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REVIEW

Conventional radiation therapy for brain metastases

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Abstract Conventional radiotherapy in the form of whole brain radiation treatment has been a longstanding treatment for brain metastases, and it continues to provide effective palliation as monotherapy and in combination with local and systemic treatments. Advances in systemic therapy have improved survival with metastatic disease, and in those patients with better prognostic factors, more aggressive local therapeutic approaches for brain metastases appear to benefit their survival and intracranial tumor control. Increased treatment intensity and longer survival following treatment of brain metastases have raised concerns about persistent treatment-related neurocognitive toxicities and the resulting impact on quality of life. Technological advances in conventional radiotherapy planning and delivery have led to novel approaches that may increase intracranial tumor control while minimizing the treatment-related toxicities of therapy. These innovative approaches include intensity-modulated radiotherapy, new image-guidance techniques, and volumetric modulated arc therapy, which allow for the delivery of whole brain radiotherapy with integrated boost treatment to the visible disease while sparing the hippocampal regions or delivery of hypofractionated radiotherapy to larger metastatic targets that may not be amenable to radiosurgery boost or salvage treatment.

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Introduction

Historically, conventional radiotherapy in the form of whole brain radiation therapy (WBRT) has been utilized as the main treatment for the management of brain metastases [1]. With advances in surgical techniques, radiosurgery treatments, and systemic therapies, multidisciplinary and multimodality treatment is increasingly used in the management of brain metastases. Whole brain radiotherapy continues to play a significant role in the treatment and prophylaxis of brain metastases, but advances in conventional radiotherapy planning and delivery are introducing more targeted approaches that may provide better intracranial tumor control while minimizing treatment-related toxicity.

Whole brain radiotherapy

There have been several systematic reviews evaluating the role of WBRT in the management of newly diagnosed brain metastases. In the most recent systematic review by Gaspar et al. [2], nine randomized control trials comparing different doses and fractionation schedules for WBRT were identified. Dose and fractionation schedules of WBRT ranged widely from 10 Gy in 1 fraction up to 50.4 Gy in 28 fractions delivered twice daily. The majority of studies compared an alternate dose and fractionation regime to 30 Gy in ten daily fractions as the control arm. Despite promising results from a number of individual studies in favor of hypofractionation and/or dose escalation, the meta-analysis failed to show a significant difference in survival with any alternate dose and fractionation schedule compared with the control [2]. This conclusion is consistent with a prior Cochrane systematic review by Tsao et al. [3].

Subsequent to these systematic reviews, Rades et al. have reported two retrospective cohort studies suggesting that dose escalation of WBRT beyond 30 Gy in ten fractions improves overall survival of patients with metastatic melanoma and renal cell carcinoma [4, 5]. A randomized study of 40 Gy in 20 twice-daily fractions compared with 20 Gy in 4 daily fractions showed that patients treated with the higher dose twice-daily treatment had better intracranial tumor control (intracranial progression in 44 % with 40 Gy in 20 twice-daily fractions vs. 64 % with 20 Gy in 4 daily fractions, $p=0.03$) with similar quality of life measures using the European Organization for Research and Treatment of Cancer Quality of Life 30-item questionnaire. This improvement in intracranial tumor control did not result in significant improvement in overall survival with median survival of 6.1 vs. 6.6 months for 40 Gy in 20 twice-daily fractions vs. 20 Gy in 4 daily fractions, respectively [6]. Numerous prospective trials have failed to reveal any effect upon survival between alternative fractionation schemes (Table 1). In contrast, elderly patients or those with limited performance status and survival, who are unlikely to receive systemic therapy, have had similar local brain tumor control and survival with hypofractionated courses of WBRT using 20 Gy in five fractions compared with 30 Gy in ten fractions [7, 8].

Various prognostic indices have been formulated in an effort to estimate survival of patients with newly diagnosed brain metastases [9–13]. The three characteristics which are common to all of the prognostic indices are patient age and performance status as well as extracranial disease status. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) delineated three prognostic groups: class I—Karnofsky performance status (KPS) ≥70, age less than 65 years, controlled primary disease, and no extracranial metastases; class III—KPS <70; and class II—all others. Median survival was 7.1, 4.2, and 2.3 months for class I, II, and III, respectively [9, 10].

Alternatively, the graded prognostic assessment (GPA) is a prognostic instrument developed from evaluation of a group of patients who received treatment with more up-to-date technology than is true for those in the RTOG study [11–13]. The GPA scoring system tabulates prognostic

Table 1 Randomized controlled trials of dose fractionation for whole brain radiotherapy

Trial	Fractionation	No. of patients	Survival	Comments
Borgelt (1981) [72] (first trial)	10 Gy/1 vs. 30–40 Gy/10–20	138	15 weeks 21 weeks (ns)	
Borgelt (1981) [72] (second trial)	12 Gy/2 vs. 20 Gy/5	64	13 weeks 12 weeks (ns)	
Kurtz (1981) [73]	30 Gy/10 vs. 50 Gy/20	255	18 weeks 17 weeks (ns)	Pts had no extracranial metastases
Chatani (1985) [74]	30 Gy/10 vs. 50 Gy 20	69	4 months 3 months (ns)	Lung cancer primary disease
Komarnicky (1991) [75]	30 Gy/10 vs. 30 Gy/6 vs.	779	4.5 months 4.1 months	
	30 Gy/6+MISO vs. 30 Gy/10+MISO		3.1 months 3.9 months	
Haie-Meder (1993) [76]	18 Gy/3 vs. 18 Gy/3 repeated once or 25/10	216	4.2 months 5.3 months (ns)	Interval of 4 weeks between those who received 18 Gy/3 times two
Chatani (1994) [77]	30 Gy/10 (nl LDH) vs. 50 Gy/20 (nl LDH)	92	5.4 months 4.8 months (ns)	Lung cancer primary disease
	30 Gy/10 (high LDH) vs. 20 Gy/5 (high LDH)	70	3.4 months 2.4 months (ns)	
Priestman (1996) [78]	12 Gy/2 vs. 30 Gy/10	533	77 days 84 days ($p=0.04$)	
Murray (1997) [79]	30 Gy/10 vs. 54.4 Gy/34 BID	429	4.5 months 4.5 months (ns)	
Davey (2008) [80]	20 Gy/5 vs. 40 Gy/20 BID	90	19 weeks 19 weeks (ns)	
Graham (2010) [6]	20 Gy/4 vs. 40 Gy/20 BID	113	6.6 months 6.1 months (ns)	

ns not statistically significant, *MISO* misonidazole, *LDH* lactate dehydrogenase, *BID* twice per day

factors related to the patient (age and KPS) as well as the disease status (presence of extracranial metastases and number of brain metastases). In addition, a disease-specific graded prognostic assessment (DS-GPA) was developed to include the histology of the primary tumor [11, 12]. The DS-GPA appears to better define those patients with the potential for lengthier survival than does the RPA, as is evidence by the range from 2.8 to 25.3 months median survival for patients with the lowest and highest scores, respectively. With advances in diagnostic imaging that allow for the detection of smaller volume brain metastases that may have better response to WBRT and with improvements in systemic therapy that can achieve better extracranial disease control, approaches to improve brain metastatic control may have a greater impact on overall survival.

Although many studies continue to evaluate the impact of WBRT on survival, it is recognized that one of the primary goals of WBRT are to palliate symptoms and improve quality of life. A number of recent studies have used various measures of functional status and quality of life as key outcomes reflecting the clinical impact of WBRT. Wong et al. prospectively evaluated patient-reported symptoms and quality of life using the Spitzer Quality of Life questionnaire in 129 consecutive patients treated with WBRT for brain metastases. In this study, 43 % of patients had stable or decreased fatigue, and 47 % had stable or improved neurological function following WBRT [14]. Even in patients with poor performance status, WBRT (20 Gy in five daily fractions) resulted in improvement in patient-reported symptoms at 1 month following treatment ($p=0.02$) and improvement in KPS in 57 % of patients. The KPS remained stable in another 17 % of patients with only 26 % of patients experiencing deterioration in KPS [15].

Prophylactic cranial irradiation

Prophylactic cranial irradiation (PCI) has been shown to improve both overall survival by 5.4 % at 3 years [relative risk (RR), 0.84; 95 % confidence interval (CI), 0.73 to 0.97; $p=0.01$) and disease-free survival (RR, 0.75; 95 % CI, 0.65 to 0.86; $p<0.001$) in patients with limited-stage small cell lung cancer (SCLC) who had a complete response following chemotherapy [16]. In patients with extensive-stage SCLC, the survival benefit was observed in patients who responded to first-line systemic therapy with the 1-year overall survival increasing from 13 to 27 % [17]. A Cochrane review of PCI in patients receiving radical treatment for non-small cell lung cancer (NSCLC) concluded that although PCI reduced the incidence of brain metastases, a survival benefit was not observed; therefore, it was concluded that there was insufficient evidence at this time to support clinical application of PCI for patients with NSCLC [18].

The impact of PCI on neurocognitive toxicity and quality of life may impact the decision to provide this treatment, even when it is indicated. In a recent retrospective review of 217 patients with limited-stage SCLC, only 61.4 % of patients had received PCI. The most commonly documented reason for omission of PCI was patient refusal due to concerns of the toxicity associated with PCI [19]. Despite concerns about the impact of the toxicities associated with PCI on quality of life, the health-related quality of life (HRQOL) measures in a recent phase III randomized study by the European Organisation for Research and Treatment of Cancer (EORTC) of PCI in extensive-stage SCLC showed that the only significant HRQOL measures that rose with PCI were fatigue and hair loss [20]. Similarly, the RTOG phase III trial of PCI in NSCLC patients demonstrated no significant differences in any measures of cognitive function (mini-mental status exam) or quality of life using EORTC-QLQC30 and brain module (QLQBN20). However, the Hopkins Verbal Learning Test did demonstrate deterioration in immediate and delayed recall at 1 year following PCI, suggesting that some of the tools used to measure quality of life and neurocognitive function may not have the sensitivity to detect subtle changes after WBRT [21]. Further investigations to determine the optimal tools to measure clinically relevant deterioration in neurocognitive function or quality of life are needed.

The ideal timing and dose of PCI have been investigated over time. Comparison of 30 Gy in 2-Gy daily fractions of PCI delivered after completion of chemoradiotherapy ("late" arm) and after thoracic radiotherapy but prior to the last cycle of chemotherapy ("early" arm) demonstrated that early PCI was associated with better outcome [22]. A recent intergroup phase III randomized study of 25 or 36 Gy PCI in 720 patients with limited-stage SCLC compared survival, intracranial tumor control, quality of life measures, and neurocognitive outcomes. There was no difference in survival or tumor control between the two doses and with 3-year follow-up, and no significant difference in quality of life or neurocognitive function was observed between the two groups. Both groups demonstrated a similar, mild deterioration in leg strength, communication, and memory [23].

Whole brain reirradiation

Although whole brain radiotherapy is an effective therapeutic and prophylactic intervention for brain metastases, a growing proportion of patients are facing intracranial recurrences as patients are surviving longer after initial treatment for brain metastases. Repeat whole brain radiation, radiosurgery, and hypofractionated high-dose radiotherapy are used, but there is no consensus regarding the appropriate salvage treatment for recurrent brain metastases following

WBRT, and there are no prospective data to support a particular intervention.

Table 2 summarizes retrospective series of patients treated with repeat WBRT after initial WBRT for brain metastases. Approximately two thirds of the patients had stable or improved clinical symptoms following reirradiation [24]. The median survival following a second course of WBRT ranged between 4 and 5 months. Prognostic factors associated with better outcomes following repeat WBRT included KPS >70, age <60, stable or absent extracranial disease, and solitary brain recurrence. The dose of the initial course of cranial irradiation varied from 20 to 50.4 Gy, and reirradiation schedules range from 25 to 30 Gy in 10–15 fractions or 20 Gy in 5–10 fractions. In general, doses greater than 20 Gy were associated with better outcome [25].

Whole brain radiotherapy with local therapy

With advances in surgical technique and introduction of radiosurgery, multimodality treatment has an increasing role in the management of patients with brain metastases. A number of studies and subsequent systematic reviews and meta-analyses have evaluated the added benefit of more aggressive local therapy, surgery, or radiosurgery, in combination with WBRT. (Table 3) Although the addition of aggressive local treatment improves local tumor control, an added survival benefit from increased local therapy has only been observed in a highly selected subset of patients who are young with a single brain metastasis and limited or well-controlled systemic disease.

The benefits of adding radiosurgery to WBRT were updated in a Cochrane review by Patil et al., which reported a meta-analysis of 358 patients enrolled into one of two prospective randomized studies of WBRT alone vs. WBRT plus radiosurgery. The meta-analysis did not show a survival benefit with the addition of radiosurgery. But in the subset of patients with a single brain metastasis, the addition of radiosurgery improved median survival to 6.5 vs. 4.9 months for the patients treated with WBRT alone (p=0.04). Combined therapy was associated with decreased steroid use and improved performance status at 6 months (p=0.03) [26]. Tsao et al. had similar conclusions, but it was noted that salvage therapies delivered to the patients were not well documented, and these could greatly impact the survival outcomes of patients thereby affecting the findings and conclusions of these meta-analyses [27].

Similar to radiosurgery, the addition of surgical resection to WBRT has improved local control but failed to demonstrate a significant survival advantage when all patients are considered [28]. A large meta-analysis of the three large randomized trials of WBRT vs. WBRT plus surgical resection confirmed these findings. However, as one of the three studies included patients with more advanced disease and this study reported worse survival following combined surgery plus WBRT compared with WBRT alone, this may reflect poor patient selection for this aggressive approach [29]. The Patchell study also reported that patients treated with surgery and WBRT maintained their functional independence for longer than those treated with WBRT alone (p=0.01) [28].

Since these meta-analyses, Kocher et al. reported the results of the EORTC 22952-26001 study of radiosurgery or surgical resection of one to three metastases followed by observation or adjuvant WBRT. This study randomized 359 patients following complete surgical resection (n=160) or radiosurgery (n=199) to WBRT, 30 Gy in ten daily fractions (n=99 following radiosurgery, n=81 following surgery) or observation (n=100 following radiosurgery, n=81 following surgery). Both arms had similar survival (median survival of 10.9 months with WBRT vs. 10.7 months with observation, p=0.89), but WBRT reduced the rate of intracranial relapse requiring salvage treatments and neurological death [30].

Treatment-related toxicities

The acute toxicities of WBRT are generally mild and well tolerated. However, as patients are living longer following WBRT, longer term neurocognitive toxicities and changes in quality of life are growing concerns for patients with brain metastases. Accurate measurements of neurocognitive function and quality of life can be challenging due to a lack of optimal measurement tools and uncertainties in the interpretation of the results, particularly in this patient population where multiple confounding factors can impact both neurocognitive function and quality of life. Nonetheless, there are rising efforts to investigate these outcomes in brain metastasis trials with recognition that these are important endpoints, particularly in palliative patient populations.

Table 2 Outcomes following cranial reirradiation

Study	WBRT (dose/fractions)	No. of patients	Median survival
Son (2012) [81]		17	5.2 months
Cooper (1990) [82]		52	22.4 weeks
Sadikov (2007) [24]		72	4.1 months
Wong (1996) [25]		86	4.0 months

Table 3 Randomized, controlled trials evaluating surgery plus radiotherapy for solitary brain metastases

Trial	Treatment	No. of patients	Median survival	Comments
Vecht (1993) [83]	40 Fy/20 BID vs. surgery+40 Gy/20 BID	63	6 months 10 months (p=0.04)	
Patchell (1990) [84]	36 Gy/12 vs. surgery+36 Gy/12	48	15 weeks 40 weeks (p=0.01)	Predominantly primary lung cancer
Mintz (1996) [24]	30 Gy/10 vs. surgery+30 Gy/10	84	6.4 months 5.6 months (ns)	

BID twice per day, *ns* not statistically significant, *TID* three times per day

As part of a phase III trial, neurocognitive function (NCF) and quality of life (QoL) measurements were acquired serially in 208 patients treated with WBRT. The changes in NCF and QoL were correlated to each other such that a decline in neurocognitive function in terms of executive function and fine motor coordination was associated with deterioration in quality of life [31]. However, it is possible that other factors including progressive extracranial disease can affect NCF and QoL measures. In order to determine the impact of WBRT in the absence of brain metastases, Welzel et al. serially measured neurocognitive function in patients receiving WBRT therapeutically for brain metastases from breast cancer and prophylactically in patients with small cell lung cancer. Both groups had impaired verbal memory at 6–8 weeks following WBRT, but the patients with brain metastases had verbal memory impairment as early as a few days after starting WBRT. In this study, other measures of cognitive function including visual memory and attention were not influenced by WBRT [32]. These findings support the hypothesis that WBRT may have differential effects on various neurocognitive domains, and this may reflect differential radiosensitivity of different regions of the brain.

Aoyama et al. evaluated changes in neurocognitive function in patients treated with WBRT plus radiosurgery or radiosurgery alone for brain metastases to determine whether the omission of WBRT may impact the neurocognitive outcome of patients. Using MMSE, the greatest impact on neurocognitive function was due to tumor progression rather than treatment effects [33]. In contrast, a more recent randomized, controlled trial by Chang et al. investigating the neurocognitive effects of stereotactic radiosurgery (SRS), with or without whole brain radiation therapy (WBRT) for brain metastases reported significant reductions in learning and memory, associated with the addition of WBRT to SRS. However, the poor results of the WBRT arm and the proximity in time of the last neurocognitive assessment to patient death in WBRT arm likely impacted the findings of this study [34]. This raises a major challenge in our ability to assess the impact of brain treatment on neurocognitive function in patients with brain metastases as patients with overall deterioration in performance due to intra- and/or extracranial disease progression are likely to perform well on neurocognitive assessments due to multifactorial reasons including general fatigue, pain, analgesics, and other medications including chemotherapy.

In addition to clinical symptoms, the toxicity of radiation has also manifested radiologically as leukoencephalopathy and white matter changes. These changes have been associated with cognitive and functional decline and development of radiation-induced dementia [35]. Several risk factors for the development of these radiological changes following WBRT have been identified including older age, preexisting leukoaraiosis, hyperglycemia, and hypertension [35, 36].

Advances in radiotherapy delivery

Major advances in conventional radiation planning and delivery over the past 10 years including the introduction of intensity-modulated radiotherapy (IMRT), new image-guidance techniques, and volumetric modulated arc therapy (VMAT) have introduced new potential approaches to the management of brain metastases. These include novel approaches to delivery of whole brain radiotherapy with integrated boost treatment to gross tumor volumes as well as sparing dose to structures such as the hippocampal regions in order to maximize intracranial control while minimizing toxicity. These advances also facilitate targeted radiotherapy including the delivery of radiosurgery or fractionated radiotherapy for the initial or salvage treatment of brain metastases in selected patients.

It has been recognized that the central role of the hippocampus is to support memory function. Recent preclinical and clinical studies have suggested that radiation-induced damage to the hippocampal regions may contribute to radiation-induced neurocognitive decline, particularly in the memory domain [37–40]. Specifically, the subgranular zone appears to be more radiosensitive, resulting in increased apoptosis in this region following low doses of radiation that result in no apoptosis in other areas of the brain [41].

Based on these findings, there have been recent studies investigating methods to deliver whole brain radiotherapy

while limiting the dose to bilateral hippocampal areas. Several groups have demonstrated the feasibility of delivering WBRT while limiting the dose to bilateral hippocampal regions to less than 6 Gy using tomotherapy, LINAC-based IMRT, and VMAT [42–44]. Similarly, the use of tomotherapy, IMRT, and VMAT to limit the dose to neural stem cell regions to 55 % of the full prescription dose of whole brain radiotherapy has been demonstrated as a feasible approach for delivering prophylactic cranial irradiation [45]. However, the clinical impact of these approaches is yet unknown. There is an ongoing RTOG phase II trial evaluating the clinical benefit of hippocampal avoidance during WBRT in terms of neurocognitive outcome. This study aims to treat the brain with a dose of 30 Gy in ten daily fractions while limiting the dose to 100 % of bilateral hippocampal volumes to 9 Gy or less and limiting the maximum dose in either hippocampal regions to 16 Gy or less.

In addition to limiting dose to the hippocampal regions, studies of tomotherapy and VMAT have demonstrated the feasibility of delivering simultaneous integrated boosts to the visible metastases. Using tomotherapy, a whole brain dose of 32.25 Gy was delivered in 15 fractions with a simultaneous boost to visible metastases using differential boost doses up to 63 Gy for lesions 2.0 cm or greater and up to 70.8 Gy for lesions less than 2.0 cm in diameter [42]. A subsequent study reported that VMAT can also achieve adequate dose distributions when the same prescription doses for whole brain and boost radiation and the same dose constraints to the hippocampal regions are used to treat patients with one to three brain metastases [43]. Although a simultaneous integrated boost seems technically feasible, the appropriate dose to utilize in this setting is yet uncertain. A phase I dose escalation study has investigated the maximum tolerated dose for a simultaneous integrated boost with whole brain radiotherapy using helical tomotherapy. In this study, a boost dose of 60 Gy in ten fractions to one to three brain metastases was successfully delivered synchronously with 30 Gy in ten fractions of WBRT without any dose-limiting toxicity [46]. There is an ongoing phase II study to evaluate the efficacy of this maximum tolerated boost dose with WBRT. More recently, a novel radiobiological modeling suggested the potential of using nonuniform dose prescriptions in order to address the nonuniform distribution of microscopic brain metastases for different tumor histologies. For example, colorectal cancers have a higher predisposition to metastasize to the posterior fossa [47].

There has been rising interest in spatially targeted treatments that may offer effective intracranial control while avoiding the toxicities associated with WBRT. This has predominantly been led by studies of radiosurgery with and without WBRT, which have shown better intracranial control with combined therapy but no difference in survival [48–50]. Other targeted radiotherapy techniques such as hypofractionated radiotherapy have been explored and may serve a particular role in the treatment of larger brain metastases that are not be amenable to radiosurgery. For example, large recurrent metastases following initial WBRT or large surgical cavities that may benefit from more intense local therapy may benefit from a hypofractionated approach that may provide superior local control while minimizing the neurocognitive toxicities of initial or repeat whole brain radiotherapy. Numerous series of hypofractionated radiotherapy for brain metastases have been reported, each showing promising outcomes of good tumor control and minimal toxicity. The dose and fraction schedules ranged from 18 to 35 Gy in three to six daily fractions delivered with or without whole brain radiotherapy (30 Gy in ten daily fractions). Several prospective studies evaluating the efficacy and toxicity of hypofractionated stereotactic radiotherapy have shown similar conclusions that these targeted treatments are generally well tolerated and are associated with good local tumor control. Aoyama et al. used 35 Gy in four fractions to each metastasis in 87 patients who presented with four or fewer brain metastases. The 1-year local control was 81 %, and median survival was 8.7 months with minimal associated toxicity [51]. A subsequent phase II trial of hypofractionated stereotactic radiotherapy utilized 35 Gy in daily five fractions without whole brain radiotherapy or 30 Gy in five daily fractions with whole brain radiotherapy. The median survival was 11 months, and local control at 12 months was 76 %. This treatment was well tolerated as long as the maximum volume of normal brain receiving >4 Gy per fraction was 20 cc [52]. Therefore, hypofractionated treatment allows for aggressive local treatment for lesions that are too large for safe radiosurgery treatment, but there appears to be a maximum volume beyond which this treatment may not be beneficial due to excessive treatment-related toxicity.

Combination with systemic therapy

Multiple chemotherapeutic agents and radiosensitizers have resulted in promising responses in conjunction with whole brain radiotherapy, but none have resulted in a survival improvement to date [53–59]. Two agents, temozolomide (TMZ) and motexafin gadolinium (MGd), have shown greater promise and therefore had been studied more extensively.

Temozolomide is an orally administered alkylating agent with nearly 100 % bioavailability. This agent can reach cerebrospinal fluid concentrations that are nearly 30 % of plasma concentrations, supporting that temozolomide crosses the BBB [60]. Temozolomide has resulted in a significant survival benefit with an acceptable toxicity profile when combined with radiotherapy for primary glioma,

which has peaked interest in the use of this drug in the setting of brain metastases [61]. There have been variable responses for combined TMZ plus WBRT compared with WBRT alone. While Antonadou et al. [62] demonstrated a significantly better response rate of 96 % in the TMZ plus WBRT group compared with 67 % in the WBRT alone arm, Verger et al. [63] were unable to replicate these response rates. A subsequent phase II study of TMZ monotherapy for brain metastases demonstrated variable responses for different tumor histologies: 40 % for melanoma, 24 % for NSCLC, and 19 % for breast cancer [64]. This has led to studies investigating the benefit of TMZ and WBRT in patients with brain metastases from specific tumor histologies, including phase II and III trials of TMZ in brain metastasis from NSCLC and melanoma. In a randomized study of TMZ with or without WBRT in patients with unresectable brain metastases from primary melanoma, TMZ with radiotherapy resulted in a survival benefit over WBRT alone [65].

MGd is a metalloporphyrin that can interact synergistically with radiation by generating reactive oxygen species by catalyzing the oxidation of several intracellular reducing metabolites to induce apoptosis and depleting enzymes involved in postradiation DNA repair [66]. A phase III randomized trial of 401 patients randomized to WBRT with or without concurrent MGd demonstrated no significant increase in median survival (5.2 vs. 4.9 months; p=0.48) [67]. In this study, the subset of patients with NSCLC had significantly better outcomes with combined treatment, which led to a subsequent study of MGd with radiotherapy in 554 NSCLC patients randomized to WBRT with or without MGd. This failed to show a statistically significant difference between the two arms, but in the subset of patients treated with MGd and WBRT, where the WBRT was initiated within 3 weeks of diagnosis (n=348), the interval to neurological progression was improved from 8.8 months for WBRT to 24.2 months for the combined treatment (p=0.004) [68]. These results have led to further investigation of the role of MGd in patients with brain metastases from NSCLC.

With the introduction of targeted therapeutic agents that have shown effect in brain metastases, there has been further investigation combining these agents with radiotherapy. As human epidermal growth factor receptor 2 (HER-2) breast cancer is associated with a higher risk of brain metastases, there have been studies of HER-2 inhibitors in conjunction with WBRT. Combined trastuzumab (2 mg/kg weekly or 6 mg/kg every 21 days) and WBRT (30 Gy in ten daily fractions) resulted in an 87.1 % response rate and a median survival of 18 months with no grade 2 toxicities [69]. Lapatinib, a tyrosine kinase inhibitor of the HER-2 receptor, has demonstrated activity against brain metastases as monotherapy [70]. A multi-institutional study of lapatinib and WBRT in patients with brain metastases from HER-2-positive breast cancer is planned to start in the near future. In patients with NSCLC, a phase II study by Pesce et al. randomized 59 patients to WBRT (30 Gy in ten daily fractions) with either gefitinib (250 mg/day) or temozolomide 75 mg/m^2 daily. The median overall survival was 6.3 months with gefitinib and 4.9 months with temozolomide, which is not any greater than the expected outcomes of WBRT alone [71].

Discussion

As patients with brain metastases are living longer with improvements in extracranial tumor control, the impact of effective treatment and prophylaxis of brain metastases has become greater. There is a greater need to develop treatment approaches that provide longer intracranial tumor control while minimizing the treatment-related acute and late toxicities of therapy. For example, whole brain radiotherapy can now be delivered with integrated boost radiotherapy and hippocampal-sparing techniques. However, prior studies have demonstrated that significant benefits of more aggressive therapeutic approaches are only seen in patients with better prognostic factors. As technological advances of radiotherapy delivery, surgery, and systemic agents introduce a growing complexity to treatment options, there is a growing demand to develop better methods to select patients for the appropriate treatments.

Conflict of interest None.

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