

Gamma-Knife Radio Surgery in Brain Metastasis

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INTRODUCTION

Brain Metastasis (BM) is the most common type of intracranial malignancies in adult. Lung, breast cancer and melanoma are the malignancies which contribute up to 80% of BM [1]. Until recently, the median overall survival for patients with BM has been troubled, and in general the expected survival is at most 6 months after diagnosis [2]. However, owing to the advance of sensitive imaging modalities and various effective treatment strategies, the prognosis of patients with BM, at least in a selected group of patients, had become better.

BM represents a heterogeneous group, with different survival after various treatment strategies. Important prognostic factors are: age (<65 years), performance status (most common designed by the Karnofsky Performance Status (KPS) score ≥ 70), number of brain metastases (single or multiple), primary tumor type (lymphoma, germ cell, and breast or other), and primary tumor activity (under control or not). The treatment strategy mainly depends on the primary disease status. In guidelines, Whole-Brain Radiotherapy (WBRT), rather than Stereotactic Radio Surgery (SRS) is recommended for patients with more than four metastatic lesions [3]. Because

of the strict targeting in SRS radiation dose given in a large, single fraction, normal tissues outside a treated lesion receive doses that fall off fast, so the doses the tissue receive are much lower (frequently less than 50%) than prescribed dose.

PROGNOSTIC FACTORS

The Prognostic Factor (PF) is defined as “a situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease or the chance of the disease recurring” [4]. Numerous patient and tumor-related factors have been identified as PFs; including the KPS, age at presentation, the status of primary tumor, presence/absence of extracranial metastases, and the number and size of BM [2,5-7].

Most commonly preferred scoring system for identifying the prognosis for patients with BM, is the ‘Recursive Partitioning Analysis’ (RPA) methodology. In the RPA classification the stratification of risk groups is as follows: Patients with KPS \geq 70, age <65 years, primary tumor under control, and no extracranial systemic metastasis were included in RPA class I and had the best prognosis (median survival 7.1 months). All patients with KPS<70 were classified as class III with worst survival (median survival 2.3 months) and all remaining patients were classified as RPA II with intermediate survival rates (median survival 4.2 months) [8].

Another prognostic scoring system, Score Index For Radio Surgery (SIR), includes the variables of RPA and other factors including the number of BM (1,2 and \geq 3), volume of the largest BM (<5, 12-5, and 13cm³), location of BM and WBRT after radio surgery [7]. Lorenzoni et al., [9] proposed a new scoring system, Basic Score for Brain Metastases (BSBM) that compared RPA with SIR. In order to keep the scoring simple, this novel system included only three factors; KPS (>70, and 50-60), control of primary tumor and presence of extracranial disease.

The number of BM was demonstrated to be a significant prognosticator by RTOG 9508 investigators. However BM number was not included in the prognostic score by the previously reported RPA, BSBM, and Rotterdam scores [10,11]. Therefore, in 2007, another prognostic index called ‘Graded Prognostic Assessment’ (GPA) was proposed, that incorporated age (>60, 50-59, <50), KPS (<70, 70-80, >80), extracranial metastases (present, absent) and number of BM (>3, 2-3, 1) in the scoring system, after analyzing the outcomes of 1960 patients treated with WBRT alone, WBRT plus radio sensitizers, or WBRT plus SRS in five RTOG trials (RTOG 7916, 8528, 8905, 9104, and 9508) [12]. Each factor was given a score of 0, 0.5 or 1.0 and GPA was calculated as a sum score of all four factors with resultant four groups (score 0, 1, 2 respectively). According to this prognostic index, median survival for patients with GPA score 0-1, GPA score 1.5-2.5, GPA score 3, and GPA score 3.5-4 were 2.6 months, 3.8 months, 6.9 months and 11 months, respectively. Recently, GPA has become one of the most commonly used prognostic indexes for prognostic stratification of patients with BM.

SRS

The aim of the SRS is to destruct the all tissue residing in the target volume. In SRS the Target Volume (TV) is usually smaller, and the fraction dose is relatively high (8-30Gy/fraction). With increased technology, the delivery of large doses to tumors with reduced margin became possible and high dose gradient outside of the target volumes were observed. With this technique, lower doses to surrounding normal tissue were achieved, which in turn reduces toxicities [13].

The tumor volume is crucial during SRS delivery, because the primary goal for the best radiobiological effect is to target the TV precisely by one shot of ionizing radiation. In this setting, SRS with its rapid dose fall-off properties beyond the TV, allows the physician to achieve ultrahigh doses and to a large extent resolves the radio resistance problem [14]. Other possible mechanism is the radio biologic advantage; the benefit of reoxygenation may disappear or even totally becomes negligible. Because most of the tumors may not be hypoxic. Thus, antitumoral affects of single fraction high-dose regimes which are not predicted by classic radiobiology, such as endothelial injury and enhanced antitumor immunity after single fraction SRS was observed [13].

GAMMA KNIFE TECHNIQUES

Technically, SRS can be performed in different ways by using Gamma-Knife (GK) or high capacity novel linear accelerators. As defined by Larsson et al., [15], the term SRS transport any way of application of ionizing radiation with the end aim of destruction of an objective volume absolutely and totally without any toxicities to adjacent tissues. This ionizing radiation can be obtained either from the radioisotope sources or from X- ray generating machines such as Cobalt-60 teletherapy or linear accelerators (LINAC).

The GK has developed in 1967. Three generated models are now used worldwide. In first models (model U or A), 201 radioisotopes of ^{60}Co source that are channeled through a tungsten collimator helmet generating narrow radiation pencil beam to coincide within 0.1mm of each other at geometric center of the helmet. Multiple circular collimators are used to shot to fill a particular volume using one or multiple isocenters. Generally, prescription doses of [18-25] Gy are applied in SRS for BM. In GK treatment, the dose is usually prescribed to the 50-80% is dose line that explains the greater dose in homogeneity within the target volumes and an immediate initial dose fall off outside the prescription is dose [16]. Generally this minimum dose corresponds to 50% of the maximally applied dose (50% is dose), with maximum doses ranging between 36 and 50 Gy [17] (Table 2). A focus helmet provided with the GK can be four helmet used to produce a shot of radiation that is 4, 8, 14 or 18mm in diameter. These models present challenging ^{60}Co loading and reloading matter. In order to eliminate this problem, the model was redesigned so that source were arranged in a circular (O-ring) configuration (model B, C, and 4-C). The total number of isocenters may modify depending upon the size, shape and location of the target volume. The intended therapeutic dose is achieved by focusing many beam lines simultaneously on the target

volume with each isocenters has a set of three x, y, z stereotactic coordinates corresponding with its location in three-dimensional space as defined using a rigidly fixed stereotactic frame, while the dose derived from each source is clinically insignificant. In addition, the frame should be placed on the head in such a way to place the target as close to the center in the axial plane as possible. In 2005, the fourth-generation Leksell Gamma Knife, model 4-C was presented. This model is equipped increment designed to improve workflow, rising precision, and supply integrated imaging capabilities.

Table 1: Dose tolerance limits for Stereotactic radio surgery [77-79].

Organs	Volume (cc)	Volume (%)	Volume limit (Gy)	Max. dose limit (Gy)		Reference
Brainstem		1		10	15.8	77-77 Tradition
Chiasma (also for Optic Nerve)					15.13-12 11-10*	78-79-79 79-77
Cochlea					12	77
Brain			100	20		79
Lens					3	79

*77% probability of optic neuritis if $D_{max} > 15$ Gy; No risk of optic neuritis if $D_{max} < 10$ Gy.

After the frame is fixed, a stereotactic Magnetic Resonance Imaging (MRI) is delivered. This means, MRI with a volume uptake or fine slice with no space between slices, through the region to be examination. This MRI is used for delineation of Gross Tumor Volume (GTV) and Organs at Risk (OAR). Because MRI often provides better tumor and critical organ visualization than Computerize Tomography (CT) scanning. However, MRI alone does not provide a sufficient database for GK treatment planning, because magnetic field non-uniformity, gradient field nonlinearity, eddy current effects, and susceptibility artifact at air/tissue interface can introduce significant geometric image distortions that affect the accuracy of treatment plans. After obtaining the CT scan with helmet, MRI is fused onto the CT image space through correlation of anatomic benchmarks in both image sets. GTV should include only the visible contrast-enhanced tumor volume on MRI without encompassing the surrounding edema, and additional margins are not necessary for the creation of clinical- (CTV) or Planning Target Volume (PTV). Therefore, GTV is equivalent to CTV and PTV in GK-SRS.

EVALUATION OF TREATMENT

Aim of SRS is to avoid irradiation of healthy tissues and the adequate delivery of prescription dose to target volumes, thus steeper dose gradient around the target volume. Evaluation for treatment generally quantified using the Conformity Index (CI), which reflected the amount of normal tissue within the prescription is dose. A CI is the volume of prescription is dose line divided by the target volume, which would ideally be one, meaning that no healthy tissue were irradiated [16]. Polymer gel measurement verified the planned dose distribution in the GK models study suggested that with a CI value of 1.17 [17].

TARGET DOSE SELECTION

Generally the prescribed SRS dose depends on the tumor size and location, and also close proximity to the surrounding critical tissues. The doses for BM were defined by the RTOG 90-05 dose escalation trial [18]. According to selected parameters, the rate of grade 3 or higher neurotoxicity for SRS in combination with WBRT was reported to be less than 20%. Recommended dose for BM diameter are delineated which 24, 18, and 15 Gy were settled as the standard dose recommendations for lesions sized ≤ 20 mm, 21-30 mm, and 31-40 mm, respectively [18]. In 468 BM with a size of ≤ 20 mm, SRS doses higher than 20 Gy causes an increase of grade 3-4 neurotoxicity (5.9% vs. 1.9%, $p=0.078$), with no favorable effect on tumor control rates [19]. In addition, RTOG 95-08 investigated WBRT (37.5 Gy/15 fraction) with or without SRS in a randomized trial, and the authors showed a survival benefit for patient a single metastasis (median survival 6.5 vs. 4.9 months, $p=0.0393$) [10]. Moreover, subgroup analyses suggest an improved median survival with up to three BM in patients younger than 50 years, who have non-small cell lung cancer, or recursive partitioning analysis class 1 disease [10]. Yet, currently eliminating WBRT in SRS with BM patients is still controversial.

Previous retrospective series have suggested that omitting WBRT, increases the likelihood of central nervous system relapse but does not affect survival rates [20,21]. Subsequently, this data was confirmed in randomized trial by Japanese Radiation Oncology Study Group (JROSG 99-11) [22]. With reference to this study, median survival was 7.5 months for WBRT plus SRS vs. 8.0 months for SRS alone arm. In this study, the one-year brain tumor recurrence rate was 46.8% in the WBRT plus SRS group and 76.8% for SRS alone group ($p<0.001$) [22]. In EORTC study, the OS rates did not differ significantly between the radio surgery/surgery arm when WBRT was added versus omitted; the median survival were 10.9 months and 10.7 months, respectively ($p=0.89$), and neurologic deaths were more common in observation arm compared to WBRT added arm (44% vs. 28%, $p=0.002$). Additionally, the need for salvage therapies was more common in the single modality treatments than their combinations with WBRT [23]. In meta-analysis, SRS alone could be recommended as initial therapy for patient with one to four BMs, and survival advantage was observed especially in patients with ≤ 50 years of age [24]. Other retrospective review from Columbia University evaluated the patients with either single or multiple BM and was treated with GK-SRS alone, GK-SRS plus WBRT, GK-SRS plus surgery, or GK-SRS plus WBRT plus surgery. Irrespective of the number of BM, the results were significantly advantageous for the multimodality treatment arms over GK-SRS alone arm in terms of OS [25]. Most relevant explanations defining WBRT/SRS in treatment of BM that have been formulated in American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based guideline [26]. According to this guideline,

1. The addition of SRS after WBRT does not improve OS or duration of functional independence, but improves treated BM control and overall brain control.
2. In patients with good prognosis and single <3 cm BM, both WBRT and SRS improve brain control as compared with WBRT alone.
3. For patients with multiple BM, there is no OS benefit with the use of addition SRS boost.

Several prospective randomized trials demonstrated no survival advantage with SRS added to WBRT in patients with multiple metastases [3]. In a prospective randomized study; patients with two to four BM were randomized to initial brain tumor management with WBRT alone or WBRT plus GK-SRS [27]. The study was stopped early after an interim analysis, due to 1-year local failure rate of 100% after WBRT alone but 8% in patient who had boost radio surgery arm. Although ASTRO, the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) agree that SRS is performed in a single session, but can be performed in up to five sessions [28,29]. The most important prognostic factors for BM patients with ≤ 4 metastases are KPS, age, extent of extracranial metastatic disease, extent of systemic disease control, number of intracranial lesions, and intracranial tumor burden [10,30-33]. Moreover, the tumor volume gains significant importance in prognosis, which has been expressed among other inclusion criteria for SRS qualifications by the National Health Service commissioning criteria (Table 2) [34,35].

Table 2: National Health Service commissioning criteria for stereotactic radio surgery and stereotactic radiotherapy for brain metastases.

Criteria	Recommendation
Patient selection	Patients should be selected by local multidisciplinary team with understanding of the systemic and neurological disease processes and neurosurgical options, as well as discussion by the specialist stereotactic radio surgery multidisciplinary team
Performance status	Karnofsky performance score ≥ 70
Cancer diagnosis	Established
Primary disease	Absent or controllable
Life expectancy	≥ 6 months from extracranial disease
Total tumor volume	≤ 20 cm ³

GK-SRS has been widely utilized as a primary treatment or in combination with WBRT. Even with multiple BM, GK-SRS can be effective for selected patient [36-39]. Although, treatment of multiple BM by the GK-SRS is feasible and become less time consuming with improved models, but it is very important to carefully consider the treatment options in each individual patient [40].

GK radio surgery is a standard treatment modality for patient with a limited number (≤ 4 lesion) of brain metastasis, but recently, there has been increasing interest in proposing GK-SRS to patients with ≥ 5 BM treated with GK-SRS [23,41]. Current evidence is limited to a few data, in which overall survival after radio surgery was evaluated [42-44]. Serizawa et al., [45] performed a retrospective study in 778 patients with 1-10 metastases who were treated SRS and concluded that the number of BM has no impact on survival. In a combined series of 1508 patients treated by GK-SRS, the authors found no significant survival difference between the patients with 2-4 or 5-10 BM [46]. Karlsson et al., [47] reported a series of 1855 patients with BM (1-8 lesions) treated with SRS over a 30-year period, and the authors found no survival difference in patient with >2 metastases. In another study by Chang et al., [48], 323 BM patients were treated by GK-SRS and categorized into 4 groups according to the number of BM: the median OS for patients with 1-5, 6-10, 11-15, and >15 BM were 10, 13, 10, and 8 months, respectively ($p > 0.05$).

The MD Anderson Cancer Center GK-SRS alone series (251 patients) showed that the number of BM was not predictive of distant brain failure, local control, and OS [49]. Similarly, in the Stanford University retrospective post-WBRT GK-SRS series (310 patients) following exclusion of the patients with single BM, and the authors did not show any significant correlation between the number of BM and OS [50]. In contrast, Yamamoto et al., [46] reported a series of 1676 patients with 1-8 BM and concluded that the number of lesions did have a statistically significant effect on survival.

Current evidence suggests that WBRT may not be only therapeutic option for patients with ≥ 5 BM, and multiple retrospective data have revealed no significant survival difference in patient with multiple BM as the number of metastases as the number of metastases increased [44-46,49,50].

GK-SRS TO THE TUMOR BED

The current standard treatment for patients presenting with large BM and mass-related significant neurological symptoms is surgery, which is based on the literature demonstrating superior OS and better functional outcomes after neurosurgery, compared to long-course fractionated WBRT [51,52]. The European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 study, found that WBRT reduced the 2-year relapse at the initial site of operation from 59% to 27% ($p < 0.001$) [25].

In literature numerous reports show that postoperative GK-SRS to the tumor bed is effective treatment modality for brain metastases [53-55]. One prospective study demonstrated that, this treatment option resulted in excellent local control, particularly for small metastases without superficial pail involvement [56,57]. Moreover, other reports suggested that postoperative GK-SRS was a good treatment option for BM and could even delay WBRT delivery [58,59]. According to previous studies, patients were successfully treated with postoperative GK-SRS to the tumor bed with 1-year local progression free survival rates of 71.8-94.2% [60-62].

SRS is usually not recommended for BM of $>3-4$ cm because of higher likelihood of irradiation-induced edema progression. In RTOG 90-05, patients with BM <4 cm (regardless of the cystic component) were enrolled on the study, and 15 Gy was determined to be the MTD of SRS for lesions sized 3.1 to 4 cm [20].

TREATMENT OF RECURRENT BM

Unfortunately, local or distant in brain recurrences of BM occur in a majority of patients treated with either of WBRT, surgery, or both. In a retrospective analysis by Kurtz et al., [63], 279 recurrent BM patients after WBRT were evaluated. Of them, 106 patients were treated with GK-SRS, which a median dose of 21 Gy (range, 12-24 Gy). The 6-months, 1-year, and 3-year local control rates were 82.8%, 60.1%, and 46.8%, respectively. Median OS was 11.7 months after salvage SRS [63]. Another study reported 54 consecutive patients presenting with 97 BM relapses after WBRT were treated with salvage SRS [64]. At a median follow-up of 9 months, and

median GK-SRS dose of 16.2 Gy (11.8-23 Gy), the 1- and 2-year local control rates were 91.3% and 84.0%, respectively, and the 1- and 2-year OS rates were 31 and 28%, respectively. Authors recommended that the dose not exceeding 14 Gy should be delivered to a dose representing 70% of the maximal dose, since local control rates were similar to that of previously published reports.

QUALITY OF LIFE

The association between WBRT and adverse neurocognitive outcomes in patient treated upon the development of BM has been reported by Chang et al., [43]. This randomized trial demonstrated that the addition of WBRT to SRS is associated with a significant decline in learning and memory at four months [43]. The EORTC randomized trial comparing observation versus WBRT, after either SRS or surgery, demonstrated worse quality of life outcomes with addition of WBRT after SRS [65]. However, all of these trials have steadily shown higher rates of intracranial relapse when WBRT is omitted. The preservation of neurocognitive function is vigorously correlated with tumor control rates with more extended follow-up [66]. Another study, which uses mini-mental state examination in order to assess the cognitive functions, revealed no significant difference in cognitive functions between the SRS and WBRT plus SRS groups, with successful tumor control rates. The authors also reported that the most important factor associated with preservation of cognitive function was local control [67]. Conversely, the results of the latest study evaluating the cognitive function in patients with 1 to 3 BM disclosed significant dismal effects to learning and memory function with addition of WBRT to SRS [43].

Limitations of GK-SRS contain accessible range, treatment field size of lesions, and radiation-induced adverse effects, which occur in 5% to 20% of patients [68-71]. Large lesions cannot be effectively treated with single fractionated radio surgery because high dose irradiation at one session for larger tumors increases the effect of undesirable irradiation to the normal brain tissue. The three-staged GK-SRS treatment (3 fractions with margin dose of 10Gy at 2-week interval) for unrespectable BM more than 10cm³ was effective, achieving 1-year tumor control rate of 76% [72].

ACUTE COMPLICATIONS

Acute complications within the first week of SRS treatment are rare. Most common complications are headache after frame removal, infection of pin sides, nausea, vomiting, seizures, transient neurologic symptom deterioration, and fatigue. The incidence of severe headaches is very rare [73]. Although majority of complications are temporary and self-limiting, seizures may be problematic with an incidence range of 2% to 6% which tends to further increase in patients undergoing SRS for cortical lesions and for those with history of seizures [73,74]. Peritumoral edema is generally associated with SRS of larger lesions or excessive doses beyond the target volume. Therefore, single session SRS in larger BM is generally not recommended due to the increased risk of a later formation of edema with associated delayed side effects [17]. Corticosteroids may effectively manage edema in most cases [75].

SUB ACUTE COMPLICATIONS

Sub acute complications occur within the first six months after treatment. Alopecia has been reported in 5-6% of patients [73]. Most of these patients had superficial lesions, and scalp received median dose of 4.4Gy. Sometimes neurologic deterioration can occur in patients, which is generally resolved with steroid.

Chronic Complications

Chronic complications may exhibit from months to years, the incidence peaks after 12 to 15 months of the SRS treatment. Radiation Necrosis (RN) is most serious chronic complications and incidence increases with higher radiation doses, prior RT history, and irradiation of larger and/or multiple tumor volumes. This symptom can be difficult to recognize from tumor recurrence even with the currently available imaging techniques [73].

RTOG 90-05 was determined the Maximum Tolerated Doses (MTD) of SRS dose for patients with previously irradiated recurrent primary brain tumors or brain metastases an adjunct to WBRT for BM [20]. According to this trial MTD were inversely correlated with the maximum tumor diameter, which were determined as 24 Gy, 18 Gy, and 15 Gy for tumors \leq 20 mm, 21-30 mm, and 31-40 mm, respectively. The actual ratios of RN were 5%, 8%, 9% and 11% at 6, 12, 18 and 24 months after SRS, respectively [20].

The generally management for RN is to decrease the edema and necrosis. High dose steroids are used to minimize neurologic deterioration. If the patient becomes symptomatic despite steroid, surgical resection may be considered. In some patient, hyperbaric oxygen has been used for patients who are poor surgical candidates, have multiple fields of RN, or have a surgical inaccessible lesion [76].

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