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Special Article

Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline

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Abstract

Purpose: To systematically review the evidence for the radiotherapeutic and surgical management of patients newly diagnosed with intraparenchymal brain metastases.

Methods and Materials: Key clinical questions to be addressed in this evidence-based Guideline were identified. Fully published randomized controlled trials dealing with the management of newly diagnosed intraparenchymal brain metastases were searched systematically and reviewed. The U.S. Preventative Services Task Force levels of evidence were used to classify various options of management.

Results: The choice of management in patients with newly diagnosed single or multiple brain metastases depends on estimated prognosis and the aims of treatment (survival, local treated lesion control, distant brain control, neurocognitive preservation).

Single brain metastasis and good prognosis (expected survival 3 months or more): For a single brain metastasis larger than 3 to 4 cm and amenable to safe complete resection, whole brain radiotherapy (WBRT) and surgery (level 1) should be considered. Another alternative is surgery and radiosurgery/radiation boost to the resection cavity (level 3). For single metastasis less than 3 to 4 cm, radiosurgery alone or WBRT and radiosurgery or WBRT and surgery (all based on level 1 evidence) should be considered. Another alternative is surgery and radiosurgery or radiation boost to the resection cavity (level 3). For single brain metastasis (less than 3 to 4 cm) that is not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered (level 1). For nonresectable single brain metastasis (larger than 3 to 4 cm), WBRT should be considered (level 3).

Multiple brain metastases and good prognosis (expected survival 3 months or more): For selected patients with multiple brain metastases (all less than 3 to 4 cm), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered, based on level 1 evidence. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered (level 3).

Patients with poor prognosis (expected survival less than 3 months): Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT (level 3).

It should be recognized, however, that there are limitations in the ability of physicians to accurately predict patient survival. Prognostic systems such as recursive partitioning analysis, and diagnosis-specific graded prognostic assessment may be helpful.

Conclusions: Radiotherapeutic intervention (WBRT or radiosurgery) is associated with improved brain control. In selected patients with single brain metastasis, radiosurgery or surgery has been found to improve survival and locally treated metastasis control (compared with WBRT alone).

Introduction

Brain metastases represent a significant health care problem. It is estimated that 20% to 40% of cancer patients will develop brain metastases during the course of their illness.[1]

Systematic reviews based on randomized phase III controlled trials for the management of single or multiple brain metastases in adult patients have been published.[1-8] Various treatment modalities exist, including whole brain radiotherapy (WBRT), resection, stereotactic radiosurgery, and best supportive care with the use of dexamethasone. A series of articles performing a systematic review and evidence-based clinical practice guidelines have been published from the perspective of the modalities listed above under the auspices of the American Association of Neurological Surgeons/Congress of Neurosurgeons (AANS/CNS).[4-8] The conclusions from this American Society for Radiation Oncology (ASTRO) Guideline are congruent with the conclusions put forth by the AANS/CNS. While these articles are important in that they are modality-based, it was also felt important to develop guidelines from an international perspective with international representation on the Brain Metastases Task Group. Additional key questions are posed (not necessarily previously addressed) such as prognostic classification systems, radiotherapy fractionation schemes, comparison of surgery and radiosurgery, neurocognition as an outcome variable in decision-making, palliative supportive care, and radiation sensitizers.

Treatment recommendations are based on patient factors (such as age, performance status), tumor factors (such as number and size of brain metastases, tumor type, extracranial disease activity), and available treatment options (such as access to neurosurgery or stereotactic radiosurgery).

This Guideline builds on the previous ASTRO Health Services Research Committee publication, "The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases."[1] This present guideline has been endorsed by the CNS.

Methods and materials

Process

The Guidelines Subcommittee of the Clinical Affairs and Quality Committee, in accordance with established ASTRO policy, recruited a Task Group composed of recognized experts in the fields of radiotherapy, surgery, and radiosurgery for brain metastases. These experts represent radiation oncology, neurosurgery, physics, outcomes, and health services research. The Task Group was asked to systematically review the literature on the radiotherapeutic and surgical management for patients with newly diagnosed metastatic disease to the brain.

In June 2009, the ASTRO Board of Directors approved a proposal to develop a Guideline on radiotherapeutic and surgical management for newly diagnosed brain metastases. In January 2010, the Board authorized the Task Group membership. The Task Group participated in a series of communications by e-mail and conference calls to review the relevant publications, to discuss controversial issues, and formulate the Guidelines contained herein. The Task Group agreed by consensus on the various recommendations based on the randomized trials and relevant publications. The initial draft of the manuscript was reviewed by 3 expert reviewers and was placed on the ASTRO website during the month of April 2011 for public comment. Upon integration of the feedback, the document was then submitted to the ASTRO Board of Directors for their final review and approval in October 2011.

Literature search

MEDLINE (1966-Nov. 3, 2010), EMBASE (1980-2010 week 46), and the CENTRAL databases (issue 4, 2010) were searched (Appendix 1). The search strategies resulted in 1826 publications, 597 publications, and 425 publications from MEDLINE, EMBASE, and CENTRAL, respectively (search strategy courtesy of the Cochrane Library). Only randomized phase III trials pertinent to the management of newly diagnosed brain metastases were included. Trials dealing with the use of WBRT, surgery, radiosurgery, chemotherapy, radiosensitizers, and palliative care alone were considered. Trials that examined the use of prophylactic cranial irradiation were excluded. A total of 36 randomized controlled trials were retrieved. One trial was excluded as it was published in abstract form in the year 2000 but never fully reported.[9] Two duplicate publications of the same trial[10,11] were included.

Lead representatives from international radiation oncology groups, ASTRO, Canadian Association of Radiation Oncology (CARO), European Society for Therapeutic Radiology and Oncology (ESTRO), and Trans-Tasman Radiation Oncology Group (TROG), reviewed the 36 retrieved trials.

As a result of feedback received from public comments, the literature search was further expanded to include nonrandomized studies (prospective or retrospective) dealing with the use of either radiosurgery or fractionated radiation to the postoperative surgical cavity. The MEDLINE (1947 to May week 2, 2011) search resulted in 1549 nonrandomized publications and EMBASE (1980-2011 week 20) gave 3721 nonrandomized publications. The CENTRAL search resulted in 0 randomized controlled trials. Titles and abstracts were screened and a final total of 15 relevant publications were retrieved.

Of note, all the radiosurgery trials used frame-based single fraction radiosurgery techniques with either a linear accelerator or gamma knife unit.

Management options were graded by the level of evidence available using the U.S. Preventative Services Task Force levels.[12] Due to the lack of high-quality studies, management of patients with recurrent metastatic disease to the brain is not included in this report.

The U.S. Preventative Services Task Force levels of evidence[12] are as follows.

> Level I: Evidence obtained from at least 1 properly designed randomized controlled trial.
> Level II-1: Evidence obtained from well-designed controlled trials without randomization.
> Level II-2: Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than 1 center or research group.
> Level II-3: Evidence obtained from multiple time series with or without the intervention.

Dramatic results from uncontrolled trials might also be regarded as this type of evidence.

> Level III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

The medical management issues associated with brain metastases will not be addressed by this Guideline as they are outside the scope of this review. Optimal follow-up brain imaging for patients with brain metastases has not been evaluated using high-quality trials. Based on expert opinion, in patients with good prognostic features and where there is potential for future salvage brain metastases treatment, enhanced magnetic resonance imaging follow-up every 2 to 4 months should be considered.

Results

Table 1 and Table 2 summarize common scenarios related to patients presenting initially with either single or multiple brain metastasis(es). These tables include not only the level 1 evidence but also other treatment options based on panel opinion and supported by literature of lower quality evidence.

Table 1 Single brain metastasis—initial management

Prognostic category ([a])	Other features	Treatment options (evidence grade) references	Clinical benefit			
			S	LC	WB control	Neurocognition
Good prognosis Expected survival 3 mo or more	Complete resection possible	If brain metastasis ≤3-4 cm: • Surgery and WBRT (level 1)[10,11,22,23,42,43,b]	✓	✓	✓	
		• Radiosurgery and WBRT (level 1)[51,53]	✓	✓	✓	
		• Radiosurgery alone (Level 1)[23,54]		✓		✓
		• Surgery with radiosurgery/radiation boost to the resection cavity with or without WBRT (level 3)[26-41,b]		✓	✓ (with WBRT)	
		If brain metastasis >3-4 cm: • Surgery and WBRT (level 1)[10,11,22,23,42,43,b]	✓	✓	✓	
		• Surgery with radiosurgery/radiation boost to the resection cavity with or without WBRT (level 3)[26-41,b]		✓	✓ (with WBRT)	
Good prognosis Expected survival 3 mo or more	Not resectable	If brain metastasis ≤3-4 cm: • Radiosurgery and WBRT (level 1)[51,53]	✓	✓	✓	
		• Radiosurgery alone (level 1)[23,54]		✓		✓
		If brain metastasis >3-4 cm: • WBRT (level 3), with consideration of biopsy, if primary unknown[59,85,86]	✓	✓	✓	
Poor prognosis Expected survival less than 3 mo		• WBRT (level 3)[59,85]		✓	✓	
		• Palliative care without WBRT (level 3)[59,85]				

KPS, Karnofsky performance status; LC, local control; S, survival; WB, whole brain; WBRT, whole brain radiotherapy.
Surgery may be favored if the diagnosis is uncertain (eg, no known primary cancer or remote history of cancer and no known extracranial metastases or metastasis).

[a] Prognostic category based on known prognostic factors (see clinical question 1, references 13-21).

[b] Excluding radiosensitive histologies (eg, small cell lung cancer, leukemia, lymphoma, germ cell tumor). A 6%-9% minority of patients in Radiation Therapy Oncology Group (RTOG) 9508 trial had small cell lung cancer.

The questions and guideline statements regarding the radiotherapeutic and surgical management for newly diagnosed brain metastases are listed below.

1. What prognostic factors are important for assessing and managing patients with newly diagnosed brain metastases?

Interpretative summary

Several prognostic indices have been reported in the literature[13-21] for survival duration among patients with newly diagnosed brain metastases. These are useful in categorizing patients into survival time strata for treatment decisions, for predicting the results of therapeutic interventions, and for comparing treatment results.

The Radiation Therapy Oncology Group (RTOG) devised 3 prognostic groups using recursive partitioning analysis[13,14] based on 1200 patients treated on prospective clinical trials with WBRT alone or additionally with radiosensitizers: class I, patients with Karnofsky performance status (KPS) ≥70 years, less than 65 years of age with controlled primary (3-month stability on imaging or newly diagnosed), and no extracranial metastases; class III, KPS <70; class II, All others. Median survival was 7.1 months, 4.2 months, and 2.3 months for class I, II, and III, respectively.

Brain metastases are a heterogeneous population. The purpose of the graded prognostic assessment (GPA) was to identify significant diagnosis-specific prognostic factors in an updated era (1985-2007) as compared with the RTOG recursive partitioning analysis (RPA) (1979-1993). The original GPA was based on 4 criteria[15]: age, KPS, number of brain metastases, and presence or absence of extracranial metastases. Each of the 4 criteria is given a score of 0, 0.5, or 1.0 and these 4 scores are summed to determine the GPA score. Patients with the best prognosis have a GPA score of 4.0. The authors established this prognostic index based on 1960 patients treated with WBRT alone, WBRT and radiosensitizers, or WBRT and radiosurgery in the

Table 2 Multiple brain metastases-initial management

Prognostic category ([a])	Other features	Treatment options (evidence grade) references	Clinical benefit			
			S	LC	WB control	Neurocognition
Good prognosis Expected survival 3 mo or more	All brain metastases ≤3-4 cm[b]	• Radiosurgery and WBRT (level 1)[51,53] • Radiosurgery alone[23,54] (level 1) • WBRT (level 1)[59,85]		✓ ✓ ✓	✓ ✓	 ✓
Good prognosis	Brain metastasis/ metastases causing significant mass effect[c]	• Safe surgical resection of the brain metastasis/metastases causing significant mass effect and postoperative WBRT (level 3)[25,b]		✓	✓	
Expected survival 3 mo or more		• WBRT (level 3)[59,85]	✓	✓	✓	
Poor prognosis Expected survival less than 3 mo		• WBRT (level 3)[59,85] • Palliative care without WBRT (level 3)[59,85]		✓	✓	

KPS, Karnofsky performance status; LC, local control; S, survival; WB, whole brain; WBRT, whole brain radiotherapy.
Surgery may be favored if the diagnosis is uncertain (eg, no known primary cancer or remote history of cancer and no known extracranial metastases or metastasis).

[a] Prognostic category based on known prognostic factors (see clinical question 1, references 13-21).

[b] Excluding radiosensitive histologies (eg, small cell lung cancer, leukemia, lymphoma, germ cell tumor). A 6%-9% minority of patients in RTOG 9508 trial had small cell lung cancer.

[c] The maximum number or total volume of brain metastases best treated with radiosurgery (or surgery) is unknown. Randomized trials which have examined the use of radiosurgery, included selected patients with up to 4 brain metastases, while retrospective reports document use of radiosurgery that exceed 4 brain metastases.[52,55] A retrospective study[25] suggested that surgery significantly improves survival if all brain metastases can be removed.

RTOG database, with all patients and data coming from prospective clinical trials.

The GPA was then refined based on a multi-institutional analysis of 4259 other patients with brain metastases treated with surgery, WBRT, radiosurgery, or various treatment combinations. New diagnosis-specific prognostic indices (diagnosis-specific graded prognostic assessment) were defined based only on the

Table 3 Diagnosis-specific GPA[15,20,21]

GPA	Significant prognostic factors	GPA scoring criteria				
NSCLC/SCLC		0	0.5		1	
	Age	>60	50-60		<50	
	KPS	<70	70-80		90-100	
	ECM	Present	—		Absent	
	#BM	>3	2-3		1	
Melanoma/RCC		0	1		2	
	KPS	<70	70-80		90-100	
	#BM	>3	2-3		1	
Breast cancer		0	0.5	1.0	1.5	2.0
	KPS	<60	60	70-80	90-100	
	ER/PR/Her2	Triple negative		ER/PR + Her2 -	ER/PR – Her2 +	Triple positive
	Age	≥ 70	<70			
GI		0	1	2	3	4
	KPS	<70	70	80	90	100

ECM, extracranial metastases; ER, estrogen receptor; GPA, graded prognostic assessment; Her2, human epidermal growth factor receptor 2; KPS, Karnofsky performance status; #BM, number of brain metastases; NSCLC, non-small cell lung cancer; PR, progesterone receptor; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

Table 4 Median survivals stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed brain metastases[15,20,21]

Diagnosis	Overall median survival (mo)	Diagnosis-specific GPA			
		GPA: 0-1 Median survival (mo)	GPA: 1.5-2.0 Median survival (mo)	GPA: 2.5-3.0 Median survival (mo)	GPA: 3.5-4.0 Median survival (mo)
NSCLC	7.0	3.0	5.5	9.4	14.8
SCLC	4.9	2.8	4.9	7.7	17.1
Melanoma	6.7	3.4	4.7	8.8	13.2
Renal cell	9.6	3.3	7.3	11.3	14.8
GI	5.4	3.1	4.4	6.9	13.5
Breast	13.8	3.4	7.7	15.1	25.3
Total	7.2	3.1	5.4	9.6	16.7

GI, gastrointestinal; GPA, graded prognostic assessment; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

statistically significant prognostic factors for each individual diagnosis.[20] A subsequent analysis of 400 breast cancer patients refined the breast-GPA scoring system.[21]

Table 3 shows the GPA scoring criteria for each of the significant prognostic factors by diagnosis. Table 4 shows the associated range of median survival by GPA and diagnosis.

Other prognostic indices such as the score index for radiosurgery, the basic score for brain metastases, the Golden grading system, and the Rades prognostic scoring system have also been published.[16-19]

Caveats

Most published randomized trials that deal with the management of patients with brain metastases included patients with various primary cancers (non-small cell lung cancer, breast cancer, etc). Physicians should consider histology-specific indices in regard to clinical decision making. The use of histology-specific indices help guide estimated prognosis, useful in deciding on whether aggressive therapies (eg, radiosurgery, surgery) for selected patients should be considered (Tables 1 and 2). At present, there are insufficient level 1 data to recommend protracted WBRT schedules for certain histologies or higher radiosurgery doses for "radioresistant" lesions (such as melanoma, renal cell carcinoma). Future clinical trials should consider these histology-specific indices for purposes of stratification.

It should be noted that the original RTOG RPA system did not find histology to be statistically significant for survival prediction. However, the revised GPA has found histology to be statistically significant based on retrospective data in a more recent era (1985-2007) compared with the database used to derive the RTOG RPA (1979-1993). The difference may be due to newer and more effective chemotherapy used to treat systemic disease.

Newly diagnosed brain metastases: Single brain metastasis, role for surgery

2. For patients with single brain metastasis (excluding radiosensitive histologies such as small cell lung cancer, leukemia, lymphoma, and germ cell tumor), does surgical resection and whole brain radiotherapy improve survival or brain control compared with whole brain radiotherapy alone or compared with surgical resection alone?

Interpretative summary

For selected patients with good performance status (eg, KPS $\geq$70), limited extracranial disease, and a resectable brain metastasis, complete resection of the single brain metastasis improves the probability of extended survival. The addition of postoperative whole brain radiotherapy improves treated brain metastasis control and overall brain control without improving overall survival or duration of functional independence. These interpretations are consistent with the AANS guidelines on the use of surgery.[5]

Phase III randomized trials evidence summary

WBRT and surgery versus WBRT alone

Three randomized controlled trials[10,11,42,43] examined the use of WBRT with or without resection for a single brain metastasis. [References 10 and 11 are duplicate publications of the same trial]. Two of the 3 trials[10,11,43] found significant improvement in survival with the addition of surgery to WBRT as compared with WBRT alone.

The benefit for surgery may be lost in patients with poor prognostic factors such as advanced extracranial disease or lower performance status. Decreased median

survival was reported in 2 randomized trials[10,11,42] in patients with a greater systemic involvement of their primary malignancy. Noordijk et al[10] reported a 5-month median survival in patients with progressive systemic disease in both the WBRT plus surgery versus WBRT alone arms. Patients with stable systemic disease had a 12-month survival with WBRT and surgery versus 7 months with WBRT alone. Mintz et al[42] reported a significant difference ($P = .009$) in the Cox regression analysis for mortality in patients having extracranial metastases versus no evidence of primary tumor (risk ratio 2.3). Forty-five percent of the patients in the study by Mintz et al[42] had extracranial metastases compared with only 37.5% in the trial by Patchell et al[43] and 31.7% in the trial by Vecht et al.[11]

WBRT and surgery versus surgery alone

Two randomized trials[22,23] have been completed that found a significant improvement in brain control (primary endpoint) in patients treated with WBRT and surgery as compared with surgery alone. The first trial[22] showed that postoperative WBRT significantly prevented brain recurrence at the site of the original metastasis (10% vs 46%, $P < .001$) and at other sites in the brain (14% vs 37%, $P < .01$). The authors found no difference in survival with the use of WBRT and surgery versus surgery alone, although the study was not powered for survival (a secondary endpoint of this trial).[22]

The second trial,[23] the European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 study, found that WBRT reduced the 2-year relapse at the initial site of surgery from 59% to 27% ($P < .001$), and at new sites from 42% to 23% ($P = .008$). In addition, salvage therapies were used more frequently after observation, compared with after WBRT.[23]

Caveats

There are 2 completed randomized trials that examine WBRT and surgery versus surgery alone.[22,23] The first trial[22] was small and not powered for survival. The second trial by the EORTC[23] included patients randomized to receive postoperative WBRT. A total dose of 30 Gy in 10 fractions at 3 Gy per fraction within 6 weeks of surgery was administered.

The Trans-Tasman Radiation Oncology Group trial (TROG 98.05) was closed early due to poor accrual.[24] The accrual target was a total of 130 patients. The authors reported on the 9 patients randomized to observation after surgery or radiosurgery and 10 patients randomized to WBRT after surgery or radiosurgery for single brain metastasis. However, no conclusions could be made from this severely underpowered study.

No prospective studies have evaluated whether resection of more than one metastasis conveys meaningful clinical benefit. A retrospective case control series suggests the hypothesis that resection of multiple metastases may convey a similar benefit as conferred by resection of a single brain metastasis.[25] Furthermore, the benefit of excising multiple brain metastases causing mass effect has not been definitively proven with level 1 evidence. However, it was felt by the guideline authors that safe resection of multiple brain metastases causing mass effect should be included as an option for good prognosis patients.

There is a lack of level 1 evidence relating to the use of surgery and radiation boost to the surgical cavity with or without WBRT, although there are publications (with lower level of evidence) supporting its use.[26-41] Fourteen publications[27-40] reported on the use of surgery and local radiation (radiosurgery in 10 series and conformal fractionated radiation therapy in 4 series), with the rationale to defer or avoid WBRT, without compromising survival. One publication reported on the use of surgery, WBRT, and radiosurgery to the surgical cavity, with the rationale to maximize whole brain and local tumor bed control.[26]

However, due to the paucity of randomized data, it is unknown whether the omission of postoperative WBRT (with a strategy of close radiographic and clinical follow-up and the use of salvage radiosurgery or WBRT at relapse) reduces neurocognitive decline compared with patients undergoing immediate postoperative WBRT. On the other hand, in a post hoc analysis of a randomized trial, distant brain metastases recurrence (a higher risk with radiosurgery alone) may have a bigger impact on neurocognitive decline.[57]

Newly diagnosed brain metastases: Single brain metastasis, surgery versus radiosurgery

3. Is survival or brain control different in selected patients with single brain metastasis (excluding radiosensitive histologies such as small cell lung cancer, leukemia, lymphoma, and germ cell tumor) treated with surgery or radiosurgery?

Interpretative summary

There have been no high quality randomized trials that have assessed whether selected patients with a small single brain metastasis, in surgically accessible sites, should undergo radiosurgery or resection. Adding WBRT did not improve overall survival or functional independence.

Evidence summary

WBRT and surgery versus radiosurgery alone

One trial[44] randomized patients with single (less than 3 cm) resectable brain metastasis to resection plus WBRT versus radiosurgery alone. Due to poor patient accrual, the

trial was stopped early and reported 33 patients in the surgery and WBRT arm and 31 patients in the radiosurgery alone arm. This trial was too underpowered for any conclusions to be made.

WBRT and radiosurgery versus WBRT and surgery

One randomized trial examined the use of radiosurgery and WBRT versus surgery and WBRT.[45] This trial was closed due to slow accrual. Results were reported for 11 patients randomized to radiosurgery and WBRT and 10 patients randomized to surgery and WBRT. Unfortunately, the trial was too underpowered to make any conclusions.

There have been 2 retrospective series[46,47] and 2 retrospective matched pair analyses[48,49] that examined the use of WBRT and radiosurgery versus WBRT and surgery for a single brain metastasis. These publications suggested no difference in overall survival between the 2 study groups.

Radiosurgery for "radioresistant" histologies

A phase II trial of radiosurgery for 1 to 3 newly diagnosed brain metastases (4 cm or less in maximum dimension) from histologies (renal cell carcinoma, melanoma, and sarcoma) that historically have been deemed radioresistant to fractioned external beam radiotherapy, was reported by the Eastern Cooperative Oncology Group.[50] Thirty-one eligible patients were treated with radiosurgery alone. Three-month intracranial failure with radiosurgery alone was 25.8%; in-field failure rate at 3 months was 19.3%.

Distant intracranial failure rate at 3 months was 32.2%. Survival was consistent with other published series of similar patients treated with surgery, radiosurgery, WBRT, or a combination of these therapies. The intracranial relapse rate was moderately high in this study of patients treated with radiosurgery alone. Whether surgery has better local control or survival as compared with radiosurgery for "radioresistant" single brain metastasis could not be answered by this study due to lack of direct comparisons with a surgical group.

Caveats

In good prognosis patients with single brain metastasis (less than 3 to 4 cm in maximum dimension and amenable to gross total resection), either surgery or radiosurgery may be considered. Surgery may be favored in patients with unknown primary, or in patients with single brain metastasis causing significant mass effect. In good prognosis patients with single brain metastasis less than 3 to 4 cm in maximum dimension (in eloquent brain areas not amenable to safe total resection or in patients who are unfit for surgery), radiosurgery may be considered.

Newly diagnosed brain metastases: Single or multiple brain metastasis(es), WBRT with or without radiosurgery boost

4. Is there a survival or brain control difference in patients treated with WBRT and radiosurgery boost versus WBRT alone?

Interpretative summary

For good prognosis patients with single brain metastases (less than 4 cm in size, in patients with good performance status and controlled extracranial disease), the use of radiosurgery added to WBRT improves survival, treated brain lesion control, and overall brain control as compared with WBRT alone.

In good prognosis patients with multiple brain metastases (all less than 4 cm in size and up to 4 brain metastases in number), radiosurgery boost when added to WBRT improves treated brain lesion and overall brain control as compared with WBRT alone. As there is no survival advantage with radiosurgery added to WBRT in patients with multiple brain metastases, WBRT alone may be considered.

One randomized trial[51] (RTOG 9508) that included patients with up to 3 brain metastases found an improvement in KPS and decreased steroid use at 6 months with the use of radiosurgery boost added to WBRT. These interpretations are consistent with the AANS guidelines on the use of radiosurgery boost.[7]

Phase III randomized trials evidence summary

WBRT alone versus WBRT and radiosurgery boost

The multi-institutional, cooperative RTOG 9508 trial[51] examined the use of WBRT and radiosurgery boost (n = 167) versus WBRT alone (n = 164). This trial included selected patients with 1 to 3 newly diagnosed brain metastases with a maximum diameter of 4 cm (for the largest lesion) and additional lesions not exceeding 3 cm in diameter. Median survival was significantly improved in patients with single brain metastasis treated with radiosurgery boost (6.5 months) as compared with 4.9 months in patients treated with WBRT alone. Higher response rates at 3 months and better control of treated lesions at 1 year were observed in the WBRT and radiosurgery group versus WBRT alone (82% vs 71%, $P = .01$).

One single institution fully published trial[53] stopped at an interim evaluation of 60% accrual (14 patients randomized to WBRT alone and 13 patients randomized to WBRT plus radiosurgery). There was no survival benefit with the use of radiosurgery boost as compared with WBRT alone in patients with multiple brain metastases. Patients treated with WBRT and radiosurgery boost were reported to have better brain control versus those patients treated with WBRT alone.

Caveats

None of the trials have examined validated quality of life outcomes with patients managed with WBRT alone versus WBRT and radiosurgery boost. Given no expected survival benefit, either option of WBRT alone with possible salvage treatment or upfront WBRT and radiosurgery boost may be offered for selected patients with multiple brain metastases. It is unclear from these published trials whether there is benefit with radiosurgery boost to more than 4 lesions.

However, there are level 3 data on patients undergoing radiosurgery for 4 or more intracranial metastases suggesting a survival benefit, and that total intracranial volume rather than number of brain metastases may be the more important predictor of survival.[52] At present, there are insufficient high-quality data on whether certain histologies benefit from the use of radiosurgery to treat more than 4 intracranial metastases.

When new brain metastases are seen on the planning scan the day of radiosurgery, it may be reasonable to proceed and complete the radiosurgical procedure to all the lesions visualized even if they exceed a total of 4 brain metastases. Alternatively, not performing radiosurgery and proceeding with WBRT would also be considered a reasonable option in these patients.

Newly diagnosed brain metastases: Single or multiple brain metastasis(es), radiosurgery alone versus WBRT and radiosurgery

5. Is there survival, brain control difference, or neurocognitive difference in patients treated with radiosurgery alone versus WBRT and radiosurgery?

Interpretative summary

Selected patients with brain metastasis(es) may be treated with radiosurgery alone. A further alternative is WBRT and radiosurgery boost. A third option for selected patients with multiple brain metastases is WBRT alone. There have been no convincing survival differences among the 3 options listed above, although none of the trials have been adequately powered to detect anything other than very large survival differences.

More trials are needed to assess whether there are differences in neurocognitive and quality of life outcomes when WBRT is omitted in selected patients who are treated with radiosurgery alone. There is level 3 evidence that the increased risk of brain recurrence with a strategy of radiosurgery alone (if patients are not monitored and followed adequately) may be associated with symptomatic recurrence, which may not recover fully despite salvage treatment.[88]

Evidence summary

Radiosurgery alone versus WBRT and radiosurgery

One fully published trial[56] reported on the use of radiosurgery alone versus WBRT and radiosurgery in selected patients with 1 to 4 brain metastases. The number of patients with single brain metastases (n = 68) was too small to perform meaningful subset analyses.

As such, results were reported for both single and multiple brain metastases patients. No overall survival difference between the 2 groups was found, with a median survival of 7.5 months (WBRT and radiosurgery) versus 8 months (radiosurgery alone) ($P = .42$).

However, the 12-month brain tumor recurrence rate was 48.6% in the WBRT and the radiosurgery group compared with 76.4% for the radiosurgery alone group ($P < .001$).

Deterioration in mini-mental score examination (MMSE) occurred in 14 of 36 WBRT and radiosurgery patients (39%) versus 12 of 46 radiosurgery alone patients (26%; $P = .21$), and there was no difference in actuarial curves of freedom-from-3-point drop in MMSE ($P = .73$). Among patients with MMSE decline, the average duration until deterioration of the MMSE was 16.5 months in the WBRT and radiosurgery group as compared with 7.6 months in the radiosurgery alone group ($P = .05$). The shorter duration to neurocognitive decline (as measured by the MMSE) was felt by the authors to be attributable to the increased risk of brain relapse in the radiosurgery alone group.[57] It should be noted, however, that the MMSE is a poor measure of neurocognition as it lacks adequate sensitivity.[58]

Chang et al[54] reported a randomized trial that examined patients with 1 to 3 brain metastases treated with WBRT and radiosurgery versus radiosurgery alone. The study was stopped according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive WBRT and radiosurgery were more likely to show a decline in learning and memory at 4 months compared with patients assigned to receive radiosurgery alone. At 4 months, patients treated with WBRT and radiosurgery had measurable decline in learning and memory as compared with patients treated with radiosurgery alone (52% vs 24%, respectively) despite higher rates of local and distant brain control in patients treated with WBRT and radiosurgery. It remains to be reported whether neurocognitive outcomes are different between the strategy of radiosurgery alone versus WBRT and radiosurgery at different time points (other than 4 months).

Additionally, there was a survival difference between the 2 arms not readily explained by treatment selection, raising the possibility of inadvertent randomization or selection differences between the 2 groups. An imbalance in the arms of the trial with respect to medications (such as anti-seizure medications and benzodiazepines) may also affect neurocognitive outcomes.

The subset of patients with single brain metastasis was not analyzed separately.

Radiosurgery or surgery alone versus WBRT and radiosurgery or surgery

The EORTC 22952-26001 trial[23] included patients with 1 to 3 brain metastases. Three hundred fifty-nine patients were recruited. One hundred ninety-nine patients underwent radiosurgery and 160 underwent surgery. For the radiosurgery group, 100 patients were allocated to post-radiosurgery observation and 99 patients were allocated to post-radiosurgery WBRT. In the surgery group, 79 patients were allocated to postsurgery observation and 81 patients were allocated to adjuvant WBRT. Patients eligible for radiosurgery had 1 to 3 metastases of solid tumors (small cell lung cancer, lymphoma, leukemia, myeloma, and germ cell tumors were excluded) and brain metastasis size ≤3.5 cm in diameter for a single lesion (≤2.5 cm for 2 to 3 lesions). A complete resection was required for patients who underwent surgery.

Overall survival (10.9 months vs 10.7 months) was similar in both arms ($P = .89$). WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, $P < .001$; radiosurgery: 31% to 19%, $P = .040$) and at new sites (surgery: 42% to 23%, $P = .008$; radiosurgery: 48% to 33%, $P = .023$). In well-performing patients with stable systemic disease and 1 to 3 brain metastases, treated with initial radiosurgery or surgery, WBRT can be withheld if serial imaging for follow-up is performed. For patients undergoing surgery for a single brain metastasis, postoperative local irradiation is an option that should be investigated as adjuvant irradiation substantially reduces the risk of tumor bed recurrence.

Caveats

There is a suggestion based on 1 randomized trial[54] that omission of WBRT after radiosurgery for single brain metastasis is associated with better neurocognitive outcomes based on formal neurocognitive testing. More trials addressing the question of neurocognitive outcomes in the setting of radiosurgery alone and omission of upfront WBRT are needed.

These radiosurgery trials assessed selected patients with small oligometastases to the brain (up to 4 metastases). It is unknown if there is a cutoff for the maximum number of targets appropriate for radiosurgery. Total target volume as well as number of targets may be important for safety and efficacy. A prospective nonrandomized series of patients[55] with 1 to 10 brain metastases treated with initial radiosurgery (without WBRT) required less than 10 cc volume for the largest tumor and less than 15 cc total tumor volume. Median survival was 0.83 years, 0.69 years, 0.69 years, 0.59 years, and 0.62 years for 1, 2, 3-4, 5-6, and 7-10 metastases, respectively.

A phase II trial of radiosurgery for 1 to 3 newly diagnosed brain metastases from histologies (renal cell carcinoma, melanoma, and sarcoma), which historically have been deemed radioresistant to fractioned external beam radiotherapy, was reported by the Eastern Cooperative Oncology Group[50] (ECOG) as discussed previously. Because the intracranial relapse rate was moderately high in this study using radiosurgery alone (25.8% at 3 months and 48.3% at 6 months), the authors concluded that delaying WBRT may be appropriate for some subgroups of patients with "radioresistant" histologies, but routine avoidance of WBRT should be approached judiciously. Whether WBRT should be routinely omitted in radiosurgery eligible patients with "radioresistant" histologies remains controversial. There is level 3 evidence that the increased risk of brain relapse with radiosurgery alone may be associated with symptomatic recurrences that may not be reversible with salvage brain treatment.[88] In this ECOG trial, the actuarial incidence of failure within the radiosurgery field at 3 months was 19.3% and at 6 months was 32.2%. The brain relapse rate and radiosurgery failure rate in the ECOG trial were similar to the radiosurgery alone arm in the Aoyama et al,[56] Kocher et al,[23] and Chang et al[54] trials.

The trials reported have examined the use of radiosurgery alone versus WBRT and radiosurgery boost. There have been no trials that have examined patients treated with radiosurgery alone versus WBRT alone.

Newly diagnosed brain metastases: Multiple brain metastases

6. What is the role of comfort measures or palliative supportive care alone versus WBRT in patients with multiple brain metastases?

Interpretative summary

For selected patients with poor life expectancy (less than 3 months), the use of whole brain radiotherapy may or may not significantly improve symptoms from brain metastases. Comfort measures only, or short course (20 Gy in 5 daily fractions) whole brain radiotherapy, are reasonable options.

Evidence summary

WBRT plus supportive care versus supportive care alone

Only 1 older randomized trial,[59] performed in the precomputed tomographic era, compared WBRT plus supportive care versus supportive care alone (oral prednisone). Median survival in the prednisone alone arm was 10 weeks as compared with 14 weeks in the combined arm (P value not stated).

There is 1 on-going Medical Research Council trial (Quartz)[87] that randomizes patients to optimal supportive care using dexamethasone versus optimal supportive care using dexamethasone and whole brain radiotherapy for patients with inoperable brain metastases from non-small cell lung cancer. Outcomes of interest include quality of life, overall survival, and side effects.

Caveats

There are consistent predictors for poor survival of brain metastases patients that include poor performance status and active uncontrolled disease.[13-21] Until better therapy is available for these poor prognostic patients, supportive comfort measures without WBRT can be considered.

7. What is the optimal WBRT dose fractionation schedule?

Interpretative summary

No differences in overall survival or symptom control have been demonstrated among the commonly used fractionation schemes, including 30 Gy in 10 daily fractions or 20 Gy in 5 daily fractions. Other common dose fractionation schedules of WBRT are 37.5 Gy in 15 daily fractions and 40 Gy in 20 daily (or twice daily) fractions. This interpretation is consistent with the AANS guideline on whole brain radiotherapy.[4]

Evidence summary

Altered WBRT dose fractionation schedules

Numerous trials have examined various dose fractionation schedules of WBRT.[60-69] No altered dose fractionation scheme has shown improvement in either survival or symptom control (neurologic functional status, neurologic symptom relief, palliative index, or performance status) as compared with 20 Gy in 5 fractions or 30 Gy in 10 fractions of daily WBRT. One trial randomized patients of good performance status with brain metastases not suitable for surgical excision to either 40 Gy in 20 fractions of 2 Gy twice daily versus 20 Gy in 5 daily fractions.[68] There was no difference in median survival (19 weeks in both arms). Another randomized trial examined the use of 40 Gy in 20 twice daily fractions versus 20 Gy in 4 daily fractions.[69] The primary endpoint of brain progression favored patients treated with 40 Gy in 20 twice daily fractions (44% vs 64%, $P = .03$). The secondary endpoint of death from brain progression was no different between the 2 groups, $P = .17$. The authors concluded that intracranial disease control was improved in patients treated with 40 Gy in 20 twice daily fractions as compared with 20 Gy in 4 daily fractions.

Caveats

Differences in neurocognitive outcomes have not been well studied among the different fractionation schemes. These trials also did not examine different dose fractionation schedules in the setting of single brain metastasis treated with surgery. In addition, optimal dose fractionation schedules of WBRT were not examined in the setting of upfront WBRT with radiosurgery or in the setting of WBRT at the time of salvage after radiosurgery alone.

8. What is the role of WBRT and radiosensitizers versus WBRT alone in the management of patients with brain metastases?

Interpretative summary

There is no evidence of survival benefit with the use of radiosensitizers and whole brain radiotherapy.

Evidence summary

WBRT plus radiosensitizers versus WBRT alone

There have been a few randomized trials[70-76] that have examined the use of radiosensitizers (lonidamine, metronidazole, misonidazole, bromodeoxyuridine, motexafin gadolinium, and efaproxyn or RSR-13). Overall, no radiosensitizer has improved survival.

Although, the use of motexafin gadolinium was reported to reduce neurologic progression in patients with non-small cell lung cancer metastatic to the brain,[76] the U.S. Food and Drug Administration did not approve the use of motexafin gadolinium for non-small cell lung cancer patients with brain metastases in 2007.

A subset analysis of breast cancer patients treated with RSR-13 and WBRT was reported to show an improvement in survival and quality of life as compared with WBRT alone.[70] However, the subsequent larger trial designed specifically with breast cancer patients failed to show benefit with the use of RSR-13 and WBRT.[71] In 2004, the U.S. Food and Drug Administration Oncologic Drugs Advisory committee did not recommend approval of RSR-13 as an adjunct to WBRT in patients with brain metastases from breast cancer.

Caveats

More trials are needed to assess the role (if any) of novel radiosensitizers in patients with brain metastases.

9. What is the role of chemotherapy and WBRT?

Interpretative summary

Although chemotherapy trials reported improved brain response rates with the use of combined chemotherapy and WBRT, this was at the cost of toxicity and no overall survival advantage was found with the addition of chemotherapy.[77-82] There currently is no high quality evidence to support the routine use of chemotherapy in the management of brain metastases.

Evidence summary

Chemotherapy and WBRT

There have been 8 trials examining the use of chemotherapy for brain metastases.[77-84] The chemotherapy agents used were chloroethylnitrosoureas, teniposide, fotemustine, temozolomide, thalidomide, and topotecan. One trial examined the use of early versus delayed WBRT with chemotherapy in patients with metastatic non-small cell lung cancer.[83] No survival difference was seen between early versus delayed WBRT with chemotherapy. Another trial[84] examined the use of primary chemotherapy for newly diagnosed non-small cell lung cancer with synchronous brain metastases (with delayed WBRT at brain relapse) versus WBRT administered first. No survival difference was reported between the 2 arms.

Caveats

Further trials are needed to assess the role of chemotherapy (including novel systemic agents) in the management of patients with brain metastases.

Conclusions

Treatment options for brain metastases more than 30 years ago were limited to steroids and whole brain radiotherapy and rarely surgery. Management options today have expanded to include comfort measures (including the use of steroids), WBRT and, in selected patients, surgery or radiosurgery. Optimal management depends on patient factors (such as age, performance status), tumor factors (such as extracranial cancer activity, as well as number, size, location, and histopathology of brain metastases) and available treatment options (such as experienced radiosurgery services and neurosurgeons).

The most important endpoint should be the deciding factor for which treatment is most appropriate. For selected patients with single brain metastasis, the use of surgery or radiosurgery has been shown to improve survival and this should be the primary consideration.

Treatment options which have been shown to improve whole brain control (such as the use of WBRT) or local brain control (such as the use of radiosurgery) without survival benefit for selected multiple brain metastases patients are more difficult in terms of best treatment choice. The most important outcome likely is quality of life (taking into account the morbidity of symptomatic brain recurrence and the morbidity of treatment such as neurocognitive decline, which may be associated with the use of WBRT or the side effects associated with the prolonged use of dexamethasone). Quality of life has inconsistently been measured in these trials and drop-outs are a problem with assessing this endpoint.

Numerous research opportunities exist to improve outcomes (survival, quality of life, brain control, and neurocognitive function) not only in the initial management of patients with brain metastases but also in the area of salvage treatment.

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This document was prepared by the Guidelines Subcommittee of the Clinical Affairs and Quality Committee (CAQC) of ASTRO in coordination with the Third International Consensus Conference on Palliative Radiotherapy.

Adherence to this Guideline will not ensure successful treatment in every situation.

Furthermore, this Guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its Guidelines. In addition, this Guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.

This Guideline was prepared on the basis of information available at the time the Task Group was conducting its research and discussions on this topic. There may be new developments that are not reflected in this Guideline, and that may, over time, be a basis for ASTRO to consider revisiting and updating the Guideline.

Appendix 1

MEDLINE search strategy:
Medline Ovid 1966 to Nov. 3, 2010

1. exp Brain Neoplasms/
2. ((brain or brainstem or intracranial or posterior fossa) adj3 (cancer* or carcinom* or tumor* or tumour* or neoplasm*)).mp.
3. 3 1 or 2
4. exp Neoplasm Metastasis/ or metastas*.mp.
5. Radiotherapy/
6. Radiotherapy, Adjuvant/
7. (radiotherapy or radiat* or radiosurg*).mp.
8. Combined Modality Therapy/
9. Radiosurgery/
10. gamma knife.mp.
11. or/5-10
12. 3 and 4 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. radiotherapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. 12 and 21
23. limit 22 to yr = "1966 - 2010"
24. (animals not (humans and animals)).sh.
25. 23 not 24

key:
mp = title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
fs = floating subheading
sh = subject heading

EMBASE search strategy:
Embase Ovid 1980 to 2010 week 46

1. exp Central Nervous System Tumor/
2. exp brain cortex/
3. ((brain or brainstem or intracranial or posterior fossa) adj3 (neoplasm* or cancer* or carcinoma* or tumor* or tumour*)).mp.
4. or/1-3
5. Brain Metastasis/ or metastas*.mp.
6. 4 and 5
7. exp radiosurgery/
8. multimodality cancer therapy/
9. Radiotherapy/
10. Cancer radiotherapy/
11. (radiotherap* or radiosurg*).mp.
12. gamma knife.mp.
13. radiat*.mp.
14. or/7-13
15. 6 and 14
16. random*.ti,ab.
17. factorial*.ti,ab.
18. (crossover* or cross over* or cross-over*).ti,ab.
19. placebo*.ti,ab.
20. (doubl* adj blind*).ti,ab.
21. (singl* adj blind*).ti,ab.
22. assign*.ti,ab.
23. allocat*.ti,ab.
24. volunteer*.ti,ab.
25. crossover procedure/
26. double blind procedure/
27. randomized controlled trial/
28. single blind procedure/
29. or/16-28
30. 15 and 29
31. animal/ or nonhuman/ or animal experiment/
32. human/
33. 31 and 32
34. 31 not 33
35. 30 not 34
36. limit 35 to yr = "1980 - 2010"

key:
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name
ti = title
ab = abstract

CENTRAL search strategy:
CENTRAL Issue 4, 2010

#1. MeSH descriptor Brain Neoplasms explode all trees
#2. brain* near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#3. brainstem near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#4. intracranial near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#5. posterior fossa near/3 (cancer* or carcinoma* tumor* or tumour* or neoplasm*)
#6. (#1 OR #2 OR #3 OR #4 OR #5)
#7. MeSH descriptor Neoplasm Metastasis explode all trees
#8. metastas*
#9. (#7 OR #8)
#10. MeSH descriptor Radiotherapy explode all trees
#11. MeSH descriptor Radiotherapy, Adjuvant explode all trees
#12. radiotherapy or radiat* or radiosurg*
#13. MeSH descriptor Combined Modality Therapy explode all trees
#14. MeSH descriptor Radiosurgery explode all trees
#15. gamma knife
#16. (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17. (#6 AND #9 AND #16)
#18. (#17), from 1980 to 2010
(Literature search courtesy of the Cochrane Library.)

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