Radiotherapy and Oncology 102 (2012) 168–179

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Treatment of brain metastases: Review of phase III randomized controlled trials

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ARTICLE INFO

Article history:
Received 25 March 2011
Received in revised form 18 July 2011
Accepted 29 August 2011
Available online 11 October 2011

Keywords:
Brain metastases
Radiotherapy
Whole brain radiation therapy
Radiosurgery
Neurocognitive impairment
Quality of life

ABSTRACT

The optimal management of brain metastases remains controversial. Both whole brain radiotherapy (WBRT) and local treatment [surgery (S) or radiosurgery (RS)] are the cornerstones of treatment. The role of systemic therapy is also being explored. Randomized controlled trials (RCT) have tried to assess the individual and combined effects of different therapeutic strategies.

(1) *RCT in oligometastatic patients:* WBRT alone vs. local treatment + WBRT. Combined treatment may improve both overall survival and local control in patients with a single metastasis, but it also leads to a local control benefit in patients with two to four lesions.

Exclusive local treatment vs. WBRT plus local treatment. The addition of WBRT to local treatment may result in improved local control, improved freedom from new brain metastases and improved overall brain control.

S + WBRT vs. RS + WBRT. There is no evidence of superiority of a combined treatment over the other one.

(2) *RCT addressing the point of improving WBRT outcome:* differences in WBRT fractionation do not significantly alter outcome of treatments. Only a few systemic drugs may cause some significant advantages.

(3) *RCT that assessed neurocognitive impairment and quality of life:* the baseline cognitive performance of most patients is significantly impaired. Intracranial tumor control is an essential factor in stabilizing neurocognitive function. The data on neurocognitive toxicity related to WBRT are still contradictory. Impairment of both neurocognitive function and quality of life of patients with brain metastases needs to be further addressed in RCT.

Brain metastases develop in up to 30% of patients with cancer [1]. With the best supportive care, median survival time is 1–2 months [2]. The cornerstones of treatment are surgery (S), whole brain radiotherapy (WBRT), and radiosurgery (RS) [3]. The chances of using a local therapy (S or RS) depend on the number, the size, and the site of brain lesions. The main prognostic factors for patients with brain metastases are Karnofsky performance status (KPS) ($\geqslant$70 vs. <70), age (<65 vs. $\geqslant$65 years), control of primary tumor, absence of extracranial metastases, and number of brain lesions. All of these factors, except for number of brain metastases, are included in the Recursive Partitioning Analysis (RPA) classification [4]. Sperduto et al. [5], analyzing more than 4200 patients with newly diagnosed brain metastases, found that the significance of prognostic factors varied by the primary tumor; consequently, no single prognostic index might be appropriate for all patients with brain metastases, and different prognostic factors should be weighed differently in the clinical decision-making processes of such a heterogeneous population.

It is worth noting that most of the patients treated for brain metastases die of extracranial disease [6]. This is an important consideration because, although most studies have used overall survival as the main endpoint, survival is probably not the best parameter to measure the efficacy of the existing therapeutic modalities [7].

Materials and methods

An extensive literature search was undertaken to identify published randomized controlled trials (RCT) for brain metastases. Data were identified by searching the PUBMED database using the keywords "brain metastases", "randomized trial", "radiotherapy", "whole brain radiation therapy", "radiosurgery", and "surgery". Only papers published in English were included. Meeting proceedings were used when they concerned RCT that had not yet been published in full-text format. The results of the different treatments in terms of brain tumor control (either local control or freedom from new brain metastases), neurological death rate, overall survival and quality of life were reported. All data were extracted and tabulated from the articles' text, tables, and figures.

We divided our appraisal into three main issues. The first issue concerned RCT on oligometastatic patients, assessing the role of local treatment with or without WBRT. The second issue consisted of RCT addressing the point of improving WBRT outcome. The third

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doi:10.1016/j.radonc.2011.08.041

issue dealt with RCT that assessed the neurocognitive impairment and quality of life of patients with brain metastases.

The tables summarize the main results of the RCT issue by issue.

Results

Randomized controlled trials on oligometastatic patients

Several trials have assessed the role of a more aggressive combined approach compared with WBRT alone in the management of brain oligometastatic disease. Other trials have assessed the role of WBRT as an adjuvant treatment after surgery or radiosurgery, comparing the combined approach with the exclusive local treatment. These trials explored the possibility of WBRT withdrawal, based on the rationale of avoiding putative neurotoxicity due to WBRT. The results of a small trial that compared the combined treatment (RS + WBRT vs. S + WBRT) for solitary brain metastases were recently published.

WBRT alone vs. WBRT + local treatment (surgery or radiosurgery) in patients with brain oligometastatic disease (Table 1)

WBRT vs. S + WBRT. The trial from Patchell et al. [8] showed that surgical treatment of brain metastasis was related to a reduced rate of recurrence at the original site of metastasis ($p < 0.02$), with a longer local relapse-free survival ($p < 0.0001$), a longer survival rate ($p < 0.01$), a longer functionally independent survival ($p < 0.005$) and a lower risk of death from neurological causes ($p < 0.0009$). Multivariate analysis showed that surgical treatment of the brain metastasis was associated with increased survival ($p < 0.04$), whereas the presence of disseminated disease and increasing age were associated with decreased survival ($p < 0.02$ and $p < 0.01$, respectively).

A Dutch trial [9,10] reported that survival was significantly longer for the combined treatment (S + RT) group than for the radiotherapy group ($p = 0.04$). This benefit was confined to patients with stable or absent extracranial disease (median survival 12 vs. 7 months, $p = 0.02$), whereas for patients with active disease, survival was equally poor (median survival of 5 months for both treatment arms). Age was a strong prognostic factor: patients older than 60 years had a hazard ratio (HR) of dying of 2.74 ($p = 0.001$) compared with younger patients. In the younger patient group, median survival was much better in the S + RT arm than in the RT arm (19 vs. 9 months); in older patients, median survival was poor and similar in both arms (6 vs. 5 months) [10]. Functionally independent survival (defined as WHO performance status $\leqslant 1$ and neurological condition $\leqslant 1$) was better for patients who were treated with surgery and postoperative WBRT, without reaching statistical significance ($p = 0.06$).

On the contrary, Mintz et al. [11] did not find any significant advantage in terms of median survival between patients randomized to WBRT alone and those who underwent S + WBRT (6.3 and 5.6 months, respectively; $p = 0.24$). There was no difference between the two arms in how long patients maintained functional independence (KPS $\geqslant 70$) or in terms of neurological death rate.

In summary, two of the three trials [8–10] show that the combined approach (S + WBRT) improves treatment outcomes compared with exclusive WBRT in patients with a single brain metastasis. This benefit is most pronounced for patients with favorable prognostic factors.

WBRT vs. RS + WBRT. Kondziolka et al. [12] randomized patients with two to four brain lesions (maximum diameter $\leqslant 25$ mm) to WBRT alone or RS + WBRT. The trial was closed according to predefined stopping rules following an interim analysis that showed a

Table 1
Trials comparing whole brain radiotherapy vs. (whole brain radiotherapy + local treatment).

Author	*Treatment arms*	*Prescribed dose*	*n*	*Inclusion criteria*	*Local control*	*Freedom from new brain metastases*	*Brain tumor control*	*Neurologic death*	*Survival*	
								Time to neurologic death		
Patchell [8]	WBRT	WBRT: 36 Gy in 12 fr	48	Single lesion, all the primaries	48.0%	NS	n.a.	26 w	3.6 m	
	S + WBRT	WBRT: 36 Gy in 12 fr			80.0%			62 w	9.5 m	
Vecht and Noordijk [9,10]	WBRT	WBRT: 40 Gy in 20 fr b.i.d.	63	Single lesion, all the primaries	n.a.	n.a.	n.a.	NS	6.0 m	
	S + WBRT	WBRT: 40 Gy in 20 fr b.i.d.							10.0 m	
Mintz [11]	WBRT	WBRT: 30 Gy in 10 fr	84	Single lesion, all the primaries	n.a.	n.a.	n.a.	NS	NS	
	S + WBRT	WBRT: 30 Gy in 10 fr								
					Time to local failure		*Time to any brain failure*			
Kondziolka [12]	WBRT	WBRT: 30 Gy in 12 fr	27	2–4 lesions, all the primaries	6 m	n.a.	5 m	n.a.	NS	
	RS + WBRT	RS: 16 Gy WBRT: 30 Gy in 12 fr			36 m		34 m			
									All	*Single BM*
Andrews [13]	WBRT	WBRT: 37.5 Gy in 15 fr	331	1–3 lesions, all the primaries	71.0%	n.a.	NS	NS	NS	4.9 m
	RS + WBRT	RS: <2 cm: 24 Gy; 2–3 cm: 18 Gy; 3–4 cm: 15 Gy WBRT: 37.5 Gy in 15 fr			82.0%					6.5 m

S, surgery; WBRT, whole brain radiotherapy; RS, radiosurgery; fr, fractions; b.i.d., twice a day; w, weeks; m, months; y, year; n.a., not available; NS, not statistically significant difference; BM, brain metastases.

strong benefit in brain tumor control for patients treated with RS + WBRT. The rate of local failure at 1 year was 100% after WBRT alone, but only 8% after RS + WBRT ($p = 0.0016$). Significant differences were shown in terms of median time to both local failure ($p = 0.0005$) and any brain failure ($p = 0.002$). No difference in overall survival was noted between the two groups ($p = 0.22$).

The Radiation Oncology Group (RTOG) 9508 trial randomly assigned patients with one to three brain metastases either to WBRT or to WBRT followed by RS boost [13]. Maximum allowed diameter was 4 cm for the largest lesion and 3 cm for the additional lesions. Patients with KPS <70 were excluded.

The local control rate was superior for the RS arm ($p = 0.01$). Surprisingly, higher radiosurgery doses were not related to better control of the treated lesion. Patients with a solitary metastasis who received radiosurgical boost had significantly better survival ($p = 0.04$), whereas survival did not differ between the treatment arms for patients with two or three lesions ($p = 0.97$). It should be noted that the difference in terms of median survival for single metastasis was only 1.6 months (4.9 months for WBRT alone vs. 6.5 months for RS + WBRT). Patients in the RS arm were more likely to have stable or improved KPS score at 6 months after treatment than were patients treated exclusively with WBRT ($p = 0.03$). On multivariate analysis, RPA class 1 resulted in a significant prognostic factor, independently of number of metastases. Multivariate analysis indicated that RS + WBRT provided only a borderline survival benefit to patients with a solitary lesion ($p = 0.053$). It is worth nothing that no statistically significant improvement in survival was found between patients treated with different treatment units (Linac vs. Gammaknife) ($p = 0.94$). Early and late toxicity did not differ between the two arms.

These two trials demonstrate that the addition of radiosurgery improves local control [12–13] and functional autonomy measured by KPS [13] for oligometastatic patients. Furthermore, the RTOG 9508 trial suggests that the combined treatment (RS + WBRT) may cause a slight improvement of survival for patients with a solitary brain lesion.

Thus, it may be concluded from the results of these trials that the addition of local treatment (S for single lesion, RS for one to four brain metastases) to WBRT might represent a superior treatment modality in terms of improving local tumor control for oligometastatic patients ($n \leqslant 4$). For patients with a single metastasis, the use of local treatment (S or RS) plus WBRT may result also in a better survival, especially for patients with good prognostic factors.

Exclusive local treatment (surgery for single brain lesion or radiosurgery for ⩽4 lesions) vs. WBRT + local treatment (surgery or radiosurgery) (Table 2)

S vs. S + WBRT. In 1998, Patchell et al. [14] published the results of a trial that compared exclusive surgery with surgery plus adjuvant WBRT for patients with a solitary brain metastasis. Multivariate analysis showed that postoperative WBRT was associated with a lower risk of brain recurrence ($p < 0.001$), a reduced risk of developing recurrence of the original brain metastasis ($p < 0.001$) and a lower rate of recurrence of distant brain metastasis ($p = 0.02$). Although adjuvant radiotherapy prevented death due to neurological causes ($p = 0.003$), the median survival was not significantly different. Furthermore, no significant difference in terms of functionally independent survival (defined as time with KPS $\geqslant 70$) was found.

RS vs. RS + WBRT. In a Japanese trial [15], 132 patients with one to four brain metastases, each with a maximum diameter <3 cm, were randomly assigned to receive RS alone or RS + WBRT. The multivariate analysis demonstrated that RS + WBRT was associated with a reduced risk of brain local recurrence ($p < 0.001$) and distant relapse ($p < 0.001$). The authors did not find any significant difference in terms of survival rate (1-year actuarial survival for RS alone, 28.4%; 1-year actuarial survival for RS + WBRT, 38.5%) and neurological death rate (RS alone, 19.3%; RS + WBRT, 22.8%). At 12 months the systemic functional preservation rates (KPS $\geqslant 70$) and actuarial rates of neurological preservation (i.e., any worsening of the neurological performance) were not statistically different. Symptomatic late neurological symptoms were reported in seven patients in the RS + WBRT arm and in three cases in the radiosurgery arm ($p = 0.20$).

Table 2
Trials comparing exclusive local therapy vs. (whole brain radiotherapy + local treatment.

Author	Treatment arms	Prescribed dose	*n*	Inclusion criteria	Local control	Freedom from new brain metastases	Brain tumor control	Neurologic death rate	Survival
Patchell [14]	S	–	95	Single lesion	54.0%	63.0%	30.0%	44.0%	NS
	S + WBRT	WBRT: 50,4 Gy in 28 fr		All the primaries	90.0%	86.0%	82.0%	14.0%	
Aoyama [15]	RS	RS:⩽2 cm: 22–25 Gy;>2 cm: 18–20 Gy	132	1–4 lesions	72.5% @ 1 y	36.3% @ 1 y	23.6% @ 1 y	NS	NS
	RS + WBRT	RS: dose reduction by 30% WBRT: 30 Gy in 10 fr or 12 fr		All the primaries	88.7% @ 1 y	58.5% @ 1 y	53.2% @ 1 y		
Chang [16]	RS	RS:<2 cm: 18 Gy; 2–3 cm: 15 Gy; 3–4 cm: 12 Gy	58	1–3 lesions	67.0% @ 1y	45.0% @ 1y	27.0% @ 1y	NS	15.2 m
	RS + WBRT	RS:<2 cm: 18 Gy; 2–3 cm: 15 Gy; 3–4 cm: 12 Gy WBRT: 30 Gy in 12 fr		All the primaries	100.0% @ 1y	73.0% @ 1y	73.0% @ 1y		5.7 m
Mueller and Kocher [20,21]	RS or S	RS: 20 Gy	359	1–3 lesions	68.7% @ 2 y	67.6% @ 2 y	46% @ 2y	44.0%	NS
	RS or S + WBRT	RS: 20 GyWBRT: 30 Gy in 10 fr		All the primaries	83.6% @ 2 y	82.4% @ 2 y	68.6% @ 2 y	28.0%	
Roos [22]	RS or S	RS: n.a.	19	Single lesion	n.a.	n.a.	NS	n.a.	NS
	RS or S + WBRT	WBRT: 36 Gy in 18 fror 30 Gy in 10 fr		All the primaries					
Muacevic [23]	RS	RS: mean dose 21 Gy (range 14–27 Gy)	64	Single lesion	NS	74.2% @ 1 y	n.a.	NS	NS
	S + WBRT	WBRT: 40 Gy in 20 fr		All the primaries		97.0% @ 1 y			

S, surgery; WBRT, whole brain radiotherapy; RS, radiosurgery; fr, fractions; w, weeks; m, months; y, year; n.a., not available; NS, not statistically significant difference.

In a recently, published trial, Chang et al. randomized 58 patients with one to three newly diagnosed brain metastases to exclusive RS or RS + WBRT [16]. Although the primary endpoint was neurocognitive assessment at 4 months, the authors also reported the results in terms of tumor control: patients who were treated with RS + WBRT had a significant improvement in terms of local tumor control ($p = 0.012$), distant brain tumor control ($p = 0.02$), and freedom from central nervous system (CNS) recurrence ($p = 0.0003$). Surprisingly, higher survival was observed in the RS group ($p = 0.003$). This survival advantage for the RS group has been attributed to a meaningful imbalance of the study groups in terms of prognostic factors and with strong differences in salvage therapy between the two cohorts, with a more aggressive approach for patients treated with RS only [17–19].

S or RS vs. S or RS + WBRT. The recently closed European Organization for Research and Treatment of Cancer (EORTC) 22952–26001 trial addressed the role of WBRT after local treatment, whatever that treatment was (surgery or radiosurgery) [20,21]. After local treatment, 359 patients with one to three brain metastases were randomized for adjuvant WBRT (RS + WBRT, $n = 99$; S + WBRT, $n = 81$) or observation (RS alone, $n = 100$; S alone, $n = 79$). Only patients with no or stable extracranial disease or with asymptomatic synchronous primary tumor and with European Cooperative Oncology Group (ECOG) performance score of 0–2 were eligible. For radiosurgery, the maximum diameter of the brain lesion could measure 3 cm for patients with single brain metastasis and 2.5 cm for cases with two or three lesions. The prescribed marginal dose was 20 Gy. No differences in survival or in the time period of functional independence (i.e., time to ECOG PS deterioration to <2) were found (HR = 0.98, $p = 0.89$, and HR = 0.96, $p = 0.71$, respectively). Postsurgical WBRT reduced the probability of relapse at initial site (27% vs. 59%, $p < 0.001$), as well as at new sites (23% vs. 42%, $p = 0.008$). In patients who received WBRT after radiosurgery, the progression rate both at the original site (19% vs. 31%, $p = 0.04$) and at new sites (33% vs. 48%, $p = 0.02$) was reduced.

Another randomized trial evaluated adjuvant WBRT after surgery or radiosurgery for single brain metastases [22]. The study was prematurely suspended due to slow accrual after the enrollment of 19 patients. There was no statistically significant difference in terms of median CNS failure-free survival, median progression-free survival, and median overall survival. Time to deterioration of WHO performance status to >1 was not different between the two arms. Although there was a trend toward reduced CNS relapse with WBRT (30% for patients treated with combined approach vs. 78% for patients treated with exclusive S or RS), the difference was not significant ($p = 0.12$). Considering the small number of patients, the authors concluded that their results support the use of postoperative WBRT to improve CNS control.

RS vs. S + WBRT. Only one trial compared exclusive radiosurgery with S + WBRT [23]. The combined treatment provided only a superior brain distant control ($p = 0.04$), whereas local control (1-year local control rate: 82% in the S + WBRT group and 96.8% in the RS group), neurologic death rate, and survival did not significantly differ. There was no significant difference in length of time with stabilized or improved KPS. Treatment groups did not differ in terms of late severe toxicity.

From the above-mentioned trials, it may be concluded that in oligometastatic patients ($n \leqslant 4$), class I evidence supports lower rates of intracranial failure (both at the original site of the metastasis and in the brain overall) when WBRT is added to local treatment.

Comparison of combined treatments: WBRT + surgery vs. WBRT + radiosurgery for solitary brain metastasis (Table 3)

Only one recently published randomized trial [24] was designed to assess whether a combined approach with RS + WBRT is as effective as S + WBRT for patients with a single brain lesion. The trial was closed early due to slow accrual, mainly because few patients proved to be truly suitable for both treatment modalities (RS or S). Even though no definitive conclusions can be drawn due to the small number of patients ($n = 21$), no significant differences were found in terms of median overall survival ($p = 0.20$) or median failure-free survival time ($p = 0.20$).

Randomized controlled trials addressing the point of improving the WBRT outcome

Since the majority of patients with brain metastases are not potential candidates for radiosurgery or neurosurgery due to the number of lesions, tumor location, or performance status, WBRT remains the standard treatment in most patients.

Thus, different total doses and fractionation schedules were assessed in several RCT to improve the outcome of WBRT in terms of survival or symptomatic effect. Another potential approach to improve the benefits of WBRT is the addition of systemic therapy.

Comparison of different WBRT fractionation schedules (Table 4)

Between 1971 and 1976 the RTOG conducted two randomized phase III trials to study the palliative effects of different fractionation schemes. The first study included 910 patients randomly assigned to four treatment arms (30 Gy in 2 or 3 weeks and 40 Gy in 3 or 4 weeks) [25]. The second study enrolled 902 patients randomized to three treatment arms (20 Gy in 1 week, 30 Gy in 2 weeks, and 40 Gy in 3 weeks) [25]. Patients were considered ineligible only for recent changes in the patient's anticancer treatment and for factors that would prohibit adequate follow-up. No significant differences among treatment schedules were found with respect to response rate, duration of improvement, palliative effect, time to progression, and survival. The conclusions of these two studies was that schedules such as 20 Gy in 1 week or 30 Gy in 2 weeks had the same effectiveness of schemes requiring higher total doses over long periods.

Some institutions participated in a separate section of these studies involving a randomization to ultrarapid high-dose

Table 3
Trial comparing combined therapy (S + whole brain radiotherapy vs. RS + WBRT).

Author	Treatment arms	Prescribed dose	*n*	Inclusion criteria	Local control	Freedom from new brain metastases	Brain tumor control	Neurologic death rate	Survival
Roos [24]	S + WBRT RS + WBRT	WBRT: 30 Gy in 10 fr RS:⩽2 cm: 20 Gy; 2.1–3.0 cm: 18 Gy; 3.1–4.0 cm: 15 Gy WBRT: 30 Gy in 10 fr	21	Single lesion All the primaries	n.a.	NS	n.a	n.a.	NS

S, surgery; WBRT, whole brain radiotherapy; RS, radiosurgery; fr, fractions; n.a., not available; NS, not statistically significant difference.

Table 4
Trials comparing different fractionation schedules of whole brain radiotherapy.

Author	Treatment arms	Prescribed dose	n	Inclusion criteria	Brain tumor control	Neurologic death rate	Survival
					Median time to progression		
Borgelt [25]	WBRT	WBRT 30 Gy in 10 fr	910	–	NS	n.a.	NS
	WBRT	WBRT 30 Gy in 15 fr					
	WBRT	WBRT 40 Gy in 15 fr					
	WBRT	WBRT 40 Gy in 20 fr					
					Median time to progression		
Borgelt [25]	WBRT	WBRT 20 Gy in 5 fr	902	–	NS	n.a.	NS
	WBRT	WBRT 30 Gy in 10 fr					
	WBRT	WBRT 40 Gy in 15 fr					
Borgelt [26]	WBRT	WBRT 30 Gy in 10 fr	138	–	WBRT 10 Gy in one fr: shorter time to progression and duration of clinical improvement	NS	NS
	WBRT	WBRT 30 Gy in 15 fr					
	WBRT	WBRT 40 Gy in 15 fr					
	WBRT	WBRT 40 Gy in 20 fr					
	WBRT	WBRT 10 Gy in one fr					
Borgelt [26]	WBRT	WBRT 20 Gy in 5 fr	64	–	WBRT 20 Gy in 5 fr: shorter time to progression	NS	NS
	WBRT	WBRT 12 Gy in 2 fr					
					Median time to progression		
Kurtz [27]	WBRT	WBRT 30 Gy in 10 fr	255	No evidence of extracranial metastases, controlled primary tumor, neurologic function classes I–III	NS	NS	NS
	WBRT	WBRT 50 Gy in 20 fr					
					Retreatment		
Komarnicky [28]	WBRT	WBRT 30 Gy in 10 fr	393	KPS >40, age 18–75 y	NS	NS	NS
	WBRT	WBRT 30 Gy in 6 fr					
Haie-Meder [29]	WBRT	WBRT 18 Gy in 3 fr	216	KPS >30, Age $\leqslant$70 y, life expectancy >4 w	n.a.	n.a.	NS
	WBRT	WBRT 18 Gy in 3 fr + (18 Gy in 3 fr or 25 Gy in 10 fr)					
							6-month survival rate
Priestman [30]	WBRT	WBRT 12 Gy in 2 fr	533	ECOG PS <4, MRC neurologic status <4	n.a.	NS	17%
	WBRT	WBRT 30 Gy in 10 fr					25%
Murray [31]	WBRT	WBRT 54.4 Gy in 34 fr b.i.d.	445	KPS $\geqslant$70, neurologic function classes 1 or 2	n.a.	n.a.	NS
	WBRT	WBRT 30 Gy in 10 fr					
					Time to retreatment		
Davey [32]	WBRT	WBRT 20 Gy in 5 fr	90	ECOG PS <3, life expectancy >6 w	14 w	n.a.	NS
	WBRT	WBRT 40 in 20 fr b.i.d.			32 w		
Graham [33]	WBRT	WBRT 20 Gy in 4 fr	113	ECOG PS <3, life expectancy >8 w	36%	52%	NS
	WBRT	WBRT 40 in 20 fr b.i.d			56%	32%	

WBRT, whole brain radiotherapy; fr, fractions; b.i.d., twice a day; w, weeks; m, months; y, year; n.a., not available; NS, not statistically significant difference; Neurologic function class I, able to work, neurologic findings minor or absent; class II, able to be at home although nursing care may be required. Neurologic findings present but not serious; class III, requiring hospitalization and medical care with major neurologic findings; class IV, requiring hospitalization and in a serious physical or neurological state.

irradiation schedules (10 Gy in a single fraction in the first study or 12 Gy in two fractions in the second one) [26]. No differences in response rate, morbidity, or survival were found, but time to progression was shorter for patients receiving short course irradiation in both the studies. The authors concluded that these ultrashort high-dose radiation schedules may not be so effective as higher dose schedules.

A third RTOG study was conducted between 1976 and 1979: this trial investigated the use of a higher dose scheme (50 Gy in 4 weeks) compared with 30 Gy in 2 weeks in a highly selected favorable subgroup of patients with brain metastases [27]. Even in this relatively good-prognosis patient population, 30 Gy in 2 weeks was found to be as effective as higher doses (palliation of symptoms, rate of clinical improvement, time to progression, cause of death, and survival were not influenced significantly by the treatment group).

The RTOG 7916 trial randomized 779 patients to four treatment arms: 3 Gy $\times$ 10 fractions with or without misonidazole vs. 5 Gy $\times$ 6 fractions with or without misonidazole [28]. A total of 393 patients who did not receive misonidazole were analyzed. Fractionation schedule did not show any statistical significance in terms of survival, time to deterioration of KPS, neurological death rate, and retreatment for brain disease rates.

A French trial compared patients treated with one course of WBRT (18 Gy in three fractions) with cases treated with two courses of radiotherapy (18 Gy in three fractions followed by 18 Gy in three fractions or 25 Gy in 10 fractions) [29]. The treatments were equivalent in terms of survival, change of KPS score, duration of clinical improvement or stabilization, and presence of neurological symptoms at 6 months of follow-up. No neurologic complication was observed.

The Royal College of Radiologists Trial [30] compared two WBRT schedules (30 Gy in 10 fractions vs. 12 Gy in two fractions on consecutive days) in 533 patients. Response rate, median time to response, median duration of response, and neurological death rate did not statistically differ between the two treatment arms. A slight but statistically significant advantage in terms of survival for the 10-fraction schedule was found ($p = 0.04$). The reported side effects (drowsiness, headache, nausea/vomiting, dizziness/ataxia, cerebral hemorrhage, blurred vision, and fits) did not differ between the two treatment arms (8% for the 10-fraction vs. 12% for the two-fraction schedule).

In the RTOG 91.04 trial [31], 445 patients were randomized between receiving 30 Gy in 3 Gy fractions or accelerated hyperfractionation (32 Gy to the entire brain plus 24.4 Gy to a boost field, in 1.6 Gy fractions b.i.d.) without any significant difference in

Table 5
Trials comparing WBRT vs. WBRT + systemic therapy.

Author	*Treatment arms*		*n*	*Inclusion criteria*	*Response rate*		*Brain control*		*Neurologic death rate*		*Survival*	
Komarnicky [28]	WBRT WBRT + Misonidazole	WBRT: 30 Gy in 6 or 10 fr WBRT: 30 Gy in 6 or 10 fr Misonidazole 10–12 mg/m^2	779	All the primaries	n.a.		n.a.		NS		NS	
					All	*Breast +NSCLC*					*All*	*Breast*
Suh [34]	WBRT WBRT + Efaproxiral (RSR13)	WBRT: 30 Gy in 10 fr WBRT: 30 Gy in 10 fr RSR13 75 or 100 mg/Kg/d	515	Single or multiple lesions; all the primaries	NS	41.0% 54.0%	NS		NS		NS	4.5 m 9.0 m
							Time to progression					
							All	*NSCLC*	*All*	*NSCLC*		
Mehta [35]	WBRT WBRT + Motexafin Gadolinium (MGd)	WBRT: 30 Gy in 10 fr WBRT: 30 Gy in 10 fr MGd 5 mg/Kg/d	401	Single or multiple lesions; all the primaries	NS		NS	5.5 m 3.7 m	NS	51.4% 36.4%		
							Time to progression					
							All	*WBRT within 28 d*				
Mehta [36]	WBRT WBRT + Motexafin Gadolinium (MGd)	WBRT: 30 Gy in 10 fr WBRT: 30 Gy in 10 fr MGd 5 mg/Kg/d	554	Single or multiple lesions; NSCLC as primary tumor	n.a.		NS	8.8 m 24.2 m	n.a		NS	
							Time to progression					
							All	*NSCLC*	*All*	*NSCLC*		
Antonadou [37]	WBRT WBRT + Temozolomide (TMZ)	WBRT: 30 Gy in 10 fr WBRT: 30 Gy in 10 fr Concomitant TMZ 75 mg/m^2/d + Sequential TMZ 200 mg/ m^2/d for 5 d every 28 for 6 cycles	134	All the primaries	33.3.% 53.4%		NS	6.0 m 7.5 m	NS	28% 13%	NS	
Guerrieri [38]	WBRT WBRT + Carboplatin (CBDCA)	WBRT: 20 Gy in 5 fr WBRT: 20 Gy in 5 fr CBDCA 70 mg/m^2/d	43	Single or multiple lesions; NSCLC as primary tumor	NS		n.a.		n.a		NS	
							Progression Free Survival					
Neuhaus [39]	WBRT WBRT + Topotecan	WBRT: 40 Gy in 20 fr WBRT: 40 Gy in 20 fr Topotecan 0.4 mg/ m^2/d	96	Single or multiple lesions; lung as primary tumor	NS		NS		n.a.		NS	
							Progression Free Survival					
Knisely [40]	WBRT WBRT + Thalidomide	WBRT: 37.5 Gy in 15 fr WBRT: 37.5 Gy in 15 fr Thalidomide during WBRT 200–600 mg/d followed by post-RT therapy for a maximum of 2 y	183	Multiple lesions; all the primaries	n.a		NS		n.a.		NS	

WBRT, whole brain radiotherapy; fr, fractions; m, months; y, years; n.a., not available; NS, not statistically significant difference; NSCLC, not small cell lung cancer.

survival time. There was also no difference in the incidence of ⩾G3 late toxicity.

More recently, two trials compared the same accelerated schedule (40 Gy in 20 fractions b.i.d.) with a hypofractionated schedule (20 Gy in four or five daily fractions). In both of these trials the eligibility criteria selected patients with relatively good prognosis. Davey et al. [32] failed to demonstrate an overall survival benefit for accelerated WBRT over hypofractionated treatment ($p = 0.418$). Patients included in the accelerated arm had a longer time to retreatment for intracranial relapse ($p = 0.03$). There was no difference in terms of toxicity and in terms of functional autonomy (measured with Barthel index score). The recently published Australian trial [33] enrolled 113 patients with stable extracranial disease or with newly diagnosed primary cancer with brain metastases. This trial also stated that intracranial disease control was improved in the accelerated schedule (median interval to CNS progression, 9.3 months for patients treated with accelerated WBRT vs. 5.1 months for patients treated with 20 Gy in 5 Gy fractions). Patients included in the accelerated arm had significant advantages also in terms of death from CNS progression rate ($p = 0.03$), whereas the median survival did not significantly differ between the two arms (6.1 vs. 6.6 months, $p = 0.17$). Late toxicity >G2 was uncommon (accelerated fractionation arm, $n = 2$; hypofractionation arm, $n = 1$).

It may be concluded that despite the extreme heterogeneity in the fractionation schedules, none of the trials demonstrated a meaningful improvement of survival, palliative effect, or toxicity. Available data suggest avoiding ultra-rapid high-dose treatment. Two trials reported some advantages in terms of intracranial control when accelerated fractionation was used, suggesting that this schedule could be considered for the subgroups of patients with better prognosis.

WBRT alone vs. WBRT and systemic therapy (Table 5)

The already cited RTOG-7916 trial failed to demonstrate any significant advantage from the addition of misonidazole, a hypoxic cell radiosensitizer, to WBRT [28]. Specifically, misonidazole did not improve survival, cause of death, percent of brain retreatment, or median time to the deterioration of KPS.

Efaproxiral (RSR13) is a modifier of hemoglobin that leads to a reduction in hemoglobin oxygen-binding affinity, resulting in enhanced tumor oxygenation and radiation sensitivity. In the RT009 trial, Suh et al. [34] tested the hypothesis that adding efaproxiral to WBRT would improve survival in patients with brain metastases. There were no differences between the two arms in terms of survival ($p = 0.16$), time to brain progression ($p = 0.21$), and proportion of death caused by neurologic progression ($p = 0.46$). A significant benefit in terms of response rate was shown in the efaproxiral arm for breast cancer patients and for non-small cell lung cancer (NSCLC) patients ($p = 0.01$), whereas a significant effect on survival was observed only in patients with breast cancer ($p = 0003$).

An RCT was designed to determine whether the addition of motexafin gadolinium (MGd) would improve the outcome of WBRT [35]. MGd is a drug that disrupts redox-dependent pathways by targeting oxidative stress-related proteins. More than 60% of the 401 enrolled patients had CNS metastases from NSCLC. Only among the NSCLC patients were there some benefits in terms of time to neurological progression ($p = 0.04$) and in terms of neurological death rate ($p = 0.03$). Furthermore, a favorable trend in time to loss of functional independence, measured by the Barthel Index, was found for NSCLC patients (HR 0.73). Some years later, the same authors published the results of a second trial, designed to confirm the benefits of MGd in patients with brain metastases from NSCLC [36]. The intent-to-treat analysis of 554 patients showed a rather large trend favoring the MGd group in the time to neurological progression (WBRT arm, 10.0 months; WBRT + MGd arm, 15.4 months); this difference did not reach the statistical significance ($p = 0.12$). The authors found that treatment delay was the major negative variable associated with inferior outcomes: a significant MGd benefit in terms of neurological progression was seen in all the patients enrolled within 28 days of brain metastasis diagnosis ($p = 0.038$).

The results of an RCT that assessed WBRT plus temozolomide (TMZ) vs. WBRT were published only as an abstract from the ASTRO 2002 meeting proceedings [37]. The addition of TMZ resulted in a better response rate ($p = 0.04$), without any difference in survival. Only in the subgroup of NSCLC ($n = 108$) did patients treated with WBRT + TMZ also have a lower risk of neurologic death ($p = 0.03$) and a longer time to progression ($p = 0.01$). It has to be noted that this series has never been published in full-text format.

There are two further RCT that assessed the addition of chemotherapy (carboplatin [38] in brain metastases from NSCLC and topotecan [39] in CNS lesions from NSCLC or SCLC) and one trial that evaluated the combination of WBRT with antiangiogenic therapy (thalidomide [40]). None of these RCT provided any benefit.

It may be concluded that the few positive data regarding the use of adding systemic therapy to WBRT are limited to NSCLC and breast cancer. A benefit in terms of survival was only reached in breast cancer patients treated with efaproxiral. In patients with NSCLC, better results in terms of intracranial control can be obtained with the addition of motexafin gadolinium.

Randomized controlled trials that assessed the neurocognitive function and quality of life (Table 6)

The potential neurocognitive morbidity of treatment remains a poorly understood concern. Quality of life and/or neurocognitive outcomes were assessed in a number of randomized trials [11,16,20,22–24,33,36,41–46].

Only three of these trials [16,36,42] used standardized batteries of neurocognitive tests exploring the main domains of neurofunction. Four trials [22,41,44,45] used the Mini Mental Status Examination (MMSE) to measure neurological impairment, although it has been suggested that this test has low specificity and sensitivity [47]. Quality of life was assessed by questionnaires on physical, psychological, social and symptom domains [11,22–24,33, 43,44,46]. A common concern in these analyses was the patient drop-off when having to comply with the completion of questionnaires and detailed tests during follow-up. Another problem was that most of the studies did not include data about other factors influencing neurocognitive performance (i.e., chronic use of steroids and antiepileptic drugs).

Among the trials that assessed the efficacy of surgery in addition to WBRT, only the Canadian trial [11] reported data regarding quality of life assessment. The mean Spitzer Quality of Life Index score was not significantly different for a period of up to 6 months between patients treated with WBRT alone and those treated with combined treatment (S + WBRT). In the recently published Australian trial that compared RS + WBRT with S + WBRT [24], quality of life was assessed using EORTC QOL-C30 and brain cancer module BN20. No differences were found between the two arms about 2 months after starting treatment in the 14 patients who completed the questionnaires. There were too few evaluable patients for analysis thereafter.

Two studies reported the neurocognitive outcome of patients randomized between different fractionation schedules. More than 350 patients out of 445 cases enrolled in the RTOG 91.04 trial (30 Gy in 10 fractions vs. 54.4 Gy in 34 fractions twice a day) [31] were assessed with MMSE at baseline and in the follow-up. No difference was found in terms of neurocognitive performance between the two arms [41]. In the trial by Graham et al. [33], EORTC QOL-C30

Table 6
Trials assessing Quality of life and impairment of neurocognitive function.

Author	*Treatment arms*	*Evaluable/ enrolled patients*	*Test/Questionnaires*	*Baseline impairment*	*Follow up evaluation*	*Neurocognitive progression by treatment arm*		*Neurocognitive impairment at intracranial progression*
Mintz [11]	WBRT S + WBRT	43/84	SQLI	n.a.	Monthly for 6 m and, then, every 3 m until death or lost to follow up	NS		n.a.
Roos [24]	RS + WBRT S + WBRT	14/21	EORTC QOL-C30, BN-20	n.a	2 and 3 m after starting treatment and, then, every 3 m until death or lost to follow up	NS		n.a
Regine [41]	WBRT 30 Gy in 10 fr WBRT 54.4 Gy in 34 fr	359/445	MMSE	Yes	2 and 3 m after WBRT	NS		Yes
Graham [33]	WBRT 20 Gy in 5 fr WBRT 40 Gy in 20 fr b.i.d.	93/113	EORTC QOL-C30	Yes	Monthly for 12 m and every 2 m until 24 m and, then, every 5 m until 60 m	NS		n.a.
Meyers [42]	WBRT WBRT + Motexafin Gadolinium	401/401	HVLT-R, Trail Making Test, COWA, Pegboard test	Yes	Monthly for 6 m and, then, every 3 m until death or lost to follow up	NS		Yes
Mehta [36]	WBRT WBRT + Motexafin Gadolinium	n.a./554	HVLT-R, Trail Making Test, COWA	n.a.	Monthly for 8 m and, then, every 2 m until death or lost to follow up	NS		n.a.
						SQLI scores over the first 6 m	*Quality Adjusted Survival*	
Scott [43]	WBRT WBRT + Efaproxiral	106/515	SQLI	Yes	WBRT day 10, 1 m after WBRT, and, then, every 3 m until death or lost to follow up	p = 0.019	p = 0.001	n.a.
Corn [44]	WBRT WBRT + Thalidomide	156/183	SQLI, MMSE	Yes	End of WBRT, 4 m and 6 m after treatment	NS		n.a.
						Improvement @ 6 w assessment	*Improvement @ 6 m assessment*	
Muacevic [23]	RS S + WBRT	48/64	EORTC QOL-C30, BN-20	n.a.	6 w and 6 m after treatment	p < 0.05	NS	Yes
						Time to neurocognitive deterioration		
Aoyama [45]	RS RS + WBRT	92/132	MMSE	Yes	1 and 3 m after treatment, and, then, every 6 m until death or lost to follow up	6.8 m 13.6 m		Yes
						Deterioration in HVLT-R total recall		
Chang [16]	RS RS + WBRT	58/58	FACT-BR, HVLT-R, WAIS III, Trail Making Test, COWA, Pegboard test	Yes	4 m after treatment	20% 64%		n.a.

(*continued on next page*)

Table 6 (*continued*)

Author	*Treatment arms*	*Evaluable/ enrolled patients*	*Test/Questionnaires*	*Baseline impairment*	*Follow up evaluation*	*Neurocognitive progression by treatment arm*	*Neurocognitive impairment at intracranial progression*
Roos [22]	RS or S	18/19	EORTC QOL-C30, BN-20, MMSE	n.a.	2 and 5 m after treatment, and, then, every 6 m until death or lost to follow up	NS	n.a.
	RS or S + WBRT						
Soffietti [46]	RS or S	317/359	EORTC QOL-C30, BN-20	Yes	2 m after treatment and, then, every 3 m until death or lost to follow up	S or RS + WBRT: Deterioration in global HR-QoL @ 9 m assessment, in physical functioning @ 2 m assessment and in cognitive function @ 2 m and 12 m evaluation	n.a.
	RS or S + WBRT						

WBRT, whole brain radiotherapy; RS, radiosurgery; S, surgery; fr, fractions; MMSE, mini mental state examination; SQLI, Spitzer Quality of Life Index; EORTC QOL-C30, EORTC quality of life 30-item questionnaire C30; MGd, motexafin gadolinium; BN-20, brain cancer module 20; FACT-BR, functional assessment of cancer therapy brain; HVLT-R, Hopkins verbal learning test-revised (total recall, delayed recall and delayed recognition; WAIS III, Wechsleradult intelligence scale III; COWA, Controlled Oral Word Association; w, weeks; m, months; NS not significant; n.a. not available.

questionnaires were administered to the patients. Quality of life was not impaired by the hyperfractionated treatment.

Patients who were included in four different trials assessing the addition of systemic drugs to WBRT [34–36,40], were evaluated for neurocognitive and/or quality of life outcomes. In the analysis of standardized neurocognitive tests performed on 401 patients who were enrolled in the first MGd trial [35], Meyers et al. did not find any significant difference in terms of neurocognitive progression [42]. Anyway, this trial pointed out some important issues. First, the authors found that more than 90% of patients with brain metastases had impairment of one or more neurocognitive tests at baseline. Second, the authors showed that tumor volume strongly correlates with severity of neurocognitive deficits. Third, patients with radiologic evidence of progressive disease had greater median changes in scores for each neurocognitive test. In other words, this study confirmed the baseline deterioration and stated that brain progression would be the most important factor in determining cognitive impairment. In the most recent trial on MGd [36], detailed tests exploring the main cognitive domains were administered to patients. The interval of neurocognitive progression was prolonged in the overall study population (HR 0.78) even though statistical significance was not reached ($p = 0.057$). The quality of life of a subgroup of 106 breast cancer patients that had been randomized into RT009 trial [34] was assessed with baseline Spitzer Quality of Life Index. Both quality of life and quality-adjusted survival were improved in the WBRT plus efaproxiral arm compared with the WBRT alone arm [43]. Finally, Corn et al. [44] analyzed quality of life and neurologic performance in patients enrolled in the RTOG 0118 trial, where WBRT was compared with WBRT plus thalidomide [40]. No differences between the two treatment arms were shown based on either the Spitzer Quality of Life Index or the MMSE.

Moreover, five RCT compared the neurocognitive outcome in patients who received local treatment with the neuroperformance of patients who received local treatment plus WBRT. These trials, in other words, are of utmost importance to assess the putative role of WBRT in deteriorating the cognitive function of patients with brain metastases. In the German trial that compared exclusive RS with postoperative WBRT [23], better scores for the role functioning domain and for quality of life were found 6 weeks after treatment for patients treated with RS. This difference was lost 6 months after the treatment. In the prematurely closed randomized Trans-Tasman Radiation Oncology Group trial [22], despite the small number of enrolled patients, the authors found that upfront WBRT did not cause a deterioration in MMSE or in overall quality of life, as measured with the EORTC QOL-C30 questionnaire. The neurocognitive MMSE-based assessment of patients included in the Japanese trial published by Aoyama et al. [15] was reported by the same authors [45]. Time to neurocognitive deterioration was marginally prolonged in patients who received combined treatment ($p = 0.05$). Of note, patients treated with RS + WBRT did significantly better in the first month of follow-up. Among patients who survived longer, the neurocognitive performance of patients treated with RS + WBRT was worse than that of patients treated exclusively with radiosurgery. This study confirms that the addition of WBRT protected patients from an early recurrence and, consequently, from an early deterioration of cognitive function. Otherwise, the long-term adverse effects of radiation therapy could be not negligible and could explain the worst outcome in the longer survivors. In the already cited trial by Chang et al. [16], patients treated with RS + WBRT had a significant impairment in learning and memory function as measured with the Hopkins Verbal Learning Test – Revised total recall at 4 months. Although a formal neurocognitive testing was scheduled at baseline and at each follow-up visit, the trial has been strongly criticized for the timing of the neurocognitive evaluation: the primary endpoint of cognitive function was indeed assessed at a single time point of 4 months [17,18]. A temporary drop-off of

neurocognitive function has been shown for some months after the end of radiation treatment [48]; the lack of a confirmed significant difference in long-term follow-up is a meaningful shortcoming of this study. Furthermore, the significant imbalance of the study groups in terms of brain disease volume could explain the worse cognitive outcome in the combined treatment arm. Patients enrolled in the EORTC 22285–26001 trial [21] were evaluated with the EORTC QOL-C30 BN20 questionnaire to assess the effects of adjuvant WBRT [46]. Differences in role functioning, emotional function, and fatigue were not significant. Conversely, some significant differences were found for global health-related quality of life, cognitive function, and physical ability. Something noteworthy is that these differences reached clinical relevance (i.e., $\geqslant$10 points of difference) only in some specific time points during the follow-up.

Therefore, it may be concluded that nearly all patients with brain metastases have some degree of baseline neurocognitive impairment, whereas brain progression is the most important factor in determining cognitive deterioration. To our knowledge, based on the few existing data, the neuroperformance of the patients is not impaired by the addition of surgery to WBRT or by the different WBRT fractionation (at least for what concerns the schedules used in the trials above). Efaproxiral appeared to improve the quality of life of patients with brain metastases from breast cancer who were treated with WBRT. Although the evidence of WBRT-related neurotoxicity of a clinically significant degree is arguable, the risk of long-term effects of WBRT on neurocognitive function cannot be excluded.

Future directions

There are five major areas of future investigation. First, we need to improve the outcome of WBRT by adding new radiosensitizers or targeted agents. Second, methods to reduce the potential neurotoxicity of the treatment should be evaluated. Intensity-modulated whole-brain irradiation with the avoidance of areas where neural stem cells are located (hippocampus and subependymal areas) could be offered to highly selected patients to reduce the risk of neurocognitive radiation-induced damage [49,50]. The estimated risk of disease progression within the avoidance region related to such approach is reasonably low [51]. Third, a recently published systematic review [52], assessing the dose–effect relationship in stereotactic radiotherapy (SRT), showed that, assuming an α/β value of 12 Gy for brain metastases, a biologically effective dose (BED) of at least 40 Gy is necessary to achieve a 12-month local control rate of >70%. A BED12 value of 40 Gy translates into a single fraction of 20 Gy, 2 fractions of 11.6 Gy, or three fractions of 8.5 Gy. These data need to be confirmed in prospective trials that explore appropriate dosage for safe and effective SRT for radiosurgery and, even more, for hypofractionated stereotactic radiotherapy, the dose–effect prospective data being even more scarce for the latter [53]. Fourth, another important point to explore is to assess the possibility to deliver synchronous boost treatments to multiple targets concurrent with WBRT, without the need for separate stereotactic procedures [54]. Last, further confirmation of performance of the frameless image-guided radiosurgery system for various patient anatomies, isocenter localizations and immobilization systems are needed [55,56].

Conclusions

RCT in oligometastatic patients

WBRT vs. S + WBRT

The combined treatment may improve local control [8] and may prolong time to neurologic death [8]. Survival benefit from the addition of surgery may exist but it is more pronounced for better prognosis patients [8–10].

WBRT vs. RS + WBRT

The addition of radiosurgery may improve local control [12,13] but it also might prolong time to any brain failure [12]. A slight improvement in survival may be obtained in patients with single brain lesions [13].

S vs. S + WBRT

Patients who receive WBRT may have a better brain tumor control [14,20,21] both in terms of local control and freedom from new brain metastases [14,20,21]. The addition of WBRT may reduce neurologic death rate [14,20,21] but it does not alter the survival rate [14,20–22].

RS vs. RS + WBRT

Upfront WBRT may decrease brain recurrence [15,16,20,21] both in terms of better local tumor control rate [15,16,20,21] and improved distant brain tumor control rate [15,16,20,21]. Neurologic death rate may be reduced [20,21] in patients treated with the combined treatment, but no survival benefit is reached [15,16,20–22].

S + WBRT vs. RS + WBRT

There is no evidence of superiority of a combined treatment over the other one [24] but no definitive conclusions can be made in this regard because only a small, prematurely closed trial was undertaken.

RCT addressing the point of improving WBRT outcome

Comparison of different WBRT fractionation schedules

Different fractionation schemes do not show any statistical significance in terms of brain tumor control [25,27,28], neurologic death rate [27,28] and survival [25,27–29,31]. Ultrashort high-dose radiation schedules are not recommended because of worse results [26,30] and because of increasing risk of neurotoxicity. Accelerated WBRT may improve intracranial control in patients with favorable prognostic factors [32,33].

WBRT alone vs. WBRT and systemic therapy

The addition of efaproxiral to WBRT may improve survival in patients with brain metastases from breast cancer [34]. In patients with NSCLC, better results in terms of brain tumor control and reduced neurologic death rate may be obtained with the addition of motexafin gadolinium [35].

RCT that assessed neurocognitive impairment and quality of life

Baseline cognitive impairment is frequently reported [16,33,41–46]. Intracranial disease progression is a strongly significant factor in worsening neurocognitive performance [23,41,42,45]. Some degrees of neurocognitive impairment [16] and deterioration of quality of life [46] have been reported in patients who received the addition of WBRT to the local treatment. Efficacy of WBRT in improving intracranial tumor control seems to be stronger than the evidence of a clinically significant neurotoxicity related to brain irradiation. Impairment of both neurocognitive function and quality of life in patients with brain metastases needs to be further addressed in RCT, using standardized cognitive testing and questionnaires. Furthermore, adequate correlation of clinical signs of neurocognitive impairment with imaging assessment during follow up should be provided.

New generation of RCT will be necessary to clarify the role of new techniques (frameless stereotactic radiosurgery, WBRT with concomitant boost) and new systemic treatments.

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