Stereotactic radiosurgery (SRS) and stereotactic radiation therapy (SRT) for neurooncological and neurological diseases: state of the art and future perspectives

Abstract: Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (SRT) are well established in a high number of neurooncological and neurological lesions. Modern technologies discussed in this review, especially the integration of multimodality imaging in the daily clinical routine, will further improve the results of SRS and SRT. Currently, the different technical methods used are comparable regarding the clinical results in different clinical indications. The technological advances allow high treatment flexibility, and therefore, new treatment indications can be established based on the new technologies. In the future, it has to be defined more clearly whether a single fraction, hypofractionated concepts, or fractionated stereotactic radiotherapy is more effective regarding the clinical results and side effects of the therapy. The main area of development for radiosurgery will be stereotactic body radiosurgery. More randomized clinical studies for all possible indications are needed in the next few decades in order to establish radiosurgery more precisely, and also to determine its true value, especially in normal-fractionated radiotherapy. In technological development, the next step has been completed and proton or particle based stereotactic radiosurgery may have increased use in the future.

Keywords: Neurooncology; radiosurgery; radiotherapy; stereotactic.

Introduction

Within the last few decades, stereotactic radiosurgery (SRS) has become established as one therapeutic option in the treatment of various malignant or benign lesions in the brain, skull base, spine, and other sites in the body. SRS is applied very precisely in high doses of radiation, which eradicates or inactivates a tumor without the need for a surgical approach. In the early days, SRS was limited to the head only. For several years, stereotactic radiosurgery has been established for extracranial targets [stereotactic body radiotherapy (SBRT)]. The treatment of extracranial lesions is not limited to primary or metastatic lesions of the spine but can also be applied to tumors or metastases in the lung or liver. Until today, the main field of application of SRS however, is still neurooncological diseases.

Lars Leksell established stereotactic radiosurgery in the last century. With the use of computed tomography (CT) data and frame-based stereotactic methods, radiosurgery became more and more a part of clinical routine. New image modalities, that is, positron emission tomography, magnetic resonance imaging (MRI), or functional MRI, could be integrated into the treatment planning process by either using various co-registration techniques and/or by integrating localization frames for various imaging modalities. New algorithms for exact dose calculation were developed in the past few years and allowed a higher dosimetric accuracy in the actual radiation delivery. Modern linear accelerators are equipped with X-ray sources, which allow performing a CT for set-up control prior to SRS, and therefore, ensure precise patient positioning. As the standard availability of on-board kV and MV imaging tools, image-guided radiotherapy (IGRT) has become a standard procedure in radiotherapy. Despite the fact that modern image modalities show high diagnostic quality and accuracy, histological determination of the
lesions before SRS should be attempted if it is clinical relevant in order to compare clinical results of SRS with surgical treatment modalities. Actually, in most cases of SRS in the head, pathology is not obtained prior to treatment (e.g., all functional disorders, metastases when an extracranial cancer is documented, meningiomas, acoustic neuromas). SRS is a complex treatment approach, which should be performed in specialized centers with close interdisciplinary collaboration, especially between neurosurgery and radiation oncology. Depending on histology, location, tumor volume, and clinical aspects, the adequate treatment modality for each patient needs to be established: radiosurgical approach (SRS) or a fractionated stereotactic treatment concept (SRT) with image-guidance.

However, clinical concepts in SRS are changing, as there is a trend from a single shot therapy to hypofractionated approaches in 3–5 fractions with the benefit of higher therapeutic ratio concerning surrounding normal tissues. In some clinical situations, mainly for extra cranial approaches in the lung or liver, up to ten fractions are used.

In order to apply SRS safely and effectively, normal tissue tolerances need to be respected. Clinical data regarding critical structures are mainly available for fractionated radiotherapy, thus, little is known of the true tolerance dose of normal tissue for hypofractionated SRS.

Using stereotactic techniques in a fractionated manner is defined as stereotactic radiotherapy (SRT). For SRT the same accuracy and quality assurance has to be ensured as for SRS.

Technical aspects and system configurations

Various technical solutions can currently be used for SRS. Each system offers different methods for accurate delivery of highly focused radiation doses and various immobilization techniques are available. Some more common systems will be explained in detail.

Over previous decades, abundant data for SRS has been accumulated for the treatment of neurooncological malignancies using the Gamma-Knife® system (Elekta AB, Stockholm, Sweden). This dedicated system allows a highly precise application using multiple cobalt sources. Patient positioning is achieved by either invasive frame-based, or more recently, a non-invasive immobilization technique for head lesions. The Gamma-Knife consists of approximately 200 sources of cobalt-60 (energy on average: 1.25 MeV), which can be opened or closed by a shielding system in order to achieve precise dose distribution. The treatment planning process defines the number and position of necessary sources in order to achieve the optimal dose distribution. The disadvantage of the Gamma Knife® system is that the cobalt sources have to be regularly replaced after a few years and the radioactive waste needs to be disposed. With the introduction of linear accelerators (LINAC) in standard clinical routine, LINAC-based treatment systems were established for SRS. All systems are highly precise with positioning accuracy (isocenter) of approximately 1.0 mm. Apart from the independence of radioactive material, the main advantage of LINAC-based systems is the possibility of performing cranial radiosurgery as well as extracranial radiosurgery. The commercially available Novalis Linac (BrainLab, Munich, Germany), which is probably the most frequently used stereotactic device, is a 6-MeV or higher energies Linac that is equipped with a motorized micromultileaf collimator and an in-room stereoscopic kilovoltage X-ray device as part of the system. These two tubes can be used for isocenter localization prior to treatment and positioning control during SRS. This information can be fused with the reference image from the treatment planning CT, therefore, the exact treatment position can be defined. Furthermore, the system is equipped with an infra-red camera system (ExacTrac system) able to detect infra-red-sensitive markers. This system can additionally monitor patient position during therapy. The radiosurgery elements of the Novalis linear accelerator can now be added individually to a variety of Elekta (Elekta AB) and Varian (Varian Medical Systems, Palo Alto, CA, USA) linacs.

Other commercially available modern linear accelerators can also be used for stereotactic applications. These LINACs are equipped with integrated on-board imaging devices, such as the Elekta (Elekta AB) or the Varian (Varian Medical Systems) systems. The mentioned vendors offer special dose calculation algorithms and positioning devices for SRS and SRT in the head and in the body. Both systems can be used for SRS/SRT as well as standard radiotherapy. CyberKnife (Accuray, Inc., Sunnyvale, CA, USA) is a dedicated radiosurgery tool with a small and lightweight LINAC attached to a robotic arm. This construction is extremely flexible and allows a high number of non-isocentric and non-coplanar beam directions. The system also has the ability to “track” moving targets and allows dissociation between imaging and treatment isocenters. CyberKnife uses an in-room stereoscopic imaging device comparable to the ExacTrac system in order to exactly control cranial and extra cranial targets.
**Skull base tumors**

Lesions of the skull base comprise a heterogeneous group of tumors with benign clinical behavior in many cases. Resections of the skull base are technically challenging and might cause severe neurological deficits. As a result of anatomical limitations, complete resections are not always possible. Stereotactic fractionated radiotherapy or SRS has been established as a treatment alternative for these indications in the previous two decades. A large number of clinical publications demonstrated that these techniques are efficient, safe, and have a minimally invasive treatment approach. In many indications, surgery and stereotactic radiotherapy/radiosurgery achieve similar success rates; however, prospective randomized trials comparing these methods are not available. Furthermore, no prospective trials are performed that compare SRS with fractionated approaches. Combined concepts might be necessary for larger lesions, and after a subtotal resection, radiotherapy should be integrated in the treatment concept.

Acoustic neuromas (AN) were treated mainly by surgery in the past [13]. In recent years, an increasing number of publications for stereotactic radiotherapy were published and showed that radiotherapy can achieve comparable results as surgery [2, 8, 10, 34, 48, 52], and is therefore a minimally invasive and safe alternative. By using stereotactic radiotherapy, a good hearing preservation can be achieved in some patients and the trigeminal and facial nerve toxicity is relatively low [46]. From recent literature, it can be concluded that the local control rates are always in excess of 90%. Many studies found control rates of 100% [7, 48, 52]. Hearing preservation rates range between 57% and 93% [7, 34, 48].

There is also data for SRS in meningioma. In a recent publication on more than 400 patients with low-grade meningioma treated by single-fraction radiosurgery, local control rates of 96% at 5 years and 89% at 10 years were presented [40]. The median follow-up for these patients was 60 months. Main risk factors for radiation-related complications after single fraction RT were increasing tumor volume and tumors of the parasagittal/falx/convexity region. After 1 year and 5 years, the rate for radiation-related complications were 6% and 11%, respectively. Other authors reported comparable results [11, 12, 32]. SRS is therefore commonly used for small lesions (<3 cm) while larger lesions, and lesions with a close proximity to the brain stem or other organs at risk, are treated by fractionated stereotactic radiotherapy. The mean doses for fractionated concepts ranges between 50 and 57.6 Gy in 1.8 to 2.0 Gy per fraction. For SRS, mean prescribed doses ranges from 14 to 16 Gy (Figure 1).

Additionally radiosurgery in the skull base region could be used for lesions of the glomusjugulare and tympanicum. Lee et al. showed local control rates of 100% (n=14/14) after gamma knife radiosurgery. All patients had a significant tumor regression with a median volume reduction of 34.0% [33]. The authors concluded that radiosurgery is a good alternative to a microsurgical resection of these lesions.

Good clinical results of SRS and SRT can be achieved for adenoma of the pituitary gland, especially for secreting pituitary adenoma resulting in an acromegaly, and many studies showed that radiation therapy is highly effective in patients with persistent active acromegaly after surgery and/or during medical therapy [24, 25, 50].

**Metastases**

SRS is well established in the treatment of brain metastases of various cancer types. It is well known that Karnofsky performance score (KPS), patient age, uncontrolled primary tumor, and extracranial metastases are the main prognostic factors in the treatment of patients with metastases of the brain [16]. In patients with one or more unfavorable prognostic factors, it has to be discussed individually whether patients will still benefit from treatment of cerebral lesions. There is no difference in the clinical outcome whether radiotherapy or neurosurgery is used as an intervention. SRS is mainly advocated in situations with one to three metastases [6, 27, 38, 41], while some studies allow up to five lesions [3, 49]. Commonly, a single lesion is treated by a surgical approach. After local approach, a whole-brain radiotherapy (WBRT) has to be discussed. A currently published EORTC trial addressed the questions of WBRT after local treatment of the brain metastases [27]. Microsurgical resection or SRS were possible as local treatment for patients with one to three brain lesions. The maximum diameter for a single metastasis eligible for SRS was 3.5 cm, for more lesions 2.5 cm and the prescribed marginal dose was 20 Gy. Comparing surgery and SRS, there was no difference in survival or the functional outcome. WBRT could significantly reduce the probability of relapse at the original site or at new sites for both local procedures. A second randomized trial also revealed no difference in the examined endpoints after WBRT, when the patients were treated with either SRS or surgery for single brain metastases [47]. Only one randomized trial compared SRS in one arm with surgery and WBRT in the second arm. Patients aged between 18 and 80 years harboring a single, resectable metastasis ≤3 cm.
were randomly assigned to microsurgery plus WBRT or gamma knife surgery alone. Local control rates at 1 year were 82% in the combined group and 96.8% in the radiosurgery group [35]. Therefore, there is no evidence of superiority of a surgical approach over SRS. WBRT was able to reduce the local failure rate and prolong the time to any brain failure for both local modalities [1, 27, 30, 37] but did not influence overall survival. Therefore, indication for WBRT should be individually discussed for every patient.

Currently, some investigations focus on SRS of the postoperative resection cavity and replacement of WBRT in patients with an oligometastatic disease [45]. Wang et al. recently published an approach with hypofractionated SRT (8 Gy in three fractions) for patients with large cerebral resection cavities [51]. Median overall survival for 37 patients with large cerebral metastasis was 5.5 months, which is inferior to the results of other investigators. Another group published a single dose stereotactic approach at a median follow-up of 12.7 months in a local control of 16 out of 18 patients treated [26]. Whether SRS of the postoperative surgical cavity can replace WBRT was under investigation in a randomized prospective trial [43].

**Brain glioma**

Primary brain gliomas are generally treated by surgery. Depending on the histology, further adjuvant therapy may be indicated. Chemotherapy, radiation therapy, or a combination of both are applied as postoperative treatment concepts. SRS or fractionated stereotactic radiotherapy is rarely performed in the primary setting. A current publication performed SRS with a median margin dose of 15 Gy in patients for recurrent or unresectable pilocytic astrocytoma [20]. Eighteen patients with 20 lesions were treated, 56% of the patients had previously received fractionated linac-based radiotherapy. The median follow-up was 8 years and the 10 year overall survival was 71%.

Prior radiotherapy was associated with an inferior clinical result according the examined end-points, interestingly...
the tumor-related symptoms improved in nine out of 11 patients after therapy. The authors did not see late radiation morbidity.

In contrast to the primary treatment situation, stereotactic concepts are often used in locally recurrent malignant glioma, where surgery is associated with high morbidity. Risks of radiation-induced side effects increase with an increasing dose and treatment volume, hence SRS is limited to smaller lesions and lower doses as patients already receive one course of radiation therapy. Alternatively, hypofractionated stereotactic radiotherapy can be an option [44]. This concept allows the exploitation of the radiobiological advantage of fractionation, reducing the treatment time compared to a regular fractionation of 1.8 or 2.0 Gy and combining radiotherapy with chemotherapy. For recurrent high-grade glioma, radiochemotherapy may further increase the treatment efficiency. There are many studies delivering hypofractionated SRS with doses between 3 and 5 Gy per fraction for local relapse after prior conventional radiotherapy doses of 60 Gy [9, 14, 15, 18]. The resulting overall survival after hypofractionated stereotactic re-irradiation ranges from 10 months for high-grade tumors to 20 months for low-grade lesions. Radiation-related toxicity was higher in the 5 Gy fraction group by 10% as compared to the 3 Gy group (about 1%). Based on these data, fractionated radiotherapy is a good treatment option for the recurrent clinical situation in malignant gliomas. However, we wish to state that the current prospective data of a phase III study demonstrating the benefit of re-irradiation is lacking.

Arteriovenous malformation (AVM)

Inoperable or incomplete resected AVMs can be treated with SRS in order to obliterate the complete lesion. As AVMs are benign lesions, radiotherapy has to be performed with great caution. Complex treatment integrating CT, MRI, and digital subtraction angiography and a frame-based fixation device are necessary for the most accurate treatment delivery. Sophisticated algorithms for dose calculation and high-resolution collimators are necessary to perform SRS. In a current publication of Han et al. [21], AVMs were divided into small (<4 cm³), medium (4–14 cm³), and large (>14 cm³) sized lesions. Over 200 patients with a follow-up of more than 2 years were evaluated. For small and medium size lesions, doses of 25 Gy were applied, and 10 Gy were applied for large lesions. However, the dose prescription was not uniform and ranged between 10.0 and 25.0 Gy for all sizes. Overall obliteration rate was 66.4%, with 12.5% for large AVMs, and 81.7% and 53.1% for small and medium size lesions, respectively. Particularly for medium-sized AVMs, a high rate (33.3%) of postradiosurgery imaging (PRI) changes was evident. For small AVMs, the PRI changes were 9.5%, and 11.4% for large AVMs. Various working groups were able to confirm these findings [22, 55–57].

Functional radiosurgery

Functional neurosurgery has been established over the years for movement disorders, pain syndromes, psychiatric illness, or trigeminal neuralgia. In previous decades, initial clinical studies, based on animal experiments, were performed to use functional stereotactic radiosurgery for the above-mentioned indications. Highly focused radiation is a non-invasive method to create a necrotic lesion in the brain. Functional radiosurgery needs highly precise imaging and therefore the development of MRI, functional MRI imaging, and exact matching algorithm between these image modalities are essential [29, 54]. Furthermore, very small collimators (4–8 mm at isocenter) and high single doses between 100 and 200 Gy were necessary for this kind of treatment [23, 28, 54]. Treatment of trigeminal neuralgia by radiosurgery has become a common indication in the last few years [31, 36, 39, 42]. This technique can achieve comparable results as more invasive treatment techniques for facial pain (Figure 2). In the treatment of trigeminal neuralgia, lower doses can be used (range 70–90 Gy) [53]. For the other indications mentioned above, functional radiosurgery is still an experimental method and only limited data is currently available [4, 23, 28].

Spinal metastasis and primary tumors of the spine

Currently, radiosurgery can be established in many extracranial anatomic sites and indications. Extracranial sites have a high impact for the future development of stereotactic radiosurgery. It is currently unclear whether a single fraction or a hypofractionated approach might be more effective. Body radiosurgery is used for lung, liver, or pancreatic lesions in either palliative or curative treatment concepts. In neurooncology, spinal metastases are of major interest. A current evidence-based review of Hall et al. reviewed 1388 patients with 1775 lesions treated with stereotactic body radiosurgery [19]. Over 50% of these patients received radiosurgery as a second course of radiotherapy. The pain control rate in the presented...
pooled analysis was 79%, with a local control rate of 90% and a myelopathy rate of 0.4%. The authors of the review concluded that 15–20 Gy in a single fraction was safe and effective. For lesions very close to the spinal cord, a hypofractionated approach should be considered.

Moreover, stereotactic radiosurgery is increasingly utilized for the treatment of the rare indication of primary spinal tumors. The treatment is performed in malignant as well as benign lesions. An image-guided approach should be used and the number of fractions normally ranged from 1 to 5. A small series reported high local control rates with a good overall pain reduction and no subacute or long-term toxicity [5, 17].

**Summary**

Stereotactic radiosurgery and fractionated stereotactic radiotherapy are well established in a high number of neurooncological and neurological indications. Modern technologies discussed in this review are already able to improve results of SRS and SRT and will continue to do so, especially the integration of multimodality imaging in the daily clinical routine. Currently, different technical methods in clinical use are comparable regarding the clinical results of the various clinical indications. The technological advances allow high treatment flexibility, and therefore, new treatment indications can be established based on the new technologies. In the future, it has to be defined more clearly whether a single fraction, hypofractionated concepts, or fractionated stereotactic radiotherapy is more effective concerning the clinical results and side effects of the therapy. The main area of development for radiosurgery will be stereotactic body radiosurgery. More randomized clinical studies for all possible indications are needed in order to determine its use compared to standard fractionated radiotherapy. In technological development, the next step has been completed and proton or particle based stereotactic radiosurgery may have increased use in the future.

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**Figure 2** Magnetic resonance imaging planned stereotactic radiosurgery for trigeminal neuralgia (iPLAN; BrainLab, Munich, Germany).
References


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