Original article

Strahlenther Onkol 2014 · 190:521–532
DOI 10.1007/s00066-014-0648-7
Received: 21 January 2014
Accepted: 25 February 2014
Published online: 9 April 2014


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# Stereotactic radiosurgery for treatment of brain metastases

## A report of the DEGRO Working Group on Stereotactic Radiotherapy

## Stereotactic radiosurgery in brain metastases

### Definition and rationale

Stereotactic radiosurgery (SRS), which was introduced by the neurosurgeon Lars Leksell in 1951, is a radiation therapy method that is frequently used to irradiate small tumors in the brain and body. To date, different techniques exist (gamma-knife, modified linear accelerator, protons, robotic radiosurgery), which all share a number of common properties: An ensemble of convergent beams or arcs is used to target a circumscribed, well defined lesion. A high, typically nonuniform dose inside the planning target volume (PTV), a steep dose gradient at the margin, and a low dose outside is sought, and the radiation dose is applied within a single fraction. Target localization is referenced to an external or internal coordinate system, and every effort is made to either immobilize the target or to track its position during treatment.

Brain metastases represent an ideal target for radiosurgery [1]. They are typically well demarcated, have a limited size, do not move with respect to the skull, and infiltrate normal brain tissue only to a very limited extent, which is why the lesions do not contain normal brain tissue. This report defines the role of radiosurgery for treatment of brain metastases by summarizing the available evidence for patient selection, treatment techniques, dose prescription, adjuvant therapy, appropriate endpoints, and clinical endpoint.

### Evidence-based indications and clinical results

With increasing incidence, brain metastases occur in 20–40 % of patients suffering from primary solid extracerebral tumors [2], of which the most common primary tumor types are lung cancer (36–64 %), breast cancer (15–25 %), and melanoma (5–20 %) [3]. Brain metastases represent the most frequent brain tumor and are an important cause of morbidity and mortality [4, 5]. Approximately 40–50 % of patients present with a single brain metastasis, whereas in 50–60 % of patients multiple lesions are diagnosed [2]. In the majority of patients, effective palliation is transient as median survival is restricted to 6–7 months [6, 7], although subsets of patients can survive for prolonged periods. Overall survival seems mainly determined by the activity of extracerebral disease as well as effective systemic treatment options [8, 9].

Treatment of metastatic tumors to the brain continues to be a significant challenge in attempting to prevent disease progression, deterioration of the neurological status, and quality of life and in trying to limit treatment-associated morbidity. Historically, the best possible supportive care or whole-brain radiotherapy (WBRT) were the standard of care [4] aiming at temporary symptom relief. For WBRT, efficacy in symptom relief but also in prolongation of the median survival time by 3–6 months is well documented [2, 10]. Both options are still valid for patients with unfavorable prognostic factors. With improved imaging possibilities for diagnosing patients with minimal or no symptoms, and better systemic treatment options, the focus of treatment changed from symptom management to prolonged local tumor control but also to avoiding long-term side effects. To date, microsurgical approaches and SRS, both proved to be safe and efficient, offer alternative treatment options that potentially meet these concerns.

However, the number of randomized clinical trials performed to evaluate the therapeutic options for brain metastases is still limited, leaving evidence-based management of this condition to be an active field of clinical research. In addition, the limited number of patients included in these trials, the heterogeneity of patient populations, and the dominance of patients with relatively good prognostic criteria limit the conclusions that can be drawn from these trials.

## Stereotactic radiosurgery as boost to whole-brain irradiation

Historically, SRS was first added to WBRT to locally enhance the dose to the lesions ("boost") aiming at an optimized local control. The benefit of adding SRS to WBRT was investigated in three prospective trials (two fully published, one abstract) [11–13].

The first trial was conducted by the Radiation Therapy Oncology Group (RTOG) [11] randomizing 333 patients with one to three newly diagnosed brain metastases to either WBRT or WBRT followed by SRS boost. Patients were stratified by number of metastases and status of extracranial disease. Primary endpoint was survival; secondary endpoints were tumor response and local control rates, overall intracranial recurrence rates, cause of death, and performance measurements. The SRS boost improved survival in patients with a single brain metastasis (median survival time 6.5 vs. 4.9 months; $p=0.0393$), a recursive partitioning analysis (RPA) class 1 ($p<0.0001$), or a favorable histological status ($p=0.0121$). The addition of SRS for patients with a Karnofsky Performance Scale (KPS) score of ≥70 lowered the rate of local failures [hazard ratio (HR)=0.27; 95 % confidence interval (CI)=0.14–0.52], statistically significantly improved the KPS score at the 6-month follow-up (43 vs. 27 %; $p=0.03$), and allowed for the administration of decreased doses of steroids.

Kondziolka et al. [12] randomized patients with two to four brain metastases to WBRT alone or WBRT + radiosurgery. The study was stopped at an interim evaluation at 60 % accrual (27 patients). The rate of local failure at 1 year was 100 % after WBRT alone but only 8 % after WBRT + SRS. The median time to local failure was 6 months after WBRT alone in comparison to 36 months after WBRT + SRS ($p=0.0005$). The median time to any brain failure was improved in the radiosurgery group ($p=0.002$). Patients who received WBRT alone lived a median of 7.5 months, while those who received WBRT + SRS lived 11 months ($p=0.22$). Survival did not depend on histology or number of metastases, but was related to the extent of extracranial disease ($p=0.02$). There was no neurologic or systemic morbidity related to additional SRS.

A meta-analysis [14] of these three randomized controlled trials revealed no general difference in overall survival (HR=0.82; 95 % CI=0.65–1.02), but a significant survival benefit after WBRT + SRS was found in a subgroup of patients with single brain metastasis (6.5 vs. 4.9 months; $p=0.04$) and in RPA class I patients in the RTOG 9508 trial (11.6 vs. 9.6 months) [11, 14]. Also, only Andrews et al. [11] reported disease-specific survival and found no significant difference in the risk of death form cerebral metastases in both treatment groups. Treatment-related morbidity did not significantly change through the addition of SRS to WBRT, with common side effects being skin toxicity, nausea/vomiting, and CNS toxicity/deficit, whereas neurocognition and quality of life (QoL) were assessed adequately in neither trial [14].

Wang et al. [15] included 463 patients with one to six metastases (diameter <4 cm) and KPS score of 40–90 in a retrospective cohort study. The study differs from many other evaluations, as patients with unfavorable prognostic factors were included [2]. The study confirmed in this patient collective similar local control rates after 1 month (95.6 vs. 88.3 %) in both treatment groups, but the median survival significantly favored the addition of SRS (91 vs. 37 weeks). Another large retrospective cohort study was published by Sanghavi et al. [16] comparing endpoints of 502 patients with historical controls based on RPA of an RTOG database. The study reveals statistically significant improvement in survival of patients in all three RPA classes by the addition of SRS, indeed also suggesting a survival benefit of WBRT + SRS even for patients with unfavorable prognostic factors [2].

## Stereotactic radiosurgery as stand-alone therapy for brain metastases

After proving its efficacy in achieving local tumor control in the treated volume, SRS was used as a stand-alone treatment option in patients with oligometastases (one to four metastases) in the brain.

The question of whether additive WBRT is needed to destroy microscopic tumor spread in the infiltrated zone around the treated metastasis and distant microscopic intracranial lesions was addressed in two randomized trials [17, 18], one prospective cohort study [19], and several retrospective investigations [20–28]. Studies analyzed survival, local control, and/or brain control as primary endpoints after SRS alone or SRS plus additive WBRT. Some investigations, including one randomized trial, included neurologic endpoint and neurocognition as secondary endpoints [29]. Two randomized trials evaluated primarily functional independence [18] and neurocognition [30], with tumor control and survival being secondary endpoints.

In the Japanese trial [17], 132 patients with one to four metastases were randomly assigned to receive WBRT + SRS or SRS alone. The SRS dose was reduced by 30 %, when added to WBRT, whereas the SRS dose if used alone and the WBRT dose were standard. The study did not show a significant difference between the treatment groups in terms of median survival (8.0 months for the SRS group vs. 7.5 months; $p=0.42$), and neurologic cause of death (19.3 % for the SRS group vs. 22.8 %; $p=0.64$) [17]. However, the 12-month actuarial rate of developing new brain metastases was 63.7 % in the SRS-alone group, but significantly reduced in the WBRT + SRS group (41.5 %; $p<0.01$) and the 1-year actuarial local control rate was reduced in the SRS group (72.5 % for the SRS group vs. 88.7 %; $p=0.002$). The authors did not find significant differences in normal tissue complications. The study was criticized for a large bilateral crossover rate in the intent-to-treat analysis [2].

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# Stereotactic radiosurgery for treatment of brain metastases. A report of the DEGRO Working Group on Stereotactic Radiotherapy


## Abstract

**Background.** This report from the Working Group on Stereotactic Radiotherapy of the German Society of Radiation Oncology (*Deutsche Gesellschaft für Radioonkologie*, DEGRO) provides recommendations for the use of stereotactic radiosurgery (SRS) on patients with brain metastases. It considers existing international guidelines and details them where appropriate.

**Results and discussion.** The main recommendations are: Patients with solid tumors except germ cell tumors and small-cell lung cancer with a life expectancy of more than 3 months suffering from a single brain metastasis of less than 3 cm in diameter should be considered for SRS. Especially when metastases are not amenable to surgery, are located in the brain stem, and have no mass effect, SRS should be offered to the patient. For multiple (two to four) metastases—all less than 2.5 cm in diameter—in patients with a life expectancy of more than 3 months, SRS should be used rather than whole-brain radiotherapy (WBRT). Adjuvant WBRT after SRS for both single and multiple (two to four) metastases increases local control and reduces the frequency of distant brain metastases, but does not prolong survival when compared with SRS and salvage treatment. As WBRT carries the risk of inducing neurocognitive damage, it seems reasonable to withhold WBRT for as long as possible.

**Conclusion.** A single (marginal) dose of 20 Gy is a reasonable choice that balances the effect on the treated lesion (local control, partial remission) against the risk of late side effects (radionecrosis). Higher doses (22–25 Gy) may be used for smaller (< 1 cm) lesions, while a dose reduction to 18 Gy may be necessary for lesions greater than 2.5–3 cm. As the infiltration zone of the brain metastases is usually small, the GTV–CTV (gross tumor volume–clinical target volume) margin should be in the range of 0–1 mm. The CTV–PTV (planning target volume) margin depends on the treatment technique and should lie in the range of 0–2 mm. Distant brain recurrences fulfilling the aforementioned criteria can be treated with SRS irrespective of previous WBRT.



## Keywords

Brain tumor · Metastases · Stereotactic radiosurgery · Whole-brain radiotherapy · DEGRO


# Stereotaktische Radiochirurgie zur Behandlung von Hirnmetastasen. Ein Bericht der Deutschen Gesellschaft für Radioonkologie (DEGRO)


## Zusammenfassung

**Einleitung.** Dieser Bericht der Arbeitsgruppe „Stereotaktische Radiotherapie" der Deutschen Gesellschaft für Radioonkologie (DEGRO) gibt Empfehlungen für die Behandlung von Patienten mit Hirnmetastasen mittels stereotaktischer Radiochirurgie (SRS). Internationale Leitlinien werden berücksichtigt und, wenn nötig, ergänzt.

**Ergebnisse und Diskussion.** Die wichtigsten Empfehlungen lauten: Patienten mit soliden Tumoren außer Keimzelltumoren und kleinzelligem Bronchialkarzinom und einer Lebenserwartung von mindestens 3 Monaten sollten bei Vorliegen von singulären Hirnmetastasen < 3 cm für die SRS in Betracht gezogen werden. Insbesondere bei inoperablen Metastasen, Hirnstammmetastasen und bei Metastasen ohne Masseneffekt sollte die SRS angeboten werden. Patienten mit multiplen Metastasen (2–4), alle mit einem Durchmesser < 2,5 cm, sollten bei einer Lebenserwartung von > 3 Monaten ebenfalls primär eine SRS (statt einer Ganzhirnbestrahlung, „whole brain radiotherapy", WBRT) erhalten. Eine adjuvante WBRT nach SRS von 1–4 Hirnmetastasen erhöht die lokale Kontrolle und reduziert die Häufigkeit distanter Hirnmetastasen, verlängert aber das Überleben im Vergleich zu einer primären alleinigen SRS und Rezidivtherapieverfahren nicht. Da die WBRT das Risiko von neurokognitiven Spätfolgen mit sich trägt, erscheint es sinnvoll, sie solange wie möglich zurückzustellen.

**Schlussfolgerung.** Eine Einzeldosis von 20 Gy stellt einen sinnvollen Kompromiss zwischen dem zu erreichenden therapeutischen Effekt (lokale Kontrolle, partielle Remission) und den möglichen Spätnebenwirkungen (Strahlennekrose) dar. Höhere Dosen (22–25 Gy) können für kleinere Läsionen (< 1 cm) verwendet werden, bei größeren Metastasen (> 2,5–3 cm) ist evtl. eine Dosisreduktion auf 18 Gy erforderlich. Da die Infiltrationszone von Hirnmetastasen klein ist, sollte der Abstand zwischen GTV („Gross Tumor Volume") und CTV („Clinical Target Volume") 0–1 mm betragen. Der Abstand zwischen CTV und PTV („Planning Target Volume") sollte abhängig von der Bestrahlungstechnik 0–2 mm betragen. Distante Hirnmetastasen, welche die genannten Kriterien erfüllen, können auch nach vorangegangener WBRT mittels SRS behandelt werden.



## Schlüsselwörter

Hirntumor · Metastasen · Stereotaktische Radiochirurgie · Ganzhirnbestrahlung · DEGRO


In the EORTC 22952-26001 trial [18], 359 patients with one to three brain metastases of solid tumors with stable systemic disease or asymptomatic primary tumors and WHO performance status of 0–2 were treated with complete surgery or radiosurgery and randomly assigned to adjuvant WBRT or observation. Consistent with the aforementioned data, in the EORTC trial, overall survival was similar in the WBRT and observational arms (median, 10.9 vs. 10.7 months, respectively; $p = 0.89$), however, neurologic death occurred more frequently in the observational arm (44 % without WBRT vs. 28 % with WBRT; $p = 0.002$) [2, 18]. WBRT reduced the 2-year relapse rate both at initial sites (radiosurgery, 31–19 %; $p = 0.040$) and at new sites (radiosurgery, 48–33 %; $p = 0.023$). Acute toxicity of WBRT was generally mild, 2 % of patients had grade 3 late effects (SOMA–LENT scale), and 1 % grade 4 late effects without clear differences between treatment arms.

Chang et al. [30] prospectively evaluated neurocognition in 58 patients with one to three newly diagnosed brain metastases. Patients were randomly assigned to SRS + WBRT or SRS alone and stratified by RPA class, number of brain metastases, and radioresistant histology. The trial was terminated according to stopping rules. At the 4-month follow-up, 13 % of patients in the SRS-alone group died, and 29 % in the group that received SRS + WBRT. At 1 year, 73 % of patients in the SRS + WBRT group were free from CNS recurrence compared with 27 % of patients who received SRS alone ($p = 0.0003$). Comparably to the Aoyama trial and the EORTC trial, tumor growth outside of the SRS volume was more frequent in the SRS-only group (29 vs. 11 patients), but death from neurological cause was comparable between both groups (26 % SRS and 25 % WBRT + SRS patients). Two patients in the SRS-alone group were diagnosed with radiation necrosis.

In the prospective cohort trial by Li et al. [19], two of three treatment arms evaluated SRS vs. SRS + WBRT, recruiting exclusively patients with a single brain metastasis of small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC). The study did not reveal a statistically significant difference concerning median survival (9.3 vs. 10.6 months) or recurrence and progression at the treated site. Distant brain relapse was not investigated.

Most retrospective studies investigating patients with one to four brain metastases of varying histologies confirm comparable patient survival after SRS or SRS + WBRT, which range between 7 and 13.9 months for SRS vs. 6.4 and 14.9 months for SRS + WBRT [2]. Consistent with the prospective studies, most retrospective series do not reveal a significant difference between the two treatment strategies in terms of local recurrence at the sites treated with SRS [2, 19, 27, 28]. The majority of studies also showed a significantly greater risk of distant brain relapse or increased recurrence rates in the brain, if WBRT is avoided [2, 20, 22, 24, 25, 28]. Salvage therapy is therefore required more frequently for patients treated exclusively with SRS [17, 18, 20].

## Neurocognitive side effects of whole-brain irradiation added to radiosurgery

The study by Aoyama et al. [29] investigated neurocognition by use of the Mini Mental State Examination (MMSE), which can reliably test dementia [31] but is rather insensitive to all but the most severe cognitive dysfunction. A bi-phasic difference was found in the long-term follow up: In the first 18 months, the MMSE results were better in the WBRT + SRS group. However, this trend was reversed in the long-term survivors [5]. Of the 82 patients with a baseline MMSE score of ≥ 27 or whose baseline MMSE score was ≤ 26 but had improved to ≥ 27 after the initial brain treatment, the 12-, 24-, and 36-month actuarial free rate of the 3-point drop in the MMSE was 76.1, 68.5, and 14.7 % in the WBRT + SRS group and 59.3, 51.9, and 51.9 % in the SRS-alone group, respectively. The average duration until deterioration was 16.5 months in the WBRT + SRS group and 7.6 months in the SRS-alone group ($p = 0.05$) [29]. The data suggest that during the first month tumor control in the brain was important to stabilize neurocognitive function in most patients. However, WBRT had deleterious effects on the neurocognitive function of long-term survivors (> 24 months after treatment) [29]. It is important to note that of the 44 patients in the study who survived longer than 1 year, MMSE data were available for 28 patients only, so that these conclusions are based on a small patient number. The authors did not find significant differences in systemic and neurologic functional preservation of patients treated with SRS alone vs. SRS + WBRT [29].

One randomized study [30] investigated neurocognition by means of a test battery as the primary endpoint in 58 patients after SRS or SRS + WBRT in patients with one to three newly diagnosed cerebral metastases. The trial was stopped based on the observation of a high probability (96 %) that patients assigned to receive SRS + WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52 %) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24 %). The study has been criticized as no long-term follow-up was available beyond 4 months, which seems premature for understanding the full trajectory of neurocognitive changes following WBRT [5]. Secondly, the patients were not stratified to groups based on cognitive performance (and there was a trend toward worse baseline cognition in the WBRT + SRS group). Moreover, patients in the SRS + WBRT group survived significantly shorter than in the SRS group, suggesting patient selection bias, which might also be an explanation for the observed effect [5]. Evaluation of performance status or neurologic status was not provided.

The EORTC22952-26001 study focuses on the duration of functional independence after surgery or radiosurgery of brain metastases with or without WBRT as measured by the time to WHO performance status deterioration to more than 2 (primary endpoint) [18]. The authors found that WBRT failed to improve the duration of functional independence with a median time to WHO performance status deterioration of 10.0 months (95 % CI, 8.1–11.7 months) after observation and 9.5 months (95 % CI, 7.8–11.9 months) after WBRT ($p = 0.71$) [18]. The study additionally investigated quality of life and cognitive function with the EORTC QoL-C30 and BR20 brain cancer module questionnaires considering: global health status; physical, cognitive, role, and emotional functioning; and fatigue. Compliance was only 45.0 % at 1 year; thus, only the first year after treatment was analyzed. Overall, patients who received WBRT reported worse HRQOL scores than the group of patients receiving SRS or surgery. The differences were statistically significant and clinically relevant mostly during the early follow-up period (for global health status at 9 months, physical functioning at 8 weeks, cognitive functioning at 12 months, and fatigue at 8 weeks) [32].

## Radiosurgery versus surgery

Radiosurgery and surgery are alternative and partly complementary treatment options in patients with a limited number of brain metastases (usually one to three me-

tastases), both being standard options in this group of patients [2, 33]. The advantages of SRS over neurosurgical resection are the noninvasive approach and the possibility to treat multiple lesions even on an outpatient basis [10]. Also, patients with significant comorbidities benefit from SRS. Radiosurgery might be preferred in patients with lesions of < 3–3.5 cm in diameter (volume < 15 ml) without mass effect (less than 1 cm midline shift) [2, 34, 35] especially if located in eloquent brain regions or surgically inaccessible regions. SRS is effective in radiosensitive as well as radioresistant histologies due to the single high radiation dose [2, 12, 36, 37] although differences seem to exist [38].

SRS and surgery have only been compared for efficacy and toxicity in one small randomized trial where treatment results did not differ in terms of survival, neurological death rates, and freedom from local recurrence [39]. Retrospective series as well as results from the EORTC 22952-26001 study suggest at least equal efficacy in achieving local tumor control (60–90 %) and also in overall patient survival [2, 10, 12, 18, 20, 40–46]. Although not designed to test efficacy, in the EORTC trial, the probability for relapse at the initial sites at 2 years was 31 % after SRS but 59 % after surgery. The results of all investigations are biased by the process of assigning patients to one or the other treatment, thus direct comparison is hardly possible.

Surgical treatment is required for histological confirmation of the malignancy and in cases of large metastasis in the posterior fossa, brainstem compression, and symptomatic hemorrhagic metastases [47]. Surgery also has advantages if mass effects cause symptoms and it is often preferred for patients with single metastasis, controlled extracranial disease, and good performance status [48]. SRS and surgery can be combined in cases of one large (symptomatic) metastasis and a limited number of small metastases.

## Radiosurgery to the resection cavity

Several retrospective series assessed the efficacy and safety of postoperative SRS to the resection cavity [49] aiming at an enhanced local tumor control but also at avoidance of the late effects of WBRT [37, 50–54]. Such a multidisciplinary treatment regime leads to 1-year local control rates of 70–93 %, which is comparable to results after surgery followed by WBRT. Median survival was 12–18 months with a 1-year incidence of new metastases in the brain of 45–60 % [37]. Fractionated regimes (FSRT) have been used especially for resection cavities > 3 cm, building on the potential advantages of fractionation with respect to radiobiology and normal brain protection [37]. Such regimes yield comparable results in terms of local control and survival as compared to single-dose SRS with favorable toxicity rates. Challenges of postoperative SRS include the optimal definition of the target volume (margins of 1–10 mm around the resection cavity are reported [37, 50]), total dose, and fraction dose, and definition of the maximal volume, which can be safely treated. Postoperative SRS or FSRT in selected patients seems to be an effective option for achieving local control and maintaining acceptable functional independence with low toxicity; however, it carries the risk of development of new distant metastases in the brain. This treatment option thus also warrants assessment in prospective clinical trials [37, 50–54].

## Radiosurgery for recurrent metastases

The decision of treating recurrent lesions should mainly be guided by the overall clinical situation of the patient at the time of recurrence, as multiple options for salvage are available but no randomized trials examining retreatment of brain metastases help in making the decisions [10, 55, 56]. Size, timing, location histology, performance status, patient age, and extracranial disease status should all be considered when choosing the appropriate modality. Surgery can be indicated in progressive and/or hemorrhagic lesions causing mass effect [56].

In cases of isolated brain recurrence, salvage SRS is possible and produces high local control rates. In patients undergoing SRS for recurrence after initial WBRT, 1-year local control rates of 70–90 % and 2-year rates of 60–84 % can be achieved [25, 57, 58]. Treating recurrences located at a site previously treated with SRS with a second SRS carries an increased risk of radionecrosis of up to 50 % [10, 59, 60]. On the contrary, in patients with multiple recurrent lesions, poor performance status, or systemic disease progression, WBRT may be the preferred salvage option. Of note, the effect of salvage treatment options such as serial SRS or WBRT on neurocognition or functional independence has not been evaluated.

## Recommendations for clinical practice of radiosurgery in brain metastases

### Physical aspects of stereotactic radiosurgery in brain metastases

In SRS, large single doses of typically 15–25 Gy are applied to the target volumes. Such high doses require highly conformal and focal dose distributions and precise localization and targeting with high demands on the equipment used and the methods applied. Comprehensive quality assurance is mandatory [61]. Only medical physicists with experience in SRS should perform radiosurgical procedures. The responsibilities of the medical physicist cover many aspects of radiosurgery and are laid out in a recent practice guideline for the performance of SRS of the American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) [62].

Today, a variety of different systems and methods are used for SRS in brain metastases. The procedure is performed either by frame-based stereotactic guidance or frameless by image-guided radiation therapy techniques. MV bremsstrahlung photons from a linear accelerator, gamma-ray photons from a stereotactic cobalt-60 unit, or protons or ions from a particle accelerator can be used [61]. Special attention is required in beam definition, beam guidance, and dosimetry.

In photon fields, the beam penumbra is minimized by use of (tertiary) collimators mounted close to the patient and by small focal spot sizes or small source diameters. A set of circular collimators with fixed apertures or a micro-multileaf colli-

mator with leaf width of less than 3 mm [63] is used for precise beam definition. Focal irradiation is used to concentrate the dose in the target volume and minimize the dose in the surrounding brain tissue. Both isocentric and non-isocentric beam-delivery techniques can be used for focusing. A high targeting accuracy of the focal beam distribution of 1–1.5 mm or better [64] is required as well as a high precision of the beam superposition. If isocentric irradiation is used, the diameter of the isocenter sphere may not exceed 1–2 mm, and for linear accelerators the distance axes of rotation of the gantry and couch should be less than 1 mm [65]. Conformal fields, multiple isocenters, and intensity modulation can be used for dose conformation to the target volume. Non-isocentric beam application can be regarded as a special technique for intensity modulation. Several guidelines and DIN standards for quality assurance in SRS are available [61, 65–69] as for IMRT using fluence modulation [70–73].

In the dosimetry of small photon fields the volume effect, i.e., the averaging of the signal within the sensitive volume of the dosimeter may cause severe deviations in output factors, dose profiles, and depth-dose curves from the true values. Therefore, small diode detectors are frequently used for dose measurements. A recent report of the Institute of Physics and Engineering in Medicine (IPEM) [74] as well as the upcoming DIN standard (DIN 6809-8) [75] give detailed guidance in performing accurate measurements in small-field MV photon beams.

Most important and common to all methods of SRS is an end-to-end test (also termed complete system integration test) including imaging, localization, dose planning, targeting, and beam delivery using an anthropomorphic phantom. A variety of different solutions adapted to the radiosurgical equipment are available [61, 65–68]. Unfortunately, the evaluation of the end-to-end test still lacks standardization. This limits comparability between different systems and institutions. There is an ongoing debate over whether submillimeter accuracy is possible in radiosurgery [76]. As stated by the ACR and ASTRO guidelines, a targeting accuracy to intracranial metastases of approximately 1 mm must be aimed at [62].

## Patient immobilization and set-up

The main goal in SRS is to deposit a high dose to a defined target and to reduce the dose to the surrounding healthy tissue with the use of a steep dose gradient [33]. The basic requirement to achieve this goal is to assure a high level of accuracy in patient immobilization and set-up. Patient immobilization is of utmost importance to minimize intrafractional error. The following aspects have to be addresses separately: (1) accurate localization, (2) mechanical precision, (3) accurate and optimal dose distribution, and (4) patient safety [61]. It is noteworthy that errors in localization contribute most to treatment error [69, 77].

Historically, radiosurgery has exclusively been performed using an invasive head frame. With such an approach, the frame is fixed invasively onto the patient's skull typically using four metal screws. A fiducial reference box is fixed on the frame during imaging to provide stereotactic coordinates. Based on these coordinates the target can be localized. This invasive approach enables an effective patient immobilization and simultaneously accurate target localization. A substantial disadvantage is the invasiveness resulting in patient discomfort caused by pain, risk of bleeding and infection, and the need of local anesthetics and anxiolytics. Further, an invasive technique is only acceptable for single-fraction radiosurgery.

In recent years, new technical developments were introduced, such as noninvasive precise mask systems, bite blocks, and image guidance including orthogonal planar x-ray techniques [78, 79] and cone beam computed tomography (CT) [80, 81]. Bite-block devices (i.e., HeadFix®- or EXtend™-system, Elekta, Stockholm, Sweden) are another innovative noninvasive approach. With the help of a dental impression, an individual dental mold is placed into the mouth and is fixed applying a vacuum between the bite block and the hard palate. This approach can be combined with a revocable thermoplastic mask to optimize patient positioning.

Considering patient movement, two aspects are of importance: the interfractional and the intrafractional motion. With immobilization systems such as uniframe/monolayer thermoplastic masks systems (i.e., Raycast-HP mask system, Orfit Industries), an intrafractional motion of 1.6± 0.8 mm is feasible as reported by Fuss et al. [82], but other authors reported inferior intrafractional errors up to 3.9 mm [81, 83, 84]. Dedicated mask systems, such as the BrainLab mask system, may contribute to optimizing the overall accuracy. Gaevert et al. reported a 1.9-mm overall accuracy using a dedicated mask system (BrainLab™) [85].

The interfractional positioning based on stereotactic coordinates alone is poor. Baumert et al. [83] analyzed the accuracy and reproducibility of patient repositioning using a stereotactic mask in combination with dental fixations. The overall isocenter deviation was 3.7 mm using the mask immobilization alone. Remarkably, by using a bite block in combination with a mask, the isocenter deviation was reduced to 2.2 mm. Using a comparable system, Minniti et al. even reported a very high accuracy of 0.5 mm±0.7 mm [86]. These excellent data (without using an image-guided technique) are in contrast to the other data and should be confirmed.

To optimize the overall patient set-up accuracy, which is the main determinant of interfractional motion, image guidance seems to be the best option [81]. The advantage of adding image guidance was demonstrated by Guckenberger et al. [84]. The set-up error could be reduced from 3.9 ± 1.7 mm to 0.9 ± 0.6 mm by adding image guidance, where a residual deviation of 0.9 mm was caused by the intrafractional movement. Using image-guidance techniques, the error is reduced to the mechanical error of the image-guidance device. Consequently, the authors stated that "intra-fractional patient movement is considered as the weakest link in frame-less image-guided radiosurgery" [84].

Recently, Ramakrishna et al. [87] compared the patient set-up and intrafraction motion using frame-based radiosurgery versus a frameless image-guided radiosurgery system and concluded that the

**Table 1** Accuracy of different noninvasive stereotactic immobilization systems

| Immobilization system | Positioning technique | Overall set-up error (mean ± SD) | Author |
|---|---|---|---|
| Dedicated thermoplastic mask (BrainLab) with bite block | Stereotactic coordinates, localizer box | 0.5 mm ± 0.7 mm | Minniti et al. [86, 88] |
| Thermoplastic mask (mono- or dual layer) | Cone-beam CT | 0.9 mm ± 0.6 mm | Guckenberger et al. [84] |
| Dedicated thermoplastic mask (BrainLab) with bite-block | Stereotactic coordinates, localizer box | 1.16 ± 0.68 | Theelen et al. [89] |
| Dedicated thermoplastic mask (BrainLab) | Stereotactic coordinates, localizer box | 1.7 ± 0.83 | Theelen et al. [89] |
| Thermoplastic mask with bite block | Stereotactic coordinates, localizer box | 2.2 mm ± 1.1 mm | Baumert et al. [83] |

overall system accuracy of the frameless, image-guided system is similar to that seen for invasive frame-based approaches. In summary, with the available noninvasive immobilization techniques, SRS can be performed with high accuracy. Distinct differences in overall treatment accuracy exist depending on the immobilization and localization procedure.

In our opinion, the overall set-up accuracy should be held within 2.0–2.4 mm [61]. This can be achieved using the following techniques (examples; ◘ **Table 1**):

## Patient selection and staging

For patients with brain metastases, treatment decisions should be based on age, performance status, and extracranial tumor activity, as these are the dominant factors predicting live expectancy. Median life expectancy can be estimated from a number of prognostic scores [6, 90]. Patients with single brain metastases of < 3 cm and two to four metastases all of < 2.5 cm and a life expectancy of > 3 months (median of the prognostic group) should be offered radiosurgery. In patients with poor performance status, systemic disease progression, or a life expectancy of < 3 months, radiosurgery may still be a treatment option for short-term palliation. Metastases from radiosensitive tumors (germinoma, lymphoma, small cell lung cancer) should be treated with WBRT first.

The maximum volume of lesions that can be safely treated is still unclear so that currently, a diameter of lesions of 3–3.5 cm is accepted as the upper bound for single-fraction treatments. Some authors have investigated fractionated stereotactic radiotherapy (FSRT) in large lesions, but delivered the dose in multiple fractions to avoid excessive toxicity to adjacent tissues. Although further investigation of optimal fractionation schemes, doses, and volume effects is warranted, FSRT seems to be a safe and efficient option in lesions not amenable to SRS, which has comparable overall survival and progression-free survival with low treatment-related toxicity [91, 92].

The question of whether multiple (> 4) lesions should be treated with SRS is unsolved, although SRS is increasingly used in this group of patients [42, 93, 94]. Comparative studies of SRS or WBRT in this group of patients do not exist. Some retrospective series indicate that SRS can be safely applied due to its conformity and sharp dose gradients as long as established dose constraints to the normal brain are respected [10]. In one study, total treatment volume rather than the number of metastases was the most significant predictor of survival, so that the authors suggest using metastases volume to identify appropriate radiosurgery candidates [94]. In favor of treating multiple but small lesions with SRS are the high local tumor control, the possibility of repeated SRS for remote recurrences or new metastases even after WBRT, preservation of cerebral functions, short hospitalization, and the option to continue systemic chemotherapy [42].

Staging for extracranial disease including the primary tumor and other metastases should be done according to appropriate procedures valid for the different tumor entities. If the disease history and/or magnetic resonance imaging (MRI) findings are equivocal with respect to the diagnosis of brain metastases, a stereotactic biopsy of the brain metastasis is necessary.

## Target volume definition

For definition of the target volumes, contrast-enhanced MRI of the brain is considered necessary since MRI is more sensitive and specific than CT in detecting brain metastases [95–97]. For decision making, MRI images should be available in axial, sagittal, and coronal axes [98]. The diagnostic MRI sequences should include pre-gadolinium T1- and T2-weighted, post-gadolinium T1-, and FLAIR sequences. The standard dose of the gadolinium-based contrast agent is 0.1 mmol/kg body weight. A doubled dose may be helpful in uncertain cases [98]. A minimal field strength of 1.5 T and slice thickness of 2 mm are recommended. Anzalone et al. suggest a standardized MRI protocol for pretreatment and follow-up assessment of brain metastases radiosurgery [98].

The target volume definition should be based on MRI, coregistered with the radiation treatment planning CT. The planning CT slice thickness should be ≤ 2 mm. The integration of functional imaging and white matter tractography in stereotactic radiation treatment planning may be helpful in protecting eloquent areas, such as the motor cortex or parts of the optic pathway [99].

The gross tumor volume (GTV) should encompass the contrast-enhanced tissue in the planning CT and the MRI. The CTV should be defined with a margin of 0–1 mm added to the GTV, as the microscopic tumor invasion into the brain was found to be within this range from the solid tumor margin except in small-cell carcinomas [100]. A 1-mm margin added to the GTV to generate the PTV improved local control in one study, but in this series marginal doses of only 14 Gy were used [101]. Adding a 2-mm margin to the GTV to define the PTV resulted in increased local complications without improving local control [102].The PTV-to-CTV margin depends on the treatment technique as described below. In SRS with invasive fixation or other means to achieve submillimeter precision (robotic radiosurgery) it is general practice to use: GTV=CTV=PTV.

## Dose planning and normal tissue tolerance

Although the local control rate after SRS of brain metastases is generally high (60–90 %), there is disagreement regarding the risk of local recurrence at the treated site, which indicates the need for further optimizing the prescribed irradiation dose [2]. The dose–response relationship for local tumor control but also for normal tissue toxicity has been evaluated on the basis of the incidence of focal cerebral radionecrosis [103, 104], which occurs in 2–10 % of cases [104]. Neuroradiological changes such as progressive contrast enhancement on follow-up serial MRI can occur in up to 45 % of cases with the highest incidence 10–15 months after SRS [104–107].

The dose escalation trial RTOG 90-05 established the diameter of lesions to be directly correlated with the risk of side effects, especially radionecrosis and vasogenic edema. The maximum tolerated doses of single-fraction radiosurgery were 24 Gy, 18 Gy, and 15 Gy for tumors of ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter. However, the maximal tolerated dose in small lesions remained unclear, as for tumors of < 20 mm, the investigators' reluctance to escalate to 27 Gy, rather than excessive toxicity, determined the maximum tolerated dose in the trial [10, 38]. A median dose of 20 Gy in a single fraction has been prescribed to lesions of ≤ 2 cm in most published series, while dose escalation above 20 Gy resulted in improved local control at the expense of a higher complication rate [104, 105, 107, 108].

Predictive factors associated with a higher incidence of radionecrosis include total absorbed dose, fraction size, volume of the target, number of treated isocenters, and prescription isodose volume [104]. Normal brain tissue toxicity increases significantly with increasing radiation dose applied to volumes above 8–10 $cm^3$, where the volume of brain receiving 12 Gy (V12) seems to be the most relevant dosimetric parameter [37, 38, 107]. It was also found that the risk of brain necrosis increases if the volume of surrounding brain tissue irradiated with a single dose of 10 Gy or more exceeds a threshold of 10 ml [109].

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) trial confirmed a clear correlation between the target size and the risk of adverse events; however, substantial variation among reported endpoints prevented toxicity–risk predictions in this analysis [110]. Moreover, the dose effects on the most sensitive structures of the brain (optic pathways, cranial nerves, brainstem) should always be recorded, and recommended dose limits should not be exceeded [111].

## Isodose level and conformity index

The aim of treatment planning is high conformity of the dose distribution with the target volume (PTV), and a steep dose gradient on the edge of the PTV. Since the dose gradient is steepest at the level of 60–80 % of the maximal dose, these isodose levels are mainly used for dose prescription. The prescribed isodose should cover at least 95 % of the target volume and the Paddick conformity index [112], which is computed as (target volume within the prescribed isodose)$^2$/(prescription isodose volume * target volume), should not be less than 0.5–0.6.

## Dose planning for brain stem metastases

The steep dose gradients allow for the treatment of lesions that are directly adjacent to critical structure such as the brain stem. Metastases located within the brain stem occur in approx. 3–5 % of patients with brain metastases. Due to the increased surgical risk, SRS has become the standard of care [113]. Smaller treatment volumes correlate with improved survival in this patient group, which might be due to less pressure and distortion on the normal tissue but also due to the usually greater marginal dose leading to improved tumor control [113]. Vogelbaum et al. [114] found a local control of 85 % if a marginal dose of 25 Gy was applied, but only 49 % for a marginal dose of 18 Gy and 45 % for a marginal dose of 15 Gy.

There are no definitive criteria regarding normal tissue toxicity to the brain stem or even more subtle dose-volume effects or effects after hypofractionated treatments [115]. Sharma et al. [116] reported that exposition of 12 Gy to a volume of 0.01 $cm^3$ may lead to neurological deficits. Mayo et al. [113, 115] suggest a similar dose limit of 12.5 Gy. However, other authors have applied considerably higher marginal doses of 17.6–20 Gy without excessive toxicity [113]. Most reports agree that the benefits of treating brain stem metastases with SRS far outweigh the risk of treatment, which has proven safe and efficient and can reduce neurological deficits and increase patient survival [113].

## Patient monitoring and follow-up

Just before and after radiosurgery, steroids are applied to prevent perifocal edema. After SRS, patients should be scheduled for follow-up according to organ-specific guidelines. After radiosurgical treatment, most brain metastases remain stable or get smaller in the subsequent months [117]. However, some lesions may increase in size 3–6 months after treatment and new metastases may develop during this period. Interestingly, Patel et al. [117] found that the median survival of patients whose lesions temporarily increased in size after radiosurgery was superior to that of patients whose lesions remained stable or decreased in size.

Such follow-up is mainly important for response evaluation and early detection of new metastases, especially when WBRT is omitted during first-line therapy. Follow-up imaging should be based on contrast-enhanced MRI performed every 3 months. In case of expected early dissemination of new metastases to the brain (three to four metastases treated, melanoma, extracranial progression), the first imaging interval should be shortened to 6–8 weeks [56].

A reactive edema with consecutive worsening of the patient's condition can develop in the weeks after brain radiosurgery. This transient phenomenon is called "pseudoprogression" in glioma radio(chemo)therapy [118–121] and should be taken note of to avoid misinterpretations.

In case of enlarging, contrast-enhancing lesions with perifocal edema, it may be difficult to differentiate between tumor

recurrence and radionecrosis of the surrounding brain tissue. Analysis of the frequency of radionecrosis is complicated by the absence of imaging features that can reliably distinguish radionecrosis from tumor recurrence [104]. Magnetic resonance spectroscopy, positron emission tomography (including amino acid PET), single photon emission tomography, perfusion MR, or perfusion CT has not been fully validated for this purpose so that standards are not available. In special cases, the use of fluoroethyl-l-tyrosine-PET (FET-PET) may be helpful to differentiate between radionecrosis and true progression [122]. Recently, Galldiks et al. [123] found that the use of specific parameters of $^{18}$F-FET can differentiate local brain metastasis recurrence from radionecrosis with high accuracy. Although all methods have shown some advantages, there is no evidence that any of these modalities is superior in terms of sensitivity or specificity [104, 106, 124, 125]. Therefore, use of stereotactic biopsy for histological assessment of indistinguishable lesions in imaging studies remains the most reliable method to differentiate local tumor recurrence from radionecrosis after SRS [126].

## Consensus statements and guidelines

A number of official guidelines concerning the general management of brain metastases [4, 127–129] and reviews [33, 130, 131] or consensus statements [2, 132] focusing on SRS for brain metastases have been published.

## Recommendations

From the existing guidelines and clinical studies, the following recommendations can be made:

- For patients with brain metastases, treatment decisions should be based on age, performance status, and extracranial tumor activity, as these are the dominant factors predicting life expectancy. Median life expectancy can be estimated from a number of prognostic scores [6, 90].
- For single brain metastases less than 3 cm in diameter in patients with a life expectancy of more than 3 months, radiosurgery should be considered. Especially when metastases are not amenable to surgery, located in the brain stem, and have no mass effect, radiosurgery should be offered to the patient.
- For multiple (2–4) metastases—all less than 2.5 cm in diameter—in patients with a life expectancy of more than 3 months, radiosurgery should be used rather than WBRT.
- Adjuvant WBRT after radiosurgery for both single and multiple (2–4) metastases reduces the number of distant brain metastases and increases local control but does not prolong survival when compared with radiosurgery and salvage treatment. As WBRT carries the risk of inducing neurocognitive damage, it seems reasonable to withhold WBRT for as long as possible.
- A single (marginal) dose of 20 Gy is a reasonable choice that balances the effect on the treated lesion (local control, partial remission) against the risk of late side effects (radionecrosis). Higher doses (22–25 Gy) may be used for smaller (< 1 cm) lesions, while a dose reduction to 18 Gy may be necessary for lesions greater than 2.5–3 cm.
- As the infiltration zone of the brain metastases is usually small, the GTV-CTV margin should be in the range of 0–1 mm. The CTV-PTV margin depends on the treatment technique and should lie in the range of 0–2 mm. Care has to be taken not to increase the GTV-PTV margin too much, as this may lead to increased toxicity.
- Distant brain recurrences fulfilling the above-mentioned criteria can be treated with SRS irrespective of previous WBRT.
- Retreatment with radiosurgery of a local recurrent brain metastasis pretreated with radiosurgery carries a substantial risk of radiation necrosis.


## Summary

**In summary, SRS is a core treatment option for cerebral metastases. Treatment decisions should consider both risks and benefits, to ensure the best patient endpoint with regard to disease and functional status. SRS aims at local control, WBRT aims at brain control. Treatment variables, such as total and fractional dose, target volume, and irradiation technique, can dramatically affect SRS safety and efficacy so that optimizing these parameters is one approach to further improve endpoint and to reduce neurotoxicity [133].**

**It seems that withholding WBRT after SRS does not compromise survival and local tumor control for patients with one to four brain metastases. However, adjuvant WBRT increases intracranial control as it addresses microscopic disease in the brain. Consequently, salvage treatment is frequently required if WBRT is not used as first-line therapy. These results challenge the reflective use of WBRT in patients with a limited number of newly diagnosed cerebral metastases. SRS alone should be considered a routine treatment option due to favorable neurocognitive endpoints with less risk of late side effects, and because delaying or avoiding use of WBRT does not adversely affect the patients performance status [2, 132].**

**The possibility of finishing therapy within 1 day may also impact on the quality of life in the palliative treatment situation where more protracted radiotherapy regimes represent a significant percentage of the patient's remaining life time [134]. SRS may also have advantages as compared with WBRT in situations where systemic therapy is delayed or withheld during the course of WBRT. Further studies are needed to investigate which patients benefit from this approach, e.g., by use of tumor-specific prognostic scores.**



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## Compliance with ethical guidelines

**Conflict of interest.** M. Kocher, A. Wittig, M. D. Piroth, H. Treuer, H. Seegenschmiedt, M. Ruge, A-L. Grosu, and M. Guckenberger state that there are no conflicts of interest.

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