Brain Metastases

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Abstract

In many patients with brain metastases, the primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a small selected cohort, long-term survival and even cure are possible. Central nervous system failures might develop after initial treatment, either locally (regrowth of a previously treated lesion), regionally (elsewhere in the brain parenchyma), or even in the form of leptomeningeal dissemination, the latter carrying the worst prognosis. Some of these failures will not require local therapy because they develop in the terminal phase of general cancer progression where active brain metastasis treatment is neither expected to prolong survival nor improve the patient's quality of life. At the other end of the spectrum, patients with limited, brain-only, relapse require effective intracranial disease control as a prerequisite for extended survival. The present chapter reviews reirradiation with brachytherapy, stereotactic radiosurgery, fractionated stereotactic radiotherapy and whole-brain radiotherapy.

1 Outcome and Relapse Rates After First-Line Radiotherapy

Patients with brain metastases present with a variable number, size, and location of brain metastases, with different patterns and activity of

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extracranial disease and with a wide range of comorbidities and performance status. Therefore, they represent a heterogeneous group with large variations in survival, often influenced by the molecular characteristics, and the availability of targeted therapies for the underlying neoplasm. The number of available treatment options has increased since the era of corticosteroids and 2-D radiotherapy, now including but not limited to resection, whole-brain radiotherapy (WBRT), radiosurgery, chemotherapy, targeted agents, and immune checkpoint inhibitors. In general, for the vast majority, the primary therapeutic aim is symptom palliation and maintenance of neurologic function, but in a small selected cohort, long-term survival and even cure are possible. Commonly used first-line approaches include short-course palliative WBRT, stereotactic radiosurgery (SRS) with or without additional WBRT, and surgical resection with or without postoperative WBRT or focal radiotherapy including SRS to the resection cavity or even delivered preoperatively, prior to resection. Specific histologic and molecularly defined types of tumors do respond to systemic chemotherapy or targeted agents, the role of which is evolving. Immune checkpoint inhibitors, either singly, or in combination with SRS are also being used, currently mostly in melanoma, but with likely application in non-small cell lung cancer as well. Central nervous system failures might develop after each of these approaches, either locally (regrowth of a previously treated lesion), regionally (elsewhere in the brain parenchyma), or even in the form of leptomeningeal dissemination, the latter carrying the worst prognosis. Some of these failures will not require local therapy because they develop in the terminal phase of general cancer progression where active brain metastasis treatment is neither expected to prolong survival nor improve the patient's quality of life (Ammirati et al. 2010). In other words, patients in poor general condition and with untreatable and life-threatening extracranial disease will typically be managed by best supportive care. At the other end of the spectrum, patients with limited brain-only relapse require effective intracranial disease control as a prerequisite for extended survival (Nieder et al. 2015).

In the first-line setting, prospective data on the efficacy of palliative WBRT were generated by the Radiation Therapy Oncology Group (RTOG) in the trials 69-01 and 73-61. Their reports suggested that the median survival of patients treated with WBRT is longer (3–6 months) than that of patients managed with steroids without radiotherapy (1–2 months). The Medical Research Council (MRC) has recently completed a large-scale randomized trial of steroids/best supportive care alone versus the same treatment plus WBRT in patients with primary non-small cell lung cancer, which is awaiting publication. The aforementioned RTOG studies described that 43–64 % of patients experienced neurologic response by week 2 (Borgelt et al. 1980, 1981). More recently, various groups have reported responses in the same range. For example, after 30 Gy WBRT, Antoniou et al. reported benefit in 38 % of patients (Antoniou et al. 2005); Sundstrom et al. reported symptomatic relief allowing steroid dose reduction in 66 % of patients after ≥25 Gy irradiation (Sundstrom et al. 1998), and Nieder et al. reported radiographic responses in comparable proportions of patients (Nieder et al. 1997).

Radiographic responses after WBRT with 30 Gy in 10 fractions are more likely in brain metastases from lung and breast cancer (Stea et al. 2006). Responders were found to have significantly longer overall survival in many series. WBRT-induced tumor shrinkage correlated with better survival and neurocognitive function preservation in a cohort of 135 patients from a phase III trial of WBRT plus the sensitizing agent motexafin gadolinium (Li et al. 2007). Previous RTOG data also suggest that patients with controlled brain metastases after WBRT tend to experience stable mini-mental status examination (MMSE) scores, while those with uncontrolled lesions had an average drop of 6 points by 3 months (Regine et al. 2001). Overall, no correlation between radiation dose and palliation could be established in the trials that compared different fractionation schedules (Gelber et al. 1981; Chatani et al. 1994).

The WBRT dosing/fractionation question was recently addressed in a AANS/CNS Guidelines Analysis (Gaspar et al. 2010). Twenty-three

studies met the eligibility criteria for this question, and of these, 17 were unique. The 17 unique studies fell into three evidence class categories as follows: ten class I studies (nine randomized controlled trials and one randomized phase I/II trial), six class II studies (retrospective cohort studies), and one class III study (prospective cohort study with historical controls). The radiation dosages were expressed in terms of Gy_{10} biologically effective doses (BED), and no correction for accelerated repopulation was attempted. The analysis was stratified by low or high dose versus control dose. The control group consisted of patients treated with 30 Gy in 10 fractions for a BED = 39 Gy_{10} (therefore assigning the low-dose regimens as a BED <39 Gy_{10} and high-dose regimens as a BED >39 Gy_{10}). None of the trials demonstrated a meaningful improvement in any endpoint relative to dose; specifically, survival was not improved. There was considerable overlap in terms of survival even at the same dose level in different trials, underscoring the significance of host-specific variables in determining survival. There was no difference in the relative risk (RR) of mortality at 6 months in the low-dose (BED <39 Gy_{10}) group compared to that in the WBRT control group (BED = 39 Gy_{10}) (6 month mortality (RR 1.05; 95 % CI 0.90, 1.23; $p = 0.52$)). When the high-dose (BED >39 Gy_{10}) group was compared to the WBRT control group (BED = 39 Gy_{10}), no difference in 6-month mortality (RR 1.05; 95 % CI 0.94, 1.18; $p = 0.39$) was identified. Similar comparisons were made for overall survival and neurologic function, and no dose-effect was identified for either endpoint. In view of this lack of a clear dose-effect relationship, recent multi-institutional analyses are in accordance with previous recommendations of short-course treatment, e.g., 5 fractions of 4 Gy, for patients with limited life expectancy (Rades et al. 2007c), or 10 fractions of 3 Gy or 15 fractions of 2.5 Gy for patients with longer life expectancy.

Estimation of prognosis is possible by using the RTOG recursive partitioning analysis (RPA) classes, first described by Gaspar et al. 1997 (Table 1) and the newly described graded prognostic assessment (GPA) score including its diagnosis-specific variant developed by Sperduto et al. 2010 (Table 2). Recent refinements of the GPA now incorporate molecular markers for breast and non-small cell lung cancer, and a similar analysis for melanoma is underway. The impact of histology also needs to be considered. After a standard WBRT course (30 Gy in 10 fractions over 2 weeks), all metastases from squamous cell carcinoma and adenocarcinoma (primary breast cancer excluded) visible on contrast-enhanced CT scans eventually relapsed or progressed within a time period of 14 months (Nieder et al. 1997). Better results were obtained in small cell carcinoma and primary breast cancer in whom less than 50 % of the WBRT-treated brain metastases relapsed or progressed. The risk of local progression after WBRT is higher in large-volume lesions, compared to smaller lesions (≥1 cc versus <1 cc), though not to a statistically significant degree. The implication here is that in patients in whom long-term survival is anticipated, the modest doses delivered by WBRT alone are inadequate for long-term control,

Table 1 Prognostic value of recursive partitioning analysis (RPA) classes

Reference	Number of patients	RPA class I	RPA class II	RPA class III
Gaspar et al. (1997)	1,200	7.1	4.2	2.3
Lutterbach et al. (2002)	916	8.2	4.9	1.8 (IIIA 3.2)
Nieder et al. (2000)	528	10.5	3.5	2.0
Agboola et al. (1998)	125 (resected brain met.)	14.8	9.9	6.0
Tendulkar et al. (2006)	271 (resected single brain met.)	21.4	9.0	8.9
Lorenzoni et al. (2004)	110 (RS)	27.6	10.7	2.8
Sneed et al. (2002)	268 (RS only)	14.0	8.2	5.3
	301 (RS + WBRT)	15.2	7.0	5.5

Median survival in months from different publications
RPA class I age <65 years, Karnofsky performance status ≥70, controlled primary tumor, no extracranial metastases, *RPA class II* all other patients, *RPA class III* Karnofsky performance status <70

Table 2 Overview of results with the graded prognostic assessment (GPA) score

Study	Median survival class I	Median survival class II	Median survival class III	Median survival class IV
Sperduto et al. (2008a) 1,960 patients who participated in clinical trials	11.0	8.9	3.8	2.6
Nieder et al. (2009) 232 patients treated outside of clinical trials	10.3	5.6	3.5	1.9
Nieder et al. (2008) 64 patients treated with surgery and WBRT	18.9	9.8	5.5	3.7
Sperduto et al. (2008b) 140 patients treated outside of clinical trials[a]	21.7	17.5	5.9	3.0

Median survival in months from different publications

In the GPA system, 3 different values (0, 0.5, or 1) are assigned for each of these 4 parameters: age (≥60; 50–59; <50), KPS (<70; 70–80; 90–100), number of brain metastases (>3; 2–3; 1), and extracranial metastases (present; not applicable; none). Patients in class I have a sum of 3.5–4 points, those in class II have 3 points, those in class III have 1.5–2.5 points, and those in class IV have 0–1 points. Note that diagnosis-specific scores might better predict the outcome of patients with primary malignant melanoma, renal cell cancer, and various breast cancer subtypes (Sperduto et al. 2010). A nomogram derived from this data has also been published (Barnholtz-Sloan et al. 2012)

WBRT whole-brain radiotherapy

[a]Several patients were treated with radiosurgery alone or radiosurgery plus WBRT

especially for larger lesions, and squamous and non-breast adenocarcinoma histologies.

Focal treatment such as SRS improves the local control observed with WBRT. In a small randomized study, patients with two to four brain metastases (all ≤25 mm diameter) either received WBRT alone (30 Gy in 12 fractions) or WBRT plus SRS (Kondziolka et al. 1999). The rate of local failure at 1 year was 100 % after WBRT alone but only 8 % in patients who had boost SRS. Median survival was 7.5 vs. 11 months for patients who received WBRT vs. WBRT plus SRS ($p=0.22$). A randomized study by the RTOG enrolled 333 patients with one to three brain metastases (Andrews et al. 2004). WBRT dose was 37.5 Gy in 15 fractions in both groups. SRS boost dose was adjusted to lesion size (15 Gy in lesions larger than 3 cm, 24 Gy in those up to 2 cm, and 18 Gy in others). Median survival was significantly better after SRS boost in patients with single brain metastasis. By post hoc multivariate analysis, survival was also improved in RPA class I patients. SRS-treated patients were more likely to have a stable or improved performance status at 6 months (43 vs. 27 %, $p=0.03$). Central imaging review showed higher response rates at 3 months and better 1-year control of the SRS-treated lesions, $p=0.01$. The risk of developing a local recurrence was 43 % greater with WBRT alone.

The risk of serious toxicity after WBRT appears rather low, even if prospective studies have demonstrated variable degrees of neurocognitive deficits during extended follow-up (Aoyama et al. 2007; Chang et al. 2009). Furthermore one must acknowledge that any type of cancer treatment might cause measurable neurocognitive decline, including SRS alone (Rugo and Ahles 2003; Heflin et al. 2005; Chang et al. 2009) and that some post-radiation symptoms might be caused by certain drugs rather than radiation itself (Nieder et al. 1999; Klein et al. 2002).

Local control of a limited number (mostly one to three) of brain metastases can effectively be achieved by surgical resection or SRS with or without adjuvant WBRT (Table 3). Recent data suggest that local control can also be achieved with SRS in patients with more numerous metastases, for example, ten or more (Yamamoto et al. 2014). The number of patients dying from uncontrolled brain metastases despite intensive local treatment ranges from 20 to 30 %. In general,

Table 3 Results of surgery and stereotactic radiosurgery (SRS) for brain metastases

Reference	*n* (patients and lesions)	Prescribed dose (median; range [Gy])[a]	Median OS	1-year PFS (%)
Patchell et al. (1990)	25/25	Surgery	9.5	80
Patchell et al. (1998)	49/49	Surgery	11.0	82
Pirzkall et al. (1998)	236/311	20; 10–30	5.5	89
Cho et al. (1998)	73/136	17.5; 6–50	7.8	80
Kocher et al. (1998)	106/157	20; 12–25	8.0	85
Sneed et al. (1999)	62/118[b] 43/117[c]	18; 15–22 17.5; 15–22	11.3 11.1	80 86
Varlotto et al. (2003)	137/208	16; 12–25	Not given	90
Andrews et al. (2004)	164/269[d]	Not given; 15–24	6.5	82
Bhatnagar et al. (2007)	205/4–18 lesions each[e]	16; 12–20	8.0	71

OS overall survival in months, *PFS* progression-free survival
[a]Prescription isodose or point varied; some series included SRS plus WBRT
[b]SRS only
[c]SRS plus WBRT (no significant difference in OS and PFS between both groups)
[d]SRS plus WBRT
[e]SRS plus/minus WBRT

SRS doses have varied with lesion size although it is counterintuitive to treat larger tumors with lower doses of radiation. While small lesions typically receive minimum doses of 20–24 Gy to the margin of the lesion, those that measure between 2 and 3 cm are treated with 18–20 Gy and those that measure between 3 and 4 cm with 15–16 Gy and sometimes with doses as low as 12 Gy, based on location. A retrospective analysis of 375 lesions suggests that 1-year local control after 18 Gy or less is in the range of 45–49 % as opposed to 85 % after 24 Gy (Vogelbaum et al. 2006). In the Japanese SRS study of 132 patients treated with lower SRS doses, discussed in greater detail below, only 4 patients (3 %) developed radionecrosis (Aoyama et al. 2006). Prognosis of SRS patients might be estimated either by RPA classes, DS-GPA, or the score index for radiosurgery (SIR) (Weltman et al. 2001; Lorenzoni et al. 2004). The most favorable SIR group contains patients with age ≤50 years, Karnofsky performance status (KPS) >70 %, no evidence of systemic disease at the time of SRS, limited number of brain lesions, and largest SRS-treated lesion <13 ml. After many years of controversy about the role of combining WBRT with SRS and considerable variation in practice, comparable to the discussion around WBRT after surgical resection of brain metastases, four randomized trials and a meta-analysis have attempted to address the issue (Aoyama et al. 2006; Chang et al. 2009; Kocher et al. 2011; Sahgal et al. 2015; Brown et al. 2015). The Japanese prospective randomized multicenter phase III study of SRS alone vs. SRS and WBRT (Aoyama et al. 2006) was designed with the primary endpoint of survival, with an overly generous expected difference of 30 %. The trial included adult patients with Karnofsky performance score >60 % and a maximum of four brain metastases, none exceeding 3 cm diameter. WBRT was given in 10 fractions of 3 Gy. SRS dose varied with size of the lesion (up to 2 cm, 22–25 Gy; >2 cm, 18–20 Gy margin dose) and was reduced by 30 % if WBRT was given. The combined arm contained 65 patients, the SRS arm 67 patients. Almost 50 % of patients had a single lesion. Median survival was 7.5 months after SRS plus WBRT and 8 months after SRS alone. One-year survival in the combined treatment arm was actually relatively increased by 36 %, but this did not reach statistical significance due to low patient numbers (38.5 vs. 28.4 %, $p > 0.05$). After SRS alone, 2 patients developed serious late complications (radionecrosis and grade 4 seizures, respectively). After SRS plus WBRT, 3 patients developed a radionecrosis, and 3 showed signs of leukoencephalopathy. The trial

revealed statistically significant differences in local control. The rate of actuarial failure at 1 year was 47 % after combined treatment but significantly greater at 76 % after SRS alone (relative increase of 62 %; $p<0.001$). New lesions developed in 42 vs. 64 % (of SRS alone patients) ($p=0.003$). WBRT reduced the risk of failure at the site of SRS from 27 to 11 % after 1 year ($p=0.002$).

A recent reanalysis of this trial has further fueled the survival debate. Based on a handful of retrospective reviews, substantially underpowered prospective trials, and a meta-analysis based on these underpowered trials, it has been widely concluded that omission of WBRT does not decrease overall survival (OS), primarily because salvage therapies are effective, and systemic progression is the key competing cause of mortality (Sahgal et al. 2015). This assertion may perhaps be true, but diligent review of the available data would caution against jumping to such a conclusion on the basis of the relative weakness of the supporting data, as well as the recent emergence of contradictory data from the aforementioned Japanese trial. An analysis of three pieces of data in the literature should induce a degree of interpretive caution. As early as 1998, Pirzkall et al. reported a single-institution 236-patient retrospective experience of SRS with or without WBRT, demonstrating a trend for superior survival (OS) in favor of WBRT (1- and 2-year OS of 30 vs. 19 and 14 vs. 8 %), but much more impressive was the recognition that in patients without extracranial disease, i.e., in those in whom systemic progression as a competing cause of mortality is largely diminished, the median survival was impressively different at 15.4 vs. 8.3 months, in favor of WBRT (reaching only borderline significance because of the small numbers). This allows one to posit the very reasonable hypothesis that a certain proportion of patients with brain metastases are destined to succumb to intracranial progression (after all we see such compartmental progression as a cause of death in other organs such as the lungs, liver, etc.) and enhanced control of intracranial progression will lengthen their survival.

Finally, a recent reanalysis of the randomized Japanese JROSG-99 trial, using the validated graded prognostic assessment (GPA) stratification model and applied to all non-small cell lung cancer patients on the trial, reveals a median survival of 16.7 versus 10.6 months in favor of the WBRT + SRS arm (vs. SRS alone, $p=0.03$) for the favorable (GPA = 2.5–4) subgroup, without demonstrating an advantage for the inferior prognosis group, providing further support that intracranial control matters and one accepts a lower rate at the potential peril of diminishing overall survival (Aoyama et al. 2006).

A European phase III trial (EORTC 22952-26001) included 359 patients, 199 underwent SRS, and 160 underwent surgery (Kocher et al. 2011). In the SRS group, 100 patients were allocated to observation, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to observation, and 81 were allocated to adjuvant WBRT. The median time to WHO performance status more than 2 was 10.0 months (95 % CI, 8.1–11.7 months) after observation and 9.5 months (95 % CI, 7.8–11.9 months) after WBRT ($p=0.7$). Overall survival was similar in the two arms (median, 10.9 vs. 10.7 months, $p=0.9$). WBRT reduced the 2-year relapse rate both at initial sites (surgery, 59–27 %, $p<0.001$; SRS, 31–19 %, $p=0.04$) and at new sites (surgery, 42–23 %, $p=0.008$; SRS, 48–33 %, $p=0.02$). Salvage therapies were used more frequently after observation than after WBRT. Intracranial progression caused death in 44 % of patients in the observation arm and in 28 % of patients in the WBRT arm.

The randomized trial from the M.D. Anderson Cancer Center re-emphasized patient selection issues as critical for overall survival. In this trial, patients with one to three newly diagnosed brain metastases were randomly assigned to SRS plus WBRT or SRS alone, and over an almost 7-year time frame, 58 patients were recruited and stratified by RPA class, number of brain metastases, and histology (Chang et al. 2009). The primary endpoint was neurocognitive function: measured as a 5-point drop compared with baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months. An interim analysis

showed that there was a high probability (96 %) that patients assigned to receive SRS plus WBRT were more likely to show a decline in learning and memory function at 4 months than patients assigned to receive SRS alone. Further, at 4 months there were four deaths (13 %) in the group that received SRS alone, and eight deaths (29 %) in the group that received SRS plus WBRT, and 73 % of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27 % of patients who received SRS alone ($p=0.0003$). These differences in early death bring into question the generalizability of the HVLT-R score results; it is well known that a general disease-related decline due to progression, especially in the preterminal phase, will cause a significant drop in neurocognitive function, and its attribution to a single component, such as WBRT, can be misleading. Early deaths in neuro-oncology are almost invariably consequential to systemic progression of disease in this setting. In fact, there were several differences in patient characteristics between the two cohorts which could explain both the early deaths and the differences in 4-month HVLT-R scores. When the constellation of prognostic factors is evaluated collectively, the SRS alone group, compared to SRS plus WBRT, had far more favorable characteristics, such as more female patients (60 vs. 39 %), fewer patients with multiple brain metastases (40 vs. 46 %), lower intracranial disease burden (1.4 vs. 2.3 cc), superior RPA (23 vs. 11 % RPA Class 1) and GPA (10 vs. 3.5 % GPA score 3.5) distribution, fewer patients with liver metastases (7 vs. 18 %), etc.; the small patient numbers precluded any of these factors from individually reaching statistical significance, but taken collectively, the prognostic variables were substantially skewed in favor of the SRS group. As would be expected from the use of WBRT, the 1-year local tumor control rate was 67 % for patients in the SRS group but considerably superior at 100 % for patients in the SRS plus WBRT group, and additionally, the 1-year distant brain tumor control rate was 45 % for patients in the SRS group and 73 % for patients in the SRS plus WBRT group. The 1-year freedom from CNS recurrence was 27 % (95 % CI 14–51) for SRS alone and 73 % (46–100) for SRS plus WBRT. This trial therefore emphasizes three crucial points when evaluating brain metastases data:

1. Local control as well as distant control in the brain is significantly improved by WBRT as an adjunct to focal therapies.
2. Patient selection variables can significantly skew neurocognitive and survival outcomes, and small trials are unlikely to statistically pick up these differences in patient prognostic variables.
3. Early decline in some neurocognitive functions, such as memory recall as measured by HVLT-R, can be impacted by several variables, including WBRT, and the early decline is suggestive of an "early-responding" cell population.

2 Reirradiation: Whole-Brain Radiotherapy

The key issues guiding clinicians in the first-line setting remain important in selecting appropriate management options for patients who relapse after brain irradiation (Table 4). However, few prospective clinical studies formally addressing the role of reirradiation for brain metastases have been published. Salvage WBRT after previous SRS is a common treatment option with survival results indistinguishable from those of first-line WBRT, i.e., usually 3–6 months median survival (Khuntia et al. 2006). A repeat course of WBRT is less commonly employed due to concerns about lack of efficacy and the potential for neurocognitive deficits. Historical experience with WBRT dates back to a retrospective study by Shehata et al. (1974) and another study by Kurup et al. (1980), which will not be reviewed in greater detail. Both are limited by the fact that they date back to the pre-CT era and few systemic treatment options existed at that time. Thus, rapid progression of systemic disease was an even bigger problem than it is now. The first study extending into the CT era, but pre-dating the advent of SRS salvage for recurrence, was reported in 1988 (Hazuka and Kinzie 1988). It included 44 patients (34 % with non-small cell and 20 % with small cell lung cancer), all of

Table 4 Key questions when selecting between the different treatment options for recurrent brain metastases

Is the patient's performance status after initiation of steroid treatment at a level that justifies initiation of radiation therapy?
Do laboratory tests point to advanced extracranial disease status and poor tolerability/efficacy of the planned therapy?
Are extracranial disease sites absent or controlled, and if so, does one expect continued extracranial disease control?
Will systemic treatment be offered or are there no more options left?
Will brain control impact on the survival of the patient or is treatment focused on palliation of symptoms?
Will surgical intervention lead to rapid symptom improvement or effective local control, if comorbidity and other factors allow for consideration of invasive measures? Could the same goals be achieved without surgery?
Might the cumulative radiation dose to critical normal tissue structures result in serious toxicity in patients with expect prolonged survival?
What would be the functional consequence of treatment-induced injury?
How did the lesion(s) respond to initial radiotherapy and how long is the interval?

whom had previously received WBRT for brain metastases. The reasons for retreatment with WBRT (and in a small number of patients, large-volume partial brain reirradiation) were the appearance of new intracranial lesions (47 %), new lesions plus progression of pre-existing metastases (10 %), and local progression of pre-existing metastases only (43 %). The median interval between initial WBRT and reirradiation was 8 months, with a minimum of 8 weeks. The median initial dose was 30 Gy in 10 fractions of 3 Gy, and the median retreatment dose was 25 Gy (range 6–36 Gy, dose per fraction 2–4 Gy). Median survival after repeat WBRT was only 8 weeks. Partial neurological improvement was observed in 27 % of patients. Two patients most likely died as a direct consequence of brain necrosis (brain necropsy result). Both were treated to rather high cumulative doses, especially if one calculates biologically equivalent doses. In one case, WBRT to 32 Gy in 8 fractions of 4 Gy was followed by WBRT to 30 Gy in 10 fractions of 3 Gy (necrosis after 20 weeks from reirradiation). In the other case, WBRT to 30 Gy in 10 fractions of 3 Gy was followed by partial brain RT to 33 Gy in 10 fractions of 3 Gy (necrosis after 11 weeks from reirradiation). The reirradiation tolerance of the human brain is reviewed in detail in other chapters of this book.

Limited, but more recent experience with 2 courses of WBRT in 72 patients, the majority with primary lung cancers suggests that 31 % of patients experienced a partial clinical response after reirradiation (Sadikov et al. 2007). In responders, the mean duration of response was 5.1 months. The median survival after reirradiation was 4.1 months. One patient was reported as having memory impairment and pituitary insufficiency after 5 months of progression-free survival. However, assessment of toxicity in this and other similar series is hampered by their retrospective nature and the poor performance status of most patients. The most frequent dose used for the initial radiotherapy was 20 Gy in 5 fractions. The most common reirradiation schema were 25 Gy in 10 fractions, 20 Gy in 10 fractions, and 15 Gy in 5 fractions. Median interval between the two courses of brain radiation was 9.6 months, with a minimum 8 weeks. The typical patient had a performance status of 1 or 2. Patients with better performance status experienced significantly longer survival after reirradiation, comparable to the study by Aktan et al. (2015; median 2.2 months if KPS $\leq$70; 5.3 months for all 34 patients). In initial nonresponders, median survival was only 0.9 months after reirradiation, implying that this might be a crucial variable to consider. Surprisingly, the interval between the two courses had no impact on survival.

In another retrospective series of 52 patients, a slightly better clinical response rate (42 %) as well as better median overall survival (almost 5 months) was reported (Cooper et al. 1990). The major difference and potential explanation were that patients were offered reirradiation only if they maintained good general condition for at least 4 months after initial WBRT (median 30 Gy in 10 fractions of 3 Gy), excluding nonresponders, and patients experiencing early decline. The most common reirradiation regimen was 25 Gy in 10 fractions of 2.5 Gy.

Another series, published in 1996 by Wong et al. (86 reirradiated patients including 18 with partial brain fields), included an equal number of lung and breast cancer patients (31 each). The median dose of initial WBRT was 30 Gy, usually given in 10 fractions. The median interval to reirradiation was 7.6 months, with a minimum of 6 weeks. The median dose of reirradiation was 20 Gy, with a maximum 30.6 Gy. Complete or partial symptomatic neurological improvement was observed in 27 and 43 % of patients, respectively. The median response duration was 2.8 months. Median survival was 4 months. The only significant prognostic factor for survival was the absence of extracranial metastases. Scharp et al. (2014) analyzed 134 patients, of whom 60 were treated with initial prophylactic WBRT (87 % had lung cancer). The median interval was 13 months (minimum 3) and the median doses 30 plus 20 Gy, both in 2-Gy fractions. Median survival was 2.8 months, and clinical improvement was observed in 39 % of patients. Significantly shorter survival was seen in patients with small cell lung cancer, KPS <70, or progressive primary tumor. A series of 49 patients was reported from Guo et al. (2014). Median interval was 11.5 months (minimum 1.5 months), median initial dose 30 Gy, and median repeat dose 20 Gy. Median KPS was 70. Improved symptoms were reported in 27 %, and median survival was 3 months. Comparable results were reported by Ozgen et al. (2013); median survival in 28 patients was 3 months and symptomatic response rate 39 %.

Minniti et al. (2014) combined reirradiation (25 Gy, 10 fractions) with concurrent temozolomide (75 mg/m^2). They treated 27 patients whose median age was 54 years. Minimum KPS was 60. Eighteen patients had lung cancer. Median survival was 6.2 months. Seventeen patients (63 %) had improved symptoms. Severe toxicity was not observed. Survival was significantly longer in patients with stable or absent extracranial disease. Survival was slightly better than in other studies, but interstudy comparison is hampered by the heterogeneity of the different study populations. Without randomized trials, the role of temozolomide is difficult to define.

Overall, the studies reviewed here reported median survival of 2–6.2 months (median 4.0) and improvement of symptoms in 27–70 % of patients (median 35 %). Shorter survival was seen in patients with KPS <70, progressive primary tumor, or extracranial metastases.

Helical tomotherapy can also be utilized in patients who develop multiple brain metastases in spite of previous WBRT (Sterzing et al. 2009). Both patients treated with this technique had previously received 40 Gy in 20 fractions of 2 Gy. The whole-brain reirradiation dose was limited to 15 Gy, while the enhancing lesions plus a 2-mm margin received 30 Gy in 10 fractions of 3 Gy. In the first case, 8 metastases from breast cancer were present 18 months after first-line WBRT. With a follow-up of 12 months, local control was achieved. In the second case, 11 metastases from non-small cell lung cancer were present 18 months after initial WBRT. With a follow-up of 6 months, local control was achieved. No serious toxicity was recorded. In Fig. 1, we show an example of a patient with multiple recurrent brain metastases from breast cancer treated with tomotherapy. The patient had received two prior courses of WBRT, initially 30 Gy in 10 fractions and then 25 Gy in 10 fractions both achieving complete responses; five subsequent individual recurrences were treated with two courses of SRS, also resulting in complete response; the tomotherapy IMRT plan was utilized for 9 new lesions, and the dose was 30 Gy in 15 fractions; most of the normal brain was kept below 10 Gy, and the patient has sustained local control more than 8 months after this course of therapy and for over 42 months since initial presentation with brain metastases. The case illustrates that with modern and advanced radiotherapy techniques, innovative salvage options become possible, and anecdotally, in selected patients, local control and durable survival are achieved. Figures 2, 3, and 4 provide treatment details regarding three other patients at one of the authors' institutions, utilizing other unique radiotherapy approaches.

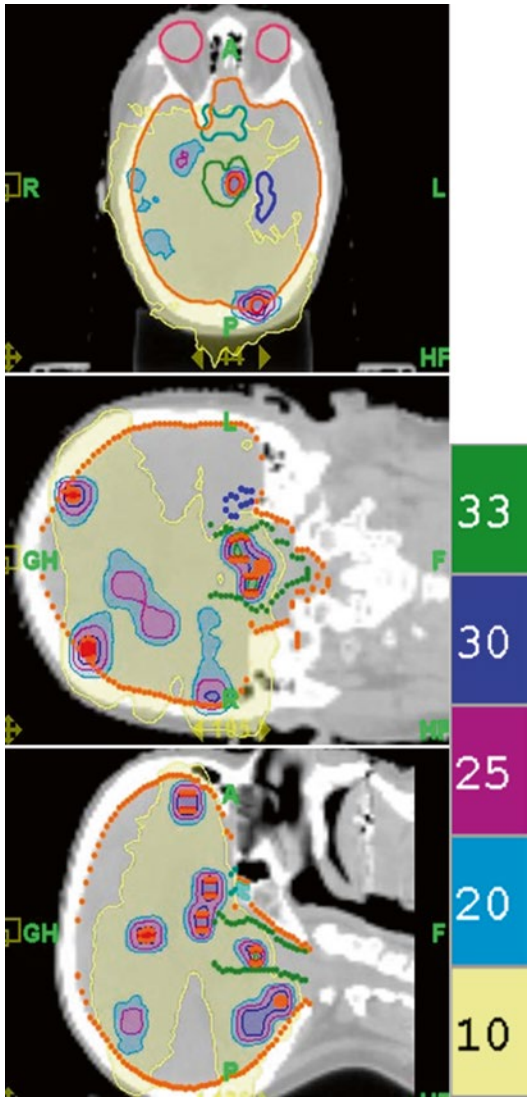


Fig. 1 An example of a patient with multiple recurrent brain metastases from breast cancer treated with tomotherapy. The patient had received two prior courses of WBRT, initially 30 Gy in 10 fractions and then 25 Gy in 10 fractions both achieving complete responses; five subsequent individual recurrences were treated with two courses of radiosurgery, also resulting in complete response; the tomotherapy IMRT plan was utilized for nine new lesions, and the dose was 30 Gy in 15 fractions; most of the normal brain was kept below 10 Gy, and the patient has sustained local control more than 8 months after this course of therapy and for over 42 months since initial presentation with brain metastases

3 Reirradiation: Stereotactic Radiosurgery

The potential advantages of SRS as salvage treatment after WBRT were realized early during the development of this technique (Loeffler et al. 1990). Several series published in the early 1990s included some patients reirradiated with SRS (Adler et al. 1992; Engenhart et al. 1993). Their results lead to recommendations that patients with recurrent lesions should be treated with stereotactic high-precision techniques. The RTOG embarked on a prospective phase I clinical trial of SRS in recurrent, previously irradiated primary brain tumors and brain metastases, one of few prospective studies in the field. RTOG study 90-05 was a dose escalation trial, which included 100 patients with brain metastases and 56 with primary brain tumors. The brain metastasis patients were included after prior WBRT to a median dose of 30 Gy (Shaw et al. 1996, 2000). SRS could be administered with a linear accelerator or Gamma Knife. Eligible patients had received first-line radiotherapy at least 3 months prior to study entry, and in the study, the actual median interval was 17 months. Their KPS was ≥60 and life expectancy ≥3 months. Seventy-eight percent had single lesions. Dose was determined by the maximum diameter of the tumor. Initial doses were 18 Gy for lesions ≤20 mm, 15 Gy for lesions measuring 21–30 mm, and 12 Gy for lesions measuring 31–40 mm. Dose was prescribed to the 50–90% isodose line, which was to encompass the entire enhancing target volume. The dose was escalated in 3 Gy increments providing there was not an excess of unacceptable toxicity. The trial eventually defined the maximum acutely tolerable SRS dose in this setting, except for lesions ≤20 mm where the dose was not escalated beyond 24 Gy because of investigators' reluctance. While small lesions ≤20 mm can be treated with up to 24 Gy to the margin of the lesion, those that measure between 21 and 30 mm might receive 18 Gy and those that measure between 31 and 40 mm 15 Gy.

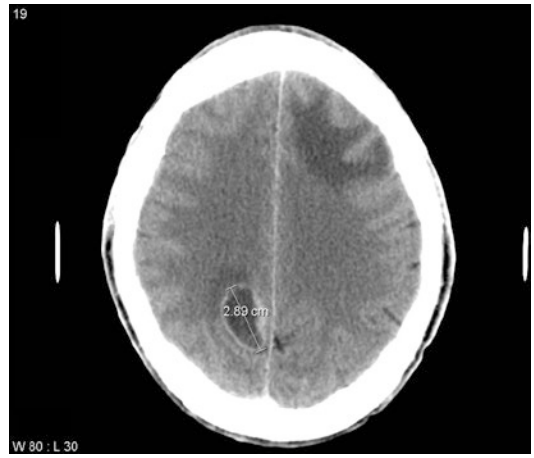


Fig. 2 An illustrative case from one of the authors' institutions (Nordland Hospital Bodø, Norway). A 63-year-old male patient was diagnosed with squamous cell lung cancer stage III B in December 2007. He received systemic platinum-based chemotherapy and thoracic radiotherapy. In November 2008, the patient collapsed, and a computed tomography (CT) scan of the brain revealed four brain metastases, maximum diameter 3.1 cm. No extracranial metastases were detected; all laboratory tests were unremarkable. The intrathoracic status was judged to be ongoing partial remission. The patients Karnofsky performance status (KPS) at that time was 70. Whole-brain radiotherapy (WBRT) was administered (10 fractions of 3 Gy). Three months later, CT scans of the brain showed partial remission of all four lesions. However, another 3 months later, all 4 lesions had increased in size. No additional new brain metastases were detected. The patient was referred for salvage treatment. When considering the key questions presented in Table 4, the following statements could be made.

Is the patient's performance status after initiation of steroid treatment at a level that justifies initiation of radiation therapy? Yes, the KPS at the time of progression was 70.

Do laboratory tests point to advanced extracranial disease status and poor tolerability/efficacy of the planned therapy? No, the only abnormal finding was slight anemia.

Are extracranial disease sites absent or controlled, and if so, does one expect continued extracranial disease control? No extracranial metastases were detected, but the primary tumor had increased slightly (less than 25 %, no clinical symptoms).

Will systemic treatment be offered, or are there no more options left? Second-line chemotherapy in case of symptomatic progression of the lung tumor was an option.

Will brain control impact on the survival of the patient or is treatment focused on palliation of symptoms? The biggest threat at that time was death from uncontrolled brain metastases.

Will surgical intervention lead to rapid symptom improvement or effective local control, if comorbidity and other factors allow for consideration of invasive measures? Could the same goals be achieved without surgery? No surgical candidate based on the number of brain metastases. None of them caused hydrocephalus or other immediately threatening complications.

Might the cumulative radiation dose to critical normal tissue structures result in serious toxicity in patients with expect prolonged survival? The probability of long-term survival was considered low.

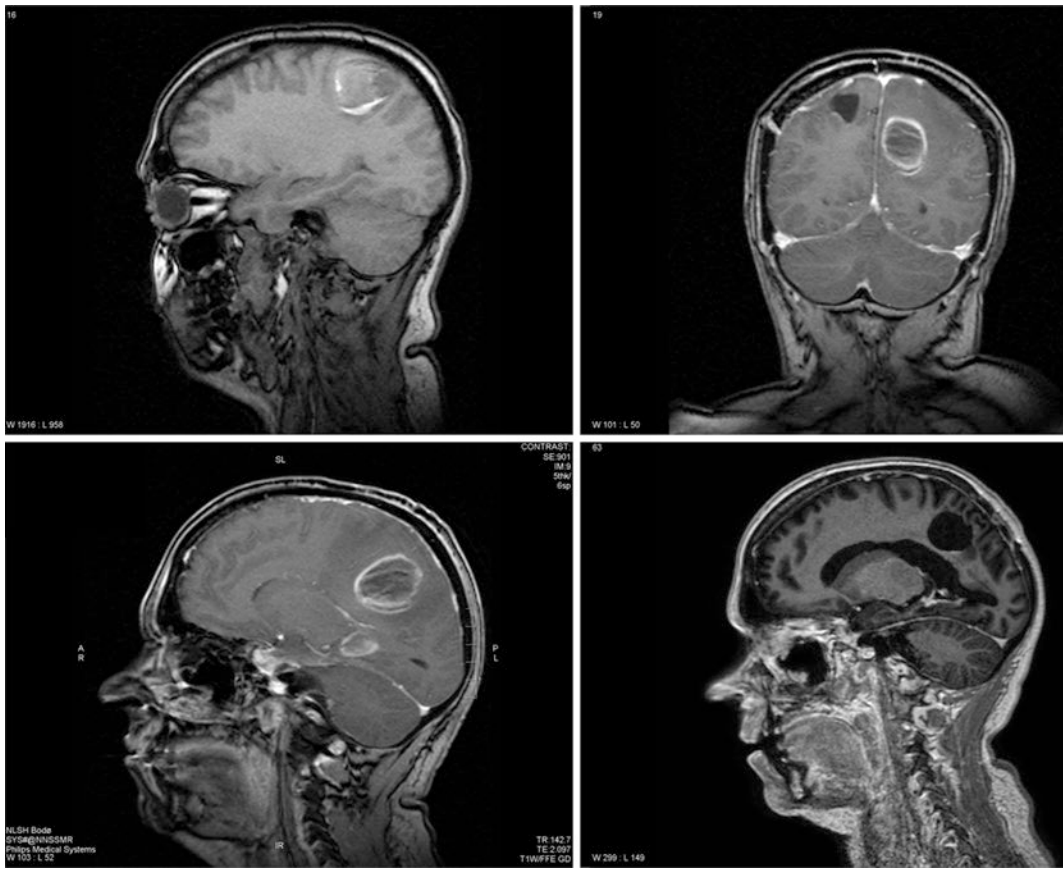
What would be the functional consequence of treatment-induced injury? Not applicable.

How did the lesion(s) respond to initial radiotherapy and how long is the interval? All 4 metastases had initially responded, the interval of 6 months did permit reirradiation.

The image above shows the second largest brain metastasis (diameter 2.9 cm, cystic lesion) and the contralateral edema indicating the presence of another lesion, which was slightly larger. When deciding between stereotactic radiosurgery (SRS) and other options in this case, the following facts were considered. Based on number and size of the lesions as well as the limited survival expectation after second-line chemotherapy in patients with relapsed non-small cell lung cancer, the patient was not an ideal candidate for SRS. Repeat WBRT was not necessary as no new lesions were present and the 4 metastases could be covered by a quite simple 3-dimensional conformal radiotherapy technique with two isocenters and two non-overlapping pairs of opposing fields, each covering two of the metastases. A dose of 30 Gy in 10 fractions of 3 Gy was given. As after the first course (30 Gy WBRT), a partial remission was obtained. The patient did not develop serious acute or late toxicity. He died without obvious neurological deficits 6.3 months after reirradiation as a result of pneumonia, which was considered a complication of the primary lung cancer

Median survival was 7.5 months. A 1-year survival rate of 26 % was observed. Some cases of further local progression in spite of SRS were observed, mainly within the first 6 months after SRS. Long-term toxicity data for brain metastasis patients are available only from the initial publication (Shaw et al. 1996). They are based on 64 patients. Four patients developed radionecrosis requiring operation 5–14 months after SRS. From the final report (Shaw et al. 2000), combined radionecrosis data on patients with brain metastases and primary brain tumors are available. The actuarial incidence was 8 and 11 % at 12 and 24 months, respectively. This study therefore provides tentative evidence that retreatment with SRS can produce local control in a certain proportion of brain metastases patients, but the approximate 10 % incidence of necrosis must be factored in. Several options can be considered to either lower this rate or possibly manage necrosis, including fractionated stereotactic radiotherapy and the recent use of bevacizumab, which might improve symptoms and imaging findings resulting from radionecrosis (Gonzalez et al. 2007; Torcuator et al. 2009; Boothe et al. 2013).

Linear accelerator-based SRS was used in 54 patients with 97 metastases (recurrent after WBRT) in another study (Noël et al. 2001). The patients' KPS was 60-100. The median interval was 9 months, with a minimum of 2 months. The median tumor volume was 1.2 cc. A median minimal dose of 16.2 Gy was prescribed, while the median maximal dose was 21.2 Gy. No serious side effects were reported with this dose prescription. Only 5 metastases recurred after salvage SRS. The 1-year survival rate was 31 %. RPA class was a significant prognostic factor for overall survival. Comparable outcomes were achieved in a retrospective series that included 111 patients (Chao et al. 2008). SRS doses were usually prescribed according to the RTOG 90-05 guidelines. Median survival was 9.9 months. Twenty-five percent of patients devel-



oped further local progression in spite of salvage SRS. Poorer local control was observed in lesions >2 cm, which usually had been treated with lower radiation doses. Gwak et al. treated 46 patients with 100 recurrent metastases with CyberKnife radiosurgery (2009). The average dose was 23 Gy in 1–3 fractions. The median interval from WBRT was 5 months. The mean volume was 12.4 cc. Median survival was 10 months, but 1-year progression-free survival was only 57 %. In these patients with quite large metastases, e.g., compared to the abovementioned series by Noël et al. (2001), acute toxicity was observed in 22 % of patients. Toxicity after >6 months occurred in 21 %.

More recent data were derived from a retrospective review of 106 patients irradiated for a median of 2 metastases (range, 1–12) with a median dose of 21 Gy (range, 12–24) prescribed to the 50 % isodose (Kurtz et al. 2014). With a median follow-up of 10.5 months, local control was 83 % at 6 months and 60 % at 1 year. Median progression-free survival was 6.2 months. Median overall survival was 11.7 months from salvage SRS and 22 months from initial diagnosis. Caballero et al. (2012) analyzed 310 patients. The median number of brain metastases was 3 and interval from WBRT to SRS 8 months. The median survival was 8.4 months overall and 12.0 vs. 7.9 months for single vs. multiple lesions ($p=0.001$). There was no relationship between number of lesions and survival after excluding patients with single metastases. Retrospective population-based data from Canada suggested that salvage SRS after WBRT was not associated with compromised survival compared to immediate boost SRS (Hsu et al. 2013).

A large analysis of 2200 metastases treated with Gamma Knife SRS also included a subgroup of 72 lesions that were reirradiated with a second SRS (Sneed et al. 2015). Prescribed dose was chosen primarily based on treatment volume or location in the brainstem, not taking into account prior WBRT or SRS. After prior SRS, the median dose was

Fig. 3 An illustrative case from one of the authors' institutions (Nordland Hospital Bodø, Norway). The patient is a 45-year-old female. In October 2004, she had noted a few days of hypesthesia in her left leg, followed by slight hemiparesis and a seizure resulting in hospitalization. A magnetic resonance imaging (MRI) scan of the brain revealed a tumor in the right parietal lobe, presumably representing a glioma. In November 2004, a partial resection (because of the proximity to the motor cortex) was performed. Histology demonstrated a malignant melanoma metastasis. Staging including examinations of the eyes, head, and neck mucosa and total skin, gynecological evaluation, bone scintigraphy, and computed tomography (CT) scans showed an enlarged left adrenal gland as the only pathological finding. The adrenal mass was removed completely by laparoscopic surgery, and histology corresponded to that of the brain metastasis. Treatment proceeded with postoperative whole-brain radiotherapy (WBRT), 10 fractions of 3 Gy, without boost. In February 2005, the patient noted headaches and a decreasing general condition. A MRI scan disclosed two new brain metastases in the left parietal and temporal lobe, respectively (see image below: previous resection cavity in the right parietal lobe, new lesions in the left hemisphere). While the parietal tumor could be resected completely, the temporal lesion was treated with Gamma Knife radiosurgery (SRS). The peripheral minimum dose was 15 Gy.

In March 2005, the patient developed abdominal symptoms, and a CT scan showed a right abdominal mass presumably representing inflammation in and around the vermiform appendix and ovary. Surgery including ovarectomy and appendectomy was performed, and the histology demonstrated again the same type of malignant melanoma. The tumor was limited to the vermiform appendix without spread to peritoneum or lymph nodes and was judged to be removed completely. After a symptom-free interval, routine MRI evaluation in November 2005 disclosed progression of the unresectable SRS-treated temporal lesion, and a second Gamma Knife procedure was performed. The interval to the previous SRS was approximately 8 months. Since then, the patient returned to repeated follow-up examinations including MRI and CT scans. The last one was performed in March 2015, i.e., more than 10 years after the first neurosurgical resection. No potential signs of disease were detectable. The patient has a Karnofsky performance status (KPS) of 80 % resulting from slight concentration and endurance problems. No radionecrosis or other serious complication was recorded in this unusual case, which illustrates the potential impact of aggressive local management in highly selected patients. Of course, the potential diagnosis of radiation necrosis after SRS must be excluded by appropriate imaging methods such as positron emission tomography (PET) with an amino acid tracer, e.g., ^{11}C-methionine, or newer MRI techniques incl. spectroscopy before proceeding to further radiation treatment. In some cases, a histopathological diagnosis of recurrent metastasis might be required. Further information on differentiation between radionecrosis and recurrent tumor can be found in the following studies and reviews: Sundgren 2009 (MR spectroscopy), Barajas et al. 2009 (dynamic susceptibility-weighted contrast-enhanced perfusion MRI), Dequesada et al. 2008 (MRI), Terakawa et al. 2008 and Chung et al. 2002 (PET), Serizawa et al. 2005 (single photon emission computed tomography), Walker et al. 2014 (overview)

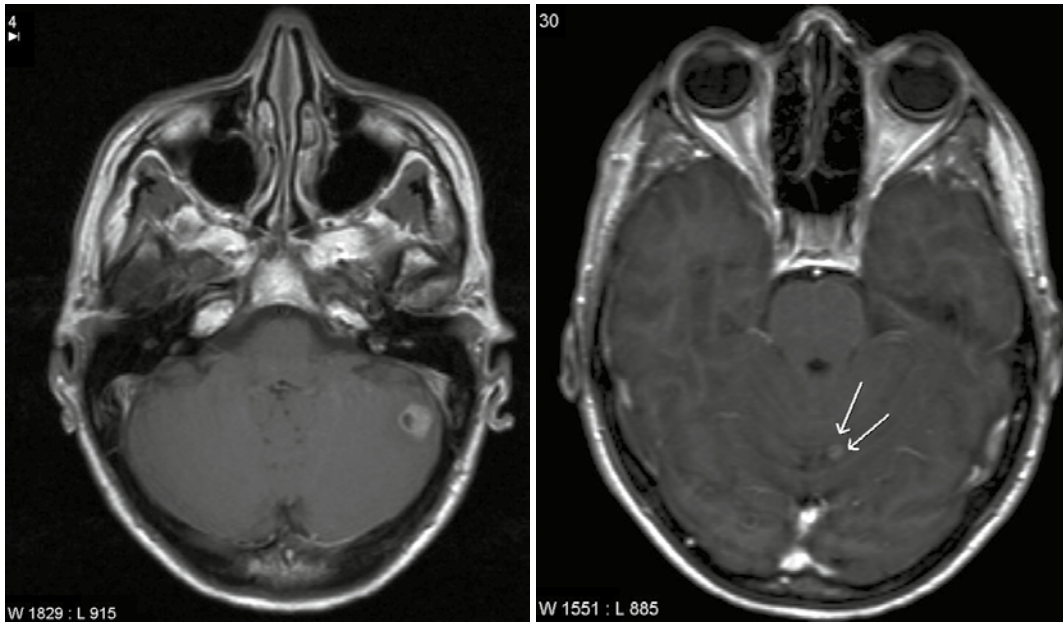


Fig. 4 An illustrative case from one of the authors' institutions (Nordland Hospital Bodø, Norway). The patient is a 46-year-old female with triple-negative breast cancer stage T1 N0 M0. Two years after the initial diagnosis and breast conserving treatment, headaches led to magnetic resonance imaging (MRI) diagnosis of a single 7-mm-large cerebellar metastasis. Pulmonary metastases were detected at the same time. *Arrows* are needed to indicate where the lesion is located

Treatment consisted of stereotactic radiosurgery and systemic chemotherapy (two different lines, anthracycline based and taxanes). Nine months later, four new brain metastases were found (supra- and infratentorial; one example is shown above).

The pulmonary metastases progressed at the same time. The patients Karnofsky performance status was 70. She received palliative whole-brain radiotherapy (WBRT), 30 Gy in 10 fractions of 3 Gy. She then started third-line chemotherapy with capecitabine. A partial remission of all 4 brain metastases was achieved, but the pulmonary disease progressed further. The patient died 5 months after WBRT from progressive pulmonary metastases with pleural and pericardiac effusions

18 Gy and the median target volume size 0.94 cc. Adverse radiation effects were judged on serial MRI scans. The 1-year cumulative incidence was 20 % for symptomatic and 37 % for overall adverse radiation effects. Compared to SRS without any prior or concomitant further radiotherapy, the hazard ratio for adverse radiation effects after re-SRS was 3.7 (95 % confidence interval 1.3–10.8; multivariate analysis). Efficacy results were not reported.

4 Reirradiation: Fractionated Stereotactic Radiotherapy (FSRT)

A normal brain tissue dose recommendation in SRS planning is to limit the volume receiving 10 Gy or more to 10–12 cc. For larger tumors, or those in proximity to critical sensitive structures, fractionated high-precision treatment with stereotactic localization and mask fixation of the head might offer a solution (Fig. 5). Only relatively small patient series are available to assess the outcomes with this approach. A Japanese series included seven patients with previously irradiated brain metastases (Tokuuye et al. 1998). The patient characteristics are comparable to those from other SRS series, but lesion size was larger. Fractionation was individualized, e.g., 33 Gy in 11 fractions of 3 Gy or 24 Gy in 4 fractions of 6 Gy. In these selected patients, results comparable to those of the RTOG SRS trial were found. In a Canadian study, SRS was used in smaller lesions ($n = 35$, maximum diameter 3 cm for supratentorial and 2 cm for posterior fossa metastases, dose of 22.5 Gy prescribed to the 90 % isodose), while a split dose was used in larger ones (29.7 Gy at the 90 % isodose surface

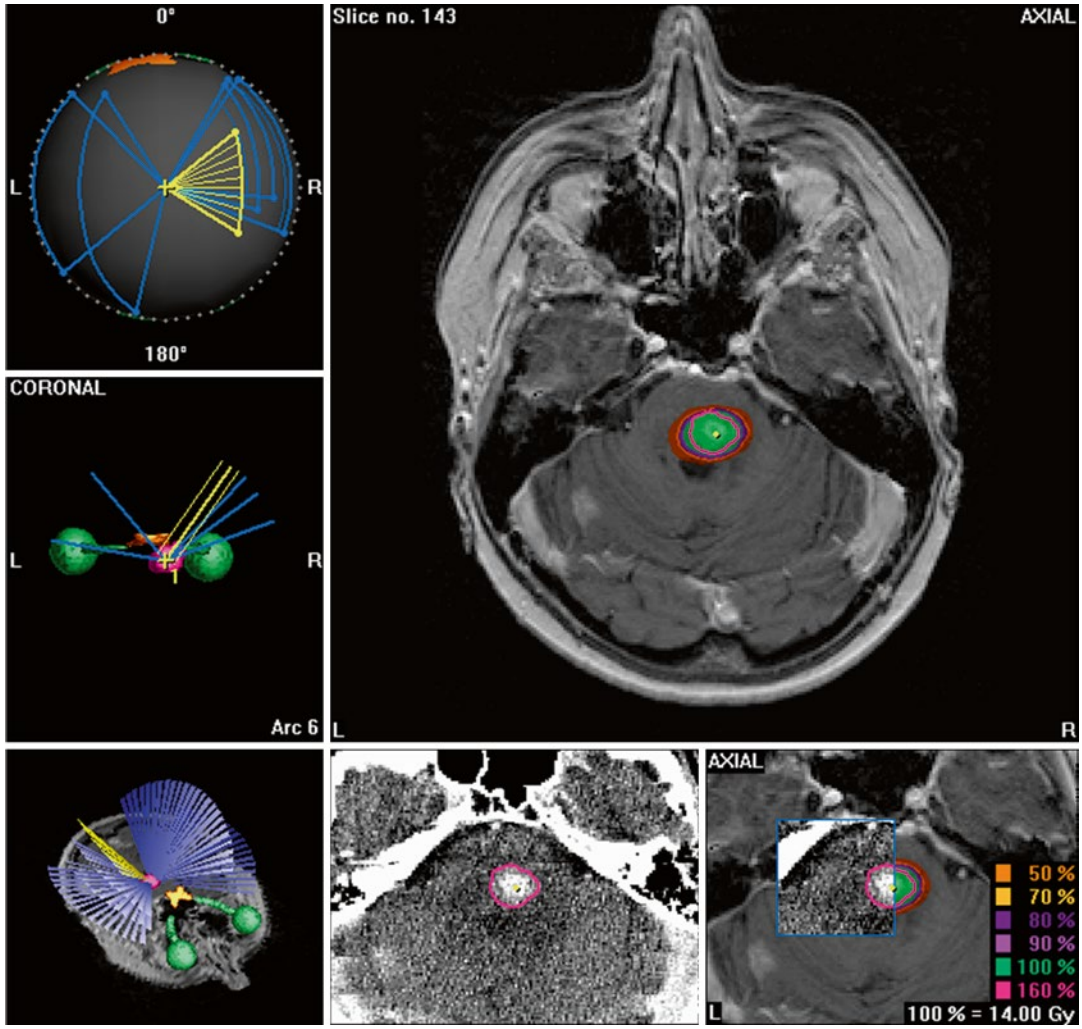


Fig. 5 A hypothetical case with a rather large metastasis in the brain stem where the therapeutic ratio of stereotactic radiosurgery is small. The long-term tumor control probability with a margin dose of 14 Gy, as displayed here, is not satisfactory. Under such circumstances, fractionated stereotactic radiotherapy might be considered

in 2 fractions, $n=69$) (Davey et al. 2007). A total of 180 metastases were treated in these 104 patients. The median time from WBRT to SRS was 7.6 months, and from WBRT to fractionated treatment, it was 6 months. Median survival after retreatment was 4 months after SRS and 6 months after 2 fractions.

The results of FSRT after SRS in 43 patients with 47 lesions were reported by Minniti et al. (2016). The patients received three daily fractions of 7–8 Gy. The 1-year survival rate was 37 % and the 1-year local control rate 70 %. Compared to NSCLC and breast cancer metastases, those from malignant melanoma were significantly less likely to be locally controlled. Better KPS and stable extracranial disease predicted for longer survival. The risk of radiological changes suggestive of radionecrosis was 34 % at 1 year (crude rate 19 % or 9/47 lesions). Fourteen percent of patients had associated neurological deficits RTOG grade 2 or 3. Figure 6 shows examples of amino acid (MET and FET) positron emission tomography (PET) after SRS.

As reported by Holt et al. (2015), surgical resection is often favored after initial SRS because it provides pathological characterization of any

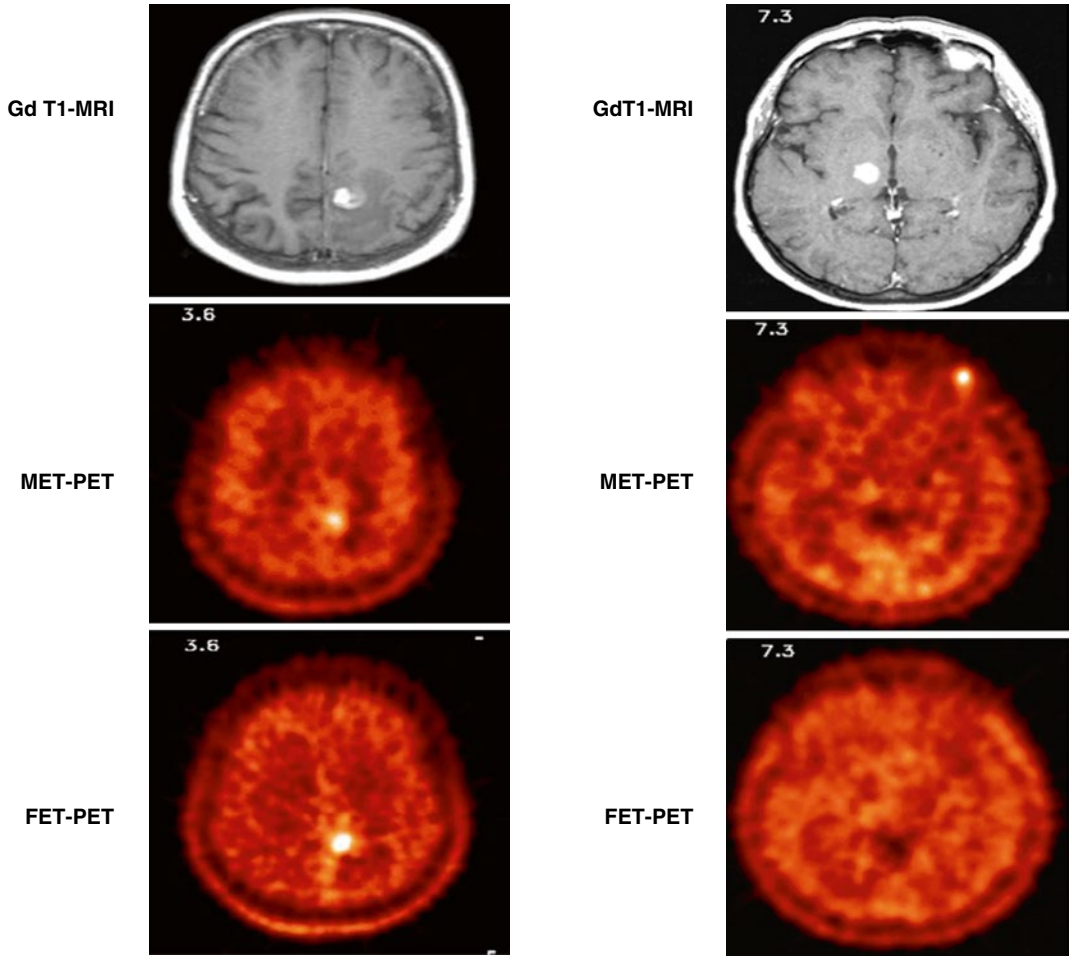


Fig. 6 After stereotactic radiosurgery for brain metastases, amino acid (MET and FET) positron emission tomography (*PET*) may facilitate differentiation between local recurrence (**a**) and radiation-induced toxicity (**b**)

residual tumor. Their experience with SRS followed by surgery and further FSRT or SRS to the tumor bed relates to 15 lesions in 13 patients. Ten lesions received adjuvant radiotherapy; the remaining 5 were treated after additional local tumor growth was detected. Malignant melanoma was the prevailing primary diagnosis (60 %). The median interval was 6 months and the median follow-up after reirradiation 9 months. Initial SRS was given to a median dose of 21 Gy (range 18–27; median size 4.3 cc). The median reirradiation dose was 21 Gy (range 16–30 in 1–3 fractions; median size 9.4 cc). Eight patients received further radiotherapy for new metastases during the disease trajectory, WBRT or SRS. Local control at 1 year was 75 %. One-year survival rate was 43 %. One patient developed grade 2 radionecrosis with grade 3 seizures and another patient grade 3 radionecrosis.

Kim et al. (2013) analyzed outcomes in patients without prior WBRT who were treated with a second course of SRS/FSRT for locally or regionally recurrent metastases, $n=32$. Multivariate analysis showed that upon retreatment, local recurrences were more likely to fail than regional recurrences (hazard ratio 8.8, $p=0.02$). Median survival for all patients from first SRS/FSRT was 14.6 and 7.9 months from second SRS/FSRT. Thirty-eight percent of patients ultimately received WBRT as salvage therapy after the second SRS/FSRT.

5 Reirradiation: Brachytherapy

The majority of reports on brachytherapy for recurrent brain metastases were published in the 1980s and 1990s, i.e., before SRS and FSRT became widely available. They are reviewed very briefly. The retrospective study from Freiburg, Germany, included 21 patients with recurrent brain metastases after previous radiotherapy with or without surgery (Ostertag and Kreth 1995). Interstitial 125-iodine implants were used. Median survival was 6 months. A Canadian series reported on 10 patients with local recurrences after surgery and WBRT (Bernstein et al. 1995). The median interval to 125-iodine brachytherapy was 8 months. Five patients died of further local progression. Median survival was almost 11 months. Two reports from the University of California San Francisco also describe the role of brachytherapy. In 1989, this group published the results of 14 patients with progressive brain metastases (13 had been treated with WBRT) (Prados et al. 1989). Twenty years later, a new report including 21 such patients was published (Huang et al. 2009). These 21 patients were treated between 1997 and 2003, i.e., approximately 3.5 patients per year. Median survival in the most recent study was 7.3 months. The 1-year local freedom from progression probability was 86 %. The brain freedom from progression probability was lower, i.e., 43 %, as a result of new lesions. Radiation necrosis might develop more often after brachytherapy than after SRS, but no randomized head-to-head comparison in patients with recurrent brain metastases is available.

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