Review

Radiotherapeutic Treatment Approaches for Brain Metastases

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Abstract. *Brain metastases represent an important healthcare problem. Approximately 20%-40% of patients develop disease metastatic to the brain over the course of their cancer history. Palliative treatment of brain metastases requires for immediate control and, at least temporarily, a remission of the symptoms because many of the symptoms associated with brain metastases reduce the patient's quality of life. Radiation therapy is used to treat this clinical circumstance. The aim of this review is to assess the efficacy and the toxicity of radiotherapeutic treatment approaches and to provide treatment recommendation for brain metastases.*

Brain metastases represent an important complication of malignant tumours. Recent progresses in modern combined modality therapy have improved survival in patients with cancer. Management of these patients is therefore a new challenge for the radiotherapist. The primary goal of therapy is to improve and preserve patient's quality of life.

Treatment Approaches

Palliative treatment of brain metastases requires for immediate control and, at least temporarily, a remission of the symptoms because many of the symptoms associated with brain metastases reduce the patient's quality of life.

Treatment approaches are evolving: nowadays lesions may be treated by surgical resection, whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS). In 1997, Gaspar *et al*. suggested three prognostic classes for brain metastases (1) using recursive partitioning analysis (RPA) of three consecutive Radiation Therapy Oncology Group (RTOG) trials. Class I includes patients with controlled primary tumors and no extracranial metastases, Karnofsky performance status ≥70 and age <65 years; class III patients have Karnofsky performance status <70; class II includes patients who do not meet requirements of class I and III.

The RPA classification should currently be utilized as a stratification factor for choosing an appropriate treatment approach (2). Radiosurgery or surgical resection, both followed by WBRT, are used to treat single metastases in class I patients. WBRT-alone is the appropriate treatment for multiple metastases for patients of any class. Class I or II patients with two or three brain metastases should be treated with single or multiple modalities (3).

Whole-brain radiation therapy. Historically, WBRT was the gold standard treatment for patients with brain metastases (4, 5). It continues to be the standard-of-care in the modern era, as treatment of choice for patients who are unsuccessful candidates for surgery or SRS, as adjuvant therapy to improve local control, and as treatment for recurrent disease. The rationale of WBRT is the assumption that haematogenous spread from the primary tumor could disseminate micrometastatic disease in the entire brain. Apart from radiation therapy indication (as single modality or in the adjuvant setting), the optimal dose and fractionation schedule are still debatable. Representative regimens tested are reported in Table I.

Graham *et al*. compared 20 Gy (500 cGy/fr) *versus* 40 Gy in 20 twice-daily fractions, in class I and II patients; the intracranial control rate was better with total dose of 40 Gy (56% *vs*. 36%) (6). Murray *et al*. compared accelerated hyperfractionated radiotherapy (160 cGy *b.i.d.*) to a total dose of 54.4 Gy *versus* accelerated fractionation of 30 Gy (300 cGy/fr), in patients with unresected brain metastases (7). The authors demonstrated equivalent survival for both regimens (median survival=4.5 months). The Royal College of Radiologists' trial compared two whole-brain radiotherapy

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Table I. *Randomized trials testing different regimens for therapy of brain metastases.*

Author	Total dose; single dose/fr	Median survival
Graham *et al.* (6)	20 Gy; 500 cGy/fr	6.6 Months
	40 Gy; 200 cGy/fr	6.1 Months
Murray *et al.* (7)	54.4 Gy; 160 cGy/fr	4.5 Months
	30 Gy; 300 cGy/fr	4.5 Months
Priestman *et al.* (8)	30 Gy; 300 cGy/fr	84 Days
	12 Gy; 600 cGy/fr	77 Days
Haie-Meder *et al.* (9)	18 Gy; 600 cGy/fr	4.2 Months
	36 Gy; 600 cGy/fr	5.3 Months
Kurtz *et al.* (10)	30 Gy; 300 cGy/fr	4.5 Months
	50 Gy; 250 cGy/fr	4.2 Months
Borgelt *et al.* (11)	30 Gy; 300 cGy/fr	21 Weeks
	30 Gy; 200 cGy/fr	18 Weeks
	40 Gy; 266 cGy/fr	18 Weeks
	40 Gy; 200 cGy/fr	16 Weeks
	20 Gy; 400 cGy/fr	15 Weeks

regimens, in patients with symptomatic brain metastases: 30 Gy (300 cGy/fr) *versus* 12 Gy (600 cGy/fr) (8). Better survival was confined to patients with good prognosis submitted to a longer radiotherapy schedule (84 days *vs.* 77 days). In the trial of Haie-Meder *et al.*, patients with brain metastases were randomized to two schedules of brain irradiation: one course of 18 Gy (600 cGy/fr) *versus* the same regime followed by a second course of radiotherapy, one month later (9). But no significant difference in survival was demonstrated (4.2 *vs.* 5.3 months). Kurtz *et al.* compared 30 Gy (300 cGy/fr) *versus* 50 Gy (250 cGy/fr) in class I patient population (10). Comparable median survival was reported between the two regimens (4.5 *vs.* 4.2 months). Five schedules of whole-brain irradiation [30 Gy (300 cGy/fr); 30 Gy (200 cGy/fr); 40 Gy (266 cGy/fr); 40 Gy (200 cGy/fr); 20 Gy (400 cGy/fr)] were evaluated in two randomized Radiation Therapy Oncology Group (RTOG) studies – RTOG 6901 and RTOG 7361 – to determine palliative efficacy in patients with metastatic brain disease. All treatment schedules had comparable outcomes (21 *vs.* 18 *vs.* 18 *vs.* 16 *vs.* 15 weeks) (11). Despite numerous studies testing numerous combinations of dose and fractionation, a total dose of 30 Gy (300 cGy/fr) continues to be the standard in clinical practice. None of the altered dose-fractionation schemes compared to 300 cGy delivered in 10 fractions found a benefit in terms of overall survival, neurological function, and symptom control (12). A significant difference in median survival was only demonstrated in the trial of Priestman *et al.* (p-value=0.04).

Toxicity. The side-effects of WBRT include hair loss, headache, nausea and vomiting, hearing loss, otitis, skin erythema, and transient neurological symptoms; therapy with corticosteroids should be continued during WBRT, to improve oedema and neurological deficits. Other complications, such as cataract formation, dry eye, dementia, memory loss and decreased concentration, are possible but the incidence is underestimated because of the short survival period of these patients. These symptoms usually develop six to 24 months after WBRT and the degree of toxicity depends on the total dose received and the time–dose-fractionation scheme. The biological rationale of the use of accelerated hyperfractionation is to reduce the effect of tumour-cell re-population between fractions, exploiting the different capacity of cells to recover from sublethal radiation damage; the aim is to improve tumour control without increasing the risk of late complications (13). The RTOG 9104 study compared acute toxicity rates between accelerated hyperfractionated radiotherapy (160 cGy *b.i.d.*) to a total dose of 54.4 Gy *versus* accelerated fractionation of 30 Gy (300 cGy/fr) (7). Acute and late side-effects were not different between the two regimens. A case of severe ototoxicity (acute toxicity) and a patient death (late toxicity) following the development of cerebral oedema were noted in the accelerated hyperfractionated group. De Angelis *et al.* reported a series of 12 patients who developed delayed complications of WBRT (14). Daily fractions of 300 to 600 cGy were employed to a total dose range from 25 to 39 Gy. Five to 36 months after therapy, all patients developed progressive dementia, ataxia, and urinary incontinence, causing severe disability. When neurological symptoms began, a Computed Tomography (CT) scan was performed: the examination did not reveal recurrent disease, but identified cortical atrophy and hypo-dense white matter. Therefore, in class I patients with a better median prognosis of seven months, a smaller dose per fraction schedule should be employed in order to reduce the risk of long-term neurological toxicity. WBRT is discussed in adjuvant setting due to potential late neurocognitive toxicity; nowadays, this toxicity can be improved with the development of techniques sparing the hippocampus (15).

Whole-brain irradiation technique. The patient should be conscious because their collaboration is needed for data acquisition during treatment planning. The patient is treated supine and is immobilized in a thermoplastic shell, fixed to the couch in at least three places, with the neck in a comfortable neutral position. CT simulation is now commonly used, but planning can be adequately carried-out with the traditional simulator. Beams are defined to cover the whole skull, from the vertex to the base. Radiation therapy is delivered with 6 MV energy photons. The patient is set-up daily.

Adjuvant whole-brain radiotherapy. Patchell *et al.* designed a multi-center randomized parallel group trial to investigate if adjuvant radiotherapy resulted in improved neurological

control of disease and increased survival (16). After complete surgical resections, Magnetic Resonance proven, patients were assigned to treatment with postoperative WBRT (50.4 Gy; 180 cGy/fr) or to observation. Adjuvant radiotherapy resulted in better tumour control than surgical resection alone. Adjuvant radiotherapy was associated with significantly less tumour recurrence anywhere in the brain (18% *vs*. 70%), at the site of surgical resection (10% *vs*. 46%), and in any other area in the brain (14% *vs*. 37%). Radiation therapy reduced death due to neurological causes (14% *vs*. 44%). Despite the reduction in brain recurrence and neurological death, adjuvant WBRT did not result in increased overall survival or the length of time patients remained independent. However, the study could be criticized due to the non-standard WBRT dose, a decrease in neurological deaths is a valid justification for the routine use of adjuvant radiation therapy.

Whole-brain radiation with/without surgery. Three randomized trials investigated the efficacy of WBRT with or without surgery in patients with single brain metastases (17-19). Patchell *et al*. conducted a prospective randomized study to determine if surgical resection of a single brain metastasis followed by WBRT resulted in improved survival and better quality of life *versus* WBRT-alone (17). Radiotherapy was delivered to a total dose of 36 Gy (300 cGy/fr) in both groups of patients. Postoperative WBRT resulted in better local tumor control: local recurrence at the site of original metastasis localization was significantly lower (20% *vs*. 52%); the median time of recurrence was increased (59 weeks *vs*. 21 weeks). The median survival was improved in postoperative WBRT group (40 weeks *vs*. 15 weeks). Duration of functional independence was significantly longer in patients treated with surgery plus WBRT than in those treated with WBRT alone (38 weeks *vs*. 8 weeks). Similarly, Wecht *et al*., in a prospectively randomized trial, compared the effect of surgical resection plus WBRT with WBRT alone. Radiation therapy was given for a total dose of 40 Gy (200 cGy/fr *b.i.d*.) (18). Combined treatment compared to WBRT alone led to longer survival (10 months *vs*. 6 months) and longer neurological functional independence (7.5 months *vs*. 3.5 months). These results were most pronounced in patients with stable disease: median survival 12 *vs*. 7 months; median functional independence 9 *vs*. 4 months. A third randomized controlled trial failed to demonstrate that the addition of surgery to WBRT improved outcome of patients with a single brain metastasis (19). Patients were randomized to surgery-plus-WBRT or to WBRT-alone. Radiation therapy consisted of 30 Gy (300 cGy/fr). No significant difference in survival was detected (5.6 months *vs*. 6.3 months) and no effect on functional independence was reported. Although the non significant results of Mintz *et al*. contradict those of others, combined therapy (surgical resection plus adjuvant WBRT) should be recommended in class I patients with solitary metastatic intracranial lesions because it guarantees better clinical outcomes. However, patients with unresectable lesions should receive WBRT as a primary therapy.

Stereotactic radiosurgery. SRS represents a valid alternative treatment modality to conventional surgical resection. SRS is a special technique that delivers a high single dose of radiation, using numerous beams of radiation aimed precisely at the target, minimizing irradiation of the adjacent normal tissue.

Potential candidates are patients not suitable for surgery due to medical contraindications, or being affected by more than one brain metastasis, or with a surgically inaccessible lesion. In patients who are good candidates for either surgical resection or SRS, there are no randomized data currently accessible to establish which is the better approach. Lesions amenable to SRS are typically defined as those measuring less than 3 cm in maximum diameter and producing less than 1 cm of midline shift mass effect (20). SRS is generally suggested to patients with small (up to 4 cm) and deep solid brain metastases (up to three in number) (21).

SRS can be performed using a multicobalt unit (Gamma Knife) or modified linear accelerators. The patient lies supine; a stereotactic head frame is used to ensure immobilization of the patient and precise localization of the lesion. Recommended doses for brain metastases are based on the maximum diameter of the lesion, according to the RTOG protocol 90-05 (22): a total dose of 21 to 24 Gy for lesions up to 2 cm; a total dose of 18 Gy for lesions measuring 2 to less than 3 cm; a total dose of 15 Gy for lesions of 3 to 4 cm.

In newly-diagnosed brain metastases, SRS should be employed as boost with WBRT, alone as initial therapy, or as adjuvant treatment to surgical resection.

SRS with/without WBRT. Fewer randomized studies have investigated the efficacy of WBRT with or without SRS boost for the initial management of patients with metastatic brain tumours (23-24). The strongest evidence comes from the RTOG 95-08 randomized trial (23). Patients with one to three newly-diagnosed brain metastases were randomized to WBRT-plus-SRS boost *vs*. WBRT-alone. All patients received WBRT to a total of 37.5 Gy (2.5 cGy/fr). Radiosurgery doses were assigned in accordance with prescriptions from RTOG 90-05. Results showed a survival benefit in the SRS boost group for patients with a single brain metastasis (median survival time 6.5 months *vs*. 4.9 months) and an improvement in functional autonomy for all patients (43% *vs*. 27%). Kondziolka *et al*. randomized patients with two to four brain metastases to WBRT-alone (30 Gy; 250 cGy/fr) or WBRT-plus-SRS (16 Gy) (24). The study was stopped at an interim evaluation at 60% accrual

because of a significant benefit in the rate of local tumor control after SRS boost *vs*. WBRT alone. Local tumor control was evaluated in terms of local failure at one year (8% *vs*. 100%) and the median time to local failure (36 months *vs*. 6 months). Sanghavi *et al*. reported a retrospective review using data from 10 Institutions to estimate the survival difference in patients with newly-diagnosed brain metastases undergoing WBRT-plus-SRS boost (25). Patients were stratified by RPA class. Results predicted for improved survival in the SRS group (16.1, 10.3, and 8.7 months for classes I, II, and III, respectively *vs*. 7.1, 4.2, and 2.3 months). However, as Metha *et al*. pointed out in their review, definitive conclusions regarding survival data and treatment effect cannot be made due to the retrospective nature of the trial and the heterogeneity of patient inclusion criteria and treatment characteristics (21). Tsao *et al*. published a review in which they analyze the treatment of newly-diagnosed multiple brain metastases: in patients treated by WBRT-plus-SRS, a benefit in local and distant brain control but no difference in overall survival were reported (12).

In the absence of a large body of randomized data, SRS boost should be considered for all patients and should be indicated in those with a single lesion; SRS boost may improve local control, although survival remains unchanged for patients with multiple brain metastases.

SRS as a single modality. SRS alone as an alternative treatment modality in patients with one to three brain metastases is still debated. The hypothesis that evidence of brain metastases, even if a single lesion, is linked to micrometastatic dissemination to the whole brain has been questioned by Aoyama *et al*. (26). They replaced WBRT by focal therapeutic irradiation. The rationale for SRS alone is to achieve brain control without possible treatment toxicity, such as neurocognitive sequelae, of WBRT (21). Aoyama *et al*. reported the first multi-institutional, prospective, randomized comparison of WBRT plus SRS *vs*. SRS alone (26). Patients with a maximum of four lesions were assigned to receive WBRT (30 Gy; 300 cGy/fr) combined with SRS or SRS alone (18 to 25 Gy depending on maximum tumour diameter). The SRS dose was lowered by 30% in the WBRT arm. The median survival time was similar in the two groups (7.5 months *vs*. 8 months); but the group treated with SRS alone was associated with a significantly increased rate of tumour recurrence (76.4% *vs*. 46.8%) and a more frequent salvage brain treatment (47% *vs*. 18 %). Li *et al*. compared WBRT alone *vs*. SRS alone *vs*. WBRT plus SRS in the management of single brain metastasis from lung cancer (27). Total radiation doses were standard. Patients treated with SRS alone and with WBRT plus SRS had similar median survival (9.3 months *vs*. 10.6 months). The comparison between SRS alone and WBRT plus SRS indicated that adding WBRT only improves freedom from new brain metastases (*p*-value=0.0392; data not available). Chang *et al*. evaluated the potential neurocognitive risks in a randomized controlled trial (28). Patients with brain metastases were treated with SRS or WBRT-plus-SRS. SRS doses were prescribed in accordance to the RTOG 90-05; the total WBRT dose was 30 Gy (250 cGy/fr). The primary end-point was neurocognitive function; the study was stopped because the group treated with WBRT plus SRS had a significant decline in learning and memory function compared to SRS alone (52% *vs*. 24%). The median survival for the whole patient group in the study was 9.2 months. SRS alone had a significantly inferior local and distant tumour control rate (67% *vs*. 100% and 45% *vs*. 73%, respectively) and freedom from brain recurrence (27% *vs*. 73%). Despite the benefit of WBRT in reducing the risk of brain tumour recurrences, the authors suggested a 'conservative' treatment – SRS plus a close follow-up – to preserve neurocognitive status.

Very few studies have compared SRS with surgical resection plus WBRT. Muacevic *et al*. evaluated SRS alone *vs*. surgical resection followed by adjuvant WBRT for the initial management of patients with single brain metastasis of small diameter in an operable site. WBRT was delivered to a total dose of 40 Gy (200 cGy/fr) (29). SRS treatment was performed using a Gamma Knife and the mean dose applied was 21 Gy (range=14-27 Gy). The study was closed prematurely due to a low rate of accrual. SRS is less invasive and toxic. Freedom from distant recurrence was significantly shorter after SRS-alone than after surgery-plus-WBRT (3% *vs*. 25.8%). Rades *et al*. compared SRS alone with surgical resection plus WBRT (30). They retrospectively analysed class I-II patients with one to two brain metastases. The SRS group received 18-25 Gy, and the surgical group received 30 Gy (300 cGy/fr) or 40 Gy (200 cGy/fr). Comparison of the two treatment approaches did not reveal any significant difference in terms of overall survival (68% *vs*. 61%), local control (74% *vs*. 67%) and distant control (84% *vs*. 74%). The results demonstrated that SRS alone is an effective and less invasive treatment for class I-II patients with one to two brain metastases. Similarly, SRS resulted in survival and local tumour control rates as good as those for surgery plus WBRT in selected patients in another retrospective study by Muacevic *et al*. (31).

Adjuvant SRS. No randomised trials have tried to address the benefit of postoperative SRS *vs*. postoperative WBRT. Results are difficult to evaluate given the small cohort and the retrospective single experience of the trials. The rationale for adjuvant SRS to the resection cavity is to affect local control without introducing the risks of acute and chronic toxicity associated with WBRT. A single-Institute

retrospective analyses was conducted by Quigley *et al*. (32). Patients received SRS boost (15 Gy) to the postoperative site in lieu of WBRT for metastatic brain disease. They recorded a 6.25% local recurrence rate. The data demonstrated comparable results to adjuvant WBRT, for which the local recurrence rate ranged from 10% to 20% (16). Karlovits *et al*. performed a retrospective review of patients with one to four intracranial metastases treated at their institution with SRS to the operative bed (33). Dose selection was based upon RTOG 90-05. The median survival was 15 months; an additional survival advantage was conferred in treatment of solitary metastases in patients with no extracranial disease (43 months). A total of 44% of patients developed distant brain recurrences at a median of 16 months after surgery. Utilizing a similar treatment approach, Soltys *et al*. reported a 79% local control rate at 12 months (34). Lacking randomized data, the choice of appropriate adjuvant radiation therapy technique following surgical resection of metastatic brain disease remains problematic.

SRS in recurrent disease. Evidence regarding SRS as salvage treatment at the time of progressive brain metastasis are insufficient. For focal recurrence, treatment depends on the previous therapeutic approach. Salvage SRS could be considered either previous SRS, provided previous good response to treatment, or after WBRT. A dose not exceeding 14 Gy is recommended (35).

Conclusion

Based on the above-mentioned data, for patients with one to three brain metastases, we recommend surgical resection followed by WBRT. WBRT plus SRS should be considered in patients with single brain metastases and good performance status. SRS plus a close follow-up or SRS boost to the postoperative site should also be considered. Patients with extracranial disease should be treated with WBRT alone. For patients with multiple (>3) brain metastases, WBRT is mandatory.

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