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Stereotactic Radiosurgery for Multiple Brain Metastases

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Abstract

Purpose of review To give an overview on the current evidence for stereotactic radiosurgery of brain metastases with a special focus on multiple brain metastases.
Recent findings While the use of stereotactic radiosurgery in patients with limited brain metastases has been clearly defined, its role in patients with multiple lesions (> 4) is still a matter of controversy. Whole-brain radiation therapy (WBRT) has been the standard treatment approach for patients with multiple brain lesions and is still the most commonly used treatment approach worldwide. Although distant brain failure is improved by WBRT, the overall survival is not readily impacted. As WBRT is associated with significant neurocognitive decline compared to stereotactic radiosurgery (SRS), SRS has been explored and increasingly utilized for selected patients with multiple brain metastases. Recent clinical data indicated the feasibility of stereotactic radiosurgery to multiple brain metastases with a similar survival in patients with more than 4 brain metastases versus patients with a maximum of 4 brain metastases. Also, neurocognitive function and quality of life was maintained after stereotactic radiosurgery which is essential in a palliative setting.
Summary The application of stereotactic radiosurgery with Gamma Knife, Cyberknife, or LINAC-based equipment has emerged as an effective and widely available treatment option for patients with limited brain metastases. Although not formally proven in

prospective studies, SRS may also be considered as a safe and effective treatment option in selected patients with multiple brain metastases. Especially in patients with a favorable prognosis, survival over several years is observed also in the setting of multiple BM. For these patients, avoidance of the neurocognitive damage of WBRT is desirable, and SRS is often a more appropriate treatment in the current multimodality treatment of BM in which systemic treatment is often the cornerstone of the treatment. For patients with an intermediate (3–12 months) and poor prognosis ($<$ 3 months), the application of WBRT becomes more and more controversial, because of its acute side effects, such as hair loss and fatigue and, thereby, detrimental effect on quality of life. For these patients, best supportive care, primary systemic treatment, and even SRS may be preferred over WBRT on an individualized patient basis.

Introduction

Brain metastases are the most common intracranial malignancy and remain a substantial source of morbidity and mortality in cancer patients [1]. The spread to the CNS is a common event in the natural course of many metastasized solid cancers like breast, lung, renal carcinoma, or melanoma with a cumulative risk of 10–30% in adults [2]. Generally the incidence of brain metastases slightly increased over the last years [3]. While the number of patients diagnosed with a single brain metastasis is furthermore decreasing, the proportion of patients diagnosed with 3 or more brain metastases is even increasing [3]. Reasons for these trends are, on the one hand, the better control of systemic cancer with prolonged survival and the increasing risk of developing BM during the natural course of the disease over time and, on the other hand, better surveillance and improved technical imaging with widespread utilization of MRI [4]. The estimated annually incidence patients with diagnosis of brain metastases reaches up to 200,000 in the USA [5].

Disease manifestation in the central nervous system may lead to significant morbidity and mortality with neurocognitive and functional deficits. The consecutive loss of autonomy may also adversely affect quality of life. Untreated, the prognosis can be dismal with only several weeks with best supportive care only [6].

Historically, brain metastases were treated primarily with whole-brain radiotherapy, as treatment of the whole sanctuary was considered necessary to prevent the development of new metastases and possibly improve overall survival. Besides, a significant portion of these patients in this era was diagnosed with symptomatic brain metastases, as CNS screening was not routinely performed, indicating a rather poor prognosis and necessitating fast symptom-oriented treatment. WBRT has significant side effects such as hair loss and fatigue and beyond that, it brings the burden of impairment in memory function and quality of life. Nevertheless, the application of WBRT is still worldwide the primary treatment approach in patients with brain metastases, despite the lack of level I evidence over best supportive care. No randomized trials have ever demonstrated a positive effect of WBRT as a primary treatment modality over best supportive care.

WBRT traditionally remains the most widely used treatment option in patients with multiple brain metastases, although the significant advances in stereotactic radiosurgery and several experience permitted radiosurgical management of multiple brain metastases [7•]. No prospective trial examining the omission of WBRT in patients with multiple brain metastases exists; consequently, upfront WBRT often remains the standard treatment approach. However, it is important to selectively choose patients qualifying for WBRT, since the QUARTZ trial showed that not all patients will eventually benefit from WBRT and best supportive care can lead to equivalent survival and quality of life [8••]. The results of the QUARTZ trial cannot be extrapolated to all BM patients, because of its inclusion criteria. Patients were eligible for this trial if the patient or the treating physician had doubts if WBRT was an appropriate treatment for this patient. Therefore, the patient population in the QUARTZ trial was a relatively poor prognostic as was expressed by the median survival in the trial. Moreover, only patients with non-small cell lung carcinoma were eligible, and usually, patients with BM of other primary tumors usually have a better prognosis, such as breast cancer and renal cell cancer patients.

With the development and clinical validation of SRS for limited brain metastases, the value of WBRT in current management strategies of brain metastases has been seriously challenged: for effective long-term local control, WBRT is deemed insufficient and with regard to possible detrimental neuro-cognitive effects considered a suboptimal treatment option, especially for patients with good clinical performance status and longer-term prognosis [9, 10].

The implementation and establishment of stereotactic radiotherapy of brain metastases with the application of high focal doses of radiation while initially using stereotactic localization and later on-machine image guidance in the last decades has evolved as the cornerstone in the treatment of brain metastases and partially displaced WBRT [11]. Important advantages of SRS over WBRT are the limited radiation dose to the uninvolved brain and the high probability of local tumor control with a single treatment. Currently, SRS alone or surgery and post-operative SRS to the resection cavity have been established as the preferred treatment option for patients with limited brain metastases [12].

Less clear is the situation in patients with multiple brain metastases [10]. In this patient group, WBRT is still often applied in clinical practice, even if these patients have good clinical performance status [13].

There is increasing, albeit retrospective or non-randomized prospective evidence that the maximum of brain metastases suitable for SRS should not be limited to 4 brain metastases and that the local control benefit is independent of the number brain metastases.

One of the most striking changes in clinical practice of the last years is the efficacy of primary systemic in the treatment of brain metastases. More and more targeted agents and immune therapies are developed. These systemic therapies are increasingly being used as a primary treatment modality, such as trastuzumab for Her2-positive breast cancer BM, and tyrosine kinase inhibitors for EGFR and ALK mutated NSCLC. Targeted therapies with BRAF and MEK inhibitors and immunotherapy with PD-1/PD-L1 or CTLA4 checkpoint inhibitors, given alone or in combination, have significantly improved survival in patients with melanoma brain metastases [14–18]. In this new clinical scenario multimodality treatment of BM, it is essential to minimize the side effects of radiotherapy. Then, SRS is often a more attractive treatment than WBRT for the patient and referring physician. WBRT is often preserved as other treatment modalities are not an option anymore.

In the following sections, we will first recapitulate current treatment recommendations for SRS of limited brain metastases and then review available retrospective and prospective evidence for SRS of multiple brain metastases to derive cautious recommendations in the absence of formal level I evidence for the latter clinical situation.

Patients with limited brain metastases

Since Lindquist in 1989 first reported that a patient was successfully treated with stereotactic radiotherapy [19], there were several randomized trials over the last decades examining treatment options with stereotactic radiosurgery in patients with brain metastases, especially in those with limited brain metastases [20••, 21, 22]. The definition of "limited brain metastases" historically includes patients with up to 4 brain metastases [21–23]. Initial trials comparing WBRT versus WBRT and added SRS confirmed a better local control for the combined treatment approach [23, 24]. Andrews et al. showed that added stereotactic radiosurgery boost to WBRT lead to improved functional autonomy of all patients and to better survival in patients with a single metastasis [23]. Still, the potential value of an intensified brain-directed treatment has been confirmed only in subset analyses of patients with a solitary brain metastasis and a presumed better prognosis [21, 23].

Further randomized trials focused on the role of SRS or surgery with or without WBRT in patients with limited brain metastases [21, 22, 25] showing no impact on survival by omitting WBRT and using SRS only [20••, 21, 22]. Aoyama et al. randomly assigned 132 patients with limited brain metastases (up to 4) to either receive WBRT plus SRS or SRS alone. The additional use of WBRT did not improve survival. Intracranial relapse occurred more frequently in the SRS alone group; thus, salvage treatment was more often required [22]. In an EORTC trial from Kocher et al., 359 patients with one to three metastases who were initially treated with SRS or complete surgery were assigned to either WBRT or observation. They also found the effect of reducing intracranial relapse after WBRT, but its addition failed to improve overall survival [21].

Extracranial disease progression is still the most common cause of death as long as brain metastases can be successfully salvaged with SRS, while less than 10% of all patients die as a result of intracranial progression alone [26].

Although distant brain control rates were greater in patients with WBRT added to SRS, WBRT was associated with a negative impact on cognition and quality of life (QoL). Brown et al. evaluated the cognitive decline among 213 patients with 1–3 brain metastases who were randomized to receive SRS alone or SRS combined with WBRT [20••]. At 6 months, for patients having cognitive evaluations, cognitive deterioration was less frequent in the SRS arm (52% vs. 85% $p = 0.00031$) reaching statistical significance for immediate memory ($p = 0.00062$), delayed memory ($p = 0.00054$), processing speed ($p = 0.023$), and executive function ($p = 0.015$). Previously, Chang et al. reported also greater rates of cognitive deterioration in patients with WBRT [25]. These findings together resulted in the ASTRO "Choosing wisely list" published in 2015 recommending SRS only without WBRT for patients with limited brain metastases. This recommendation has been made as there is no evidence that the addition of WBRT impacts on survival, but negatively influence neurocognitive functioning (www.choosingwisely.org/astro-releases-second-list) [27].

The mentioned phase 3 trials evaluating SRS with or without WBRT for 1 to 3 metastases demonstrated that after SRS alone, local and distant brain failures are approximately 10 to 30% and 40 to 70%, respectively [21, 22, 25]. Thus, approximately 40 to 70% will present with new brain metastases distant from the initial site within a year after SRS alone [21, 22, 25, 26].

In clinical practice, it is important that the reduced development of new brain metastases with the addition of WBRT to SRS is clearly communicated to the patient with respect to the rationale for surveillance MRI imaging following SRS alone [28].

Although high-level evidence data for repeated SRS is missing, several groups reported retrospective analyses of their experience with repeated courses of SRS and showed that salvage SRS is possible, safe, and effective [29]. Furthermore, upfront SRS without WBRT does not result in higher average cost, despite an increased need for salvage therapy, which was shown in a cost-effectiveness study [30].

For patients with up to 3 or 4 metastases, SRS without WBRT has evolved as the preferred treatment options [20••, 21, 22]. Surgery should be considered in metastases with larger tumor sizes, distinctive mass effect, and edema or in order to receive tissue for histopathologic or molecular investigation. Postoperative radiotherapy should be added to reduce the risk of local recurrence from roughly 60 to 30% [21, 31]. Recently, the efficacy of SRS to the resection cavity has been demonstrated by two important prospective trials showing its superiority over surgery alone, and similar survival and better cognitive function and quality of life compared to adjuvant WBRT. Therefore, SRS to the resection cavity should be adopted as the new standard of care in these patients [32••, 33••].

Currently, local brain-directed therapy (SRS or surgery) remains the guideline-recommended treatment for patients with limited brain metastases in good clinical performance status and favorable prognostic factors [34•].

Patients with multiple brain metastases

Behind the evidence of the efficacy of SRS without WBRT in patients with limited brain metastases, its use is still controversial in cases with multiple lesions. Historically, WBRT has emerged as the standard treatment approach for patients with multiple brain metastases, as prophylactic radiotherapy of the whole brain as a sanctuary was thought to be necessary due to the very high likelihood of further distant failure [7•, 35, 36]. Currently, WBRT is still one of the guideline-recommended treatments for multiple brain metastases and worldwide currently the most widely used option in clinical practice [7•]. Despite the lack of level 1 evidence for SRS in this scenario, it is increasingly adopted in daily clinical practice and more institutions expand its utilization beyond the initial target population with limited brain metastases in fear of neurocognitive side effects of WBRT.

Outcome of multiple brain metastases SRS

While there are some courageous approaches using stereotactic radiosurgery for patients with up to 100 metastases, SRS is increasingly being adopted for patients with up to 10 brain metastases as reported in a recent European survey [37•]. Depending on institutional philosophy, technical features, and equipment, some groups even treat up to a maximum of 20 brain metastases [38].

Since Moriarty et al., Young et al., and later Yamamoto et al. first reported that patients with multiple brain metastases were successfully treated with stereotactic radiosurgery[39–41], many additional, mostly retrospective studies, have evaluated this approach in the last two decades [36, 42–46]. Nevertheless, there is still no randomized trial data available and only one prospective registry analysis from Yamamoto et al. and one prospective phase 2 trial on safety and toxicity by Nichol et al. have been published [26, 47•]. Thus, generated clinical data is currently quite limited.

The most important study was reported by Yamamoto et al. in 2014 from their prospective SRS registry for brain metastases [26]. They examined whether stereotactic radiosurgery without whole-brain radiotherapy as the initial treatment for patients with 5 to 10 brain metastases is non-inferior to that for patients with 2 to 4 brain metastases in terms of overall survival. The Japanese prospective observational trial included 1194 patients (455 with a single brain metastasis, 531 with two to four brain metastases, and 208 patients with five to ten brain metastases).

Overall, the study population consisted of patients with brain metastases of a maximum diameter of 3 cm and a total cumulative volume less than 15 mL, with the majority with RPA class 2 and KPS greater than 80.

Overall survival was not compromised by the presence of multiple metastases, and therefore, non-inferiority was assumed. The median survival in the cohort of patients with 5 to 10 metastases was 10.8 months and similarly to the cohort with 2 to 4 metastases. Systemic disease progression was the predominant cause of death, and neurologic death did not exceed 10%. Local control rates—consistently high—showed furthermore no significant difference in any of the three cohorts. Distant brain failure was the lowest for patients with only a single metastasis, but there was no significant difference in distant brain failure between those with 2 to 4 metastases and 5 to 10 metastases. Summarized, Yamamoto et al. showed that patients with 5 to 10 brain metastases did not fare worth compared to patients with 2 to 4 brain metastases in terms of local tumor control, neurological deterioration, and death and therefore overall survival. They stated that SRS might be a suitable alternative for patients with up to 10 brain metastases considering the minimal invasiveness of SRS and the fewer side effects compared to WBRT. Approximately 50% of all patients received a salvage therapy due to new brain metastases diagnosed by follow-up MRI. Seventy-seven percent of patients receiving salvage therapy were treated with repeated SRS. This circumstance highlights the necessity of follow-up MRI in patients treated with sole SRS.

Still, one should consider that there were some distinctive features potentially leading to bias. First, there might be a potential imbalance between the subgroups, although the primary sites of cancer seemed to be balanced. The proportion of cancer with specific molecular subtype, e.g., SCLC, driver mutated NSCLC, and HER2-positive and triple-negative breast cancer, was unknown and might influence the outcomes in any direction. Second, the study protocol did not allow the use of volumetric MRI or double or triple doses of gadolinium for the imaging of tumors, which might have led to an underestimation of the exact number of brain metastases in the specific groups. Third, the nature of the non-randomized study design itself could have led to selection bias and generally the non-inferior design is usually only applied for randomized phase 3 studies [48, 49]. Fourth, it is debatable if overall survival is the most appropriate endpoint after radiosurgery to assess the results of these techniques facing the fact that about 90% of all patients died of extracerebral disease progression. Moreover, systemic therapies such as targeted agents are increasingly being used as primary treatment and SRS or WBRT is used as a salvage treatment. Then, survival after SRS or WBRT is not an appropriate treatment. Fifth, the data which are presented are low volume BM (largest tumor was smaller than 10 mL in volume and smaller than 3.0 cm in longest diameter, the cumulative volume of all their tumors was 15.0 mL or smaller). However, the results presented in this study are up to now the best available data examining SRS in patients with multiple brain metastases and showed convincingly that vigorous brain-metastases-directed local treatment approach is able to reduce the neurologic death rate down to 10%. This result will gain significant weight as soon as more effective systemic agents to control extracranial disease burden are available.

From there, prospective brain metastases database, Yamamoto et al. performed a dedicated case-matched study comparing patients with multiple brain metastases with 2–9 and 10 or more brain metastases undergoing SRS [50, 51]. In this study, post-SRS median survival was not significantly different, exactly as neurological death-free survival, local recurrence, repeat SRS, neurological deterioration, or SRS-related complications. They concluded that even patients with 10 or more brain metastases may be suitable candidates for SRS after careful selection, e.g., low intracranial tumor burden [51].

In the only prospective study to date, Nichol et al. reported in a multicenter, single-arm, phase 2 study on the effectivity and tolerability of SRS for patients with 1 to 10 brain metastases [47•]. Patients with life expectancy of ≥ 6 month and 1 to 10 brain metastases with a diameter of ≤ 3 cm were treated with volumetric radiosurgery. Sixty patients were enrolled and radiosurgery was delivered in five fractions with 98% target coverage, prescribed as 95% of 50 Gy (47.5 Gy in 5 fractions) to the metastases with no margin and 95% of 40 Gy (38 Gy in 5 fractions) to their 2-mm planning target volumes, concurrent with 20 Gy to the whole-brain planning target volume [47•]. The 1-year local control rate was 88%, and after 2 years, relapse was observed in 14%. They observed one grade 3 acute toxicity (case of somnolence syndrome) and one patient died of unknown neurologic cause 4 weeks after treatment, which was scored as a grade 5 radiation necrosis. Regarding late toxicity grade 3 to 5 radiation necrosis was observed in 10%, and grade 1 to 5 radiation necrosis in 17%. The cumulative incidence of symptomatic radiation necrosis (grade 2 to 5) was 13% at 3 years.

Other retrospective studies confirmed SRS as feasible and tolerable in patients with multiple brain metastases [52, 53]. Yamamoto et al. reported in their prospective trial a local recurrence after 1 year of stereotactic radiosurgery in 7% of patients with 2–4 tumors and 6.5% in patients with 5–10 tumors. Incidences of local recurrence or leukoencephalopathy did not differ significantly between the two groups of patients with more than one tumor [26].

In general, toxicity rates in studies evaluating SRS in multiple brain metastases were consistently low and local control rates were sufficient and comparable with stereotactic radiosurgery in limited brain metastases. Yamamoto et al. showed furthermore in case-matched study of stereotactic radiosurgery for patients with multiple brain metastases that there was no significant differences between the groups with tumor numbers of 1–4 (group A) and with ≥ 5 tumors (group B) in case of SRS-related complications [50].

Patient selection for multiple brain metastases SRS: predictive factors for local control and overall survival

It remains controversial which subpopulation of multiple BM patients benefits most from local treatment including SRS. Thus, patient selection in patients with multiple brain metastases is important to achieve high local control rates and prolonged survival. Predictive factors for local control comprise delivered dose, total volume of each metastasis, and histology of the primary cancer [54, 55]. These factors are independent of the total number of brain metastases, and hence, local control is theoretically guaranteed in all patients even though in patients with multiple lesions. Overall intracranial tumor volume seems to play an important role, when considering SRS in multiple brain metastases [56]. Several published results stated that survival is significantly effected by cranial tumor volume [43, 56], whereas the number of intracranial metastases is not a prognostic factor for survival [43, 56–58]. Bhatnagar et al. evaluated the outcomes after a single stereotactic radiosurgery procedure in patients with 4 or more intracranial metastases and revealed total treatment volume, age, RPA classification, and marginal dose as significant prognostic factors, whereas the number of brain metastases was not significant. Likhacheva et al. and Baschnagel et al. confirmed these results [54, 59]. However, the total number of metastases is still considered as an indicator for patients eligible for SRS in clinical practice [37•]. Interestingly, a survey of Sandler et al. has shown that the optimal "cutoff number" for SRS in brain metastases was higher for high-volume CNS centers than for low-volume CNS centers [60]. While the importance of irradiated total tumor volume is being increasingly recognized, the maximum volume to be treated remains to be defined; the use of fractionated SRS as an effective and safe treatment for large brain metastases and the favorable impact of new targeted agents and immunotherapy in patients with brain metastases are likely to improve the outcome in patients with larger tumor volumes than previously reported.

Currently, several scoring systems and prognostic scores are available to simplify and guide treatment decisions in patients with multiple brain metastases. The GPA, developed to guide these decisions, has been validated in WBRT as well as SRS-treated brain metastases patients [61, 62]. Recently, it has been expanded and validated to a disease-specific prognostic score, even incorporating information of tumor-specific mutations [63, 64, 65••]. RPA, GPA, and especially the ds-GPA proofed their value in clinical practice [66]. Scores are now being developed incorporating tumor receptors, such as the breast cancer–specific GPA and the lungmol-GPA. These models reflect potential treatment with effective systemic targeted agents which probably have large impact on survival [65••, 67]. Interestingly, in none of these available prediction models enabling a valid estimation of survival, the total intracranial tumor volume as a prognostic factor is encompassed; currently, the total number of metastases is still considered as an indicator for patients eligible for SRS in clinical practice [37•].

Various models assisting clinicians in deciding between administration of WBRT or SRS as initial treatment have been developed. All of them intend to enable estimation of risk of and time to distant brain failure [68–70]. All of these studies included the number of primarily diagnosed metastases in their scoring system, as it was significantly predictive for early DBF after initial treatment. However, the effect of the estimated number of future metastases or of the dynamics of relapse on overall survival has so far not been investigated. Therefore, an innovative and promising new metric brain metastasis velocity (BMV) has been developed.

[71]. BMV was established by analysis of 737 patients treated with upfront SRS only for new brain metastases and represents the rate of new metastases that develop over time. The value can be re-calculated over a patient's disease course multiple times and stays prognostic. A multi-institutional study with almost 3000 has recently validated the BMV as a dominant predictor for OS but the full results have not been published yet [72].

Ongoing prospective trials and perspective

A few ongoing phase III trials (NCT02353000, NCT01592968, and NCT03075072) comparing directly WBRT and stereotactic radiosurgery in patients with multiple brain metastases will hopefully bring more relevant data and evidence when the use of WBRT or SRS should be considered (Table 1). Another randomized trial (NAGKC 12–01) comparing stereotactic radiosurgery

(SRS), specifically the Gamma Knife (GK) system, and whole-brain radiation therapy (WBRT) with measuring neurocognitive outcomes in patients with 5 or more brain metastases was closed prior to enrolment due to insufficient staff (Table 1). Recently, the NCT02353000 trial was closed, because of lack of accrual after randomizing 30 patients [73].

Recent developments applying WBRT with conformal avoidance of the bilateral hippocampus have revived the interest in WBRT for multiple brain metastases and prospective trials are terminated or still ongoing (https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0933; https://clinicaltrials.gov/ct2/show/NCT02635009), as this seems to be associated with preservation of memory and quality of life at 3 months as compared with historical series of WBRT without hippocampal sparing [74, 75]. A simultaneously integrated boost may then be added to WBRT with hippocampal sparing to achieve adequate whole-brain coverage and radiosurgery-equivalent dose distributions to the brain metastases (HIPPORAD study, (NOA-14/ARO 2015-3) [76]. Nonetheless, the main advantage of SRS compared to WBRT with stereotactic boost remains the short treatment duration. While for WBRT long interruptions of systemic therapy are necessary, SRS can safely be administered in a short break of systemic therapy.

When SRS is considered in the management of patients with multiple brain metastases several additional aspects have to be considered: (a) available systemic treatment options and their efficacy if administered as sole treatment modality and (b) optimal sequencing and timing of local brain-directed therapies. Both clinical questions—especially in times of emerging effective systemic treatment options for selected cancer types like NSCLC and melanoma—are still not answered satisfyingly. Recent developments in systemic treatment for these exemplary cancer types showed promising intracranial response besides improving progression-free and overall survival in general [77, 78].

Especially, lung cancer is characterized by a high incidence of brain metastases. Around 25–40% of patients with NSCLC will experience BM during

Table 1. Currently ongoing clinical trials investigating the role of radiosurgery for multiple brain metastases

Trial	PI	Number of patients	Standard arm	Experimental arm	Number of brain metastases
NCT02353000	Jaap Zindler (MAASTRO Clinic, The Netherlands)	260 estimated	WBRT	SRS	4–10
NCT01592968	Jing Li M.D. Anderson Cancer Center	100 estimated	WBRT	SRS	4–15
NCT03075072	Ayal Aizer Brigham and Women's Hospital	196 estimated	WBRT	SRS	5–20
NAGKC 12–01, NCT01731704	Igor J Barani University of California, San Francisco	120 estimated	WBRT	SRS (Gamma Knife)	≥ 5

course of their disease. Lung cancer is the primary source of brain metastases and account for 40–65% of secondary brain malignancies [5, 79]. In metastatic NSCLC, newer TKI generations (e.g., osimertinib for EGFR-mutated NSCLC and alectinib, brigantinib, and lorlatinib for ALK-mutated NSCLC) showed superior CNS penetration and impressive treatment response [80••, 81••, 82, 83]. Upfront TKI-therapy is a potential option which is widely accepted in clinical practice and can be initiated in non-symptomatic patients with multiple brain metastases according to ESMO guidelines [84]. Thus, the value of local therapy, especially radiotherapy, has been challenged by these potent treatment options and the acute and late side effects of WBRT become less attractive in these multimodality approaches.

Although effective CNS-directed TKI treatment is available, retrospective data suggests a role of early integration of radiotherapy intervention like stereotactic radiosurgery, although the optimal timing has yet not been defined [85••].

Conclusion

So where do we stand? The role of stereotactic radiosurgery in multiple brain metastases is evolving. There exists reassuring evidence from large registry data on efficacy and from one prospective and several retrospective series on toxicity. High-level evidence is on the horizon with two randomized trials investigating this new approach. Two other randomized trials were closed prematurily because of lack of accrual. Hopefully, the two ongoing trials will shed more light on the optimal patient selection for such an approach.

For the time being, a prudent approach is reasonable and SRS for multiple brain metastases can be offered to selected patients fulfilling the criteria from the Japanese registry or—with regard to toxicity—from the prospective study by Nichols et al.

Several clinical factors may aid in the decision-making process: clinical performance status, intracranial tumor burden, and a favorable tumor specific GPA. "Brain metastases velocity" is a very new, but apparently powerful and simple tool to predict distant brain failure and aid the decision of SRS versus WBRT or even sole systemic treatment.

Eventually, the number of brain metastases may no longer be considered as the threshold for the use of SRS. Total volume of brain metastases should be more rolled into decision-making when discussing patients qualifying for SRS and a total maximal tumor volume should be defined in guidelines for easier decision-making in what kind of patient SRS is an alternative to WBRT.

Compliance with Ethical Standards

Conflict of Interest

Johannes Kraft and Matthias Guckenberger each declare no potential conflicts of interest. Nicolaus Andratschke reports grants from Brainlab AG, outside the submitted work. Giuseppe Minniti reports personal fees from BrainLAb, outside the submitted work. Jaap Zindler has no personal conflicts of interest—MAASTRO Clinic has a research agreement with Varian Medical Systems Palo Alto USA.

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