



Stereotactic radiotherapy for brain oligometastases

Marco Lupattelli¹, Paolo Tini², Valerio Nardone³, Cynthia Aristei¹, Simona Borghesi⁴, Ernesto Maranzano⁵, Paola Anselmo⁵, Gianluca Ingrosso¹, Letizia Deantonio⁶, Michela Buglione di Monale e Bastia⁷

¹Radiation Oncology Section, University of Perugia and Perugia General Hospital, Italy

²Unit of Radiation Oncology, University Hospital of Siena, Italy

³Unit of Radiation Oncology, Ospedale del Mare, Napoli, Italy

⁴Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Italy

⁵Radiation Oncology Centre, S. Maria Hospital, Terni, Italy

⁶Radiation Oncology Clinic, Oncology Institute of Southern Switzerland, Bellinzona-Lugano, Switzerland

⁷Department of Radiation Oncology, ASST Spedali Civili and Brescia University, Italy

ABSTRACT

Brain metastases, the most common metastases in adults, will develop in up to 40% of cancer patients, accounting for more than one-half of all intracranial tumors. They are most associated with breast and lung cancer, melanoma and, less frequently, colorectal and kidney carcinoma.

Magnetic resonance imaging (MRI) is the gold standard for diagnosis. For the treatment plan, computed tomography (CT) images are co-registered and fused with a gadolinium-enhanced T1-weighted MRI where tumor volume and organs at risk are contoured. Alternatively, plain and contrast-enhanced CT scans are co-registered. Single-fraction stereotactic radiotherapy (SRT) is used to treat patients with good performance status and up to 4 lesions with a diameter of 30 mm or less that are distant from crucial brain function areas. Fractionated SRT (2–5 fractions) is used for larger lesions, in eloquent areas or in proximity to crucial or surgically inaccessible areas and to reduce treatment-related neurotoxicity. The single-fraction SRT dose, which depends on tumor diameter, impacts local control. Fractionated SRT may encompass different schedules. No randomized trial data compared the safety and efficacy of single and multiple fractions. Both single-fraction and fractionated SRT provide satisfactory local control rates, tolerance, a low risk of transient acute adverse events and of radiation necrosis the incidence of which correlated with the irradiated brain volume.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; brain metastases; hypofractionation; local control; toxicity; radionecrosis

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Introduction

Brain metastases are the most common metastases in adults, accounting for more than one-half of all intracranial tumors. They are most associated with breast cancer, lung cancer, melanoma and, less frequently, colorectal and kidney carcinoma [1] and will develop in up to 40% of cancer patients

and in 15–30% of patients with metastatic breast cancer [2].

In breast cancer, the principal risk factors are young age, negative receptor status and poorly differentiated disease. Although a positive HER2 status increased the incidence of developing brain metastases in up to 30–40% of patients, the introduction of trastuzumab has changed prognosis in this

Address for correspondence: Simona Borghesi, MD, Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Via Curtatone 54, 52100 Arezzo, Italy, tel: +39 340 9125890, fax: +39 0575 254086; e-mail: s.borghesi@gmail.com

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subgroup of patients [1, 3, 4]. In lung cancer, brain metastases developed in 22–54% of non-small cell lung cancer patients with activating mutations in the epidermal growth factor receptor (EGFR) gene. Brain metastases will develop in up to 50% of patients with small cell lung cancer in their life-time [5, 6], with 10% being detected because of related symptoms. Advanced stage melanoma patients had a similar 50% risk [7]. In contrast, brain metastases developed in only about 2% of cases with renal cell carcinoma and colorectal cancer [8, 9].

Nowadays, in order to achieve durable control of brain disease, minimize the early and late adverse effects of therapy and maintain quality of life, surgery and radiotherapy are the treatment of choice. In decision-making the following prognostic factors should be considered: Karnofsky performance status, age, systemic disease status, availability of systemic treatment, patient preferences, median survival associated with the underlying histology, number and size of brain metastases, as well as their location in either eloquent or non-eloquent cerebral regions [10].

Surgery alone was insufficient for long-term local control. Adding postoperative whole brain radiation therapy improved local control rates, without providing a survival benefit and increasing the risk of cognitive deficits [11–14].

Increasingly popular options are single-fraction and fractionated stereotactic radiotherapy (SRT), with both providing satisfactory local control rates and a low risk of radiation necrosis [15]. Single-fraction SRT is used to treat patients with a good performance status and up to 4 lesions with a diameter of 30 mm or less [16–17] that are distant from crucial brain function areas. Fractionated SRT (2–5 fractions) is used for larger lesions, in eloquent areas or in proximity to crucial or surgically inaccessible areas and to reduce treatment-related neurotoxicity [18–20]. It aims at reducing the risk of adverse events with large metastases and maintaining satisfactory local control and has become widespread with the expansion of frameless techniques. In an adjuvant setting, a phase III randomized trial showed SRT significantly improved local control compared with resection alone of one to three brain metastases [18].

This overview analyzed the experience and trends in SRT in the treatment of brain oligometastases, identifying whether radiation therapy modalities impacted outcomes.

Sources of information

Up to February 2021, Pubmed and the Cochrane library were searched for relevant literature.

Imaging for staging and treatment planning

When neurological symptoms manifest, computed tomography (CT) is the first-line imaging test. When positive, the second level is the gold standard magnetic resonance imaging (MRI) which best defines size, location and number of lesions, as well as peritumoral oedema and mass effect. In MRI, T1-weighted with gadolinium and T2-weighted sequences are commonly performed [21–23]. Single-fraction SRT is performed with a Gamma Knife (Elekta AB, Stockholm, Sweden) or linear accelerators that are equipped with micro multi-leaf collimators and a high-dose rate or with a CyberKnife (Accuray, Sunnyvale, CA, USA). Linear accelerators are also used for fractionated treatments [15, 16]. For simulation purposes, the patient is placed in a supine position and a stereotactic frame is applied to the head using local anaesthesia for Gamma Knife SRT. A volumetric MRI is done after headframe placement in order to define target volumes and crucial areas. A modified stereotactic frame or frame-less approach with a 3-point thermoplastic fixation mask is often used with linear accelerator-based systems. A CT scan with 1–2 mm slice thickness is acquired from the cranial vertex to the mid-cervical spine. For contouring tumor volume and organs at risk CT images are co-registered and fused with a gadolinium-enhanced T1-weighted MRI [13, 17, 19]. Alternatively, plain and contrast-enhanced CT scans are co-registered.

The gross tumor volume (GTV) for definitive treatment and the clinical target volume (CTV) for adjuvant treatment of the surgical bed are delineated by the T1-weighted MRI with gadolinium. If a frame-based SRT is performed, planning target volume (PTV) corresponds to the GTV. When a thermoplastic fixation mask is used, the PTV is based on the set-up error and reproducibility of the patient's position; a 2–3 mm margin is commonly applied. Organs at risk, including the brain, brainstem, chiasm, optic nerves, cochlea, and hippocampus also have to be contoured [18, 19] and the planned doses are an integral part of the quality control before treatment plan approval.

The type of image-guided radiotherapy (IGRT) depends on the treatment machine. When treatments are performed on a linear accelerator, a cone beam CT is the standard. When treatments are delivered by tomotherapy, a megavoltage CT is acquired for IGRT. When dedicated machines, such as Gamma Knife and CyberKnife, are used, orthogonal kV X-rays are performed.

Doses, fraction schedules and dose-constraints

As determined by the RTOG 90-05 dose-escalation trial [24], the maximum tolerated doses of single fraction SRT were 24 Gy, 18 Gy, and 15 Gy, respectively, for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in diameter. Notably, tumors 21–40 mm were 7.3–16 times more likely to develop grade 3–5 neurotoxicity than tumors < 20 mm.

Local control after SRT depends on dose. After a single dose of 21 Gy long-term local control was achieved in 80% of patients, dropping to 50% when 15 Gy or less was administered [25]. Today, a single fraction of at least 20 Gy is standard for brain metastases of 20 mm.

The risk of radionecrosis correlated with irradiated brain volume [24]. No data from randomized trials are available comparing safety and efficacy of single and multiple fractions. A recent meta-analysis designed to evaluate the safety and efficacy of SRT in 2–5 fractions versus single-fraction SRT showed that fractionated SRT enhanced safety and was as efficacious as the single-fraction in the treatment of large brain metastases. In fact, the incidence of radionecrosis was potentially reduced by 68% in metastases measuring 4 to 14 cm³ and/or 2 to 3 cm in diameter, and by 44% in metastases measuring > 14 cm³ and/or > 3 cm in diameter [19].

Kim et al. retrospectively compared 36 Gy in 6 fractions to 20 Gy single-fraction SRT. At 1-year follow-up, no differences were found in local control while a significant reduction was observed in neurotoxicity (5% vs. 17%; $p = 0.005$) [26].

Several retrospective studies attempted to establish the best fractionation and total dose. Fahrig et al. compared 3 schedules (33.5 Gy in 5 fractions, 40 Gy in 10 fractions, 35 Gy in 7 fractions) in 150 patients with 228 brain metastases. For metastases over 30 mm in size, schedules of 5 and 7 fractions achieved a better local control [27]. After adminis-

tering 24–35 Gy in 3–7 fractions, 1-year local control rates ranged from 70 to 90% [28–31]. Notably, Martens et al. advised a treatment schedule corresponding to an equivalent dose in 2 Gy (EQD2) > 35 Gy [30]. Eaton et al. tested various schedules with a total dose of 21–30 Gy in 3–6 fractions, finding similar local control and radionecrosis rates [31]. With 30–42 Gy in 3 fractions, the 1-year local control rate was over 80%, with 12% radionecrosis [29]. Finally, a review showed that a single fraction of 20 Gy or 8.5 Gy for 3 fractions achieved a 1-year local control rate of 70% [25].

After brain metastasis resection, single-fraction SRT to the surgical cavity is preferable to adjuvant whole brain radiotherapy when patients have no or few other lesions that are suitable for SRT [11–13, 32]. In a multi-centre cooperative group trial, 194 patients with resected brain metastases were randomly assigned to postoperative single fraction SRT (12–20 Gy, depending on cavity volume) or whole brain radiotherapy (30 Gy in 10 fractions or 37.5 Gy in 15 fractions). At 6 months follow-up, SRT was associated with a lower risk of cognitive deterioration (52 vs. 85% whole brain radiotherapy), worse surgical site control rates (80 vs. 87%) and overall intracranial control rates (55 vs. 81%) [32]. Median OS was similar in both groups (12.2 vs. 11.6 months). A lower dose delivered to a larger surgical bed may account for the differences. A recent meta-analysis by Lahrer et al. addressed this issue, advising fractionated adjuvant SRT for large surgical beds of brain metastases [19]. Other dose and fractionation schedules [33–39] are reported in Table 1.

The most common late complication of SRT for brain metastases is radiation necrosis, which occurred, from six months to several years after treatment, in approximately 10% of cases [40–42]. Radiation necrosis rates after postoperative SRT ranged from 4 to 18% [43]. The irradiated brain volume was its most predictive factor: normal brain tissue volumes receiving 10–12 Gy (V10–V12) in a single dose should be under 5–15 cc [24, 44–47]. In fractionated treatments, data from a review suggested a V28 < 7 cc [43]. Since late brainstem damage is a life-threatening complication a maximum dose of 12.5 Gy is recommended in single-fraction SRT. On the other hand, a tumor volume > 1 cc was the only risk factor for brainstem complication after single-fraction SRT at a median dose of 16 Gy [48]. The optic chiasm dose should be limited to

Table 1. Selected series of brain metastases treated by single-fraction and fractionated stereotactic radiotherapy

Authors	Total dose and fractions
Mahajan et al. (2017) [18]	12 Gy/1 fraction
	14 Gy/1 fraction
	16 Gy/1 fraction
Abuodeh et al. (2016) [33]	25 Gy/5 fractions
Ling et al. (2015) [34]	22 Gy (median dose)/1–5 fractions
Minniti et al. (2013) [35]	27 Gy/3 fractions
Brennan et al. (2014) [36]	18 Gy (median dose) /1 fraction
Shaw et al. (2000) [24]	15 Gy/1 fraction
	18 Gy/1 fraction
	24 Gy/1 fraction
Kim et al. (2011) [26]	20 Gy (median dose)/1 fraction
	36 Gy/6 fractions
Fahrig et al. (2007) [27]	30–35 Gy/5 fractions
	40 Gy/10 fractions
	35 Gy/7 fractions
Martens et al. (2012) [30]	30–35 Gy/6–7 fractions
	30 Gy/5 fractions
	32–40 Gy/7–10 fractions
	25–30 Gy/5–6 fractions
Eaton et al. (2013) [31]	30 Gy/5 fractions
	24 Gy/4 fractions
	21 Gy/3 fractions
Narayana et al. (2007) [28]	30 Gy/5 fractions
Saitoh et al. (2010) [29]	42 Gy/3 fractions
	39/3 fractions
Brown et al. (2017) [32]	20 Gy/1 fraction
	12 Gy/1 fraction
Ahmed et al. (2014) [37]	30 Gy/5 fractions
	20 Gy/5 fractions
Keller et al. (2017) [38]	23.1 Gy/3 fractions
Pessina et al. (2016) [39]	30 Gy/3 fractions
Navarria et al. (2020) [76]	24 Gy/1 fraction
	24 Gy/3 fractions

8 Gy. Hearing complications, especially in acoustic neurinomas, are minimized with a mean cochlear dose threshold of 4–6 Gy. A maximum dose of 12–14 Gy is advised to maintain serviceable hearing [49–54]. Finally, although SRT dose limits for the hippocampus are still lacking, long-term memory

impairment after fractionated SRT was associated with an EQD2 over 7.3 Gy delivered to 40% of the bilateral hippocampus area [55].

Outcome evaluation

Contrast-enhanced MRI is the optimal modality for evaluating outcomes and disease recurrence in the brain. It should be performed every 2–3 months after completing radiotherapy for the first year and repeated at the same frequency if clinically indicated [18, 19].

Precise evaluation of tumor response or progression is not always easy. When imaging findings are doubtful, apparent diffusion coefficient (ADC) values can help in evaluating treatment results as they may distinguish radiation-induced necrosis from tumor recurrence [56]. MRI with dynamic contrast-enhanced (DCE) sequences as well as spectroscopy may identify metabolic changes before morphological ones [57, 58]. To differentiate radionecrosis from tumor progression in 50 brain metastases treated with single dose SRT, 6-[18F]-fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) positron emission tomography (PET) was performed, appearing more accurate than perfusion-weighted MRI [59].

Treatment toxicity

High dose per fraction SRT of brain metastases is associated with satisfactory tolerance, a low risk of transient acute adverse events and less cognitive impairment than whole brain radiotherapy. Radiation necrosis, a late complication, appears at follow-up imaging, as increased enhancement at the SRT site accompanied by surrounding oedema.

Major risk factors for radiation necrosis are lesion size, re-irradiation, and volume of healthy irradiated brain tissue. Other factors are the total dose, prescription isodose and treatment technique [24, 40]. Risk of radionecrosis correlated with V10 and V12 [24, 40, 47, 60–62]. Although radionecrosis was reported to range from 5 to 32%, reaching up to 50% in retrospective analyses [36, 47, 63], in prospective studies its risk was close to 3% [13, 64, 65] and under 10% in a series of 2200 metastases treated with GammaKnife. Median time to occurrence was 7 months, with symptoms in 60% of cases [66] correlating to > 2.1 cm tumor diameter, V12>3.3cc,

and V10 > 4.3cc. The risk of radionecrosis was not restricted to the first year after treatment as 26% of radionecrosis developed in up to 48 months of follow-up, suggesting that imaging should be repeated in patients with longer survival [67]. Brainstem radionecrosis was reported in 7.4% of 596 brainstem metastases treated by GammaKnife. Risk factors were tumor volume > 1 cc (confirming Kased's results [48]), marginal dose > 16 Gy, and radiotherapy delivered < 4.5 months previously [68].

With fractionated SRT radionecrosis occurred in 2–10% of cases [17, 26–27, 69, 70], with a higher risk in large tumors (30 mm). Radionecrosis occurred in 6% of patients after lesions of 21–30 mm and 31–50 mm were treated with, respectively, 27 Gy in 3 fractions and 32 Gy in 4 fractions [71]. At a 1-year median follow-up 8% radionecrosis was observed in 289 patients with > 20 mm brain metastases who received a total dose of 27 Gy in 3 fractions [72]. Large volumes and brain volumes receiving 18 Gy (V18) > 30 cc emerged as significant risk factors.

In general, radiation necrosis is asymptomatic and diagnosed by MRI. In some cases, it may be symptomatic with focal neurological signs and symptoms related to cerebral oedema. Corticosteroids are commonly used to treat symptoms. Hyperbaric treatment, high-dose vitamin E, heparin or warfarin are prescribed for patients with low tolerance, concomitant morbidities counter-indicating steroid use, or side effects due to long-term steroid therapy. No data on efficacy are available from controlled clinical trials. In severe cases of radionecrosis, resection or bevacizumab, an anti-angiogenic antibody may be useful [16, 67, 73–75] even though most patients relapsed when the drug was suspended and treatment resumption was not efficacious.

Conflicts of interest

The authors have no conflict of interest to declare.

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