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Title

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Permalink

https://escholarship.org/uc/item/585431dx

Journal

Journal of Neuro-Oncology, 96(1)

ISSN

0167-594X

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Publication Date

2010

DOI

10.1007/s11060-009-0060-9

Copyright Information

Peer reviewed

INVITED MANUSCRIPT

The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

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Abstract

Should whole brain radiation therapy (WBRT) be used as the sole therapy in patients with newly-diagnosed, surgically accessible, single brain metastases, compared with WBRT plus surgical resection, and in what clinical settings?

Target population

This recommendation applies to adults with newly diagnosed single brain metastases amenable to surgical resection; however, the recommendation does not apply to relatively radiosensitive tumors histologies (i.e., small cell lung cancer, leukemia, lymphoma, germ cell tumors and multiple myeloma).

Recommendation

Surgical resection plus WBRT versus WBRT alone

Level 1 Class I evidence supports the use of surgical resection plus post-operative WBRT, as compared to WBRT alone, in patients with good performance status (functionally independent and spending less than 50% of time in bed) and limited extra-cranial disease. There is insufficient evidence to make a recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.

If WBRT is used, is there an optimal dosing/fractionation schedule?

Target population

This recommendation applies to adults with newly diagnosed brain metastases.

Recommendation

Level 1 Class I evidence suggests that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control or neurocognitive outcomes when compared with "standard" WBRT dose/fractionation. (i.e., 30 Gy in 10 fractions or a biologically effective dose (BED) of 39 Gy10).

If WBRT is used, what impact does tumor histopathology have on treatment outcomes?

Target population

This recommendation applies to adults with newly diagnosed brain metastases.

Recommendation

Given the extremely limited data available, there is insufficient evidence to support the choice of any particular dose/fractionation regimen based on histopathology.

The following question is fully addressed in the surgery guideline paper within this series by Kalkanis et al. Given that the recommendation resulting from the systematic review of the literature on this topic is also highly relevant to the discussion of the role of WBRT in the management of brain metastases, this recommendation has been included below.

Does the addition of WBRT after surgical resection improve outcomes when compared with surgical resection alone?

Target population

This recommendation applies to adults with newly diagnosed single brain metastases amenable to surgical resection.

Recommendation

Surgical resection plus WBRT versus surgical resection alone

Level 1 Surgical resection followed by WBRT represents a superior treatment modality, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone.

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Rationale

Whole-brain radiation therapy (WBRT) has long been a
standard treatment for patients with brain metastases.
Based on preclinical and observational data, some physi-
cians alter dose fractionation or withhold WBRT based
upon tumor histology.

This paper will systematically review the evidence
available for altered WBRT dose fractionation and the
impact of tumor histopathology on treatment outcomes
when WBRT is used. In addition, this paper will also
systematically review the evidence for the use of surgical
resection plus WBRT compared with WBRT alone in
patients with newly diagnosed, surgically accessible, single
brain metastases. The studies identified through this process
will be used to make evidence-based recommendations for

the role of WBRT in the management of patients with
newly diagnosed brain metastases.

As WBRT has been a mainstay of the treatment
approach for patients with brain metastases, several other
papers in this guideline series also include comparisons and
recommendations regarding the use of WBRT for this
patient population. Of particular note are the papers by
Kalkanis et al. [1], (surgical resection) and Linskey et al.
[2], (stereotactic radiosurgery) for patients with newly
diagnosed brain metastases.

Methods

Search strategy

The following electronic databases were searched from
1990 to September 2008: MEDLINE®, Embase®, Coch-
rane Database of Systematic Reviews, Cochrane Con-
trolled Trials Registry, and Cochrane Database of Abstracts
of Reviews of Effects. A broad search strategy using a
combination of subheadings and text words was employed.
The search strategy is documented in the methodology

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paper for this guideline series by Robinson et al. [3] Reference lists of included studies were also reviewed.

Eligibility criteria

(a) For WBRT versus surgical resection plus WBRT question:

- Published in English with a publication date of 1990 forward.
- Patients with newly diagnosed single brain metastases.
- Fully published peer-reviewed primary comparative studies (all comparative study designs for primary data collection included; e.g., randomized controlled trials (RCTs), non-randomized trials, cohort studies or case–control studies)
- Study comparisons include: WBRT versus surgery + WBRT
- Number of participants with newly diagnosed brain metastases >5 per study arm
- Baseline information on study participants is provided by treatment group in studies evaluating interventions exclusively in patients with newly diagnosed brain metastases. For studies with mixed populations (i.e., includes participants with conditions other than newly diagnosed brain metastases), baseline information is provided for the intervention sub-groups of participants with newly diagnosed brain metastases.

(b) For optimal dosing/fractionation schedule for WBRT question:

- Published in English.
- Patients with newly diagnosed brain metastases.
- Fully published peer-reviewed primary comparative studies (all comparative study designs for primary data collection included; e.g., RCT, non-randomized trials, cohort studies or case–control studies) for studies published 1990 forward; RCTs published 1970 forward.
- Study comparisons include: WBRT dose/fractionation schedule 1 versus WBRT dose/fractionation schedule 2
- Number of participants with newly diagnosed brain metastases >5 per study arm.
- Baseline information on study participants is provided by treatment group in studies evaluating interventions exclusively in patients with newly diagnosed brain metastases. For studies with mixed populations (i.e., includes participants with conditions other than newly diagnosed brain metastases), baseline information is provided for

the intervention sub-groups of participants with newly diagnosed brain metastases.

(c) For whether tumor histopathology has an impact on WBRT treatment outcomes?

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

Study selection and quality assessment

Two independent reviewers evaluated citations using a priori criteria for relevance and documented decisions in standardized forms. Cases of disagreement were resolved by a third reviewer. The same methodology was used for full text screening of potentially relevant papers. Studies which met the eligibility criteria were data extracted by one reviewer and the extracted information was checked by a second reviewer. The PEDro scale [4, 5] was used to rate the quality of randomized trials. The quality of comparative studies using non-randomized designs was evaluated using eight items selected and modified from existing scales.

Meta-analyses

Meta-analyses of RCTs were undertaken when sufficient data for pooling was available for the outcomes of interest. For the following outcomes, 6 month mortality, overall survival and neurologic function, the altered WBRT dose/fractionation schedules were compared to conventional scheduling. The pooled relative risk (RR) was estimated using a random-effects model and each RCT was weighted

by the inverse of its variance. Chi-square heterogeneity tests were used to test for statistical heterogeneity amongst the RCTs. I^2 was calculated in order to quantify inconsistency across trials and assess the impact of heterogeneity on the meta-analysis. Publication bias was evaluated graphically with funnel plots. All statistical analyses were carried out using Revman 5.

Evidence classification and recommendation levels

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

Guideline development process

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

Scientific foundation

Overall, 24 primary studies [6–29] and seven companion papers [30–36] met the eligibility criteria for this systematic review (Fig. 1).

Fig. 1 Flowchart of studies to final number of eligible studies
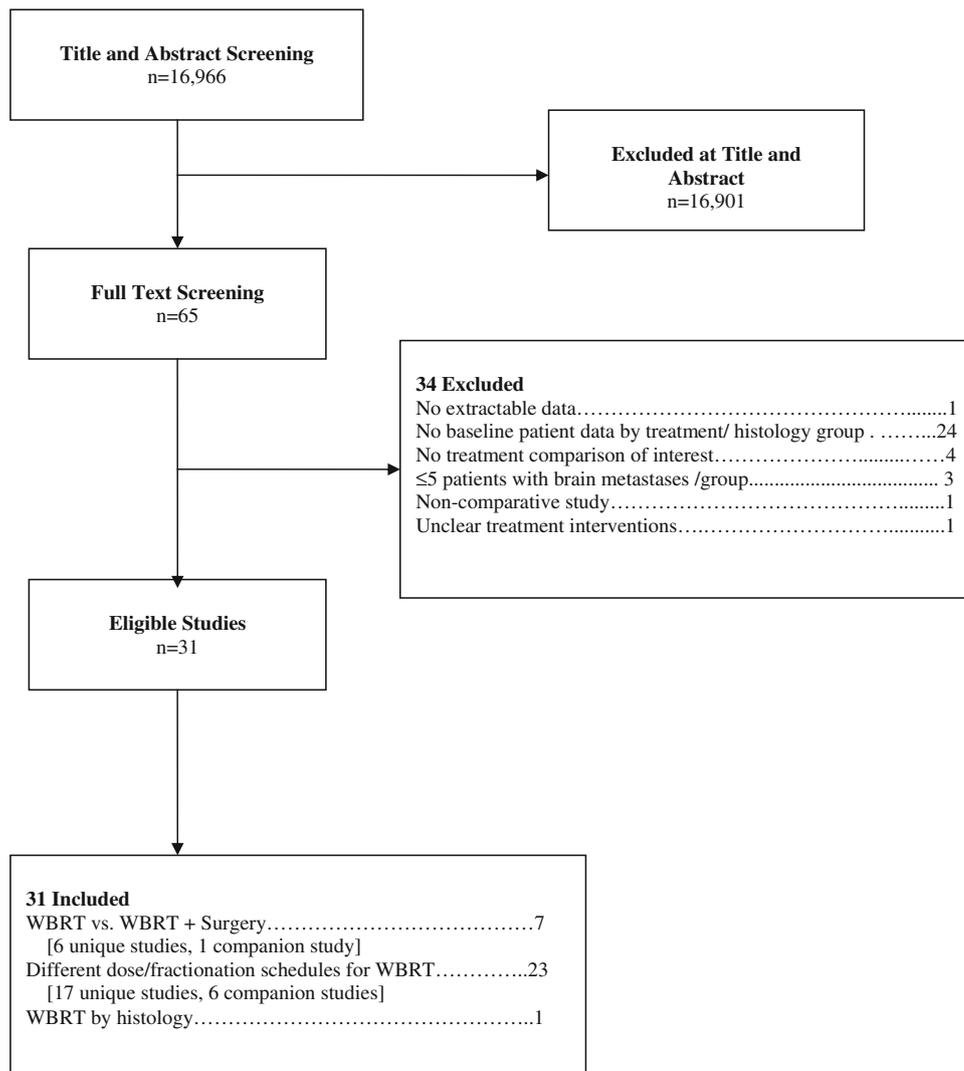
Surgical Resection plus WBRT versus WBRT alone

Seven studies met the eligibility criteria for this treatment comparison, and of these six were unique and one was a companion study [6–11, 30]. Three of these studies were prospective randomized trials [6–8] (Table 1). Given that the treatment modalities being compared included surgical resection in only one arm of each trial, all of the RCTs were non-blinded. In a randomized trial performed at the University of Kentucky [6], 48 patients with known systemic cancer were treated with either biopsy of the suspected brain metastasis plus WBRT or complete surgical resection of the metastasis plus WBRT. The radiation doses were the same in both groups and consisted of a total dose of 36 Gy given in 12 daily fractions of 3 Gy each. Patients had to be capable of caring for themselves independently, with a Karnofsky performance score (KPS) of at least 70. Patients were ineligible if they had a need for immediate treatment to prevent acute neurologic deterioration, or if they had tumors considered to be relatively radiosensitive [small cell lung cancer (SCLC), germ-cell tumors, lymphoma, leukemia, and multiple myeloma]. Patients were not excluded based on the extent of systemic disease. Randomization was performed by computer-generated random numbers. Information on allocation concealment was not reported. All the patients in the surgical group were considered to have had complete resection as assessed by postoperative computerized tomography (CT) scanning. Follow up brain CT or magnetic resonance imaging (MRI) scans were required every 3 months. There was a statistically significant increase in survival in the surgical group (40 vs. 15 weeks). In addition, the time to recurrence of brain metastases, freedom from death due to neurologic causes, and duration of functional independence were significantly longer in the surgical resection group. The 1 month mortality was 4% in each group, indicating that there was no extra mortality from surgery. Although surgical resection was the only variable positively associated with maintaining performance status, the extent of systemic disease and increased age were associated with poor performance status post-treatment.

A second randomized study [8], conducted as a multi-institutional trial in the Netherlands, contained 63 evaluable patients. Patients with single brain metastases were randomized to complete surgical resection plus WBRT or WBRT alone. Randomization was performed centrally by telephone. The WBRT schedules were the same for both treatment arms and consisted of 40 Gy given in a non-standard fractionation scheme of 2 Gy twice per day for 2 weeks (10 treatment days). Patients had to have a reasonable quality of life and neurological status, defined as spending no more than 50% of their time in bed and not requiring continuous nursing care or hospitalization.

Excluded histologies were SCLC and lymphoma. Information is not given regarding the extent of resection in the surgical group or the use and frequency of imaging in follow up. Survival was significantly longer in the surgical group (10 vs. 6 months). There was also a non-significant trend toward longer duration of functional independence in the surgically treated patients. No data concerning recurrence of brain metastases were provided. The 1 month mortality rates were 9% in the surgery group and 0% in the WBRT alone group, a statistically insignificant difference. The authors concluded that the addition of surgery to WBRT provided a survival benefit except to those patients who were 60 years of age or older, or those patients with progressive systemic disease in the 3 months prior to the diagnosis of the brain metastasis.

A third randomized trial, conducted as a multi-center trial in Canada by Mintz et al. [7], failed to find a benefit from surgical treatment. In that study, 84 patients with a single brain metastasis were randomized to receive radiotherapy alone (30 Gy given in 10 daily fractions of 3 Gy) or surgery plus radiotherapy. Randomization was performed centrally by telephone. Eligible patients had to be less than 80 years of age, and they had to have a KPS of at least 50, i.e., they could be spending more than 50% of their time in bed but had to be able to care for some personal needs. Patients were not eligible if they had leukemia, lymphoma, or SCLC. A CT scan was done in the first postoperative week to assess the extent of tumor removed. Follow up CT scans were performed monthly for 6 months and every 3 months after that. A gross total resection was achieved in 38 of the 40 patients in the surgical group. No difference was found in overall survival; the median survival time was 6.3 months in the radiotherapy alone group and 5.6 months for the surgical group. There was also no difference in causes of death or quality of life.

It is unclear why the Canadian study was not in agreement with the other two trials. In all three studies, the control arms (the radiation alone arms) had median lengths of survival in the 3–6 months range—within the expected range for patients treated with radiotherapy alone. The major difference in the studies was the poor results obtained in the surgical arm of the Canadian trial. That study contained a higher proportion of patients with extensive systemic disease and lower performance scores. It is possible that these factors resulted in more patients dying of their systemic cancer before a long term benefit of surgery was seen. Additionally, MRI was not mandatory in the Canadian study, and it is theoretically possible that patients with additional lesions not detected by CT may have been included in the study.

All three of the evidence class II studies [9–11] demonstrated a survival benefit for patients who underwent surgical resection followed by WBRT as compared to

Table 1 WBRT versus surgical resection plus WBRT

First author (year)	Study design/evidence class	Interventions	Population	Median survival	# Pts with recurrence/progression[a]	Median time to recurrence/progression
Randomized trials						
Patchell (1990) [6]	RCT Evidence class I	G1: WBRT (n = 23) G2: WBRT + surgery (n = 25)	Single BM	G1: 15 weeks G2: 40 weeks (Survival curves: log-rank; $P < 0.01$)	At original site: G1: 12/23 (52%) G2: 5/25 (20%) ($P < 0.02$) At distant or leptomeningeal sites: G1: 3/23 (13%) G2: 5/25 (20%) (P = NS)	At original site: G1: 21 weeks G2: >59 weeks (LR curves: log-rank; $P < 0.0001$)
Mintz (1996) [7]	RCT Evidence class I	G1: WBRT (n = 43) G2: WBRT + surgery (n = 41)	Single BM	G1: 6.3 months G2: 5.6 months (Survival curves: log-rank; P = NS)	NR	NR
Vecht (1993) [8]	RCT Evidence class I	G1: WBRT (n = 31) G2: WBRT + surgery (n = 32)	Single BM	G1: 6 months G2: 10 months (Survival curves: log-rank; $P = 0.04$)	NR	NR
Other study designs						
Ampil (1996) [9]	Retrospective cohort study Evidence class II	G1: WBRT (n = 34) G2: WBRT + surgery (n = 11)	Cerebellum BM	G1: 3 months G2: 15 months (Wilcox on rank sum; $P = 0.005$)	NR	NR
Rades (2008) [10]	Retrospective cohort study Evidence class II	G1: WBRT (n = 96) G2: Surgery + WBRT (n = 99)	Single BM	G1: 6 months G2: 11.5 months (Survival curves: log-rank; $p < 0.001$)	NR	At original site: NR (LR curves: log-rank; $P < 0.001$) At distant site: NR (DR curves: log-rank; P = NS) At any site: NR (BR curves: log-rank; $P < 0.001$)
Sause (1990) [11]	Prospective non-randomized trial Evidence class II	G1: WBRT (n = 55) G2: WBRT + surgery (n = 25)	Single BM	G1: 6.7 months G2: 15.5 months (Survival curves: log-rank; $P = 0.004$)	NR	NR

BM brain metastases, *BR* brain recurrence (local + distant), *DR* distant recurrence in brain, *G1* group 1, *G2* group 2, *LR* local recurrence at original site in brain, *NR* not reported, *NS* not significant, *Pts* patients, *RCT* randomized control trial, *WBRT* Whole-brain radiation therapy

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

WBRT alone. Ampil et al., published a single institution experience with either surgery plus WBRT (11 patients) versus WBRT alone (34 patients) in 45 patients who had a cerebellar metastasis. The majority of the patients in the WBRT alone arm had additional supratentorial brain metastases. Although there was a significant difference in survival noted between the two groups, the authors concluded that the outcome of patients with a brain metastasis within the cerebellum was improved with surgical resection if the primary was not from the lung.

WBRT dosing/fractionation schedule

Twenty-three studies met the eligibility criteria for this question, and of these, 17 were unique [12–28] and six [31–36] were companion publications (Table 2). The 17 unique studies fell into three AANS/CNS evidence class categories as follows: ten class I studies (nine RCTs [12–20] and one randomized phase I/II trial [21]), six class II studies [22–24, 26–28] (retrospective cohort studies) and one class III study [25] (prospective cohort study with historical controls).

The radiation dosages have been expressed in terms of the tumor response biologically effective dose (BED) in order to quantitatively capture the observed biological effect between treatment arms. This was calculated from the linear quadratic equation:$BED = nd[1 + d/(\alpha/\beta)]$ where n = number of treatments, d = dose per fraction; the calculation assumes $\alpha/\beta = 10$ Gy for tumor effects of each schedule, however it is uncorrected for treatment regimes of two fractions/day. The BED units are referred to in terms of Gy_{10} to indicate that the BED values are single-point calculations for tumor response [37, 38] and no correction for accelerated repopulation was made.

Expressing radiation dosages in terms of the BED takes into account the total dose of radiation, fraction size, and overall time to deliver the radiation, and presumed repair of irradiated tissue. The analyses are stratified by low or high dose versus control dose. The control group consists of patients treated with 30 Gy in 10 fractions for a BED = 39 Gy_{10} (therefore assigning the low dose regimens as a BED < 39 Gy_{10}, and high dose regimens as a BED > 39 Gy_{10}).

None of the trials demonstrated a meaningful improvement in any endpoint relative to dose; specifically, survival was not improved. There was considerable overlap in terms of survival even at the same dose level in different trials, underscoring the significance of host-specific variables in determining survival.

The data from the randomized trials, stratified by the BED are shown in Table 3.

The meta-analyses were stratified by low or high dose versus control dose. Studies lacking a comparable control were excluded from meta-analyses, due to the inherent dosing variability amongst the study's control group.

Figure 2 indicates the RR of mortality at 6 months in the low dose (BED < 39 Gy_{10}) group compared to that in the WBRT control group (BED = 39 Gy_{10}). Only data from two trials (Chantani et al. [13] and Priestman et al. [20]) were robust enough to be considered for this end-point. When combined, no difference (P = 0.52) was found for 6 month mortality (RR 1.05; 95% CI 0.90, 1.23). Figure 3 presents the same analysis, but for the comparison of the high dose (BED > 39 Gy_{10}) group to the WBRT control group (BED = 39 Gy_{10}). Data from five trials were robust enough to be considered for this end-point. Combining data for Chantani et al. [13, 14], Komarnicky et al. [17], Kurtz et al. [18], and Murray et al. [19], yielded no difference (P = 0.39) in 6 month mortality (RR 1.05; 95% CI 0.94, 1.18). A 1981 trial by Borgelt et al. [12] was excluded from the meta-analyses for lack of a comparable control. Since the administered dosage ranged from 20 to 40 Gy over 1–4 weeks, the resulting permutations and combinations of plausible radiation schedules in this group varied too substantially (22–72 Gy_{10}) to function as a true control. The inherent dosing variability disqualified this control group thereby making the trial ineligible for comparison.

Similar comparisons were made for overall survival and neurologic function, and no dose–effect was identified for either end-point. Figures 4 and 5 depict the overall survival for the respective comparisons of low and high BED values versus the control BED. In Fig. 4, the pooling of two studies, Chantani et al. [13] and Priestman et al. [20], for the comparison of low dose WBRT (BED < 39 Gy_{10}) to a control dose (BED = 39 Gy_{10}) yielded no difference (P = 0.07) in overall survival (RR 0.86; 95% CI 0.73, 1.01). In Fig. 5, overall survival data from Chantani et al. [13, 14], Komarnicky et al. [17], Kurtz et al. [18], and Murray et al. [19], were pooled for the comparison of high dose WBRT (BED > 39Gy_{10}) versus WBRT control dose (BED = 39 Gy_{10}). No difference (P = 0.26) in overall survival was found (RR 1.06; 95% CI 0.96, 1.18). The hazard plots for neurologic function are not presented.

Impact of tumor histopathology on WBRT treatment outcomes

Using the AANS/CNS evidence classification, no papers with class I or II evidence were identified by the systematic literature review that met the eligibility criteria for this question. In fact, only one paper, providing class III evidence, met the inclusion criteria (Table 4). The only data is provided by a single institution retrospective analysis with 75 cases (Sundstrom et al. [29]). In that study, there were 15 cases that were of classic "radio-resistant" histology. There were no statistically significant differences in overall survival by tumor histology. Local control by tumor type was not reported.

Table 2 Different dose/fractionation schedules of WBRT

First author (year)	Study design/evidence class	WBRT total dose/fractionation	Population	Median survival	# Pts with recurrence/progression[a]	Median time to recurrence/progression
Randomized trials						
Borgelt (1981) [12]	RCT Evidence class I	*First RCT:* G1: 10 Gy/1 fraction (n = 26) G2: 30–40 Gy over 2–4 weeks (n = 112) *Second RCT:* G3: 12 Gy/2 fractions (n = 33) G4: 20 Gy over 1 week (n = 31)	BM	*First RCT:* G1: 15 weeks G2: 21 weeks (Survival curves: log-rank; P = NS) *Second RCT:* G3: 13 weeks G4: 12 weeks (Survival curves: log-rank; P = NS)	NR	Median time to progression (measured by deterioration in neurologic function): *First RCT:* Initial NF 1: G1: 9 weeks; G2: 14 weeks Initial NF 2: G1: 9 weeks; G2: 10 weeks Initial NF 3: G1: 7 weeks; G2: 12 weeks (Cox's model; P = 0.07) *Second RCT:* Initial NF 1: G3: 9 weeks; G4: 10 weeks Initial NF 2: G3: 11 weeks; G4: 8 weeks Initial NF 3: G3: 3 weeks; G4: 3 weeks (Cox's model; P = NS)
Chantani (1994) [13]	RCT Evidence class I	*Normal LDH:* G1: 30 Gy/10 fractions (n = 46) G2: 50 Gy/20 fractions (n = 46) *High LDH:* G3: 30 Gy/10 fractions (n = 35) G4: 20 Gy/5 fractions (n = 35)	Lung cancer BM	G1: 5.4 months G2: 4.8 months (Survival curves G1 vs. G2: log-rank; P = NS) G3: 3.4 months G4: 2.4 months (Survival curves G3 vs. G4:log-rank; P = NS)	NR	NR
Chantani (1985) [14]	RCT Evidence class I	G1: 30 Gy/10 fractions (n = 35) G2: 50 Gy in 20 fractions (n = 34)	Lung cancer BM	G1: 4 months G2: 3 months (Survival curves: log-rank; P = NS)	NR	NR
Davey (2008) [15]	RCT Evidence class I	G1: 20 Gy/5 daily fractions (n = 45) G2: 40 Gy/20 fractions/twice daily (n = 45)	BM	G1: 19.1 weeks G2: 19.1 weeks (Survival curves: log-rank; P = NS)	NR	NR

Table 2 continued

First author (year)	Study design/ evidence class	WBRT total dose/fractionation	Population	Median survival	# Pts with recurrence/ progression[a]	Median time to recurrence/progression
Haie-Meder (1993) [16]	RCT Evidence class I	G1: 18 Gy/3 fractions (n = 110) G2: 18 Gy/3 fractions; 4 weeks later a second identical course or 25 Gy/10 fractions (n = 106)	BM from lung, breast, head and neck or unknown primaries	G1: 4.2 months G2: 5.3 months (Survival curves: log-rank; P = NS)	NR	NR
Komarnicky (1991) [17]	RCT Evidence class I	G1: 30 Gy/10 fractions (n = 193) G2: 30 Gy/6 fractions (n = 200) G3: 30 Gy/6 fractions + MISO (n = 196) G4: 30 Gy/10 fractions + MISO (n = 190)	BM	G1: 4.5 months G2: 4.1 months G3: 3.1 months G4: 3.9 months (Survival curves: log-rank; P = NS)	# of pts retreated for BM after protocol therapy: G1: 54/179 (30%) G2: 54/180 (30%) G3: 33/173 (19%) G4: 54/163 (33%) (P = NS)	NR
Kurtz [18] (1981)	RCT Evidence class I	G1: 30 Gy/10 fractions (n = 130) G2: 50 Gy/20 fractions (n = 125)	BM with no extra-cranial metastases	G1: 18.2 weeks G2: 16.9 weeks (Survival curves: log-rank; P = NS)	Overall in brain: G1: 109/124 (88%) G2: 105/118 (89%) (P value not reported)	Overall in brain: G1: 11 weeks G2: 10 weeks (P value not reported)
Murray (1997) [19]	RCT Evidence class I	G1: 30 Gy/10 fractions/daily (n = 213) G2: 54.4 Gy/34 fractions/twice daily (n = 216)	BM	G1: 4.5 months G2: 4.5 months (Survival curves: Prentice modified Wilcox on; P = NS)	NR	NR
Priestman (1996) [20]	RCT Evidence class I	G1: 12 Gy/2 fractions (n = 270) G2: 30 Gy/10 fractions (n = 263)	BM	G1: 77 days G2: 84 days (Survival curves: log-rank; P = 0.04)	NR	NR
Sause [21] (1993)	Randomized phase I/II trial Evidence class I	G1: 32 Gy in 1.6 Gy fractions + boost to 48.0 Gy] (n = 62) G2: 32 Gy in 1.6 Gy fractions + boost to 54.4 Gy] (n = 115) G3: 32 Gy in 1.6 Gy fractions + boost to 64.0 Gy] (n = 104)	BM	G1: 4.2 months G2: 5.2 months G3: 4.8 months G4: 6.4 months (Survival curves: log-rank; P = NS)	NR	NR

Table 2 continued

First author (year)	Study design/ evidence class	WBRT total dose/fractionation	Population	Median survival	# Pts with recurrence/ progression[a]	Median time to recurrence/progression
		G4: 32 Gy in 1.6 Gy fractions + boost to 70.4 Gy] (n = 53) Fractions administered twice daily				
Other study designs						
Bach (1996) [22]	Retrospective cohort study Evidence class II	G1: 22 Gy/4 fractions[b] (n = 57); G2: 50.4 Gy/28 fractions[b] (n = 44)	BM from SCLC	G1: 88 days; G2: 160 days (Survival curves: log-rank; P = 0.00001)	NR	NR
Conill [23] (2006)	Retrospective cohort study Evidence class II	G1: 20 Gy/5 fractions + TMZ based chemotherapy (n = 11); G2: 30 Gy/10 fractions + TMZ based chemotherapy (n = 10)	BM from melanoma	G1: 4.0 months; G2: 4.0 months (Survival curves: log-rank; P = NS)	Data not reported by group; no statistically significant difference between groups (P = NS)	NR
Nieder (1995) [24]	Retrospective cohort study Evidence class II	G1: WBRT [40 Gy in 20 fractions ± local boost 10–20 Gy] (n = 39); G2: WBRT [30 Gy in 10 fractions] (n = 39) [matched to G1]	BM	G1: 3.5 months; G2: 2.5 months (Survival curves: log-rank; P = NS)	*# Pts with local CR/PR*: G1: CR 5/39 (13%); PR 25/39 (64%); G2: CR 4/39 (10%); PR 15/39 (38%) (CR or PR G1: 77% vs. G2: 48%; P = 0.037)	*Median time to BM progression:* G1: 3.0 months; G2: 2.5 months (Progression-free curves: log-rank; P = NS)
Nieder (1997) [25]	Prospective cohort study with historical controls Evidence class III	G1: Surgery + WBRT [30 Gy/ 2.5 Gy fractions/twice daily] (n = 11); G2: WBRT [50.4 Gy/1.8 Gy fractions/twice daily] (n = 15); G3: WBRT [30 Gy/2.5 Gy fractions/twice daily] (n = 36); G4: Historical group WBRT [30 Gy/3 Gy fractions/daily] (n = 246); G5: Historical group surgery + WBRT [30 Gy/ 3 Gy fractions/daily] (n = 37)	BM	G1: 3.3 months; G2: 2 months; G3: 2 months; G4: 2.5 months; G5: 7.3 months (Survival curves G2, G3, G4: log-rank; P = NS)	*# of pts with follow up CT with BM progression/ recurrence anywhere in brain:* G1: 3/9 (33%); G2: 4/11 (36%); G3: 11/25 (44%); G4: 29/202 (14%); G5: 5/35 (14%)	*Median time to any recurrence in brain:* Not reported BR curves G3 vs. G4: log-rank; P = 0.0001; BR curves G2 vs. G3: log-rank; P = NS; BR curves G2 vs. G4: log-rank; P = NS

Table 2 continued

First author (year)	Study design/ evidence class	WBRT total dose/fractionation	Population	Median survival	# Pts with recurrence/ progression[a]	Median time to recurrence/progression
Rades (2007) [26]	Retrospective cohort study Evidence class II	G1: 20 Gy/5 fractions (n = 140) G2: 30 Gy/10 fractions or 40 Gy/20 fractions (n = 264)	BM from NSCLC	Median survival: Not reported 6 month survival rate: G1: 40% G2: 30% (Survival curves: log-rank; P = NS)	NR	NR
Rades (2007) [27]	Retrospective cohort study Evidence class II	G1: 30 Gy/10 fractions (n = 257) G2: 45 Gy/15 fractions or 40 Gy/20 fractions (n = 159)	≥2 BM	Median survival: NR 6 month survival rate: G1: 33% G2: 29% (Survival curves: log-rank; P = NS)	6 month local control rate: G1: 39% G2: 41% (LR curves: log-rank; P = NS)	NR
Rades (2008) [28]	Retrospective cohort study Evidence class II	G1: 20 Gy/5 fractions (n = 387) G2: 30 Gy/10 fractions or 40 Gy/20 fractions (n = 698)	BM	Median survival: Not reported 1 year survival rate: G1: 20% G2: 18% (Survival curves: log-rank; P = NS)	NR	NR

BM brain metastases, BR brain recurrence (local + distant), CR complete response, CT computed tomography, DR distant recurrence in brain, G1 group 1, G2 group 2, G3 group 3, G4 group 4, KPS Karnofsky performance score, LDH lactate dehydrogenase, LR local recurrence at original site in brain, MISO misonidazole, NF neurologic function, NR not reported, NS not significant, NSCLC non-small cell lung carcinoma, PR partial response, Pts patients, RCT randomized control trial, TMZ temozolomide, WBRT whole-brain radiation therapy

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

[b] WBRT use similar at baseline in both groups

Table 3 Randomized trials stratified by the BED for different treatment schedules

Author	Year	Total dose (Gy)	Fractions	BED (Gy; $\alpha/\beta = 10$)	n	Median survival (weeks)
Borgelt	1981	12	2	19.2	33	13
Priestman	1996	12	2	19.2	270	11
Borgelt	1981	10	1	20	26	15
Borgelt	1981	20	5	28	31	12
Chatani	1994	20	5	28	35	10.4
Davey	2008	20	5	28	45	19.1
Haie-Meder	1993	18	3	28.8	110	18.3
Chatani	1994	30	10	39	46	23.5
Chatani	1994	30	10	39	35	14.8
Chatani	1985	30	10	39	35	17.4
Komarnicky	1991	30	10	39	193	19.5
Komarnicky	1991	30	10	39	190	16.9
Kurtz	1981	30	10	39	130	18.2
Murray	1997	30	10	39	213	19.6
Priestman	1996	30	10	39	263	12
Komarnicky	1991	30	6	45	200	17.8
Komarnicky	1991	30	6	45	196	13.5
Davey	2008	40	20[a]	48	45	19.1
Sause	1993	48	30[a]	55.7	62	18.3
Haie-Meder	1993	–	–	50.8	106	23
Chatani	1994	50	20	62.5	46	20.9
Chatani	1985	50	20	62.5	34	13
Kurtz	1981	50	20	62.5	125	16.9
Murray	1997	54.4	34[a]	63.1	216	19.6
Sause	1993	54.4	34[a]	63.1	115	22.6
Sause	1993	64	40[a]	74.2	104	20.9
Sause	1993	70.4	44[a]	81.7	53	27.8
Borgelt	1981	30–40	10–20	34.5–56	112	21

[a] Treatment regimes of two fractions/day (BED uncorrected)
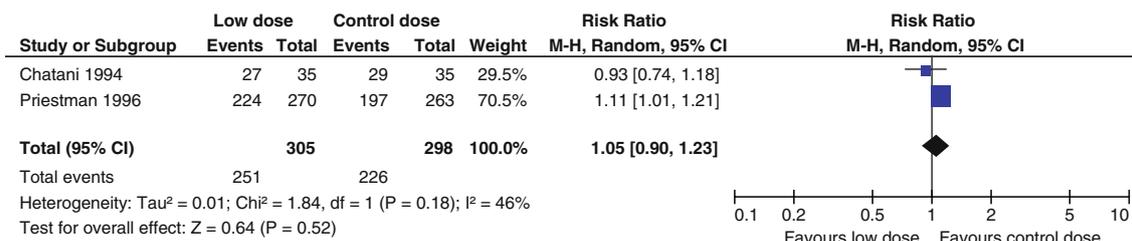
Fig. 2 Comparison of low dose WBRT (BED < 39 Gy$_{10}$) versus WBRT control dose (BED = 39 Gy$_{10}$): mortality at 6 months

Conclusion

Surgical resection plus WBRT versus WBRT alone

Based on the available class I and class II evidence, surgical resection followed by WBRT is an effective treatment for patients with single, surgically accessible, brain metastases who have controlled extra-cranial disease and are in good general condition. Good general condition in the relevant studies was defined as functional independence and spending less than 50% of time in bed. Patients with disease progression in the 3 months preceding the diagnosis of the brain metastases have a relatively poor survival and poor functional status but still had a significant improvement in survival as a result of surgical resection. Due to the risk of fourth ventricle compression and the
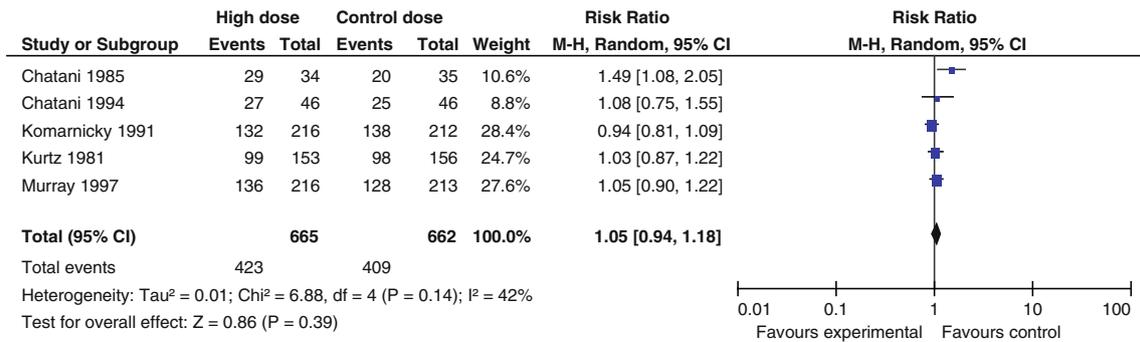
	High dose		Control dose			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chatani 1985	29	34	20	35	10.6%	1.49 [1.08, 2.05]	
Chatani 1994	27	46	25	46	8.8%	1.08 [0.75, 1.55]	
Komarnicky 1991	132	216	138	212	28.4%	0.94 [0.81, 1.09]	
Kurtz 1981	99	153	98	156	24.7%	1.03 [0.87, 1.22]	
Murray 1997	136	216	128	213	27.6%	1.05 [0.90, 1.22]	
Total (95% CI)		665		662	100.0%	1.05 [0.94, 1.18]	
Total events	423		409				

Heterogeneity: Tau² = 0.01; Chi² = 6.88, df = 4 (P = 0.14); I² = 42%

Test for overall effect: Z = 0.86 (P = 0.39)

0.01   0.1   1   10   100
Favours experimental   Favours control

Fig. 3 Comparison of high dose WBRT (BED > 39 Gy_{10}) versus WBRT control dose (BED = 39 Gy_{10}): mortality at 6 months (*Note*: extraction of data for Komarnicky trial is based on the K–M curve)
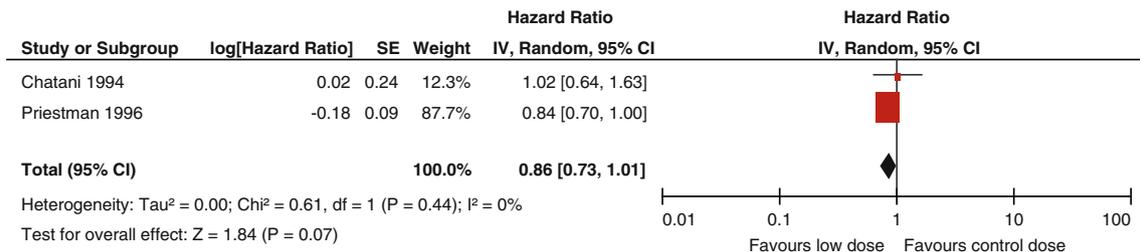
				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chatani 1994	0.02	0.24	12.3%	1.02 [0.64, 1.63]	
Priestman 1996	-0.18	0.09	87.7%	0.84 [0.70, 1.00]	
Total (95% CI)			100.0%	0.86 [0.73, 1.01]	

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0%

Test for overall effect: Z = 1.84 (P = 0.07)

0.01   0.1   1   10   100
Favours low dose   Favours control dose

Fig. 4 Comparison of low dose WBRT (BED < 39 Gy_{10}) versus WBRT control dose (BED = 39 Gy_{10}): overall survival

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chatani 1985	0.42	0.2	7.0%	1.52 [1.03, 2.25]	
Chatani 1994	0.04	0.21	6.4%	1.04 [0.69, 1.57]	
Komarnicky 1991	0	0.08	43.9%	1.00 [0.85, 1.17]	
Kurtz 1981	0.06	0.12	19.5%	1.06 [0.84, 1.34]	
Murray 1997	0.07	0.11	23.2%	1.07 [0.86, 1.33]	
Total (95% CI)			100.0%	1.06 [0.96, 1.18]	

Heterogeneity: Tau² = 0.00; Chi² = 3.82, df = 4 (P = 0.43); I² = 0%

Test for overall effect: Z = 1.13 (P = 0.26)

0.01   0.1   1   10   100
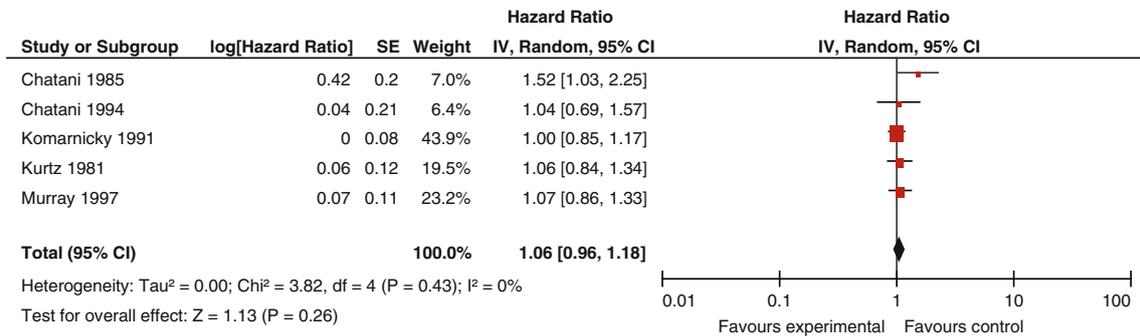Favours experimental   Favours control

Fig. 5 Comparison of high dose WBRT (BED > 39 Gy_{10}) versus WBRT control dose (BED = 39 Gy): overall survival

subsequent increase in intracranial pressure, surgery should be particularly considered if there is a brain metastasis situated within the posterior fossa.

Surgical resection plus WBRT versus surgical resection alone

The surgical resection guideline paper by Kalkanis et al. [1] outlines in detail the evidence supporting the addition of WBRT after surgical resection. Please refer to this paper for a further discussion of why the combined modalities of surgical resection followed by WBRT represent a superior treatment option, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone

If WBRT is used, is there an optimal dosing/ fractionation schedule?

There is class I evidence that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control or neurocognitive function when compared to "standard" WBRT dose/fractionation. (i.e., 30 Gy in 10 daily fractions or a BED of 39 Gy_{10}).

If WBRT is used, what impact does tumor histopathology have on treatment outcomes?

Only one small case series (class III evidence) met the eligibility criteria for the question addressing the impact of histopathology on WBRT treatment outcomes. Further

Table 4 Study evaluating WBRT treatment outcome by histopathology

First author (year): Sundström (1998) [29]

Study characteristics	Study outcomes	Study quality
Study design: case series	*Primary outcome*: survival	*Quality assessment*: N/A as non-comparative study
Inclusion criteria:	*Median survival by primary tumor type*:	*AANS/CNS evidence classification*: class III
Pts treated with WBRT for BM diagnosed by CT or MRI	*Breast*: 7 months (range 1–62 months)	
Minimum midline dose to the whole brain of at least 25 Gy	*Lung*: 4 months (range 1–21 months)	
	Renal cell: 4 months (range 2–34 months)	
	Melanoma: 3 months (range 1–6 months)	
	Other primaries: 4 months (range 1–9 months)	
	(Survival curves: *P*-value not reported)	
Interventions:	*Tumor control*: not reported	
WBRT [mean dose 30 Gy (range 25–40 Gy) in 1.8–3 Gy fractions]		
Median follow-up: not reported	*Median time to recurrence of brain metastases*: not reported	
# Male:		
Breast: 0/19, lung: 26/35, renal cell: 4/9, melanoma: 6/6, other: 6/6		
Median age (range):	*Functional performance*: not reported by histology	
Breast: 53 years (39–77 years)	*Cause of death*: not reported	
Lung: 64 years (43–78 years)	*Adverse events*: not reported by tumor type	
Renal cell: 61 years (41–69 years)		
Melanoma: 61 years (39–62 years)		
Other: 61 years (50–71 years)		
# Of brain metastases:		
Breast: 1 BM 9/19, 2 BM 4/19, >2 BM 6/19		
Lung: 1 BM 15/35, 2 BM 5/35, >2 BM 15/35		
Renal cell: 1 BM 3/9, 2 BM 2/9, >2 BM 4/9		
Melanoma: 1 BM 3/6, 2 BM 0/6, >2 BM 3/6		
Other: 1 BM 3/6, 2 BM 2/6, >2 BM 1/6		
Extra-cranial disease: Extra-cranial metastases:		
Breast: 17/19		
Lung: 6/35		
Renal cell: 5/9		
Melanoma: 4/6		
Other: 5/6		
Baseline functional performance:		
WHO classification (0 (best) to 4 (worst)		
Performance status (PS):		
Breast: PS 0–1 9/19, PS 2 5/19, PS 3 5/19		
Lung: PS 0-1 10/35, PS 2 16/35, PS 3 9/35		
Renal cell: PS 0–1 2/9, PS 2 5/9, PS 3 2/9		
Melanoma: PS 0–1 6/6		
Other: PS 0–1 3/6, PS 2 1/6, PS 3 2/6		

AANS American Association of Neurological Surgeons, *BM* brain metastases, *CNS* Congress of Neurological Surgeons, *CT* computed tomography, *MRI* magnetic resonance imaging, *NA* not available, *Pts* patients, *WBRT* whole brain radiation therapy, *WHO* World Health Organization

studies in this area are needed before any recommendations can be made.

Key issues for future investigation

There have been numerous studies comparing various dose/fractionation schemes for WBRT. Unless future studies incorporate more sophisticated measures of neurocognitive outcome there is little need to repeat these studies. There are, however, very few studies evaluating the effectiveness of WBRT for one histopathological type versus another. Future studies of WBRT explicitly addressing treatment outcomes for well-defined patient groups by different tumor types are needed.

The following is a list of major ongoing or recently closed randomized trials pertaining to the use of whole brain radiation therapy that evaluate treatment comparisons addressed by this guideline paper for the management of newly diagnosed brain metastases.

1. Brain metastases study: radiotherapy schemes in the treatment of brain metastases
   Official Title: To determine which of two radiotherapy brain fractionation schemes is superior in the treatment of brain metastases
   Status: Completed
   Clinicaltrials.gov Identifier: NCT00138788
   Principal Investigator: Associate Professor, Peter H Graham, Cancer Care Centre, St George Hospital
   Location: Australia
   Sponsors and Collaborators: St George Hospital, Australia

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

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