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Management of Brain Metastases: Role of radiotherapy alone or in combination with other treatment modalities

Practice Guideline Report #13-4

M.N. Tsao, N.S. Laetsch, R.K.S. Wong, N. Laperriere, and the Supportive Care Guidelines Group and Neuro-oncology Disease Site Group

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SUMMARY

Guideline Questions

What is the role of radiotherapy alone or in combination with other treatment regimens in adult patients with single or multiple brain metastases? If radiotherapy is offered, what is the optimal radiotherapy regimen? Outcomes of interest are survival, intracranial progression-free duration, tumour response, neurological function, quality of life, symptom control, and toxicity.

Target Population

The recommendations apply to adult patients with a clinical and radiographic diagnosis of brain metastases (single or multiple) arising from cancer of any histology (except for choriocarcinoma and other germ cell tumours, and hematologic malignancies).

Recommendations

Radiotherapy and Surgery for Single Brain Metastasis:

- Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision.
- Postoperative whole brain radiotherapy should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis.

Radiotherapy for Multiple Brain Metastases:

- It is recommended that the whole brain be irradiated for multiple brain metastases. Commonly used dose fractionation schedules are 3000 cGy in 10 fractions or 2000 cGy in five fractions.
- Altered dose fractionation whole brain radiotherapy schedules have not demonstrated any advantages in terms of overall survival or neurologic function relative to more commonly used fractionation schedules.
- The use of radiosensitizers is not recommended outside research studies.
- The optimal use of radiosurgery in the treatment of brain metastases remains to be defined. In patients with one to three brain metastases (less than 3 cm in size) and limited or controlled extracranial disease, radiosurgery may be considered to improve local tumour control either as boost therapy with whole brain radiation or at the time of relapse after whole brain radiotherapy.

Chemotherapy and Whole Brain Radiotherapy:

- The use of chemotherapy as primary therapy for brain metastases (with whole brain radiotherapy used for those whose intracranial metastases fail to respond) or the use of chemotherapy with whole brain radiotherapy to treat brain metastases remains experimental.

Supportive Care and Whole Brain Radiotherapy

- Supportive care alone without whole brain radiotherapy is an option (for example, in patients with poor performance status and progressive extracranial disease). However, there is a lack of Level 1 evidence to guide practitioners as to which subsets of patients with brain metastases should be managed with supportive care alone without whole brain radiotherapy.

Qualifying Statements

- The number of patients included in the two trials comparing 3000 cGy in 10 fractions versus 2000 cGy in five fractions for multiple brain metastases was small.
- In the trials examining the use of surgery and whole brain radiotherapy for single brain metastasis, the whole brain radiotherapy doses were 3000 cGy in 10 fractions daily, 4000 cGy in 20 fractions given twice daily, 3600 cGy in 12 fractions daily, and 5040 cGy in 28 fractions daily. As such, the use of 2000 cGy in five fractions of whole brain radiotherapy has not been studied directly in this scenario.
- The results of the studies may not be generalizable to all tumour types. The majority of the patients in the studies (except the chemotherapy studies) had lung, breast, or colorectal cancer primaries.

Methods

Entries to MEDLINE (1966 through January 2003), CANCERLIT (1975 through October 2002), EMBASE (1980 through 2002), CINAHL (1982 through February 2003), and Cochrane Library (2002, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2002) and the American Society for Therapeutic Radiology and Oncology (1997-2002) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Supportive Care Guidelines Group and methodologists. This practice guideline report has been reviewed and approved by the Supportive Care Guidelines Group, which comprises palliative care physicians, nurses, radiation oncologists, psychologists, medical oncologists, a chaplain, an anaesthetist, a surgeon, methodologists, and administrators. The Neuro-oncology Disease Site Group, which includes neuro-oncologists, neurosurgeons, radiation oncologists, medical oncologists, a neuroradiologist, a neuropathologist, an oncology nurse, and a patient representative, also reviewed this practice guideline report.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report will be obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. The process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Two randomized controlled trials examined patients with good performance status (Karnofsky Performance Status 70-90 or World Health Organization 0, 1) and a surgically accessible single brain metastasis. Surgical excision combined with whole brain radiotherapy were found to improve duration of functional independence and overall survival compared to radiotherapy

alone (mortality at six months 33% versus 61%, respectively, relative risk 0.54 (95% confidence interval 0.31, 0.93). Perioperative mortality (30 days) ranged from 4-10%.

- One randomized study of postoperative whole brain radiotherapy following excision of a single brain metastasis detected a significant reduction in intracranial tumour recurrence rates, but no difference in overall survival as compared to surgery alone was detected.
- Nine randomized controlled trials showed no benefit of altered dose-fractionation schedules as compared to a standard control fractionation schedule (3000 cGy in 10 fractions) of whole brain radiotherapy for probability of survival at six months and neurological improvement. Two trials showed no difference between 3000 cGy in 10 fractions and 2000 cGy in five fractions. Both fractionation schemes are commonly used in Canada.
- For conventional external beam radiotherapy, the volume of radiotherapy studied in randomized controlled trials has been whole brain radiotherapy. There have been no randomized trials investigating the use of radiotherapy to the whole brain versus conventional external beam radiotherapy to only part of the brain volume.
- The addition of radiosensitizers, as assessed in five fully published randomized controlled trials, did not confer additional benefit to whole brain radiotherapy in terms of overall survival or the frequency of response to radiotherapy of the tumour metastases.
- One randomized trial detected a benefit in terms of local control of brain metastases with the addition of radiosurgery to whole brain radiotherapy for two to four brain metastases all less than 25 mm in maximum diameter. However, overall survival was not improved. Fully published results of two further randomized trials examining the use of radiosurgery for brain metastases are pending. The optimal timing of radiosurgery (e.g. boost after whole brain radiotherapy, as salvage after whole brain radiotherapy relapse or as primary treatment followed by whole brain radiotherapy at the time of relapse of brain metastases remains to be defined.
- One older randomized trial examined the use of whole brain radiotherapy versus supportive care alone (via the use of oral prednisone). Results were not conclusive. Further randomized controlled trials are needed to assess the benefit of whole brain radiotherapy versus supportive care alone particularly in patients with brain metastases who have poor performance status or uncontrolled extracranial malignant disease.

Related Guideline

Practice Guidelines Initiative's Practice Guideline Report #9-1: *Treatment of Single Brain Metastasis*.

For further information about this practice-guideline-in-progress report, please contact Dr. Rebecca Wong, Co-Chair, Supportive Care Guidelines Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, M5G 2M9; TEL 416-946-2919; FAX 416-946-4586, Email rebecca.wong@rmp.uhn.on.ca.

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
http://www.cancercare.on.ca/access_PEBC.htm
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

FULL REPORT

I. QUESTIONS

What is the role of radiotherapy alone or in combination with other treatment regimens in adult patients with single or multiple brain metastases? If radiotherapy is offered, what is the optimal radiotherapy regimen? Outcomes of interest are survival, intracranial progression-free duration, tumour response, neurological function, quality of life or symptom control, and toxicity.

II. CHOICE OF TOPIC AND RATIONALE

Brain metastases represent a significant health care problem. It is estimated that 20-40% of patients with cancer will develop metastatic cancer to the brain during the course of their illness (1). The burden of brain metastases impacts on the quality and length of survival. Presenting symptoms include headache (49%), focal weakness (30%), mental disturbances (32%), gait ataxia (21%), seizures (18%), speech difficulty (12%), visual disturbance (6%), sensory disturbance (6%), and limb ataxia (6%) (2).

Brain metastases may develop from any primary tumour site. The most common primary site is lung followed by breast then gastrointestinal (3). Eighty-five percent of brain metastases are found in cerebral hemispheres, 10-15% in the cerebellum, and 1-3% in the brainstem (4). The literature suggests that patients with breast cancer and lung cancer metastatic to brain are likely to respond to whole brain radiotherapy (WBRT) both clinically and radiographically. Patients with melanoma or renal cancer metastatic to brain are less likely to respond to WBRT (5).

Important prognostic factors for patients with brain metastases include whether the metastasis is single or not, and whether there is active systemic disease. Management of patients with brain metastases can be broadly divided into single versus multiple brain metastases. For patients with a single brain metastasis, surgery and whole brain radiotherapy (S+WBRT) is the common approach. The practice guideline for management of single brain metastasis will examine the evidence in support of S+WBRT, and will look at how S+WBRT compares with other treatment approaches. For patients with multiple brain metastases, WBRT is the common approach in clinical practice. As such, the practice guideline will examine the evidence in support of WBRT and how WBRT compares with other treatment approaches, and will look at the optimal dose fractionation scheme.

Due to the prevalence of brain metastases, its impact on patients, and the implications for health care resources, this practice guideline was initiated to summarize the evidence and to provide recommendations on the management of brain metastases.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (6). Evidence was selected and reviewed by members of the PGI's Supportive Care Guidelines Group (SCGG) and methodologists. Members of the SCGG disclosed potential conflict of interest information. The PGI's Neuro-oncology Disease Site Group (DSG) also reviewed this practice guideline report.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the role of radiation therapy in adult patients with brain metastases, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the SCGG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report will be was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. The process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 to January 2003), CANCERLIT (1975 to October 2002), CINAHL (1982 to February 2003), EMBASE (1980 to 2002), and the Cochrane Library (2002, Issue 4) databases were searched through Ovid. The terms “brain neoplasms” (Medical subject heading [MeSH]), “metastas#s” (text word), and “metastatic brain” were combined with "radiotherapy" (MeSH), “radiotherapy, adjuvant” (MeSH), “combined modality therapy” (MeSH), “chemotherapy” (MESH), “surgery” (MESH), and “radiosurgery” (MeSH). These were then combined with the search terms for the following study designs: practice guidelines, meta-analyses, randomized controlled trials, clinical trials, cohort studies, and retrospective studies. In addition, the Physician Data Query (PDQ) clinical trials database (http://www.cancer.gov/search/clinical_trials/) and the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2002), the American Society for Therapeutic Radiology and Oncology (1997-2002), and the European Society for Therapeutic Radiology and Oncology (1997-2202) were also searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed and the reference lists from these sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Design: published randomized or quasi-randomized controlled studies including abstracts.
2. Population: adult patients with single or multiple brain metastases from cancer of any histology.
3. Interventions: external beam radiotherapy or radiosurgery in one study arm.
4. Outcomes: survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, toxicity.

Exclusion Criteria

Studies were excluded if they were:

1. Studies that used prophylactic radiotherapy for brain metastases.
2. Phase I or II because of the availability of randomized controlled trials.
3. Published in languages other than English.

Synthesizing the Evidence

Since the types of patients, prognosis, and treatment strategy are different between patients with a single brain metastasis compared to those with multiple brain metastases, studies addressing these two groups of patients were examined separately. The studies were further divided by study design, based on the question the trials were intended to address. The quality of the studies was assessed using the Jadad quality assessment tool (7).

Study characteristics, including inclusion criteria, intervention, number analysed, types of outcomes reported, and results, were extracted in duplicate. Specifically, data on outcomes of

interest, including survival, intracranial progression-free duration, response of brain metastases to therapy, quality of life, symptom control, neurological function, and toxicity, were extracted.

The proportion of patients with brain response and progression is dependent on the imaging modality used (computed tomography [CT] or magnetic resonance imaging [MRI]). Similarly, neurological symptom response and quality of life are sensitive to the tool used for evaluation. These details were tabulated.

For the evaluation of dose response, many different dose fractionation schedules were compared. The most commonly employed "control" regimen was 3000 cGy in 10 fractions. The concept of Biological Equivalent Dose (BED) was used to facilitate comparison among different dose fractionation regimens. BED can be calculated using the equation BED = nd (1+ d/α/β) where n = number of fractions, d = dose per fraction, and α/β = 10 for tumour (8). For the purpose of assessing dose response, studies were divided into those comparing lower doses to 3000 cGy in 10 fractions, and higher doses compared with 3000 cGy in 10 fractions. As 2000cGy in five fractions is most commonly employed in Canada, and this is the second most commonly employed standard regimen, outcomes comparing 2000cGy in five fractions versus 3000cGy in 10 fractions are also presented.

For the pooled analysis of brain tumour response, the number of patients with a complete or partial response was abstracted from the tables or text in published reports. Tumour response was determined by the proportion of patients achieving complete response (CR) or partial response (PR). Patients were considered to have responded (CR + PR) if there was a 50% or greater decrease in lesion size and they were on a stable or decreasing dose of corticosteroids. Intracranial progression-free duration was defined as the duration during which there was no intracranial tumour growth and no new brain metastases.

Mortality data were obtained by estimating, from the Kaplan-Meyer probability curves presented in each report, the number of patients who died within six months after randomization.

The statistical package Revman 4.1 (Metaview © Update Software) provided by the Cochrane Collaboration was used for all analyses. Relative risk (RR) with 95% confidence intervals (CI) using the random effects model was reported as the more conservative estimate of effect. Analyses were primarily conducted on an intention-to-treat basis; however, when the number of patients randomized per study arm was not reported, the number of patients evaluable was analyzed. For tumour response, a RR > 1.0 indicates that the patients in the experimental treatment group experienced better response compared with those in the control group. For mortality analyses, a RR < 1.0 indicates that the patients in the experimental treatment group experienced fewer deaths compared with those in the control group.

IV. RESULTS

Literature Search Results

Studies that met the inclusion criteria are presented in Tables 1 and 2. These were divided into studies dealing with single brain metastasis versus multiple brain metastases.

Single Brain Metastasis

Trials assessing the effectiveness of surgical interventions for single brain metastasis are listed in Table 1. Three trials evaluated the role of S+WBRT compared with WBRT alone (9-11). One trial reported on S+WBRT versus surgery alone (12).

Table 1. Studies evaluating the role of surgery plus WBRT versus WBRT alone and surgery plus WBRT versus surgery alone.

Comparisons	Number of studies	Reference numbers
WBRT ± surgery	3	9-11
Surgery ± WBRT	1	12

Multiple Brain Metastases

Trials assessing the effectiveness of *WBRT compared with supportive care alone, WBRT (control dose fractionation) compared with other dose fractionation schemes, and WBRT compared with WBRT plus other modalities* for multiple brain metastases are listed in Table 2.

There was one randomized controlled trial examining the use of supportive care alone (through oral prednisone administration) versus supportive care and WBRT (13). Nine studies examined the use of altered WBRT dose/fractionation schedules (14-22). Five fully published trials reported the use of radiosensitizers in addition to WBRT (23-27,36). Four trials reported on chemotherapy and WBRT. One randomized trial (28) compared early versus delayed WBRT with concurrent chemotherapy in inoperable brain metastases from non-small-cell lung cancer. Another trial (29) randomized patients to WBRT alone, WBRT and chloroethylnitrosoureas (methyl-CCNU or ACNU), or WBRT and a combination of chloroethylnitrosoureas and tegafur. Results of a randomized trial published in abstract form on the use of WBRT with or without chemotherapy are also included in this guideline report (30). One randomized controlled trial examined the use of WBRT with or without radiosurgery for two to four brain metastases (31). Another trial, reported in abstract form, randomized patients with one to three brain metastases to gamma knife radiosurgery (GK RS), WBRT, or both (32). A randomized phase III trial by the Radiation Therapy Oncology Group (RTOG) examined the use of WBRT alone versus WBRT plus radiosurgical boost for two to four brain metastases (33,34). The preliminary results were published in abstract form.

Table 2. Studies evaluating the role of WBRT compared with supportive care, altered dose fractionation schedules, and other treatment modalities.

Comparisons	Number of studies	Reference numbers
Supportive care (oral prednisone) ± WBRT	1	13
Altered dose/fractionation schedules	9	14-22
WBRT ± radiosensitizer	5	23-27, 36
Chemotherapy and WBRT	3 + 1 (abstract)	28, 29, 30, 35
WBRT ± radiosurgery	1 + 3 (abstracts)	31, 32, 33, 34

Study Characteristics

Tables 3-8 summarize the study characteristics (study arms, number of patients, patient characteristics, exclusion criteria, imaging modality, duration of follow-up, and study quality) of the trials included in this practice guideline report.

SINGLE BRAIN METASTASIS

Table 3. Studies addressing the effectiveness of surgery plus WBRT compared with other treatment approaches.

Study (Ref)	Study arms	No. of pts random-ized (eval)	Patient characteristics	Exclusion criteria	Imaging modality[1]	Duration of follow-up	Study quality[2]
Mintz 1996 (9)	3000 cGy/ 10fr + sx 3000 cGy/ 10fr	41 43	-mean age: 58y -KPS 50-70: 18% (RT + sx);15% (RT) -extracranial mets: 17% (RT + sx); 21% (RT) Primaries: NSCLC (54%); colon or rectum (15%); breast (12%)	-KPS < 50 -leukemia, lymphoma, SCLC, skin cancer other than melanoma -meningeal carcinomatous -previous cranial irradiation -co-morbid condition precluding FU -lesion in brainstem or basal ganglia -emergency decompression -previous brain mets	CT	Not stated	3
Noordijk 1994 (10)	4000 cGy/20fr BID + sx 4000 cGy/20fr BID	(32)[3] (31)[4]	-mean age: 59y -WHO 0-1: 75% (RT +sx); 71% (RT) -status of progressive disease: 31% (RT + sx); 32% (RT) Primaries: NSCLC (52%); breast (19%); melanoma (10%)	-SCLC, malignant lymphoma, leptomeningeal disease -WHO <2 -life expectancy <6m -neurologic function class IV	CT (MRI optional)	Not stated	2
Patchell 1990 (11)	3600 cGy/12fr + sx 3600 cGy/12fr	(25)[5] (23)[4]	-median age: 60y -median KPS 90 (range 70-100) -extent of disseminated disease: 36% (RT + sx); 39% (RT) Primaries: NSCLC (77%); breast (6%); GI (6%)	-age <18 y; KPS < 70 -brain lesions not potentially resectable -leptomeningeal disease, previous cranial radiation -need for immediate decompression -SCLC, germ cell tumours, lymphoma, leukemia, multiple myeloma	CT and MRI	Overall median FU: 40w 15w	2
Patchell 1998 (12)[6]	5040 cGy/ 28fr + sx sx	(49) (46)	-median age: 60y (RT + sx); 58y (sx) -KPS: 90 (both arms) -extent of disease-primary only: 39% (both arms) -extent of disease-disseminated: 24% (RT +sx); 26% (sx) Primaries: NSCLC (60%); breast (9%); GI (8%)	-brain mets not completely removed with sx -leptomeningeal metastases -previous cranial RT -need for urgent treatment due to acute neurologic deterioration -concomitant second malignancy -KPS <70 -SCLC, germ-cell tumour, lymphoma, leukemia, multiple myeloma	MRI	Median follow-up: 48w 43w	3

Notes: BID – twice daily, cGy – centigray, CT – computed tomography, eval (evaluable), fr – fraction(s), FU – follow up, GI – gastrointestinal, KPS- Karnofsky performance status, m – month(s), mets – metastases, MRI – magnetic resonance imaging, No. – number, NSCLC – non-small cell lung cancer, pts – patients, Ref – reference, SCLC – small cell lung cancer, sx – surgery , RT-radiotherapy, w – week(s), WHO – world health organization, y – years

1- all included patients have a single brain metastasis based on CT and/or MRI; 2 – study quality by the Jadad score; 3 – total randomized = 66; 4 – overall survival at 6 months based on number of patients evaluable; 5 – total randomized = 54; 6 – total randomized = 95, eligible patients = 146

MULTIPLE BRAIN METASTASES

Table 4. Studies addressing the effectiveness of WBRT compared with supportive care alone.

Study (Ref)	Study arms	No. of pts randomized	Inclusion criteria	Exclusion criteria	Duration of follow-up	Study quality[2]
Horton et al. 1971 (13)	Supportive care[1] + WBRT Supportive care alone	28 19	-histologically proven cancer -parenchymal brain metastases (radioisotope brain scan, EEG, echo encephalogram, angiogram, spinal fluid cytology and chemistry) Primaries: lung (63%); breast (15%); melanoma (8%)	-all gross brain tumour surgically excised	Not stated	2

Notes: EEG – electroencephalogram, No. – number, pts – patients, Ref – references, WBRT – whole brain radiotherapy
1 – oral prednisone; 2 – study quality by the Jadad score

Table 5. Studies addressing the effectiveness of WBRT using altered dose fractionation.

Study (Ref)	Study arms	No. of pts randomized (eval)	Patient characteristics[1]	Exclusion criteria	Duration of follow-up	Study quality[2]
Borgelt, et al. 1980 (15)	Study 1: 4000 cGy/20fr 4000 cGy/15fr 3000 cGy/15fr 3000 cGy/10fr Study 2: 4000 cGy/15fr 3000 cGy/10fr 2000 cGy/5fr	Study 1[3]: (227) (233) (217) (233) Study 2[4]: (227) (228) (447)	-brain mets diagnosed by clinical symptoms and EEG, radioisotope brain scans, arteriograms, pneumoenceph-alograms, or biopsy -performance score (1+2) 55% (Study 1) 47% (Study 2) -brain as the only site of mets 56% (Study 1) 43% (Study 2)	-medical condition precluding adequate FU -new anti-cancer treatment within 2w -lesions too numerous -symptoms too vague for adequate assessment	Not stated	2
Borgelt et al. 1981 (16)	Study 1: 1000 cGy/1fr 3000-4000 cGy/10-20fr Study 2: 1200 cGy/2fr 2000 cGy/5fr	Study 1[5]: 26 (26) 129 (112) Study 2[6]: (33) (31)	-brain mets diagnosed by clinical symptoms and EEG, radioisotope brain scans, arteriograms, pneumoencephalograms, or biopsy -performance score (1+2) Study 1: 62% (1000 cGy/1fr) 55% (3000-4000 cGy/ 10-20 fr) Study 2: 46% (1200 cGy/2fr) 52% (2000 cGy/5 fr)	-see Borgelt 1980	Not stated	2

Chatani et al. 1985 (17)	5000 cGy/20fr 3000 cGy/10fr	34 35	-brain mets diagnosed by clinical symptoms and CT; lung cancer; age > 60y 65% (5000 cGy/20 fr) 51% (3000 cGy/10fr) -extracranial mets 74% (both arms) -performance score (1+2) 32% (5000 cGy/20 fr) 34% (3000 cGy/10fr)	Not stated	Minimum FU 6 m	1
Chatani et al. 1994 (18)	**Normal LDH:** 5000 cGy/20fr 3000 cGy/10fr **Elevated LDH:** 3000 cGy/10fr 2000 cGy/5fr	Normal LDH: 46 46 Elevated LDH: 35 35	- brain mets diagnosed by clinical symptoms and CT **Normal LDH:** NFC (1+2) 63% (both arms) Extracranial mets: 41% (5000cGy/20fr) 39% (3000cGy/10fr) **Elevated LDH**: NFC (1+2) 57% (3000cGy/10fr) 51% (2000cGy/5fr) Extracranial mets: 66% (3000cGy/10fr) 51% (2000cGy/5fr)	Not stated	Not stated	1
Haie-Meder, et al. 1993 (14)*	**One course of RT:** 1800 cGy/3fr/3d **Two courses of RT:** 1800 cGy/3fr/3d followed 1m later by another 1800 cGy/3fr/3d ***Or*** 1800 cGy/3fr/3d followed 1m later by another 2500 cGy/10 fr/14d	One course of RT: 111 (110) Two courses of RT: 109 (106)	-brain mets diagnosed by CT -mean age 54y -69% KPS >70 -other distant mets 62% (1 course of RT) 46% (2 courses of RT; p<0.02	-solitary brain mets surgically removed -previous cranial irradiation or intra-arterial chemo -KPS< 20 -life expectancy <1m	Not stated	3
Harwood et al. 1977 (19)*	1000 cGy/ 1fr 3000 cGy/10fr	(51) (50)[7]	- no previous chemo nor brain RT during the proceeding 3w; pts stratified by functional status and histology of primary tumour	-extensive extracranial disease; previous cranial irradiation; chemo within 3w	Not stated	4

Kurtz et al. 1981 (20)	5000 cGy/20fr 3000 cGy/10fr	153 (125) 156 (130)	-cancer pts with positive radioisotope brain scans; KPS 70-100 18% (5000cGy/20fr) 23% (3000cGy/10fr) -status of primary (present or unknown) 16% (5000cGy/20fr) 15% (3000cGy/10fr)	-NFC IV; anti-cancer treatment within the previous 2w; progressive untreated primary	Not stated	3
Murray et al. 1997 (21)*	5440 cGy/34fr BID (over 17d) 3000 cGy/10fr (over 10d)	(216) (213)[8]	- proof of underlying primary tumour and measurable brain lesions by CT; mean age 59.8 y -KPS <80 52% (5440cGy/34fr BID) 62% (3000cGy/10fr) -primary tumour controlled 26% (5440 cGy/34 fr BID) 27% (3000cGy/10fr)	-KPS < 70 -NFC III, IV - primary site hematopoietic, lymphoma or meningeal involvement	Not stated	3
Priestman et al. 1996 (22)*	1200 cGy/2fr 3000 cGy/10fr	274 (270) 270 (263)	- brain mets diagnosed by CT, unequivocal radioisotope brain scan or intracranial biopsy -median age 60y -WHO PS (0+1) 38% (1200cGy/2fr) 34% (3000cGy/10fr) -solitary brain mets 39% (1200cGy/2fr) 40% (3000cGy/10fr)	-WHO PS 4 -neurologic status 4 -cytotoxic chemo in the previous 4w	Not stated	3

Notes: BID – twice daily, cGy – centigray, chemo – chemotherapy, CT – computed tomography, d – day(s), EEG – electroencephalogram, eval – evaluable, fr – fraction(s), FU – follow up, KPS – Karnofsky performance status, LDH – lactate dehydrogenase, m – month(s), mets – metastases, NFC – neurologic function classification, No. – number, PS – performance status, pts – patients, Ref – reference, RT – radiotherapy, w – week(s), WHO – World Health Organization, y – year(s)

1 – All studies included patients with various primary histologies except for Chatani 1994 (18) that included only lung cancer patients (non-small cell and small cell lung cancer) and Chatani 1985 (17) that included only non-small cell lung cancer patients; 2 – study quality by the Jadad score; 3 – Total randomized = 993; 4 – Total randomized = 1001; 5 – Total randomized = 155; 6 – Total randomized = 78; 7 – Total randomized = 108; 8 – Total randomized = 445; * Number of fractions given daily Monday through Friday unless otherwise stated

Table 6. Studies addressing the effectiveness of WBRT ± Radiosensitizers.

Study (Ref)	Study arms	No. of pts randomized (eval)	Patient characteristics[1]	Exclusion criteria	Duration of follow-up	Study quality[2]
DeAngelis et al. 1989 (23)	3000 cGy/10fr + lonidamine 3000 cGy/10fr	31 (19) 27 (20)	-histologically proven cancer; brain mets by CT Median age: 60y (RT); 57y (RT + LON) -KPS 50-70 52% (RT) 45% (RT + LON) -30% of pts had melanoma	-prior WBRT	Not stated	1

Eyre et al. 1984 (24)[3]	3000 cGy/10fr + metronidazole 3000 cGy/10fr	(57) (54)	-histologically proven cancer -brain mets by radioisotope brain scans , CT scan, neurologic symptoms -age ≥ 60 46% (RT) 32% (RT + MET) -neurologic function (1+2) 81% (RT) 81% (RT + MET) -systemic mets: 50% (RT); 51% (RT + MET)	-prior cranial radiation -expected survival less 4w - use of systemic chemo known to cross the blood brain barrier	Not stated	2
Komarnicky et al. 1991 (25)	3000 cGy/6fr + misonidazole 3000 cGy/6fr 3000 cGy/10fr + misonidazole 3000 cGy/10 fr	 220 /(196) 216 /(200) 211 /(190) 212 /(193)	-measurable brain mets on CT; neurologic function class I-III -age > 60 42%, 44%, 46%, 40% (by study arm respectively) -KPS 70-100 78%, 80%, 74%, 78% (by study arm respectively) -brain and other mets 50%, 47%, 44%, 45% respectively	-< 18y or >75y -KPS <40 -neurologic function class IV -chemo changed within 2w	Not stated	3
Mehta et al. 2002 (27, 36)	3000 cGy/10fr + MGd 3000 cGy/10fr	193 (193) 208 (208)	-histologically proven solid tumors; MRI-demonstrated brain mets -KPS≥70	-SCLC , lymphoma or germ-cell tumors -brain mets partially or completely resected -prior cranial irradiation leptomeningeal mets -two or more sites of extracranial mets except with primary breast cancer -chemo given with WBRT or within 14 days of WBRT -radiosurgery given as initial therapy	Not stated	2
Phillips et al. 1995 (26)	3750 cGy/15fr + BrdUrd 3750 cGy/15fr	35 (34) 37 (36)	- biopsy proven cancer -measurable brain lesions -age ≥ 60y 58% (RT) 65% (RT + BrdUrd) -KPS 70-100 – all -primary controlled: 56% (RT); 47% (RT +BrdUrd)	-prior brain RT; KPS < 70; age <18y; central nervous system primaries or leukemias; primary unresected or uncontrolled; concurrent chemo; white count over 4000 per mm^3 and platelets more than 125000 per mm^3	Not stated	3

Notes: BrdUrd – Bromodeoxyuridine, cGy – centigray, chemo – chemotherapy, CT – computed tomography, eval – evaluable, fr – fraction(s), KPS – Karnofsky performance status, LON – lonidamine, m – month(s), MET – metronidazole, mets – metastases, MGd – motexafin gadolinium, No. – number, pts – patients, Ref – reference, RT – radiotherapy, SCLC – small cell lung cancer, w – week(s), WBRT – whole brain radiotherapy, y – year(s)
1 – All studies included patients with various primary histologies; 2 – study quality based on Jadad criteria; 3 – Total randomized = 116

Table 7. Studies addressing the effectiveness of WBRT and chemotherapy.

Study (Ref)	Study arms	No. of pts randomized (eval)	Patient characteristics	Exclusion criteria	Duration of follow-up	Study quality[1]
Antonadou et al. 2002 (30) (abstract)	WBRT (3000 cGy/10 fr) and temozolamide chemo WBRT(3000 cGy/10fr)	134 eligible pts -numbers per arm not described	- previously untreated brain mets -details not available	-previously treated brain mets	Not stated	Not assessed
Postmus et al. 2000 (35)	Teniposide Teniposide and WBRT (3000 cGy/10fr)	(60) (60)	-histologic or cytologic diagnosis of SCLC -brain mets by contrast enhanced CT -age < 76y	-previous treatment by chemo or radiotherapy -previous treatment with teniposide	Not stated	3
Robinet et al. 2001 (28)	-early vs. delayed WBRT (3000 cGy/10fr) with chemo (cisplatin and vinorelbine)	(86) delayed WBRT (85) early WBRT	- histologic or cytologic diagnosis of NSCLC; at least one measurable (diameter >10 mm) and inoperable brain mets either by CT or MRI; ECOG 0-2; median age 57y (both arms) -PS (0+1): 71% (delayed); 76% (early) -extracranial disease: 53% (delayed); 48% (early)	-previous malignancy except nonmelanoma skin cancer, in situ carcinoma cervix -age <18y or >75y; ECOG PS>2 -good renal, hepatic and hematologic function -no recent (<3m) heart disease	Not stated	3
Ushio et al. 1991 (29)	Group A: WBRT (4000cGy/20-27fr) Group B: WBRT[2] + chloroethylnitrosoureas Group C: WBRT[2] + chloroethylnitrosoureas + tegafur	31 (25) 36 (34) 33 (29)	- brain metastases from lung cancer (non-small cell and small cell)	-life expectancy estimated to be <4m -patients deemed to be unable to tolerate radiotherapy or chemotherapy for at least 1m	Not stated	3

Note: cGy – centigray, chemo – chemotherapy, CT – computed tomography, ECOG **–** Eastern Cooperative Oncology Group, eval – evaluable, fr – fraction(s), KPS **–** Karnofsky performance status, mets – metastases, m – month(s), mm – millimetres, MRI – magnetic resonance imaging, No. – pts, NSCLC – non-small cell lung cancer, PS – performance status, pts – patients, Ref – reference, vs. – versus, WBRT – whole brain radiotherapy, y – year(s)
1 – study quality by Jadad, 2 – same dose/schedule as Group A

Table 8. Studies addressing the effectiveness of WBRT with or without radiosurgery.

Study (Ref)	Study arms	No. of pts Randomized	Patient characteristics	Exclusion criteria	Duration of follow-up	Study quality[1]
Chougule et al. 2000 (32) (abstract)	GK alone GK and WBRT(3000 cGy/10fr) WBRT (3000cGy/10fr)	36 37 31	-≤3 lesions -tumour volume ≤ 30cc -minimum life expectancy 3m	Not stated	Not stated	Not stated
Kondziolka et al. 1999 (31)	WBRT (3000 cGy/12fr) WBRT (3000 cGy/12fr) and radiosurgery	14 13	- histologic confirmation of cancer (various primary histologies); ≤ 25 mm brain mets; > 5 mm from optic chiasm; 2-4 brain mets -mean age:58y (WBRT), 59y (WBRT + radiosurgery) -systemic disease: 71% (WBRT); 62% (WBRT + radiosurgery) - KPS ≥ 70 (all)	-pts unable to undergo MRI	Not stated	3
Sperduto et al. 2002 (34) (abstract)	WBRT (3750 cGy/15fr) WBRT (3750 cGy/15fr) and radiosurgery	144 pts randomized -numbers per arm not described	-2 to 3 brain mets -details not provided	Not stated	Not stated	Not assessed

Notes: cc – cubic centimetre, cGy – centigray, GK – gamma knife, fr – fraction(s), KPS – Karnofsky performance status, m – months, mets – metastases, mm – millimetres, MRI – magnetic resonance imaging, No. – number, pts –patients, Ref – reference, WBRT – whole brain radiotherapy, y – year(s)
1 – study quality by Jadad criteria

Outcomes

Trial results for single brain metastasis and multiple brain metastases are presented in Tables 9-16. Overall survival, tumour response, intracranial progression-free duration, neurological function, quality of life, and toxicity outcomes are presented where available.

Single Brain Metastasis

WBRT plus surgery versus WBRT alone

The results of three randomized controlled trials examining the use of WBRT with or without surgical resection for single metastasis to brain are presented in Table 9. The results are heterogeneous (p= 0.022) cautioning against pooling of the data. As a post hoc analysis, the effect of performance status and extracranial disease was explored as a possible source of heterogeneity. The Mintz et al. (9) trial had a higher proportion of patients with poorer performance status and extracranial disease. The six-month mortality outcome for the two trials where patients had a higher performance status and a lower proportion of extracranial disease were pooled and are presented in Figure 1. A summary statistic for the Mintz et al. trial is shown as a comparison.

Based on the subgroup of studies (10,11) consisting of patients with a higher performance status and lower proportion of patients with extracranial disease, there was a statistically significant difference in overall mortality at six months favouring the surgical resection and WBRT arm (RR, 0.54; 95% CI, 0.31 to 0.93; p=0.03).

Assessment of tumour response was not applicable since the single brain metastasis was grossly resected. None of the three trials reported on intracranial progression-free duration. Two of the three trials reported on changes in neurological function (10,11). There was a statistically significant difference favouring surgery and WBRT for duration of functional independence in two (10,11) of the trials. The Noordijk et al. study (10) detected a significant improvement in functionally independent survival for the surgery and radiotherapy arm compared with the radiotherapy-alone arm. The Patchell et al. study (11) found that patients in the surgical group maintained Karnofsky performance status (KPS) scores $\geq$ 70 longer than patients treated with radiotherapy alone (median 38 weeks versus 8 weeks; p< 0.005).

Only one trial reported on quality-of-life outcomes. The Mintz et al. trial (9) did not detect a statistically significant difference in the number of days KPS was at least 70 or in mean Spitzer quality-of-life scores. Table 10 summarizes the toxicities reported in the trials examining WBRT with or without surgery for the treatment of a single brain metastasis.

Table 9. Randomized studies of WBRT with or without surgical resection for single brain metastasis.

Study (Ref)	Study arms	No. of pts randomized (eval)	Overall median survival	Overall survival at 6 months (no. of pts)
Mintz et al. 1996 (9)	3000 cGy/10fr + sx	41	5.6m	19 (46%)
	3000 cGy/10fr	43	6.3m NS	23 (53%)
Noordijk et al. 1994 (10) [1] *	4000 cGy/20fr BID + sx	(32)	10m	21 (66%)
	4000 cGy/20fr BID	(31)	6m p=0.04	16 (52%)
Patchell et al. 1990 (11) [2] *	3600 cGy/12fr + sx	(25)	9.2m	17 (68%)
	3600 cGy/12fr	(23)	3.5m p<0.01	5 (22%)

Notes: BID – twice daily, cGy – centigray, eval – evaluable, fr – fraction(s), m – month(s), no. – number, NS – not significant, pts – patients, Ref – reference, sx – surgery 1 – total randomized = 66; 2 – total randomized = 54; * overall survival at six months based on number of patients evaluable

Figure 1. Overall mortality at six months for surgery and WBRT versus WBRT alone for single metastasis to the brain.

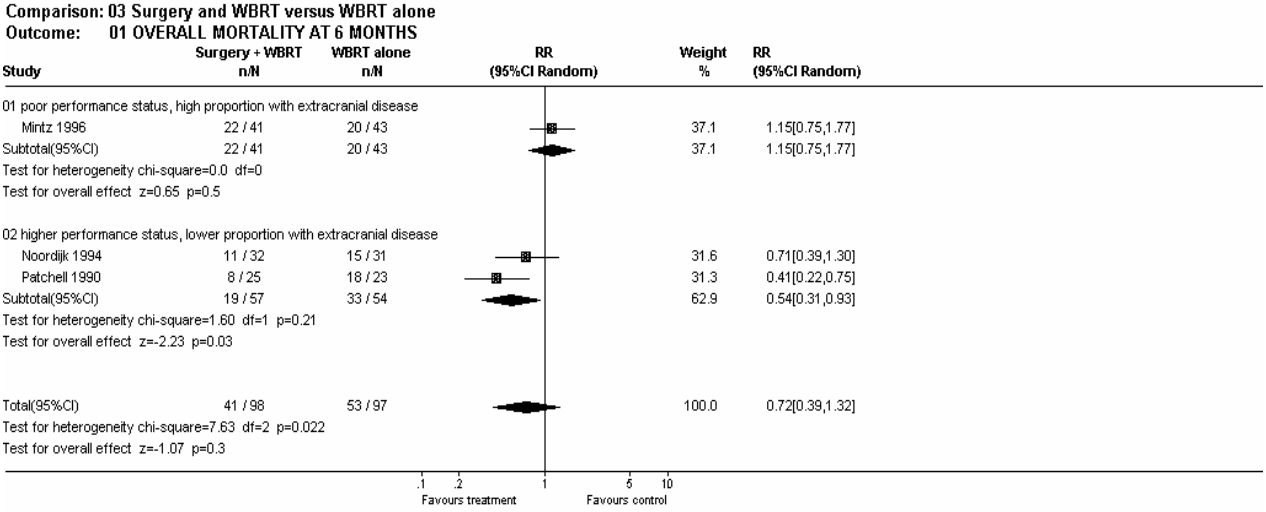

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Table 10. Toxicities reported in trials assessing WBRT with or without surgery.

Study (Ref)	Surgery and WBRT	WBRT alone
Mintz et al. (9)	surgical mortality (30 days from surgery): 9.8% (4/41)	no toxicity data
Noordijk et al. (10)	1-month mortality: 9% (3/32) postoperative morbidity: 41% (13/32) serious postoperative morbidity: 12.5% (4/32) headache, nausea, vomiting (10/32)	headache, nausea, vomiting (9/31)
Patchell et al. (11)	operative mortality (30 days from surgery): 4% (1/25) operative morbidity: 8% (2/25)	1-month morbidity (not defined): 17% (4/23)

Notes: Ref – reference, WBRT – whole brain radiotherapy

Surgery plus WBRT versus surgery alone

There was only one randomized controlled trial (12) that examined the use of surgery alone versus S+WBRT for single metastasis to brain. The postoperative WBRT dose used was 5040 cGy in 28 fractions given daily over 5.5 weeks. There was no significant difference in overall survival. Assessment of tumour response was not applicable as the single brain metastasis was grossly resected. A statistically significant difference in brain tumour recurrence was detected in this trial by Patchell (12): 18% of 49 patients in the surgery and radiation group recurred versus 70% of 46 patients in the surgery alone group ($p<0.001$). There was no significant difference in the length of time patients remained functionally independent. Data on quality of life and toxicity were not reported in this trial.

Multiple Brain Metastases

WBRT plus supportive care versus supportive care alone

Only one trial by Horton et al. (13) compared WBRT plus supportive care (oral prednisone) versus supportive care alone. Median survival in the prednisone alone arm was 10 weeks compared with 14 weeks in the combined arm (p-value not stated). The proportion of patients with an improvement in performance status was similar in the prednisone alone and combined WBRT and prednisone arms (63% vs. 61% respectively). Data on tumour response, intracranial progression-free duration, quality of life, and toxicity were not reported.

Altered WBRT dose fractionation schedules

The results of randomized trials examining altered WBRT dose fractionation schedules are presented in Table 11. The dose fractionation and its equivalent BED for each trial is tabulated in Table 12. In order to explore if a dose response relationship is present, we used 3000cGy in 10 fractions relative biological effectiveness (RBE) = 39Gy as the control and presented outcome comparisons between RBE <39Gy versus 39Gy, and 39Gy versus >39Gy.

Eight of the nine trials (15-22) included either 3000 cGy in 10 daily fractions or 2000 cGy in five fractions of WBRT as the standard arm. Overall survival at six months was obtainable from six trials (17-22). None of the trials reported on intracranial progression-free duration, tumour response, or quality of life using a validated quality of life instrument. Data on neurological function and toxicity are presented in Tables 13a, 13b, 14a, and 14b and in Figures 4 and 5.

RBE <39Gy versus 39Gy

Three trials (18,19,22) compared lower dose radiation (1000 cGy in a single fraction, 1200 cGy in 2 fractions or 2000 cGy in five fractions) with a standard dose of WBRT of 3000 cGy in 10 fractions. The six-month mortality outcome for these three trials was pooled and is presented in Figure 2. When the three trials were combined, there was no significant difference in overall mortality at six months (RR, 1.09; 95% CI, 0.98 to 1.21; p=0.12).

RBE 39Gy versus >39Gy

Four trials (17,18,20,21) compared higher dose WBRT (5000 cGy in 20 fractions or 5440 cGy in 34 fractions twice daily [BID]) with a standard dose of 3000 cGy in 10 fractions. The six-month mortality results of these four trials are pooled in Figure 3. When the four trials in Figure 3 were pooled, there was no statistically significant difference (p=0.16) in overall mortality at 6 months (RR, 1.10; 95% CI, 0.96 to 1.27; p=0.16).

39Gy (3000cGy in 10 fractions) versus 28Gy (2000cGy in five fractions)

Two studies provided data directly comparing these two commonly employed fractionation schedules. Neither Borgelt et al. (15,16) nor Chatani et al. (18) detected a significant difference in overall survival between fractionation schedules of 3000 cGy in 10 fractions or 2000 cGy in five fractions. The number of patients in each arm (3000 cGy in 10 fractions or 2000 cGy in five fractions) was small. Although these two fractionation schedules are commonly used regimens in Canada, they have not been evaluated as being equivalent in large trials.

Table 11. Randomized studies of altered whole brain dose/fractionation radiotherapy schedules for metastatic cancer to the brain (overall survival).

Study (Ref)	Study arms[1]	No. of pts randomized (eval)	Overall median survival	Overall survival at 6 m (no. of pts)
Borgelt, et al. 1980 (15)	Study 1: 4000 cGy/20fr 4000 cGy/15fr 3000 cGy/15fr 3000 cGy/10fr Study 2: 4000 cGy/15fr 3000 cGy/10fr 2000 cGy/5fr	Study 1[3]: (227) (233) (217) (233) Study 2[4] (227) (228) (447)	Study 1: 4.2m (range 3.7-4.6m) (p>0.05) Study 2: 3.5m (range 3.2-3.5m) (p>0.05)	NR
Borgelt et al. 1981 (16)	Study 1: 1000 cGy/1fr 3000-4000 cGy/10-20fr Study 2: 1200 cGy/2fr 2000 cGy/5fr	Study 1[5]: 26 (26) 129 (112) Study 2[6]: (33) (31)	Study 1: 3.5m 4.8m (p>0.05) Study 2: 3.0m 2.8m (p>0.05)	NR
Chatani et al. 1985 (17)	5000 cGy/20fr 3000 cGy/10fr	34 35	3m 4m (p>0.05)	5 (15%) 15 (43%)
Chatani et al. 1994 (18)	Normal LDH: 5000 cGy/20fr 3000 cGy/10fr Elevated LDH: 3000 cGy/10fr 2000 cGy/5fr	Normal LDH: 46 46 Elevated LDH: 35 35	Normal LDH: 4.8m 5.4m p=0.841 Elevated LDH: 3.4m 2.4m p=0.943	19 (41%) 22 (48%) 7 (20%) 7 (20%)
Haie-Meder, et al. 1993 (14)[2]	One course of RT: 1800 cGy/3fr/3d Two courses of RT: 1800 cGy/3fr/3d followed 1m later by another 1800 cGy/3fr/3d ***or*** 1800 cGy/3fr/3d followed 1m later by another 2500 cGy/10fr/14d	One course of RT: 111 (110) Two courses of RT: 109 (106)	One course of RT: 4.2m Two courses of RT: 5.3m (p>0.05)	53 (48%) 41 (38%)
Harwood et al. 1977 (19)[2]	1000 cGy/1fr 3000 cGy/10fr	(51) (50)[7]	4.4m 4.0m p=0.082	14 (27%) 20 (40%)
Kurtz et al. 1981 (20)	5000 cGy/20fr 3000 cGy/10fr	153 (125) 156 (130)	3.9m 4.2m p value not stated	55 (36%) 59 (38%)
Murray et al. 1997 (21)[2]	5440 cGy/34fr BID (over 17d) 3000 cGy/10fr (over 10d)	(216) (213)[8]	4.5m 4.5m p=0.52	84 (39%) 88 (41%)
Priestman et al. 1996 (22)[2]	1200 cGy/2fr 3000 cGy/10fr	274 (270) 270 (263)	2.5m 2.8m p=0.04	46 (17%) 66 (24%)

Notes: BID – twice daily, cGy – centigray, d – day(s), fr – fraction(s), LDH – lactate dehydrogenase, m – month(s), no. – number, NR – not reported, pts – patients, Ref – reference, RT – radiotherapy

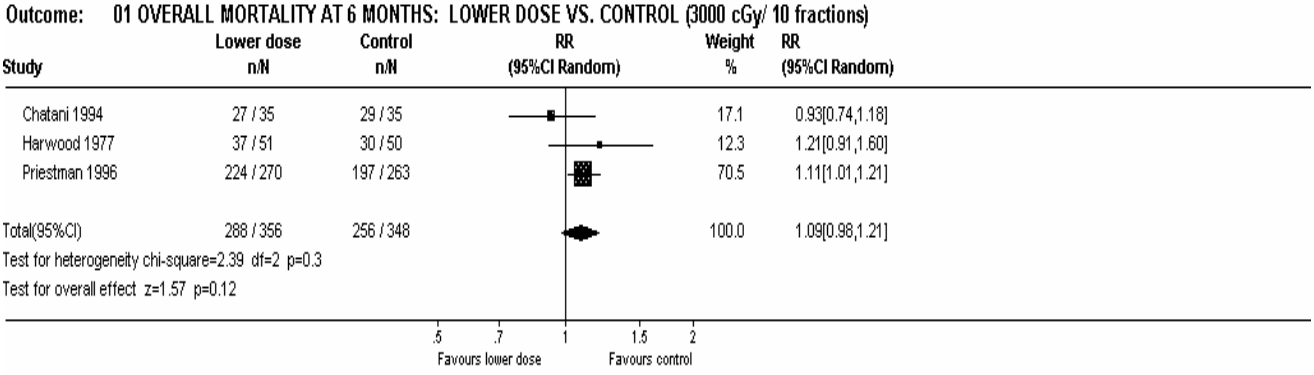
1 – number of fractions given daily Monday through Friday unless otherwise stated; 2 – overall survival at 6 months based on number of patients evaluable; 3 – total randomized = 993; 4 – total randomized = 1001; 5 – total randomized = 155; 6 – total randomized = 78; 7 – total randomized = 108; 8 – total randomized = 445

Table 12. Biological equivalent doses.

Study (Ref)	12Gy in 2	10Gy in 1	20Gy in 5	18Gy in 3	30Gy in15	30Gy in 10	40Gy in 20	40Gy in 15	18Gy in 3 + 18 Gy in 3 or 25Gy in 10	50Gy in 20	54.4Gy in 34 BID
BED	19.2	20	28	28.8	36	39	48	50.7	57.6-60.05	62.5	63
Borgelt, et al. 1980 (15) Study I					+	+	+	+			
Borgelt, et al. 1980 (15) Study II			+			+		+			
Borgelt et al 1981 (16) Study I		+				+					
Borgelt et al. 1981 (16) Study II	+		+								
Chatani et al. 1985 (17)						+				+	
Chatani et al. 1994 (18) Normal LDH						+				+	
Chatani et al 1994 (18) Elevated LDH			+			+					
Haie-Meder, et al. 1993 (14)				+					+		
Harwood et al. 1977 (19)		+				+					
Kurtz et al. 1981 (20)						+				+	
Murray et al. 1997 (21)						+					+
Priestman et al. 1996(22)	+					+					

Notes: BED – biological equivalent dose, BID – twice daily, Gy – gray, LDH – lactate dehydrogenase, Ref – reference

Figure 2. Pooled results of overall mortality for randomized studies using lower dose WBRT for metastatic cancer to brain compared to 3000 cGy in 10 fractions.



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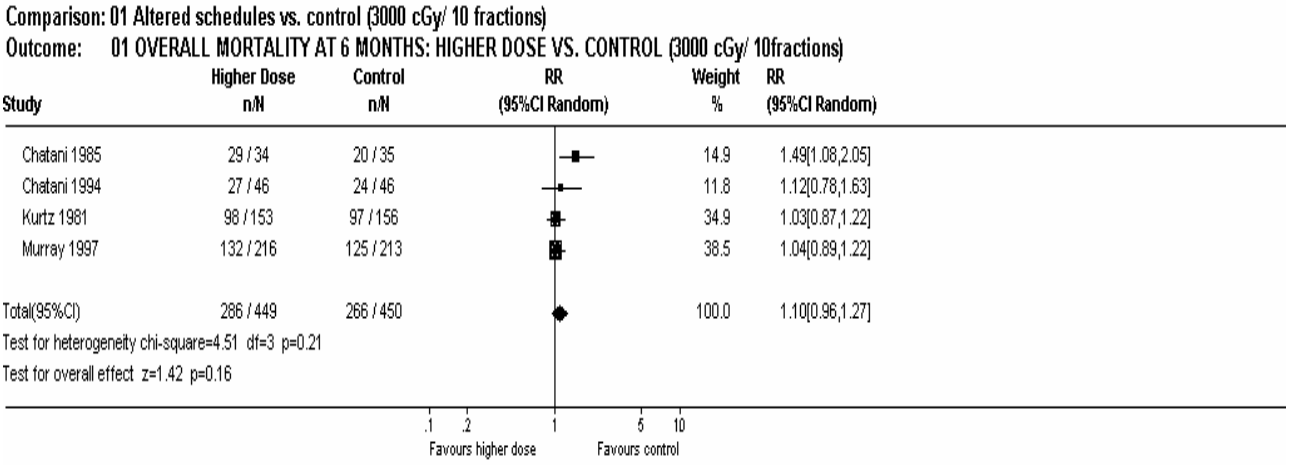
Notes: Five trials (15,16,18,19,22) compared lower biological dose to 3000 cGy in 10 fractions. One trial (14) did not have a standard arm of 3000 cGy in 10 fractions. Six-month mortality was obtainable in only three trials (18,19,22).

Figure 3. Pooled results of overall mortality for randomized studies using higher dose WBRT for metastatic cancer to brain compared with 3000 cGy in 10 fractions.



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Notes: Six-month mortality was not obtainable from the Borgelt trial (15). One trial (14) did not have a standard arm of 3000 cGy in 10 fractions.

Symptom control was assessed in seven (15-20,22) of the nine trials comparing altered whole brain dose/fractionation radiotherapy schedules. A variety of scales were used (neurologic functional status, neurologic symptom relief, palliative index, and performance status). None of the seven trials detected a difference in symptom control with altered dose fractionation schedules compared to conventionally fractionated schedules (i.e., 3000 cGy in 10 fractions).

In terms of symptom outcomes, neurological function improvement was reported in 7 studies. The grading systems employed were similar across the studies and are outlined in Table 13a. The scales were typically based on a 4-point scale ranging from (1) minimal interference to (4) where the patient is in a coma or requires constant nursing care. Data on neurological function improvement for the trials that measured this outcome are presented in Table 13b.

For three studies (15,16,20), neurological function improvement was only reported for patients with neurological function grade 2 or 3. The denominator for these three studies represents the number of patients with grade 2 or 3 neurologic status pre-treatment rather than the entire group randomized. Data for neurological function improvement are therefore available for this selected subgroup only (Table 13b).

Within this limitation, the response rate was 47% (419/894), 48% (342/707 or 342/719), and 45% (325/722) in neurologic function improvement for those treated with biologically lower dose, control dose, and higher dose, respectively (Figure 13b). Figures 4 and 5 demonstrate that, overall, there was no statistically significant difference in neurologic function improvement with lower dose versus control dose (RR, 0.95; 95% CI, 0.86 to 1.06; p=0.3) or for higher dose versus control (RR, 0.95; 95% CI, 0.85 to 1.06; p=0.3) (Figure 5). The duration of improvement was not consistently reported.

Trials that reported toxicities are summarized in Tables 14a and 14b. Because numbers are small, definitive conclusions cannot be made.

Table 13a. Neurological function classification system

Study (Ref)	Neurological function evaluation	Detailed definition
Altered whole brain dose/fractionation		
Borgelt et al. 1980, 1981 (15,16)	4-point scale	1 - able to work or to perform normal activities; neurological findings minor or absent 2 - able to carry out normal activities with minimal difficulty; neurological impairment does not require nursing care or hospitalization 3 - seriously limited in performing normal activities; requiring nursing care or hospitalization; patients confined to bed or wheelchair, or have significant intellectual impairment 4 - unable to perform even minimal normal activities; requiring hospital and constant nursing care and feedings; patients unable to communicate or in coma.
Chatani et al. 1985, 1994 (17,18)	4-point scale	Class I - able to work; neurologic findings minor or absent Class II - able to be at home although nursing care may be required; neurologic findings present but not serious Class III - requiring hospitalization and medical care with major neurologic findings Class IV - requiring hospitalization and in serious physical or neurologic state including coma
Haie-Meder et al. 1993 (14)	NA	NA
Harwood et al. 1977 (19)	4-point scale	Level I - intellectually and physically able to work; neurologic abnormalities minor/absent Level II - intellectually intact (oriented, normal conversation); able to be at home though nursing care may be required Level III - major neurologic disability requiring hospitalization and medical care Level IV - profound neurologic disability
Kurtz et al. 1981 (20)	4-point scale	Same as Chatani (16,17)
Murray et al. 1997 (21)	NA	NA
Priestman et al. 1996 (22)	4-point scale (MRC)	MRC Scale 0 - no neurological deficit 1 - some neurological deficit but function adequate for useful work 2 - neurological deficit causing mod functional impairment (e.g., able to move limbs only with difficulty, mod dysphasia, mod paresis, some visual disturbances (e.g., field defect) 3 - neurological deficit causing major functional impairment (e.g., inability to move limb(s) gross speech or visual disturbances) 4 - no useful function; inability to make conscious response

Notes: mod – moderate, MRC – Medical Research Council, NA – not assessed, Ref – reference

Table 13b. Neurological function improvement (altered whole brain dose/fractionation).

Study (Ref)	Neurological function evaluation tool	Control fractionation (3000 cGy/10fr) No. with improvement/ No. in group	Lower dose fractionation No. with improvement/ No. in group	Higher dose fractionation No. with Improvement/ No. in group	
Borgelt et al. 1980, 1981 Study I (4 arms) (15,16)	4-point scale Proportion with improvement, time frame not stated	3000 cGy/10fr 84/181/233	3000 cGy/15fr 96/185/217	4000 cGy/15fr 88/193/233	4000 cGy/20fr 80/182/227
Borgelt et al. 1980, 1981 Study II (3 arms) (15,16)	4-point scale	3000 cGy/10fr 96/178/228	2000 cGy/5fr 181/353/447	4000 cGy/15fr 93/181/227	
Chatani et al. 1985 (17)	4-point scale " show definite improvement"	3000 cGy/10fr 9/35	-	5000 cGy/20fr 9/34	

Chatani et al. 1994 Normal LDH group (18)	4-point scale Improved neurological function, time not stated	3000 cGy/10fr 15/46	-	5000 cGy/20fr 14/46
Chatani et al. 1994 High LDH Group (18)	NR	3000 cGy/10fr 9/35	2000 cGy/5fr 6/35	-
Haie-Meder et al. 1993 (14)	NR	NR	NR	NR
Harwood et al. 1977 (19)	4-point scale "improvement" no definition given, no time given	3000 cGy/10fr 32/50	1000 cGy/1fr 29/51	-
Kurtz et al. 1981 (20)	4-point scale Improvement of neurological class ≥1G	3000 cGy/10fr * 54/98/156	-	5000 cGy/20fr * 41/86/153
Murray et al. 1997 (21)	NR	NR	NR	NR
Priestman et al. 1996 (22)	4-point scale (MRC) Improvement of neurological class ≥1G maintained for ≥4w	3000 cGy/10fr 121/263	1200 cGy/2fr 107/270	-

Notes: cGy – centigray, fr – fraction(s), G – grade, LDH – lactate dehydrogenase, MRC – Medical Research Council, no. – number, NR – not reported, Ref – reference, w – week(s); * Number with improvement in neurological status 2, 3 pre-treatment / No. with neurological status 2, 3 pre-treatment/evaluable patients in group

Figure 4. Neurological function improvement (lower dose versus 3000cGy/10fr).

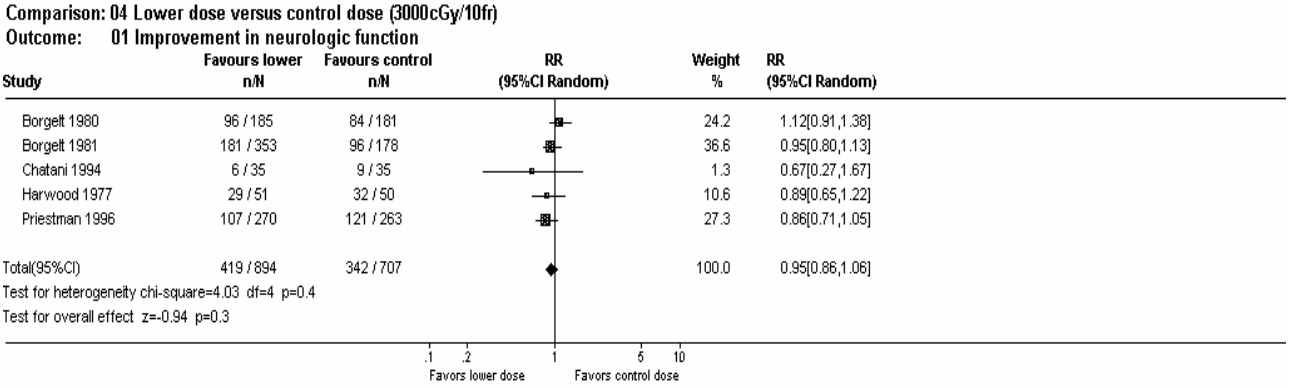

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Figure 5. Neurological function improvement (higher dose versus 3000cGy/10fr).

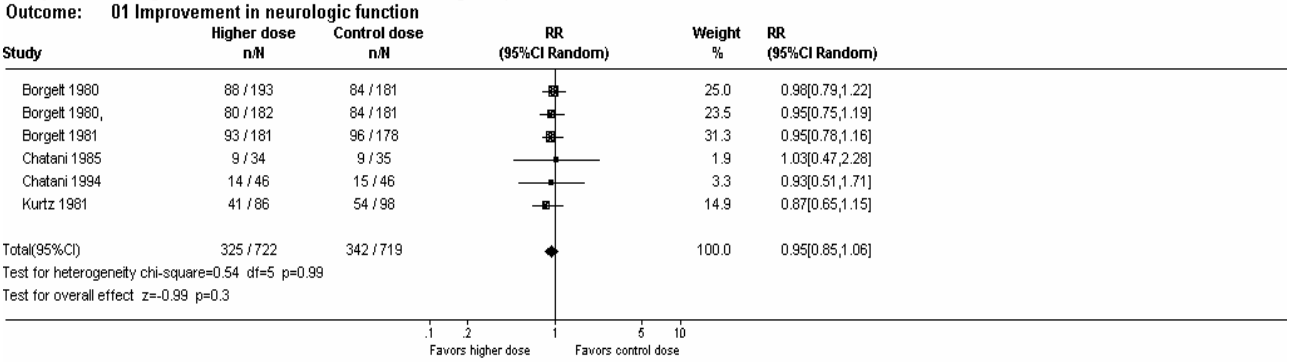

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Table 14a. Toxicity data for studies comparing 3000cGy in 10 fractions versus lower dose.

Study (Ref)	Definition of toxicities	Lower dose	Control dose (3000cGy in 10fr)
Borgelt et al. 1981 (16)	No definition given	No difference	
Chatani et al. 1994 (18)	Nausea, vomiting or headache	45% (14/35) (2000 cGy/5fr)	23% (8/35)
Harwood et al. 1977 (19)	Nausea, vomiting, headache, increased neurologic deficit or fall in level of consciousness	40% (1000 cGy/1fr)	27% p=0.254
Priestman et al. 1996 (22)	Nausea, vomiting, headache, increased neurologic deficit, fall in level of consciousness, cerebral hemorrhage	12% (22/188) (1200 cGy/2fr)	8% (13/167)

Notes: cGy – centigray, fr – fraction(s), Ref – reference

Table 14b. Toxicity data for studies comparing 3000cGy in 10 fractions versus higher dose.

Study (Ref)	Definition of toxicities	Control dose (3000cGy in 10fr)	Higher dose as compared to control dose
Borgelt et al. 1981 (16)	Not stated	No difference	
Chatani et al. 1994 (18)	Nausea, vomiting, or headache	35% (16/46)	21% (10/46) (5000 cGy/20fr)
Murray et al. 1997 (21)	Not stated	No difference in the incidence of acute G3 or late G3/4 toxicity as compared to control One G4 ototoxicity and one G5 toxicity (death due to cerebral edema) in the hyperfractionation arm (5440 cGy/34fr BID).	

Notes: BID – twice daily, cGy – centigray, fr – fraction(s), G – grade, Ref – reference

WBRT plus radiosensitizer versus WBRT alone

Table 15 presents the results of five randomized controlled trials (23-27) that examined the use of radiosensitizers in addition to WBRT. Overall survival at six months was obtainable in three of the five trials. The pooled results are presented in Figure 6. When the three trials were combined, there was no significant difference in mortality at six months (RR, 1.06; 95% CI, 0.93 to 1.20; p=0.4).

Three of the five trials reported on brain response rate (CR + PR). The definition used to define response was a 50% or greater decrease in lesion size, and patients were on a stable or decreasing dose of corticosteroids. The pooled results of patients who achieved CR or PR are presented in Figure 7. There was no significant difference in response rate between treatment arms (RR, 1.00; 95% CI, 0.69 to 1.44; p=1.00). Intracranial progression-free duration was not reported in any of the trials.

Only one trial (25) reported on symptom control with the use of misonidazole and WBRT. Multiple endpoints were reported. These include percentage of patients who spent 90-100% of their survival time in an improved or stable neurological state, median time to deterioration of KPS, and percentage of total survival time spent in an improved or stable KPS. There was no significant difference in any of these endpoints between the treatment arms.

In the trial by Mehta et al. (27,36), no significant difference was detected in median time to neurologic progression (9.5 months [motexafin gadolinium (MGd) + WBRT] versus 8.3 months [WBRT alone]). Subgroup analysis was conducted on 214 patients with lung cancer, recursive partitioning analysis (RPA) class 2 patients. Median time to neurologic progression was not reached for the combined arm and was 6.3 months for the WBRT alone group

(p=0.013). Neurologic progression-free survival at 1 year was 18.6% (MGd + WBRT) and 10.5% (WBRT alone) for lung cancer patients. It was concluded that MGd did not confer an overall advantage in survival or time to neurologic progression for the entire cohort. Based on the subgroup analysis, *there is a suggestion that* patients with lung cancer may benefit.

The gadolinium trial (36) found that there was no significant difference in time to progression of brain-specific quality of life (Functional Assessment of Cancer Therapy-Brain [FACT-BR]) assessment in any of the treatment groups.

Four of the five trials reported on toxicity. In the study by DeAngelis et al. (23), the most common side effects from lonidamine were myalgia (68%), testicular pain (42% of men), anorexia (26%), and ototoxicity (26%), malaise/fatigue (26%) and nausea/vomiting (19%). No acute or subacute radiation-related neurotoxicity was observed in either treatment group. WBRT combined with metronidazole in the Eyre et al. study (24) resulted in a 51% incidence of nausea/vomiting compared with 3.2 % in the WBRT-alone arm. In the study by Komarnicky et al. (25), misonidazole administration was well tolerated and produced no grade 3 neuro- or ototoxicity. However, several grade 3 symptoms of nausea and vomiting (defined as occurring one to three times daily) were noted. There was no increased radiation skin reaction or central nervous system (CNS) injury in the bromodeoxyuridine (BrdUrd) arm in the study by Phillips et al. (26). Three fatal toxicities with BrdUrd were noted. One was a severe Stevens-Johnson skin reaction, and two were due to neutropenia and infection.

Table 15. Randomized studies of WBRT and radiosensitizers versus WBRT alone.

Study (Ref)	Study arms	No. of pts randomized/ (eval)	Overall median survival	Overall survival at 6 months	Response rates (CR + PR)
DeAngelis et al. 1989 (23)	3000 cGy/10fr + lonidamine	31 (19)	4.0m	NR	37% (11.5 pts)
	3000 cGy/10fr	27 (20)	5.4m		55% (15 pts)
Eyre et al. 1984 (24)[1] *	3000 cGy/10fr + metronidazole	(57)	2.8m	14	27% (15 pts)
	3000 cGy/10fr	(54)	3.2m	13	24% (13 pts)
Komarnicky et al. 1991 (25)	3000 cGy/6fr + misonidazole	220 /(196)	3.1m	68	NR
	3000 cGy/6fr	216 /(200)	4.1m	83	
	3000 cGy/10fr + misonidazole	211 /(190)	3.9m	65	
	3000 cGy/10fr	212 /(193)	4.5m	72	
Mehta et al. 2002 (27,36)	3000 cGy/10fr +MGd	193	5.2m	82	NR
	3000 cGy/10fr	208	4.9m	85	
Phillips et al. 1995 (26)	3750 cGy/15fr + BrdUrd	35 (34)	4.3m	12	63% of 22 pts eval for response (14pts)
	3750 cGy/15fr	37 (36)	6.12m	20	50% of 24 pts eval for response (12pts)

Notes: BrdUrd – bromodeoxyuridine, cGy – centigray, CR – complete response, eval – evaluable, fr – fraction(s), m – month(s), MGd-motexafin gadolinium, no. – number, NR – not reported, PR – partial response; pts – patients; Ref – reference, WBRT – whole brain radiotherapy

1 – total Randomized = 116; * Overall survival at 6 months based on number of patients evaluable

Figure 6. Overall mortality at six months for WBRT and radiosensitizers versus WBRT alone.

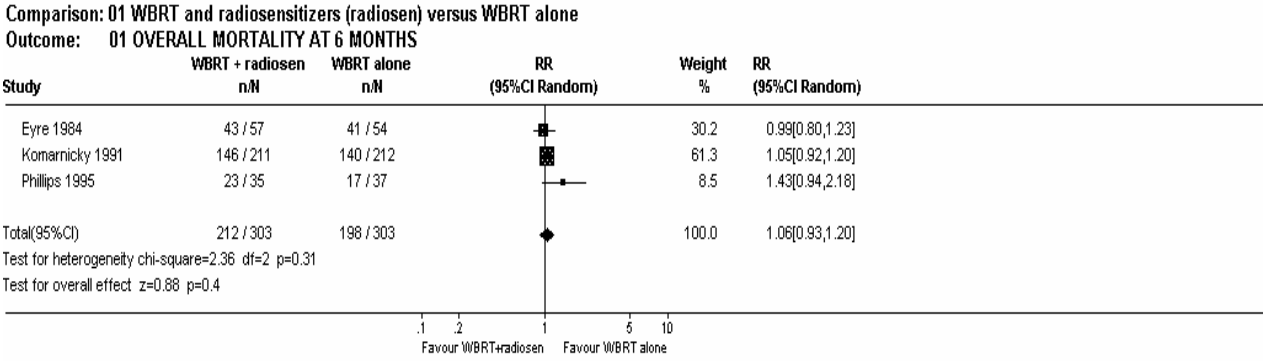

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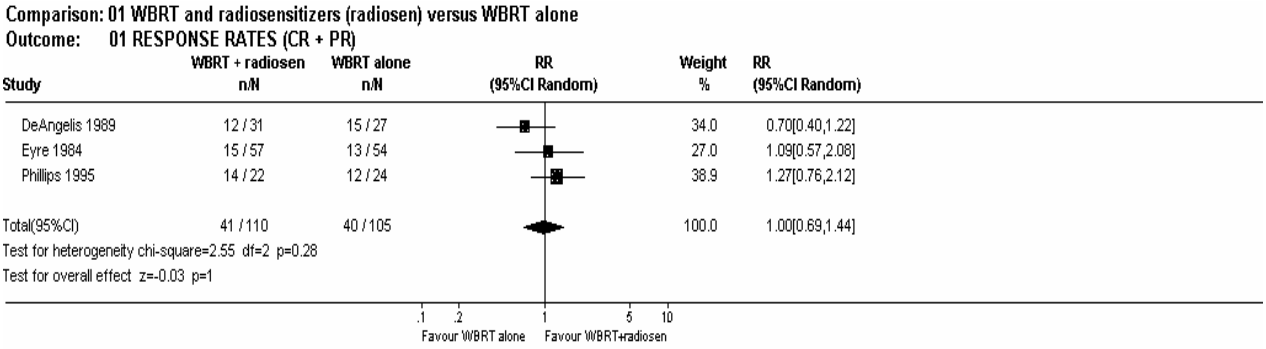
Figure 7. Pooled response rates (CR + PR) from randomized trials of WBRT and radiosensitizers versus WBRT alone.



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Chemotherapy and WBRT

Of the four trials reporting on chemotherapy and WBRT, Postmus et al (35) examined the use of teniposide versus teniposide and WBRT in 120 patients with metastatic small cell lung cancer to the brain. Robinet et al. (28) examined early versus delayed WBRT with concurrent cisplatin and vinorelbine chemotherapy in 176 patients with metastatic non-small cell lung cancer. WBRT was either given early (on day 1-12 during the first cycle of chemotherapy) or delayed (after two to six cycles of chemotherapy for intracranial non-responders). In the randomized controlled trial by Ushio et al. (29), 100 patients were randomized to one of three treatment arms: WBRT alone, WBRT plus chloroethylnitrosoureas (methyl-CCNU or ACNU), or WBRT plus chloroethylnitrosoureas plus tegafur. Antonadou et al. (30) randomized 134 patients to WBRT with or without temozolamide chemotherapy. Results were published in abstract form.

Median survival was 3.5 months in the teniposide plus WBRT arm and 3.2 months in the teniposide alone arm of the Postmus trial (35). Overall survival was not significantly different between these two groups (p=0.087). Robinet et al. (28) did not detect a significant difference in survival between the two arms (median survival 21 weeks versus 24 weeks in the early and delayed radiotherapy arms, respectively). Ushio et al. (29) also failed to detect a significant difference in median survival time between groups (27, 29, and 30.5 weeks, respectively). Median survival was not significantly different between the two arms in the trial reported by Antonadou et al. (8.3 months WBRT + temozolamide versus 6.3 months WBRT alone, p=0.179) (30).

In the trial by Postmus et al. (35), a 57% response rate was seen in the teniposide and

WBRT arm as compared to 22% in the teniposide-alone arm (p<0.001). In the delayed WBRT arm, there was a 21% overall response (CR + PR) after 2 cycles of chemotherapy alone and 20% overall response to chemotherapy and early WBRT (28). Ushio et al. (29) reported tumour regression (more than 50% regression) in 36%, 69%, and 74% of patients receiving WBRT alone, WBRT plus chloroethylnitrosoureas, and WBRT plus chloroethylnitrosoureas plus tegafur, respectively. Response rates were significantly different between the WBRT-alone arm and the WBRT plus chloroethylnitrosoureas plus tegafur arm (p>0.05). Antonadou et al. (30) detected a significantly improved brain response rate in the combined arm (53.4%) compared to the WBRT-alone arm (33.3%, p=0.039).

Postmus (35) reported that time to progression in the brain was longer in the teniposide and WBRT arm compared to the teniposide-alone arm (p=0.005). Intracranial progression-free duration and neurological function were not reported in the other trials. None of the trials reported on quality of life.

Toxicities were said to be “mild” in the Postmus trial (35). The predominant form of toxicity was hematologic. There were 13 toxic deaths in the trial by Robinet et al. (28): seven with the early chemotherapy arm (8.2%) and six with the delayed chemotherapy arm (6.9%). Ten of these deaths were due to sepsis during severe neutropenia. One patient in each arm died of pneumonia without neutropenia after the second cycle of chemotherapy. Another patient died of renal failure in the delayed chemotherapy arm after the first cycle. Two patients died in the trial by Ushio et al. of probable side-effects from chemotherapy (29). Antonadou et al. did not report on toxicity.

WBRT plus radiosurgery versus WBRT alone

Results of three trials examining the use of WBRT with or without radiosurgery are summarized in Table 16. There was only one fully published randomized controlled trial (31) that compared WBRT plus radiosurgery for two to four brain metastases (all no larger than 25mm in size). This study was stopped at 60% accrual (outcomes of 27 patients were reported).

None of the trials that assessed WBRT with or without radiosurgery detected a significant difference in overall survival. In a subsequent abstract (34), the Radiation Therapy Oncology Group (RTOG) performed subgroup analyses on multiple subgroups:

1. Solitary brain metastasis (median survival time 6.5 versus 4.9 months, p=0.04)
2. Recursive Partitioning Analysis (RPA) class I (median survival time 11.6 versus 9.6 months, p=0.05)
3. Age < 50 (9.9 versus 8.3 months, p=0.04)
4. Patients with non-small cell lung cancer or any squamous cell carcinoma (5.9 versus 3.9 months, p=0.05).

Although the subgroup analyses were statistically significant in favour of solitary brain metastases, RPA class I, age <50, and patients with non-small cell lung cancer or squamous cell carcinoma, the clinical significance of the observed differences need to be included in the decision-making process. In addition, the findings should be considered suitable for hypotheses generation rather than confirmatory evidence, since the primary study result was negative and the study was not powered to address these subgroups separately. Further trials are needed to confirm whether survival is improved when using WBRT and radiosurgery boost as compared to WBRT alone in these specific patient populations

None of the three trials reported on tumour response or neurological function. Kondziolka et al. (31) found the rate of local brain failure was 100% after WBRT and 8% in those treated with boost radiosurgery. The RTOG (33) detected a slight but not statistically significant advantage in the WBRT and radiosurgery arm. The failure rate was 21% in the

WBRT and radiosurgery arm versus 37% in the WBRT-alone arm at 1 year (p=0.107). While local control was 87% and 91% in the two radiosurgery arms (versus 62% in the WBRT alone arm) in the trial by Chougule et al., the occurrence of new brain lesions was lower in the two arms receiving WBRT (43%, 19%, and 23% for gamma knife, GK and WBRT, and WBRT alone, respectively).

Quality of life will be reported when the full report of the RTOG trial (33) becomes available. The other two trials did not report on quality of life. In terms of toxicity, Kondziolka et al. (31) found no neurologic or systemic morbidity related to stereotactic radiosurgery. The RTOG reported no grade 4 or 5 toxicities in either group. Four percent (3/69) of patients treated with WBRT and stereotactic boost had acute grade 3 toxicity compared with 0% (0/70) of patients treated with WBRT alone. Late grade 3 toxicity occurred in 5% (2/39) of patients treated with WBRT and stereotactic boost compared with 2% (1/51) treated with WBRT alone. All grade 3 toxicities were neurologic in origin. The fully published article is pending.

Table 16. Results of studies assessing WBRT with or without radiosurgery.

Study (Ref)	Study arms	No. of pts randomized (eval)	Overall median survival	One year local brain control
Chougule et al. 2000 (32) [1] (abstract)	GK alone	36	7m	87%
	GK and WBRT(3000 cGy/10fr)	37	5m	91%
	WBRT (3000cGy/10fr)	31	9m NS	62% no p value stated
Kondziolka et al. 1999 (31)	WBRT (3000 cGy/12fr)	14	7.5m	0%
	WBRT (3000 cGy/12fr) and radiosurgery	13	11m p= 0.22	92% p=0.0016
Sperduto et al. 2002 (33) [2] 2002 (34) (abstract)	WBRT (3750 cGy/15fr)	No. pts per arm not reported	6.7m	63%
	WBRT (3750 cGy/15fr) and radiosurgery		5.3m p=0.59	79% p=0.107

Notes: cGy-centigray, fr – fraction(s), GK – gamma knife, m – months, No. – number, NS – not significant, WBRT– whole brain radiotherapy;
1 – total number evaluable = 96; 2 – total no. of patients randomized = 144 (139 evaluable)

V. INTERPRETIVE SUMMARY

Single Brain Metastasis

Two of the three trials using WBRT with or without surgical excision of a single brain metastasis detected an overall survival benefit favouring the addition of surgery. The trial that did not detect a benefit (9), however, included more patients with poorer performance status and a higher proportion of patients with extracranial disease as compared to the other two trials.

The randomized trial by Patchell et al. (12) reported on the use of surgery with or without WBRT. A significant improvement in brain recurrence rates was detected in the S+WBRT arm, but there was no significant difference in overall survival.

The methodologic quality of the studies was similar. However, description of withdrawals and dropouts was variable. Only the Patchell trials (11, 12) required MRI-confirmed single metastasis. As such, those trials which relied on brain CT may have included patients with multiple brain metastases rather than single. The benefit of adding surgery in these patients with truly multiple brain metastases may have been diminished.

In the trials examining the use of S+WBRT for single brain metastasis, the WBRT doses were 3000 cGy/10 fractions daily (9), 4000 cGy/20 fractions given twice a day (10), 3600 cGy/12 fractions daily (11) and 5040 cGy/28 fractions daily (12). As such, the use of 2000 cGy/5 fractions of WBRT has not been studied directly in this scenario.

The evidence provided in this report suggests that surgical resection of a single brain metastasis in a patient with good performance status (KPS $\geq$ 70) and stable or no extracranial disease may improve overall survival. The addition of WBRT after surgical resection of a single brain metastasis decreases brain recurrence rates.

Multiple Brain Metastases

There was only one randomized trial (13) that examined the use of prednisone with or without WBRT. This was an older trial reported in the pre-CT era with a small sample size of 48 patients. The diagnosis of brain metastases was based on older outdated criteria and not based on contemporary CT or MRI criteria. The proportion of patients with an improvement in performance status was similar in the steroid alone and combined WBRT and steroid arms (63% and 61% respectively). The median survival of the steroid-alone arm was 10 weeks as compared to the combined-arm median of 14 weeks (p value not stated). The methodologic quality of this study was poor. Sample size calculations were not described a priori, and a description of dropouts and withdrawals was not provided. Statistics were not performed. As such, the magnitude of benefit with the use of WBRT over supportive care alone, in terms of symptom control, quality of life, or survival, remains unclear, particularly in patients with poor performance status and/or active extracranial disease.

In several randomized controlled trials included in this review, a significant benefit in terms of overall survival or symptom control was not detected with altered dose-fractionation schedules as compared with a standard dose-fractionation schedule (3000 cGy in 10 fractions). The methodologic quality of included studies was similar. Details of randomization (e.g., blinding of randomization) were rarely provided. Complete follow-up was variable among the studies. None of the trials reported on the blinding of outcomes. Furthermore, none of the negative trials commented on confidence intervals or power calculations. A lack of sufficient high quality evidence precludes recommendations on which treatment regimen(s) provide the greatest improvement in symptom control.

In an attempt to improve the response of brain metastases to treatment, radiosensitizers have been added to WBRT. However, of the four randomized controlled trials reported, none detected a benefit in terms of overall survival or brain response (CR + PR). None of the trials examining the use of radiosensitizers were double-blind. However in the gadolinium trial (27, 36), the events review committee (ERC) were blinded to treatment assignment and reviewed baseline and follow-up data. Based on subgroup analysis, there was a suggestion that RPA Class II lung cancer patients with metastatic cancer to brain may benefit from the use of motexafin gadolinium and WBRT. This is being studied in a phase III trial (UCLA 0302038). This trial specifically examines the population of patients with metastatic non-small cell lung cancer and randomizes them to WBRT with or without motexafin gadolinium.

For metastatic small cell lung cancer, Postmus (35) found no difference in overall survival in patients treated with teniposide alone versus teniposide and WBRT. Although the combined arm had higher brain response rates, there is no comparison with WBRT alone. This study showed that chemotherapy alone is inferior to the use of WBRT and chemotherapy for improved brain metastases response rates. However, it does not address the question of whether WBRT alone is superior or equivalent to WBRT and chemotherapy for the brain response and neuropsychological outcomes.

For metastatic non-small cell lung cancer, Robinet (28) found no difference in overall survival with early versus delayed WBRT when given with chemotherapy. Delayed WBRT was given to intracranial non-responders to chemotherapy. This non-blinded study was powered to detect a 25% improvement in six-month survival rate. Approximately 13% of patients were not evaluable for intracranial or extracranial response. However, withdrawals and dropouts were described in terms of numbers and reasons per group. There was 21% overall response (CR + PR) after two cycles of chemotherapy alone and 20% overall response to chemotherapy and

early WBRT. Six-month survival was no different between the two arms. The results confirmed that chemotherapy alone may reduce the size of brain metastases from metastatic non-small cell lung cancer. The timing of WBRT in relation to chemotherapy did not affect survival. However, it was not possible to establish from the results of this trial the optimal timing of WBRT when given concurrently with chemotherapy.

In a non-blinded study, Ushio et al. (29) randomized patients with metastatic lung cancer to the brain to one of three groups (WBRT alone, WBRT + chloroethylnitrosoureas, or WBRT + chloroethylnitrosoureas + tegafur). No difference in overall survival was seen among the three groups. Brain response rates were statistically different between the WBRT-alone arm and the WBRT plus chloroethylnitrosoureas plus tegafur arm. However, twelve patients were excluded from the evaluation due to protocol violations that may have skewed the results of the study, given the small number of patients. Two patients died of probable side effects of chemotherapy.

Antonadou (30) found no difference in overall survival in patients treated with WBRT and temozolamide chemotherapy versus WBRT alone. However, an improved brain response rate was seen in the combined arm. These results were published in abstract form. Further trials are needed to confirm a benefit in the durability of brain metastases response with the addition on chemotherapy to WBRT.

There has been only one published randomized trial reporting the use of radiosurgery in addition to WBRT (31). The trial was small (n=27), and the results were reported early at 60% accrual. Furthermore, the 100% recurrence rate in the WBRT-only arm was unusually high. A reduction in brain recurrence rate was found with the addition of radiosurgery, but no difference in overall survival was noted. A preliminary report of the RTOG 95-08 trial (33) examining WBRT with or without radiosurgical boost for patients with two or three brain metastases found no survival benefit, and an analysis of brain failure rates showed a slight, but not statistically significant, advantage in the WBRT and radiosurgery arm (21% versus 37% at 1 year; p=0.107). The full published report is pending. Another trial published in abstract form (32) examined the use of GK RS, WBRT, or both in the treatment of one to three brain metastases. There was no difference in overall survival. Local control rates were superior for the GK RS and GK RS plus WBRT arms. Thus, the use of radiosurgery may improve local control of brain metastases when used in conjunction with WBRT. However, overall survival is not improved. The optimal timing of radiosurgery has not been elucidated. The question of whether radiosurgery should be used as boost treatment with WBRT, at the time of relapse after WBRT, or used alone, reserving WBRT for future extensive brain relapse, remains unanswered.

VI. ONGOING TRIALS

The Supportive Care Guidelines Group is aware of the following trials:

Protocol ID(s)	Title and details of trial
RTOG-9508 trial (33,34)	Trial comparing WBRT with or without stereotactic radiosurgical boost is closed. The full published report is pending.
ACOSOG-Z0300	The American College of Surgeons Oncology Group is conducting a phase III randomized study of radiosurgery with or without WBRT in patients with one to three cerebral metastases. Protocol amendment June 2003. This trial is still open.
ALLOS-RSR13RT-009	A phase III trial of WBRT with or without RSR13 in patients with brain metastases. Completed accrual September 2001. Published results are pending.
EORTC-18981	Phase III randomized trial examining the use of temazolamide chemotherapy with or without WBRT in 250 patients with stage IV melanoma with asymptomatic brain metastases. This trial closed in May 2003. Published results are pending.

EORTC-22952 -26601	Randomized phase III trial examining the use of convergent-beam radiotherapy followed by adjuvant WBRT compared to no further radiotherapy for brain metastases. Projected accrual 340 patients. This trial is still open.
RTOG-BR-0118, RTOG-DEV-1006	A phase III randomized RTOG trial on conventional radiotherapy with or without thalidomide in patients with multiple brain metastases. Projected accrual 332 patients. This trial is still open
UCLA-0302038	A phase III randomized trial of whole brain radiotherapy with or without motexafin gadolinium in patients with non-small cell lung cancer metastatic to brain. Projected accrual 550 patients.

VII. SUPPORTIVE CARE GUIDELINES GROUP CONSENSUS

A draft outline of this practice guideline report was discussed at the Neuro-oncology DSG meeting in February 2002, with a view to submit the final form of these guidelines under the auspices of the SCGG. The Neuro-oncology DSG felt that the guideline should include sections on single brain metastasis and refer readers to Practice Guideline Report #9-1 for more detail on single brain metastases. The group also suggested including surgical options for patients with multiple brain metastases. As such, the title of the guideline was changed from *Radiotherapy for Brain Metastases* to *Management of Brain Metastases*.

At the next Neuro-oncology DSG meeting in September 2002, the Neuro-oncology DSG learned that the Protocol on this topic was accepted by the Cochrane Library. The guideline report was discussed at the SCGG meeting in November 2002, at which time some concerns about the methodology and interpretation of the studies were raised. A suggestion was made to include a statement that the numbers of patients in the studies that had 3000 cGy in 10 fractions versus 2000 cGy in five fractions was small. The authors included a qualifying statement in response to this comment. Further modifications to the draft report as a result of feedback from the SCGG included adding a bullet to the recommendations to state that there is no advantage of other altered-dose-fractionation WBRT schedules, adding subtitles to the recommendations relating to the intervention, and modifying the guideline question to include radiotherapy *alone or in combination with other treatment regimens*.

The Neuro-oncology DSG discussed the guideline again in May 2003, since much new information and tables had been added. The DSG questioned the relevance of having separate guidelines on similar topics by two different guideline groups. Dr. Tsao maintained that two guidelines were necessary as the SCGG's guideline has a greater palliative focus than does the one by the Neuro-oncology DSG. The information in the two guidelines is consistent. The Neuro-oncology DSG suggested revising the recommendation under "Radiotherapy and Surgery for Single Brain Metastasis" from "postoperative WBRT is recommended…" to "postoperative WBRT *should be used*…", since the evidence is available to make a stronger statement. Modifications were made in response to the group's suggestion.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the SCGG, with the opinions of the Neuro-oncology DSG, drafted the following recommendations:

Target Population

These recommendations apply to adult patients with a clinical and radiographic diagnosis of brain metastases (single or multiple) arising from cancer of any histology.

Radiotherapy and surgery for single brain metastasis:

- Surgical excision is recommended, in addition to whole brain radiotherapy, for patients with

good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision.
- Postoperative whole brain radiotherapy should be used to improve brain control for patients who have undergone resection of a single brain metastasis.

Radiotherapy for multiple brain metastases:
- Whole brain radiotherapy is the recommended volume of treatment for multiple brain metastases. Commonly used dose fractionation schedules are 3000 cGy in 10 fractions or 2000 cGy in five fractions.
- There are no advantages of other altered dose fractionation whole brain radiotherapy schedules in terms of overall survival or neurologic function.
- The use of radiosensitizers is not recommended outside research studies.
- The optimal use of radiosurgery in the treatment of brain metastases remains to be defined. In patients with one to three brain metastases (less than 3 cm in size) and limited or controlled extracranial disease, radiosurgery may be considered to improve local control either as boost therapy with whole brain radiation or at the time of relapse after whole brain radiotherapy failure.

Chemotherapy and whole brain radiotherapy:
- The use of chemotherapy as primary therapy for brain metastases (with whole brain radiotherapy used for intracranial non-responders) or the use of chemotherapy with whole brain radiotherapy to treat brain metastases remains experimental.

Supportive Care and whole brain radiotherapy
- Supportive care alone without whole brain radiotherapy is an option for patients with poor performance status or widely disseminated progressive cancer.

Qualifying Statements
- The number of patients included in the two trials comparing 3000 cGy in 10 fractions versus 2000 cGy in 5 fractions for multiple brain metastases was small.
- In the trials examining the use of surgery and WBRT for single brain metastasis, the WBRT doses were 3000 cGy/10 fractions daily, 4000 cGy/20 fractions given twice daily, 3600 cGy/12 fractions daily, and 5040 cGy/28 fractions daily. As such, the use of 2000 cGy/5 fractions of WBRT has not been studied directly in this scenario.

Related Guideline
Practice Guidelines Initiative's Practice Guideline Report #9-1: *Treatment of Single Brain Metastasis*.

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 246 practitioners in Ontario (26 neurosurgeons, 137 medical oncologists, and 83 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 14, 2003. Follow-up reminders were sent at two weeks (post card)

and four weeks (complete package mailed again). The SCGG reviewed the results of the survey.

Results

One hundred nine responses were received out of the 246 surveys sent (44% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 85 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 17.

Table 17. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	82 (98%)	1 (1%)	1 (1%)
There is a need for a clinical practice guideline on this topic.	70 (83%)	12 (14%)	2 (2%)
The literature search is relevant and complete.	77 (94%)	5 (6%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	81 (96%)	3 (4%)	0
The draft recommendations in this report are clear.	81 (96%)	1 (1%)	2 (2%)
I agree with the draft recommendations as stated.	79 (94%)	2 (2%)	3 (4%)
This report should be approved as a practice guideline.	77 (92%)	6 (7%)	1 (1%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	57 (68%)	6 (7%)	21 (25%)

Summary of Written Comments

Twenty-three respondents (27%) provided written comments. The main points contained in the written comments were:

1. Nine practitioners commented that they agreed with the draft guideline report and found the recommendations to be reflective of current practice in their center.
2. One practitioner commented that the recommendation on radiosurgery has implications in terms of availability of services in Ontario.
3. One practitioner felt that treating patients with ≥2 metastases with radiosurgery would not be beneficial.
4. Two practitioners suggested combining this guideline report with Practice Guideline Report #9-1 on the treatment of single brain metastasis.
5. One practitioner noted that the there is not enough evidence to recommend WBRT over supportive care alone even for patients with good performance status and limited extracranial disease.
6. A comment was made that because of the radiation resource implications, the guideline should clearly recommend 2000 cGy in five fractions as standard.
7. One practitioner noted that the guideline should clearly state that it does not apply to the management of choriocarcinoma and the other germ cell tumours and hematologic malignancies. He/she also suggested noting that the trials are most applicable to lung, breast, and colorectal cancer patients with brain metastases and that other cancers require individualized management. Two other practitioners also commented that the results may

not be generalizable to all tumour types and that the main problem with interpreting the literature (with the exception of the chemotherapy studies) is that patients with a wide variety of tumours (and hence radiosensitivities) are included.

8. One practitioner questioned whether any trials have assessed WBRT in one to two fractions for patients with brain metastases with adequate performance status.
9. One practitioner suggested including RTOG BR-0119, a randomized phase II study of a.m. and p.m. melatonin for brain metastasis in RPA class II patients.
10. One practitioner commented that he/she found the report very informative and noted that he/she would like to see some evidence on stereotactic radiosurgery, noting that in his/her experience patients did better than with conventional WBRT.
11. One practitioner suggested clarifying the recommendations on the role of stereotactic radiotherapy for two to four small brain metastases.
12. One practitioner commented that not all patients should have treatment (i.e., patients with poor performance status and systemic metastases should not have radiotherapy).
13. One practitioner suggested rewording the language used to describe the clinical circumstance, such as brain control.

Modifications/Actions

1. No modifications required.
2. Radiosurgery resources in Ontario are available in specialized centers. The recommendations are written on the basis of evidence rather than resource limitations. It is recognized that the optimal use of radiosurgery in selected patients remains to be defined.
3. Whether or not treatment of two or more brain metastases with radiosurgery would be beneficial has not been evaluated in the context of Level 1 evidence.
4. While there is an overlap between the guideline reports on single and multiple brain metastases, it is felt that the current guideline provides more detail on radiotherapy management while the guideline on single brain metastasis has a greater emphasis on surgical issues.
5. It is agreed that there are not enough data to recommend radiotherapy over supportive care alone even for patients with good performance status and limited extracranial disease. As such, the recommendation on supportive care alone without WBRT was revised.
6. The studies of altered dose fractionation schemes used 3000 cGy in 10 fractions as the standard arm. Only two trials examined the use of 2000 cGy in five fractions versus 3000 cGy in 10 fractions. In the Borgelt trial (15), 447 patients were randomized to 2000 cGy in five fractions versus 228 patients to 3000 cGy in 10 fractions. In the Chatani trial (18) only 35 patients were randomized to 2000 cGy in five fractions and 35 patients were randomized to 3000 cGy in 10 fractions. The sample size for the studies examining the use of 2000 cGy in five fractions was smaller as compared to the standard regimen of 3000 cGy in 10 fractions. Furthermore, various histologies were included in these studies. The trials were not powered to detect differences in outcome based on histology and therefore may not be generalizable to all tumour types. As such, either 3000 cGy in 10 fractions or 2000 cGy in five fractions are the recommended dose fractionation schedules.
7. A qualifying statement that the site of the primary tumour may impact the recommendations was added. An exception was made to the target population for clarification in response to this comment. The limitations of the studies with regard to management based on specific tumour type have been added to the guideline report.
8. One trial included in this guideline report by Harwood (19) assessed single fraction WBRT in patients stratified by functional status.
9. The eligibility criteria state that only phase III randomized trials were included.

10. The randomized trials pertaining to radiosurgery are described in this guideline report.
11. Only three randomized trials examined the use of WBRT with or without radiosurgery of which only one small trial has been fully published. Fully published results of the other two trials may enable further treatment recommendations. In general, radiosurgery boost after WBRT may be associated with a reduction in brain recurrence rates, but studies to date have not demonstrated survival benefit. The optimal use of radiosurgery remains to be elucidated.
12. The recommendations state that supportive care alone is an option for patients with poor performance status.
13. Where appropriate, the term "brain control" was revised to "intracranial progression-free duration".

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Four of eight members of the PGCC returned ballots. Three PGCC members approved the practice guideline report as written, while one member approved the guideline and provided a suggestion for consideration by the Supportive Care Guidelines Group. The member suggested revising the wording under the recommendation for single brain metastasis to "considered" rather than "recommended" as the evidence for benefit is not compelling.

Modifications/Actions

The SCGG agreed and made the suggested revision.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Supportive Care Guidelines Group and by the Practice Guidelines Coordinating Committee.

Target Population

The recommendations apply to adult patients with a clinical and radiographic diagnosis of brain metastases (single or multiple) arising from cancer of any histology (except for choriocarcinoma and other germ cell tumours, and hematologic malignancies).

Recommendations

Radiotherapy and Surgery for Single Brain Metastasis:

- Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision.
- Postoperative whole brain radiotherapy should be considered to reduce the risk of tumour recurrence for patients who have undergone resection of a single brain metastasis.

Radiotherapy for Multiple Brain Metastases:

- It is recommended that the whole brain be irradiated for multiple brain metastases. Commonly used dose fractionation schedules are 3000 cGy in 10 fractions or 2000 cGy in five fractions.
- Altered dose fractionation whole brain radiotherapy schedules have not demonstrated any advantages in terms of overall survival or neurologic function relative to more commonly used fractionation schedules.
- The use of radiosensitizers is not recommended outside research studies.

- The optimal use of radiosurgery in the treatment of brain metastases remains to be defined. In patients with one to three brain metastases (less than 3 cm in size) and limited or controlled extracranial disease, radiosurgery may be considered to improve local tumour control either as boost therapy with whole brain radiation or at the time of relapse after whole brain radiotherapy.

Chemotherapy and Whole Brain Radiotherapy:

- The use of chemotherapy as primary therapy for brain metastases (with whole brain radiotherapy used for those whose intracranial metastases fail to respond) or the use of chemotherapy with whole brain radiotherapy to treat brain metastases remains experimental.

Supportive Care and Whole Brain Radiotherapy

- Supportive care alone without whole brain radiotherapy is an option (for example, in patients with poor performance status and progressive extracranial disease). However, there is a lack of Level 1 evidence to guide practitioners as to which subsets of patients with brain metastases should be managed with supportive care alone without whole brain radiotherapy.

Qualifying Statements

- The number of patients included in the two trials comparing 3000 cGy in 10 fractions versus 2000 cGy in five fractions for multiple brain metastases was small.
- In the trials examining the use of surgery and whole brain radiotherapy for single brain metastasis, the whole brain radiotherapy doses were 3000 cGy in 10 fractions daily, 4000 cGy in 20 fractions given twice daily, 3600 cGy in 12 fractions daily, and 5040 cGy in 28 fractions daily. As such, the use of 2000 cGy in five fractions of whole brain radiotherapy has not been studied directly in this scenario.
- The results of the studies may not be generalizable to all tumour types. The majority of the patients in the studies (except the chemotherapy studies) had lung, breast, or colorectal cancer primaries.

Related Guideline

Practice Guidelines Initiative's Practice Guideline Report #9-1: *Treatment of Single Brain Metastasis*.

X. JOURNAL REFERENCE

The systematic review was submitted to the Cochrane Collaboration and is currently undergoing review. Publication of the practice guideline is in progress.

XI. ACKNOWLEDGEMENTS

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For a complete list of the Supportive Care Guidelines Group and Neuro-oncology Disease Site Group members, and the Practice Guideline Coordinating Committee members, please visit our web site at: http://www.cancercare.on.ca/access_PEBC.htm.

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