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INVITED MANUSCRIPT

The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline

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Abstract

Question

What evidence is available regarding the use of whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?

Target population

This recommendation applies to adults with recurrent/progressive brain metastases who have previously been treated with WBRT, surgical resection and/or radiosurgery. Recurrent/progressive brain metastases are defined as metastases that recur/progress anywhere in the brain (original and/or non-original sites) after initial therapy.

Recommendation

Level 3 Since there is insufficient evidence to make definitive treatment recommendations in patients with recurrent/progressive brain metastases, treatment should be individualized based on a patient's functional status, extent of disease, volume/number of metastases, recurrence or progression at original versus non-original site, previous treatment and type of primary cancer, and enrollment in clinical trials is encouraged. In this context, the following can be recommended depending on a patient's specific condition: no further treatment (supportive care), re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy.

Question

If WBRT is used in the setting of recurrent/progressive brain metastases, what impact does tumor histopathology have on treatment outcomes?

No studies were identified that met the eligibility criteria for this question.

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Rationale

Untreated brain metastases have a median survival of about 4 weeks with almost all patients dying from neurological rather than systemic causes [1]. The majority of studies which have compared different modalities for the treatment of brain metastases have focused on the management of newly diagnosed patients. The role of WBRT, surgical excision, SRS and chemotherapy for patients with newly diagnosed brain metastases are addressed by other guideline papers in this series (Gaspar et al., Kalkanis et al., Linskey et al., and Mehta et al.).

For those individuals who survive long enough to experience recurrence/progression of previously treated brain metastases, no consensus on treatment exists. The overall objective of this guideline paper is to systematically review the existing data relevant to the treatment of patients who develop recurrent/progressive brain metastases after initial therapy and to provide recommendations based on this evidence.

The questions specifically addressed by this guideline paper are:

1. What evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?
2. If WBRT is used in this setting, what impact does tumor histopathology have on treatment outcomes?

Methods

Search strategy

The following electronic databases were searched from 1990 to September 2008: MEDLINE®, Embase®, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, Cochrane Database of Abstracts of Reviews of Effects. A broad search strategy using a combination of subheadings and text words was employed. The search strategy is documented in the methodology paper for this guideline series by Robinson et al. [2] Reference lists of included studies were also reviewed.

Eligibility criteria

(a) *What evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent and/or progressive brain metastases?*

- Published in English with a publication date of 1990 forward.
- Patients with recurrent and/or progressive brain metastases.
- Fully-published primary studies (all study designs for primary data collection included; e.g., RCT, non-randomized trials, cohort studies, case–control studies or case series).

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- Any study evaluating the use of WBRT, SRS, surgical excision, or chemotherapy alone or in combination.
- Number of study participants with recurrent and/or progressive brain metastases >5 per study arm for comparative studies and >5 overall for non-comparative studies.
- For studies evaluating interventions exclusively in patients with recurrent and/or progressive brain metastases, baseline characteristics of study participants are provided by treatment group for comparative designs and overall for non-comparative studies. For studies with mixed populations (i.e., includes participants with conditions other than recurrent and/or progressive brain metastases), baseline characteristics are provided for the sub-group of participants with recurrent and/or progressive brain metastases, and stratified by treatment group for comparative studies.

(b) *If WBRT is used, what impact does tumor histopathology have on treatment outcomes?*

- Published in English with a publication date of 1990 forward.
- Patients with recurrent and/or progressive brain metastases.
- Fully-published peer-reviewed primary studies (all study designs for primary data collection included; e.g., RCT, non-randomized trials, cohort studies, case–control studies or case series).
- Any study evaluating the outcome(s) of WBRT by tumor histopathology (or primary tumor type).
- Number of study participants with recurrent and/or progressive brain metastases >5 per study arm for comparative studies and >5 overall for non-comparative studies.
- For studies evaluating the outcome(s) of WBRT by histopathology (or primary tumor type) exclusively in patients with recurrent and/or progressive brain metastases, baseline characteristics are presented and stratified by histologic/primary tumor group. For studies with mixed populations (i.e., includes participants with conditions other than recurrent and/or progressive brain metastases), baseline characteristics are presented and stratified by histologic/primary tumor group for the sub-group of participants with recurrent and/or progressive brain metastases.

Study selection and quality assessment

Two independent reviewers evaluated citations using *a priori* criteria for relevance and documented decisions in standardized forms. Cases of disagreement were resolved by a third reviewer. The same methodology was used for full text screening of potentially relevant papers. Studies which met the eligibility criteria were data extracted by one reviewer and the extracted information was checked by a second reviewer. The PEDro scale [3, 4] was used to rate the quality of randomized trials. The quality of comparative studies using non-randomized designs was evaluated using eight items selected and modified from existing scales.

Evidence classification and recommendation levels

Both the quality of the evidence and the strength of the recommendations were graded according to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) criteria. These criteria are provided in the methodology paper accompanying this guideline series.

Guideline development process

The AANS/CNS convened a multi-disciplinary panel of clinical experts to develop a series of practice guidelines on the management of brain metastases based on a systematic review of the literature conducted in collaboration with methodologists at the McMaster University Evidence-based Practice Center.

Scientific foundation

What evidence is available regarding the use of WBRT, SRS, surgical resection or chemotherapy for the treatment of recurrent/progressive brain metastases?

In total, 30 studies met the eligibility criteria for this question (Fig. 1). Of these studies, three evaluated the use of WBRT [5–7], four addressed the role of surgical resection [8–11], 13 reported on the use of radiosurgery [12–24] and 10 evaluated chemotherapeutic agents [25–34] for the treatment of recurrent/progressive brain metastases. The details of each are outlined in Tables 1, 2, 3, 4.

No class I or II evidence was identified that specifically addressed the question of which therapies (i.e., repeated WBRT, SRS, surgery or chemotherapy) were beneficial in the setting of recurrent/progressive metastatic brain. In fact, only one of the 30 included studies compared different modalities for the treatment of recurrent/progressive brain metastases [15]. The remaining 29 papers provide non-comparative outcome data on the treatment of recurrent/progressive brain metastases.

WBRT

Three case series addressed the question of whether re-administration of WBRT was beneficial for patients in

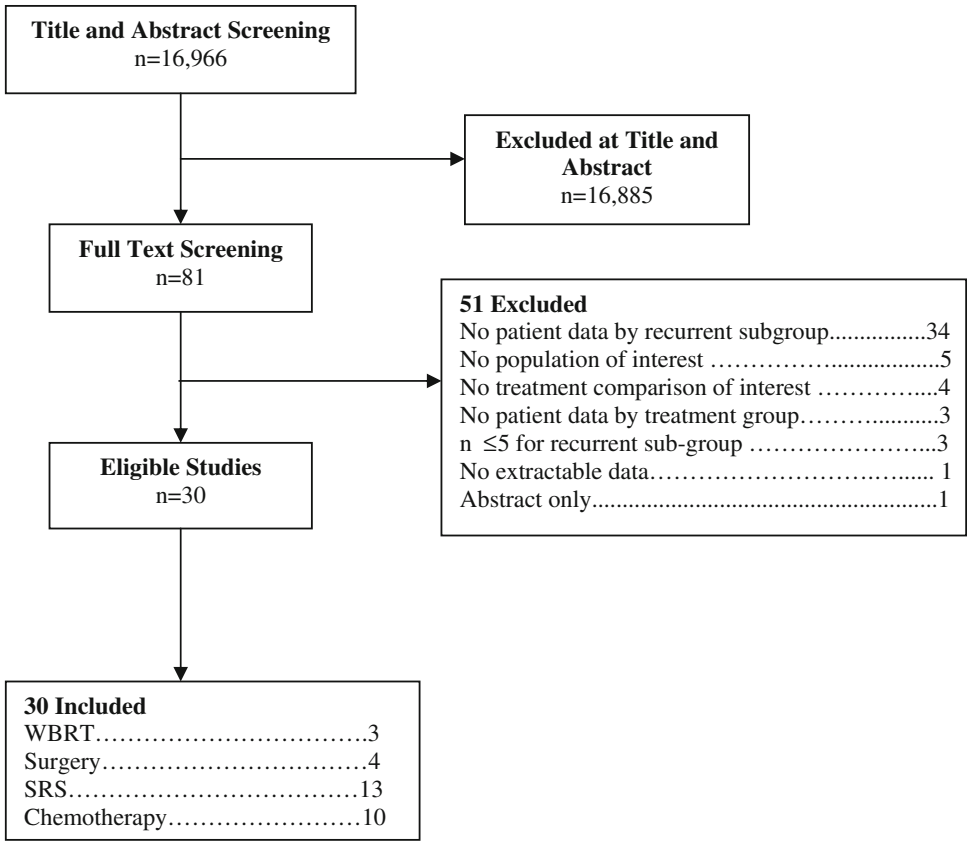

Fig. 1 Flow of studies to final number of eligible studies of retreatment of recurrent brain metastases

Table 1 Re-irradiation with WBRT for recurrent/progressive brain metastases

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/ progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Cooper [5] (1990)	Case series Evidence class III	WBRT ($n = 52$)	Recurrent/progressive BM Initial treatment: WBRT	Median: NR Mean survival: 22.4 weeks	NR	NR
Sadikov [6] (2007)	Case series Evidence class III	WBRT ($n = 72$)	Recurrent/progressive BM Initial treatment: WBRT	4.1 months	NR	NR
Wong [7] (1997)	Case series Evidence class III	WBRT ($n = 86$)	Recurrent/progressive BM Initial treatment: WBRT	4.0 months	NR	NR

BM Brain metastases, *NR* Not reported, *Pts* Patients, *WBRT* Whole-brain radiation therapy

[a] Number of pts with recurrence/progression of brain metastases, unless otherwise specified

whom previously treated brain metastases recurred/progressed [5–7] (Table 1). These studies are retrospective analyses of 52, 72 and 86 patients, respectively, and they offer only very limited data as to whether patients died from neurologic causes versus systemic disease progression. The average re-irradiation dose for these patients was in the range of 20–25 Gy over multiple fractions. The post-re-irradiation median survival was 4 or 5 months in all of the series.

In the largest of the case series ($n = 86$), 70% of patients had either complete or partial resolution of neurological symptoms following re-irradiation. In the two other case series, the percentage of patients whose neurologic function improved following re-irradiation was 42% and 31%, respectively [5, 6].

One patient experienced symptoms of dementia attributed to radiation therapy in each of the two series reporting information on longer term adverse effects [6, 7].

Table 2 Surgical resection for recurrent/progressive brain metastases

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/ previous treatment	Median survival	# Pts with recurrence/ progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Arbit [8] (1995)	Case series Evidence class III	Surgery ($n = 32$)	Recurrent BM from NSCLC Initial treatment included surgical resection	10 months	NR	NR
Bindal [9] (1995)	Case series Evidence class III	Surgery ($n = 48$)	Recurrent BM Initial treatment: surgical resection ± WBRT	11.5 months	At original site only: 18/48 (38%) At distant brain site only: 3/48 (6%) At original + distant sites: 5/48 (10%) Overall in brain: 26/48 (54%)	Overall in brain: 7.7 months
Truong [10] (2006)	Case series Evidence class III	Surgery ($n = 32$)	Recurrent/progressive BM BM had been previously treated with SRS (either as initial or salvage treatment)	8.9 months	At original site: 9/32 (28%)	At original site: 6.2 months
Vecil[11] (2005)	Case series Evidence class III	Surgery ($n = 61$)	Recurrent/progressive ≤3 BM Initial treatment: SRS	11.1 months	At original site only: 4/61 (7%) At distant brain site only: 19/61 (31%) At original + distant sites: 9/61 (15%)	Overall in brain: 5 months At distant sites in brain: 8.4 months At original site: Median: could not be estimated

BM Brain metastases, *NR* Not reported, *NSCLC* Non-small cell lung cancer, *Pts* Patients, *SRS* Stereotactic radiosurgery, *WBRT* Whole-brain radiation therapy

[a] Number of pts with recurrence/progression of brain metastases, unless otherwise specified

No studies were identified that evaluated the use of WBRT in the setting of recurrent/progressive brain metastases for patients whose initial management did not include WBRT.

Surgical resection

Four cases series addressed the use of surgical resection for recurrent/progressive brain metastases [8–11], as outlined in Table 2. Two of these retrospective studies reported outcomes for patients who underwent surgical resection for recurrent/progressive brain metastases who also had previously been treated with SRS ± WBRT [10, 11]. In the study by Vecil et al. 61 patients with three or fewer recurrent brain metastases underwent surgical resection for at least one index brain metastasis [11]. Treatment of non-index brain metastases varied. Major surgical complications occurred in seven patients. From the date of resection, median survival was 11.1 months and median time to any recurrence in the brain was 5 months. Cause of death was neurologic in 15% of patients and neurologic/systemic combined in 34%. The second study, conducted by Truong et al., included 32 patients who had previously been treated with SRS and who had MRI and/or clinical evidence of brain metastasis progression. To be considered for surgical resection, patients needed to have a KPS ≥60 and stable or absent systemic disease. Median survival from the time of resection was 8.9 months. Seven patients experienced surgical complications. Cause of death was neurologic in 48% of patients [10].

Two case series evaluated the outcome of re-operation for recurrent brain metastases [8, 9]. Bindal et al. reported on 48 patients who had surgical resection of a brain metastasis as part of their initial treatment and then underwent resection for recurrent disease. From the time of re-operation, median survival was 11.5 months and the median time to recurrence was 7.7 months. Of the 26 patients who developed a second recurrence, 17 underwent another surgical resection. For the 25 patients in which cause of death was known, it was neurologic in 48% and combined neurologic/systemic in 12% [9]. As part of a larger study, Arbit et al., provide retrospective data on 32 patients with non-small cell lung cancer (NSCLC) who underwent re-operation for recurrent brain metastases. From

Table 3 SRS for recurrent/progressive brain metastases

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Akyurek [12] (2007)	Case series Evidence class III	SRS ($n = 15$)	Recurrent/progressive BM from breast cancer Initial BM treatment: WBRT	14 months	At original site: 1 year local Control rate: 77% At distant brain sites: 1 year distant control rate: 57%	NR
Chen [13] (2000)	Case series Evidence class III	SRS ($n = 45$)	Recurrent/progressive BM Initial BM treatment included SRS ± WBRT	28 weeks	Local control (by lesion for 84% of lesions with data): 90% 1 year freedom from tumor progression: 94%	NR
Combs [14] (2004)	Case series [For the recurrent group (G3) only] Evidence class III	SRS for recurrent BM ($n = 39$)	Recurrent/progressive BM from breast cancer Initial BM treatment: WBRT	19 months	NR	At original sites: 9 months At distant brain sites: 7 months
Davey [15] (2007)	Retrospective cohort study with historical controls Evidence class III	G1: SRS ($n = 35$) G2: Fractionated SRS (2 fractions) ($n = 69$)	Recurrent/progressive BM Initial BM treatment included WBRT	G1: 16 weeks G2: 30 weeks (Survival curves: log-normal; univariate $p = 0.0155$)	NR	NR
Davey [16] (1994)	Prospective single arm phase I/II trial Evidence class III	SRS ($n = 12$ pts)	Recurrent/progressive BM Initial BM treatment: WBRT	6 months	# pts with local recurrence: 9/12 (75%) Radiological response at 4 weeks (by lesion): Complete response 3/19 (16%) Partial response 6/19 (32%) No change 10/19 (53%) Progression 0/19	NR
Hoffman [17] (2001)	Case series [For the recurrent group (G3) only] Evidence class III	SRS for recurrent BM ($n = 53$)	Recurrent/progressive BM from lung cancer Initial BM treatment: WBRT	10.0 months	1 year freedom from LR rate: 36% 1 year freedom from DR rate: 55% 1 year freedom from any intracranial recurrence: 27%	At original site: 9.2 months At distant site: 16.5 months Overall in brain: 5.8 months
Kwon [18] (2007)	Case series Evidence class III	SRS ($n = 43$)	Recurrent/progressive BM Initial BM treatment included SRS	32 weeks	6 month local control rate: 91% 6 month overall brain control rate: 86%	NR
Loeffler [19] (1990)	Case series Evidence class III	SRS ($n = 18$)	Recurrent/progressive BM Initial BM treatment: WBRT ± surgery (except in 1 pt who refused WBRT)	NR	At original site: # of lesions that decreased or stabilized: 21/21 (100%)	NR
Noel [20] (2003)	Case series [For the recurrent group (G3) only] Evidence class III	SRS for recurrent group($n = 36$)	Recurrent/progressive BM Initial BM treatment: WBRT	8 months	1 year local control rate: 86%	Overall in brain: Median: not reached

Table 3 continued

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Noel [21] (2001)	Case series Evidence class III	SRS ($n = 54$)	Recurrent/progressive BM Initial BM treatment: WBRT	7.8 months	1 year local control rate (by lesion): 91% 1 year overall brain control rate: 65%	Median time to development of new BM or leptomeningeal carcinomatosis: 24.5 months
Sheehan [22] (2005)	Case series Evidence class III	SRS ($n = 27$)	Recurrent/progressive BM from SCLC Initial BM treatment included WBRT	4.5 months	Local tumor control (Of 21 lesions in 14 pts with data): 17/21 (81%) lesions; 12/14 (86%) pts	NR
Shuto [23] (2004)	Case series Evidence class III	SRS ($n = 16$)	Recurrent/progressive BM Initial BM treatment included SRS	22.4 months (from 1st SRS treatment)	Tumor response:[Of 173/242 (72%) lesions with data]: Complete response 121/173 (70%) Partial response or no change 47/173 (27%) Progression 5/173 (3%)	NR
Yamanaka [24] (1999)	Case series Evidence class III	SRS ($n = 41$)	Recurrent/progressive BM Initial BM treatment included SRS	15 months (from first SRS treatment)	Overall local control rate after 2nd SRS (by lesion): 93% Response after 2nd SRS [Of 61 lesions evaluable]: Disappeared 16/61 (26%) Decreased 40/61 (66%) Unchanged 1/61 (2%) Increased 4/61 (7%)	NR

BM Brain metastases, *BR* Brain recurrence (local + distant), *DR* Distant recurrence in brain, *G1* Group 1, *G2* Group 2, *LR* Local recurrence at original site in brain, *NSCLC* Non-small cell lung cancer, *NR* Not reported, *PR* Partial response, *Pts* Patients, *SCLC* Small cell lung cancer

[a] Number of pts with recurrence/progression of brain metastases, unless otherwise specified

the date of re-operation, median survival was 10 months. Time to recurrence/progression was not reported [8].

SRS

Thirteen studies addressed the role of SRS for recurrent/progressive brain metastases [12–24]. Nine studies evaluated the use of SRS for recurrent/progressive disease in patients whose initial management included WBRT [12, 14–17, 19–22]. One of these studies was prospective [16]. This single-arm phase I/II study enrolled 12 patients whose life expectancy was $\geq$3 months and who had both clinical and radiologic evidence of brain metastases progression following treatment with WBRT. All patients were followed to recurrence at the SRS treated site or until death. In total, 20 brain metastases in the 12 patients were treated by radiosurgery. From the date of SRS treatment, median survival was 6 months. Nine patients developed evidence of progressive disease at SRS treated sites. Time to progression was not reported. Of the other eight studies that addressed the role of SRS for recurrent disease in patients whose upfront treatment included WBRT, four specifically evaluated SRS treatment for recurrent/progressive brain metastases from particular primary tumor types–breast cancer (2 case series [12, 14]), small cell lung cancer (SCLC) (1 case series [22]) and lung cancer, predominantly NSCLC (1 case series [17]). See Table 3 for details.

The only comparative study that met the eligibility criteria for the systematic review evaluated single-dose SRS versus split-dose (2 dose) SRS for recurrent/progressive disease in 104 patients whose initial management included WBRT [15]. In this retrospective cohort study with historical controls, median survival was significantly longer for patients who received split-dose SRS compared to single-dose SRS (30 vs. 16 weeks; $p = 0.015$). Time to recurrence/progression was not reported.

Four case series evaluated the use of SRS for recurrent/progressive brain metastases in patients whose previous treatment included radiosurgery [13, 18, 23, 24], as outlined in Table 3. Only two of these case series provide survival data from the date of SRS for recurrent disease [13, 18]. In the series by Kwon et al., of 43 patients who underwent salvage SRS, median survival from the time of SRS for recurrent/progressive disease was 32 weeks and the local control rate at 6 months was 91% [18]. In the case series by Chen et al., of 45 patients, median survival from the time of SRS for recurrent brain metastases was 28 weeks [13]. The 1 year freedom from progression rate was 94%.

Chemotherapy

Ten studies evaluated the role of chemotherapy in patients with recurrent/progressive metastatic brain disease [25–34]. Of these, five are prospective single arm phase II studies [25, 27, 29, 31, 32] and five are case series [26, 28, 30, 33, 34]. Refer to Table 4 for details. The agents used in these studies varied from intracarotid administration of cisplatin, to temozolomide alone or with thalidomide, vinorelbine, fotemustine or cisplatin. Five of the studies investigated the role of chemotherapy specifically for patients with recurrent/progressive brain metastases from particular primary tumor types—melanoma (3 studies) [26, 28, 31], NSCLC (1 study) [29], and SCLC (1 study) [30].

Median survival in patients with recurrent/progressive brain metastases treated with chemotherapy ranged from 3.5 to 6.6 months [25–34]. The median time to recurrence after retreatment with chemotherapy in these studies ranged from 2 to 4 months. These studies indicate that some patients with recurrent or progressive brain metastases will have an objective radiographic response and/or improvement in functional status after treatment with chemotherapy.

If WBRT is used in the setting of recurrent and/or progressive brain metastases, what impact does tumor histopathology have on treatment outcomes?

No studies were identified that met the eligibility criteria for this question.

Discussion and conclusions

No studies that provide class I or II evidence were identified which met the eligibility criteria and specifically addressed the question of which adjuvant therapies (i.e., WBRT, SRS, surgical resection or chemotherapy) are beneficial in the setting of recurrent/progressive metastatic brain tumors. Furthermore, all but one of the included studies that provide class III evidence on this topic are non-comparative. While multiple randomized clinical trials have examined the benefits for up-front combined therapies (e.g., WBRT plus SRS, WBRT plus surgery), none have been performed specifically to address the question of the benefits of further SRS, surgery or chemotherapy in cases of recurrent/progressive brain metastases. Therefore, no level 1 or level 2 recommendations can be made.

Given that none of the included studies compared the different modalities (WBRT, SRS, surgical resection or chemotherapy) for the treatment of recurrent/progressive brain metastases, the relative merits of one approach versus another are yet to be determined. Furthermore, retrospective studies of patients with recurrent/progressive brain metastases who have previously undergone WBRT, and then received subsequent re-irradiation, show conflicting results with regard to neurologic improvement and quality of life.

It is recommended that treatment of recurrent/progressive brain metastases be individualized based on functional status, extent of disease, volume/number of metastases,

Table 4 Chemotherapy for recurrent/progressive brain metastases

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Abrey [25] (2001)	Prospective single arm phase II trial Evidence class III	TMZ ($n = 41$)	Recurrent/progressive BM Initial BM treatment varied (all received WBRT ± other modalities)	6.6 months	Response in brain: Complete response 0/41 (0%) Partial response 2/41 (5%) Stable disease 15/41 (37%) Progressive disease 17/41 (42%) Not assessed 7/41 (17%)	Overall in brain: 1.97 months
Bröcker [26] (1996)	Prospective single arm study NR		WBRT + fotemustine ($n = 13$)	Progressive multiple BM from melanoma	Overall: Not reported Evidence class III	Response in brain: (12 evaluable pts) Pts with partial response/stable disease: 6 months Complete response: 0/13 (0%) Partial response 4/13 (31%) Stable disease 3/13 (23%) Other pts: 2 months Progressive disease 6/13 (46%) Not assessable: 1/13 (8%)
Christodoulou [27] (2005)	Prospective single arm phase II trial Evidence class III	TMZ + cisplatin ($n = 32$)	Recurrent/progressive BM	5.5 months	Response both in brain + extra-cranial sites: Complete response 1/32 (3%) Partial response 8/32 (25%) Partial response in brain only 1/32 (3%) Stable disease 5/32 (16%) Progressive disease 6/32 (19%) Not evaluable 11/32 (34%)	Median time to progression for all pts: 2.9 months
Feun [28] (1990)	Case series Evidence class III	Intracarotid cisplatin-based chemotherapy ($n = 23$)	Recurrent/progressive BM from melanoma Initial BM treatment included WBRT in 22/23 pts	Median: Not reported Range: 1 to 65 weeks	Objective improvement by CT scan 7/23 (30%) Stable disease 3/23 (13%) Failed to respond 13/23 (57%)	Median time to progression in responding pts: 20 weeks
Giorgio [29] (2005)	Prospective single arm phase II trial Evidence class III	TMZ ($n = 30$)	Recurrent or progressive BM from NSCLC Previous BM treatment: WBRT and chemotherapy for BM	6 months	Response in brain: Complete response 2/30 (7%) Partial response 1/30 (3%) Stable disease 3/30 (10%) Progressive disease 24/30 (80%)	Median time to progression of brain metastases in all pts: 3.6 months

Table 4 continued

First author (Year)	Study design/ evidence class	Intervention (# pts)	Population/previous treatment	Median survival	# Pts with recurrence/progression after retreatment[a]	Median time to recurrence/ progression after retreatment
Groen [30] (1993)	Prospective single arm study Evidence class III	Carboplatin ($n = 20$)	Recurrent/progressive BM from SCLC Initial BM with teniposide, reinduction combination chemotherapy or cranial irradiation	15 weeks	Response in brain: Complete response 2/20 (10%) Partial response 6/20 (30%) Stable disease 4/20 (20%) Progressive disease 4/20 (20%) Clinically determined progressive disease 4/20 (20%)	Median duration of response: 8 weeks
Hwu [31] (2005)	Prospective single arm phase II trial Evidence class III	TMZ + thalidomide ($n = 26$)	Recurrent/progressive BM from melanoma Initial BM treatment varied Chemotherapy-naive patients	5 months	Response in brain: Complete response 2/26 (8%) Partial response 1/26 (4%) Minor response/stable: 7/26 (27%) Progressive disease: 4/26 (15%) Unknown 1/26 (4%) Not assessable 11/26 (42%)	Median duration of response or stable disease in brain: 4 months
Iwamoto [32] (2008)	Prospective single arm phase II study Evidence class III	TMZ + vinorelbine ($n = 38$)	Recurrent/refractory BM Initial BM treatment varied	5 months	Response in brain: Objective response 5% (CR 1/38; minor response 1/38) Stable disease 5/38 (13%) Progressive disease 29/38 (76%) Not evaluable 2/38 (5%)	Median progression free survival: 1.9 months
Kaba [33] (1997)	Prospective single arm study Evidence class III	TPDC-FuHu ($n = 97$ assessable/115 enrolled)	Recurrent/progressive BM Initial BM treatment: surgery and/or radiation therapy	25 weeks	Response in brain: Complete response 4/97 (4%) Partial response 14/97 (14%) Minor response 9/97 (9%) Stable disease 25/97 (26%) Progressive disease 45/97 (46%)	Median time to progression for all pts: 12 weeks
Omuro [34] (2006)	Prospective single arm phase I trial Evidence class III	TMZ + vinorelbine ($n = 21$)	Recurrent/progressive BM Initial BM treatment varied	17 weeks	Response in brain: (Of 18 evaluable pts) Partial response 1/18 (6%) Minor response 1/18 (6%) Stable disease 6/18 (33%) Progressive disease 10/18 (56%)	NR

BM Brain metastases, *NSCLC* Non-small cell lung cancer, *NR* Not reported, *NS* Not significant, *Pts* Patients, *SCLC* Small cell lung cancer, *TMZ* Temozolomide, *TPDC-FuHu* Hydroxyurea, *WBRT* Whole-brain radiation therapy

[a] Number of pts with recurrence/progression of brain metastases, unless otherwise specified

recurrence or progression at original versus non-original site, previous treatment and type of primary cancer. In this context, re-irradiation (either WBRT and/or SRS), surgical excision or, to a lesser extent, chemotherapy, can be recommended depending on a patient's specific condition and based on the judgment of the patient's treating physician.

As no studies were identified that met the eligibility criteria for the question addressing whether tumor histopathology impacts treatment outcomes when WBRT is used in the setting of recurrent/progressive brain metastases, no evidence-based recommendations can be made on this topic.

Key issues for further investigation

This systematic review of the evidence highlights the critical need for comparative studies that directly evaluate the outcome of different treatment modalities for patients with recurrent/progressive metastatic brain disease, while simultaneously addressing the role of tumor histopathology in treatment outcomes. In addition, understanding potential differences in the mode of death (neurologic versus systemic progression), will help answer the important question of whether treating recurrent/progressive lesions delays neurologic progression long enough to allow more aggressive therapy for the primary systemic disease.

Moreover, specific patient characteristics offer important clinical variables in evaluating treatment for recurrent/progressive metastases, such as if the recurrence/progression occurs at the site of the primary focal treatment (surgery or SRS) and if it is clinically symptomatic or discovered because of routine surveillance neuroimaging. Indeed, as the treatment of recurrent/progressive brain metastases is undertaken primarily with palliative intent, it is important to stress which symptoms these treatments are poised to address and how overall patient quality of life is going to be affected by any re-treatment modality.

No ongoing or recently closed randomized clinical trials addressing the re-treatment of patients with recurrent/progressive brain metastases were found that met the eligibility criteria.

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Disclaimer of liability The information in these guidelines reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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