# Complete Summary

## GUIDELINE TITLE

Leptomeningeal metastases.

## BIBLIOGRAPHIC SOURCE(S)

Dutch Neuro-Oncology Working Group. Leptomeningeal metastases. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2006 Jan 12. 71 p. [219 references]

## GUIDELINE STATUS

This is the current release of the guideline.

## ** REGULATORY ALERT **

## FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse**: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 17, 2007, Haloperidol (Haldol): Johnson and Johnson and the U.S. Food and Drug Administration (FDA) informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

- Leptomeningeal metastases secondary to extracranial solid tumors (e.g., breast cancer, lung cancer, melanoma)
- Leptomeningeal metastases secondary to primary central nervous system (CNS) tumors (primitive neuroectodermal tumor [PNET], germ cell tumor, medulloblastoma, ependymoma, pineal gland tumor/pineoblastoma, glioblastoma multiforme, esthesioneuroblastoma)

### GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Management
Risk Assessment
Treatment

### CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurological Surgery
Neurology
Nursing
Oncology
Pathology
Psychiatry
Psychology
Radiation Oncology
Radiology

### INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

### GUIDELINE OBJECTIVE(S)

Generally:

- To provide recommendations for the diagnosis treatment, and support of adult patients with leptomeningeal metastases (LM)
- To facilitate the best care for patients with LM
- To offer an initial basis for developing transmural care or local protocols to promote guideline implementation

Specifically:

- To specify the role of cerebrospinal fluid diagnostics in LM
- To specify the role of magnetic resonance imaging in the diagnosis of LM
- To specify the role of symptom management, intrathecal chemotherapy, systemic therapy, radiation therapy and neurosurgery in LM
- To provide a statement on the effect of treatment on quality of life and survival
- To provide a statement on the centralisation of care for patients with LM

## TARGET POPULATION

Adult patients (more than 16 years old) with leptomeningeal metastases (LM) of solid tumours and primary tumours of the central nervous system (excluding leukaemia, non-Hodgkin's lymphoma, and primary central nervous system (CNS) lymphoma)

## INTERVENTIONS AND PRACTICES CONSIDERED

### Diagnosis/Evaluation

1. Assessment of Karnofsky Performance Score (KPS)
2. Diagnostic imaging (magnetic resonance imaging [MRI] with or without gadolinium, computed tomography [CT])
3. Cerebrospinal fluid (CSF) analysis (cytology and cell count; fluid pressure; lactate dehydrogenase [LDH] protein, and glucose concentrations)

### Counseling/Management/Treatment

1. Intravenous, intrathecal, or systemic chemotherapy (methotrexate, cytarabine, thiotepa)
2. Systemic hormonal therapy for hormone-sensitive primary tumour
3. Systemic interferon therapy
4. Radiation therapy
5. Combination therapies
6. Neurosurgery
    - Insertion of an intraventricular reservoir (with antibiotic prophylaxis)
    - Antibiotic treatment of infection during intrathecal therapy with a ventricular reservoir
    - Monitoring of intracranial pressure and assessment for intracranial haemorrhage
    - Insertion of a ventriculoperitoneal drain for treatment of hydrocephalus
7. Consultation for treatment of primary tumors of the central nervous system (medulloblastomas, ependymomas, germinomas)

8. Symptomatic (palliative) treatment
    - Dexamethasone
    - Management of headache and vomiting (CSF drainage, ventriculoperitoneal shunt, radiation therapy)
    - Management of confusion (haloperidol, lorazepam)
9. Assessment of need for psychosocial support
10. Organization of care

### MAJOR OUTCOMES CONSIDERED

- Change in Karnofsky Performance Score
- Neurological, cytological, and tumour response to treatment
- Sensitivity and specificity of cerebrospinal fluid (CSF) analyses
- Complications of therapy
- Degree of symptom control
- Changes in quality of life scores
- Health care utilization
- Duration of survival

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Relevant articles were found by performing systematic searches in the *Cochrane Library*, *Medline*, *Embase*, *Cinahl* and *Psychinfo*. Manual searches were also performed. Searches were limited to articles published between 1970 and 2005. The following search terms were used for the patient population: leptomening* near metastas*, leptomening* near seeding, leptomening* near cancer*, leptomening* near dissemination, leptomening* near lymphomatosis, mening* near caricinomat*, neoplastic near meningitis, lymphomatous near meningitis, cerebrospinal fluid near seeding, CSF near seeding. Articles were selected based on the following criteria: (a) predominantly English, German or Dutch publications and (b) full articles whenever possible. Case reports and preclinical research were excluded, except for topics where no other literature was available. The quality of the articles was evaluated by members of the working group using evaluation forms created by the evidence-based guideline development (evidence-based richtlijnontwikkeling, EBRO). Articles of mediocre or poor quality were excluded. After this selection process, the remaining articles were used as the basis for the various conclusions stated throughout the guideline.

### NUMBER OF SOURCE DOCUMENTS

- 5 articles on cerebrospinal fluid (CSF) cytology
- 36 articles on clinical-chemical analysis of CSF
- 25 articles on clinical-chemical markers in CSF

- 7 articles on the efficacy of intrathecal therapy
- 20 non-comparative studies of intrathecal therapy
- 16 articles on the toxicity of intrathecal therapy
- 8 articles on the incidence and treatment of leptomeningeal metastases from primary central nervous system tumors
- 2 systematic reviews on communication training
- 2 surveys on coordination of care/transmural care
- 3 meta-analyses of psychological intervention

## METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

## RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

### Levels of Evidence

| For Articles Regarding Intervention | |
|---|---|
| **A1** | Systematic reviews covering at least some A2-level studies in which the results of the individual studies are consistent |
| **A2** | Randomised comparative clinical studies of good quality (double-blind, controlled), sufficient size and consistency |
| **B** | Randomised clinical trials of moderate quality or insufficient size, or other comparative studies (non-randomised, comparative cohort studies, patient-control studies) |
| **C** | Non-comparative studies |
| **D** | Expert opinion from, for example, working group members |
| **For Articles Regarding Diagnosis** | |
| **A1** | Studies on the effects of diagnosis on clinical outcomes in a prospectively followed, well-defined patient population with a predefined protocol based on the results of the study test, or decision theory studies on the effects of diagnosis on clinical outcomes based on the results of A2-level studies with sufficient consideration given to the interaction between diagnostic tests |
| **A2** | Studies that include a reference test with predefined criteria for the study test and the reference test and a good description of the test and the clinical population studied; a sufficiently large series of consecutive patients must be included, predefined cut-off values must be used and the results of the test and the gold standard must be evaluated independently. For situations in which multiple diagnostic tests are involved, there is in principle interaction and the analysis should take this into account by using, for example, logistical regression |
| **B** | Comparison with a reference test and description of the study test and population, but lacking the other characteristics of A-level studies |
| **C** | Non-comparative studies |
| **D** | Expert opinion from, for example, working group members |

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The selected articles were graded according to the degree of evidence. The degree of evidence and level of evidence are given in the conclusion section of each chapter in the original guideline document. In this way, the most important literature upon which the conclusions are based is reported.

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus
Expert Consensus (Consensus Development Conference)

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

### Composition of the Working Group

A multidisciplinary working group was formed that consisted of representatives of all relevant specialities involved in the diagnosis and treatment of leptomeningeal metastases (LM) of solid tumours. In composing the study group, consideration was given to the geographic distribution of the group members, the proportional representation of various concerned associations and authorities, as well as distribution among those with and without an academic background. Further details are provided in the original guideline document.

### Formation of Basis Questions

The working group that produced the guideline formulated a number of basis questions after examining the existing problem areas of the neuro-oncological working groups of the integrated cancer centres (see appendix 1 in the original guideline document). The questions encompass problems that arise in daily practice regarding diagnostic, therapeutic and counselling procedures for patients with LM or suspected LM. The questions address the incidence of LM for various types of cancer, pathogenesis, relation to disease stage and other sites of metastatic disease, symptomatology and factors that may influence further treatment decisions, diagnostic and treatment options and their efficacy and influence on quality of life. The basis questions form the foundation for the various chapters in this guideline. The guideline is not intended to be comprehensive.

### Methods of the Working Group

Given the scale of the task, a number of subgroups were formed with representatives from relevant disciplines. In addition, an editorial team that consisted of a chair, the Dutch Institute for Healthcare Improvement (CBO) advisor and a project manager from the Dutch Association of Comprehensive

Cancer Centres (ACCC; Vereniging voor Integrale Kanker Centra [VIKC]) was responsible for the coordination and mutual agreement among the subgroups.

The working group spent approximately 18 months developing text for the draft guideline. Working group members wrote text individually or in subgroups, which was discussed during meetings and agreed upon after the incorporation of comments. The working group met 15 times to intercorrelate the results of the subgroups. The text developed by the subgroups was combined by the editorial team and standardised to create once document: the draft guideline. The draft guideline was presented for discussion on 16 March 2005 at a members meeting of the Dutch Neuro-Oncology Working Group (Landelijke Werkgroep Neuro-Oncologie, LWNO).

**Other Considerations**

In addition to the scientific evidence, there are often other important aspects to consider in the development of a recommendation, including patient preferences, the availability of special techniques or expertise, organisational factors, social consequences and costs. These factors are addressed in the section 'Other considerations' following the 'Conclusion' in the original guideline document. In this section, the conclusion that was based on the literature is placed in the context of daily practice and the advantages and disadvantages of the various protocol options are weighed. The final formulated recommendation is the result of the available evidence in combination with these considerations.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

| Level of Evidence for Conclusions | |
|---|---|
| **1** | At least one systematic review (A1) or two independently conducted A2-level studies |
| **2** | At least two independently conducted B-level studies |
| **3** | At least one A2-, B- or C-level study |
| **4** | Expert opinion from, for example, working group members |

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After incorporation of comments from the meeting of the Dutch Neuro-Oncology Working Group (Landelijke Werkgroep Neuro-Oncologie [LWNO]), the guideline

was ratified by the complete working group on 28 June 2005 and sent to the LWNO and relevant associations for authorisation. The guideline was made publicly available on 12 January 2006.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

#### Prognosis

Based on the literature and clinical expertise, the working group advises using the following classification for the prognosis of patients with leptomeningeal metastases without brain metastases.

| Category | Characteristics | Prognosis |
|---|---|---|
| **1** | KPS >70, no serious encephalopathy or neurological deficit, non-threatening extra-CNS disease, tumour is not resistant to chemotherapy or hormone therapy | Not unfavourable |
| **2** | Other | Unfavourable |
| **3** | KPS <70, progressive non-treatable extra-CNS disease | Very unfavourable |

KPS = Karnofsky Performance Score, CNS = central nervous system

#### Diagnosis

#### Diagnostic Imaging

The working group is of the opinion that, if leptomeningeal metastases are suspected in a patient known to have a malignancy:

- Magnetic resonance imaging (MRI) assessment is the preferred choice over cerebrospinal fluid (CSF) assessment. If MRI is not available or

contraindicated, a computed tomography (CT) evaluation of the intracranial region can be performed.
- If the MRI (or CT) results are positive, no further assessment is necessary to make the diagnosis of leptomeningeal metastases. If the MRI (or CT) results are inconclusive or negative, CSF assessment should be conducted.
- If leptomeningeal metastases are found in the spinal canal and the intention is to treat the patient, consideration should be given to performing a brain MRI at the same time to rule out subclinical brain metastases, which could be relevant to later treatment protocols. For the performance of the MRI evaluation (see appendix 22 in the original guideline document).

**CSF Diagnosis**

If leptomeningeal metastases are suspected and the first cytological analysis of the CSF is negative, performing a second lumbar puncture is advisable.

If possible, 10 mL of fluid should be collected for cytological analysis. Depending on the intended line of inquiry, 5 mL of liquid should be collected for clinical chemistry analysis.

The amount of fluid required can differ for each clinical chemistry laboratory; the clinical chemist involved should advise on this matter.

Both cytological and clinical-chemical processing of the fluid should occur as soon as possible following puncture. Clinical-chemical markers and immunocytochemical/cytogenetic CSF analysis are adjuvant to cytology and have only limited additional value. Standard CSF analysis should include cell count and concentrations of lactate dehydrogenase (LDH), protein and glucose. Abnormalities in these factors can lend support to clinical suspicions of leptomeningeal metastases if the CSF cytology is negative.

**Organisation of Care**

The working group is of the opinion that specific procedures regarding the organisation of care for patients with leptomeningeal metastases are not strictly necessary. However, if it is decided to employ intraventricular chemotherapy, the insertion of the ventricular reservoir should take place in a neurosurgical centre with experience in this area. Treatment institutions should have adequate access to radiation therapy. In case of rare complications, it is advisable that physicians consult with a referral centre by telephone. For patients with leptomeningeal metastases of primitive neuroectodermal tumours (PNETs), consideration can also be given to consultation with paediatric oncology centres for their experience. Given the severity of the stage of disease in which leptomeningeal metastases occur, providing adequate care as close as possible to the patient's home is more important than the centralisation of care and treatment.

**Treatment**

**LM of Extracranial Solid Tumors**

*Systemic Therapy*

In patients with leptomeningeal metastases of a metastasised solid tumour, systemic drug therapy should be considered as first choice for treatment. The choice of drug is determined by the sensitivity of the tumour type in question.

If leptomeningeal metastases are the only manifestation of tumour activity, potentially effective systemic therapy is recommended as the treatment of choice. Endocrine therapy can be effective against leptomeningeal metastases of hormone-sensitive breast carcinoma.

*Radiation Therapy*

In patients with leptomeningeal metastases of solid tumours, radiation therapy is recommended as a treatment modality to reduce symptoms or, when combined with intrathecal chemotherapy, to reduce CSF flow disturbances. Radiation therapy is applied locally to sites of bulky disease. A dose of 20 to 30 Gy in 5 to 10 fractions is recommended. If brain metastases are also present, treatment should consist of brain irradiation, followed by systemic therapy if possible.

*Intrathecal Chemotherapy*

In the context of meaningful palliation (i.e., a self-sufficient existence for at least several months without disabling symptoms), systemic chemotherapy with radiation therapy to clinically relevant sites as need is preferred over intrathecal chemotherapy for patients with leptomeningeal metastases of solid tumours. If potentially effective systemic treatment is not possible, leptomeningeal metastases are the only relevant tumour activity and the primary tumour is potentially sensitive to intrathecal methotrexate, cytarabine or thiotepa, then intrathecal chemotherapy in combination with radiation therapy to clinically relevant sites and macroscopic tumour locations is recommended. The combination of intrathecal methotrexate and whole brain radiation therapy (WBRT) should be avoided if possible.

In patients with leptomeningeal metastases, the intrathecal treatment of choice is intraventricular methotrexate 10 mg given twice weekly. Treatment should stop as soon as the cytology is negative. Intrathecal treatment beyond six weeks has no further beneficial effect and can therefore be discontinued. A comparable alternative is depot cytarabine 50 mg given once every two weeks by lumbar puncture. In patients with leptomeningeal metastases and a Karnofsky Performance Score $\geq$ 70 who experience disease progression or recurrence following a clinically meaningful stabilisation or response, re-challenge with or switch to systemic therapy or intrathecal chemotherapy can be considered. If brain metastases are present in addition to leptomeningeal metastases, treatment should consist of brain irradiation followed by systemic therapy if possible.

The neurological response to treatment is preferred over the CSF cytological response as a measure for determining further actions. The working group is of the opinion that, for patients without realistic prospects for neurological/clinical improvement and tumour control, such as those who are care-dependent due to encephalopathy, have severe motor loss or progressive, non-treatable tumour activity, treatment should consist of symptom management with psychosocial support.

Complications of Intrathecal Treatment

A cumulative dose of intraventricular methotrexate treatment ≥ 150 mg is strongly advised against for patients with leptomeningeal metastases. Combination with whole brain radiation therapy is also advised against due to the high risk of late progressive leukoencephalopathy (ataxia, dementia, incontinence). During treatment with intrathecal chemotherapy, use of oral dexamethasone on days 1 to 5 is recommended to reduce the risk of chemotherapy meningitis.

*Neurosurgery*

Insertion of a Ventricular Reservoir and Antibiotic Prophylaxis

For patients with leptomeningeal metastases in whom a ventricular reservoir will be inserted, administering flucloxacillin 1 g intravenously immediately before the operation is preferred as antibiotic prophylaxis to prevent wound infections and ventriculitis.

To reduce the risk of infection, it is recommended that the insertion of a ventricular reservoir is performed in an operating room and not as a bed-side procedure in a ward or in intensive care. The working group is of the opinion that puncturing the reservoir should be carried out using a 25-gauge needle (possibly 23-gauge) under strict sterile conditions.

Infection during Intrathecal Therapy Using a Ventricular Reservoir

In patients with leptomeningeal metastases and infectious meningitis, which is often caused by *Staphylococcus epidermidis* or *aureus*, treatment with antibiotics should begin while waiting for the results of CSF cultures. The Ommaya reservoir can remain in situ as long as intraventricular treatment is needed. For optimal treatment of infectious meningitis, the reservoir should be removed as soon as possible.

Hydrocephalus

In patients with leptomeningeal metastases with symptomatic hydrocephalus, a ventriculoperitoneal drain can be considered to ameliorate symptoms. For tumours that are sensitive to radiation therapy, local irradiation may be an option in some rare cases.

Asymptomatic hydrocephalus does not require treatment.

Intracranial Haemorrhage Caused by a Ventricular Reservoir

The working group is of the opinion that, if there are signs of a sudden increase in intracranial pressure, intracranial haemorrhage should be considered and a CT or MRI scan should be performed. Intracranial haemorrhage should be treated according to standard procedures (conservative/surgical).

*Symptomatic Treatment*

The working group is of the opinion that patients with a poor prognosis should forgo tumour-directed treatment and undergo therapy aimed at symptom management instead.

The Role of Dexamethasone

The working group is of the opinion that a short course of dexamethasone can be considered if signs of irritation are present. The dose should be lower than that used in the management of oedema caused by brain metastases: 3 mg twice daily appears to be sufficient. If there is no response, dexamethasone should be discontinued; increasing the dose is not advisable.

Headache and Vomiting

The working group is of the opinion that headache and vomiting should be handled with standard approaches. For severe headache, CSF drainage by means of lumbar puncture, or possibly a ventriculoperitoneal drain, may be considered. For excessive vomiting, radiation therapy at the posterior fossa may be considered.

Confusion

Haloperidol is the treatment of choice for most cases of delirium for patients with somatic disease. For older patients and those with more severe somatic disease, a starting dose of 1 to 2 mg daily and maximum dose of 0.5 to 5.0 mg is recommended given orally (tablets or liquid), subcutaneously or intramuscularly. Intravenous administration is not recommended because of the risk of QT prolongation and sudden death.

In case of inadequate sedation, lorazepam can also be given orally, intramuscularly or intravenously at a dose of 0.5 to 2 mg daily. For delirious patients who require opiates for pain, it should be considered whether pain medication is appropriate and treatment with haloperidol might be necessary.

*Psychosocial Support*

Clinicians who treat patients with leptomeningeal metastases should acquire specific communication skills. Good communication with patients and their family members is important given the stage of disease, its severity and the threatening nature of the disorder. In all cases, it should be clear to the patient and family members who is the treating physician and/or treatment coordinator.

Active inquiry into the possible need for psychosocial support should be a part of the management strategy for patients with leptomeningeal metastases during diagnosis and planning for further treatment. It should made be clear at each institution which care provider is responsible for the patient with leptomeningeal metastases and which disciplines the patient and/or family members can call on for support. If psychosocial support is indicated, then it should also be available, regardless of the location of the patient. Good transferrals with attention to the psychosocial aspects of care are therefore required.

*Organisation of Care*

The working group is of the opinion that specific procedures regarding the organisation of care for patients with leptomeningeal metastases are not strictly necessary. However, if it is decided to employ intraventricular chemotherapy, the insertion of the ventricular reservoir should take place in a neurosurgical centre with experience in this area. Treatment institutions should have adequate access to radiation therapy. In case of rare complications, it is advisable that physicians consult with a referral centre by telephone. For patients with leptomeningeal metastases of PNETs, consideration can also be given to consultation with paediatric oncology centres for their experience. Given the severity of the stage of disease in which leptomeningeal metastases occur, providing adequate care as close as possible to the patient's home is more important than the centralisation of care and treatment.

**LM of Primary Tumours of the CNS**

*Medical Technical*

Consultation with a referral centre is recommended for the treatment of leptomeningeal metastases of medulloblastomas, ependymomas and germ cell tumours. The treatment of synchronous leptomeningeal metastases of these tumours is curative.

For PNET/medulloblastomas with leptomeningeal metastases, a combination of chemotherapy and radiation therapy should be administered. Various regimens with vincristine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), etoposide, methotrexate, cis/carboplatin and cyclophosphamide can be used. A radiation dose or 35 Gy in 20 to 22 fractions is given to the craniospinal axis with a boost of 15 to 20 Gy in 8 to 12 fractions to the posterior fossa and other macroscopic tumour locations if applicable.

Of the germ cell tumours, the germinomas are highly sensitive to chemotherapy and radiation therapy; the chance of cure of leptomeningeal metastases in this setting is probably high.

*Symptomatic Treatment*

The working group is of the opinion that patients with a poor prognosis should forgo tumour-directed treatment and undergo therapy aimed at symptom management instead.

<u>The Role of Dexamethasone</u>

The working group is of the opinion that a short course of dexamethasone can be considered if signs of irritation are present. The dose should be lower than that used in the management of oedema caused by brain metastases: 3 mg twice daily appears to be sufficient. If there is no response, dexamethasone should be discontinued; increasing the dose is not advisable.

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disease in which leptomeningeal metastases occur, providing adequate care as close as possible to the patient's home is more important than the centralisation of care and treatment.

### CLINICAL ALGORITHM(S)

The original guideline document contains clinical algorithms for:

- Diagnosis of leptomeningeal metastases of extracranial solid tumours
- Treatment of leptomeningeal metastases with and without brain metastases

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not identified or graded for each recommendation.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Improved quality of care and quality of life in patients with leptomeningeal metastases

### POTENTIAL HARMS

Iatrogenic or treatment-related complications of systemic therapy include the adverse effects of morphine, dexamethasone, radiation therapy, and chemotherapy.

Complications of intrathecal treatment:

- Ommaya reservoir-related problems (blockage, incorrect position, intracranial haemorrhage) occur in approximately 5-10% of patients, of which about 10% are fatal and about half lead to a second operation. Infectious meningitis occurs in 5-10% of patients, of which 10% are fatal; insufficient response to antibiotics necessitates surgical removal of the reservoir.
- Chemotherapy meningitis is reported in 5% to more than 20% of patients, most often following treatment with methotrexate or depot cytarabine.
- An acute reaction to intrathecal corticosteroids involving loss of consciousness, headache and vomiting has been described. Severe, often irreversible myelopathy is observed occasionally. It may occur more often following combination intrathecal therapy with methotrexate and cytarabine or following combined cytarabine and radiation therapy to the spinal column.
- Other early complications that have been occasionally described are mild, transient encephalopathy (mild transient fever, nausea and apathy) and seizures. Approximately one-third of patients experience neurological complications in the first few weeks of intraventricular treatment. These

complications will often lead to a prolonged hospital stay and they can also preclude further targeted antitumour treatment.
- In patients with longer survival, leukoencephalopathy can occur as soon as 4 months after treatment initiation (mean 8 months) and is characterised by ataxia, apathy and cognitive disorders, as well as by radiological evidence of damaged periventricular white matter. It is usually progressive, leading to overt dementia.
- Long-term treatment with intrathecal methotrexate can also produce systemic complications, such as myelosuppression and occasionally mucositis.

The most dreaded complication of irradiation is necrotising leukoencephalopathy.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Guidelines are not legal requirements, but rather scientifically founded and widely accepted views and recommendations to which healthcare providers would have to adhere to provide quality care. Given that guidelines are based on 'average patients', healthcare providers can deviate from the recommendations in the guideline as necessary in individual cases. Deviation from the guideline is in fact sometimes necessary if the patient's situation demands it. When there is deviation from the guideline, however, it must be rationalised, documented and, when necessary, discussed with the patient.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

During the various phases of development of the draft guideline, consideration was given whenever possible to the implementation of the guideline and the actual feasibility of the recommendations. The guideline will be distributed to all hospitals and oncology boards, scientific societies and comprehensive cancer centres. In addition, the guideline will be reproduced on www.oncoline.nl. In general, indicators are often developed in order to evaluate the effect of a guideline. This was not done for the guideline on leptomeningeal metastases due to the low incidence, the wide variation in treatment options of a distinctly multidisciplinary nature and the course of the disease, which is typically rapidly progressive, unfavourable and fatal within months.

### IMPLEMENTATION TOOLS

Clinical Algorithm
Foreign Language Translations
Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

End of Life Care
Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Dutch Neuro-Oncology Working Group. Leptomeningeal metastases. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2006 Jan 12. 71 p. [219 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2006 Jan

### GUIDELINE DEVELOPER(S)

Association of Comprehensive Cancer Centres - Disease Specific Society

### SOURCE(S) OF FUNDING

Association of Comprehensive Cancer Centres

### GUIDELINE COMMITTEE

Dutch Neuro-Oncology Working Group

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

A folder containing disclosures of potential conflicts of financial interests for working group members is available at the Dutch Institute for Healthcare Quality Improvement, Monitoring and Maintenance (Kwaliteitsinstituut voor de Gezondheidszorg CBO). No unusual conflicts of interest were reported.

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This is the current release of the guideline.

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Electronic copies: Available in English and Dutch from the Association of Comprehensive Cancer Centres Web site.

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## AVAILABILITY OF COMPANION DOCUMENTS

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## PATIENT RESOURCES

None available

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