INVITED MANUSCRIPT

The role of emerging and investigational therapies for metastatic brain tumors: a systematic review and evidence-based clinical practice guideline of selected topics

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Abstract

Question

What evidence is available regarding the emerging and investigational therapies for the treatment of metastatic brain tumors?

Target population

These recommendations apply to adults with brain metastases.

Recommendations

New radiation sensitizers

Level 2 A subgroup analysis of a large prospective randomized controlled trial (RCT) suggested a prolongation of time to neurological progression with the early use of motexafin-gadolinium (MGd). Nonetheless this was not borne out in the overall study population and therefore an unequivocal recommendation to use the currently available radiation sensitizers, motexafin-gadolinium and efaproxiral (RSR 13) cannot be provided.

Interstitial modalities

There is no evidence to support the routine use of new or existing interstitial radiation, interstitial chemotherapy and or other interstitial modalities outside of approved clinical trials.

New chemotherapeutic agents

Level 2 Treatment of melanoma brain metastases with whole brain radiation therapy and temozolomide is reasonable based on one class II study.

Level 3 Depending on individual circumstances there may be patients who benefit from the use of temozolomide or fotemustine in the therapy of their brain metastases.

Molecular targeted agents

Level 3 The use of epidermal growth factor receptor inhibitors may be of use in the management of brain metastases from non-small cell lung carcinoma.

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Rationale

As can be gleaned by the data collected and the questions
assessed in the other papers in this guideline series, uni-
formly successful control of brain metastases has not been
achieved. Even in those selected cases of outstanding con-
trol, toxicity from the treatment itself can result in an overall
decrement in the person's level of function. Fortunately
there is research proceeding on a number of fronts to
improve this situation. To provide some insight into these
investigative areas, modalities that have reached the point
of assessment by clinical trials warrant critical review.

The objectives of this paper are to assess both compar-
ative and non-comparative studies of the following thera-
pies that are still in the investigational stage (i.e., not
currently available outside of clinical trials). This will
include (1) the radiation sensitizers motexafin-gadolinium
and RSR 13, (2) local modalities placed at the time of
surgical excision including local irradiation with the bal-
loon-based brachytherapy, stereotactically placed radiation
sources, and local chemotherapy with BCNU-impregnated
polymers, (3) the role of the chemotherapeutic agents
temozolomide and fotemustine, and (4) the molecular tar-
geted agents against epidermal growth factor or angiogenic
receptors.

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 com-
bination of subheadings and text words was employed. The
search strategy is documented in the methodology paper
for this guideline series by Robinson et al. [1]. Reference
lists of included studies were also reviewed.

Eligibility criteria

For literature to be included for consideration in creation of
the guidelines related to this question, it needed to meet the
following criteria:

- Published in English.
- Include patients with brain metastases.
- Arise from fully-published primary studies with a
  publication date of 1990 forward or abstracts from the
  2006–2008 meetings of AANS, CNS, SNO, ASTRO,
  ASCO and the AANS/CNS joint section on tumors
  satellite symposiums (all study designs for primary data
  collection were included; e.g., randomized controlled
  trials, non-randomized trials, cohort studies, case–
  control studies, or case series).
- Evaluation of one or more or the following modalities
  was necessary:

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- Radiation sensitizers:
  - Motexafin-gadolinium
  - Efaproxiral (RSR 13)
- Local modalities placed at the time of surgical excision or biopsy:
  - Local irradiation
    - Balloon tipped catheter placement
    - Interstitial radiosurgery or brachytherapy (without hyperthermia)
  - Local chemotherapy to the resection cavity
- New chemotherapeutic agents: temozolomide or fotemustine
  - Molecular targeted agents: Gefitinib (ZD1839)
  - Anti-angiogenesis agents: Bevacizumab (Avastin)
- The number of study participants with brain metastases needed to be >5 per study arm for at least two of the study arms for comparative studies and >5 overall for non-comparative studies.
- The following criteria was applied to full-length papers, but not meeting abstracts: For studies evaluating interventions exclusively in patients with brain metastases, the baseline characteristics of study participants needed to be 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 brain metastases), baseline characteristics needed to be provided for the sub-group of participants with brain metastases, and stratified by treatment group for comparative studies.

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 [2, 3] 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 questions to be answered regarding the 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

Overall, 59 publications (53 primary studies and 6 companion papers) met the eligibility criteria for use in the discussion of the scientific foundation of this guideline (Fig. 1). A summary of the class of evidence of all the primary studies discussed in this scientific foundation are presented in Table 1.

New radiation sensitizers

Review of the literature provided five unique studies [4–8] and five companion papers [9–13] that met the criteria for support of guidelines recommendations regarding the use of new radiation sensitizers in the management of brain metastases (Table 2).
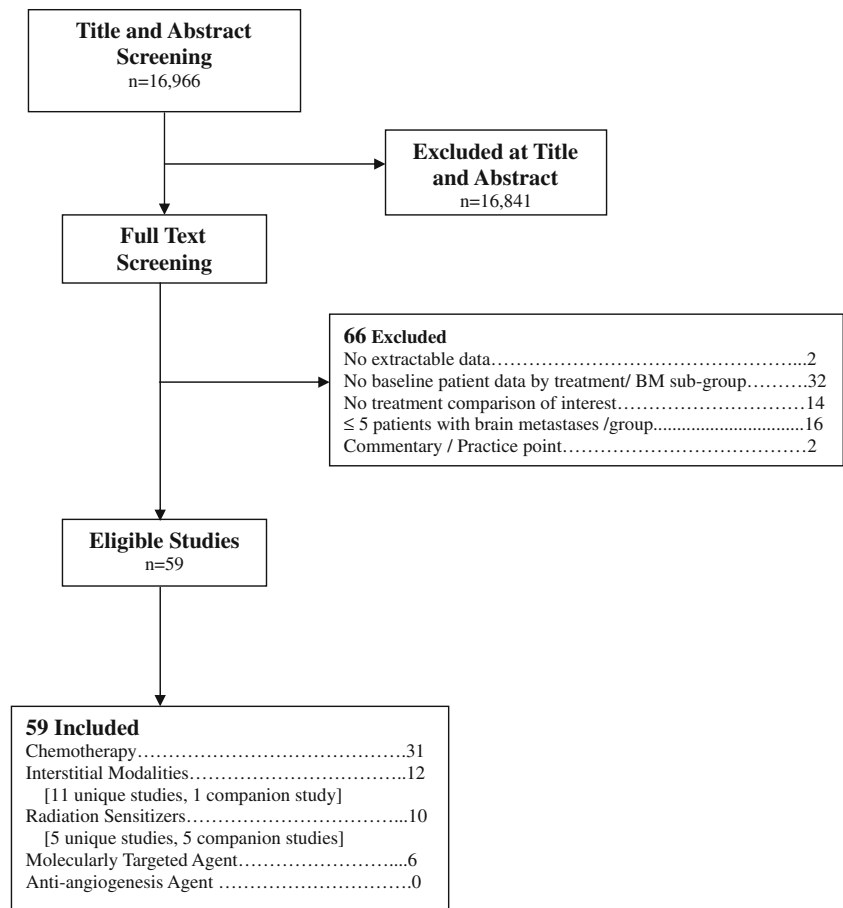
Many radiation sensitizers have been investigated to try to increase the effectiveness of whole-brain radiation therapy (WBRT). Two recent radiation sensitizers that have been extensively evaluated are motexafin gadolinium and efaproxiral.

Motexafin gadolinium

Motexafin gadolinium (MGd) is a metallotexaphrin that localizes within tumors in greater concentration than in normal tissues. This agent is detectable by magnetic resonance imaging (MRI) because it contains the paramagnetic metal ion, gadolinium. Its exact mechanism of action is not known although it is known to be involved with electron scavenging. It may act as both a radiation sensitizer and modifier.

There is one prospective single arm study [7] (class III evidence) and two randomized controlled studies [4, 6] (class I evidence) evaluating MGd as a radiation sensitizer. Carde et al. published a prospective single arm phase Ib/II study which established MGd 5 mg/kg given intravenously daily as the recommended best tolerated dose when

Fig. 1 Flow of studies to final number of eligible studies

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            ┌─────────────────────────┐
            │  Title and Abstract     │
            │       Screening         │
            │       n=16,966          │
            └─────────────────────────┘
                        │          ┌──────────────────────┐
                        │─────────▶│ Excluded at Title    │
                        │          │  and Abstract        │
                        ▼          │   n=16,841           │
            ┌─────────────────────────┐ └──────────────────────┘
            │    Full Text            │
            │    Screening            │
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66 Excluded
No extractable data……………………………………………2
No baseline patient data by treatment/ BM sub-group………32
No treatment comparison of interest……………………………14
≤ 5 patients with brain metastases /group……………………16
Commentary / Practice point………………………………………2

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            ┌─────────────────────────┐
            │   Eligible Studies      │
            │       n=59              │
            └─────────────────────────┘
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59 Included
Chemotherapy…………………………………………31
Interstitial Modalities………………………………12
  [11 unique studies, 1 companion study]
Radiation Sensitizers………………………………...10
  [5 unique studies, 5 companion studies]
Molecularly Targeted Agent………………………...6
Anti-angiogenesis Agent …………………………..0

combined with 30 Gy WBRT given in 10 fractions of 3 Gy. This yielded class III evidence regarding the feasibility and potential efficacy of MGd [7].

A subsequent randomized controlled study in 401 patients with brain metastases of various histologies, comparing WBRT alone versus WBRT with motexafin gadolinium failed to show any significant difference in median survival or tumor response [4]. However, the median time to neurologic progression as determined by the investigators was increased by 0.5 months ($p = 0.018$) for the group that received motexafin gadolinium. This effect was attributed predominantly to the lung cancer stratum. Patients were stratified by histology (lung, breast or other) and a subset analysis revealed that the time to neurological progression favored the MGd and WBRT arm for patients with lung cancer (median 5.5 months for MGd v 3.7 months for WBRT alone, $p = 0.025$), but no difference was seen in the other strata. A companion study of neurocognitive function by Meyers et al. further suggested that MGd may preserve memory and executive function and prolong time to neurocognitive and neurologic progression in patients with brain metastases from lung cancer [9].

An international phase III study was therefore conducted, randomizing 554 patients with non-small cell lung carcinoma (NSCLC) to WBRT alone (30 Gy in 10 fractions) or to WBRT with MGd [6]. The primary endpoint of the study was time to neurologic progression. Although time to neurological progression was improved in the MGd arm, it was not a statistically significant difference unless the patients enrolled outside of North America were excluded. In a subgroup analysis of the 348 North American patients, there was a statistically significant prolongation of time to neurological progression from 8.8 to 24.2 months, $p = 0.04$. This difference in outcome between the North American patients and patients treated elsewhere was attributed to the fact that patients in North America received the study treatment sooner after the diagnosis of the brain metastases. When WBRT was initiated within three weeks of diagnosis of the brain metastases, regardless of whether the patient was treated in North America or not, time to neurological progression was significantly prolonged by the addition of MGd ($p = 0.006$, HR = 0.59). A major reason for the delay to WBRT outside of North America was the use of chemotherapy. This study failed to meet its primary objective of increasing time to neurologic progression and is considered a negative study. However the subgroup analysis mentioned, though post hoc and selective in nature, can be interpreted as providing class 2 evidence.

Table 1 The evidence class provided by the included primary studies

Evidence class	Description of evidence class	Class of evidence provided by included primary studies
New radiation sensitizers: motexafin-gadolinium and efaproxiral		
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials	3 RCTs: Mehta [4], Suh [5], Mehta [6]
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)	None
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls	1 Prospective cohort study with historical controls: Shaw [8]
		1 Prospective single arm study: Carde [7]
Interstitial modalities		
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials	None
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)	1 Retrospective cohort study: Ostertag [25]
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls	3 Prospective single arm studies:
		Ewend [15], Rogers [16], Nakagawa [17]
		7 Case series: Alesch [18], Bernstein [19], Bogart [20], Dagnew [21], Schulder [22], Curry [23], Nakamura [24]
New chemotherapeutic agents: Temozolomide or fotemustine		
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials	1 RCT: Mornex [59]
		2 Randomized phase II trials: Antonadou [32], Verger [33]
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)	2 Retrospective cohort studies: Conill [34], Panagiotou [35]
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls	22 Prospective single arm studies: Abrey [36], Addeo [37], Agarwala [38], Caraglia [41], Christodoulou [42], Christodoulou [43], Cortot [56], Giorgio [44], Hwu [46], Iwamoto [47], Janinis [48], Kouvaris [49], Krown [50], Larkin [51], Margolin [52], Omuro [53], Rivera [54], Schadendorf [55], Brocker [60], Chang [61], Cotto [62], Jacquilat [63]
		2 Case series: Hofmann [45], Ulrich [64]
		2 Sub-group analyses of prospective studies: Bafaloukos (2006),
		Boogerd [40]
Molecular targeted agent: Gefitinib (ZD 1839)		
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials	None
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)	None
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls	3 Prospective single arm studies: Ceresoli [71], Chiu [72], Wu [73]
		3 Case series: Hotta [68], Namba [69], Shimato [70]

Fully published papers. Conference proceeding abstracts not included

Efaproxiral

Efaproxiral, (also known as RSR13; Allos Therapeutics, Westminster, CO) is an allosteric modifier of hemoglobin.

Efaproxiral binds to hemoglobin, causing a change in its conformational structure, leading to a reduction in hemoglobin oxygen binding affinity. This leads to an increased release of oxygen into tissue, enhancing tumor

Table 2 Summary of primary radiation sensitizer studies

First author (year)	Study design/evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/progression
Motexafin-gadolinium						
Carde [7] (2001)	Prospective single arm phase Ib/II study Evidence class III	WBRT + MGd (phase Ib $n = 39$; phase II $n = 22$)	BM	4.7 months (Phase 1b + phase II)	Radiographic response in brain: Phase Ib (23 assessable pts): CR 1/23, PR 13/23, SD 8/23, PD 1/23 Phase II (18 assessable pts): CR 0/18, PR 13/18, SD 4/18, PD 1/18	NR
Mehta [4] (2003)	RCT Evidence class I	G1: WBRT ($n = 208$) G2: WBRT + MGd ($n = 193$)	BM	G1: 4.9 months G2: 5.2 months (Survival curves: log-rank; $p =$ NS)	Response rate in brain (CR or PR): G1: 50.7% G2: 46.3% ($p =$ NS)	Median time to neurologic progression (by ERC): G1: 8.3 months G2 9.5 months (log-rank; $p =$ NS) Median time to neurologic progression (by investigators): G1: 3.8 months G2 4.3 months (log-rank; $p = 0.018$)
Mehta [6] (2008)	RCT Evidence class I	G1: WBRT ($n = 275$) G2: WBRT + MGd ($n = 279$)	BM from NSCLC	G1: 5.8 months G2: 5.1 months (log-rank; $p =$ NS)	NR	Interval to neurologic progression: G1: 10.0 months G2: 15.4 months (Neurologic progression curves: stratified log-rank; $p =$ NS)
Efaproxiral (RSR 13)						
Shaw [8] (2003)	Prospective cohort study with historical controls Evidence class III	G1: WBRT [historical controls] ($n = 1070$) G2: WBRT + efaproxiral ($n = 57$ RPA class II)	BM	G1: 4.1 months G2: 6.4 months (Survival curves: log-rank; $p = 0.0174$)	Response in brain: G1: Not reported G2: CR 7/57, PR 13/57, SD 21/57	NR

Table 2 continued

First author (year)	Study design/evidence class	Population	Interventions	Median survival	Tumor response	Median time to recurrence/progression
Suh [5] (2006)	RCT Evidence class I	BM	G1: WBRT + supplemental O_2 (n = 250) G2: WBRT + supplemental O_2 + efaproxiral (n = 265)	G1: 4.4 months G2: 5.4 months (Survival curves: log-rank; p = NS) NSCLC/breast cancer sub-group: G1: 4.4 months G2: 6.0 months (Survival curves: log-rank; p = NS)	Response rate in brain (CR or PR): G1: 96/250 (38%) G2: 121/265 (46%) (p = NS) Response rate in NSCLC/breast cancer sub-group: G1: 41% G2: 54% (p = 0.01)	Median progression-free survival: G1: 3.5 months G2: 4.0 month (log-rank: p = NS) Median progression-free survival in NSCLC/breast cancer sub-group: G1: 3.7 months G2: 4.8 month (log-rank; p = NS)

BM Brain metastases, BR Brain recurrence (local + distant), CR Complete response, DR Distant recurrence in brain, ERC Events review committee, FdUrd 5-fluoro-2'-deoxyuridine, G1 Group 1, G2 Group 2, G3 Group 3, G4 Group 4, LR Local recurrence at original site in brain, MGd Motexafin-gadolinium, NR Not reported, NS Not significant, NSCLC Non-small cell lung cancer, OR Objective response, PR Partial response, Pts Patients, RCT Randomized control trial, SRS Stereotactic radiosurgery, TMZ Temozolomide, WBRT Whole-brain radiation therapy

oxygenation leading to radiation sensitization. Shaw et al. completed a phase II study in which 57 patients with brain metastases received WBRT (30 Gy in 10 fractions of 3 Gy) with daily efaproxiral 50–100 mg/kg. This yielded class III data showing median survival was 6.4 months which compared favorably to the Radiation Therapy Oncology Group's (RTOG) historical control patients (4.1 months) [8].

This prompted a large phase III study of WBRT alone versus WBRT with efaproxiral in 515 patients [5]. This study failed to reveal a significant difference in median survival, tumor response or median time to recurrence/progression with the addition of efaproxiral although it prompted a confirmatory trial in patients with brain metastases related to breast cancer. The investigators found that patients with brain metastases related to breast cancer were more likely to receive at least 7 of the planned 10 fractions of efaproxiral and were more likely to have an increased concentration of efaproxiral in red blood cells as compared to patients with brain metastases due to other primary cancers such as lung cancer [11, 12]. However, the confirmatory phase III study in breast cancer patients of WBRT with efaproxiral versus WBRT alone failed to demonstrate an improvement in overall survival or any other prespecified endpoint [13, 14].

In summary, there is class I evidence that motexafin gadolinium (MGd) given daily during WBRT does not increase survival over survival following WBRT alone. Additionally, there is also class I evidence that efaproxiral given daily during WBRT does not increase survival over survival following WBRT alone.

Radiation sensitizers summary

Considerable effort has been put into the development of motexafin gadolinium and efaproxiral yielding class I data supporting the conclusion that these agents do not improve the therapy of brain metastases. This is not to say that radiation sensitizers are without merit. The lessons learned in the studies reviewed here provide direction for further investigation and encouraging patient participation in such studies is warranted.

Interstitial modalities

Review of the literature provided 11 unique studies [15–25] and one companion study [26] that met the criteria for support of guidelines recommendations regarding the use of interstitial modalities in the management of brain metastases (Table 3). In this discussion brachytherapy is defined as therapy placed inside of or next to the area being treated.

Table 3 Summary of interstitial modalities studies

First author (year)	Study design/evidence class	Interventions	Population	Median survival	Tumor control	Median time to recurrence/progression
Brachytherapy ± WBRT						
Ostertag [25] (1995)	Retrospective cohort study Evidence class II	G1: Temporary ^{125}Iseeds + WBRT (n = 38) G2: Temporary 125I seeds (n = 34) G3: Temporary ^{125}I seeds for recurrent BM (n = 21)	BM	G1: 17 months G2: 15 months G3: 6 months (Survival curves G1 vs. G2: Lee-Desu statistic; p = NS)	NR by treatment group	NR
Alesch [18] (1995)	Case series Evidence class III	Temporary ^{125}I seeds (n = 19)	BM	NR	Response in brain (by CT scan): Marked reduction 5/19 Slight reduction 11/19 Unchanged 2/19 Not evaluable 1/19 # of pts with LR: 1/19 # of pts with DR: 1/19	NR
Bernstein [19] (1995)	Case series Evidence class III	Temporary high-activity ^{125}I seeds (n = 10)	Single locally recurrent BM	46 weeks	NR	NR
Surgery + brachytherapy						
Bogart [20] (1999)	Case series Evidence class III	Surgery + permanent 1^{125}I seeds (n = 15)	Single newly diagnosed BM from NSCLC	14 months	LR only: 2/15 DR only: 2/15 LR + DR: 1/15	Median time to BM recurrence: 9 months
Dagnew [21] (2007)	Case series Evidence class III	Surgery + permanent ^{125}I seeds (n = 26)	Single newly diagnosed BM	17.8 months	# of pts with local control: 25/26 # of pts with DR: 10/26 (38%)	NR
Rogers [16](2006)	Prospective single arm Phase II study Evidence class III	Surgery + GliaSite balloon catheter with 125I (n = 54)	Single newly diagnosed BM	40 weeks	1 yr local control rate: 79% 1 yr distant brain control rate: 50%	Median time to distant brain recurrence: 54 weeks
Schulder [22] (1997)	Case series Evidence class III	Surgery + permanent ^{125}I seeds (n = 13)	Single BM	7.6 months overall; 9 months if exclude two post-op deaths	# of pts with local control: 9/11 # of pts with DR: 7/11	NR

Table 3 continued

First author (year)	Study design/evidence class	Interventions	Population	Median survival	Tumor control	Median time to recurrence/ progression
Surgery + local chemotherapy ± WBRT						
Ewend [15] (2007)	Prospective single arm study Evidence class III	Surgery + carmustine polymer wafers + WBRT (n = 25)	Newly diagnosed single BM	33 weeks	# of pts with LR: 0/25 (0%) # of pts with DR: 4/25 (16%)	NR
Nakagawa [17] (2001)	Prospective single arm study Evidence class III	Surgery + FdUrd intracavitary chemotherapy (n = 6 for BM sub-group)	Single BM	NR	Objective response in brain: Complete response 3/6 No change 1/6 Progressive disease 2/6	NR
Interstitial radiosurgery						
Curry [23] (2005)	Case series Evidence class III	Stereotatic interstitial radiosurgery with photon Radiosurgery system (n = 60)	BM	8 months	Of 59 evaluable BM; 13 BM not assessable Lesion with local control: 48/59 (81%) Lesions with progression: 11/59 (19%)	NR
Nakamura [24] (1994)	Case series Evidence class III	Surgery + intra-operative radiation therapy (n = 43)	Single BM	Median: NR 1 yr survival rate: 53%	# of pts with LR: 7/43 # of pts with DR: 7/43	NR

BM Brain metastases, BR Brain recurrence (local + distant), CR Complete response, DR Distant recurrence in brain, ERC Events review committee, FdUrd 5-fluoro-2'-deoxyuridine, G1 Group 1, G2 Group 2, G3 Group 3, G4 Group 4, KPS Karnofsky performance score, LR Local recurrence at original site in brain, MGd Motexafin-gadolinium, NR Not reported, NS Not significant, NSCLC Non-small cell lung cancer, OR Objective response, PR Partial response, Pts Patients, RCT Randomized control trial, SRS Stereotactic radiosurgery, TMZ Temozolomide, WBRT Whole-brain radiation therapy

Interstitial radiosurgery is defined here as brachytherapy in which the therapy specifically consists of radiation.

Brachytherapy with or without whole brain radiation therapy

One retrospective series [25] looking at three cohorts and two case series [18, 19] met criteria for inclusion of their data in this portion of the guideline.

Retrospective multiple cohort series

In a retrospective cohort study [25] of the temporary implantation of ^{125}I seeds for spherical brain metastases (from a variety of primary sites) 4 cm or smaller in diameter Ostertag et al. looked at three groups of patients that the authors refer to as A, B and C, respectively, with A being temporary ^{125}I seeds and WBRT for patients with newly diagnosed brain metastases, B being temporary ^{125}I seeds alone in patients newly diagnosed with brain metastases, and C being temporary ^{125}I seeds for patients with recurrent brain metastases treated with other modalities first. The chosen dose of interstitial radiation was 60 Gy prescribed to the rim of the lesion(s). The dose of WBRT was chosen to be 40 Gy in 2 Gy daily fractions. In terms of clinical characteristics, three cases with two lesions were treated in the first group, four cases with two lesions were treated in the second group and twelve cases with two lesions were treated in the third group. The groups were balanced except for age. The median age was 55 years, 58 years, and 47 years, by group, respectively, with a statistically significant younger age for the third group. Median survivals for the three groups were 17, 15 and 6 months, respectively. The shorter survivals in those with recurrent and longer standing disease was not considered surprising. The difference between the first two brachytherapy groups (with or without WBRT, respectively) was not significant using Lee–Desu statistic to assess the Kaplan–Meier survival curves. The authors state that the temporary ^{125}I sources utilized in the manner outlined were not associated with radiation necrosis requiring surgery in any case. They go onto advocate "interstitial radiosurgery" as a method of avoiding or postponing WBRT. The properly executed retrospective comparison of the cohorts treated here yielded class II evidence. However, the numbers treated in each group are moderate in nature and no comparison to metastatic tumors treated in a more standard method is provided. Thus, a level 2 recommendation cannot be provided [25].

Case series

In a case series of 19 patients, Alesch et al., describe their use of temporary ^{125}I seeds treating metastases from a variety of primary lesions with a tumor margin dose of 60 Gy. All but one case had one lesion. A mean dose rate of 11 cGy/hour (ranging from 5 to 22 cGy/hour) was used and the mean irradiation time before explantation was 28 days (ranging from 11 to 52 days). They utilized a simplistic plan with only one catheter per lesion. The authors point out the value of biopsy at the time of implant to rule out other processes, which excluded three cases from their series. CT was the predominant modality used for imaging and response assessment, leaving the possibility of other untreated small lesions open to question. The responses were classified as marked reduction (5 cases), slight reduction (11 cases), unchanged (2 cases) and not evaluable (1 case). Marked reduction versus slight reduction was not defined further. One patient had a temporary worsening of an existing hemiparesis. No patient died from neurologic causes. No mention of symptomatic radiation necrosis is provided. As this report is a case series it meets the criteria for class III evidence [18].

In a small series of ten cases of single brain metastases that had recurred at the same site after surgical resection and WBRT Bernstein et al. describe the use of high activity ^{125}I seeds used to administer 70 Gy or more at periphery of the lesion at a median dose rate of 67 cGy/h. Nine of the cases had lung primaries. The median time to tumor recurrence was 35 weeks. Median survival was 46 weeks. Reoperation at the implant site was necessary in three cases because of symptomatic mass effect, two for radiation necrosis and one for mixed tumor and radiation necrosis. Two early deaths occurred from pulmonary emboli. The authors point out that the cases were highly selected and conclude that a more detailed controlled and randomized study compared to other therapies is necessary to assess the real value of this mode of therapy in brain metastases. This case series with no comparative component meets the criteria to provide class III evidence [19]. This and the cases series by Alesch et al. support the feasibility of this modality but do not provide evidence of comparative efficacy necessary to more strongly support its recommendation [18].

Surgery and brachytherapy

One fully published single arm phase II study [16] and three case series [20–22] met criteria for inclusion of their data in this portion of the guideline.

Phase II single arm studies

To look at the efficacy of the Gliasite Radiation Therapy System after surgical resection of single brain metastases Rogers et al. designed a phase II study. This system entails surgical placement of a balloon that is connected to a

reservoir that is implanted subcutaneously. Liquid containing ^{125}I is then inserted postoperatively into the balloon by injection into the reservoir. Patients were required to have a single resected lesion and to have a Karnofsky performance score (KPS) of 70 or above. Fifty-four cases with tumors from a variety of primary sites were enrolled with a median age of 60 and a median KPS of 90. The planned dose of radiation was 60 Gy to a one cm depth from the balloon surface. One year local control rate was the primary outcome assessed and was 79%. Distant brain control at the same interval was 50% with median time to development of those distant lesions being 54 weeks. Histologically confirmed radiation necrosis alone was observed in nine cases and in two others in combination with tumor recurrence. They estimated the actuarial 1 year incidence of radiation necrosis without tumor at 23%. The authors made an attempt to assess functional status noting baseline median Mini-Mental Status Exam scores were 28.5. This remained stable at 29 at 6 months and 12 months amongst the patients still surviving at those intervals. Additionally the median FACT-BR score at baseline was 130 and at 12 months it was 112. Median survival was 40 weeks at the 1 year follow-up point of the report and only four of the 35 deaths that had occurred were due to tumor progression within the central nervous system and all were at sites not treated with the Gliasite. This data was obtained prospectively, but without meaningful concurrent comparative data rendering it class III evidence [16].

Sills et al. provided a preliminary report captured in a conference proceeding search of a series of patients with one to three brain metastases. One lesion was treated with "balloon brachytherapy" (presumably the Gliasite Radiation Therapy System) to a dose of 60 Gy at 5 mm and the other lesions treated with stereotactic radiosurgery. Of the 48 cases reported (of a planned enrollment of 50) one case had local recurrence at 3 months and another at 9 months. Radiation necrosis was confirmed surgically in one case 12 months after treatment and suspected by positron emission tomography in another after 15 months. The primary outcome measures planned were 6 month and 1 year local control and this was not reported. This data was obtained prospectively, but is clearly incomplete and without meaningful concurrent comparative data rendering it as class III evidence [27].

In another preliminary report captured in a conference proceeding search, a study assessing radiation necrosis in brain metastases patients by Burri et al. provided a retrospective look in their practice database of 20 cases that underwent resection followed by Gliasite implantation as initial primary therapy without WBRT. The chosen dose was 60 Gy though the depth of the dose is specified in only seven of the cases. Seven cases required surgical debridement of symptomatic progressive imaging changes that

proved to be radiation necrosis for a crude reoperation rate of 35%. They attempted to estimate an actuarial risk of reoperation in those with radiation necrosis noting it as 7% at 6 months reaching 84% at 24 months with a median time to that operation of 17 months. The authors conclude that radiation necrosis is a substantial risk with the use of the Gliasite device for the dose regimens they used for metastatic disease. The retrospective nature of this series is unable to filter for bias in case selection or nonsurgical management and provides no comparison to other modalities of radiation to determine if their findings are truly out of the ordinary for their practice. Thus this case series with limited clinical background and no comparative component meets the criteria to provide class III evidence [28]. The frequency of radiation necrosis with the use of Gliasite was substantial in the Rogers et al. [16] and the Burri et al. [28] studies. Additionally, the minimally described assessments for radiation necrosis in the Sills et al. [27] study results in the level 3 recommendation that this technique is best utilized in the clinical trial setting for metastatic brain tumors.

Case series

Bogart et al., report a series of 15 cases of solitary metastases from NSCLC treated with surgical resection and permanent ^{125}I seeds implanted on the surface of the tumor bed. Median KPS was 70 and ten of the 15 individuals had the intracranial disease as the only active site. The planned dose was 5 cGy/h with estimated cumulative doses of 80–160 cGy to the tumor bed [29]. Median follow-up and survival was 14 months. The median time to recurrence was 9 months. Recurrences within the brain were local in 2 l, distant in two and both in one. One individual succumbed to an overwhelming fungal infection. None developed symptomatic radionecrosis. The authors conclude that this modality may be useful for selected patients but that further studies in a larger number of patients were warranted [20].

When looking at a series of 26 patients with single brain metastasis with very high performance status (median KPS 90) Dagnew et al. [21], found a median actuarial survival of 17.8 months after surgical resection and placement of permanent low activity ^{125}I seeds with an estimated dose of 150 Gy to the tumor bed resection perimeter taking into account tumor cavity collapse. All cases reportedly had controlled systemic disease from a variety of primary sites. Only one patient had local recurrence and only two died of neurologic disease. Thirty-eight percent developed tumors elsewhere in the brain that on their review was higher than in patients who received WBRT as an initial part of their treatment (as previously seen in studies by Noordijk et al.

[30] and Patchell et al. [31]). One individual had deep venous thrombosis and pulmonary embolus perioperatively. Symptomatic radiation necrosis occurred in two individuals requiring surgical debridement. Both of those patients had tumors that had exceeded 3 cm in greatest diameter (3.1 and 5 cm). This case series with no comparative component meets the criteria to provide class III evidence [21].

In 1997 Schulder et al., reported their experience with 13 cases of brain metastases treated with surgical resection and implantation of permanent low activity ^{125}I seeds. Included were individuals with recurrent tumors having already failed WBRT (8 patients), or who had initially refused WBRT with metastases too large for stereotactic radiosurgery (5 patients). The median calculated dose of ^{125}I was 82 Gy. This was a good performance status group of patients with a mean KPS of 84 and absent or stable systemic disease. Two patients died early; one who required evacuation of a hematoma in the resection cavity on the day after implantation then died of pulmonary embolus 2 weeks later and one with postoperative adult respiratory distress syndrome. The mean survival of the remaining 11 was 9 months and all had local control. One individual required surgery for symptomatic radiation necrosis and another for a combination of tumor and radiation necrosis. One patient developed a symptomatic cerebrospinal fluid leak requiring repair. This case series with no relative comparison to another therapy meets the criteria to provide class III evidence [22]. The high early mortality rate in this small study suggests that the use of low activity ^{125}I seeds in brain metastases should be relegated to properly conducted clinical trials.

Surgery and local chemotherapy with or without whole brain radiation therapy

Two single arm studies [15, 17] met the criteria for inclusion of their data in this portion of the guideline.

In an assessment of an alternative modality to local radiation therapy, Ewend et al., described their experience with a prospectively evaluated group of 25 cases of newly diagnosed solitary metastatic tumors in good performance status patients treated with surgical resection and Gliadel wafer implantation followed by WBRT (44 Gy in 22 fractions). The primary goal was to assess toxicity of this combination therapy, and the serious toxicities reported included seizures ($n = 1$), seizures and respiratory failure ($n = 1$), and the moderate toxicities included nausea ($n = 2$), constipation ($n = 3$), right eye pain ($n = 1$) and fever ($n = 1$). Median follow-up was 36.1 weeks and at that point median survival was 33 weeks. No local recurrences were reported but four patients developed distant intracranial recurrences and two patients had new metastases in the spinal canal. Of the 16 deaths observed five were neurologic in nature. This data was obtained prospectively, but without meaningful concurrent comparative data rendering class III evidence [15].

In a study of the feasibility of intracavitary 5-fluoro-2′-deoxyuridine (FdUrd) Nakagawa et al., report on six brain metastases patients in a series of 13 cases with malignant brain tumors. They point out that the goal of the use of this agent is to inhibit tumor DNA synthesis by its metabolite 5-fluoro-2'deoxy-5'-monophosphate. After claiming to show intrathecal administration of FdUrd was safe, the authors placed an Ommaya reservoir in "small" fresh resection cavities and then administered 25–30 daily injections of 1–5 micrograms. They report no adverse events and three complete responses (of 3, 10 and 32 weeks, respectively), one with stable disease and two with progressive disease. However, median follow-up time is not reported. This data was obtained prospectively, but with less than usual detail on pretreatment and post-treatment data and is without meaningful concurrent comparative data rendering it as class III evidence [17].

Interstitial radiosurgery

Two case series [23, 24] met the criteria for inclusion of their data in this portion of the guideline. To assess a device termed the Photon Radiosurgery System (PRS), Curry et al., describe its use in the treatment of 60 patients with metastatic brain tumors; 37 with solitary lesions and 23 with multiple lesions. They describe the device as a light weight x-ray generator that produces a point source of low-energy photons. The median age of the subjects was 58 years (range of 18–83 years) and median KPS was 90. Prior treatment was variable. PRS was applied in cases not deemed suitable for resection due to location or which were undergoing diagnostic biopsy. Seven lesions were larger than 3 cm in diameter and only one in the entire series was in the cerebellum. The device was introduced utilizing a stereotactic frame. The median dose was 16 Gy to a point 2 mm beyond the enhancing tumor margin. The authors chose to report local control as their primary outcome and did so after a median follow-up of 6 months (with a range of 5 days to 31 months). Seventy-two lesions were treated. Local control was present in 81%. Median survival was 8 months from treatment. Of the 46 cases that went onto death, 30% were neurologic in nature. Four patients experienced perioperative seizures that were easily controlled with anticonvulsant medications and were not recurrent, three experienced transient neurological deficits thought to be associated with the biopsy or due to treatment induced cerebral edema, and two experienced biopsy related hemorrhages. Three patients experienced symptomatic radiation necrosis requiring surgical debridement and corticosteroid therapy. This case series with no concurrent comparison to another therapy meets the criteria to provide class III evidence [23].

In an attempt to avoid WBRT as an initial treatment in patients with metastatic brain tumors Nakamura et al., reported a case series of 43 patients whose solitary lesions were treated with intraoperative radiosurgery with high-energy electron beams generated by a 20 MeV betatron. Therapy was delivered over 5–10 min to a dose of 18–25 Gy with 8–16 MeV to one cm beyond the margins of a fresh resection bed. They also mention that progression was treated with additional radiation but this was not standardized. One year survival was 53%. Median follow-up was not reported, but seven patients developed local recurrence and seven patients developed brain recurrences distant from the primary site. Two individuals developed radiation necrosis at the treatment site but were managed without surgery. The authors discuss other patients treated for brain metastases at their institution utilizing various combinations of therapy but fail to provide systematic pretreatment and follow-up data so as to make a meaningful comparison. Thus the data from this paper qualifies as class III evidence [24].

Interstitial therapy summary

Interstitial therapies are appealing as their intent is to maximize treatment of the metastatic pathology and preserve surrounding normal tissue. The data presented here does not allow creation of level 1 or level 2 recommendations. The interstitial use of radiation and cytotoxic chemotherapy appears feasible but not without toxicity. Furtherance of these modalities will be dependent on truly prospective and comparative study designs in order to obtain meaningful information.

New chemotherapeutic agents

Review of the literature provided 31 unique studies that met the criteria for support of guidelines recommendations regarding the use of chemotherapeutic agents in the management of brain metastases (Table 4). The use of temozolomide was reported in 25 studies of which two were evidence class I studies [32, 33], two were evidence class II studies [34, 35], and 21 were evidence class III studies [36–56]. In most of the studies included in this discussion the primary tumor treated was melanoma, though other primary tumor sites were addressed.

Temozolomide

Prospective randomized phase II studies

In the first of the class I studies Antonadou et al., carried out a randomized phase II study of 48 individuals with lung cancer, breast cancer or unknown primaries. Group 1 received WBRT to 40 Gy in 2 Gy fractions and group 2 received oral temozolomide (TMZ, 75 mg/m^2/d) concurrent with WBRT 40 Gy in 2 Gy fractions and then continued TMZ therapy (200 mg/m^2/d) for 5 days every 28 days for an additional maximum of 6 cycles after WBRT was completed. The clinical and pathologic characteristics of the groups were well balanced. The response rate in group 2 was 96% as opposed to 67% in group 1, a significant difference ($p = 0.017$). This better response rate was at the cost of significantly more nausea and vomiting in group 2. There was no grade 3 or grade 4 myelosuppression. However, median survival was 7.0 months in group 1 and 8.6 months in group 2, a difference that did not reach significance [32].

The second class I study by Verger et al., was also a randomized phase II study of patients with newly diagnosed brain metastases from any source. Group 1 received 30 Gy WBRT in 10 fractions and group 2 received 30 Gy WBRT in 10 fractions with concurrent TMZ during radiation (75 mg/m^2/day), followed by two cycles of TMZ (200 mg/m^2/day) for 5 days of a 28 day cycle. The clinical and pathology characteristics of each group were not significantly different. Progression free survival from brain metastases 90 days after randomization was 72% in group 2 and 54% in group 1, a statistically significant advantage ($p = 0.03$). Also group 1 had a greater percentage dying a neurologic death (69%) than in group 2 (41%), again a significant difference ($p = 0.029$). Despite these differences, there was no advantage in median survival of group 2 over group 1 (4.5 months and 3.1 months, respectively) and no difference in response rates. Additionally, clinically significant toxicity was only observed in group 2 [33]. In summary, neither of these well done randomized phase II studies demonstrated a meaningful benefit to survival by adding TMZ.

Retrospective cohort analyses

Both of the class II studies regarding the use of TMZ were retrospective cohort analyses [34, 35]. In the first study Panagioutou et al., described their experience with 64 patients with melanoma brain metastases. Four groups were evaluated according to treatment. Group A was treated with surgery followed by WBRT, Group B was treated with TMZ at initial diagnosis and with WBRT at progression, Group C was treated with WBRT alone, and Group D received supportive care alone. The median survivals were 12, 5, 3, and 2 months, respectively. The survival in the TMZ at initial diagnosis and WBRT at progression group was significantly greater than the WBRT alone group ($p = 0.0267$ by log rank). Patient characteristics influenced treatment selection. Age and intracranial

Table 4 Summary of primary chemotherapy studies

First author (year)	Study design/ evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/ progression
TMZ						
Abrey [36] (2001)	Prospective single arm phase II study Evidence class III	TMZ (n = 41)	Recurrent/progressive BM	6.62 months	Response in brain: Complete response 0/41 (0%) Partial response 2/41 (4.9%) Stable disease 15/41 (36.6%) Progressive disease 17/41 (41.5%) Not assessed 7/41 (17.1%)	Overall in brain: 1.97 months
Addeo [37] (2007)	Prospective single arm phase II study Evidence class III	WBRT + TMZ (n = 59)	Newly diagnosed BM	13 months	Response in brain: OR 44% (CR: 5/59; PR 21/59) Stable Disease: 19/59 (32.3%) Progressive Disease: 14/59 (23.7%)	Median time to progression: 9 months
Agarwala [38] (2004)	Prospective single arm phase II study Evidence class III	TMZ (n = 151)	Newly diagnosed BM from melanoma	3.2 months	Response in brain: OR 6% (CR 1/151; PR 8/151) Stable disease: 40/151 (26%) Progressive disease: 73/151 (48%) Not evaluable: 29/151 (19%)	Median progression free survival: Pts with prior chemo: 1 month Chemo naïve pts: 1.2 months
Antonadou [32] (2002)	Randomized phase II trial Evidence class I	G1: WBRT (n = 23) G2: WBRT + TMZ (n = 25)	BM from lung, breast or unknown primary	G1: 7.0 months G2: 8.6 months (Survival curves: log-rank; p = NS)	Response rate in brain: (Of evaluable pts) G1: OR 67% (CR 7/21, PR 7/21) G2: OR 96% (CR 9/24, PR 14/24) (p = 0.017)	NR
Bafaloukos [39] (2004)	Sub-group analysis of two Phase II studies Evidence class III	TMZ-based chemotherapy (n = 25)	BM from melanoma	4.7 months	Response in brain: OR 24% (CR 0/25; PR 6/25) Stable disease 5/25 Progressive disease 13/25 Not evaluable 1/25	Median time to progression: 2 months
Boogerd [40] (2006)	Sub-group analysis of three prospective studies Evidence class III	TMZ ± immunotherapy (n = 52 with BM)	BM from melanoma	5.6 months	Response in brain: Only reported for sub-group of 13/52 pts who had a response to TMZ at extra-cranial sites: Complete response 3/13 Partial response 2/13 Stable disease 6/13	NR overall
Caraglia [41] (2006)	Prospective single arm phase II study Evidence class III	TMZ + pegylated liposomal doxorubicin (n = 19)	BM	10 months	Response in brain: OR36.8% (CR 3/19; PR 4/19) Stable Disease 8/19 (42.1%) Progressive Disease 4/19 (21%)	Median progression-free survival: 5.5 months

Table 4 continued

First author (year)	Study design/ evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/ progression
Christodoulou [42] (2005)	Prospective single arm phase II study. Evidence class III	TMZ + cisplatin (n = 32)	Recurrent/progressive BM	5.5 months	Response both in brain + Extra-cranial sites: Complete response 1/32; Partial response 8/32; Partial response in brain only 1/32; Stable disease 5/32; Progressive disease 6/32; Not evaluable 11/32	Median time to progression for all pts: 2.9 months
Christodoulou [43] (2001)	Prospective single arm phase II study. Evidence class III	TMZ (n = 28)	BM	4.5 months	Response in brain: Objective response 4% (CR 0/27; PR 1/27); Stable disease 4/27; Progressive disease or death: 14/27; Not assessable: 3/27	Median time to progression: 3 months
Conill [34] (2006)	Retrospective cohort study. Evidence class II	G1: 20 Gy/5 fractions + TMZ based chemotherapy (n = 11); G2: 30 Gy/10 fractions + TMZ based chemotherapy (n = 10)	Newly diagnosed BM from melanoma	G1: 4.0 months G2: 4.0 months (Survival curves: log-rank; $p = NS$)	Data not reported by group; No statistically significant difference between groups ($p = NS$)	NR
Cortot [56] (2006)	Prospective single arm phase II study. Evidence class III	TMZ + cisplatin followed by WBRT (n = 50: 68% had WBRT)	Newly diagnosed BM from NSCLC	5 months	Response in brain: Objective response (CR 2%; PR 10%); Stable disease: 42%; Progressive disease: 40%; Not assessable: 6%	Median time to progression: 2.3 months
Giorgio [44] (2005)	Prospective single arm phase II study. Evidence class III	TMZ (n = 30)	Recurrent/progressive BM from NSCLC	6 months	Response in brain: Complete response 2/30 (6.7%); Partial response 1/30 (3.3%); Stable disease 3/30 (10%); Progressive disease 24/30 (80%)	Median time to progression of brain metastases in all pts: 3.6 months
Hofmann [45] (2005)	Case series. Evidence class III	TMZ ± SRS or WBRT (n = 35)	BM from melanoma	8 months	Response in brain + extra-cranial sites: (Of 34 evaluable pts) Complete remission: 1/34 (3%); Partial remission: 2/34 (6%); Stable disease: 9/34 (26.4%); Mixed response (PR or stable disease in brain, but extra-cranial disease progression): 5/34 (14.7%); Progressive disease: 17/34 (50%)	Median progression free survival: 5 months

Table 4 continued

First author (year)	Study design/evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/progression
Hwu [46] (2005)	Prospective single arm phase II study. Evidence class III	TMZ + thalidomide ($n = 26$)	Recurrent/progressive BM from melanoma	5 months	Response in brain: Complete response 2/26; Partial response 1/26; Minor response/stable: 7/26; Progressive disease: 4/26; Unknown 1/26; Not assessable 11/26	Median duration of response or stable disease in brain: 4 months
Iwamoto [47] (2008)	Prospective single arm phase II study. Evidence class III	TMZ + vinorelbine ($n = 38$)	Recurrent/refractory BM	5 months	Response in brain: Objective response 5% (CR 1/38; minor response 1/38); Stable disease 5/38; Progressive disease 29/38; Not evaluable 2/38	Median progression free survival: 1.9 months
Janinis [48] (2000)	Prospective single arm study. Evidence class III	TMZ ($n = 11$)	BM from melanoma	NR	Response in brain: (Of 8 pts evaluable) Partial response 1/8; Minor response 3/8; Stable disease 1/8; Progressive disease: 3/8	NR
Kouvaris [49] (2007)	Prospective single arm phase II study. Evidence class III	WBRT + TMZ ($n = 33$)	Newly diagnosed BM	12 months	Response in brain: After 3 cycles of TMZ: OR 54.5% (CR 7/33; PR 11/33); After 6 cycles of TMZ: OR 57.6% (CR 8/33; PR 11/33)	Median progression-free survival: 11 months
Krown [50] (2006)	Prospective single arm phase II study. Evidence class III	TMZ + thalidomide ($n = 16$)	BM from melanoma	23.9 weeks	Response in brain: OR 0/16 (ITT analysis)	Progression-free survival: 7.3 weeks
Larkin [51] (2007)	Prospective single arm phase I/II study. Evidence class III	TMZ + lomustine ($n = 26$)	BM from melanoma	2 months	Response in brain: (In phase II; $n = 20$) Response rate 0/20	NR
Margolin [52] (2002)	Prospective single arm phase II study. Evidence class III	TMZ + WBRT ($n = 31$)	BM from melanoma	6 months	Response in brain: OR 9.7% (CR 1/31; PR 2/31)	Median progression-free survival: 2 months

Table 4 continued

First author (year)	Study design/ evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/ progression
Omuro [53] (2006)	Prospective single arm phase I study Evidence class III	TMZ + vinorelbine ($n = 21$)	Recurrent/progressive BM	17 weeks	Response in brain: (Of 18 evaluable pts) Partial response 1/18 Minor response 1/18 Stable disease 6/18 Progressive disease 10/18	NR
Panagiotou [35] (2005)	Retrospective cohort study Evidence class II	G1: Surgery + WBRT ($n = 5$) G2: TMZ (initial tx) + WBRT (after progression) ($n = 17$) G3: WBRT ($n = 28$) G4: Supportive care ($n = 14$)	BM from melanoma	G1: 12 months G2: 5 months G3: 3 months G4: 2 months (Survival curves G2 vs. G3 log-rank; $p = 0.0267$)	NR	NR
Rivera [54] (2006)	Prospective single arm phase I study Evidence class III	TMZ + capecitabine ($n = 24$)	BM from breast cancer	NR	Response in brain: (Of 22 evaluable pts) OR 18% (CR1/22; PR 3/22) Minor response or stable disease 11/22 Progressive disease 7/22	Median time to progression of brain metastases: 12 weeks
Schadendorf [55] (2006)	Prospective single arm phase II study Evidence class III	TMZ ($n = 45$)	BM from melanoma	4.1 months	Response in brain: Objective response 4.4% (CR 0/45; PR 2/45) Stable disease 5/45 Progressive disease 33/45 Not evaluable 5/45	NR overall
Verger [33] (2003)	Randomized phase II trial Evidence class I	G1: WBRT ($n = 41$) G2: WBRT + TMZ ($n = 41$)	Newly diagnosed BM	G1: 3.1 months G2: 4.5 months (Survival curves: log-rank; $p = $ NS)	Response in brain at 30 days: (by ITT) G1: OR 32% (CR 2/41, PR 11/41) G2: OR 32% (CR 2/41, PR 11/41) ($p = $ NS) Response in brain at 90 days: G1: OR 2/41 (CR 0/41, PR 2/41) G2: OR 7/41 (CR 1/41, PR 6/41) ($p = $ NS)	Median: Not reported % BM progression-free at 90 days: G1: 54% G2: 72% ($p = 0.03$)

Fotemustine

Table 4 continued

First author (year)	Study design/ evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/ progression
Bröcker [60] (1996)	Prospective single arm study; Evidence class III	WBRT + fotemustine (n = 13)	Progressive multiple BM from melanoma	Overall: Not reported; Pts with partial response/stable disease: 6 months; Other pts: 2 months	Response in brain: (12 evaluable pts); Complete response: 0/13; Partial response 4/13; Stable disease 3/13; Progressive disease 6/13; Not assessable: 1/13	NR
Chang [61] (1994)	Prospective single arm phase II study; Evidence class III	Dacarbazine + fotemustine (n = 34)	BM from melanoma	4.5 months	Response in brain: OR 12% (CR 2/34; PR 2/34); Stable disease 9/34	NR
Cotto [62] (1996)	Prospective single arm phase II study; Evidence class III	Fotemustine + Cisplatin (n = 31)	BM from NSCLC	16 weeks	Response in brain: (Of 25 evaluable pts); OR 16% (CR 2/25; PR 2/25)	NR
Jacquilat [63] (1990)	Prospective single arm phase II study; Evidence class III	Fotemustine (n = 39)	BM from melanoma	26 weeks	Response in brain: Objective response 28% (CR 2/39; PR 9/39); Stable disease 9/39; Progressive disease 19/39	NR
Mornex [59] (2003)	RCT; Evidence class I	G1: Fotemustine (n = 39); G2: Fotemustine + WBRT (n = 37)	BM from melanoma	G1: 86 days; G2: 105 days; (Survival curves: log-rank; p = NS)	Response rate in brain at day 50 (by ITT); G1: OR 5.1% (CR 0/39, PR 2/39); G2: OR 8.1% (CR 0/37, PR 3/37); (p = NS)	Median time to progression in brain: G1: 49 days; G2: 80 days; (BM progression-free curves; Wilcoxon: p = 0.03; log-rank: p = 0.069)
Ulrich [64] (1999)	Case series; Evidence class III	WBRT + fotemustine ± dacarbazine (n = 12)	BM from melanoma	Median: NR; Mean survival of responders: 8.2 months	Response in brain: Complete remission 4/12; Partial remission 2/12	Median: NR; Mean progression free survival: 6.1 months

BM Brain metastases, *BR* Brain recurrence (local + distant), *CR* Complete response, *DR* Distant recurrence in brain, *ERC* Events review committee, *FdUrd* 5-fluoro-2'-deoxyuridine, *G1* Group 1, *G2* Group 2, *G3* Group 3, *G4* Group 4, *LR* Local recurrence at original site in brain, *MGd* Motexafin-gadolinium, *NR* Not reported, *NS* Not significant, *NSCLC* Non-small cell lung cancer, *OR* Objective response, *PR* Partial response, *Pts* Patients, *RCT* Randomized control trial, *SRS* Stereotactic radiosurgery, *TMZ* Temozolomide, *WBRT* Whole-brain radiation therapy

extent of disease were not well balanced and performance status was not assessed [35]. In a study that mainly looked at differing radiation doses Conill et al., reviewed a group of 21 individuals with melanoma brain metastases who were treated with WBRT (20 Gy in 5 fractions) and TMZ-based chemotherapy ($n = 11$), or WBRT (30 Gy in 10 fractions) and TMZ-based chemotherapy ($n = 11$). The actual chemotherapy regimens varied substantially, with some patients receiving other agents in addition. The extent of disease and performance status was reasonably well balanced between the two groups and the median survival in both groups was 4 months [34]. Again, in these class II studies, one cannot conclude TMZ imparts a survival advantage.

Prospective phase II studies

Among the 21 remaining studies qualifying for inclusion in this guideline all were class III data. Five were prospective phase II studies in which TMZ was utilized alone [36, 38, 43, 44, 55]. Agarwala et al., reported their prospective experience with 151 patients with newly diagnosed brain melanoma metastases treated with TMZ (150 mg/m^2/day for patients with prior chemotherapy, or 200 mg/m^2/day for chemotherapy naïve patients, for 5 days, every 28 days for 1 year or until disease progression or unacceptable toxicity). Median survival was 3.2 months and objective response (complete response or partial response) was noted in 6% [38]. Schadendorf et al., treated 45 individuals with known melanoma who had developed new brain metastases with TMZ (125 mg/m^2/day in patients who had received prior chemotherapy or 150 mg/m^2/day in previously untreated patients, on days 1–7 and days 15–21 very 28 days). Median survival was 4.1 months with two partial responses and five patients with stable disease [55]. In another study of newly diagnosed brain metastases Christadoulou et al. looked at individuals with a wide variety of primaries that had already received substantial systemic therapy for their cancer. All ($n = 28$) received TMZ (150 mg/m^2/day for 5 days every 4 weeks until progression or unacceptable toxicity). Median survival in the entire group was 4.5 months with only one partial response [43]. Abrey et al., looked at 41 individuals with recurrent or progressive brain metastases from various primaries (22 were NSCLC) treated with TMZ (patients who had received chemotherapy before received TMZ 150 mg/m^2/day for 5 days, and chemotherapy naïve patients received 200 mg/m^2/day for 5 days with treatment cycles repeated every 28 days). Two partial responses were observed. Overall median survival was 6.62 months in all participants [36]. Giorgio et al., looked at a series of patients with NSCLC whose brain metastases had progressed after WBRT and one regimen of chemotherapy

($n = 30$). Two complete responses and one partial response were reported. Median survival was six months [44]. Though individuals with NSCLC seemed to survive slightly longer than those with melanoma in these five studies no meaningful comparison or statistical assessment can support such a conclusion.

In a sixth prospective single armed study Janinis reported on 11 patients with melanoma brain metastases who had not received radiotherapy, who were treated with TMZ (200 mg/m^2/day for 5 days every 28 days for chemotherapy naïve patients and 150 mg/m^2/day for 5 days every 28 days for patients treated with prior chemotherapy). Survivals ranged from 10 days to over 13 months but no median was reported [48]. Though this publication met the criteria for being included in this guideline, the small size and lack of comparative data does not yield information that provides direction for therapy in brain metastases.

In three of the prospective phase II studies yielding class III data, TMZ was used with WBRT [37, 49, 52]. Margolin et al., assessed 31 individuals with newly diagnosed melanoma brain metastases treated with TMZ at 75 mg/m^2/day started on day 1 and continued daily for 6 weeks and then repeated every 10 weeks along WBRT to a total dose of 30 Gy in 10 fractions on days 1–5 and 8–12. Though all cases had a WHO performance status of 0 or 1 the median survival was just 6 months and only one complete response and two partial responses were observed [52]. In a more recent study Addeo et al., describe the use of WBRT to a dose of 30 Gy in 10 fractions with concomitant TMZ (75 mg/m^2/day) for 10 days, and subsequent TMZ (150 mg/m^2/day every 28 days) for up to 6 cycles in 59 patients with newly diagnosed brain metastases from various sources. Median survival was 13 months with 5 complete responses and 21 partial responses being noted to yield a 44% objective response rate. In another study looking at brain metastases from a variety of primary sites, Kouvaris et al., reported the use of combined therapy with WBRT to a total dose of 36 Gy in 12 fractions given in 16 days along with TMZ 60 mg/m^2/day (days 1–16) followed by 6 cycles of TMZ (200 mg/m^2/day for 5 consecutive days every 28 days). Median survival was 12 months with seven complete responses and 11 partial responses being noted for an overall objective response rate of 54.5% with the objective response rate in patients with lung cancer being 78.6%. Interestingly, 45.5% of individuals in this study experienced hepatotoxicity, attributed to the use of anticonvulsants in these patients [49]. The improved survival seen here and in the Addeo et al., study as opposed to the Margolin study may be more related to the underlying primary tumor histologies than to the advantage provided by the alteration in the TMZ administration [37, 49, 52].

One other prospective phase II study of WBRT and TMZ also included the use of cisplatin but with both

cytotoxic agents administered before radiation [56]. Cortot et al., studied 50 patients with NSCLC brain metastases treated with TMZ (200 mg/m^2/day for 5 days every 28 days) and cisplatin (75 mg/m^2) on day 1 of each cycle, for up to 6 cycles followed by WBRT to a total of 30 Gy in 10 fractions. WBRT was performed at time of progressive disease (at any time) or in patients with stable disease after 4 cycles. Median survival was 5 months and one complete response and five partial responses were noted [56]. Though methodological differences prevent meaningful comparisons between this and the studies of Addeo, Kouvaris and Margolin, the addition of cisplatin did not appear to provide an overt survival or response benefit.

In the six remaining prospective phase II studies TMZ was used in combination with a variety of other systemic agents [41, 42, 46, 47, 50, 51]. These included thalidomide, cisplatin, vinorelbine, pegylated liposomal doxorubicin, and lomustine utilized for a variety of tumor types and at either new diagnosis or at recurrence. Median survival was as short as 2 months in the report by Larkin et al., who utilized TMZ at 150 mg/m^2 on days 1 through 5 every 28 days and lomustine 60 mg/m^2 on cycle day 5 every 56 days in patients with newly diagnosed melanoma brain metastases[51]. The longest median survival in this group of six studies was 10 months in the report of Caraglia et al., who used TMZ at 200 mg/m^2 on days 1 through 5 and pegylated liposomal doxorubicin at 35 mg/m^2 on day 1 of every 28 day cycle for up to 8 cycles in individuals with progressive metastases failing initial therapy. In this study, only one individual had a melanoma primary[41]. Here again, the underlying characteristics of the different studies are too disparate to allow meaningful comparisons to establish the superiority or inferiority of one regimen to another. They do, however, reflect the known poor prognosis of patients with melanoma once intracranial metastases develop [41, 42, 46, 47, 50, 51].

Prospective phase I studies

There were two prospective phase I studies utilizing TMZ and other management in the series of papers meeting this guideline's criteria [53, 54]. In the first Omuro et al., describe the use of 28 day cycles of TMZ at 150 mg/m^2 on days 1 through 7 and 15 through 21 and vinorelbine on days 1 and 8 using escalating doses with a starting dose of 15 mg/m^2 with increments of 5 mg/m^2 for each cohort of 3–6 patients until 30 mg/m^2. The maximum tolerated dose was declared at 30 mg/m^2 and, though not a primary goal of the study, it was noted median survival of the patients treated was 17 weeks [53]. In the other study Rivera et al., looked for a maximum tolerated dose of TMZ and capecitabine. Four sequential cohorts were treated at different dosing levels on days 1 through 5 and days 8 through 12 with cycles repeated every 21 days. Respective dosing ranges of capecitabine and TMZ were 1600–2000 mg/m^2 and 50–150 mg/m^2. Maximum tolerated dose was not reached. No median survival was reported but, among the 24 cases enrolled one complete response and two partial responses were noted [54]. Though these two studies meet criteria for inclusion in these guidelines, they add little to development of a consensus on how TMZ, alone or in combination with other agents would play a role in the therapy of brain metastases.

Combined subgroup analyses from multiple publications

Two of the studies involving TMZ therapy of brain metastases were subgroup analyses combined from prior prospective studies [39, 40]. Bafaloukos et al., combined the data from two publications of the Hellenic Cooperative Oncology Group evaluating patients with melanoma brain metastases. Twenty-five individuals treated with TMZ at a dose of 150–200 mg/m^2/day on days 1 through 5 every 4 weeks alone or with either docetaxel (80 mg/m^2 on day 1) or cisplatin (75 mg/m^2 on day 1). Median survival combining all patients was 4.7 months. Six partial responses were observed distributed between the three groups. No obvious superiority of one regimen was discerned over another [39, 57, 58]. In the publication by Boogerd et al., data was combined from three different studies. Fifty-two patients with brain metastases were evaluable who were treated with TMZ at doses from 150 to 250 mg/m^2/day for 5 days every 4 weeks followed by immunotherapy granulocyte–macrophage-colony stimulating factor (2.5 μg/kg), interleukin-2 (4 MIU/m^2), and IFNα (5 MIU fixed dose) for 12 days ($n = 23$) or who were treated with TMZ alone (200 mg/m^2/day for 5 days every 4 weeks) ($n = 29$). Out of the 52 patients the authors focused on the 13 with evidence of systemic response noting that their neurologic stabilization or responses seemed to be more meaningful. The median survival for all 52 was 5.6 months. The authors were unable to conclude the superiority of one regimen over the other [40].

Retrospective case series

The last class III study qualifying for inclusion in this guideline was a simple retrospective case series of 35 patients, all treated with TMZ (200 mg/m^2 for 5 days every 28 days) with 12 receiving stereotactic radiosurgery and with ten receiving WBRT. Median survival was 8 months with one complete response and two partial responses

observed; the longest duration being 16 months. The authors concluded the results were "favorable" but appropriately did not attempt to compare the groups for superiority [45].

Fotemustine

The use of fotemustine was addressed in six studies, one of which was evidence class I [59] and five of which were evidence class III [60–64]. Five of the six included only brain metastases from melanoma [59–61, 63, 64].

Randomized controlled study

The study by Mornex et al., was a randomized controlled study of 76 individuals with brain metastases from melanoma yielding class I data. Group 1 received fotemustine intravenously at a dose of 100 mg/m^2 on days 1, 8, and 15 followed by a 5 week rest period followed by a single dose every 3 weeks thereafter. Group 2 received the same dosage regimen of fotemustine with the addition of WBRT at a dose 37.5 Gy delivered in 15 fractions over 3 consecutive weeks. Gender, age, extent of systemic disease, and number of intracranial metastases were balanced. The performance status of group 2 was significantly better than in group 1 ($p = 0.019$). Utilizing intent to treat analysis there was no difference in survival, response rate (complete responses combined with partial responses) or tumor control (defined as complete responses combined with partial responses and stable disease) between the two groups. Median time to cerebral progression was longer in the patients treated with both being 49 days in group 1 and 80 days in group 2 ($p = 0.069$) [59]. No newer studies of fotemustine in this patient group have met criteria for inclusion in this guideline.

Prospective single armed phase II studies

In the class III studies an array of uses of this therapy and subsequent outcomes can be found. In one study using fotemustine alone for brain metastases from melanoma Jacquilat et al., described 39 individuals who had a median survival of 26 weeks from initiation of therapy. There were two complete responses and nine partial responses with the median duration of response being 11 weeks. The promising nature of this study, published prior to the other studies meeting criteria for inclusion in this guideline, likely spurred the additional investigations that have been noted [63]. Brocker et al., reported the use of WBRT and fotemustine in 13 patients with melanoma brain metastases not amenable to surgery or stereotactic radiotherapy, with seven achieving partial response or stable disease. Among

those seven median survival was 6 months and survival in the rest was 2 months [60]. In a somewhat larger study Chang et al., combined fotemustine with dacarbazine in a group of 34 patients with brain metastases from melanoma whose median survival was 4.5 months [61]. Cotto et al., reported a series of 31 individuals with brain metastases from NSCLC treated with fotemustine plus cisplatin. Twenty-five cases were evaluable for response with two achieving complete response and two achieving partial response. Median survival was reported as 16 weeks [62]. Hematologic toxicity in both the Chang and the Cotto studies was in excess of that seen with the use of fotemustine alone as noted by Jacquilat [61–63].

Case series

Ulrich et al., reported their case series of 12 patients with brain metastases from melanoma who were treated with induction therapy of fotemustine at 100 mg/m^2 once a week with simultaneous WBRT to a total dose ranging from 32 to 58 Gy followed by maintenance treatment with 100 mg/m^2 fotemustine every 4 weeks thereafter. Two of the 12 individuals received dacarbazine 200 mg/m^2 on days 3 and 5 of the first 2 weeks. Six individuals had complete or partial intracranial remission and amongst those the mean survival was 8.2 months [64]. Grade 3 or 4 thrombocytopenia was seen in four cases and grade 3 or 4 leukopenia was seen in four cases. The variation in radiation doses and systemic chemotherapy (16% of cases receiving dacarbazine) results in the data from this publication being classified as class III.

Chemotherapy agent summary

Although class I, II and III data could be discerned from the literature regarding the use of TMZ and fotemustine in the treatment of brain metastases, meaningful survival benefit could only be demonstrated when subjected to rigorous analysis in patients with melanoma metastases when added to WBRT. There were numerous reports of individuals who benefited in one form or another from the use of these agents and it cannot be concluded that there might not be a specific circumstance where TMZ or fotemustine are of value in the therapy of brain metastases. To improve this situation, investigations of these and other systemically administered agents is clearly warranted.

Molecular targeted agents

Review of the literature provided six unique studies that met the criteria for support of guidelines recommendations

regarding the use of molecular targeted agents in the management of brain metastases (Table 5).

There is only class III evidence that a molecular targeted agent, gefitinib, results in partial response or stable disease in approximately 80–90% of patients with brain metastases due to NSCLC.

Recent advances in the treatment of many malignancies have frequently been due to the incorporation of molecular targeted agents into the treatment regimen. In NSCLC the two categories of molecular targeted agents that have received the most attention are agents targeting the epidermal growth factor or angiogenesis pathways [65, 66]. The use of RECIST criteria [67] to measure tumor response to these agents likely underestimates their effectiveness since prolonged tumor stabilization has been noted with these agents.

Epidermal growth factor inhibiting agents

Gefitinib inhibits numerous tyrosine kinases, including the epidermal growth factor receptor (EGFR). It can be given orally and was approved for use in advanced NSCLC. Erlotinib is another widely used tyrosine kinase inhibitor of the EGFR receptor. Cetuximab is a monoclonal antibody to the EGFR receptor and is currently being evaluated in locally advanced and advanced NSCLC.

Table 5 summarizes the case reports [68–70] and small single arm prospective studies [71–73] of gefitinib for patients with brain metastases from NSCLC. Most of these have demonstrated tumor response or stabilization in the majority of the patients treated. However, it is not generally used in patients as first line treatment for symptomatic brain metastases and there is no evidence that it should be used instead of WBRT or other conventional treatments [68–73].

An area of ongoing research is in the predictive value of EGFR mutations in NSCLC [74]. In eight patients with brain metastases from lung cancer, Shimato et al., reported the association of EGFR mutations with a higher rate of tumor response/stabilization with gefitinib in a small number of patients. Most of these patients had previously undergone WBRT and this complicated the attribution of tumor response or stabilization to gefitinib alone [70].

Angiogenic-inhibiting agents

Agents targeting the angiogenesis pathway include thalidomide and bevacizumab. Bevacizumab is a monoclonal antibody against vascular epidermal growth factor receptor (VEGFR). Elevated VEGFR has been linked with development of brain metastases in murine models of NSCLC [75]. There are no prospective studies of anti-angiogenesis

agents for brain metastases in humans in part due to concern regarding the possibility of treatment-related intracranial bleeding. Prospective studies that have shown a survival benefit with bevacizumab in patients with non-squamous NSCLC excluded patients with known brain metastases [76]. A recently presented study by Akerly et al., concluded that the use of bevacizumab along with cytotoxic chemotherapy agents resulted in only one central nervous system hemorrhage in a group of 85 patients with non-small cell carcinoma and known brain metastases [77]. More studies have been proposed to evaluate the safety of bevacizumab in patients with brain metastases who undergo WBRT but no data meeting the criteria for inclusion in a recommendation are available.

Molecular targeted agent summary

The molecular underpinnings of tumor growth are better understood than ever in the past, but translation of this information to the treatment of brain metastases has not yet resulted in robust improvement in treatment outcome parameters. Isolated cases of treatment response have been observed with epidermal growth factor inhibiting agents and angiogenic-inhibiting agents. By no means should agents related to epidermal growth factor or vascular endothelial growth factor be viewed as the only candidates for the targeted therapies of brain metastases. Larger prospective and comparative studies, likely combined with more standard therapies, will be necessary to determine if such targeted agents will really contribute to tumor control and improved survival.

Investigational therapy summary

Not surprisingly, the clinical work done thus far with newer treatment modalities for metastatic brain tumors has not provided data that immediately translates into level 1 recommendations. Some progress has been made in defining the roll of TMZ in the management of brain metastases and it is clear that though there is a role it is limited as noted in the level 2 recommendation provided. Much of the clinical investigative work completed and published simply defines new problems and challenges with the techniques and agents that can be addressed in studies with properly asked questions. Thus, investigations to improve upon weaknesses identified in the above discussion continue to be reported. For example, demonstration of ongoing research activity for molecular targeted agents such as the assessment of gefitinib efficacy, as well as on a number of other fronts, is evidenced

Table 5 Summary of molecular targeted agents

First author(year)	Study design/evidence class	Interventions	Population	Median survival	Tumor response	Median time to recurrence/progression
Gefitinib						
Ceresoli [71] (2004)	Prospective single arm study. Evidence class III	Gefitinib (n = 41)	BM from NSCLC	5 months	Objective response in brain: 10% (CR 0/41; PR 4/41) Stable disease: 7/41	Median progression-free survival: 3 months
Chiu [72] (2004)	Prospective single arm study. Evidence class III	Gefitinib (n = 21) for BM sub-group	BM from NSCLC	NR for BM sub-group	Of 8 pts with measurable BM Objective response in brain: 50% (CR 0/8; PR 4/8) (Stable disease 3/8	Median progression free survival: 3.9 months
Hotta [68] (2004)	Case series. Evidence class III	Gefitinib (n = 14 for BM sub-group)	NSCLC; data extracted for BM sub-group	NR for BM subgroup	Objective response in brain: 43% (CR 1/14, PR 5/14) Stable disease 8/14 Objective response at extra-cranial sites: 7/14	NR
Namba [69] (2004)	Case series. Evidence class III	Gefitinib (n = 15)	BM from NSCLC	8.3 months	Objective response in brain: 60% (CR 1/15; PR 8/15) Stable disease 2/15	NR
Shimato [70] (2005)	Case series. Evidence class III	Gefitinib (n = 8)	BM from NSCLC	NR	Objective response in brain: 5/8 pts Of the 5 pts with an objective response: 3 pts classified as effective with gefitinib as response was in the setting of an uncontrollable BM or new BM after radiotherapy	NR
Wu [73] (2007)	Prospective single arm phase II study. Evidence class III	Gefitinib (n = 40)	BM from NSCLC sub-type adenocarinoma	15 months	Objective response in brain: 38% (CR 1/40; PR14/40) Stable disease 18/40 Progressive disease 7/40	Median progression free survival: 9.0 months

BM Brain metastases, *BR* Brain recurrence (local + distant), *CR* Complete response, *DR* Distant recurrence in brain, *ERC* Events review committee, *FdUrd* 5-fluoro-2'-deoxyuridine, *GI* Group 1, *G2* Group 2, *G3* Group 3, *G4* Group 4, *LR* Local recurrence at original site in brain, *MGd* Motexafin-gadolinium, *NR* Not reported, *NS* Not significant, *NSCLC* Non-small cell lung cancer, *OR* Objective response, *PR* Partial response, *Pts* Patients, *RCT* Randomized control trial, *SRS* Stereotactic radiosurgery, *TMZ* Temozolomide, *WBRT* Whole-brain radiation therapy

through reports at national meetings [78]. Even when no specific positive level 1 recommendations can be made, it is still appropriate to encourage enrollment in properly designed and conducted clinical trials of new treatment modalities and agents.

Key issues for future investigation

New modalities in the therapy of metastatic brain tumors need not be limited to the radiation therapy, radiation sensitizers, chemotherapy and molecular targeted agents mentioned in this guideline. Assessment of alternative types of radiation, improved radiation planning systems, improved radiation and chemotherapy targeting systems and assessment of other tumor metabolic pathways for targeting are critical to making progress against this broad ranging disease. Enrollment of patients in properly conducted studies of each of these agents and modalities is warranted in order to learn their true value.

Use of nanoparticle technology for identifying tumors, targeting therapy and assessing response early in therapy warrants particular attention. Investigation of other methods of molecular imaging, for instance with MRI or positron emission tomography, may result in better methods of early detection of therapeutic efficacy or failure helping to minimize time wasted on ineffective treatments. Improved radiation and systemic treatment planning and targeting may decrease toxicity to normal cerebral tissue improving quality of life even though disease control may not be impacted.

An exhaustive list of biologic issues that should be addressed in the therapy of cerebral metastases cannot be provided here but the following highlights should serve as inspiration to motivated investigators. Though EGFR and VEGFR are recognized as being important in many tumor types, they are but one avenue by which disordered molecular signaling provides proliferative advantage. Metastatic tumor cell resistance to standard alkylating agents is yet to be addressed effectively, especially in the central nervous system. The importance of tumor stem cells in metastatic brain lesions has yet to be defined in detail. Though the blood brain barrier is not generally an issue in larger brain metastases, the possibility of smaller clusters of cells with growth potential being shielded from therapy by this structure must be investigated.

The following is a list of major ongoing or recently closed randomized clinical trials pertaining to the use of emerging therapies that evaluate treatment comparisons addressed by this guideline paper for the management of brain metastases.

1. Temozolomide for Treatment of Brain Metastases From Non-Small Cell Lung Cancer (Study P03247AM3) (COMPLETED)

Official title: A Randomized, Open-Label Phase 2 Study of Temozolomide Added to Whole Brain Radiation Therapy Versus Whole Brain Radiation Therapy Alone for the Treatment of Brain Metastasis From Non-Small Cell Lung Cancer
Status: Completed
Clinicaltrials.gov Identifier: NCT00076856
Principal Investigator: Not provided
Location: Not provided
Sponsors and Collaborators: Schering-Plough

2. Study of Temozolomide in the Treatment of Brain Metastasis From Non-Small-Cell Lung Cancer (Study P02143) (COMPLETED)
Official title: A Phase II Study of Temozolomide (SCH 52365) in Subjects with Brain Metastasis from Non-Small-Cell Lung Cancer
Status: Completed
Clinicaltrials.gov Identifier: NCT00034697
Principal Investigator: Not provided
Location: Not provided
Sponsors and Collaborators: Schering-Plough

3. Safety and Tolerability of Low-Dose Temozolomide During Whole Brain Radiation in Patients With Cerebral Metastases From Non-Small-Cell Lung Cancer (Study P04071) (TERMINATED)
Official title: Randomized Phase II Study: Temozolomide (TMZ) Concomitant to Radiotherapy Followed by Sequential TMZ in Advanced NSCLC Patients With CNS Metastasis Versus Radiotherapy Alone
Status: Terminated (Phase II)
Clinicaltrials.gov Identifier: NCT00266812
Principal Investigator: Not provided
Location: Not provided
Sponsors and Collaborators: Schering-Plough, AES-CA Pharma GmbH

4. Radiation Therapy With or Without Temozolomide in Treating Patients With Non-Small Cell Lung Cancer That is Metastatic to the Brain
Official title: A Phase II Study Of Temozolomide (SCH 52365) In Subjects With Brain Metastasis From Nonsmall Cell Lung Cancer
Status: Active, not recruiting (Phase II)
Clinicaltrials.gov Identifier: NCT00030836
Principal Investigator: Lauren E. Abrey, MD, Memorial Sloan-Kettering Cancer Center
Location: United States
Sponsors and Collaborators: Memorial Sloan-Kettering Cancer Center, National Cancer Institute (NCI)

5. Temozolomide With or Without Radiation Therapy to the Brain in Treating Patients With Stage IV Melanoma That Is Metastatic to the Brain
Official title: Temozolomide Versus Temozolomide + Whole Brain Radiation In Stage IV Melanoma

Patients With Asymptomatic Brain Metastases
Status: Active, not recruiting (Phase III)
Clinicaltrials.gov Identifier: NCT00020839
Principal Investigator: Juergen C. Becker, MD, PhD Universitaets-Hautklinik Wuerzburg
Location: Europe (33 locations)
Sponsors and Collaborators: European Organization for Research and Treatment of Cancer

6. Radiation Therapy Combined With Either Gefitinib or Temozolomide in Treating Patients With Non-Small Cell Lung Cancer and Brain Metastases
   Official title: Whole Brain Radiotherapy in Combination With Gefitinib (Iressa) or Temozolomide (Temodal) for Brain Metastases From Non-Small Lung Cancer (NSCLC) A Randomized Phase II Trial
   Status: Recruiting (Phase II)
   Clinicaltrials.gov Identifier: NCT00238251
   Principal Investigators: Study Chair: Gianfranco Pesce, MD Oncology Institute of Southern Switzerland
   Investigator: Roger Stupp, MD Centre Hospitalier Universitaire Vaudois
   Location: Switzerland
   Sponsors and Collaborators: Swiss Group for Clinical Cancer Research

7. Radiation Therapy and Stereotactic Radiosurgery With or Without Temozolomide or Erlotinib in Treating Patients With Brain Metastases Secondary to Non-Small Cell Lung Cancer
   Official title: A Phase III Trial Comparing Whole Brain Radiation And Stereotactic Radiosurgery Alone Versus With Temozolomide Or Erlotinib In Patients With Non-Small Cell Lung Cancer And 1–3 Brain Metastases
   Status: Recruiting (Phase III)
   Clinicaltrials.gov Identifier: NCT00096265
   Principal Investigators:
   Paul Sperduto, MD, MAPP Park Nicollet Cancer Center
   Minesh P. Mehta, MD University of Wisconsin, Madison
   H. I. Robins, MD, PhD University of Wisconsin, Madison
   Location: United States and Canada (56 locations)
   Sponsors and Collaborators: Radiation Therapy Oncology Group, National Cancer Institute (NCI)

8. Comparison Study of WBRT and SRS Alone Versus With Temozolomide or Erlotinib in Patients With Brain Metastases of NSCLC
   Official title: A Phase III Trial Comparing Whole Brain Radiation (WBRT) and Stereotactic Radiosurgery (SRS) Alone Versus With Temozolomide or Erlotinib in Patients With Non-Small Cell Lung Cancer and 1–3 Brain Metastases

Status: Recruiting (Phase III)
Clinicaltrials.gov Identifier: NCT00268684
Principal Investigator: Felix Bokstein, M.D. Tel-Aviv Sourasky Medical Center
Location: Israel
Sponsors and Collaborators: Tel-Aviv Sourasky Medical Center, RTOG

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Disclosures All panel members provided full disclosure of conflicts of interest, if any, prior to establishing the recommendations contained within these guidelines.

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