Brain metastases: Is there still a role for whole-brain radiation therapy?

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Abstract

Whole-brain radiation therapy (WBRT) has commonly been prescribed to palliate symptoms from brain metastases, to reduce the risk of local relapse after surgical resection and to improve distant brain control after resection or radiosurgery. While targeting micrometastases throughout the brain can be considered advantageous, the simultaneous exposure of healthy brain tissue might cause adverse events. Attempts to mitigate the risk of neurocognitive decline after WBRT include the selective avoidance of the hippocampi, among others. Besides selective dose reduction, dose escalation to boost volumes, e.g. simultaneous integrated boost, aiming at increased tumor control probability is technically feasible. While up-front radiotherapy for newly diagnosed brain metastases often employs radiosurgery or other techniques targeting visible lesions only, sequential (delayed) salvage treatment with WBRT might still become necessary. In addition, the presence of leptomeningeal tumors or very widespread parenchymatous brain metastases might prompt clinicians to prescribe early WBRT.

Introduction

Whole-brain radiotherapy (WBRT), which was considered the standard approach for most scenarios of brain metastases (both intact and resected, and also prevention as prophylactic cranial irradiation (PCI) in patients with small cell lung cancer (SCLC)) a few decades ago, has come under gradually increasing scrutiny, after technological advances paved the way for other methods of brain irradiation.[1-4] Comparison of different WBRT fractionation regimens in various randomized clinical trials (once daily or twice daily fractionation, mostly 1-4 weeks of treatment) resulted in adoption of a 2-week regimen (10 fractions of 3 Gy) by many institutions. Others preferred shorter (5 fractions of 4 Gy) or longer (15 fractions of 2.5 Gy) regimens. Typically combined with oral steroid medication and other supportive measures, WBRT led to symptom relief and improved neurological function in a proportion of patients.[5,6] Given that both peritumoral edema and metastases themselves were targeted by the combination of steroids and WBRT, clinical improvement was not always caused by shrinkage of the metastases. In case of clinical deterioration due to lack of tumor growth suppression, survival was very short. Despite occasional long-term survival in patients with excellent response, median overall survival in different studies was 3-6 months, depending on selection criteria.[7]

A complicating factor in decision making was the presence of extracranial metastases in the majority of patients and the fact that available systemic therapies were less effective than in the present era.[8,9] Therefore, death from progressive extracranial disease within a few months was often inevitable. At the same time, gradual extracranial disease progression impacted performance status and overall symptom burden. Thus, the net effect of WBRT on functional independence and quality of life

was not necessarily very pronounced. Symptoms caused by extracranial disease progression such as worsening bone pain, dyspnea, asthenia, loss of appetite, nausea etc. may prevent patients from living an active life, despite improvement in other domains such as headache or dizziness conferred by WBRT. Currently, WBRT use is much more restricted than 20 or 30 years ago.[10] Indications include, e.g. salvage after up-front focal radiotherapy (often stereotactic radiosurgery (SRS) or repeated courses of SRS) or primary systemic treatment (Figures 1 and 2).

Characteristics of whole-brain radiotherapy and selected outcomes

As indicated in Table 1, WBRT targets both visible and microscopic cancer deposits. This would make WBRT an attractive approach, provided all normal cells and organs at risk could tolerate radiation without serious damage that translates into adverse effects. As an alternative to WBRT, some oncologists advocate leaving microscopic tumor to systemic therapy, at least for cancer types eligible for effective drugs.[11] Radiation doses sufficient to control microscopic tumor are less effective against visible and, especially, large metastases. A historical study included patients treated with WBRT (10 fractions of 3 Gy over 2 weeks) who did not receive additional treatment, for example, surgery or chemotherapy, and were imaged with at least one follow-up computed tomography (CT).[12] Three hundred thirty-six metastases from 108 patients were evaluated with regard to their volume, extent of necrosis and histology of the primary tumor. All parameters were associated with best response and time to progression. Complete remission (CR) was observed in 37% of metastases from SCLC, 35% of those from breast cancer, 25% of those from squamous-cell carcinoma, and 14% of those from non-breast adenocarcinoma. The rate was 52% for metastases

<0.5 cc and 0% for those >10 cc. In multivariate analysis, small volume and no necrosis were the most important predictors of CR.

Mehta et al. studied 401 patients (251 with NSCLC, non-small cell lung cancer) enrolled in a prospective open-label trial (WBRT regime: 30 Gy in 10 fractions).[13] Median survival was 4.9 months for WBRT without radiation sensitizer (control arm). Median time to investigator-assessed neurologic progression, a coprimary endpoint evaluated at monthly intervals for the first 6 months, was 3.8 months. The events review committee (ERC) assessed time to neurologic progression was longer (8.3 months). The ERC was blinded to the treatment assignment. Confounding factors that might affect neurologic function, such as corticosteroid use or tapering, narcotic use, or metabolic derangements were provided to the ERC. Prespecified criteria for ERC-determined progression required a worsening in two or more of the following clinical domains: neurocognitive function, neurologic signs, and neurologic symptoms. Deterioration of neurologic signs and symptoms was considered significant if it was consistent with the presence of brain metastases, not explained by confounding factors, and the findings were persistent on two consecutive visits. The ERC considered magnetic resonance imaging (MRI) results only if a patient was found to have deterioration in at least two of the three neurologic domains to confirm that the observed deterioration was related to brain metastases and not to confounding factors. MRI results were used to confirm clinical findings but were not used to determine the neurologic progression end point. In contrast to the ERC, investigator-assessed neurologic progression did not require confirmation at the next visit and could be based on MRI progression. These differences provided the investigators with more frequent assessments and more clinical information than was available to the ERC. Only 68%

of patients had follow-up MRI (21% died before the first follow-up scan). Complete and partial response was observed in 51% after WBRT alone. As also reported, only patients with at least partial response demonstrated improvement in executive function (Trail B) and visual motor scanning (Trail A) tests.[14]

Graham et al. randomized a total of 113 patients to 40 Gy in 20 twice-daily fractions (arm A) or 20 Gy in four daily fractions (arm B), stratified by resection status (n=41).[15] Overall, the actuarial central nervous system progression rate at 12 months, 24 months, and 5 years was 68%, 77%, and 82%, respectively. The median interval to progression was 9 months in arm A vs. 5 months in arm B, indicating limited long-term control also after relatively high WBRT doses. The European Organization for Research and Treatment of Cancer (EORTC) quality of life 30-item C30 QOL questionnaire was administered monthly during the first year. The patients' quality of life was not impaired by the more intense treatment in Arm A. Quality of life was largely stable during the first year. However, some patients reporting stable scores might nonetheless report adverse events, if a study collects a large amount of data through several instruments or tests.

Side effects of WBRT were also evaluated in a study by Chow et al.[16] All patients were prescribed dexamethasone at varying doses during radiotherapy (commonly 20 Gy in 5 fractions). There were statistically significant deteriorations in the mean differences from the baseline for the following ESAS (Edmonton symptom assessment system) domains: fatigue 1.0 to 1.8; drowsiness 1.2 to 1.8; and appetite 2.2 to 2.4. Increasing numbers reflect worse symptoms (minimum 0, maximum 10). Hong et al. studied adjuvant WBRT compared with observation after local treatment of melanoma brain

metastases.[17] Patients in the WBRT group had more grade 1-2 toxicity in the first 2-4 months wiith more fatigue (68% vs. 28%, p<0.001), anorexia (45% vs. 8%, p≤0.001), nausea (33% vs.16%, p<0.001), dermatitis (12% vs. 0%, p<0.001), and alopecia (62% vs.4%, p≤0.001). However, there was no difference in these types of toxicity up to 24 months after random assignment. There were no severe adverse events related to WBRT within 90 days of random assignment. Median time to deterioration in performance status was 3.8 months after WBRT and 4.4 months with observation (p=0.3). Yang et al. studied WBRT with and without concurrent erlotinib in NSCLC with brain metastases in a multicenter, open-label, randomized setting.[18] The WBRT alone arm included 99 patients (dose: 20 fractions of 2 Gy). After 1-5 months approximately 20% of patients declined in Folstein Mini-Mental State Examination (MMSE). At later time points this figure increased to approximately 30% (decline: >3-point decline).

In a prospective randomized trial investigating neurocognition in patients after SRS vs. SRS plus WBRT, patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months after treatment compared with the group that received SRS alone.[19] Besides transient or permanent neurocognitive deficits, imaging changes were observed after WBRT (white matter changes, brain atrophy, Figure 3).[20] There is not always good concordance between imaging changes, neurocognitive test results, other symptom scores and quality of life. Not all changes that are detectable by tests or questionnaires have a measurable impact on a patient's everyday life and performance status. In addition, many factors may contribute to clinically detectable changes, e.g. side effects of systemic therapy, disease progression, hyponatremia, hypercalcemia.

Trifiletti et al. reported a post hoc analysis of the NCCTG N107C [Alliance]/CEC.3 trial.[21] Among 92 patients treated with surgical resection and adjuvant WBRT, 49 were treated with 30 Gy in 10 fractions, and 43 were treated with 37.5 Gy in 15 fractions. Baseline characteristics, including neurocognitive testing, were well balanced between groups, with the exception of primary tumor type (lung cancer histology was more frequent with protracted WBRT: 72% vs. 45%, p=0.01). The 37.5 Gy in 15 fractions regime did not significantly affect time to cognitive failure, surgical bed control, intracranial tumor control, or overall survival. There was a statistically significant increase in the risk of at least 1 grade ≥3 adverse event with 37.5 Gy in 15 fractions vs. 30 Gy in 10 fractions (54% vs. 31%, respectively, p=0.03). Thus, the therapeutic ratio was not improved. The authors concluded that shorter course regimens remain the current standard of care. Implementation of 30 Gy in 10 fractions as the preferred institutional approach should not preclude individual decision making, because for example patients with radiosensitive primary malignancy such as SCLC and limited prognosis might derive servicable palliation from a one-week schedule of 20 Gy in 5 fractions.

Modified whole-brain radiotherapy

Two different strategies or a combination of both have been developed to circumvent the biggest disadvantages of WBRT. Firstly, efficacy may be increased by dose escalation through sequential SRS boost or various simultaneous integrated boost (SIB) techniques.[22,23] Ideally, equi-effective doses should be comparable to those of SRS alone, if the same tumor control probability is desirable. Secondly, to decrease the severity of neurocognitive deficits, modification of the target volume has been introduced.[24] Selective omission or avoidance of the hippocampi (HA-WBRT) might

preserve imaging-defined hippocampal volume and impact clinical endpoints, e.g. in a pivotal phase 3 trial in which also memantine was prescribed (discussed below).[25,26]

The hippocampus is involved in episodic memory processing.[27] Irradiation blocks the adult neurogenesis in the subgranular zone of the hippocampus in rodent animal models. Based on extensive pre-clinical work and translational clinical studies, prevention of neurocognitive decline by HA-WBRT has been described.[28,29] For hippocampal contouring and treatment planning in Radiation Therapy Oncology Group (RTOG) trial 0933, patients required MRI scans of the brain with axial slice thickness ≤ 1.5 mm, fused to a radiotherapy-planning CT scan with axial slice thickness ≤ 2.5 mm.[29] Bilateral hippocampal contours were manually generated on the fused MRI-CT image set and expanded by 5 mm to generate the HA regions. HA-WBRT is shown in Figure 4.

The added value of memantine has been addressed in a randomized study of WBRT plus placebo or memantine (20 mg/d), started within 3 days of initiating radiotherapy for 24 weeks.[30] Serial standardized tests of cognitive function were performed in the trial with 554 patients (508 were eligible). Grade 3 or 4 toxicities and study compliance were similar in the 2 arms. There was less decline in delayed recall in the memantine arm at 24 weeks (p=0.059), but only 149 patients contributed data at this follow-up time point, resulting in only 35% statistical power. The memantine arm had significantly longer time to cognitive decline (p=0.01). Superior results were seen in the memantine arm for executive function at 8 (p=0.008) and 16 weeks (p=0.004) and for processing speed (p=0.014) and delayed recognition (p=0.015) at 24 weeks. Due to these

encouraging data, memantine was also prescribed in the study of WBRT with or without hippocampal-avoidance.

The seminal phase 3 trial briefly mentioned above enrolled 518 adult patients with brain metastases who received WBRT (30 Gy in 10 fractions) plus memantine with or without hippocampal-avoidance.[26] The primary end point was time to cognitive function failure, defined as decline using the reliable change index on at least one of several cognitive tests. Risk of cognitive failure was significantly lower after HA-WBRT plus memantine vs. WBRT plus memantine (adjusted hazard ratio, 0.74; p=0.02). This difference was attributable to less deterioration in executive function at 4 months (23% vs. 40%, p=0.01) and learning and memory at 6 months (11.5% vs. 25%, p=0.049; and 16% vs. 33%, p= 0.02), respectively). At 6 months, using all data, patients who received HA-WBRT plus memantine reported less fatigue (p=0.04), less difficulty with remembering things (p= 0.01), less difficulty with speaking (p=0.049), less interference of neurologic symptoms with daily activities (p=0.008), and fewer cognitive symptoms (p=0.01) as compared to patients who were in the standard WBRT arm. As a consequence of limited overall survival, not all patients were evaluable at 4 and 6 months, respectively. From a dosimetric perspective, HA-WBRT dose distributions often show higher maximum doses (Dmax) in the standard target volume than conventional WBRT, which aims at a Dmax of 107%. It is currently unknown whether higher Dmax translates into clinically measurable long-term toxicity.

Importantly, patients with visible metastases near the hippocampus are not appropriate for a hippocampal avoidance strategy. The prospective German HIPPORAD trial is currently examining HA-WBRT with SIB.[31] WBRT delivers 30 Gy in 12 daily fractions

nd the SIB escalates dose to 51 Gy in 12 daily fractions for intact metastases (42 Gy to resection cavities). In parallel, treatment planning techniques that result in further reduction of the hippocampal dose are under investigation.[32]

Present roles of whole-brain radiotherapy

The complexity around decision-making requires input from dedicated multidisciplinary teams, able to address the unique challenges associated with each individual presentation of the disease.

Post-operative radiotherapy

Based on a seminal, yet small randomized trial by Patchell et al. (95 patients with single lesion, primary endpoint: recurrence in the brain, post-operative WBRT (28 fractions of 1.8 Gy) versus observation), which demonstrated significantly lower rates of brain recurrence at the site of the original metastasis (10% versus 46%, $p<0.001$) and at other sites in the brain (14% versus 37%, $p<0.01$), this treatment paradigm gained acceptance in many institutions (often by utilizing shorter fractionation regimens).[33] However, Patchell et al. reported no significant difference between the two groups in overall survival or the length of time that patients remained functionally independent. A further seminal randomized trial (EORTC 22952-26001) will be discussed below. Opponents of immediate WBRT have argued that both lack of improved survival and risk of toxicity provide reasons to study a different approach, acknowledging the desirable increase in local control. This different approach consists of surgical bed/tract radiotherapy, commonly performed in a stereotactic single-dose or fractionated manner. Randomized trials have laid the foundation for increasing utilization of this

small-volume adjuvant radiotherapy approach.[34,35] As illustrated in the next paragraph, a proportion of patients eventually requires WBRT for locoregional relapses.

Recurrent disease including new distant brain metastases

The phase 3 trial, which assessed whether adjuvant WBRT (30 Gy in 10 fractions) increases the duration of functional independence after surgery or SRS of 1-3 brain metastases (EORTC 22952-26001), might serve as an illustrative example.[36] Of 359 participants, 199 underwent SRS and 160 underwent surgery. In the SRS group, 100 patients were allocated to observation and 99 were allocated to adjuvant WBRT. After surgery, 79 patients were allocated to observation and 81 were allocated to WBRT. As displayed in Figure 5, progression was common after initial observation (78%). A third of the patients eventually received WBRT. Adjuvant (immediate) WBRT significantly reduced the likelihood of neurologic death (28 and 44%, respectively). However, neither duration of functional independence nor overall survival improved significantly.

In a study by Zindler et al. distant brain recurrence rates were evaluated in a group of patients treated with SRS alone for 1-3 brain metastases (n=443).[37] For all 127 patients with a distant brain recurrence, the median overall survival after repeat SRS was 9.9 months, after secondary WBRT 6.2 months, and without salvage treatment 3.5 months. In a smaller study of up-front systemic therapy for brain metastases from lung cancer (no targetable mutations), median survival from secondary radiotherapy was only 2.7 months.[9]

Presence of a leptomeningeal disease component

Both de novo presentation (Figure 6) or diagnosis after previous surgical resection are scenarios radiation oncologists might face. The European Association of Neuro-Oncology (EANO) – European Society for Medical Oncology (ESMO) guidelines have proposed a classification of leptomeningeal metastases from solid cancers based on clinical, MRI, and cerebrospinal fluid (CSF) cytology presentation. Imaging patterns are classified as linear, nodular, both, or neither. Type I disease is defined by positive CSF cytology (confirmed leptomeningeal metastases) whereas type II is defined by typical clinical and radiological signs (probable or possible leptomeningeal metastases). In a study by Le Rhun et al., patients with confirmed metastases had significantly inferior outcome compared with patients with probable or possible metastases.[38] Type I patients did worse than type II patients. Nodular disease on MRI was a negative prognostic factor in type II disease, but not in type I. Iglseder et al. assessed diagnostic criteria and treatment response by EANO-ESMO classification in 40 patients who were treated with combined WBRT and intrathecal cytarabine.[39] Median overall survival was 4 months. Patients with positive CSF cytology (n=26) showed worse prognosis compared to patients with negative CSF cytology (survival 2.8 vs. 6.5 months, p=0.006). Stable and responding patients (EANO-ESMO response assessment) survived significantly longer than those with progression or suspicion of progression.

Leptomeningeal disease in neurosurgical brain metastases patients was studied in a systematic review and meta-analysis of 13 studies with 2105 patients by Tewarie et al.[40] They included 386 patients who developed leptomeningeal disease. Eighteen unique risk factors were reported as significantly associated with its occurrence, including but not limited to larger tumor size, infratentorial brain metastasis location, proximity of brain metastasis to cerebrospinal fluid spaces, ventricle violation during

surgery, and subtotal or piecemeal resection. Furthermore, breast cancer as the primary tumor location and multiple brain metastases were significantly associated with a higher risk of leptomeningeal spread. The latter often presents as nodular pattern disease. If localized, salvage SRS might be feasible. Otherwise, WBRT can be prescribed. In a small study of 29 patients, WBRT for nodular disease resulted in a median overall survival of 5 months.[41] In a larger study, 125 patients with brain metastases who underwent surgical resection and postoperative SRS, and subsequently developed leptomeningeal spread were combined from seven centers.[42] The neurological death rate in these patients was 79%. Overall survival was not reported. WBRT was used in 52% of patients with nodular disease and 95% of those with other pattern. Patients with nodular pattern treated with salvage focal radiation did not have higher neurological death rates compared with WBRT.

Best supportive care or whole-brain radiotherapy

As mentioned in the previous parts of this overview, imaging response rates and median overall survival after WBRT are limited, indicating that not all patients are able to benefit. Avoiding futile treatment in the terminal phase of metastatic cancer is important and requires thorough assessment of prognostic factors.[43] Major advances have been made in the development of survival prediction tools. Scores such as the updated diagnosis-specific graded prognostic assessment (DS-GPA, Table 2) may inform treatment choices,[44] even if they simplify the complete clinical picture. Assigning a patient to the unfavorable prognostic group in any of the validated scores typically means that predicted median survival for a group of patients with similar characteristics is in the order of 2-3 months. Nevertheless, vastly different management approaches might be recommended if such a patient consults with several providers, as illustrated

in an international expert survey that focused on brain metastases from NSCLC.[51] However, the life expectancy of patients with brain metastases and adverse prognostic features is often very short, and therefore best supportive care (BSC) may be the preferable option for selected patients.[52-54]

Selection criteria are currently a matter of debate. In a landmark randomized trial (QUARTZ, limited to NSCLC), investigators were encouraged to approach potential participants about the trial if there was uncertainty in the clinicians' or patients' minds about the potential benefit of WBRT (20 Gy in 5 daily fractions, i.e. a total dose inducing limited tumor cell kill), and a multidisciplinary team that included both neurosurgeons and radiation oncologists had concluded that the patient was unsuitable for either surgery or SRS.[53] In other words, no pre-specified, defined prognostic model was required. The non-inferiority phase 3 trial included 538 patients and assessed the omission of WBRT with a primary outcome measure of quality-adjusted life-years (QALYs), which combines overall survival and quality of life. Symptoms and quality of life at baseline were similar between the two groups (using the EuroQol EQ-5D 3L questionnaire). The mean QALY for patients assigned to the BSC plus WBRT group was 46 days, and for those assigned to the BSC group was 42 days. Patients receiving BSC plus WBRT reported more moderate or severe episodes of drowsiness than those receiving BSC alone (42% vs. 28%, p=0.02), hair loss (34% vs.1%, p=0.0001), nausea (10% vs. 2%, p=0.007), and dry or itchy scalp (7% vs. 1%, p=0.006). Overall, 89 patients receiving BSC plus WBRT and 82 patients receiving BSC reported at least one serious adverse event over the course of the trial. The most commonly reported events were infections, neurological problems, and pulmonary problems, with no evidence of any difference between groups in the rate of any event. Quality of life, as

measured by the utility score generated from the EQ-5D 3L responses, remained similar over time, with no significant differences between the groups at 4, 8, or 12 weeks. The number of patients with maintained or improved quality of life compared with baseline was also similar between the groups at 4 weeks (54% of patients receiving BSC plus WBRT vs. 57% with BSC), 8 weeks (44% of patients receiving BSC plus WBRT vs. 51% with BSC), and 12 weeks (44% of patients receiving BSC plus WBRT vs. 49% with BSC). Median survival (estimated from a flexible parametric model) was 9 weeks for patients who received BSC plus WBRT and 8.5 weeks for patients who received BSC. Younger patients, particularly those aged younger than 60 years, show improved survival with WBRT. The data also suggested that WBRT might still have a role for patients with the best prognoses according to GPA categories[55] (those with scores of at least 2.5).

To confirm the latter findings that suggested a role of WBRT, a different group performed a retrospective single institution analysis of 76 patients with favorable prognosis.[56] In contrast to the QUARTZ trial, inclusion was not limited to patients with NSCLC. Furthermore, a cohort treated with a higher total dose of WBRT was included (10 fractions of 3 Gy). All study patients were younger than 60 years or had a GPA score of 2.5-3. The median survival was significantly shorter after BSC (1.2 months; 3.2 months after WBRT with 5 fractions of 4 Gy, and 3.9 months after 10 fractions of 3 Gy). In multivariate analysis, survival was also significantly better after WBRT. A separate study included patients with 0-1.5 points according to the DS-GPA (or GPA if primary tumor type was not among those represented in DS-GPA).[57] Survival curves were compared between patients treated with BSC or different radiotherapy regimens. Irrespective of point sum examined, DS-GPA by itself was not a satisfactory

selection parameter. However, we identified a subgroup of patients with short survival irrespective of management approach (only 5 % of irradiated patients survived beyond 6 months, all of whom had newly diagnosed, treatment-naïve lung cancer), i.e., patients in whom foregoing radiotherapy was unlikely to compromise survival. These were patients with i) 0-1.5 points and age 75 years or older, ii) 0-1.5 points and Karnofsky performance status ≤ 50, and iii) 0-1.5 points and uncontrolled primary tumor with extracranial metastases to at least two organs, e.g. liver plus lung(s). Also a large study of 1146 patients treated with WBRT alone identified the number of involved extracranial organs as independent prognostic factor for survival.[58] The 6-month survival rates for the involvement of 0, 1, 2, 3, and ≥4 extracranial organs were 51, 30, 16, 13, and 10%, respectively ($p<0.001$).

Summary

Selective prescription of WBRT is warranted in scenarios such as up-front treatment of widespread intracranial disease, and delayed salvage after up-front surgery/SRS/SFRT. Attempts to mitigate the risk of neurocognitive decline after WBRT include the selective avoidance of the hippocampi, among others. Besides selective dose reduction, dose escalation to boost volumes, e.g. simultaneous integrated boost, aiming at increased tumor control probability is technically feasible and under active clinical investigation. Mismatch between life-span and treatment approach or intensity should be avoided, remembering that the QUARTZ trial showed similar results for BSC and BSC plus low-dose WBRT in patients with NSCLC and uncertainty in the clinicians' or patients' minds about the potential benefit of WBRT at inclusion. Prognostic tools contribute important information in the decision-making process. Despite wide-spread

utilization of 30 Gy in 10 fractions, selected patients should be considered for less time consuming (20 Gy in 5 fractions) or more efficacious (SIB) regimens.

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Figure 1.

Whole-brain radiotherapy (WBRT), a standard of care in previous decades, has lost its dominant role as up-front treatment for patients who don't require surgical resection, because many patients are triaged to initial systemic therapy, stereotactic radiotherapy (SRS/SFRT) or best supportive care (BSC). Secondary WBRT in case of progression after up-front SRS/SFRT or systemic therapy continues to represent a useful approach.

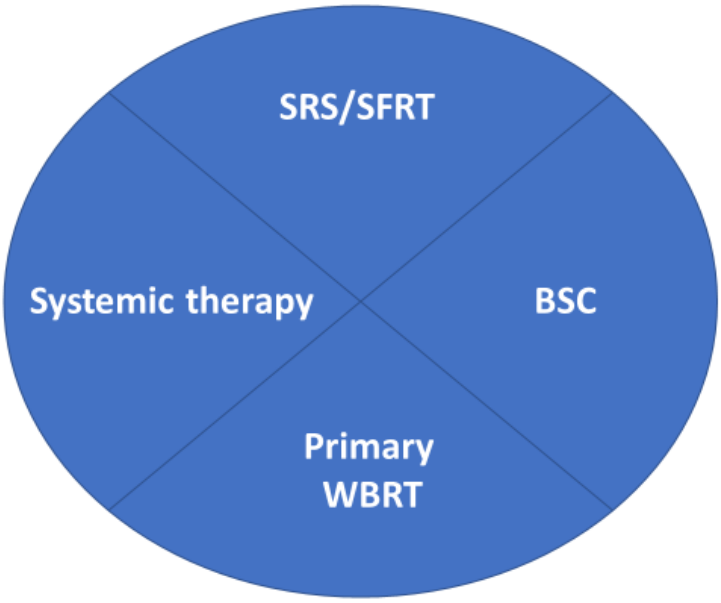


Figure 2.

Computed tomography imaging (CT, left panels), treatment planning CT and digitally reconstructed radiograph (right panels). Compared to a classical radiosurgery case (3 metastases, lower right panel), the displayed case of a 51-year-old female patient with non-small cell lung cancer, neurological symptoms and at least 25 brain metastases (no actionable targets for tyrosine kinase inhibitors) may be considered for up-front whole-brain radiotherapy (upper right panel, lateral treatment field).

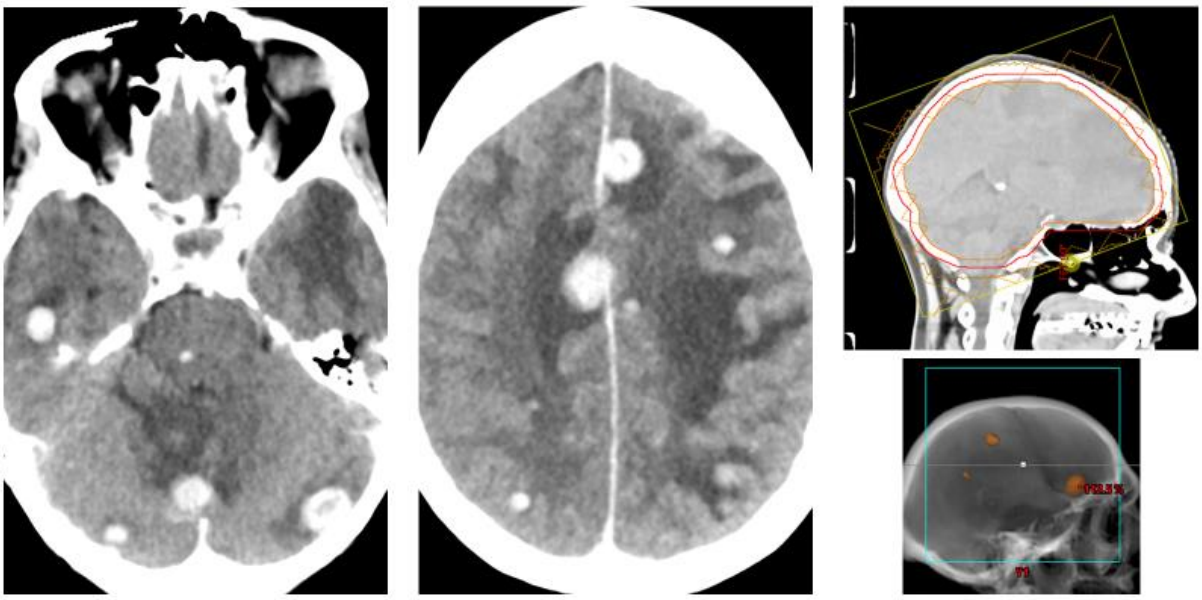


Figure 3.

Magnetic resonance imaging, axial T2 TSE sequence at diagnosis (red arrows indicate pre-existing white matter changes) and in July 2021 (blue arrow indicates more pronounced white matter changes). 67-year-old male patient with extensive disease small cell lung cancer (ED-SCLC) including brain metastases at diagnosis in January 2015, treated with platinum-doublet chemotherapy and 10 fractions of 3 Gy (whole-brain radiotherapy). Size of the ventricles increased from 35 mm (green line) to 44 mm.

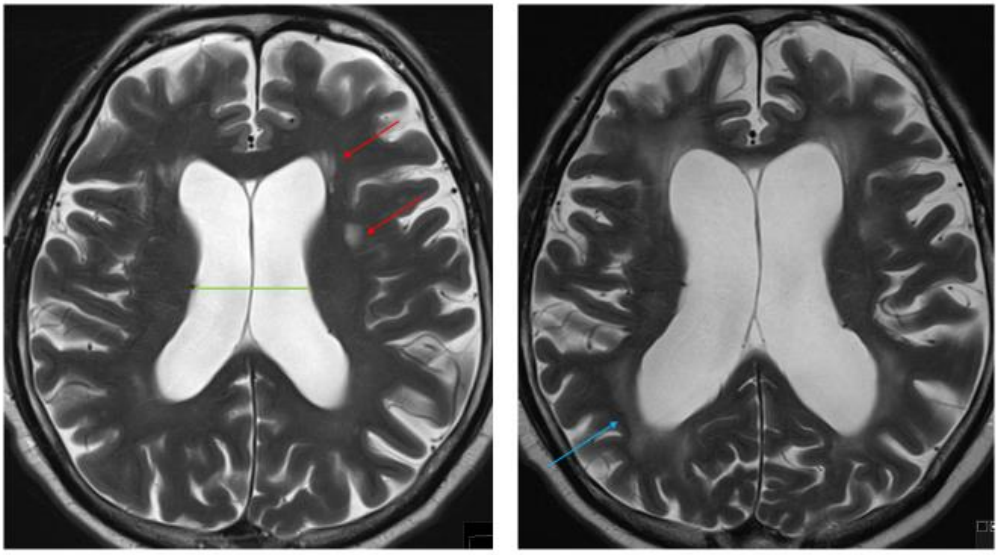


Figure 4.

Coronal planning computed tomography (CT) scan in a patient with non-small cell lung cancer managed with hippocampal-avoidance whole-brain radiotherapy. The closest metastasis is delineated in orange. The 50% isodose is the lowest level depicted here.

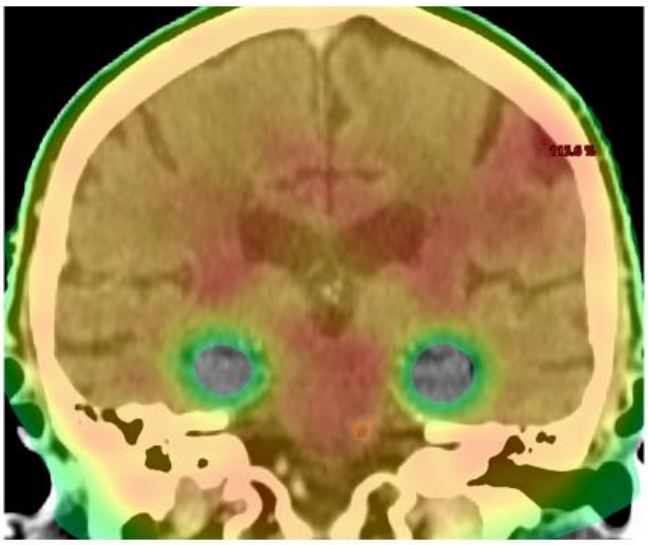


Figure 5.

Pattern of progression in a randomized trial of adjuvant whole-brain radiotherapy vs. observation after radiosurgery or surgical resection of 1-3 brain metastases (EORTC 22952-26001).

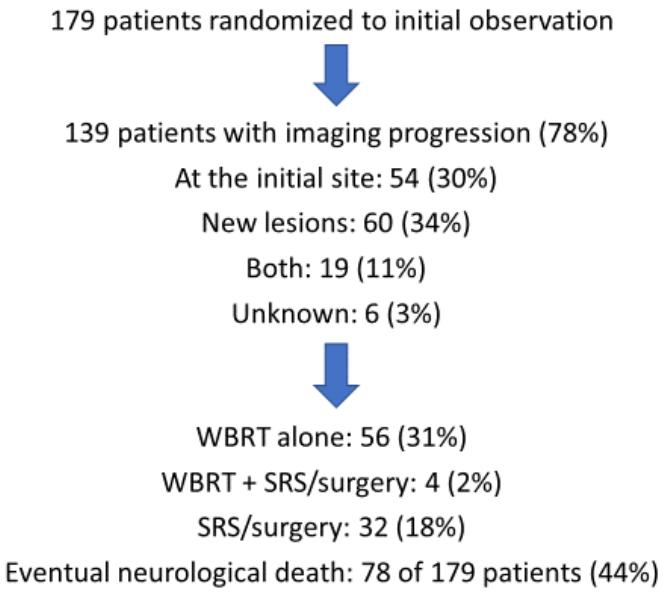
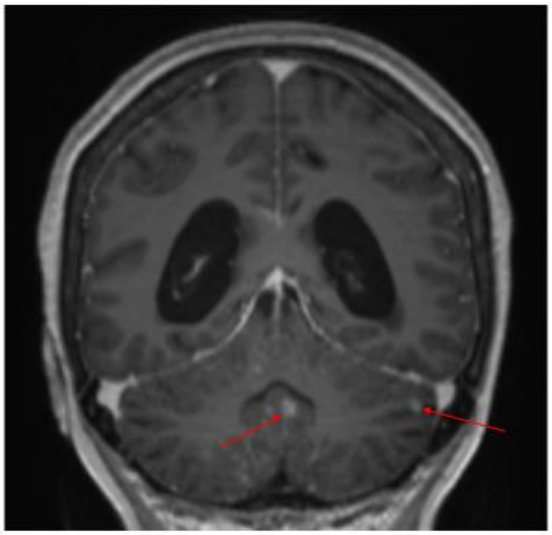


Figure 6.

Left panel: Coronal contrast-enhanced magnetic resonance imaging (MRI) scan of a 62-year-old female patient with estrogen receptor positive Her2 negative metastatic breast cancer (bones, gastric mucosa) presenting with neurological symptoms during 3rd line palliative chemotherapy (red arrows indicate the largest lesions).

Right panel: Axial contrast-enhanced MRI scan of a 43-year-old female patient with estrogen receptor positive Her2 negative metastatic breast cancer (bones, liver, pleura) presenting with neurological symptoms during 3rd line palliative chemotherapy (red arrows indicate selected parenchymal and meningeal lesions).



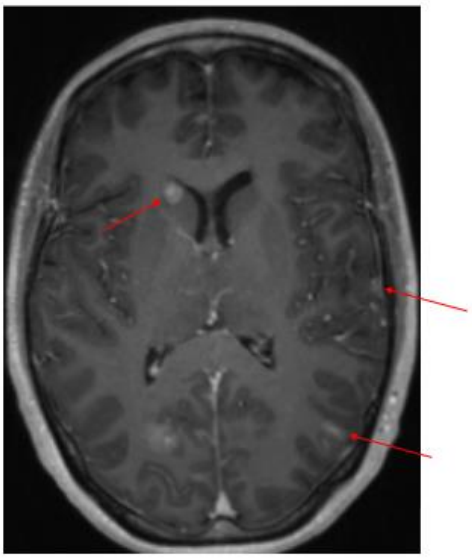


Table 1. Characteristics of whole-brain radiotherapy (WBRT)

Pro	Contra	Solution
Targets microscopic tumor in brain and meninges	Areas relevant to neurocognition receive identical dose	Restricted target volume (HA-WBRT), memantine
Virtually no risk of radionecrosis	Other side effects (eyes, ears, parotid glands, pituitary gland, skin, hair, fatigue)	
	Equi-effective dose is considerably lower than with SRS (limited TCP)	Focal dose escalation (SIB-WBRT or SRS + WBRT)
	Overall treatment time (fractionation)	

SRS: stereotactic radiosurgery; TCP: tumor control probability; HA: hippocampal avoidance; SIB: simultaneous integrated boost

Table 2. Comparison of selected prognostic scores that contribute to personalized treatment

Score	Components	Comments
Updated diagnosis-specific graded prognostic assessment[44,45]	Performance status, number of brain metastases, extracranial metastases, age, and molecular tumor features	Versions for common cancer types such as SCLC, NSCLC, breast cancer, renal cell carcinoma, gastrointestinal cancers etc.
LabBM[46]	Serum hemoglobin, platelets, albumin, C-reactive protein, lactate dehydrogenase	Purely based on site-agnostic surrogate markers of cancer burden
Rades et al. CUP[47]	Performance status, extracranial metastases	This group has also developed scores for bladder cancer, gynecological cancer etc.
Rades et al. NSCLC WBRT30[48]	Performance status, age, systemic treatment, extracranial metastases, number of brain metastases	This group has also developed diagnosis- and treatment-specific scores for other cancer types
Gaspar et al. recursive partitioning analysis classes[49]	Performance status, age, extracranial metastases, primary tumor control	Historical, yet still valid easy-to-assess three-tiered score from 1997

SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer, CUP: cancer of unknown primary, WBRT30: whole-brain radiotherapy with 30 Gy in 10 fractions

Several groups have published scores or nomograms that only include patients managed with surgical resection or stereotactic radiosurgery. Kraft et al. have recently compared numerous scores in patients managed with upfront stereotactic radiosurgery.[50] According to their data, a prognostic score solely based on the assessment of performance status performed very well (as either 3- or 4-tiered score).