Stereotactic radiosurgery for brain metastases

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Brain metastases are the most common intracranial tumors and have a poor prognosis in their natural course. Treatment options include surgical resection, whole brain radiotherapy, stereotactic radiosurgery (SRS), and systemic therapy. The applications of SRS have expanded over the last several decades, and SRS has become the most commonly used primary treatment modality for metastatic brain tumors. This review summarizes the role of SRS in the treatment of metastatic brain tumors and discusses the recommendations of guidelines.

KEY WORDS: Radiosurgery, Brain neoplasm

INTRODUCTION

Brain metastases are common intracranial tumors affecting up to 30% of cancer patients [1]. The incidence of brain metastases is increasing as more effective systemic therapies improve extracranial tumor control and result in prolongation of survival. Traditionally the central nervous system (CNS) was considered a sanctuary site due to the blood-brain barrier preventing delivery of therapeutic agents. Surgical resection in eligible patients and whole brain radiotherapy (WBRT) were main stream of treatment in the past with mostly dismal prognosis. Introduction of stereotactic radiosurgery (SRS) significantly changed paradigm of treatment and became standard or preferred therapeutic option in wide range of application. Although targeted agents and immunotherapy agents are used increasingly and some of them are effective on brain metastases, drug resistance will eventually develop in many patients and SRS continues to play a central role in the management of brain metastases.

EVOLUTION OF TREATMENT FOR BRAIN METASTASIS AND STEREOTACTIC RADIOSURGERY

The best known of the early studies on the treatment of metastatic brain tumors is a paper published by Patchell et al. [2] in 1990. In this study, the cases of single metastasis treated with radiation therapy alone and those treated with surgical resection followed by postoperative radiation therapy were compared through randomized trial. The time to recurrence and survival time after surgery were both significantly longer in the group of patients who received surgical resection followed by postoperative radiation therapy. In a paper published by Patchell et al. [3] again in 1998, patients with single metastasis treated with surgery alone and those with surgery followed by postoperative radiation therapy were compared. In the
patient group who received postoperative radiotherapy, the time to local recurrence and distant recurrence, and overall survival time were all significantly longer. Based on these studies, a combination of surgery and radiation therapy has become the standard treatment for single metastasis when possible. However, metastatic brain tumors are frequently multiple, and even for single metastasis, surgery is often not appropriate. In those situations WBRT was the only treatment available for the majority of patients in the past. In addition, systemic treatment for various cancers was not very effective, and in most cases, there was no effective treatment for the progression or recurrence of brain metastases after WBRT, so the prognosis for cancer patients diagnosed with brain metastases was usually very poor. SRS using linear accelerator for brain metastases was first published in 1987, and another case treated with Gamma knife was reported in 1989 [4,5]. The results of RTOG 9508 reported in 2004 [6] led SRS to be used routinely for the treatment of metastatic brain tumors. In this study of the patients with 1 to 3 brain metastases, the group of the patients treated with a combination of SRS and WBRT and the group of the patients treated with WBRT alone were compared in a randomized trial. For single lesions, the median survival time in the group of patients treated with addition of SRS to WBRT was 6.5 months, which was statistically significantly longer than 4.9 months in the group of patients who only received WBRT. In all the patients with lesions up to 3, the rate of KPS remaining stable at 6 months in the group of patients who received SRS and WBRT was 43%, which was significantly higher than the rate of 27% in the group of patients who only received WBRT. Subsequently, Aoyama et al. [7] reported a randomized controlled trial (RCT) which compared SRS plus WBRT with SRS alone in the patients with 1 to 4 lesions. There was no significant difference in overall survival between the two patient groups though the recurrence rate at 12 months was significantly lower in the group of patients treated with a combination of SRS and WBRT. An RCT published in 2009 reported that SRS alone was significantly more advantageous than the combination of SRS and WBRT for preserving cognitive function [8,9]. Based on these research results, SRS alone for oligometastases with 5 or less lesions have been recognized as the standard treatment. Multiple randomized trials that investigated SRS, WBRT, and SRS combined with WBRT versus observation in patients with small numbers of brain metastases are briefly summarized (Table 1) [3,6-15].

Metastatic brain tumors frequently occur as multiple lesions, and as the number of lesions increases, the probability of tumor control after SRS decreases. Therefore, there has been long lasting controversy over the number of lesions to which SRS can be applied. With the development of SRS equipment and technology, accurate and efficient treatment has become possible for an increasing number of lesions while reducing radiation exposure to normal tissue below the appropriate level. In a prospective multi-institutional prospective observational study on this issue, 1,194 patients were classified into groups with 1, 2 to 4, and 5 to 10 lesions, respectively, according to the number of lesions. The survival time in the patient group with 1 lesion was longer than in the other groups, but the survival time was same in the patient group with 2 to 4 lesions and the patient group with 5 to 10 lesions with 10.8 months. These results show that even if the number of lesions is 5 or more, SRS alone can be applied as a primary treatment when the sum of the total tumor volume is within an appropriate range and life expectancy excluding brain lesions is not expected to be too short [16].

In cases where the tumor is large and neurological symptom caused by increased intracranial pressure or mass effect is severe, surgical treatment is still the most rapid and effective treatment. WBRT after surgery has been the standard treatment for decades. When SRS instead of WBRT was given to the resection cavity, RCT proved that the local recurrence rate was significantly reduced compared to the case without additional treatment after surgical resection [10]. Postoperative SRS was superior to postoperative WBRT in preservation of cognitive function with no difference in survival time [11]. In the long-term follow-up results the intracranial tumor control rate was lower with SRS than WBRT, the rate of deterioration of cognitive function was still consistently low [17]. As SRS for the resection cavity was established as a standard treatment after surgery, the effectiveness of so-called neoadjuvant SRS, which is SRS performed before surgery, was highlighted. Although it has not yet been proven through RCT, neoadjuvant SRS is thought to have several advantages over postoperative resection cavity SRS. The relative advantages of neoadjuvant SRS include direct effects such as improvement in the local recurrence rate, reduction in the frequency of leptomeningeal disseminated metastases, and reduction in the incidence of radiation necrosis (RN), as well as indirect benefits such as the advantages of shortening the treatment period and early implementation of systemic therapy are listed [18].

In SRS for metastatic brain tumors, the volume of the lesion and the radiation dose are the two most important factors that affect the tumor control rate and the occurrence of side effects. According to the results of RTOG protocol 90-05, when single dose SRS was performed in patients who had previously received radiation therapy, a radiation dose of 24 Gy given to tumors of 20 mm or less, 18 Gy to tumors of 21 to 30 mm and 15 Gy given to 31–40 mm tumors were accompanied with grade 3 or higher CNS toxicity in 10%, 20% and 14% of cases, respectively [19]. It is obvious that the larger the tumor and the higher the radiation dose, the higher the frequency of complications in normal brain tissue.
Table 1. RCTs of SRS, WBRT, and combination therapy in patients with small numbers of brain metastases

<table>
<thead>
<tr>
<th>Authors, year, size, design</th>
<th>Treatment setting and interventions</th>
<th>Key outcomes</th>
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<tbody>
<tr>
<td>Patchell et al. [3], 1998, 95 patients, RCT</td>
<td>One resected metastasis WBRT vs. no WBRT</td>
<td>Brain recurrence rate: 18% vs. 70%, p &lt; 0.001</td>
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<td>Andrews et al. [6], 2004, 331 patients, RCT</td>
<td>1–3 newly diagnosed metastases SRS+WBRT vs. WBRT</td>
<td>Median OS: 5.7 months vs. 6.5 months; p = 0.1356</td>
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<td>Aoyama et al. [7], 2006, 132 patients, RCT</td>
<td>1–4 metastases &lt; 3 cm WBRT+SRS vs. SRS alone</td>
<td>Median OS: 7.5 months vs. 8 months (p = 0.42)</td>
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<td>Chang et al. [8], 2009, 58 patients, institution-based RCT</td>
<td>1–3 newly diagnosed metastases eligible for SRS, KPS &gt; 70 SRS vs. SRS+WBRT</td>
<td>Cognitive deterioration: 24% (of 20 evaluated) vs. 52% (of 11 evaluated) of patients experienced HVLT-R, with a total recall reduction of 5 points or more from baseline at 4 months</td>
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<td>Kocher et al. [12], 2011, 359 patients, phase III RCT</td>
<td>1–3 metastases, WHO PS 0–2 (SRS or surgery)+WBRT vs. (SRS or surgery)</td>
<td>Median survival with functional independence (WHO PS &gt; 2); 9.5 months vs. 10 months: HR, 0.96 (95% CI, 0.76–1.20; p = 0.71)</td>
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<td>El Gantery et al. [13], 2014, 60 patients, institution-based RCT</td>
<td>1–3 metastases, KPS &gt; 70 SRS vs. WBRT vs. SRS+WBRT</td>
<td>Local control rate: 22.2% vs. 19% vs. 42.9%, p = 0.04</td>
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<td>Lim et al. [14], 2015, 98 patients, institution-based phase III RCT</td>
<td>1–4 metastases, ECOG PS 0–1 SRS+chemotherapy vs. chemotherapy alone</td>
<td>Median OS: 14.6 months (95% CI, 9.2–20.0) vs. 15.3 months (95% CI, 7.2–23.4) for chemotherapy alone (p = 0.418)</td>
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<td>Brown et al. [9], 2016, 213 patients, phase III RCT</td>
<td>1–3 metastases &lt; 3 cm, ECOG PS 0–2 SRS vs. SRS+WBRT</td>
<td>Symptomatic progression 18.4% vs. 26.5% without statistical significance</td>
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<td>Brown et al. [11], 2017, 194 patients, phase III RCT</td>
<td>1–3 resected metastasis and resection cavity &lt; 5 cm, ECOG PS 0–2 SRS vs. WBRT</td>
<td>Cognitive deterioration: 63.5% vs. 91.7% experienced deterioration at 3 months, difference -28.2% (90% CI, -41.9% to -14.4%; p &lt; 0.001)</td>
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<td>Mahajan et al. [10], 2017, 132 patients, phase III institution-based RCT</td>
<td>1–3 resected metastases, KPS &gt; 70 SRS vs. no SRS</td>
<td>Time to intracranial failure: HR, 3.6 (95% CI, 2.2–5.9; p &lt; 0.001)</td>
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<td>Kayama et al. [15], 2018, 137 patients (WBRT) &amp; 134 patients (SRS) phase III noninferiority RCT</td>
<td>≤ 4 resected metastases, ECOG PS 0–2 Observation with salvage SRS vs. WBRT</td>
<td>Median OS: 15.6 months vs. 15.6 months: HR, 1.05 (95% CI, 0.83–1.33; p = 0.03 for noninferiority of SRS for margin of HR 1.385)</td>
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caused by radiation. Therefore, to maintain the incidence of complications at an acceptable level, the radiation dose should be adjusted and inevitably the tumor control rate is lowered. To solve this problem, fractionated SRS as a compromise between single fraction SRS and fractionated radiotherapy has been introduced. The tumor control probability is 75% when 18 Gy is given to a 21–30 mm tumor, and 70% when 15 Gy is given to a 31–40 mm tumor. Meanwhile the tumor control probability was reported to be 80% when a total of 27–35 Gy was given 3–5 times to a 21–40 mm tumor [20]. In addition, it has been reported that fractionated SRS in large tumors could increase not only the tumor control rate but also lower the incidence of RN compared to single fraction SRS [21]. Although not yet clearly proven by RCT, these data recommend that fractionated SRS be considered for tumors exceeding 20 mm in size. The guidelines for the appropriate number of fractions or radiation dose in fractionated SRS are not yet clear either. Probably optimal dose or number of fractions may be influenced not only by the size of the tumor but also by the histology or method of dose planning. It was reported through a dose-escalation study that the appropriate dose considering tumor control rate and RN is 9 Gy per fraction for 3 fractionated treatments [22]. It was suggested that biological effective dose (BED) 50 Gy or more is necessary for control of brain metastasis. Based on linear quadratic formula it is possible to calculate dose per fraction in fractionated SRS required to obtain BED 50 Gy. If α/β ratio = 10 is assumed for brain metastases, approximately 11.6 Gy in 2 fractions, 8.9 Gy in 3 fractions, 7.3 Gy in 4 fractions, and 6.1 Gy in 5 fractions are required. However, despite these attempts, RN still occurs at a significant rate. In single fraction SRS, the rate of RN can be kept to 20% when V12 exceeds 15 cm³, and in 5-fraction split treatment, the frequency of RN or edema can be kept below 10% when V24 is less than 20 cm³ [3,23]. In clinical context, local recurrence and RN are major important events after SRS. Following SRS, up to one-third of treated lesions will increase in size [24]. Thus, appropriate diagnosis of RN versus tumor progression (TP) is critical as this will guide next steps in management and avoid unnecessary treatments, such as surgery, re-irradiation, or discontinuation of a systemic therapy that was in fact effective. Therapeutic options for local failure after SRS are similar to those for newly diagnosed lesions including surgical resection, SRS and fractionated radiotherapy. SRS is a preferred treatment again for feasible lesions. In a report of systematic review and meta-analysis [25] pooled 1-year local failure after a second course of SRS was 24% and cumulative crude RN rate was 13%. Therefore, it is considered that second course of SRS is an effective strategy for in-site recurrence of brain metastasis previously treated with SRS. The treatment of RN is frequently empiric and decision-making are largely driven by the acuity and severity of symptoms. In the past, RN was primarily treated with corticosteroids and surgical resection was recommended in selected cases that did not respond to corticosteroid. Recently, bevacizumab was introduced as a very effective means of treating RN. According to a systematic review, 95% of 235 patients improved clinically, and 85% showed improvement in imaging findings [26]. Laser interstitial thermal therapy (LITT) is a relatively novel invasive modality that serves as an alternative to surgical resection. Though a meta-analysis performed by Palmisciano et al. [27] comparing 148 patients undergoing LITT and 143 patients receiving bevacizumab demonstrated that LITT provided improved overall survival rates and equivalent symptomatic improvement and mean T1-weighted volume reduction.

Meanwhile differential diagnosis of TP and RN is a dilemma. Histopathology is the gold standard for accurate diagnosis, but may not always be feasible due to potential complications from surgery. Diverse techniques of magnetic resonance imaging (MRI) and positron emission tomography are useful in differentiating TP from RN. However, TP versus RN is not an issue of all or none phenomenon and frequently symptomatic lesions are composed of both viable tumor tissue and RN [22]. Finally, repeated course of SRS or treatment of RN should be chosen based on clinical decision considering dominant features favoring recurrence or RN. In repeated course of SRS, the risk of RN appears lower after re-irradiation with fractionated SRS when compared to single fraction-SRS. Other potential risk factors of RN include the volume of overlap of normal tissue receiving 12 Gy at the first course and 18 Gy at the second course of SRS, maximum doses ≥ 40 Gy of the first or the second SRS courses, V12 Gy > 9 cm³ of the second course, initial treatment with single fraction SRS [28].

CURRENT TREND IN TREATMENT OF BRAIN METASTASES

Recently, a prominent trend in the treatment of metastatic brain tumors is the attempt to increase the treatment effect by combining systemic treatment and SRS. Compared to SRS alone or systemic therapy alone, the combination of SRS and systemic treatment was reported to be associated with better progression free survival and overall survival [29]. Among systemic therapies, immune checkpoint inhibitors are expected to have a synergistic effect when combined with SRS. Patients treated with immune checkpoint inhibitor (ICI) got superior efficacy to those without ICI. In terms of response and survival, concurrent administration of SRS and ICI led to better outcomes than non-concurrent or non-SRS [30].

In terms of the technical aspect of SRS, the rapid introduction
and dissemination of artificial intelligence (AI) is a notable trend. The use of AI is rapidly expanding with wide range of application such as the initial diagnosis of metastatic brain tumors, target delineation for SRS, dose planning, interpretation of follow-up images after treatment, and analysis of large amounts of data obtained from huge number of the patients.

The most recent NCCN guideline (version 1; 2024) presents general treatment principles based on research results and accumulated clinical data, and recommends a wider scope of application for SRS compared to the past. In the case of limited brain metastasis, SRS alone is favored instead of WBRT. According to the guideline, it is recommended to follow up with a brain MRI every 2 to 3 months for 1 to 2 years and then every 4 to 6 months indefinitely [31]. Even in patients with disseminated systemic disease application of SRS is not restricted and generally recommended over WBRT except for patients without systemic treatment options.

CONCLUSION

Role of SRS has grown remarkably since its introduction. Less invasive immobilization method and modified fractionation scheme are driving further expansion. A significant portion of the areas managed with WBRT in the past have been replaced by SRS, and treatment outcomes are being improved by using SRS alone or in combination with systemic therapy, which is rapidly developing in recent years. Multi-disciplinary and personalized approach is necessary for optimal outcome. Techniques of SRS and its application will continue to progress and paradigm of treatment for brain metastases will continue to evolve.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES