lethargy and somnolence may be observed approximately after 3 months. Rarely, localized demyelination resulting in nausea, vomiting, ataxia, dysphasia, and cerebellar ataxia may develop, usually in a self-limited manner.

Progressively enlarging encephalopathic changes are now well-documented effects of SRS. It tends to occur 3 to 30 months after radiation treatment of brain tumors. While radiographic differentiation between encephalopathic changes and recurrent tumor is of high clinical relevance, confident interpretation of post-radiosurgery imaging changes can be challenging or even impossible in some cases.

Radiation Necrosis

Radiation necrosis (RN) is a serious late complication of radiation therapy (RT) for brain tumors and may develop after 6 months to 3 years after treatment. RN may occur in up to 50% of lesions treated by SRS and represents the most important late toxicity. The incidence of neurological complications due to RN is quite variable, ranging from 2 to 32% of SRS treated patients. RN has a wide spectrum of clinical manifestations, varying from purely imaging-based diagnosis in asymptomatic patients to highly symptomatic individuals with mass effect and subsequently increased intracranial pressure, and symptoms traceable to the anatomic location. It is generally accepted that RN becomes symptomatic in only 40% of MRI diagnosed patients. MRI imaging RN abnormalities does not always correlate with clinical symptoms such as seizure, motor deficits, cognitive decline, and speech problems. The contrary is also true because some patients with moderate symptoms might have minimal changes on imaging.

Radiation tolerance of normal brain is dependent of patient profile, lesion and clinical parameters. As previously stated, tumor volume and location of the lesion are the most important factors.
predictive variables for the development of RN after SRS. Radiation dose also seems to be an important factor, although some authors have described nonlinear dose dependence for RN.

Discriminating RN from neoplasm recurrence with imaging can be challenging because in both cases there are regions with avid uptake of contrast material on T1-weighted images that can cause mass effect with local edema. Several times RN can frequently emulate the disease treated by SRS. The following imaging criteria were proposed as indicative of radionecrosis:

1) increased T1 contrast enhancement located in the irradiated area with central hypointensity and increased peripheral edema;
2) substantial regression or stability (for at least 4 months) of enhancing areas on serial follow-up MRI scans without additional treatment;
3) a clear absence of perfusion (black hole), in the absence of any nodular highly vascularized area within the contrast-enhanced lesion at perfusion MRI.

Magnetic Resonance Spectroscopy (MRS) measuring concentration of specific metabolites (and comparing their ratio) emerged as a helpful tool to improve diagnostic yield. Diffusion-Weighted imaging (DWI) is also useful to try to differentiate tumor recurrence and RN because necrotic areas have higher diffusion coefficients. MRI imaging and follow-up can strongly suggest RN diagnosis but many times only histology can confirm the diagnosis. In addition to RN other significant late CNS complications have been described, especially after SRS for AVM, including cyst formation and diffuse white matter changes.

The physiopathological intricacies of RN have not been fully understood, although they are believed to be, to some extent, the result of endothelial cell dysfunction, tissue hypoxia and increased vascular endothelial growth factor (VEGF) release resulting in capillary leakage, progressive blood-brain barrier dysfunction, and brain edema.

The goal of RN treatment is to reduce clinical symptoms and the neurological risks of edema and increased intracranial pressure. In asymptomatic and slightly symptomatic RN patients conservative treatment may be the best option. For patients bearing more symptoms or larger lesions one or several treatments may be needed. Steroids are a first line of medication to treat radiation induced edema and RN. Steroids probably reduce the vascular inflammatory changes that precede necrosis, possibly reducing and delaying, when applied early, subsequent necrosis. The optimal dose and timing of corticosteroids must be tailored by clinical symptoms, as early as possible. After symptoms improve the steroid dose should be tapered as tolerated. Medical complications of steroid therapy should be monitored and avoided. Hyperbaric oxygen therapy can increase tissue oxygenation and angiogenesis, improving capillary bed function. Some patients may largely benefit from this therapy, while others might not improve. Anticoagulants and antiplatelet medications have also been used to try to minimize vascular changes that lead to ischemia in RN. More than 60% of patients not responding to steroids may improve on anticoagulation therapy. Bleeding risk, the major concern of anticoagulation, needs to be monitored. Other medications such as antioxidants and memantine have been subject of investigation but their role in RN treatment remains unknown.

Surgical treatment is indicated as RN becomes progressively larger and symptomatic despite all above treatments. Surgery aims to resect the RN nidus, relief mass effect and allow decompression. Surgery is less effective for diffuse necrotic lesion.

Cognitive Decline

Radiation induced cognitive decline is becoming more important with the prolonged survival allowed by oncological treatment. Brain radiation is known to lead to a subcortical type of cognitive deterioration. Reduction in hippocampal neurogenesis and the occurrence of neuroinflammation are viewed as playing a major role in radiation-induced cognitive impairment. Cognitive deterioration can also be associated to radiation-induced leukoencephalopathy, noticeable on brain MRI. In these circumstances sequential imaging highlight a mineralizing angiopathy, caused by injury to small vessels and characterized by loss of white matter, enlarged ventricles, and microcalcifications. Microvascular abnormalities and reduction of hippocampal-dependent cognitive function may clinically result in impairment of intellectual function, especially memory, attention, executive function and mathematical ability.

Radiation induced neurocognitive impairment evolves in a biphasic pattern: a subacute transient decline...
with a peak at four months, and a late delayed irreversible impairment of neurocognitive function several months or years after completion of radiation\textsuperscript{64}. In severe cases it may also result in significant dementia, ataxia, and confusion.

The exact incidence of neurocognitive impairment after SRS remains inadequately quantified, mostly because of shorter survival of patients with malignant neoplasms. Even the data on neurocognitive toxicity related to Whole brain RT are still contradictory\textsuperscript{24}. White matter changes and cognition problems after SRS have been reported to occur in 0 to 12\% of patients\textsuperscript{5,50,97,119,131,151}. There are several identified predisposing factors that contribute to overall neurocognitive decline after brain irradiation, including tumor histology, volume and location, surgery, RT and chemotherapy. In addition, underlying diseases, especially those characterized by microvascular changes, including diabetes, hypertension, smoking, stroke, cardiovascular insufficiency, and other conditions, also contribute to the greater incidence\textsuperscript{63,64,120}. The larger individual risk factors for neurocognitive impairment after SRS are older age and multiple brain metastases. Once again the total volume and dose of irradiation play important role in the genesis of the phenomenon. Cognitive symptoms can occasionally be ameliorated with memantine and other Alzheimer-type medication\textsuperscript{93}. SRS induced impairment of both neurocognitive function and quality of life of patients with larger lesions or multiple brain metastases needs to be further addressed in RCT.

**Peripheral Nervous System**

There is a radiation tolerance difference among the areas of the brain and various cranial nerves. Special sensory nerves (optic and acoustic nerves), being fiber tracts of the central nervous system, have the least toleration to radiation and may not recover fully from injury. Dose tolerances of the most critical and eloquent brain regions to SRS irradiation are: 8Gy to optic nerve and chiasm, 10 Gy to brainstem and spinal cord and 12 Gy to visual pathway\textsuperscript{61,146}. Nerves in the parasellar region, the facial nerves, and the lower cranial nerves tolerate higher radiation doses.

SRS treatment of tumors in close proximity to cranial nerves often require limited doses. The distance between the nerve and the lesion being treated should be assessed carefully. The tolerable distance is a function of the degree to which a dose plan can be designed to deliver a suitable radiation dose to the tumor and yet spare the more radiosensitive nerves. Norén analyzed risk factors for facial and trigeminal neuropathy in patients with tumors receiving 12 to 20 Gy and concluded that the most significant factor is the length of the nerve irritated, not the volume of tumor or dose\textsuperscript{124}. Tishler reported that the it was the maximum dose delivered to the cranial nerves that was associated with neurologic deficits in LINAC and Gamma Knife radiosurgery\textsuperscript{14}. In contrast patients with AVMs, meningiomas, and pituitary adenomas, receiving SRS cranial nerves doses between 20 and 25 Gy might have no complications\textsuperscript{121}.

The mechanism of radiation injury to cranial nerves seems to be the damage to small vessels, oligodendroglia or protective Schwann cells.

The delayed onset of trigeminal numbness or facial weakness after acoustic neuroma SRS seems to be around 25\%, while for SRS for benign tumors near to parasellar nerves and low cranial nerves appears to be about 4\%\textsuperscript{31,51,54,57,70,107,114}.

**CSF Circulation**

Hydrocephalus has been reported as an occasional complication of SRS. It may result for acute edema or late white mater changes. Lesions closer to the brainstem are more likely to be related to post SRS hydrocephalus. Published data on hydrocephalus development due to SRS for acoustic nerve tumors ranges around 6 to 16\%\textsuperscript{78,84,105,116,159}.

**Bone Skin and Muscles**

With SRS technology, skin and muscle such as dry desquamation, erythema reactions and myositis are usually rare and clinically readily manageable. If ear canals or lacrimal gland is included in the radiation field, otitis media may develop. Keratoconjunctivitis and otitis have been reports after SRS\textsuperscript{1,54}.

**Conclusions**

SRS offers, when adequately indicated, a high rate of tumor control, with acceptable preservation of neurological functions, and a good or reasonable quality of life. Despite all
technology SRS side effects are rather frequent. For instance radiation-induced imaging changes occur in half of SRS treated cases (only 20% of those will develop side effects) and up to one fourth of the patients can experience self-limiting early toxicity. Normal tissue complication probability and tumor control probability after SRS depend on factors such as treatment modality, size, shape, and location of the target, and complexity of treatment planning. Better treatment planning, better selection of candidates and targets, preferably the ones with small diameter and volume, may reduce the future risk of SRS complications. It is very important to emphasize that an organized team of neurosurgeons, radiation oncologists and medical physicists is always required to achieve optimum SRS planning, dosing, and long-term outcomes.

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**CORRESPONDING AUTHOR**

Dr. Luiz Claudio Modesto Pereira  
Hospital de Base do Distrito Federal  
Hospital de Santa Luzia  
Brasilia - DF  
Telephones: +5561 99705646; +5561 81815656  
E-mail: modesto.luizclaudio@gmail.com