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REVIEW ARTICLE

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Radiosurgery for metastatic brain tumors

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Abstract Stereotactic radiosurgery (SRS) precisely delivers high-dose radiation to a small target (usually less than 3–4 cm in diameter), in a single session with steep dose-fall, employing various radiation methods. SRS provides good tumor control for small brain metastases from various primary cancers, with minimal untoward effects on surrounding normal brain. This excellent tumor control prevents neurological death and maintains good activity of daily life. Although surgery with whole-brain radiation therapy (WBRT) remains an important option for patients with a solitary brain metastasis, SRS with or without WBRT should be considered in patients with a limited number of small tumors and a good prognosis. Many reports, as well as both retrospective and prospective reviews, have shown WBRT before or after SRS to improve local control and reduce new distant lesion emergence. However, upfront WBRT does not improve survival. There are two major delivery techniques, Gamma Knife (GK; Elekta AB, Stockholm, Sweden) SRS and linear accelerator (LINIAC)-based SRS. They are based on quite different concepts, and have different techniques and clinical applications. These differences complicate the discussion of the limitations of and indications for SRS and the necessity for prophylactic WBRT. This review discusses numerous aspects of SRS, its value as compared with other treatment modalities, the necessity for prophylactic WBRT with SRS, the limitations of and indications for SRS, and the difference between GK and LINIAC SRS, based on the literature and our experience, and proposes a new strategy for the treatment of brain metastases in view of the available clinical data and experience.

Key words Metastatic brain tumor · Stereotactic radiosurgery · Gamma Knife · Whole-brain radiation therapy

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Introduction

Stereotactic radiosurgery (SRS) for metastatic brain tumors offers many benefits as compared to surgery, with less invasive procedures, and it can also be performed during a few days of hospitalization, or even in an outpatient clinic. In the same session, SRS may be used to treat multiple lesions in widely disparate or eloquent locations not conducive to open surgical approaches. Two types of devices are commonly used for brain SRS: the multisource cobalt-60 unit known as the Gamma Knife (GK; Elekta AB, Stockholm, Sweden) and the specially modified or dedicated linear accelerator (LINIAC). Charged-particle irradiators are limited in number because of their high initial and running costs. The most commonly used SRS system for intracranial lesions is the Leksell GK. The GK consists of 192 (Perfexion; Elekta AB, Stockholm, Sweden) or 201 (models U, B, C, and 4-C) cobalt-60 sources that emit gamma irradiation. The isocenter of delivery of each dose (or "shot") of radiation is always in the center of the spherically arranged collimator helmet. The GK is designed to treat intracranial targets only, such as brain tumors (e.g., metastatic brain tumor, vestibular schwannoma, meningioma, pituitary adenoma, and craniopharyngioma) and vascular diseases (arteriovenous malformation, arteriovenous fistula, cavernous angioma), as well as functional disorders (e.g., trigeminal neuralgia involuntary movement, and epilepsy), to provide the highest level of accuracy. The second method for delivering SRS is a modified or dedicated LINIAC that generates high-energy photons. The LINIAC systems are of two types, those with a tracking system [such as the Novalis Tx (Brain LAB, Kapellenstr, Germany) and Cyberknife (Accuray, Sunnyvale, CA, USA)] and those without one, such as Trilogy (Varian, Palo Alto, CA, USA) and Synergy (Elekta AB, Stockholm, Sweden), which may have cone beam computed tomography (CT) for precise position checking. LINIAC SRS systems may have various collimators, from simple round types to modern multileaf devices. LINIAC can be used for SRS by focusing the beams through a variety of fixed, shaped fields at the target,

Table 1. Differences between GK SRS and LINIAC SRS

	Gamma Knife SRS	LINIAC SRS
Radiation beam	Gamma ray	X-ray
Images for treatment planning	MRI (CT available)	CT (fused MRI available)
Skull fixation	Frame with skull pins	Mask (frame available)
Treatment plan	GTV = PTV (no margin)	GTV < PTV (1-to 2-mm margin)
Irradiation methods	Static 201 or 196[b] Co-source 4 (3[b]) different collimators Beam-blocking multi-isocenter; common angle change	Dynamic or static arc angle collimator Multileaf collimator[a] Single-isocenter: common[a] tracking system[c]
Setup margin of machine	No (PTV = CTV)	Yes (PTV ≤ CTV)
Primary care physicians	Neurosurgeon	Radiation oncologist
Fractionation	Nearly impossible	Possible
Limited number in a single session	10–25 (if TTV < 15 cc)	3–4

MRI, magnetic resonance imaging; CT, computed tomography; GK, Gamma Knife (Elekta); LINIAC, linear accelerator; GTV, gross target volume; PTV, planning target volume; TTV, total tumor volume
[a] Excluding the Cyberknife system (Accuray)
[b] Perfexion (new-type Gamma Knife)
[c] Novalis TX (Brain LAB) and Cyberknife

or by a variety of arcs at the axis of rotation. Thus, LINIAC SRS systems consist of many types with different dose-planning software, position checking systems, head fixation systems, and so on. These differences may lead to different clinical results, though GK SRS is essentially unique. LINIAC technology focuses on targets within the entire body but may not provide the same accuracy within the brain as GK SRS technology. Proton beam systems use fixed high-energy beams that are either cross-fired (non-Bragg peak) or use the Bragg peak effect to deposit radiation in the tumor.[1,2]

General aspects of SRS for metastatic brain tumors

Surgical resection of a single brain metastasis has been shown to improve tumor control and prolong survival, particularly when combined with whole-brain radiation therapy (WBRT).[3,4] However, surgical resection may be contraindicated in many patients because of poor general condition or unresectable tumor locations.[5,6] For more than two decades, SRS has provided patients who have metastatic brain tumors with an alternative local treatment to surgery. Studies have shown that SRS is very effective in controlling brain metastases and that it prevents neurological death and maintains good activities of daily life (ADL).[7–18] Moreover, SRS is minimally invasive and can be performed with a short hospitalization, important considerations for quality of life (QOL) and health care economics when compared with surgery.[19,20]

On the other hand, we must understand the differences in SRS devices between GK and LINIAC, including the radiation beams, images for treatment planning, planning software, irradiation methods, set-up margin, frame fixation, practitioners, the availability of fractionation, and limitations in lesion number and size to be irradiated in a single session, as shown in Table 1.[12,19–34] A Radiation Therapy Oncology Group (RTOG) study (RTOG 9005) reported better local brain tumor control for GK than for LINIAC.[9,17] However, that study was not randomized, and LINIAC technology has improved recently. Thus, the results of the RTOG 9005 study are difficult to interpret and the difference does not seem to be clinically relevant. The most important difference between GK and LINIAC is the potential tumor number that can be irradiated in a single session. The GK can irradiate 10–25 brain metastases very safely, if the lesions are diffusely scattered and the total tumor volume is less than 15–30 cc.[12,21–25] On the contrary, the upper limit of the brain lesion number for LINIAC SRS is only 3 or 4, because arc radiation methods may cause a hot spot outside target volumes. Furthermore, treatment planning images are different, i.e., enhanced thin-sliced magnetic resonance imaging (MRI) for GK SRS and enhanced CT scan for LINIAC SRS. The detectability of tiny metastatic lesions on MRI is far superior to that on CT. These situations result in different treatment strategies for brain metastases, such as the indications for and limitations of SRS, and the necessity for prophylactic WBRT. GK users tend not be concerned about tumor number and prefer SRS-alone treatment. On the contrary, the most important indications for LINIAC SRS users are tumor numbers (up to 3–4), and prophylactic WBRT tends to be introduced for tumors that are not visible on CT. Without understanding the differences between GK and LINIAC SRS, the aforementioned discussions would be meaningless.

Nonrandomized studies of SRS for metastatic brain tumors

The majority of evidence supporting the use of SRS for brain metastases comes from prospective nonrandomized trials (class 2 data) and retrospective studies (class 3 data). Table 2 summarizes large retrospective series.[26–31,35–41] These reports suggest that SRS is more effective than WBRT and that it is comparable to or superior to surgery.[26–32,35–43] SRS as the sole initial management or as a boost before or after WBRT has emerged as a widely practiced treatment modality for brain metastases. The goal of SRS without WBRT is to achieve brain control without the possible long-term neurotoxic or cognitive side effects of WBRT.[11,44,45] The rationale for SRS, when used as a boost after WBRT, is to

Table 2. Recent retrospective studies of radiosurgery for brain metastases

First author	Year	No. of patients	Primary organ	Median survival (months)	Median margin dose (Gy)	Local control
Serizawa[26]	2006	1030	Mixed	9	20	96%
Gaudy-Marqueste[27]	2006	106	Melanoma	5.09	25	84%
Bhatnagar[35]	2002	205	Mixed	8	16	71% at 1 Year
Chang[36]	2005	109	NSCLC	7.5	18	64% Renal 47% Melanoma
Nam[28]	2005	130	Mixed	8.75	17.9	64%
Pan[29]	2005	191	All lung	14	18	91%
Gerosa[30]	2005	504	All NSCLC	14.5	21.4	95%
Lippitz[31]	2004	215	Mixed	7.8–13.7	22	94%
Hasegawa[37]	2003	121	Mixed	8	18.5	79%
Petrovich[38]	2002	458	Mixed	9	18	87%
Sheehan[39]	2002	273	All NSCLC	7	16	86%
Amendola[40]	2000	68	All breast	7.8	15–24	94%
Simonova[41]	2000	237	Mixed	6–12	21.5	95%

NSCLC, non-small cell lung cancer

achieve improved local brain tumor control. SRS boost seems to improve survival in selected patients in whom the predominant problem is brain disease rather than extracranial disease. SRS is also used as salvage treatment for local recurrence and new distant lesions after surgery or WBRT, even after SRS.[46] Traditionally radioresistant histologies tend to be more responsive to SRS than to conventional fractionated radiation treatment.[36,47] Despite a relatively high risk of new metastases outside the SRS volume in patients who have SRS alone, retrospective studies have not confirmed a survival benefit versus adjuvant WBRT.[7,10,26,33,34,48–50] As mentioned above, the clinical application of GK is widespread throughout the world, and it is used extensively in Japan (see Table 2 for a recent Japanese report[7,12,13,21–24,26,33,34,51]).

Tumor control

Retrospective series have consistently revealed local control of target lesions in the range of 80%-95% or even higher, with a very acceptable rate of untoward effects, depending on such factors as tumor size, volume, pathology, location, and radiation methods.[12,26,33,34,39,47,51–53] Serizawa et al.,[26] reporting a large series with 10 163 lesions treated with GK SRS alone, found the most important prognostic factor for tumor control to be tumor volume. According to that report, the tumor control rate at 1 year was 99.5% for 8573 tiny lesions (≤1 cc in tumor volume), 92.6% for 977 small lesions (1<, ≥4 cc), 87.3% for 441 medium-sized lesions (<4, ≥10 cc), and 65.5% for 172 large lesions (>10 cc). Several retrospective studies have compared local brain control rates in patients receiving initial SRS alone with those receiving WBRT.[16,18,54–57] Most reports suggested upfront WBRT to improve local control. Chidel et al.[56] found a statistically significant improvement in 2-year brain lesion control with the use of WBRT in addition to SRS boost: 80% vs 52% in patients treated with SRS alone ($P = 0.034$). Pirzkall et al.[10] found 1-year local control rates to be inferior in the SRS-alone group: 89% vs 92% in the WBRT and SRS-boost group. Shehata et al.[57] reported that patients who received WBRT had superior local tumor control rates (97%) as compared with patients treated with SRS alone (87%; $P = 0.0001$).

A prospective, single-arm, multi-institutional Eastern Cooperative Oncology Group (ECOG) phase II study of SRS alone for "radioresistant" histologies (melanoma, sarcoma, renal cell carcinoma) in patients with one to three brain metastases has also been reported.[59] Inclusion criteria were one to three newly diagnosed brain metastases with a maximum diameter of 4 cm. In patients with multiple lesions and any lesion more than 3 cm, all remaining lesions were required to be less than 3 cm. Of 36 patients accrued, 31 were eligible and evaluable; 14 had melanoma, 14, renal cell carcinoma; and 3, sarcoma. Three of the 31 patients (10%) had a partial response, 10 (32%) had stable disease, 14 (45%) had progressive disease, and 4 (13%) were not evaluable. At 6 months, 39.2% showed failure within the SRS volume and 39.4% failure outside the SRS volume.

Overall survival

However, excellent local control by SRS with or without WBRT for metastatic brain tumors does not translate into improved overall survival, because corresponding survival rates were notably lower and the majority of patients in these studies died of systemic disease progression.[26–31,33,35–41,58–60] In addition to systemic disease status, other factors may contribute to the discrepancy between the high rate of local tumor control and the lower rates of survival. Other retrospective studies reported median survivals to range from 8 to 15 months. Chidel et al.[56] reported the median survival of patients treated with SRS alone to be 10.5 months, as compared with 6.4 months in patients treated with radiosurgery boost and WBRT (P value not stated). Sneed et al.[54] reported that the median survival of patients treated initially with SRS alone was 11.3 months, which was not significantly different from the survival of those treated with WBRT + SRS boost (11.1 months). Pirzkall et al.[10] found no difference in overall survival between patients treated with SRS alone versus those treated with SRS and

WBRT; however, in the subset of patients without extracranial disease, omitting WBRT resulted in a decrease in survival from 15.4 to 8.3 months.

Various prognostic factors impacting overall survival after SRS have been reported.[7,10,15,18,21–24,26–31,33,34,36–41,48–56,58–60] A multicenter retrospective analysis was performed by Sneed et al.,[55] with 502 patients treated at ten institutions in which all of the patients were treated with WBRT and SRS. The patients were stratified by recursive partitioning analysis (RPA) class and compared with similar patients from the RTOG database who had been treated with WBRT alone.[61] The study revealed that patients with higher Karnofsky performance status (KPS), controlled primary tumors, absence of extracranial metastases, and lower RPA class had significantly superior survival. The three classes were: class I, patients with KPS more than 70, less than 60 years of age with controlled primary tumor, and no extracranial metastases; class III, KPS less than 70; and class II, all others. From the historical database, the best survival was noted in class I patients (median, 7.1 months), with intermediate survival in class II patients (median, 4.2 months), and the worst survival in class III patients (median, 2.3 months).[61] The addition of an SRS boost resulted in median survivals of 16.1, 10.3, and 8.7 months, respectively, for RPA classes I, II, and III. This is in comparison to 7.1, 4.2, and 2.3 months for similar RPA class patients from the RTOG database. This improvement in overall survival, stratified by RPA class, with an SRS boost, was statistically significant. In a recent study, SRS alone was found to be as effective as resection plus WBRT in the treatment of one or two brain metastases for patients in RPA classes I and II.[14] Lutterbach et al.[8] performed a prospective study using SRS alone for the initial management of brain metastases.

Several retrospective studies have reported on the use of SRS alone as the initial management of selected patients with brain metastases.[7,8,10–13,21–24,26–27,33,34,37–40,49–57] Serizawa et al.[26] reported from their experience, treating 1030 patients with GK SRS alone, that median survival was 2.2 years in class 1, 0.71 years in class 2, and 0.29 years in class 3, using the RTOG RPA classification. Moreover, in another study by the same group, multivariate analysis revealed three significant prognostic factors for survival in an analysis of more than 2000 patients treated with GK alone in a multi-institute study: sex (male), extracranial disease status (active), and initial KPS score (<70).[51] Intracranial factors such as tumor number, size, and location did not affect survival. Other authors have reported RTOG RPA class 1 patients to have the strongest likelihood of longer survival.[26,30,33,37,42,50,56]

However, we must pay attention to primary tumor type. Lutterbach et al.[8] reported renal cancer to be associated with a reduced risk of death as compared with other primary tumor types. Furthermore, retrospective studies by Petrovich et al.[38] demonstrated better survival for patients with metastatic breast cancer compared with other types of metastatic tumors. Hasegawa et al.[37] found that metastatic melanoma was associated with poorer survival than other metastatic tumor types.

New distant lesions

Published series of patients treated with SRS have demonstrated a risk of distant brain failure at 1 year ranging from 43% to 57%.[8,37,48,54] In general, the risk of new metastasis in patients with solitary tumors is approximately 37% (crude), but the actuarial risk is 50% at 1 year.[3,7,26,33,48] Sneed et al.[54] reported a statistically significant improvement in 1-year freedom from brain tumor progression in patients receiving WBRT + SRS boost (69%) compared to those treated with initial SRS only (28%). It was noted that the 1-year brain control rate allowing for salvage (using WBRT or serial SRS) at first failure did not differ significantly between those treated with initial WBRT + SRS boost (73%) vs those treated initially with SRS alone (62%). These retrospective studies suggest that WBRT will improve local and distant control in the brain, but do not clearly demonstrate a survival advantage for this treatment. Serizawa et al.[26] reported the incidence of new distant lesions in 1030 patients with 1–25 brain metastases treated with GK SRS alone to be 49.3% at 1 year. According to multivariate analysis, the significant risk factors for new distant lesions were more than four brain metastases and active extracranial diseases. In their series of more than 429 deceased patients who had received GK SRS alone, 35.5% had required GK SRS salvage treatment (one procedure in 134, two in 62, three in 26 and more than three in 37) for limited numbers of new distant lesions and 4.1% had required salvage WBRT for cerebral dissemination and/or cerebrospinal fluid (CSF) dissemination.

Neurological survival

There are few reports concerning neurological survival (NS). Serizawa et al.[26] also reported that in 87% of patients with 1–25 brain metastases (total tumor volume <15 cc) treated by GK, with a meticulous follow-up protocol, SRS alone prevented neurological death. The main causes of neurological death were carcinomatous meningitis, tumor recurrence, and cerebral dissemination. The only significant poor prognostic factor for NS was a finding of CSF dissemination on dose planning thin-slice (2-mm) MRI ($P < 0.0001$). This retrospective study suggested that GK alone with meticulous follow up would prevent neurological death in most patients with 1–25 brain metastases, if the total tumor volume is less than 15 cc, leading to the proposal of a 10-Joule total skull integral dose (3 Gy whole-skull irradiation).[12]

Quality of life

Auchter,[15] in a retrospective study, reported on QOL and symptom control outcomes; for patients treated with WBRT and SRS, the median time during which the KPS score was maintained above 70 was 44 weeks. Serizawa et al.[26] reported that at 1 year, 82.1% of patients with 1–25 brain lesions treated with GK alone maintained ADL, until death or dependence due to systemic causes.

Untoward effects

The untoward effects of SRS are limited but can occasionally be serious. There are very few acute side effects of SRS related to the radiation. SRS may cause mild fatigue and sometimes a temporary patch of hair loss, if the tumor is close to the skull and scalp. In the ECOG phase II trial,[58] two grade 3 events in 31 patients (one seizure and one fatigue) were thought to be possibly related to SRS. The prospective study by Lutterbach et al. found that 13% of patients experienced complications with SRS alone as initial treatment for brain metastases; 9% were acute toxicities and 4% were late toxicities.[8] Varying degrees of toxicities were reported in a retrospective series examining the outcomes of patients treated with SRS alone.[7,11–13,21–27,33,34,37,39,49,51,55]

There is a risk of late side effects, the most common and serious of which is radiation injury.[13] Radiation injury consists of damage to the tumor and/or radiation necrosis of adjacent brain tissue in the high-dose area. This can result in increasing enhancement of the area with surrounding edema, shown on enhanced MRI, which may cause seizures and neurological deficits. Radiation injury can often be managed with corticosteroids, though sometimes surgical intervention is required to reduce the mass effect. The risk of symptomatic radiation injury is usually less than 5% depending on such factors as treatment volume, treatment dose, pathology, interval from treatment, dose distribution conformity, and previous radiation history.[9,17,57] A multicenter phase I RTOG trial involving SRS documented this procedure to be safe in patients previously treated with standard external-beam radiation therapy.[9,17]

This radiation injury must be differentiated from tumor recurrence, which has similar MRI findings, increasing the enhanced area accompanying edema in the surrounding brain. The efficacies of various modalities such as magnetic resonance spectrography (MRS), thallium single photon emission computed tomography (SPECT), or positron emission tomography (PET) using fluorodeoxyglucose (FDG) or methionine, have been reported.[52,62,63] However, it is sometimes difficult to differentiate between tumor recurrence and radiation injury, because mixed lesions containing both tumor recurrence and radiation injury may exist.[65]

Necessity for prophylactic whole-brain radiation therapy

The use of prophylactic WBRT with SRS has been somewhat controversial because the benefit seems to be limited to improving tumor control and reducing the risk of new distant lesions,[10,18,48,54,55] whereas its use is associated with serious late-term complications, such as radiation-induced dementia or subacute brain atrophy.[44,45] Although randomized surgical studies have demonstrated a clear survival benefit with upfront WBRT in selected patients,[3,4] retrospective studies indicate that the addition of WBRT to SRS does not significantly improve survival.[10,18,33,34,45–51,53–55] In view of the serious long-term side effects associated with WBRT plus SRS, some investigators have suggested that WBRT should be omitted in patients undergoing SRS.[7,10,21–27,33,34,48,51,52,54,55,61] Amazingly, Serizawa et al.[34] found that there were no significant differences between small cell lung cancer (34 patients) and non-small cell lung cancer (211 patients), in overall, neurological, or qualitative survival. The emergence of new distant lesions of small cell lung cancer tends to be more frequent than that of non-small cell lung cancer (not significant), though most patients with new distant lesions can be managed by salvage GK treatment without WBRT.

These retrospective studies suggest that upfront WBRT be considered, case by case, depending on the machine (GK or LINIAC) used, economic circumstances, and follow-up protocols, as well as the following factors:

1. Tumor number and size
2. Presence of CSF dissemination
3. Pathology of the primary cancer
4. Patient age
5. Symptoms
6. Status of systemic disease
7. Current neurological status
8. General medical condition
9. Presence or absence of other organ metastases
10. History of prior WBRT
11. History of prior brain procedures
12. Patient's concerns and risk tolerance for neurocognitive functions
13. Patient's wishes

Radiosurgery combined with WBRT: level 1 evidence

There have been three randomized trials examining the use of WBRT + SRS boost compared with WBRT alone and one randomized trial comparing SRS alone with SRS + WBRT, as shown in Table 3. Three of these trials were reported in peer-reviewed published literature,[4,16] and one has been reported only in abstract form with the final report pending.[64] In addition, one randomized trial comparing SRS with WBRT to SRS alone has been published[65] (Table 3).

Trial carried out by Kondziolka et al.[16]

Kondziolka et al.[16] randomized patients with two to four brain metastases (all <25 mm) to WBRT alone (30 Gy in 12 fractions) or WBRT + SRS. The study was discontinued at 60% accrual when only 27 patients had been randomized. The results were reported for 14 patients in the WBRT group and 13 in the WBRT + SRS boost group. The two groups were well balanced with respect to age, sex, tumor type, number of tumors, and extent of extracranial disease. Local brain control was defined as no tumor growth based on MRI scans and no increase in clinical symptoms associated with the lesion. This study noted superior intracranial control with the use of SRS. Median survival did not differ

Table 3. Randomized trials of WBRT + SRS versus WBRT alone or SRS alone

First author	Management modalities	No. of tumors	Maximum tumor size (cm)	No. of patients	Patient eligibility	Median survival (months)	Statistical significance
Andrews[14] 2004	WBRT WBRT + SRS	1–3	4	94 92	Patients with prior surgery included; patients with active disease excluded WBRT 37.5 Gy in 15 fractions; SRS 15–24 Gy, linear accelerator or GK	4.9[a] 6.5[a]	$P = 0.0393$
Kondziolka[16] 1999	WBRT WBRT + SRS	2–4	2.5	14 13	Patients with active disease included WBRT 30 Gy in 12 fractions; study stopped at 60% accrual	7.5 11	$P = 0.22$
Chougule[64] 2000	SRS WBRT + SRS WBRT	1–3	3	36 37 31	Patients with minimum life expectancy of 3 months were included WBRT, 30 Gy in 10 fractions; SRS, 30 Gy to tumor margin; SRS + WBRT, SRS 20 Gy to margin + WBRT 30 Gy in 10 fractions	7 5 9	NA
Aoyama[65] 2006	SRS WBRT + SRS	4	2	60 60	30 Gy in 10 fractions over 2–2.5 weeks Patients with SCC, lymphoma, germinoma, and multiple myeloma were excluded	8 7.5	$P = 0.42$

WBRT, whole-body radiation therapy; NA, not available; SCC, squamous cell carcinoma
[a] Patients with single brain metastases (unresectable or inoperable)

significantly between the two groups (7.5 months for WBRT alone vs 11 months for WBRT with SRS boost; $P = 0.22$). Survival was dependent on the extent of extracranial disease ($P = 0.02$), but was not dependent on histology or the number of tumors. In summary, this randomized trial detected an improvement in local brain control in patients treated with WBRT and SRS boost compared with WBRT alone, though there was no statistically significant improvement in overall survival with the use of SRS boost compared with WBRT alone. This trial demonstrated "no neurologic or systemic morbidity related to SRS".

Report of Andrews et al.[14] (RTOG 9508)

The RTOG 9508 trial reported by Andrews et al.[14] randomized 164 patients to WBRT and SRS boost and 167 to WBRT alone. Patients with one to three newly diagnosed brain metastases were included. The arms of the trial were well balanced for baseline characteristics known to affect survival, such as age, KPS score, and status of extracranial metastases. Brain metastases with the largest lesion up to a maximum diameter of 4 cm and additional tumors less than 3 cm in size were included. Median survivals for the WBRT arm ranged from 5.7 to 7.5 months (mean, 5.7 months) and those for the WBRT and SRS boost arm range from 5 to 11 months (mean, 6.5 months; $P = 0.1356$). The RTOG 9508 trial also used RPA classification of prognostic factors to analyze the relative contributions of pretreatment variables to the survival of patients and to identify subgroups of patients with homogeneous prognostic characteristics predictive of survival. This RTOG 9508 trial explored survival outcomes in certain subsets of patients. By multivariate analysis, WBRT and SRS boost improved survival in RPA class I patients ($P < 0.0001$) and in patients with favorable histological status, i.e., squamous cell or non-small cell lung tumors ($P = 0.0121$). In patients with single brain metastases (unresectable or inoperable) the median survival was 6.5 months with SRS boost compared with 4.9 months with WBRT alone ($P = 0.0393$). The RTOG 9508 trial reported that patients in the SRS boost group were more likely to have a stable or improved KPS at 6 months follow up than patients in the WBRT alone group (43% vs 27%, respectively; $P = 0.03$). Steroid use 6 months after treatment had decreased in 41 of 76 patients treated with SRS boost, compared with 25 of 75 patients treated with WBRT alone ($P = 0.0158$). Andrews et al.[14] reported a statistically nonsignificant increase in the risk of toxicity with SRS boost, i.e., 3% acute grades 3 and 4 toxicities and 6% late grades 3 and 4 toxicities.

Trial carried out by Chougule et al.[64]

The Chougule et al.[65] trial randomized patients with one to three brain metastases to GK SRS alone (30 Gy to the tumor margin), WBRT (30 Gy in ten fractions) plus GK boost (20 Gy to the tumor margin), and WBRT alone (30 Gy in ten fractions). Patients with a total tumor volume less than 30 cc and minimum life expectancy of more than 3 months were included. The results of this trial were published only in abstract form. The local brain control rate was higher in the two SRS arms: 87% for GK SRS alone and 91% for GK SRS and WBRT, compared with 62% in the WBRT-only arm. Overall median survivals were 7, 5, and 9 months in the three arms, respectively. Survival reportedly did not differ among the three arms.

Study carried out by Aoyama et al.[65] (JROSG 99-1)

The only published study of SRS alone versus SRS + WBRT, from the Japan Radiation Oncologist Study Group (JROSG), was conducted by Aoyama et al.[66] in 2006. Aoyama and colleagues reported the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs SRS alone for patients with limited (defined as ≤4) brain metastases with a maximum

diameter of 3 cm on contrast-enhanced MRI scan. Patients with metastases from small cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded. Eligible patients had a KPS score of 70 or higher. The WBRT dosage schedule was 30 Gy in ten fractions over 2–2.5 weeks. Metastases with a maximum diameter of up to 2 cm were treated with SRS doses of 22–25 Gy and those larger than 2 cm were treated with doses of 18–20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion. The primary endpoint of the study was overall survival. Secondary endpoints were cause of death, functional preservation, brain tumor recurrence, salvage treatment, and toxic effects of radiation. One hundred and thirty-two patients were randomized (65 to WBRT + SRS and 67 to SRS alone). The interim analysis was performed with 122 patients (approximately 60 in each group). This trial reported an actuarial 1-year local tumor control rate of 88.7% in the WBRT + SRS group and 72.5% in the SRS-alone group ($P = 0.002$). The 1-year actuarial rate of developing new brain metastases was 41.5% in the WBRT + SRS group and 63.7% in the SRS-alone group ($P = 0.003$).

The Japanese trial found no significant survival difference between the group receiving WBRT + SRS versus the group receiving SRS alone. The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. In addition, no significant difference in the frequency of death due to neurological causes was observed. Death was attributed to neurological causes in 22.8% of the WBRT + SRS group and in 19.3% of the SRS alone group. No formal comparisons between SRS alone vs competing management options such as WBRT have been made in terms of QOL or symptom control in any of the studies cited here. The only study reporting KPS outcomes has been this Japanese randomized trial. The actuarial 1-year KPS preservation rate (KPS > 70) was 25% in the SRS-alone arm and 37% in the WBRT + SRS arm. No formal neurological functional tests were prospectively performed. However, validated QOL outcomes have not been reported in any of the cited studies examining the use of SRS alone (without WBRT) as upfront treatment for brain metastases.

Summary of level 1 evidence in the Japanese trial[65]

1. SRS boost with WBRT, compared with SRS alone, significantly improved local brain control rate for patients with up to four metastases.
2. SRS boost with WBRT improved survival in selected patients with a single brain metastasis.
3. The tapering of steroid doses and KPS improvement were statistically significantly better in the SRS arm at 6 months.
4. There was no statistically significant difference in any grade of either acute or late radiation toxicities between the SRS-alone arm and the SRS + WBRT arm.
5. The addition of WBRT in patients treated with SRS for one to three newly diagnosed brain metastases did not improve survival, compared with SRS alone, with WBRT reserved for salvage therapy.
6. The omission of WBRT resulted in decreased tumor control, both at the site of SRS and also in the remaining untreated brain, though upfront WBRT did not improve survival.

Conclusions

The roles of surgery and SRS may be complementary in patients with multiple metastases, particularly in those whose largest lesion causes mass-effect symptoms and in those with unresectable lesions, i.e. small-size lesions or lesions with a deep location. In this context, the ideal treatment may be surgical resection of the larger or more symptomatic lesions combined with SRS for the surgically

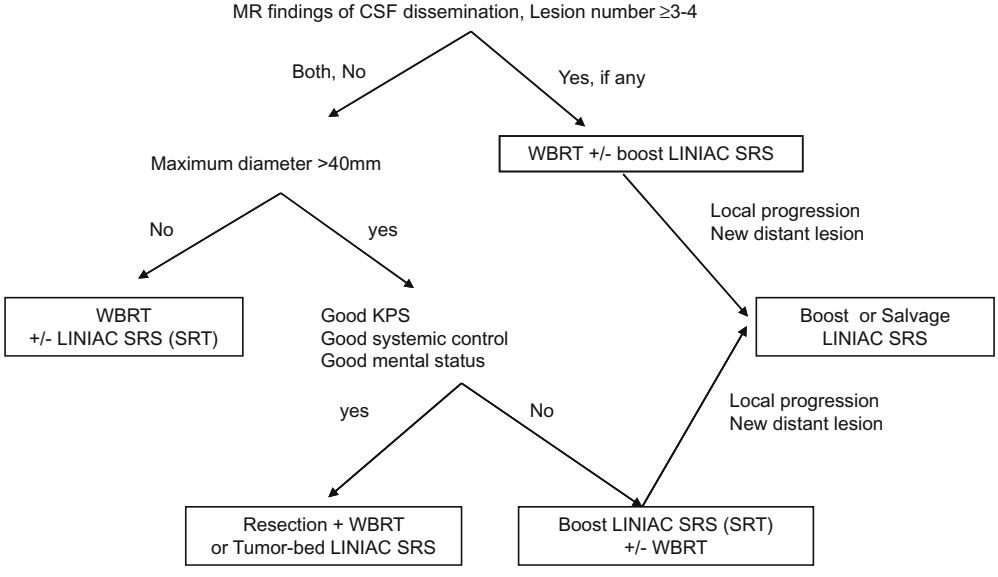

Fig. 1. Strategy for limited number (1–3 or 4) of brain metastases to be irradiated by linear accelerator stereotactic radiosurgery (*LINIAC-SRS*). *MR*, Magnetic resonance; *CSF*, cerebrospinal fluid; *WBRT*, whole-brain radiation therapy; *SRT*, Stereotactic radiotherapy; *KPS*, Karnofsky performance status

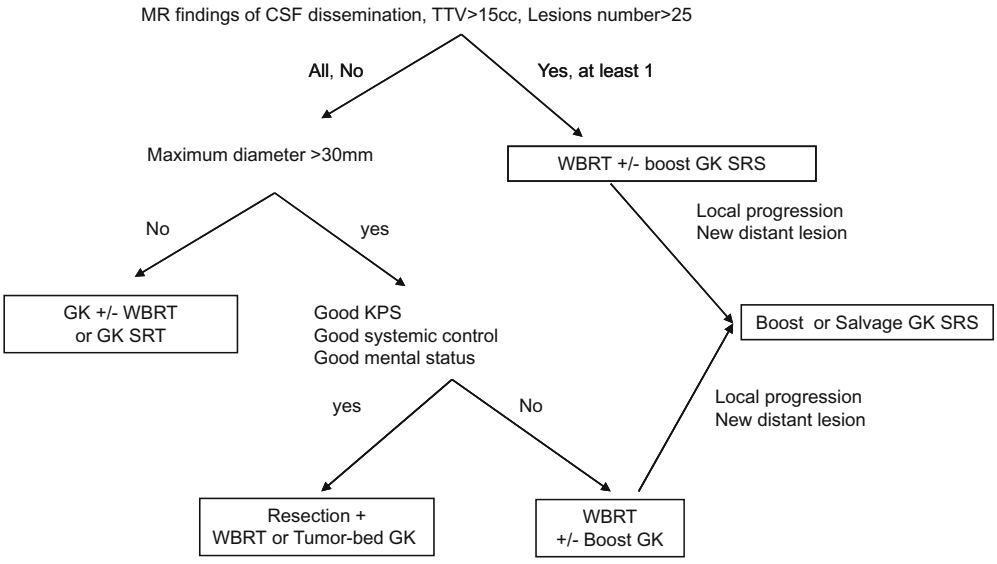

Fig. 2. Strategy for limited total tumor volume (≤15 cc) of brain metastases to be irradiated by Gamma Knife (*GK*)-SRS. *TTV*, Total tumor volume; *SRT*, Stereotactic radiotherapy

inaccessible lesions. This combination approach allows for local treatment of all brain lesions, which may be the critical factor for a successful outcome. Since the time that the University of Kentucky study clearly demonstrated the need for adjuvant therapy after the resection of a brain metastasis, WBRT has been mandatory for these patients.[3,4]

SRS as the sole initial management or as a boost before or after WBRT has emerged as a widely practiced treatment modality for brain metastases. The new treatment strategies, depending on which SRS device is available, GK or LINIAC, are outlined in Figs. 1 and 2. These strategies do not represent a guideline, and we must be flexible depending on the factors outlined above, which are variable, summarizing our knowledge from large series of retrospective and prospective nonrandomized and randomized studies.

Conflict of interest statement

The author has no conflict of interest.

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