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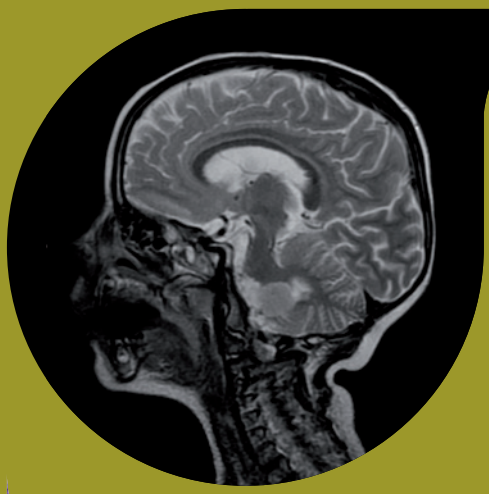
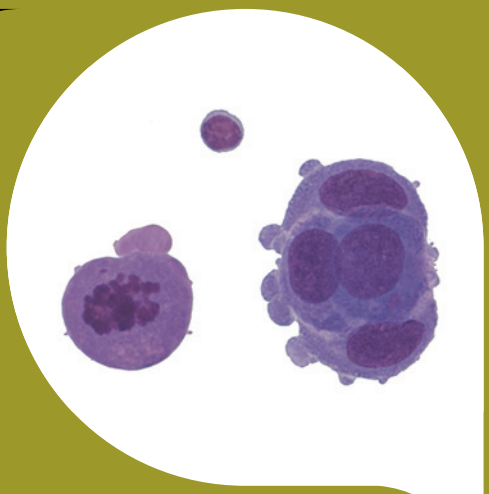
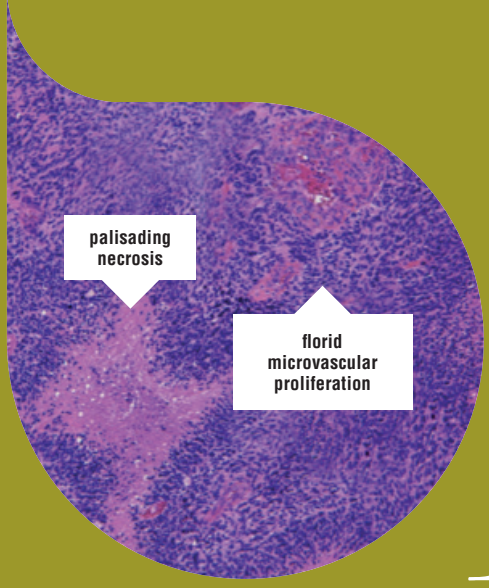
edited by
Matthias Preusser
& Michael Weller

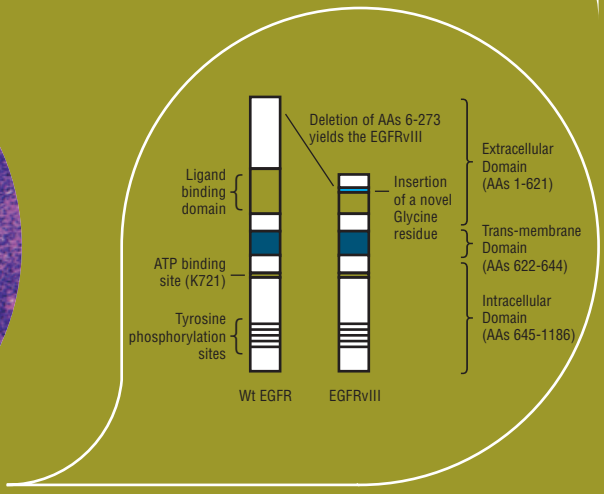
NEURO-ONCOLOGY

ESSENTIALS *for* CLINICIANS









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Neuro-Oncology
Essentials for Clinicians

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Preface

For the last ten years, few new therapies have been found to be useful for the treatment of neuro-oncological diseases. Nevertheless, many improvements have been made in the recognition of pathological and clinical entities based on molecular alterations that drive the outcome and response to treatment of central nervous system malignancies, leading to refinement of therapeutic strategies and treatment indications. These advances, together with the general consensus on radiological, clinical and response assessment rules, which should be part of clinical investigations done by the RANO group, promise a future of excellent investigations that will surely lead to improvements in the diagnosis and treatment of these diseases.

This volume of *Essentials for Clinicians*, masterfully supervised by recognised experts Drs Matthias Preusser and Michael Weller, contributes in summarising the state-of-the-art of neuro-oncology from different perspectives ranging from epidemiology to treatment strategies. To summarise means, in fact, to describe the essential information that each clinician wants to know about a disease, as well as the starting point from which to expand further knowledge on neuro-oncology. The ESMO *Essentials for Clinicians* initiative meets this objective well, with a friendly and illustrative way of transmitting information.

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Abbreviations

5-ALA	5-Aminolevulinic acid
ALK	Anaplastic lymphoma kinase
AQP4	Aquaporin 4
ATRX	Alpha thalassaemia/mental retardation syndrome X-linked gene
BBB	Blood–brain barrier
CCNU	Lomustine
CE	Contrast enhancement
ChT	Chemotherapy
CIMP	CpG island methylator phenotype
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTLA	Cytotoxic T lymphocyte-associated antigen
CVA	Cerebrovascular accident
D/N	Desmoplastic/nodular
DC	Dendritic cell
DGIIG	Diffuse Grade 2 glioma
DGIIIG	Diffuse Grade 3 glioma
DIPG	Diffuse intrinsic pontine gliomas
EEG	Electro-encephalogram
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
FET	O-(2-[^{18}F]fluoroethyl)-L-tyrosine
FLAIR	Fluid attenuation inversion recovery
FLT	[^{18}F]fluorothymidine
fMRI	Functional MRI
FSRT	Fractionated stereotactic RT
GFAP	Glial fibrillary acidic protein
HGG	High-grade gliomas
IDH	Isocitrate dehydrogenase
iMRI	Intraoperative MRI
IMRT	Intensity-modulated RT
iUS	Intraoperative ultrasound
KPS	Karnofsky Performance Status
LGG	Low-grade glioma
LINAC	Linear accelerator
LOH	Loss of heterogeneity
MAPK	Mitogen-activated protein kinase
MB	Medulloblastoma
MBEN	Medulloblastoma with extensive nodularity
MGMT	O6-Methylguanine-DNA methyltransferase
MRI	Magnetic resonance imaging
MSP	Methylation-specific polymerase chain reaction
mTOR	Mechanistic target of rapamycin
MVP	Microvascular proliferation
NF2	Neurofibromatosis Type 2
NOS	Not otherwise specified
OPG	Optic pathway gliomas
OS	Overall survival
PCV	Procarbazine/ lomustine/vincristine
PD	Programmed death
PET	Positron emission tomography
PFS	Progression-free survival
PI	Phosphatidyl-inositol
PREM	Patient-related experience measures
PROM	Patient-related outcome measures
QoL	Quality of life
RANO	Response Assessment in Neuro-Oncology Criteria
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SCLC	Small cell lung cancer
SHH	Sonic Hedgehog
SRS	Stereotactic radiosurgery
TMS	Transcranial magnetic stimulation
TMZ	Temozolomide
VEGF	Vascular endothelial growth factor
VTE	Venous thromboembolism
WBRT	Whole brain radiotherapy
WHO	World Health Organization
wt	Wildtype

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Matthias Preusser and Michael Weller

A

What every oncologist should know

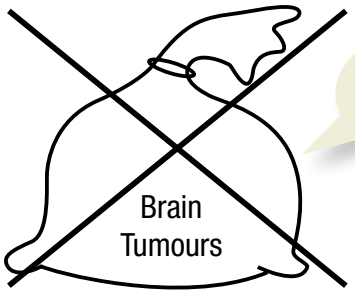
1 Epidemiology, pathogenesis and risk factors of brain tumours

Introduction; definition

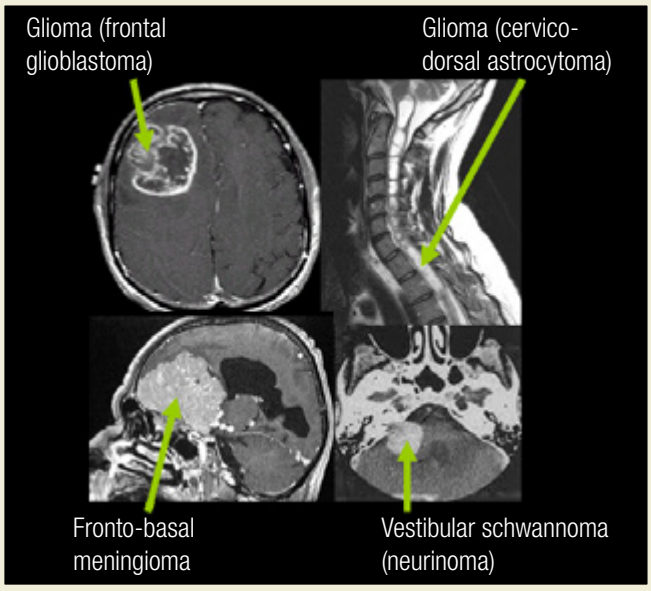
"Brain tumours" is the common term to define central nervous system (CNS) neoplasms, or CNS tumours.

The global incidence of all CNS tumours is unknown but higher than 45/100 000 patients a year.

The 2016 World Health Organization classification of CNS tumours is based on histopathological and molecular criteria and includes malignant, benign and borderline tumours. They are categorised as primary or secondary.



Brain tumours are not one entity, but diverse histological entities with different causes, prognosis and treatments.



Primary CNS tumours include all primary tumours located in the CNS, the envelopes of the CNS and the beginning of the nerves localised in the skull and spine.

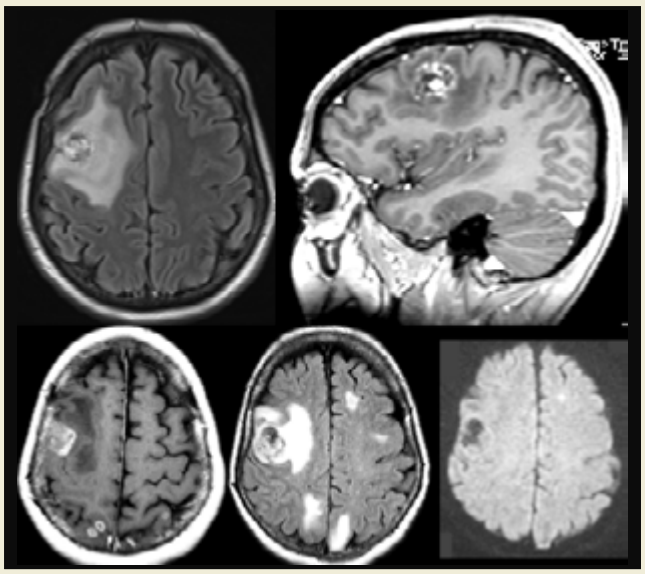
In the USA, the incidence rate of all primary malignant and non-malignant CNS tumours is 21.42/100 000 (7.25/100 000 for malignant and 14.17/100 000 for non-malignant tumours).

In the USA, among the various histological groups of primary CNS tumours, meningiomas account for 36%, gliomas for 28%, nerve sheath tumours for 8% and lymphomas for 2%.

Secondary CNS tumours are CNS metastases; they are all malignant. CNS metastases are single or multiple.

Metastatic tumours are the most frequent type of CNS tumour in adults. The reported incidence of metastatic CNS tumours is increasing but the exact incidence is unknown.

In general, the sources of brain metastases (in descending order) are: cancers of the lung, breast, skin (melanoma), kidney and gastrointestinal tract.



REVISION QUESTIONS

1. Do brain tumours always have the same origin?
2. Name the two most common histological groups among primary tumours.
3. Which brain tumours are more frequent: primary or secondary?

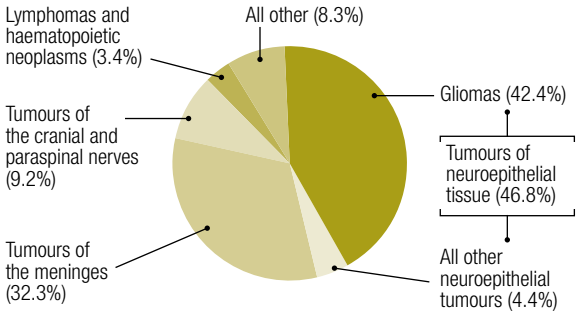
Primary CNS tumours – descriptive epidemiology

Epidemiological data on primary CNS tumours come from registries and population studies. But registration guidelines and population vary among registries and countries, so results from the literature should be analysed according to these differences.

Primary CNS tumours are divided into major histological groups.

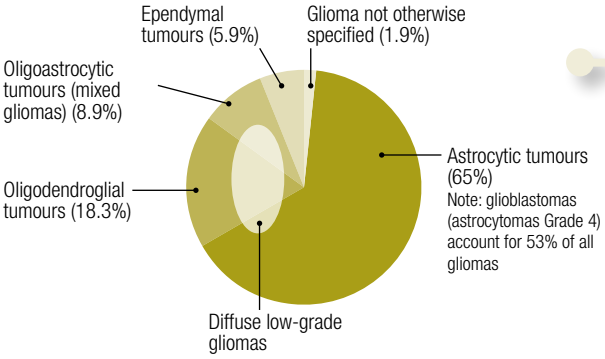
More than 90% of neuroepithelial tissue tumours are malignant, and more than 90% of meningeal tumours are non-malignant.

Distribution of all primary CNS tumours by major histology groupings in France



CNS, Central nervous system.

Distribution of gliomas by major histological subgroups in France



In adults, the male/female ratio for diffuse gliomas is approximately 1.5. Among these, glioblastoma (Grade 4 glioma) is the most frequent. The median age at diagnosis is 64 years.

Diffuse Grade 2 gliomas (DGIIGs, often named diffuse low-grade gliomas) and diffuse Grade 3 gliomas (DGIIIGs, often named anaplastic gliomas) account for approximately 30% of all gliomas.

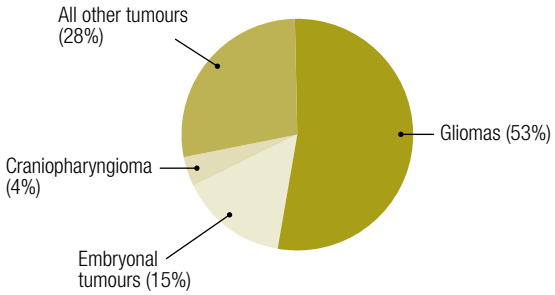
Median age at diagnosis is 43 years for DGIIG and 56 years for DGIIIG.

In the USA, the incidence rate of paediatric (<15 years old) primary CNS tumours is 5.3 cases per 100 000. These tumours are the most common paediatric solid tumours.

Paediatric gliomas include pilocytic astrocytomas (Grade 1 glioma, 33%), Grade 3 and 4 gliomas (21%), ependymal tumours (10%) and all other gliomas (36%).

All embryonal tumours are malignant. Medulloblastoma is the most important subgroup of embryonal tumours (62%).

Distribution of all paediatric primary CNS tumours by major histology groupings (0-14 years) in USA



CNS, Central nervous system.

REVISION QUESTIONS

1. Why can epidemiological data differ from one country to the next?
2. Are diffuse gliomas more frequent in women or men?
3. What is the most frequent grade of glioma in children?

Primary CNS tumours – clinical epidemiology

Prognostic factors and therapeutic measures (resection, radiotherapy, chemotherapy, new therapy) impact survival in primary CNS tumour patients.

Multivariate analysis is one method used to take into account different prognostic factors for the survival analysis.

Usually, median survival in population studies (all patients [with good or poor prognostic factors] are included) is shorter than in clinical trials (only selected patients are included).

Main prognostic factors for primary CNS tumours

Age
Performance status (e.g. Karnofsky performance status)
Comorbidity
Appearance of the tumour by MRI (topography, volume, delimitation, enhancement, etc.)
Features of the new tumour imaging techniques (multimodal MRI, PET scan, etc.)
Tumour growth rate
Histological type and subtype
Histological grade
Biology
Etc.

CNS, Central nervous system; MRI, magnetic resonance imaging; PET, positron emission tomography.

Survival rate (SR) for selected gliomas and age groups (years) in USA

Histology	Age group	1-Year SR (%)	10-Year SR (%)
Pilocytic astrocytoma	0-14	98.8	95.9
	15-39	97.2	90.2
	40+	95.3	72.4
Oligodendroglioma	0-14	96	90.9
	15-39	98.6	69.7
	40+	90.3	54.6
Glioblastoma	0-14	49.9	14.9
	15-39	71.7	13.2
	40+	34.2	1.6

See CBTRUS table for 95% confidence intervals: http://www.cbtrus.org/reports/reports.html

Glioblastoma is the most frequent glioma with the worst prognosis (median survival ≈10 months in population studies, and 14.6 months in the group of patients treated with radiotherapy and temozolomide in the pivotal study of Stupp et al).

Most children with pilocytic astrocytoma who have a complete resection are cured without further oncological treatment.

The quality of life (QoL) of oligodendroglioma patients is often preserved for several years with surgery(ies) and oral chemotherapy.

The QoL of primary CNS tumour patients is often affected by a variety of symptoms, depression and fatigue. Diagnosis of a brain tumour is a life-changing event for patients and families.

Helping these patients, treating symptoms and improving QoL at all stages of illness are important goals for the multidisciplinary care team.

Supportive care teams can improve the patient's QoL, symptom burden and even survival.

Signs and symptoms (%) in a series of 7786 primary CNS tumour patients

	Ep	Ha	RI	MD	FD	Ot	As
Gliomas	31	29	22	30	41	7	3
Other NET	26	38	49	11	17	11	3
Meningiomas	24	33	14	20	34	18	7
Lymphomas	14	27	19	53	48	7	1

As, Asymptomatic; CNS, central nervous system; Ep, epilepsy; FD, focal deficit; Ha, headache; MD, mental status disorders; NET, neuroepithelial tumours; Ot, other; RI, raised intracranial pressure.

REVISION QUESTIONS

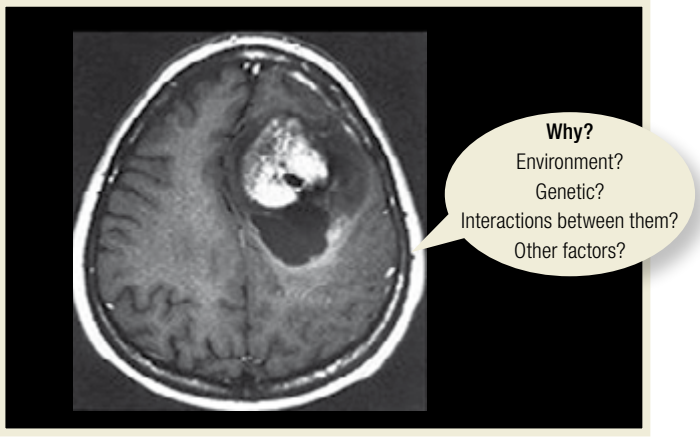
1. Age at diagnosis is the only prognostic factor in gliomas. True or false?
2. What is the median survival for glioblastoma patients in population studies?
3. What are the main clinical symptoms in primary CNS tumour patients?

Gliomas and meningiomas – risk factors

High-dose ionising radiation is the only unequivocal environmental risk factor that was identified for glial and meningeal neoplasms. An association was observed in A-bomb studies, nuclear test fallout data, therapeutic radiation, and occupational and environmental studies.

In 2011, the International Agency for Research on Cancer classified mobile phone use and other radiofrequency electromagnetic fields as a possible carcinogenic agent (Group 2B).

Many environmental risk factors (non-ionising radiation, e.g. mobile phones, pesticides, solvents, etc.) have been examined as potential contributors to glioma risk, with inconclusive results until now.



Monogenic Mendelian disorders associated with increased risk of glioma

Gene	Disorder/syndrome
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
TSC1,TSC2	Tuberous sclerosis
MSH2, MLH1, MSH6, PMS2	Lynch syndrome
TP53	Li-Fraumeni syndrome
p16/CDKN2A	Melanoma-neural system tumour syndrome
IDH1/IDH2	Ollier disease/Maffucci syndrome

A heritable genetic contribution to glioma genesis was initially suggested by the increased incidence of these tumours in families with Mendelian cancer syndromes.

But a very small portion of these tumours are caused by Mendelian disorders, including neurofibromatosis, tuberous sclerosis and Li-Fraumeni syndrome.

Excluding genetic syndromes, familial cases of primary CNS tumours represent less than 5% of cases.

Epidemiological studies consistently suggest that allergic conditions, including asthma, hay fever, eczema and food allergies, are associated with reduced glioma risk.

In the USA, incidences of glioblastoma and oligodendroglioma are approximately 2 times greater in white people than in black people, but the incidence of meningioma is higher in black people than white people.

Genome-wide association studies have identified heritable risk alleles within 7 genes that are associated with increased risk of glioma.

Candidate genes	Chromosome location
TERT	5p15.33
EGFR	7pl1.2
CCDC26	8q24.21
CDKN2B	9p21.3
PHLDBI	11q23.3
TP53	17pl3.1
RTELI	20ql3.33

REVISION QUESTIONS

1. What is the only identified environmental risk factor that increases the risk of glioma or meningioma?
2. What are the rare genetic syndromes associated with gliomas?
3. Allergy is associated with a reduced risk of glioma. True or false?

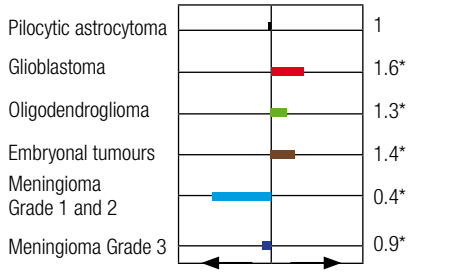
Gliomas and meningiomas – risk factors (continued)

Across countries and populations, the incidence of brain tumours is related to gender, with opposite patterns for meningiomas and gliomas. The male/female ratio for meningioma is approximately 0.4 (1 man for 2.5 women).

This difference suggests that sex hormones and/or genetic differences between males and females may play a role in the occurrence of these tumours.

Hormonal receptors were identified in meningioma tissues: ≈80% of meningiomas have progesterone receptors, 40% oestrogen receptors and 40% androgen receptors.

Incidence rate ratios by gender (males/females) in USA



Higher incidence in females I Higher incidence in males
*Significant difference

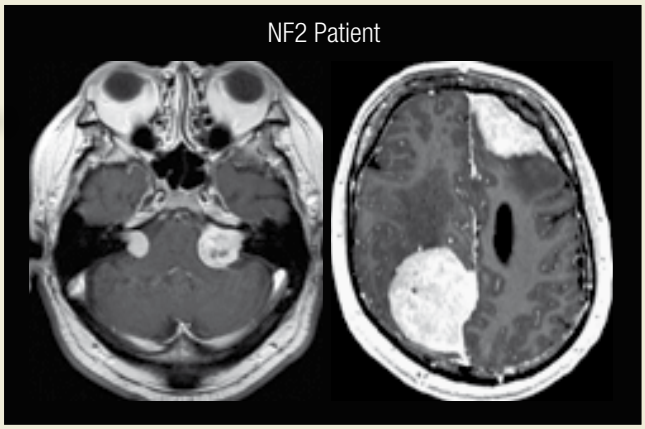
Menopausal hormone therapy is associated with an increased meningioma risk. A recent meta-analysis suggests an increased risk in users of oestrogen-only hormone therapy.

Oral contraception and breast-feeding do not appear to increase the risk of meningioma.

To date, among exogenous suspected factors (electromagnetic fields, nutrition, pesticides, etc.), the only established causal link with risk of meningioma is high doses of ionising radiation.

Increased risk of meningioma is observed in rare hereditary syndromes, mainly neurofibromatosis Type 1 and 2 (NF1 and NF2), and possibly in Turner's syndrome and Werner's syndrome.

Germline and somatic mutations in meningiomas: a significant increase in risk of meningiomas is associated with neurofibromatosis Type 2 disease through mutation of the *NF2* gene, and approximately 5% of individuals with schwannomatosis develop meningiomas, through mutation of the SWI/SNF chromatin remodeling complex subunit, SMARCB1.



NF2, Neurofibromatosis Type 2.

REVISION QUESTIONS

1. Which primary CNS tumour has the lowest sex ratio (male/female)?
2. It is recommended to prescribe hormone therapy to menopausal women with meningioma. True or false?
3. What are the two main histological types of primary CNS tumour associated with *NF2* gene mutation?

Summary: Epidemiology, pathogenesis and risk factors of brain tumours

- Primary CNS tumours are diverse histological entities with different causes
- Primary CNS tumours include malignant, benign and borderline tumours
- Meningiomas and gliomas are the two main histological types of primary CNS tumours
- Secondary CNS tumours (metastases) are more frequent than primary CNS tumours
- Glioblastoma is the most frequent glioma with a median age at diagnosis of 64 years
- Paediatric primary CNS tumour is the most frequent paediatric solid tumour
- Age, Karnofsky performance status, comorbidity, tumour growth rate, magnetic resonance imaging, histology and biology are important prognostic factors
- Symptomatology and QoL must be taken into account in the medical care management
- High-dose ionising radiation is the only unequivocal risk factor that was identified for glial and meningeal neoplasms
- Increased risk of glioma and meningioma is observed in rare hereditary syndromes

Further Reading

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2 Clinical presentation, differential diagnosis and response assessment of gliomas

Clinical presentation

The most common symptoms of brain tumours are headache, epileptic seizures, focal deficiency symptoms and/or more diffuse mental or thought-compulsive symptoms.

With acute symptoms pointing to incipient obstruction of cerebrospinal fluid (CSF) flow (e.g. severe headache, disorientation, unilaterally dilated light rigid pupils), urgent contact with a neurosurgeon is needed.

Suspicion of a primary brain tumour should occur when at least one of the five criteria in the table are met.

Alarm symptoms	
1	First-time seizures (focal or generalised)
2	The onset of focal neurological deficit symptoms progressing over days or weeks without other plausible explanation (e.g. hemiplegia, balance problems, numbness, loss of vision)
3	Changes in personality or cognitive impairment (weeks to months)
4	New episodes and pattern of headache (especially with distinct character of increased intracranial pressure; morning headache, nausea/vomiting, papillo-oedema) that progresses over weeks and where thorough medical history and clinical neurological examination has not revealed other plausible explanations
5	Computed tomography (CT) or magnetic resonance imaging (MRI) (performed in other indications) indicates suspicion of primary malignant brain tumour

Analysis of a potential brain tumour patient
• Age of the patient

• Localisation:
  • Intra- vs extra-axial
  • What structures?
  • Midline crossing

• CT and MRI features:
  • Calcification, fat, cystic
  • T1, T2, DW1

• Contrast enhancement
• Effect on surrounding structures   • Mass effect – oedema
• Solitary – multiple?
• Pseudotumour?

CT, Computed tomography; MRI, magnetic resonance imaging.

Patients may present with generalised symptoms of increased intracranial pressure (headaches, nausea and cognitive impairment) or signs that reflect the location of the tumour.

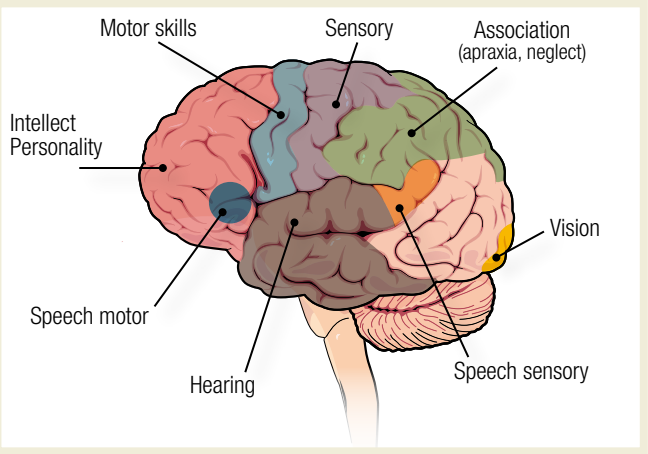
Headache, rarely alone as initial symptom, can vary in intensity and quality. It is frequently more severe on awakening, due to pain-sensitive meninges and blood vessels.

Psychiatric symptoms, e.g. anxiety and depression, seem to be underdiagnosed. Tumours in less critical areas (anterior frontal or temporal lobe) may be associated with subtle personality changes and memory problems.

Weakness and sensory hemineglect (more prominent in right hemispheric lesions) are the hallmarks of tumours arising in the frontal or parietal lobes and thalamic region.

Seizures of varying patterns (partial or generalised) are a common presentation of tumours in the frontoparietal regions and temporal lobe and are more often reported in low-grade glioma.

Occipital lobe tumours may present with slow onset of visual field defects. Bilateral crossed neurological deficits (weakness on one side with contralateral cranial nerve palsy) can be an initial indicator of brainstem glioma.



REVISION QUESTIONS

1. What are the alarm symptoms of a brain tumour?
2. What is important to consider when analysing a patient with a potential brain tumour?
3. Give one example of symptoms reflecting the location of the tumour.

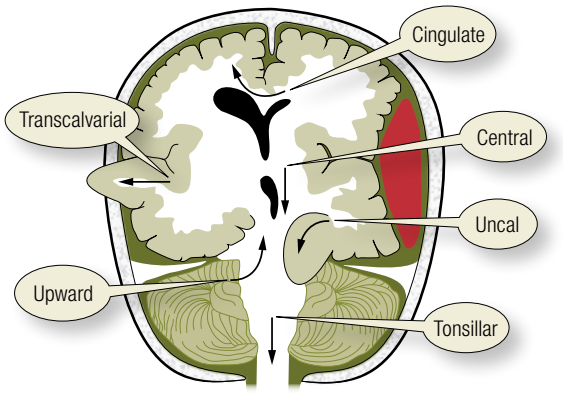
Clinical presentation (continued)

If the liquor flow is compromised (obstructive hydrocephalus), a Valsalva manoeuvre, coughing and position change of the head may cause sudden short-term intensive headache associated with nausea and loss of consciousness.

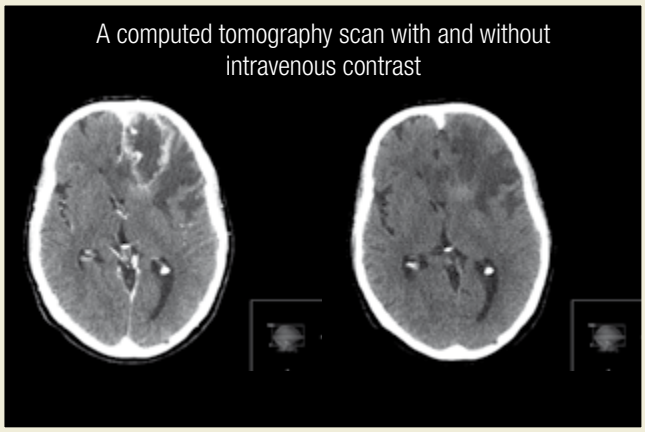
Particular attention and early contact with neurosurgery is required in case of an expansive process in the posterior cranial fossa, due to the risk of herniation of the medulla oblongata.

Brain herniation, caused by a mass effect and increased intracranial pressure, occurs when a part of the brain is squeezed across structures, such as the falx cerebri, the tentorium cerebelli and through the foramen magnum.

Types of brain herniation



A computed tomography scan with and without intravenous contrast



The clinical history of patients with primary glioblastoma (90% of glioblastomas) is usually short, less than 3 months in half of patients. Secondary glioblastoma (usually younger patients) typically develops from lower grade gliomas and has a longer clinical history.

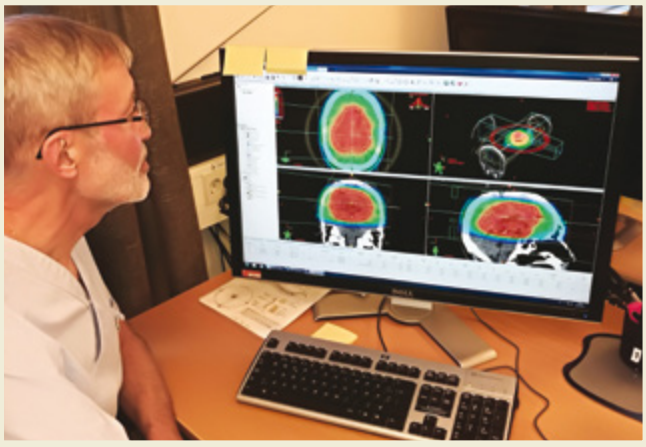
Rapidly growing high-grade glioma causes focal loss of function symptoms, rarely seen in low-grade glioma due to the plasticity of the brain, except in cases of bleeding in the tumour, when the onset is rapid, as in stroke.

Contrast agent will not leak into the brain unless the blood–brain barrier (BBB) is damaged. Enhancement is seen when a central nervous system (CNS) tumour destroys the BBB or when no BBB is present (meningioma, pituitary and pineal region).

A proper evaluation of a patient with a suspected brain tumour requires a detailed history, neurological examination, and appropriate diagnostic neuroimaging studies.

On suspicion of a brain tumour, magnetic resonance imaging (MRI) is the gold standard. If in need of urgent investigation, or if MRI is not available, computed tomography (CT) scan with and without contrast enhancement can be used.

If MRI/CT confirms the suspicion of brain tumour, the patient should be referred to a regional multidisciplinary therapy conference or to the neurosurgical clinic.



REVISION QUESTIONS

1. What is the risk of a glioma in the posterior fossa?
2. When are focal loss of function symptoms seen?
3. What is the gold standard when a brain tumour is suspected?

Differential diagnosis

Brain tumours are often overlooked in differential diagnosis. Most physicians/general practitioners meet very few patients with a brain tumour. The confusion of tumour symptoms with other disease symptoms is a challenge.

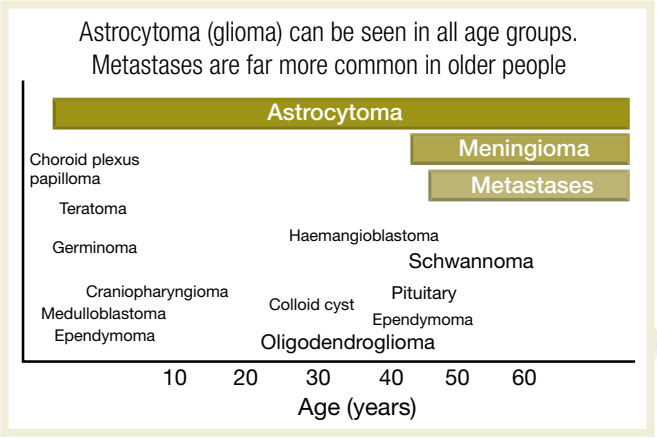
The most effective means of ensuring early identification is to bear the possibility of a brain tumour constantly in mind in differential diagnosis.

A varied spectrum of different conditions, from benign lesions to more severe neurological associated disorders, have to be considered in the differential diagnosis of glioma.

Differential diagnosis of glioma

- Aneurysm
- Benign brain tumour
- Brain abscess
- Cavernous sinus syndrome
- Cluster headache
- CNS lymphoma
- Encephalitis
- Head injury
- Haematoma
- Hydrocephalus
- Metastasis
- Metabolic dysfunction
- Multiple sclerosis
- Radiation necrosis
- Stroke

CNS, Central nervous system.



When analysing a potential brain tumour, many questions arise:

- different tumours occur in different age groups
- the location of the lesion
- solitary mass or multifocal disease?

Less malignant gliomas occur at any age, but glioblastoma is mostly seen in older people.

Multiple tumours in the brain indicate metastatic disease. Some primary brain tumours like lymphomas, multicentric glioblastomas and gliomatosis cerebri can be multifocal.

Cerebral metastasis may look identical to malignant gliomas, multifocal or as a solitary lesion. Metastases are much more common, especially infratentorially.

Functional MRI and magnetic resonance spectroscopy (MRS) can provide important information about the tumour, such as metabolic phenotyping, microvasculature and cellularity.

Positron emission tomography (PET) using various tracers (transmitter ligands) for molecular evaluation are of value to characterise tumours, and also to differentiate between low-grade glioma and non-tumour causes.

Common intra-axial tumours in adults

Supratentorial	Infratentorial
Metastases ++	Metastases +++++
Gliomas (25%)	Haemangioblastoma
• Fibrillary astrocytoma	
• Anaplastic astrocytoma	
• Glioblastoma multiforme	
• Oligodendroglioma	

REVISION QUESTIONS

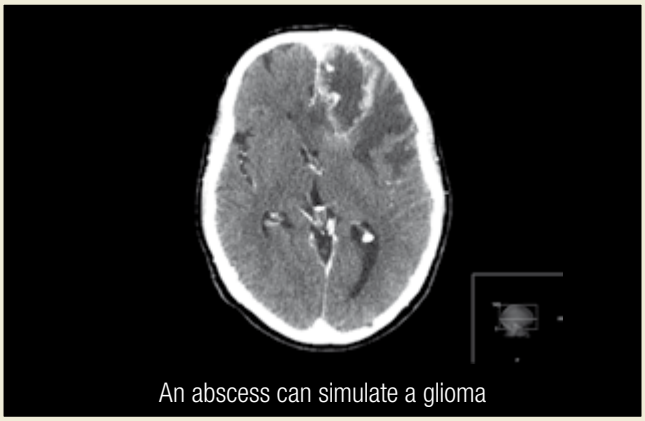
1. Give examples of differential diagnoses to malignant glioma
2. Why may a brain tumour be overlooked in daily practice?
3. What can be a clue to the diagnosis of malignant glioma?

Differential diagnosis (continued)

Infections (abscesses) can mimic a brain tumour with confusing symptoms: headache, seizures, disorientation, unilateral weakness and, usually, fever.

Vascular lesions may be the first sign of a glioma by acute bleeding into or in the vicinity of the tumour, causing a neurological deficit. Stroke can also imitate a primary brain tumour.

In the parasellar region, one should always consider the possibility of an aneurysm.



An abscess can simulate a glioma

Epileptic manifestations can sometimes be misinterpreted and delay tumour diagnosis. The clinician should therefore be aware of the possibility of a brain tumour, regardless of the type of underlying epileptic seizure.

Epileptic aura could be indicated by a sudden transient dysphasia in the absence of other symptoms, transient focal deficiency symptoms (numbness and paresis), sudden emotional, autonomic or hallucinatory symptoms.

Contrast enhancement
Extra-axial tumours: meningioma, schwannoma
High-grade gliomas
Low-grade gliomas: ganglioglioma
Lymphoma
Metastases
Infection, abscess, multiple sclerosis, vascular

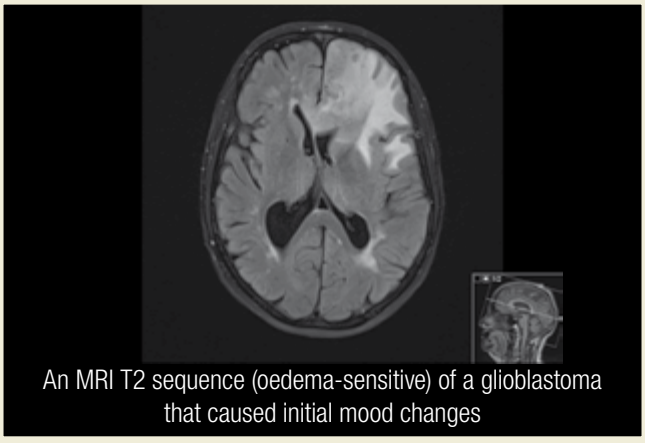
MRI, Magnetic resonance imaging.

Contrast enhancement on CT or MRI does not always differentiate low-grade glioma from non-tumour causes. Characteristics on MRI/CT (calcifications, fat, signal intensity) may be a clue to diagnosis.

Affective disorders may be due to causes other than glioma, e.g. side effects of any treatment given, or occur as a reaction to other aspects of life, including adjustment to a brain tumour diagnosis.

Excessive anxiety of having a tumour in the brain is not uncommon in patients with severe headache.

Although chronic headache very rarely leads to the detection of a brain tumour, in some explicit cases it can be an indication for a CT/MRI to alleviate the patient's concerns.



An MRI T2 sequence (oedema-sensitive) of a glioblastoma that caused initial mood changes

MRI, Magnetic resonance imaging.

REVISION QUESTIONS

1. What are the symptoms of an intracranial abscess?
2. Give examples of epileptic auras that can be a sign of tumour.
3. What about affective disorders and glioma?

Assessment

Accurate response measurements are needed to ensure the continuation of effective therapy, and modify or discontinue an ineffective treatment in non-responding patients.

For clinical trials enrolling brain tumour patients, overall survival or survival at specified time points are usually considered as the most reliable endpoints. However, these endpoints may be prone to the confounding effects of salvage therapy.

Quality of life endpoints, i.e. PROM (patient-related outcome measures) and PREM (patient-related experience measures), including neurological and cognitive symptoms, are of great value and should be used in clinical brain tumour studies.

Commonly used patient-related outcome instruments	
FACT-G/Br	Functional Assessment of Cancer Therapy – General/Brain Modules
FBrSI	FACT Brain Symptom Index
EORTC	European Organisation for Research and Treatment of Cancer
- QLQ-C30	- Quality of Life Questionnaire Core 30
- QLQ-BN20	- Quality of Life Brain Module

RANO
The RANO criteria divide responses into 4 types of response based on imaging (MRI) and clinical features:
1. Complete response
2. Partial response
3. Stable disease
4. Progression

MRI, Magnetic resonance imaging; RANO, Response Assessment in Neuro-Oncology.

Response rate and progression-free survival using MRI/CT for evaluating tumour burden are valuable endpoints when attempting to isolate the relative efficacy of a given treatment, and to increase the knowledge of the nature of follow-up on study.

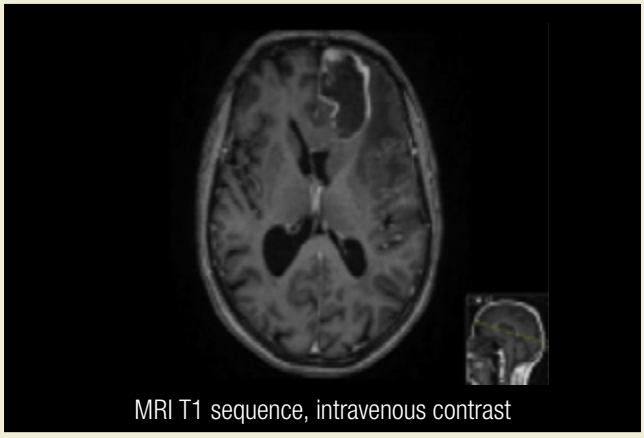
Currently the most widely used system to assess first-line treatment response in glioma is the Response Assessment in Neuro-Oncology (RANO) criteria.

These surrogate markers present limitations, including the potential for variability, the potential for false-positive signals and the discordance in radiographic interpretation between radiologists.

An improved understanding of tumour biology and novel imaging techniques, e.g. PET and functional MRI, have opened new windows for the evaluation of tumours, even at the molecular level.

The introduction of targeted therapies and immunotherapies directly affecting contrast enhancement have also highlighted the need for new endpoints.

Response assessments (clinically and MRI/CT) are in general conducted every second or third month for patients during the initial 1–2 years after primary treatment, thereafter every six months or at the discretion of patient and physician.



MRI T1 sequence, intravenous contrast

MRI, Magnetic resonance imaging.

REVISION QUESTIONS

1. What is the gold standard when evaluating the efficacy of a given treatment?
2. What is the value of using surrogate markers in evaluating treatment?
3. How often should a response assessment be done?

Summary: Clinical presentation, differential diagnosis and response assessment of gliomas

- Patients may present with generalised symptoms or signs that reflect the location of the tumour
- Common symptoms are headache, nausea and various signs of cognitive impairment
- Tumours in the anterior frontal or temporal lobe may cause subtle or severe changes in personality and memory
- Partial or generalised seizures may indicate a glioma
- Weakness and sensory hemineglect are common deficits
- Different brain disorders have to be considered in the differential diagnosis of glioma
- Cerebral metastasis may look like malignant gliomas; furthermore, abscess and stroke mimic malignant glioma
- The most accepted endpoints for clinical trials in neuro-oncology are overall and progression-free survival and quality of life
- MRI is the gold standard for evaluation of tumour burden
- Increased knowledge in tumour biology gives new predictive and prognostic markers

Further Reading

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3 Histology and molecular pathology of gliomas

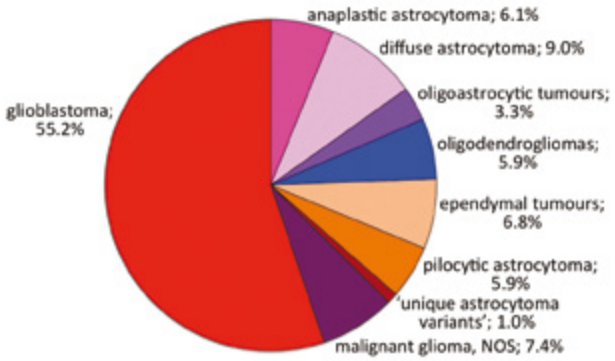
Classification; typing and grading

Gliomas are the most frequent primary central nervous system (CNS) tumours. They originate from glial cells or progenitor cells showing glial characteristics upon neoplastic transformation.

Gliomas form a very heterogeneous group of tumours. For over a century, histological diagnosis formed the basis for assessment of prognosis and therapy.

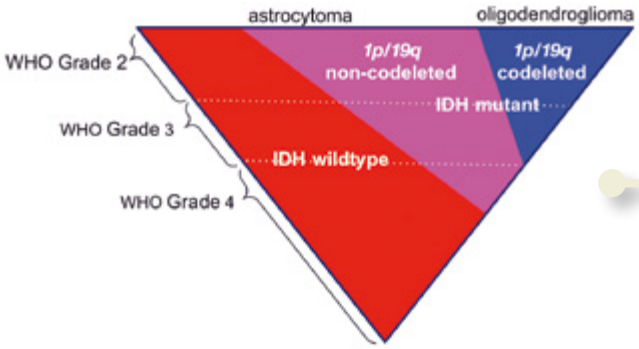
Testing for underlying molecular aberrations now often leads to a more robust diagnosis. The World Health Organization (WHO) 2016 classification integrates histological and molecular aspects.

Distribution of gliomas by histological subtypes



NOS, Not otherwise specified.

Diffuse gliomas



IDH, Isocitrate dehydrogenase; WHO, World Health Organization.

Gliomas in adults are mostly diffuse gliomas, with diffuse growth in cerebral hemispheres. Histological subtypes are diffuse astrocytoma and oligodendroglioma.

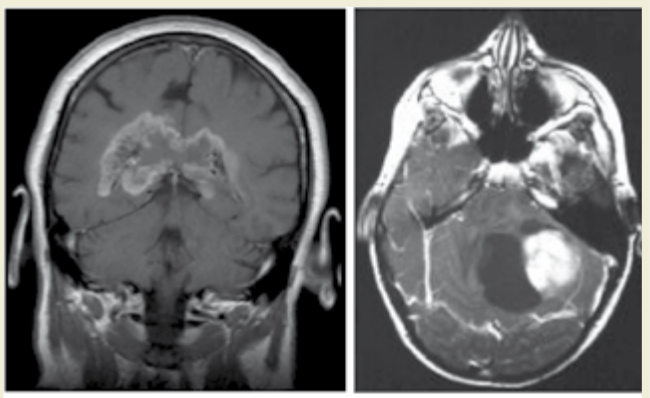
Based on histology, a WHO malignancy grade is assigned to diffuse gliomas: Grade 2 = low grade, Grade 3 = anaplastic and Grade 4 = glioblastoma.

Three main molecular subgroups of diffuse gliomas are recognised: (1) IDH (isocitrate dehydrogenase) wildtype; (2) IDH mutant & *1p/19q* non-codeleted; (3) IDH mutant & *1p/19q* codeleted.

Non-diffuse gliomas typically show more circumscribed growth; pilocytic astrocytomas and ependymomas are the most frequent examples.

In clinical practice, achieving a histological diagnosis of gliomas can be challenging because of imprecise diagnostic criteria and inadequate tissue sampling.

Clinical and radiological findings (especially tumour location, growth pattern, presence/absence of contrast enhancement) provide clues to the right diagnosis.



Glioblastoma | Pilocytic astrocytoma

REVISION QUESTIONS

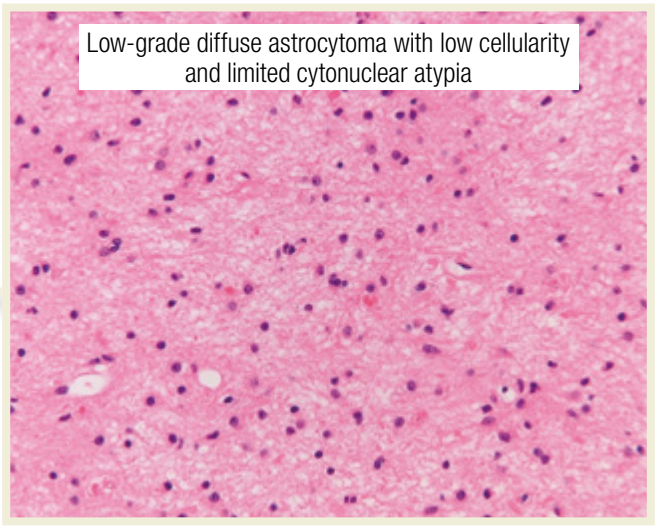
1. Why are diffuse gliomas called “diffuse”?
2. What are the two major histological subgroups of diffuse glioma?
3. What are the three main molecular subgroups of diffuse glioma?

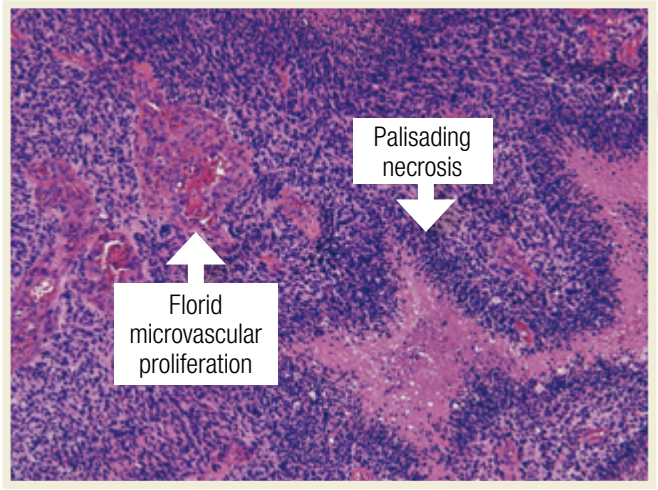
Diffuse astrocytomas, IDH wildtype

Tumour cells in diffuse astrocytomas often resemble non-neoplastic astrocytes with variable eosinophilic cell processes blending into the neuropil.

Like guerrilla warriors, these tumour cells tend to invade extensively the surrounding CNS parenchyma. Visualisation of the invasive front is problematic.

Diffuse astrocytomas lacking "brisk" mitotic activity, necrosis and florid microvascular proliferation (MVP) are diagnosed as low-grade (WHO Grade 2).


Low-grade diffuse astrocytoma with low cellularity and limited cytonuclear atypia



Increased mitotic activity leads to a diagnosis of anaplastic astrocytoma (Grade 3); presence of necrosis and/or florid MVP means glioblastoma (Grade 4).

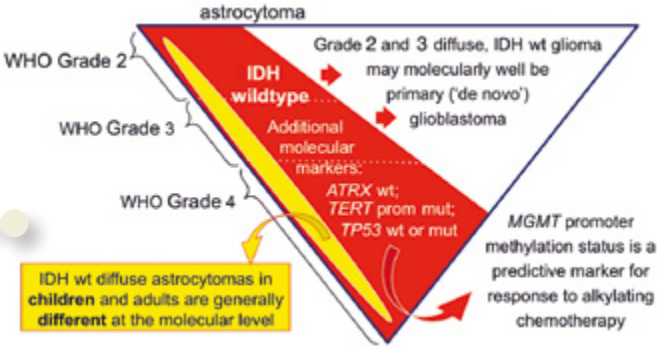
Immunohistochemical staining for glial fibrillary acidic protein (GFAP) is a helpful but non-specific tool for recognising astroglial differentiation of tumour cells.

Glioblastoma is not only the most malignant, but also by far the most frequent diffuse astrocytoma. Furthermore, about 90% of glioblastomas are IDH wildtype.

IDH wildtype diffuse astrocytomas in adults are typically *ATRX* wildtype and *TERT* promoter mutant; *TP53* in these tumours may be wildtype or mutant.

Grade 2 or 3 IDH wildtype astrocytomas in adults with gain of chromosome 7, loss of chromosome 10, and/or *EGFR* amplification/*EGFR variant III* may in fact be glioblastomas.

Most diffuse gliomas in children are different at the molecular level; markers like Histone H3 K27M mutation indicate high-grade malignancy irrespective of histology.



IDH, Isocitrate dehydrogenase; mut, mutant; prom, promoter; WHO, World Health Organization; wt, wildtype.

REVISION QUESTIONS

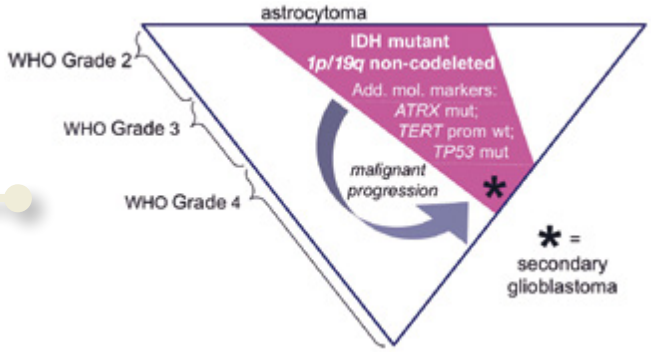
1. Which histological features are used for grading diffuse astrocytomas?
2. What is by far the most frequent diffuse glioma?
3. Which molecular markers in diffuse, IDH wildtype astrocytoma indicate glioblastoma?

Diffuse astrocytomas, IDH mutant & *1p/19q* non-codeleted

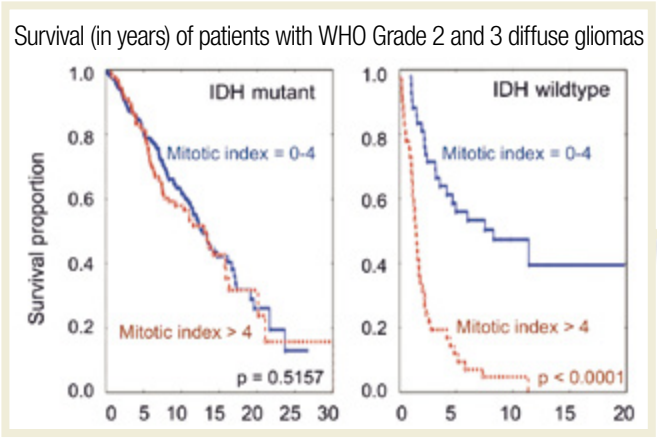
The vast majority of Grade 2 and 3 diffuse gliomas are *IDH1* or *IDH2* mutant; around 90% of these tumours are *IDH1* R132H mutant.

The approximately 10% of glioblastomas that are IDH mutant are nowadays considered "secondary glioblastomas" (i.e. derived from a lower grade precursor tumour).

Diffuse IDH wildtype and IDH mutant astrocytomas cannot be delineated with routine histology. Currently, grading of these tumours is performed in the same way.



IDH, Isocitrate dehydrogenase; mut, mutant; prom, promoter; WHO, World Health Organization; wt, wildtype.



IDH, Isocitrate dehydrogenase; WHO, World Health Organization.

However, patients with IDH mutant astrocytomas are on average younger, have a better prognosis and may need different management than those with IDH wildtype tumours.

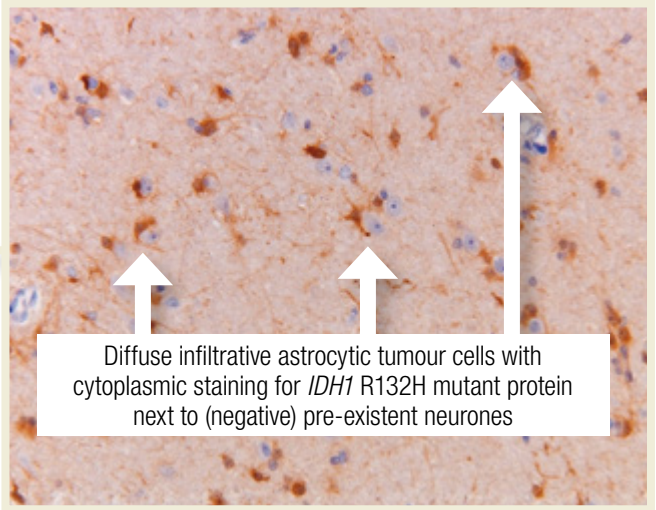
Histological criteria for grading within molecularly defined glioma categories will need modification: e.g. the impact of mitotic activity may differ between these groups.

Sequencing analysis of the *IDH1* and *IDH2* hotspot regions (*IDH1* R132, *IDH2* R172) is the gold standard to demonstrate the IDH mutant status of diffuse gliomas.

Molecular features supporting the diagnosis of IDH mutant astrocytoma are: presence of *TP53* and *ATRX* mutation, absence of *TERT* promoter mutation.

An antibody specifically targeting mutant *IDH1* R132H protein nowadays allows for easy recognition of the most frequent IDH mutant form of diffuse glioma.

Lack of nuclear *ATRX* expression correlates well with *ATRX* mutation. Immunohistochemical stainings may be of great help when molecular testing is not possible.



Diffuse infiltrative astrocytic tumour cells with cytoplasmic staining for *IDH1* R132H mutant protein next to (negative) pre-existent neurones

REVISION QUESTIONS

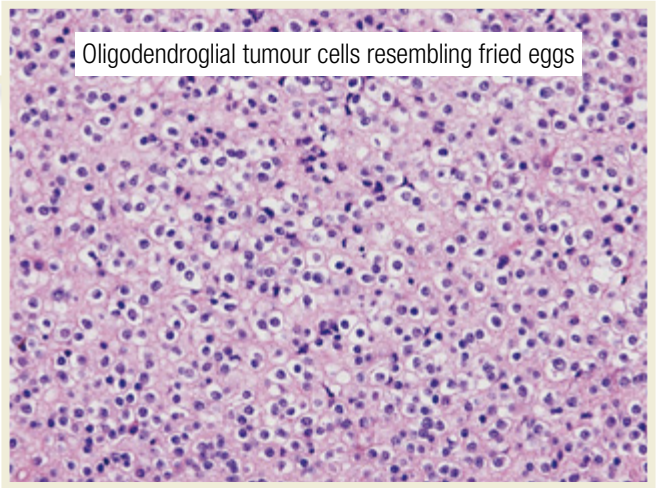
1. Which subgroups of diffuse astrocytomas are frequently IDH mutant?
2. What is the most frequent IDH mutation found in diffuse gliomas?
3. Which molecular markers support the diagnosis of IDH mutant astrocytoma?

Oligodendrogliomas, *1p/19q* codeleted (& IDH mutant)

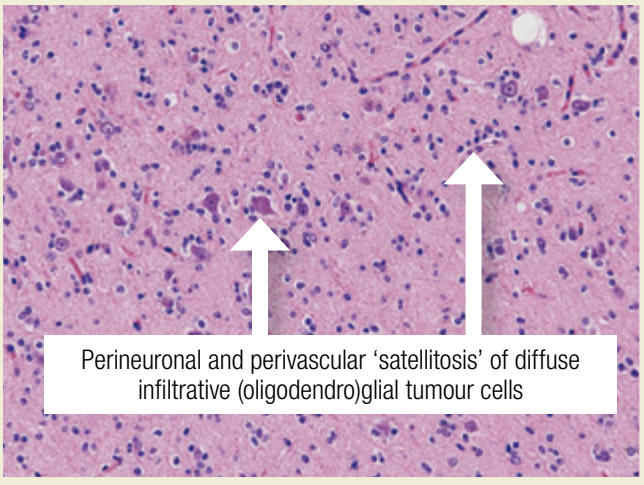
Oligodendrogliomas typically show round nuclei with a clear perinuclear halo, resulting in a "fried egg" appearance and a "honeycomb" aspect of tumour cell clusters.

Unequivocal recognition of oligodendrogliomas is hindered by the lack of specific immunohistochemical markers for these tumours.

Aggressive oligodendrogliomas typically show marked mitotic activity, even in the presence of necrosis and/or florid MPV. However, these tumours are still Grade 3.



Oligodendroglial tumour cells resembling fried eggs



Perineuronal and perivascular 'satellitosis' of diffuse infiltrative (oligodendro)glial tumour cells

Especially in the periphery of the (often highly cellular) oligodendrogliomas, the diffuse infiltrative growth in surrounding brain tissue is generally easily identified.

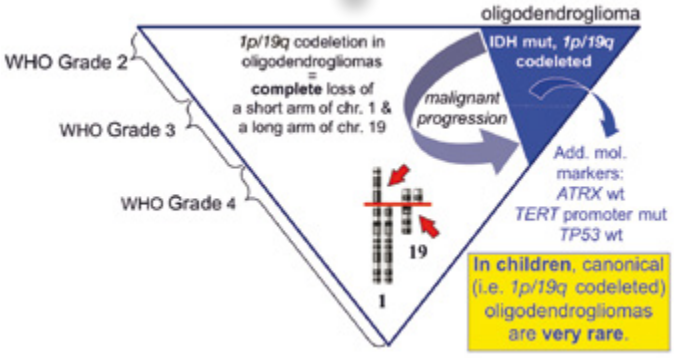
Virtually all oligodendrogliomas are IDH mutant. As in diffuse IDH mutant astrocytomas, *IDH1* R132H is by far the most common IDH mutation in oligodendrogliomas.

Complete *1p/19q* codeletion (loss of the entire chromosome arms!) is the hallmark of oligodendrogliomas and indicates a better prognosis and therapy response.

Molecular tests for detection of molecular aberrations (including *1p/19q* codeletion) may differ between centres and may yield false-positive or false-negative results.

With the integration of molecular aspects in the diagnosis of diffuse gliomas, the need for a separate/mixed oligoastrocytic glioma category will largely disappear.

CIC and *FUBP1* gene mutations (located on chromosome 19q and 1p, respectively) are found in a subset of *1p/19q* codeleted tumours; their impact on outcome is presently unclear.



Chr, Chromosome; IDH, isocitrate dehydrogenase; mut, mutant; WHO, World Health Organization; wt, wildtype.

REVISION QUESTIONS

1. What is the WHO malignancy grade assigned to the most malignant oligodendroglioma?
2. Why will the diagnosis of mixed glioma/oligoastrocytoma largely disappear?
3. What is the molecular hallmark of oligodendrogliomas?

Non-diffuse gliomas

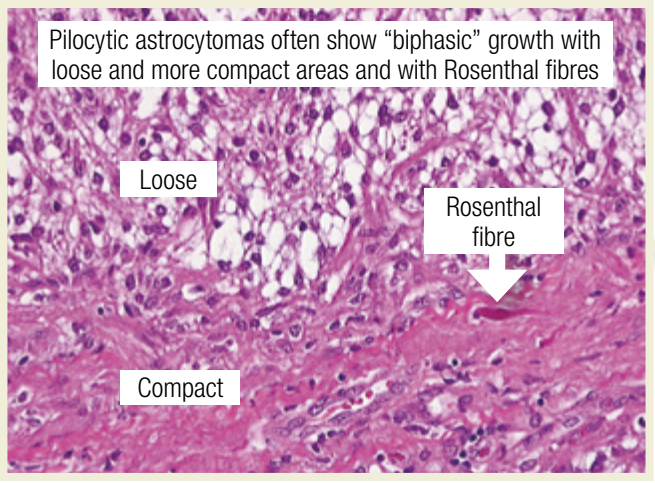
Non-diffuse gliomas include a wide spectrum of neoplasms with 3 larger subgroups: non-diffuse astrocytic tumours, ependymal tumours, "other gliomas".

Apart from pilocytic astrocytomas and ependymomas, these gliomas are rare. Most of them are slow growing, but occasionally more aggressive examples occur.

In neuronal-glial tumours, the tumour cells show a mixture of neuronal and glial differentiation; discrimination from gliomas with entrapped neurones may be difficult.

WHO grade	Other astrocytic tumours	Ependymal tumours	Other gliomas
1	Pilocytic astrocytoma Subependymal giant cell astrocytoma	Subependymoma Myxopapillary ependymoma	Angiocentric glioma Chordoid glioma of the 3rd ventricle Astroblastoma
2	Pleiomorphic xanthoastrocytoma	Low-grade ependymoma	
3	Anaplastic pleiomorphic xanthoastrocytoma	Anaplastic ependymoma	

WHO, World Health Organization.



Pilocytic astrocytomas, the most common gliomas in children, are preferentially located in the cerebellum, optic pathways, hypothalamic region and brain stem.

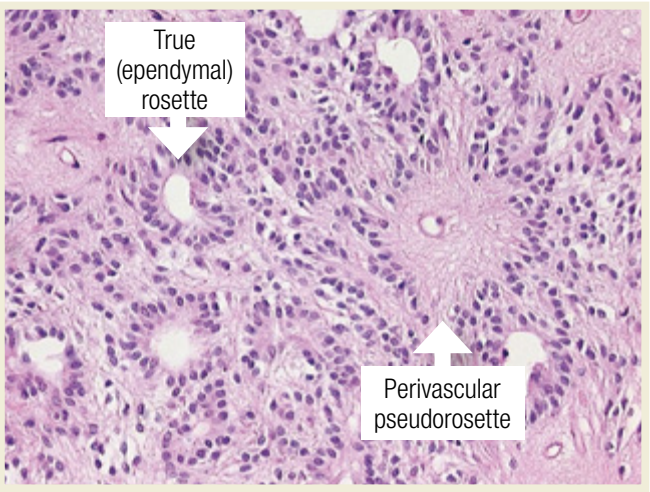
They typically show alternating compact and loosely structured areas (biphasic growth), with a subset of the cells having long, hair-like (piloid) cell processes.

Most pilocytic astrocytomas carry a molecular defect affecting the BRAF pathway (most frequently a *BRAF* fusion gene, sometimes the BRAF V600E mutation).

A histological hallmark of ependymomas is pseudorosette formation (perivascular nuclear-free zones). True rosettes (without a central vessel) are generally less frequent.

Most ependymomas are "classic" ependymomas (WHO Grade 2 or 3); subependymomas and myxopapillary ependymomas (both Grade 1) are relatively rare.

Nowadays, improved ependymoma classification can be achieved by combining information on tumour location, histology and molecular features.



REVISION QUESTIONS

1. What are the two most frequent categories of "non-diffuse" glioma?
2. Which pathway is often affected in pilocytic astrocytomas?
3. What are the two histological features that indicate ependymal differentiation in a glioma?

Summary: Histology and molecular pathology of gliomas

- Gliomas form a very heterogeneous group of tumours, with regard to both histology and clinical behaviour
- Based on histology, gliomas are traditionally typed as astrocytic, oligodendroglial and ependymal neoplasms, and graded as low grade (WHO Grade 2), anaplastic (WHO Grade 3), or (only for astrocytic tumours) glioblastoma (WHO Grade 4)
- The vast majority of astrocytomas and oligodendrogliomas in adult patients are so-called diffuse gliomas, characterised by diffuse infiltrative growth in the CNS parenchyma
- Three major molecular categories of diffuse gliomas are recognised: IDH wildtype; IDH mutant & *1p/19q* non-codeleted; IDH mutant & *1p/19q* codeleted
- IDH wildtype and IDH mutant & *1p/19q* non-codeleted diffuse gliomas generally show an astrocytic phenotype, most IDH mutant & *1p/19q* codeleted gliomas exhibit oligodendroglial features
- According to the WHO 2016 classification, demonstration of *1p/19q* codeletion is required for the diagnosis of "canonical" oligodendroglioma
- Most glioblastomas (about 90%) are IDH wildtype; IDH mutant glioblastomas often originate from lower grade (Grade 2 or 3) diffuse astrocytomas
- The majority of the lower grade diffuse astrocytomas and all oligodendrogliomas are *IDH1* or *IDH2* mutant (*IDH1* R132H being by far the most frequent mutation)
- Diffuse gliomas in children are generally IDH wildtype and have a different molecular pathogenesis compared to histologically similar tumours in adults
- Non-diffuse gliomas are more frequent in children. The most common representatives of this group are the relatively benign pilocytic astrocytomas and the variably aggressive ependymomas

Further Reading

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4 Treatment strategies for anaplastic astrocytoma and glioblastoma

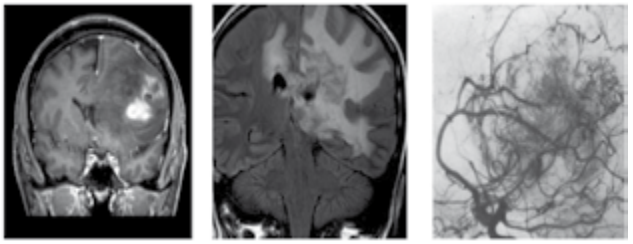
Surgery

Neurosurgical interventions are commonly performed initially to obtain tissue for histological and molecular diagnosis.

If lesions are not resectable, then a serial biopsy to obtain representative tissue samples should be considered.

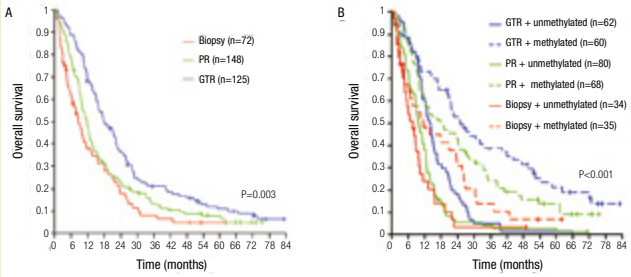
Management decisions should almost never be made without histological confirmation of the suspected diagnosis.

Coronal MRI (T1 plus contrast left, T2/FLAIR middle) and cerebral angiography (right) of a left hemispheric glioblastoma



FLAIR, Fluid attenuation inversion recovery; MRI, magnetic resonance imaging.

Association of extent of resection (PR, partial resection, GTR, gross total resection) with overall survival in all patients (left) or by MGMT promoter methylation status



MGMT, O6-Methylguanine-DNA methyltransferase.

Childhood diffuse intrinsic pontine gliomas (DIPG) are still commonly treated without histological confirmation.

Gross total resection is associated with improved outcome.

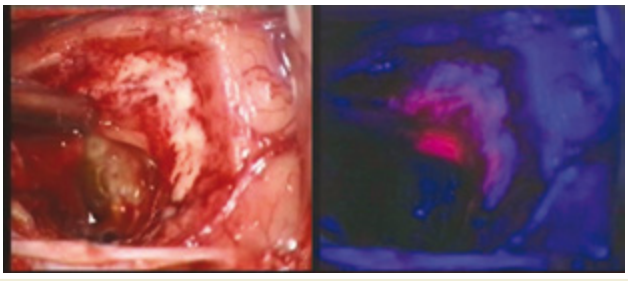
The superiority of partial tumour resection over biopsy alone has not been demonstrated.

If the goal is gross total resection, various techniques for maximising the safety of resective surgery are available, including ultrasound, intraoperative magnetic resonance imaging (MRI) and the use of fluorescent dyes to label tumour tissue.

The role of surgery in recurrent gliomas remains controversial, but selected patients with resectable tumours recurring more than a few months after the first surgery may benefit.

Recurrent gliomas are likely to exhibit significant differences in their molecular profile compared with the primary tumours, probably justifying more surgical reinterventions in the future.

Resection cavity of a glioblastoma (left) under the surgical microscope, white light mode, and (right) fluorescent tumour remnants visible in red (5-ALA mode)



5-ALA, 5-Aminolevulinic acid.

REVISION QUESTIONS

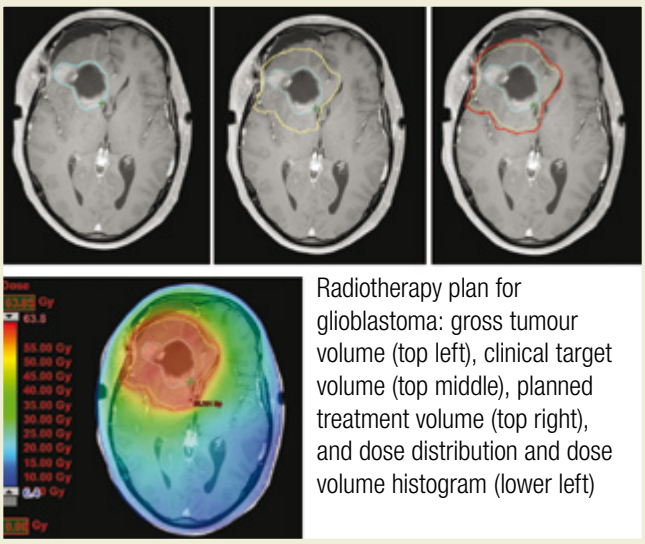
1. In which clinical situations is clinical decision-making feasible without verification of the histological diagnosis?
2. Which technical means can be used to achieve a gross total resection?
3. Which patients are candidates for re-resection of anaplastic astrocytoma or glioblastoma?

Radiotherapy

Radiotherapy (RT) was shown to double median survival in adult malignant glioma patients several decades ago.

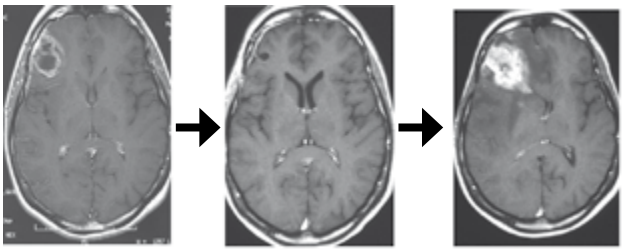
The introduction of involved-field RT as opposed to whole brain RT has not compromised overall survival.

The involved field, defined with a safety margin of 2–3 cm, is important to capture the infiltration zone around the primary radiologically defined lesion.



Radiotherapy plan for glioblastoma: gross tumour volume (top left), clinical target volume (top middle), planned treatment volume (top right), and dose distribution and dose volume histogram (lower left)

Axial MRI (T1 plus contrast) before (left) and after resection (middle) and at relapse after radiochemotherapy (right) of right temporal glioblastoma



MRI, Magnetic resonance imaging.

The optimal dose regarding tolerability, safety and efficacy has been identified as 30 × 2 Gy, or hypofractionated variations thereof at a biologically equivalent dose, e.g. 15 × 2.66 Gy.

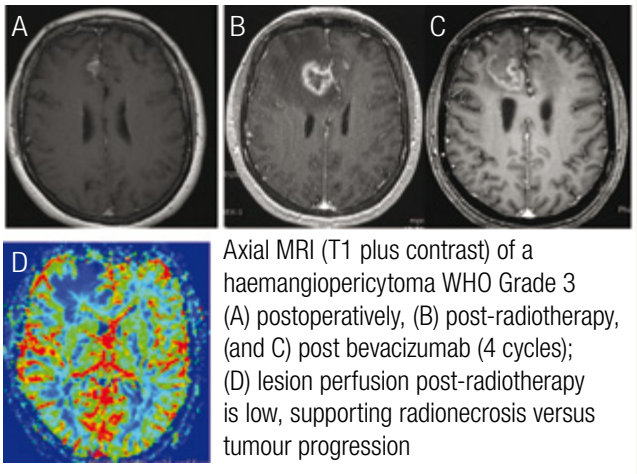
Dose escalations beyond 30 × 2 Gy or radiosurgical boosts do not improve local control.

More than 90% of glioblastomas recur within the irradiated target volume.

Re-irradiation is feasible in patients with circumscribed lesions, but has not been shown to improve overall survival.

Radiation necrosis is seen less frequently with modern RT fractionations and techniques.

Bevacizumab may be more active than corticosteroids in treating symptomatic radiation necrosis.



Axial MRI (T1 plus contrast) of a haemangiopericytoma WHO Grade 3 (A) postoperatively, (B) post-radiotherapy, (and C) post bevacizumab (4 cycles); (D) lesion perfusion post-radiotherapy is low, supporting radionecrosis versus tumour progression

MRI, Magnetic resonance imaging; WHO, World Health Organization.

REVISION QUESTIONS

1. What is the typical target volume of RT for anaplastic astrocytoma and glioblastoma?
2. Which patients should be considered candidates for re-irradiation?
3. What is the most effective pharmacological treatment for radiation necrosis?

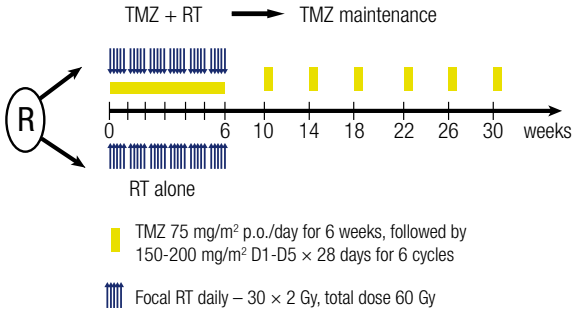
Pharmacotherapy

Temozolomide (TMZ) concomitant with RT, followed by six cycles of maintenance TMZ (TMZ/RT→TMZ), is the standard of care for glioblastoma.

In glioblastoma and IDH wildtype anaplastic glioma, benefit from TMZ is largely restricted to patients with tumours with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.

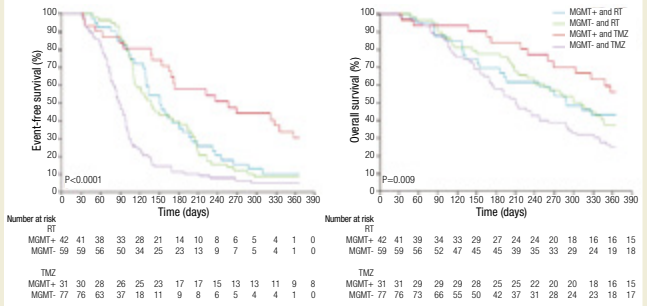
The MGMT status needs to be determined with a validated test. Methylation-specific polymerase chain reaction (MSP) is the standard method; pyrosequencing is an alterative option.

Study design of the randomised (R) phase III trial for temozolomide in newly diagnosed glioblastoma



Gy, Gray; p.o. orally; RT, radiotherapy, TMZ, temozolomide.

Event-free (left) and overall (right) survival in the NOA-08 trial comparing temozolomide (TMZ) alone versus radiotherapy (RT) alone in elderly patients with newly diagnosed glioblastoma



MGMT, O6-Methylguanine-DNA methyltransferase.

Elderly glioblastoma patients are treated based on MGMT status, either with RT (unmethylated) or TMZ with or without RT (methylated).

Anaplastic astrocytoma without *IDH*1/2 mutation is increasingly treated like glioblastoma.

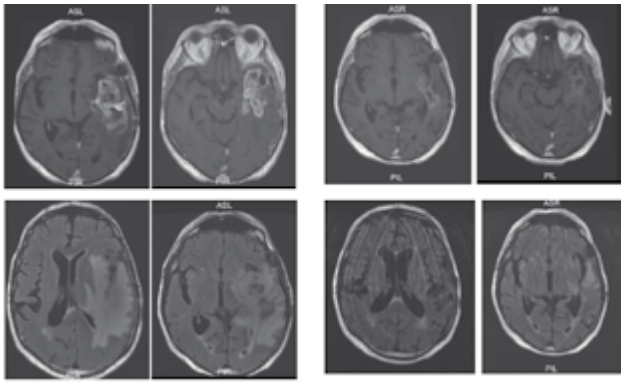
Typical anaplastic astrocytoma (*IDH*1/2 mutant, no *1p/19q* codeletion) is treated with RT alone or TMZ/RT→TMZ.

In newly diagnosed glioblastoma, bevacizumab prolongs progression-free survival but not overall survival.

Nitrosoureas, mostly lomustine (CCNU), are commonly selected as the standard of care systemic treatment at recurrence.

Bevacizumab is approved for recurrent glioblastoma in the USA and many other countries, but not in the European Union (EU).

Almost complete radiological response to bevacizumab administered for 2 months from 1/2011 (left) to 3/2011 (right) in a 71-year-old patient with recurrent glioblastoma (upper row: T1 plus contrast, lower row T2/FLAIR)



FLAIR, Fluid attenuation inversion recovery.

REVISION QUESTIONS

1. What is the standard duration of maintenance temozolomide in newly diagnosed glioblastoma?
2. What is the predictive marker for benefit from temozolomide in glioblastoma and IDH wildtype anaplastic glioma?
3. Why did the EU not approve bevacizumab for recurrent glioblastoma?

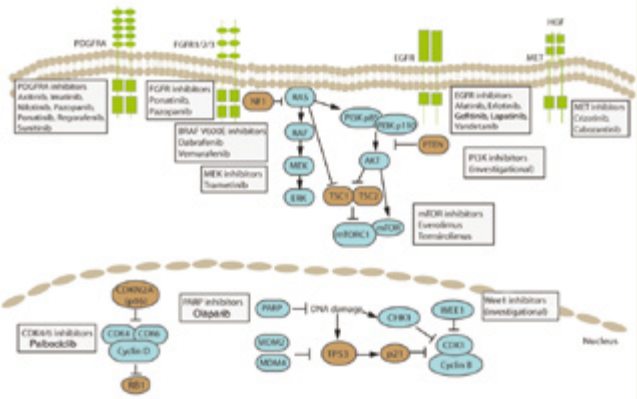
Experimental treatment approaches

Various novel antiangiogenic agents targeting vascular endothelial growth factor (VEGF)-dependent and VEGF-independent pathways are being tested, mostly in recurrent glioblastoma.

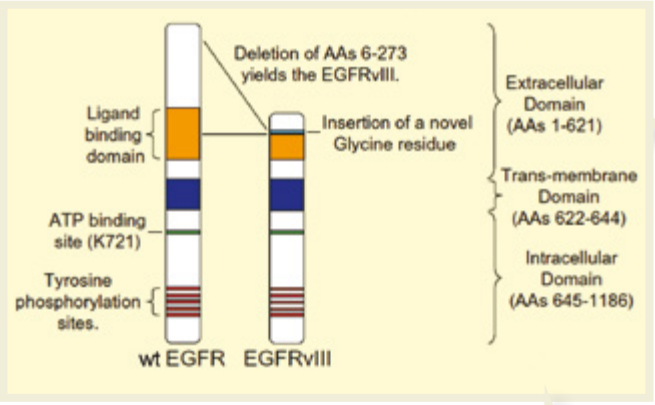
Epidermal growth factor receptor (EGFR), phosphatidyl-inositol (PI)-3 kinase, mechanistic target of rapamycin (mTOR) and c-MET are typical pathways for targeted therapy in glioblastoma.

There is increasing interest in exploiting aberrant metabolic pathways for therapeutic purposes.

Pathways and molecular targets for pharmacological intervention in glioblastoma



Schematic of the epidermal growth factor receptor (EGFR) vIII truncation



ATP, Adenosine triphosphate; EGFR, epidermal growth factor receptor.

The EGFRvIII variant receptor is characterised by a deletion of exons 2–7 of the wildtype (wt) EGFR gene. This results in an in-frame truncation of amino acids (AA) 6 to 273 in the extracellular domain of the full length protein, yielding a constitutively active variant receptor that cannot bind ligand. The EGFRvIII also contains a novel glycine residue inserted at the fusion junction

Rindopepimut is a vaccine targeting a specific deletion mutation of *EGFR* referred to as vIII or delta-EGFR.

ICT-107 is a cocktail of six peptides used for autologous dendritic cell (DC) vaccination.

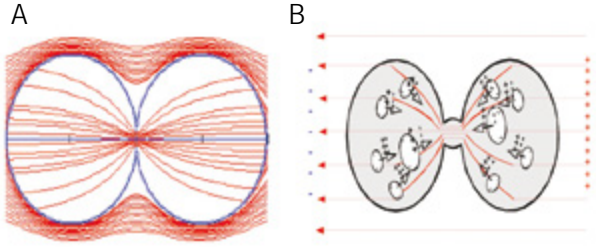
Checkpoint inhibitors, e.g. antibodies to cytotoxic T lymphocyte-associated antigen (CTLA)-4, or programmed death (PD)-1, or PD-1 ligand, are being explored as novel treatments.

Tumour-treating fields are a novel treatment approach based on electrical fields that may prolong survival in newly diagnosed glioblastoma.

Oncolytic viruses continue to be explored and may induce therapeutic inflammation linked to improved outcome.

The role of cytomegalovirus (CMV) in the aetiology or as a target in glioblastoma remains controversial.

Putative mode of action of tumour-treating fields based on cell culture studies: A, Electrical fields focus at the neck formed during cellular division. B, Inhomogeneous field at the neck generates forces which push all polar and charged structures (organelles, macromolecules) towards the neck, resulting in cell damage and death



REVISION QUESTIONS

1. What are the main pathways of intervention for targeted therapy?
2. What are the main approaches of immunotherapy for anaplastic astrocytoma and glioblastoma?
3. What precisely is EGFRvIII?

Symptomatic treatment and supportive care

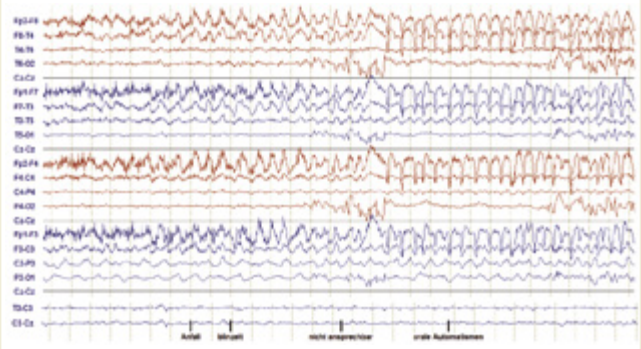
Corticosteroids are powerful anti-oedema agents in brain tumour patients.

Chronic exposure to corticosteroids has a broad range of side effects.

Anti-VEGF agents have strong steroid-sparing properties.

Adverse events and side effects of corticosteroids
Cushing syndrome
Immunosuppression
Myopathy
Osteoporosis
Vascular complications
Depression, psychosis, cognitive decline

Electroencephalogram showing left temporal slowing with rhythmic delta activity of increasing amplitude and frequency consistent with epileptic activity



Approximately 50% of affected patients develop symptomatic epilepsy.

The choice of antiepileptic drug needs to consider the high risk of cognitive side effects and drug–drug interactions.

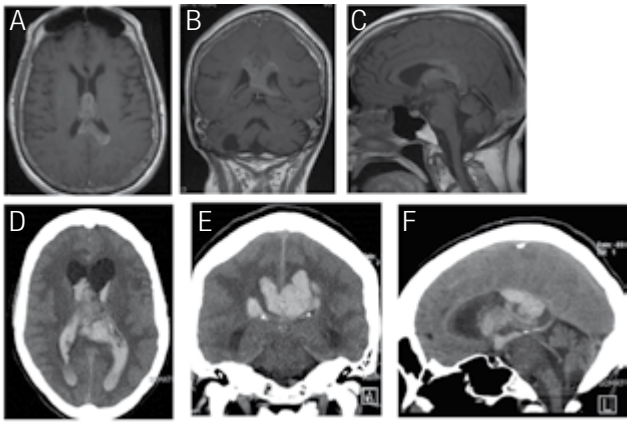
Levetiracetam, lamotrigine and pregabalin, for example, have a favourable benefit-risk profile in brain tumour patients.

Deep vein thrombosis or pulmonary embolism may affect more than 50% of patients.

Interactions of novel drugs, notably antiangiogenic agents, and antiplatelet agents and anticoagulants require consideration.

Neurorehabilitation assumes increasing importance as the number of long-term surviving patients increases.

Top: Axial (A), coronal (B) and sagittal (C) MRI (T1 plus contrast) of an anaplastic oligodendroglioma, initially localised in the right cerebellum, then spread to the corpus callosum; bottom: axial (D), coronal (E) and sagittal (F) CT scan (native) demonstrating extensive tumour bleeding after one dose of bevacizumab



CT, Computed tomography; MRI, magnetic resonance imaging.

REVISION QUESTIONS

1. What is the mode of action of corticosteroids in brain tumour patients?
2. What are the antiepileptic drugs of choice in brain tumour patients?
3. What are the most common cardiovascular complications in brain tumour patients?

Summary: Treatment strategies for anaplastic astrocytoma and glioblastoma

- Clinical decision-making should be based on a histologically verified diagnosis
- Molecular markers (IDH, *1p/19q,* MGMT, EGFR status) assume increasing importance for diagnostic and therapeutic concepts
- Gross total resection is associated with improved outcome
- Partial resections may not improve outcome over biopsy alone
- Involved-field RT, e.g. 60 Gy in 1.8–2 Gy fractions, doubles survival, but is not curative
- The alkylating agent TMZ prolongs progression-free and overall survival when combined with RT
- The benefit from TMZ added to RT in patients with IDH wildtype anaplastic glioma and glioblastoma is probably limited to patients with MGMT promoter methylation
- Bevacizumab prolongs progression-free, but not overall, survival in newly diagnosed glioblastoma
- Bevacizumab has clinical value as a salvage treatment in recurrent anaplastic astrocytoma and glioblastoma
- EGFRvIII-targeted vaccination, DC vaccination and electrical tumour-treating fields are emerging treatment approaches

Further Reading

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5 Treatment strategy for low-grade gliomas

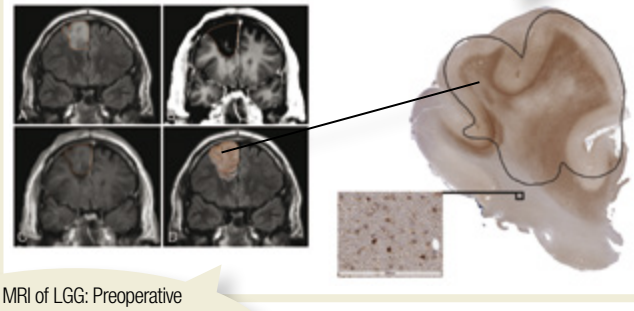
Pathology and biology; molecular markers

Low-grade gliomas (LGGs) are infiltrative diseases of the central nervous system (CNS), with cells found throughout the brain. The majority of tumour cells are found within 1–2 cm around the visible tumour on magnetic resonance imaging (MRI).

LGGs diffusely infiltrate the brain parenchyma and cannot be cured by surgery alone. The extent of tumour infiltration may be shown by isocitrate dehydrogenase (IDH) immunostaining: large dots = 10%–15% tumour cells, small dots = less than 10% tumour cell fraction.

Right, IDH1 immunostaining from the peripheral part of the tumour shows the brown-stained, infiltrating tumour cells; brown dots = positive IDH1 staining, which is found throughout the brain.

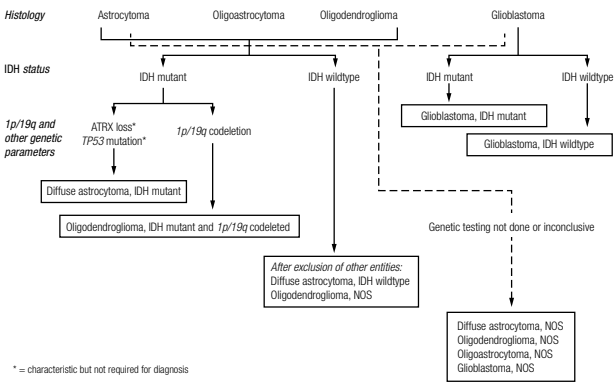
Infiltrating glioma made visible



Left, MRI of LGG: Preoperative delineated tumour on coronal T2-FLAIR (A), postoperative cavity (B), overlay of the preoperative tumour and postoperative cavity showing resected peritumoural margins (C) and overlay of IDH1 image (D).

FLAIR, Fluid attenuation inversion recovery; IDH1, isocitrate dehydrogenase gene 1; LGG, low-grade glioma; MRI, magnetic resonance imaging.

The 2016 WHO classification of CNS tumours integrating molecular markers



IDH, Isocitrate dehydrogenase; NOS, not otherwise specified.

Until 2016, the World Health Organization (WHO) classification of LGGs was based on histopathological features, and divided them into astrocytoma, oligodendroglioma and oligoastrocytoma. The 2016 WHO classification integrates for the first time histological and molecular features for glioma subtyping.

The 2016 WHO classification of CNS tumours is based both on histological and molecular features. It separates LGGs into 3 categories:

- Diffuse astrocytoma with mutation of the IDH gene 1 or 2 (*IDH1* or *2*)
- Astrocytoma IDH wildtype (wt)
- Oligodendroglioma IDH mutant (IDHmt), and codeleted for chromosomal arms 1p and 19q (*1p/19q* codeleted)

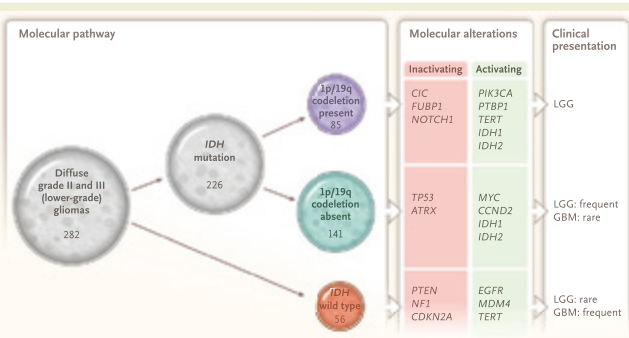
Or, in the absence of genetic information, astrocytoma or oligodendroglioma not otherwise specified (NOS).

Mutations of *IDH1* or *2* are gain of function mutations and result in the formation of a CpG island methylator phenotype (CIMP). This results in the silencing of numerous genes, including tumour suppressors.

1p/19q codeletion results from an unbalanced whole-arm translocation between chromosomes 1 and 19 with loss of the derivative chromosome t(1p:19q). IDHmt and *1p/19q* codeleted tumours are usually associated with *TERT* promoter mutations.

IDHwt LGGs are associated with intact alpha thalassaemia/mental retardation syndrome X-linked gene (*ATRX*) expression. This gene, like *p53*, is involved in telomere maintenance.

Schematic representation showing 3 distinct LGG groups strongly correlated with IDH mutation and *1p/19q* codeletion status with specific molecular alterations



GBM, glioblastoma; IDH, isocitrate dehydrogenase; LGG, low-grade glioma.

REVISION QUESTIONS

1. What are the histological subtypes of LGGs?
2. Which are the two most relevant molecular markers of LGGs?
3. What is the typical molecular profile of an oligodendroglioma?

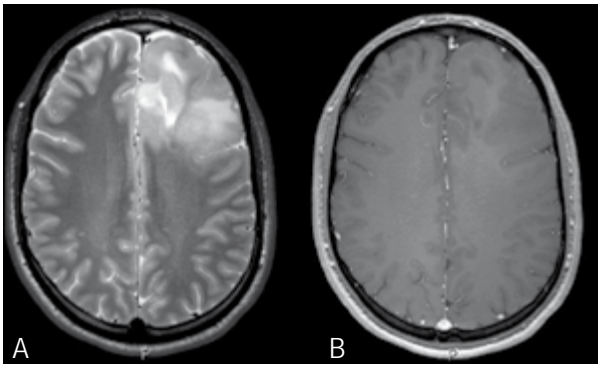
Clinical presentation and clinical prognostic markers

LGGs account for 5%–10% of all gliomas and typically arise in individuals aged 30–50 years. Most patients present with seizures only and show no other neurological deficit.

MRI appearance may be highly suggestive for the presence of a LGG. The majority of LGGs show T2 hyperintensity, without uptake of contrast media.

Comparison of imaging (MRI, FLAIR [fluid attenuation inversion recovery] sequences) over long periods of time (typically >1 year) will show progression.

Typical MRI appearance of an oligodendroglioma: (A) T2 sequence showing left frontal hyperintensity and (B) absence of contrast enhancement following gadolinium administration



MRI, Magnetic resonance imaging.

NCCTG/RTOG/ECOG trial: Prognostic factors (multivariate analysis)

Patient subset	No.	2 Years (%)	5 Years (%)	Log rank P
Arm				
A (low-dose)	101	94	72	0.48
B (high-dose)	102	85	65	
Age				
<40 years	100	97	77	0.0245
≥40 years	103	82	60	
Astro, mixed A>O	64	80	56	0.0001
Oligo, mixed O>A	139	94	74	
Tumour size				
<5 cm	72	94	81	0.0008
≥5 cm	131	87	61	
Gross total resection	29	100	88	0.0151
Subtotal resection	71	88	56	
Biopsy only	103	87	71	

Factors associated with worse outcome include:

- Age ≥40 years
- Astrocytic histology
- Tumours ≥5 cm
- Tumour crossing the midline
- Neurological deficit before surgery

The European Organisation for Research and Treatment of Cancer (EORTC) developed a clinical prognostic score, based on two randomised, multicentre trials: EORTC 22844 and 22845.

This score defined 0 to 5 points as unfavourable prognostic factors. Survival decreased with each unfavourable factor.

Patients with unfavourable risk factors should be treated, while patients with mainly favourable prognostic factors may not need immediate treatment; a watch-and-wait strategy is an option.

Prognostic score for patients with a LGG based on clinical factors. A score of ≥3 factors presents a higher risk for recurrence

		Construction set (n=281)		Validation set (n=253)	
Score	Risk group	Group No.	Median survival (years) (95% confidence interval)	Group No.	Median survival (years) (95% confidence interval)
0-2	Low	200	7.72 (6.55-9.25)	195	7.8 (6.77-8.90)
3-5	High	81	3.2 (2.95-3.99)	58	3.67 (2.89-4.69)

LGG, Low-grade glioma.

REVISION QUESTIONS

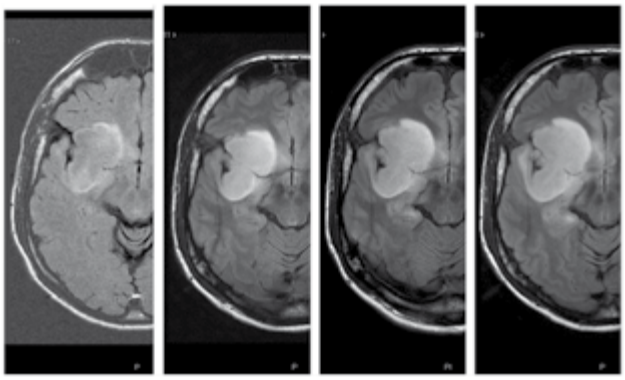
1. What is the typical appearance of LGG on MRI?
2. Why is it not sufficient to compare MRI images over a 3–6 month period for LGG?
3. What defines a “high risk“ LGG patient?

Treatment: radiotherapy

For patients presenting with seizures only and with typical radiographic features of LGG, follow-up can consist of serial MRIs.

In the presence of unfavourable prognostic factors or progressive disease on MRI, treatment is warranted.

The first step should be surgery to obtain tissue for establishing a definite diagnosis. Maximal safe resection should be aimed for, whenever feasible.



Baseline 6 months later 6 months later 6 months later

Images 2–4: progression over a 1-year time period

Randomised multicentric and prospective trials for patients with a high-risk LGG

Study	Treatment Arms	No.	Survival 5-yr OS %	Survival 5-yr PFS %	Survival 10-yr OS %	Survival 10-yr PFS %	*P* OS/PFS
Timing of RT							
EORTC 22845	S vs S+RT	140 150	66 68	35 55			NS <0.0001
Dose of RT							
EORTC 22844	S+RT 45 Gy S+RT 59.4Gy	171 172	58 59	47 50			NS NS
NCCTG/RTOG/EGOG	S+RT 50.4 Gy S+RT 64.8 Gy	102 103	73 68	55 52			NS —
Chemotherapy and RT							
RTOG 98-02	Watch & wait favourable pts	111	94	50			NS
	RT vs RT and PCV	126 125			40 60	21 51	0.002 OS <0.001 PFS
Chemotherapy or RT							
EORTC 22033-26033	RT 50.4 Gy TMZ	240 237	Not reached	40 29			— *NS*

LGG, Low-grade glioma; NS, not significant; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; S, surgery; TMZ, temozolomide.

Once the diagnosis is established, the optimal management of patients with LGGs remains challenging and controversial, as neither timing nor sequence of treatment have been unambiguously resolved.

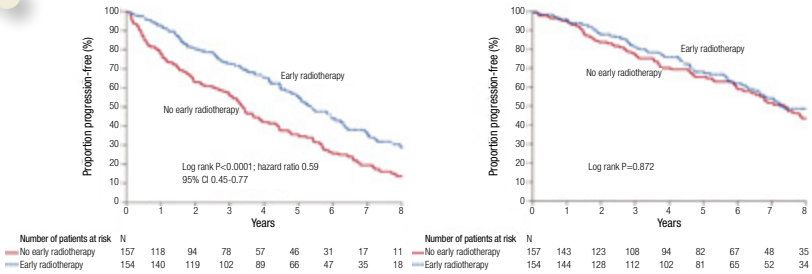
Postoperative follow-up may be an option for some patients. This approach is supported by the results of EORTC Trial 22845, which showed similar overall survival (OS) for patients having radiotherapy (RT) or "simple" follow-up (although progression-free survival [PFS] was in favour of RT).

Current accepted standard doses for radiation are 50.4–54 Gy in fractions of 1.8 Gy.

Early RT also resulted in significantly better control and improvement of epilepsy at 1 year (EORTC 22845), compared to delayed RT.

The main concern with RT is long-term cognitive sequelae. However, most adverse effects of RT are linked to higher total doses, larger treatment fields and older RT techniques. With modern RT techniques (intensity-modulated RT [IMRT], stereotactic RT, image-guided RT) and doses, limited neurocognitive damage is expected.

EORTC 22845 trial showing improved PFS for patients receiving early postoperative RT vs patients receiving RT at progression, but no difference in OS



CI, Confidence interval; PFS, progression-free survival; OS, overall survival; RT, radiotherapy.

REVISION QUESTIONS

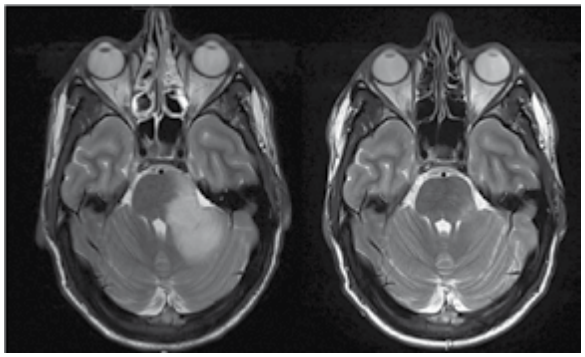
1. Can surgery be delayed in patients with LGGs?
2. What is the accepted standard RT dose?
3. Does RT alone improve survival in LGG patients?

Treatment: chemotherapy

Given the theoretical long-term risks associated with RT, chemotherapy (ChT) has been widely evaluated as a treatment of LGG. In small phase II trials, ChT resulted in similar PFS, OS and response rates as RT.

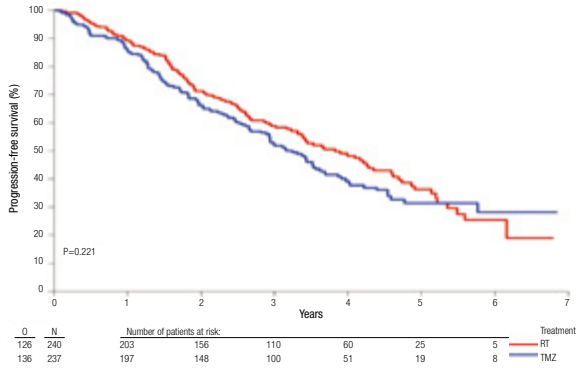
Most trials used procarbazine, lomustine and vincristine (PCV), which was later replaced by temozolomide (TMZ), showing a better tolerability and fewer side effects.

WHO Grade 2 *IDH1* mutated astrocytoma, (left) before and (right) after 12 cycles of TMZ



*IDH*1, Isocitrate dehydrogenase gene 1; TMZ, temozolomide; WHO, World Health Organization.

EORTC 22033-26033 trial: no difference between treatment with RT alone or TMZ alone for PFS in high-risk LGGs

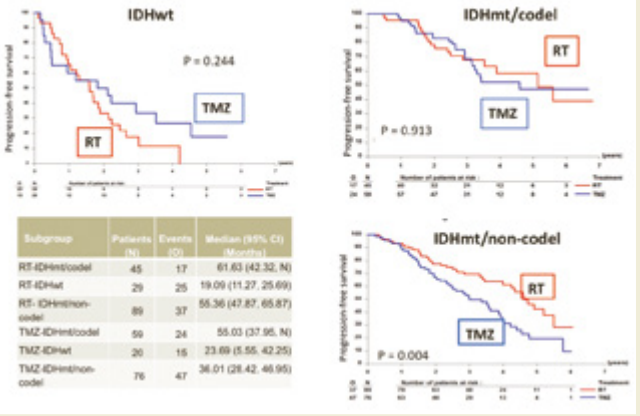


LGG, Low-grade glioma; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

To validate this impression, a randomised phase III trial of high-risk LGG patients (age >40 years, neurological deficit or progredient lesion) compared the outcomes of standard RT versus 12 cycles of TMZ (EORTC 22033-26033). After a median follow-up of 4 years, PFS was similar in both groups. OS data are not yet mature.

Molecular subgroup analysis of this study showed that for patients with IDHmt *1p/19q* codeleted tumours, no difference in PFS was present between TMZ and RT. For these patients, treatment with ChT first would allow delaying RT. However, patients with IDHmt *1p/19q* non-codeleted tumours showed significantly longer PFS when treated with RT compared with TMZ.

EORTC 22033-26033 trial: analysis of molecular subgroups of patients with high-risk LGGs



IDH, Isocitrate dehydrogenase; LGG, low-grade glioma; mt, mutant; RT, radiotherapy; TMZ, temozolomide; wt, wildtype.

REVISION QUESTIONS

1. Is ChT superior to RT to treat LGGs?
2. Should patients be treated based on the molecular profile of their tumour?
3. Which subgroup of LGGs is most likely to benefit from ChT?

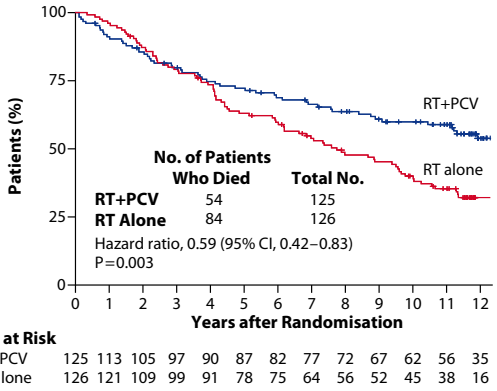
Treatment: multimodality treatment

The next question is whether combined treatment modalities might be superior to single treatment for LGGs.

This question was addressed in the RTOG 9802 trial. High-risk patients (age >40 years or incomplete resection) were randomised to either RT or RT plus adjuvant ChT with PCV (6 cycles).

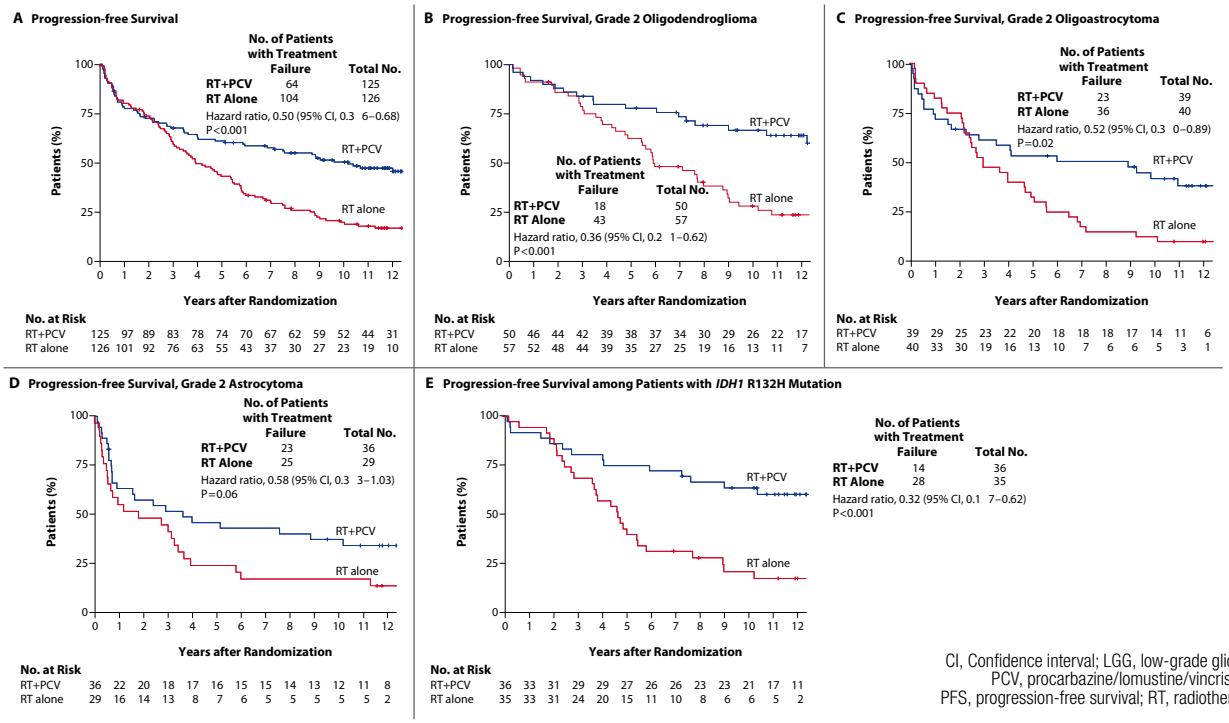
Adjuvant PCV after RT prolonged PFS and OS compared with RT alone: median survival was increased by 5.5 years, and the 5-year and 10-year survival rates increased by 9% and 20%, respectively. Molecular subgroup analyses in this trial are, however, incomplete.

RTOG 9802 trial: OS significantly increased with adjuvant PCV after RT: difference of 5.5 years between study arms



OS, Overall survival; PCV, procarbazine/lomustine/vincristine; RT, radiotherapy.

RTOG 9802: PFS according to histology of LGG



CI, Confidence interval; LGG, low-grade glioma; PCV, procarbazine/lomustine/vincristine; PFS, progression-free survival; RT, radiotherapy.

Combined treatment with RT and PCV therefore has a significantly greater effect than single-modality treatment with RT alone.

It must however be noted that this study provides incomplete information on the molecular status of the patients, as *1p/19q* codeletion status was not evaluated.

It remains highly debated whether PCV can be replaced by TMZ, which is much better tolerated and associated with fewer side effects.

REVISION QUESTIONS

1. Is combined therapy superior to single-modality treatment for LGG?
2. How would you treat a low-risk LGG patient with a small resectable tumour?
3. How would you treat a high-risk LGG patient with an unresectable tumour?

Summary: Treatment strategy for low-grade gliomas

- The optimal management of LGGs remains controversial
- To date, no compelling evidence demonstrates that early intervention with surgery improves outcome over observation in low-grade gliomas
- The current evidence supports treating patients with LGG based on their molecular and clinial characteristics: intensive therapeutic strategies for poor-prognosis patients while avoiding overtreatment in indolent disease
- For a slowly proliferating tumour causing few or no symptoms and in a patient with a low-risk profile, a watch-and-wait policy may be adequate
- Once progression is established, maximal safe resection should be favoured over biopsy
- Significant differences in outcome between molecular subgroups have led to the integration of molecular markers into the 2016 WHO classification of brain tumours
- IDH mutated, *1p/19q* codeleted LGGs present the best prognosis, IDH wildtype LGGs the worst
- Younger age, smaller tumour, absence of neurological symptoms, oligodendroglial histology, presence of *1p/19q* codeletion and IDH mutation are favourable prognostic factors
- If it is decided that the patient must be treated after surgery, options include RT, ChT or a combination of both. Recent data suggest that a combination of RT followed by ChT is superior to RT alone
- Direct postoperative monotherapy with RT probably improves PFS, but not OS

Further Reading

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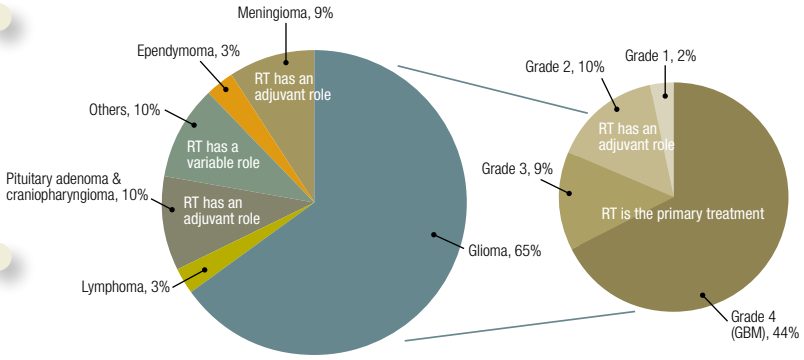
6 The essentials in radiation oncology for brain tumours

Practice of radiotherapy

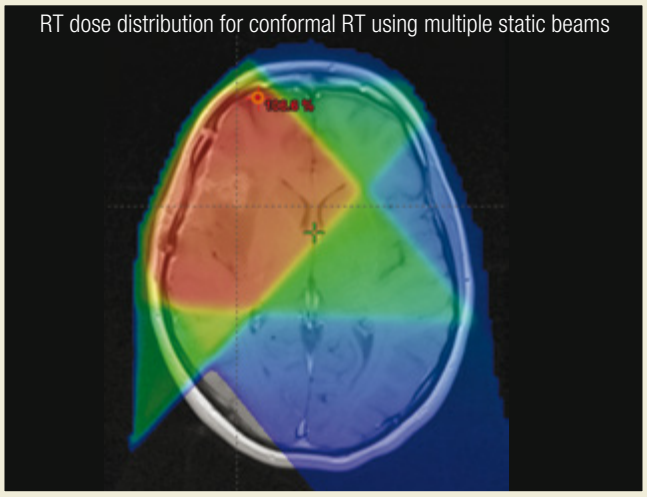
Radiotherapy (RT) using photons (X-rays) is the mainstay of treatment in the majority of brain tumours not cured by surgery.

Radiotherapy applications in brain tumours	Examples of tumour type
Cure	Cranial germinoma
Lifelong tumour control	Benign tumours (e.g. in optic pathway glioma and meningioma)
Pivotal component of curative treatment	Malignant brain tumours (e.g. medulloblastoma)
Survival prolongation	Malignant glial tumours
Effective palliative treatment	Brain metastases

Role of radiotherapy in common brain tumours



GBM, Glioblastoma; RT, radiotherapy.



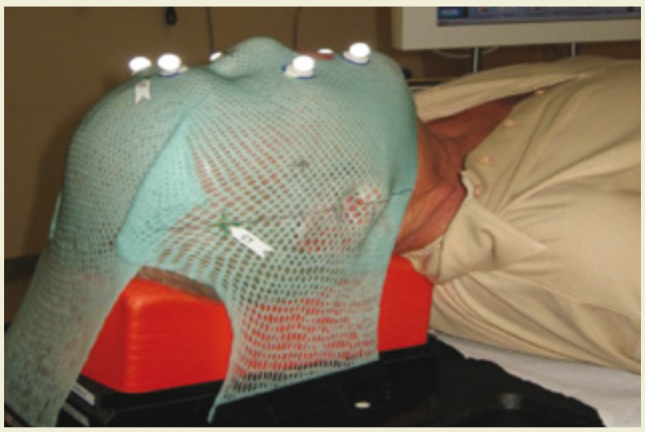
RT, Radiotherapy.

Cranial RT is delivered mostly as fractionated external beam RT using a linear accelerator (LINAC). The high-dose volume of radiation, delivered by multiple static or moving beams, conforms to the shape of the tumour, avoiding normal tissues, the technique being known as conformal RT. Intensity-modulated RT (IMRT) is a variant of conformal RT which allows for avoidance of specific structures.

For disseminating tumours such as medulloblastoma, RT is given to the whole craniospinal axis (brain and spinal cord). For extensive tumours or multiple tumours such as brain metastases, it is given as whole brain RT (WBRT). For the majority of brain tumours requiring RT, it is delivered as localised conformal RT.

Small targets can be given with high precision as single-dose RT, described as stereotactic radiosurgery (SRS). If given in multiple treatments, it is described as fractionated stereotactic RT (FSRT). Stereotactic RT can be delivered with a LINAC, dedicated multi-headed cobalt unit (Gamma knife®) or robotic arm-mounted small LINAC (Cyberknife®).

To achieve precision, patients are immobilised in a thermoplastic mask or a non-invasive frame system and the positioning is checked with image guidance.

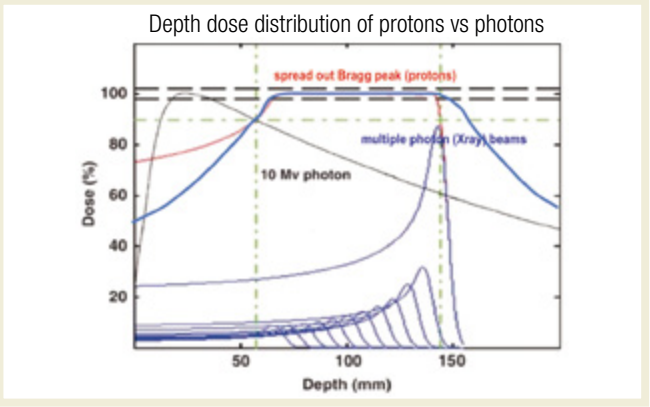


REVISION QUESTIONS

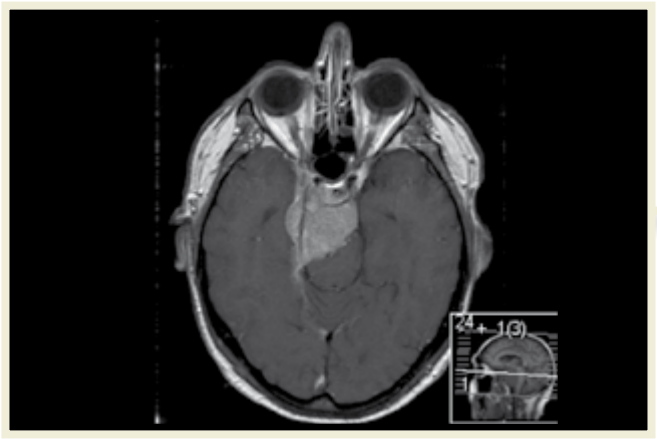
1. Name two brain tumours that can be cured with RT.
2. What are the different techniques for RT?
3. What are the methods used to deliver SRS?

Practice of radiotherapy (continued)

Proton beam RT, which has the same biological effect as photon RT, is increasingly explored in cranial irradiation, due to the potential reduction in radiation dose beyond the target. Currently proton RT remains a complex treatment with many uncertainties and no single indications showing superior results compared with modern photon RT.



Radiotherapy in benign tumours



RT is highly effective in benign tumours which cannot be surgically removed. Treatment is usually reserved for progressive, rather than stable tumours.

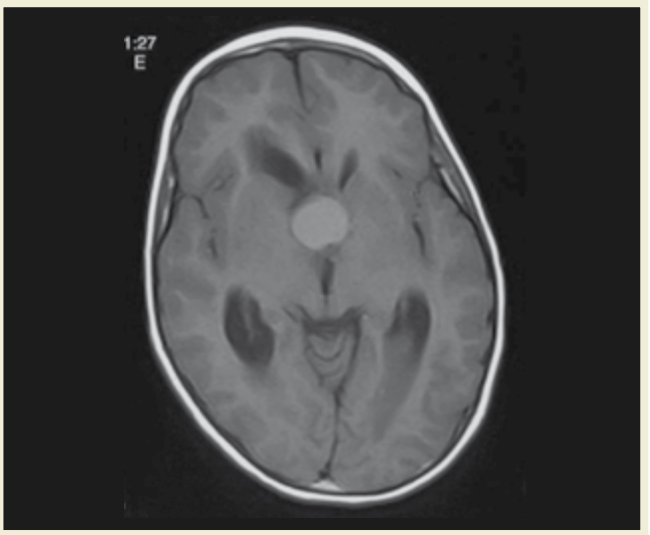
In Grade 1 meningiomas, usually in skull base location, high-precision fractionated treatment achieves excellent tumour control with little toxicity. Small meningiomas are also effectively treated with single-fraction SRS.

RT is highly effective in the control of residual/recurrent pilocytic astrocytoma, particularly when used for optic pathway glioma and tumours in surgically poorly accessible locations.

RT also achieves excellent tumour control of progressive residual or recurrent non-functioning pituitary adenomas and craniopharyngiomas, and leads to hormone normalisation in the majority of secreting tumours, albeit with a delay.

Fractionated high-precision RT and single-fraction SRS (for small lesions) achieve 90% control rate of VIIIth nerve schwannomas (acoustic neuromas).

Cystic components of benign tumours, particularly craniopharyngioma and acoustic neuroma, may enlarge during or shortly after RT, causing mass effect and hydrocephalus. They require close monitoring and appropriate and timely treatment.

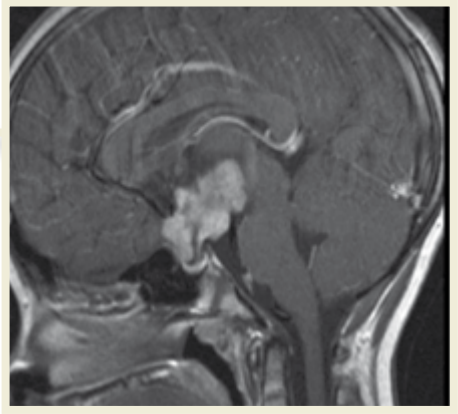


REVISION QUESTIONS

1. Name six benign tumours that can be treated with RT.
2. What is the indication for SRS in acoustic neuroma?
3. What precaution is needed during or after treatment of benign tumours with cystic component and why?

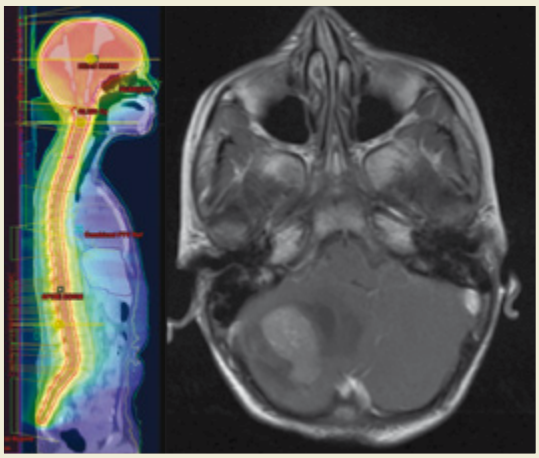
Radiotherapy in germ cell tumours

RT is a curative treatment in cranial germinomas, which principally occur in the pineal or suprasellar regions. It is given as low-dose craniospinal irradiation or as low-dose whole ventricular radiation, followed by a boost to the primary tumour site.



Craniospinal RT and a boost are used as adjuvant treatment in cranial non-germinomatous germ cell tumours, following chemotherapy (ChT) and surgery.

Radiotherapy in medulloblastoma and ependymoma

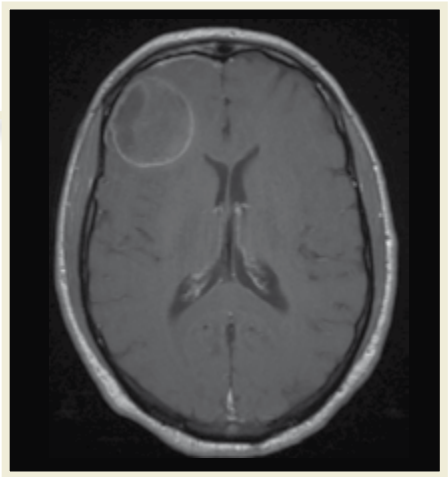


Craniospinal RT after complete excision of medulloblastoma, followed by a boost to the primary site, results in high cure rates. Adult protocols use conventional-dose craniospinal RT, while children with low-risk disease receive low-dose RT.

Fractionated localised RT is of value following excision of both Grade 2 and Grade 3 ependymomas. Craniospinal irradiation is used only in the presence of dissemination.

Radiotherapy in astrocytic tumours

RT is the primary treatment of malignant glioma. As fractionated conformal RT to a dose of 60 Gy in 30 fractions, it is associated with a survival gain in the region of 6 months, shown in randomised trials in glioblastoma (Grade 4 astrocytoma). Patients aged over 70 years benefit from a shorter, less intensive treatment, resulting in a better outcome than an intensive 6-week course. The addition of ChT provides further survival benefit.



Elderly patients with known methylated O6-methylguanine-DNA methyltransferase (MGMT) may alternatively be treated with conventional dosing of temozolomide.

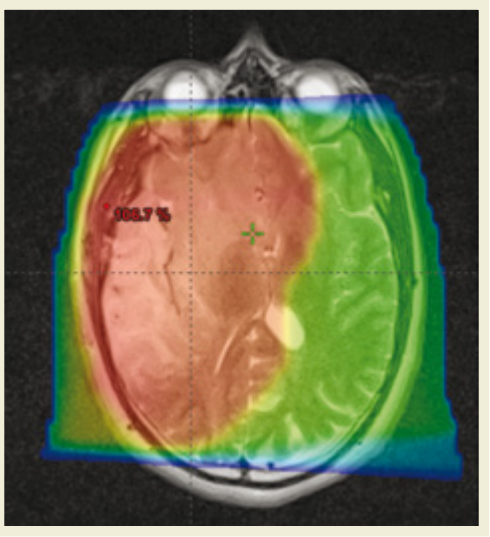
The role and timing of RT in patients with Grade 2 astrocytoma is still debated. Conventionally, it is offered as fractionated conformal RT to patients with progressive and/or transforming tumours following a period of surveillance, and is given at a dose of 54–60 Gy in 25–33 fractions at ≤2 Gy per fraction.

REVISION QUESTIONS

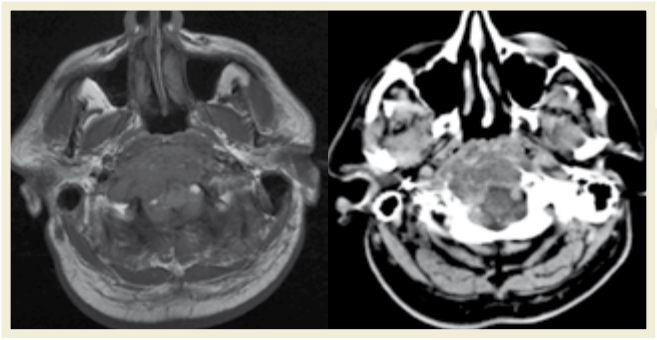
1. Name three situations where craniospinal RT is indicated.
2. What are the treatment options for elderly patients with glioblastoma?
3. What are the indications for RT in patients with Grade 2 astrocytoma?

Radiotherapy in oligodendroglioma

Grade 3 *1p/19q* codeleted oligodendrogliomas (anaplastic oligodendrogliomas) are traditionally treated with primary RT and adjuvant nitrosourea-containing ChT (usually the PCV [procarbazine, lomustine and vincristine] regimen). Conformal RT is given to a dose of 59.4 Gy in 33 fractions (1.8 Gy per fraction). The combination achieves the best long-term survival and disease control.



Radiotherapy in skull base tumours



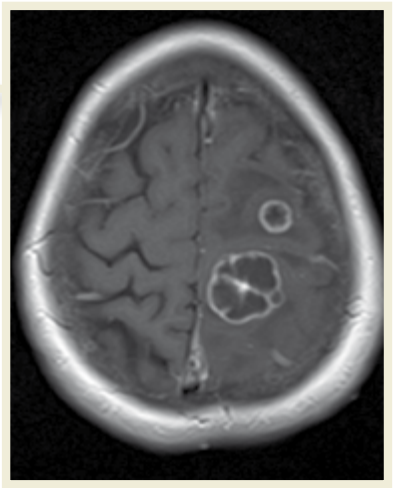
Progressive chordomas and chondrosarcomas invading surrounding structures and poorly accessible by radical surgery are treated with fractionated conformal RT or, if small, with stereotactic high-precision techniques.

Although proton therapy is frequently employed, there is no evidence that it offers superior results either in terms of efficacy or toxicity. The most important prognostic factor is the extent of surgery.

Radiotherapy for brain metastases

RT is the mainstay of treatment in brain metastases. Patients with symptomatic multiple brain metastases from a variety of tumours can be treated with WBRT, generally given as 20 Gy in 5 fractions.

Patients with solitary lesions which are not excisable are effectively treated with single-fraction radiosurgery. WBRT is no longer recommended as an additional treatment following surgery or radiosurgery. It is also not used in patients with adverse prognostic factors and short life expectancy, as it is not associated with a survival gain or quality of life gain compared with supportive care alone. The addition of concomitant ChT is not associated with a survival gain.

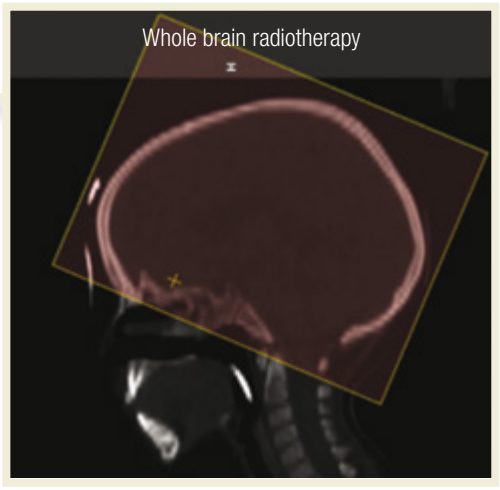


REVISION QUESTIONS

1. What is the common genetic abnormality in oligodendrogliomas?
2. What are the challenges of treatment for chordoma and chondrosarcoma?
3. What are the RT treatment options for brain metastases?

Radiotherapy dose fractionation

Standard RT practice: small daily fractions of 1.6–2.0 Gy per fraction up to 60 Gy in 30 fractions (being considered the limit of radiation tolerance with a risk of radiation-induced structural damage <5%). Increasing the dose or dose per fraction is associated with a marked increase in the risk of damage.



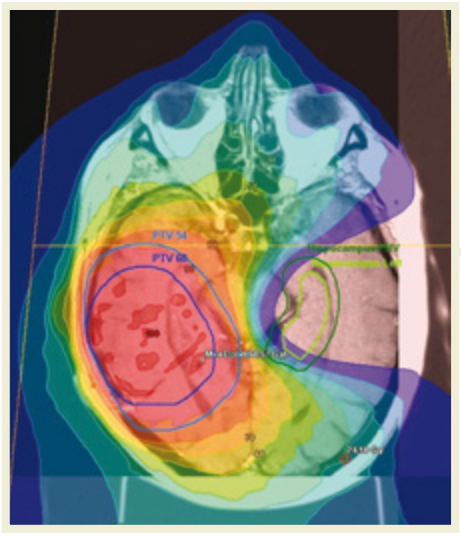
Toxicity-"equivalent" altered fractionation regimens:

- Hypofractionation: larger doses per fraction over a shorter treatment time to an overall lower dose, OR
- Hyperfractionation: Multiple smaller doses, generally twice a day over the same or shorter period.

Such regimens require testing for equivalent effectiveness in terms of survival and tumour control.

Adverse effects of radiotherapy

Dose distribution for potential hippocampal avoidance



Fractionated RT is well tolerated, with principal acute side effects including hair loss and tiredness. Doses beyond tolerance can lead to radiation necrosis (more frequently seen following large single doses of radiation; it is uncommon following conventional fractionated RT).

Conventional doses may lead to mild functional impairment, noted as decline in cognitive function; it is more pronounced in young children, following treatment of large volumes of brain and with the use of large doses per fraction. Avoidance of hippocampus is being tested as a potential means of sparing cognitive function.

Cranial RT is associated with a small risk of developing a second radiation-induced tumour, and with an increased risk of cerebrovascular accident (CVA).

Medical management during radiotherapy

Fractionated cranial RT is generally well tolerated without the need for prophylactic corticosteroids or anticonvulsants.

Low-dose corticosteroids such as dexamethasone can be used for symptoms of increased intracranial pressure and for apparent deterioration of a focal deficit specific to the site of the tumour, all assumed to be due to radiation-induced oedema.

For large single-fraction radiosurgery, a short course of corticosteroids is generally recommended. No specific treatment is required or recommended for post-treatment tiredness/somnolence, as this is a transient phenomenon with full spontaneous recovery.

REVISION QUESTIONS

1. What different fractionation regimens can be used for radical RT of malignant glioma?
2. What dose of corticosteroids (dexamethasone) should be given during RT?
3. Is hypofractionated RT safer or more toxic than conventional fractionated RT?

Summary: The essentials in radiation oncology for brain tumours

- RT is used for both curative and palliative treatment of brain tumours
- Craniospinal RT is an essential component of the curative treatment of medulloblastoma
- Low-dose RT is a curative treatment for intracranial germinomatous germ cell tumours
- RT has an established role in the adjuvant treatment of high-grade brain tumours
- RT is used to improve local control of benign brain tumours and tumours not accessible by surgery
- RT dose fractionation and extent of irradiation depend on the tumour histology and treatment intent
- Long-term side effects of RT include cognitive impairment, pituitary dysfunction and an increased risk of CVA and secondary tumours
- Single-fraction radiosurgery is an effective treatment for small solitary brain metastases
- Corticosteroids and anticonvulsants should not be used prophylactically
- Corticosteroids at low doses should be reserved for symptom control

Further Reading

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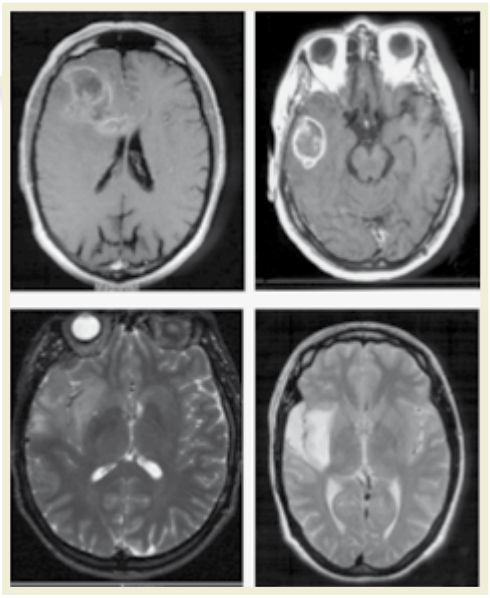
7 Surgery, indications and limitations

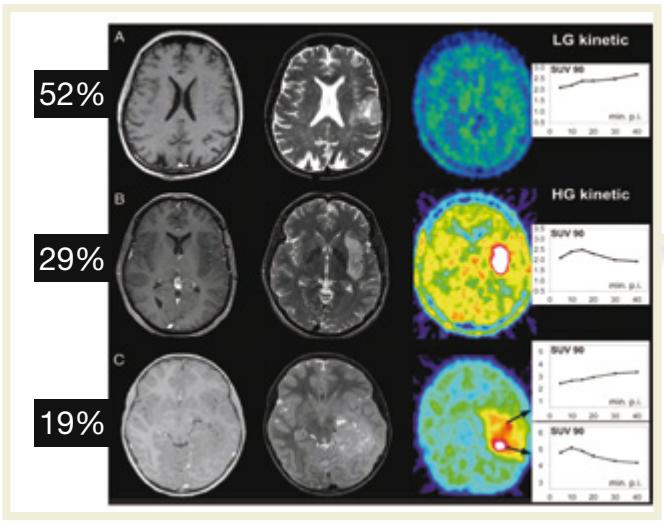
Basic considerations

T1-weighted magnetic resonance imaging (MRI) with contrast enhancement (CE) in all three planes plus T2/FLAIR-weighted images are mandatory to properly delineate brain anatomy.



Magnetic resonance spectroscopy (MRS) or diffusion-weighted images may provide more information about the anatomical boundaries, and about functional areas within the brain.

Differentiation between the tumour infiltration zone and normal brain remains insufficient based on this information alone.



HG, High-grade; LG, low-grade; SUV, standardised uptake value.

Non-contrast enhancing parts of the tumour contribute significantly to the overall outcome in patients with malignant gliomas.

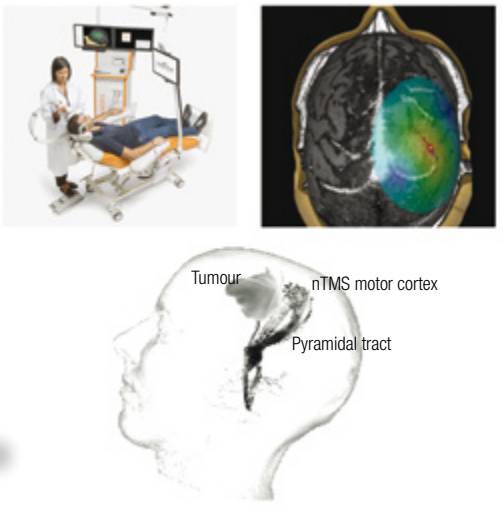
Positron emission tomography (PET) with amino acid tracers like O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) may, to some extent, differentiate between tumour and brain.

^{18}F-FET PET along with other markers such as [^{18}F]fluorothymidine (FLT) may also provide additional information about tumour volume and prognosis.

Preservation of the functional integrity is absolutely mandatory for every surgical approach in malignant glioma surgery.

Functional MRI is unreliable with regard to language testing, and should therefore not be used without intraoperative mapping.

Transcranial magnetic stimulation (TMS) preoperatively correlates neurocognitive and neuropsychological testing by stimulating cortical areas transcranially with MRI.



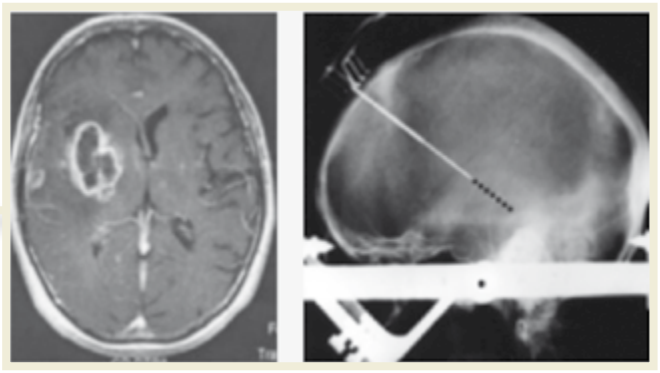
nTMS, Navigated transcranial magnetic stimulation.

REVISION QUESTIONS

1. What are the main prerequisites to consider before glioma surgery?
2. Which diagnostic procedures should be performed before surgery?
3. What are the indications and limitations of these methods?

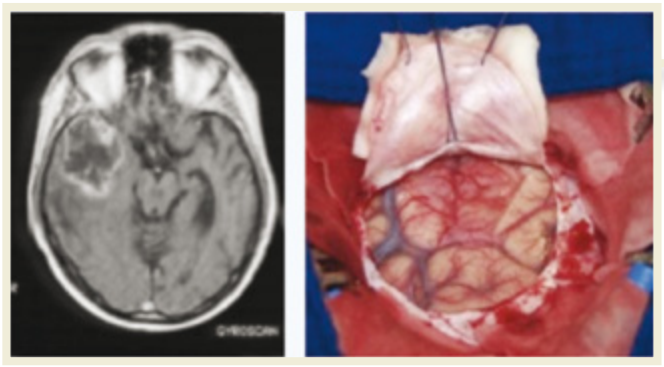
Tissue acquisition: surgery versus biopsy

The goal of surgery in suspected glioblastoma is histological (+ molecular genetic) confirmation, and cytoreduction with the aim of safely removing the solid tumour volume.



Indications for either tumour resection or stereotactic biopsy in glioblastomas should take into account risk factors and relevant comorbidities in older patients.

Molecular genetic analyses (e.g. MGMT promoter methylation, IDH mutation or loss of heterogeneity *1p/19q*) can be performed reliably from small biopsy specimens.



Surgical resection is considered the treatment of choice if complete resection of at least all contrast-enhancing tumour on MRI can be achieved safely.

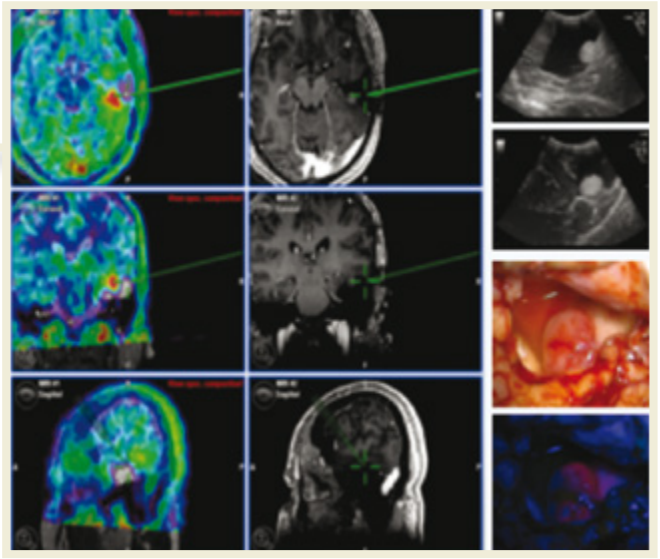
Only complete resection has prognostic benefit, whereas partial tumour resection does not seem to improve prognosis compared with biopsy alone.

Tumour debulking, in order to realise external beam radiation and to avoid the risk of brain herniation in cases of existing mass effects, may sometimes be necessary.

In the case of tumour recurrence, surgical resection may be an option, depending on the tumour biology (including molecular profile, previous treatment and location).

Different studies have revealed younger age, a good preoperative clinical status (Karnofsky Performance Status [KPS]) and greater extent of resection as prognostically favourable.

However, the DIRECTOR trial indicated that only complete resection of contrast-enhancing tumour at first recurrence of glioblastoma improves patient outcome.



REVISION QUESTIONS

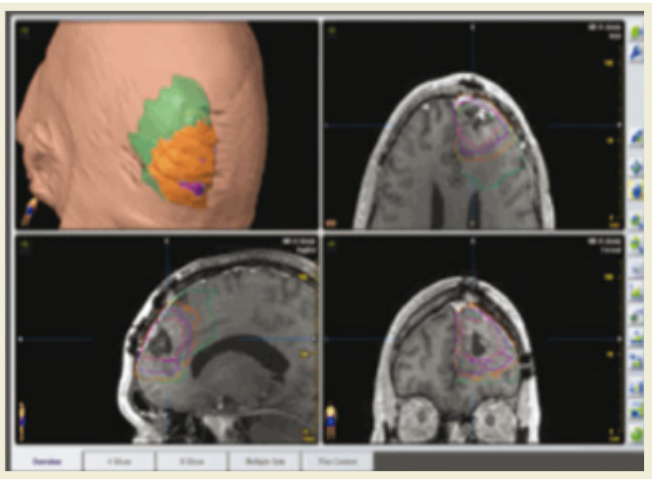
1. Describe indications for tumour resection versus biopsy for suspected malignant gliomas.
2. What are the primary goals and limitations of the different surgical procedures?
3. Which prognostic factors are favourable/unfavourable for tumour resection in recurrent gliomas?

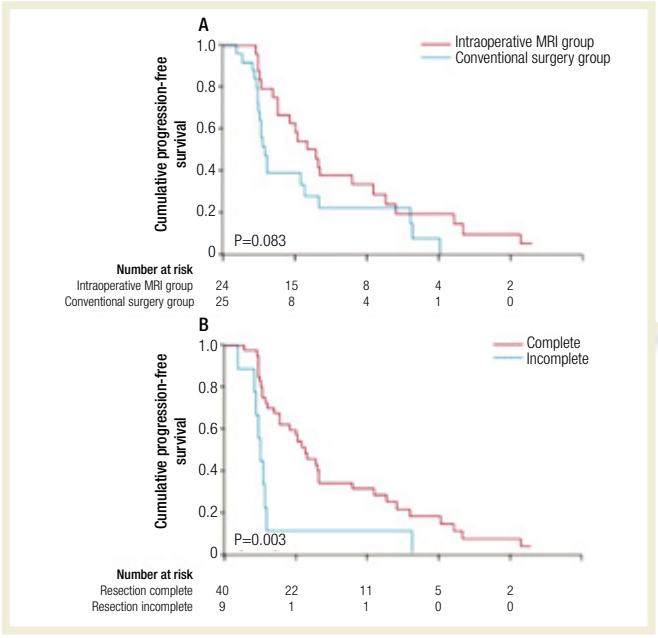
Anatomical orientation using neuronavigation

Very few randomised, controlled trials have studied the use of standard MRI-based neuronavigation.

Information about biological tumour extent is very important during the neurosurgical approach to the tumour, and metabolic imaging should be added to basic MRI at preoperative evaluation.

Dural opening and loss of cerebrospinal fluid leads to loss of accuracy, due to brain shift, and removal of tumour mass with the ongoing resection.





MRI, Magnetic resonance imaging.

Preoperative imaging methods are indirect diagnostic methods only and not suitable for intraoperative real-time analysis.

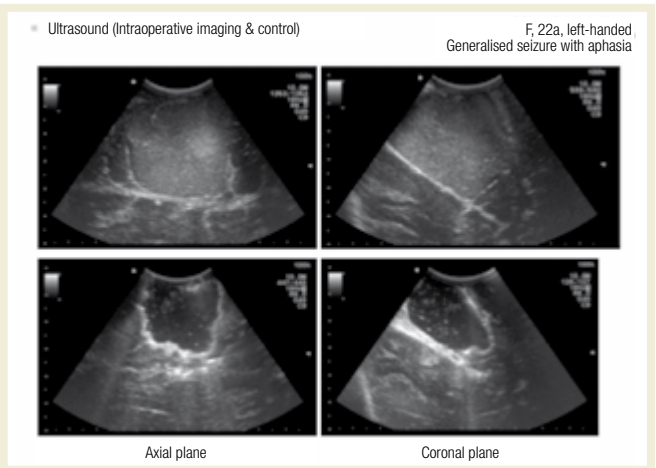
Significant improvement in the extent of resection could be achieved by using intraoperative MRI (iMRI) in up to 96% of patients, compared with 68% in patients in the control arm (NCT01394692).

However, this significant difference did not persist after stratification for complete resection. Therefore, extent of resection rather than use of iMRI was prognostic.

Intraoperative ultrasound (iUS) can be used repeatedly without significantly disturbing or interrupting the surgical workflow.

iUS is the only tool for real-time acquisition of the intraoperative resection status. It can be easily integrated into standard neuronavigation systems.

Moreover, it allows freehand acquisition of a 3D-reconstruction during surgery without substantial time consumption.

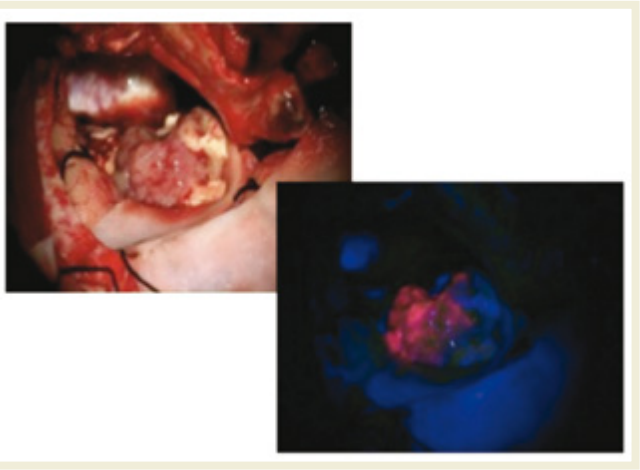


REVISION QUESTIONS

1. What are the indications and limitations in the use of neuronavigation in glioma surgery?
2. Which intraoperative imaging methods can be used and what are their benefits?
3. Why is intraoperative imaging update so important in glioma surgery?

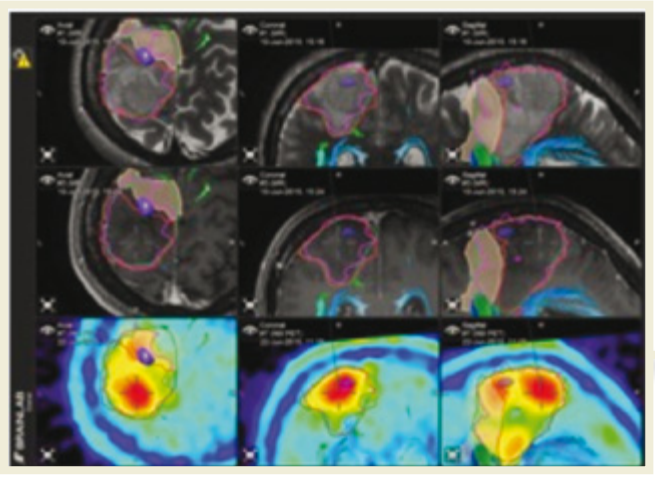
Detection of biologically relevant tumour areas

Complete resection of a malignant glioma can be facilitated by use of 5-aminolevulinic acid (5-ALA) fluorescence-guided tumour resection, more often than by using white light only.



Fluorescence-guided tumour resection has therefore become a major and widespread standard for tumour resection in malignant gliomas in Europe.

To preserve functional activity within the respective brain areas, other tools such as neuronavigation or intraoperative (sub)cortical stimulation techniques should be used.

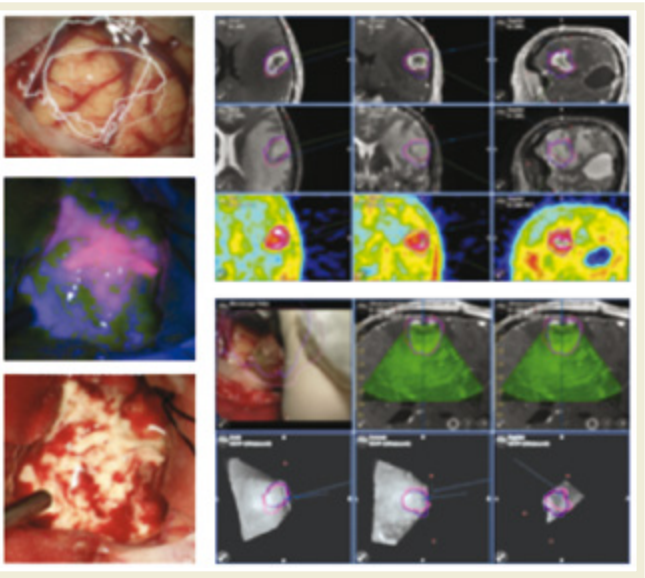


Biological tumour activity may reach far beyond CE displayed by conventional T1-weighted MRI, and can be detected by use of amino acid PET.

PET with amino acid tracers better differentiates between tumour and normal brain, but also between tumour recurrence and treatment-associated changes.

The combination of FET-PET with neuronavigation helps to assess biologically active tumour, as well as the risks and benefits of tumour resection during surgery.

Application of 5-ALA fluorescence in glioma surgery presents some risks, since it is enriched not only in tumour cells but also in the ependymal lining of the ventricles.



The same risk applies to tumours within eloquent brain areas, since 5-ALA fluorescence or FET-PET does not distinguish functional from non-functional tissue.

Close to eloquent areas, use of other surgical instruments such as neuronavigation or intraoperative mapping and monitoring are recommended.

REVISION QUESTIONS

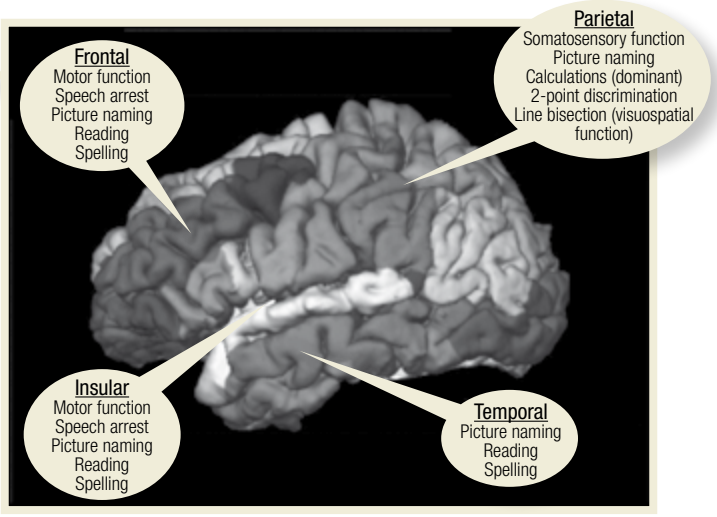
1. Why should 5-ALA fluorescence-guided tumour resection be a standard of care in malignant gliomas?
2. Which other imaging methods may be useful to delineate the biological tumour volume?
3. What are the surgical risks and benefits when using 5-ALA- or FET-PET-guided neuronavigation?

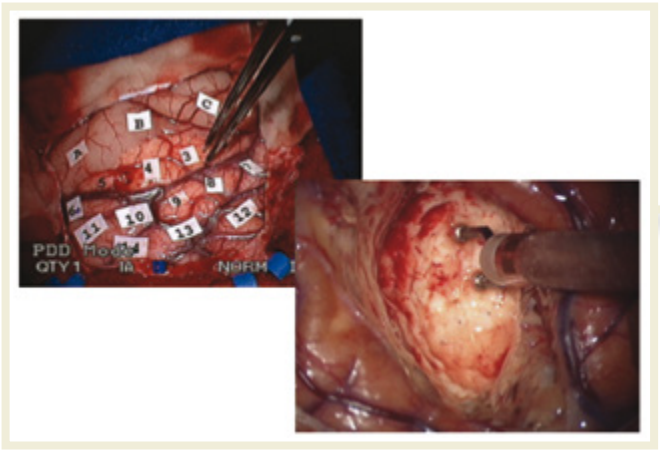
Functional integrity by using intraoperative mapping and monitoring

Our understanding about certain brain modalities like language and its regional distribution has changed substantially over recent years.

Due to large interindividual differences, functional eloquence cannot be determined by anatomical landmarks alone.

All imaging methods have the great disadvantage that they do not provide information about brain functioning during tumour resection.





The gold standard to obtain reliable information about functionally relevant areas within the brain remains intraoperative neurophysiological examination.

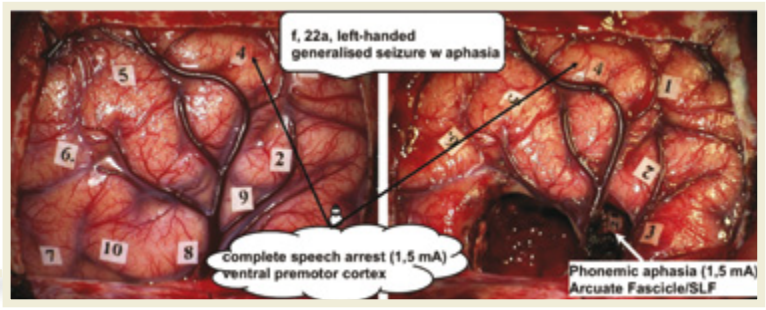
Brain mapping and monitoring via (sub)cortical stimulation allows for the determination of eloquent areas at every time point during surgery.

Higher rates for extent of resection can be achieved more safely in gliomas of different World Health Organization grades by using these neurophysiological techniques.

Higher cognitive functions cannot be monitored in anaesthetised patients. However, awake surgery allows for localisation of language, calculation or spatial orientation.

According to special protocols, certain preoperatively trained tasks, like picture naming, can be tested safely in awake patients to detect aphasic disorders.

Triggered by the presentation of a task, the (sub)cortical surface is irritated by a standardised electrophysiological stimulation, possibly leading to functional disorders.



SLF, Superior longitudinal fasciculus.

REVISION QUESTIONS

1. Why should intraoperative mapping and monitoring be used for glioma surgery?
2. Describe the indications for awake surgery of intracerebral tumours.
3. How can patients be tested reliably during awake surgery?

Summary: Surgery, indications and limitations

- Information about brain anatomy, tumour biology and cerebral function is essential
- Histopathology and biomarker profile should be determined for every glioma
- FET-PET allows detection of “hot-spot“ areas in low-grade gliomas
- Stereotactic biopsy is a safe and minimally invasive procedure
- Only complete tumour resection has a positive prognostic impact in gliomas
- Different imaging modalities can be integrated in modern neuronavigation systems
- Intraoperative imaging update helps to achieve maximal safe resection
- Use of 5-ALA increases the rate of complete resection in malignant gliomas
- Intraoperative electrophysiological testing reduces long-term neurological deterioration
- Awake craniotomy allows tumour resection in eloquent areas for speech

Further Reading

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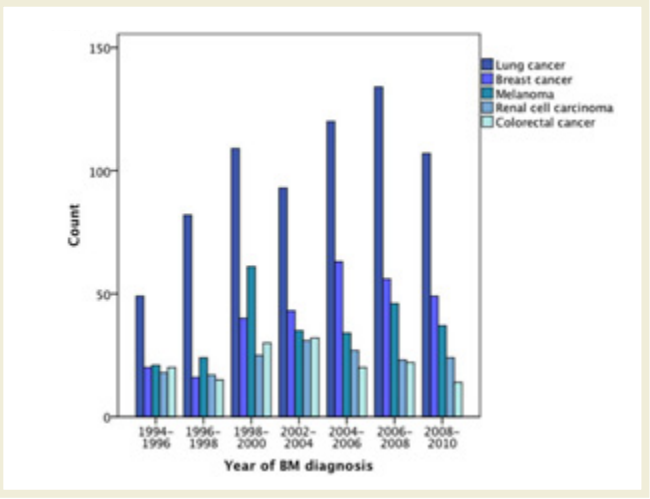
8 Management of CNS metastases

Epidemiology, clinical presentation, diagnosis, prognosis

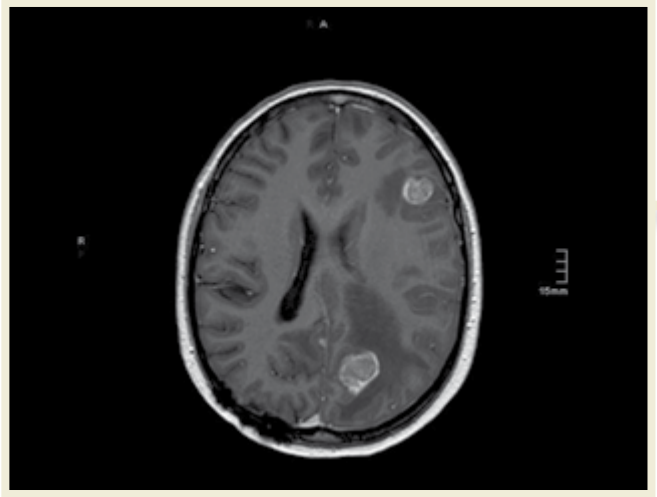
The most common primary tumours causing central nervous system (CNS) metastases are lung cancer, breast cancer and melanoma.

CNS metastases are the most common intracranial tumours and are approximately 10 times more common than primary brain tumours.

The incidence of CNS metastases is increasing due to novel therapies improving the survival time of cancer patients and the increasing availability of neuroimaging.



BM, Brain metastasis.



CNS metastases may cause symptoms and signs of increased intracranial pressure (headache, nausea/vomiting), seizures and focal deficits.

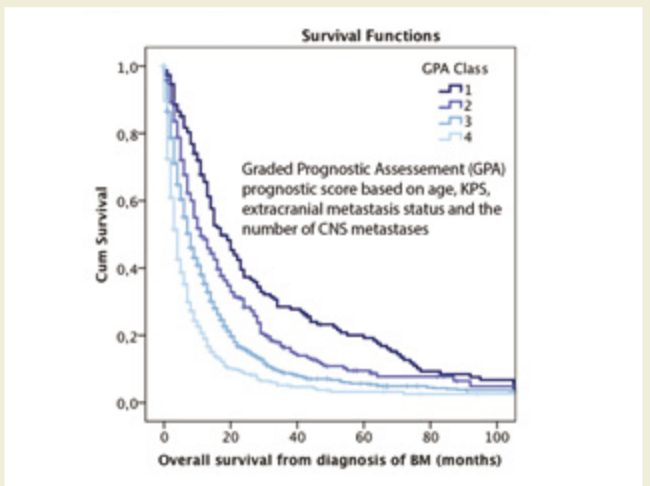
The method of choice for the detection of CNS metastases is contrast-enhanced magnetic resonance imaging (MRI).

CNS metastases typically present as single or multiple contrast-enhancing space-occupying lesions, often with surrounding brain oedema.

The prognosis of CNS metastases is limited, with median overall survival times ranging from a few weeks to months.

The most important clinical prognostic parameters are patient age, Karnofsky Performance Status, number of brain metastases and extracranial tumour status.

Long-term survivors exist, with patients with brain metastases of HER2-positive breast cancer showing the most favourable median survival times.



BM, Brain metastases; CNS, central nervous system, KPS, Karnofsky Performance Status.

REVISION QUESTIONS

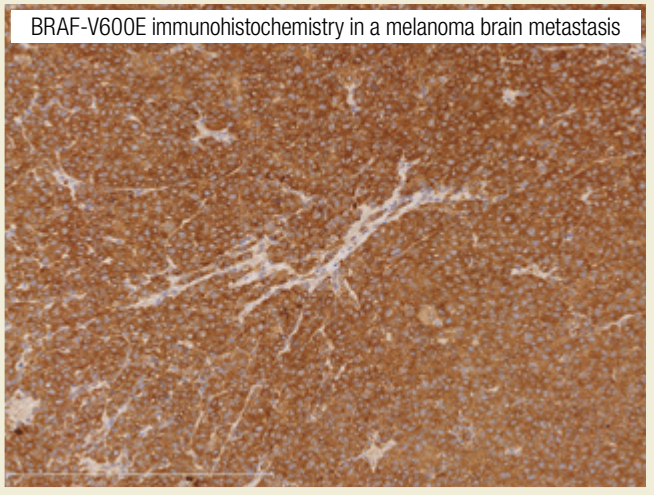
1. CNS metastases occur most frequently with which tumour types?
2. What is the method of choice for the detection of CNS metastases?
3. Name the important clinical prognostic parameters for patients with brain metastases.

Local therapies: radiation and resection

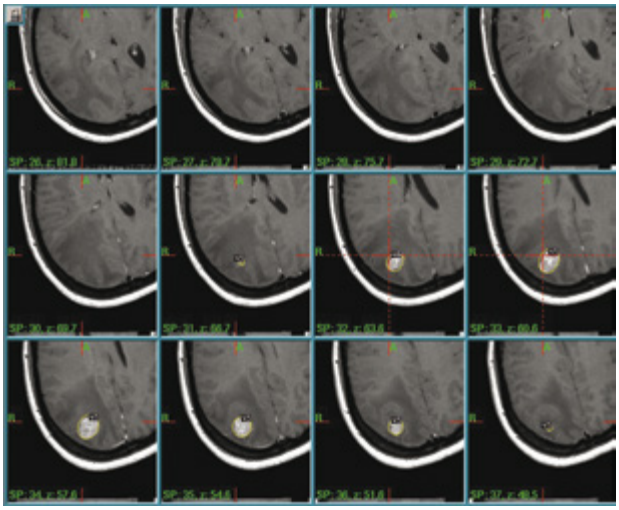
Neurosurgical resection of CNS metastases is performed in selected patients.

Indications include one or few brain metastases, controlled extracranial disease, unknown primary tumour and acute decompression need.

Tumour tissue derived from neurosurgical intervention may help to guide systemic therapy by securing a histological diagnosis or enabling biomarker analysis.



BRAF-V600E immunohistochemistry in a melanoma brain metastasis



Stereotactic radiosurgery (SRS) delivers single-dose high-precision focused radiotherapy (RT).

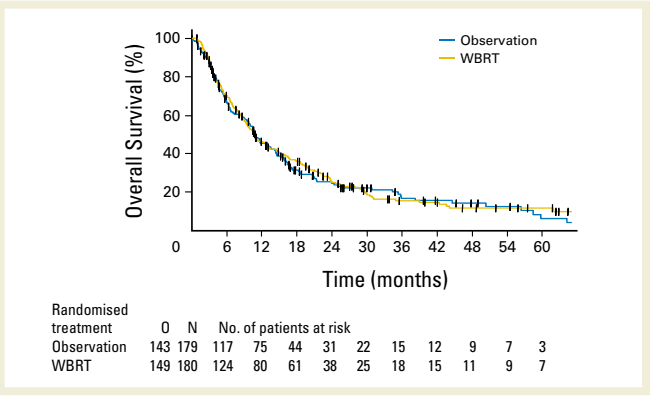
SRS is typically considered for small (maximal diameter up to 3 cm) CNS metastases.

SRS may achieve good local control, but can induce significant radiation necrosis with brain oedema.

Whole brain radiotherapy (WBRT) is a treatment option in patients with multiple brain metastases and is used for prophylaxis of small cell lung cancer (SCLC) brain metastases.

WBRT is associated with significant neurotoxicity and a high risk of neurocognitive decline.

In patients treated with neurosurgical resection or SRS for few brain metastases, postoperative WBRT can be omitted in favour of radiological follow-up.



WBRT, Whole brain radiotherapy.

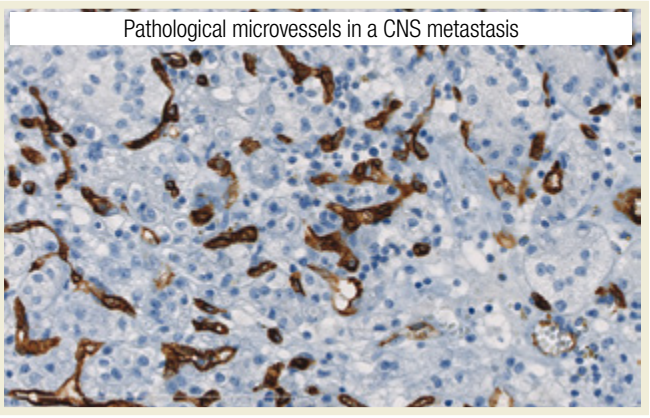
REVISION QUESTIONS

1. Discuss the indications and contraindications for neurosurgical resection of CNS metastases.
2. Up to which CNS metastasis size is SRS feasible?
3. What is the main adverse event associated with WBRT in patients with CNS metastases?

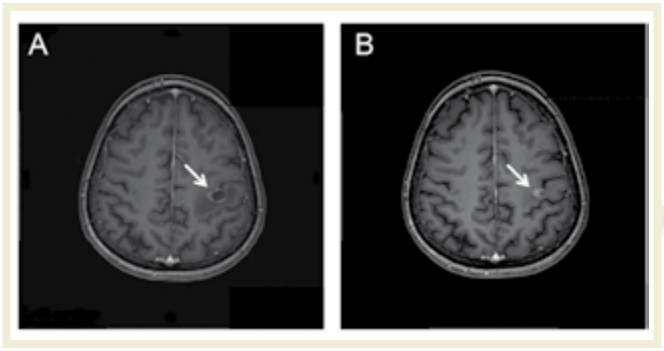
Systemic antineoplastic and supportive therapy

The blood–brain barrier (BBB) limits drug penetration into the CNS. However, pathological microvessels in CNS metastases may allow adequate drug penetration.

Responses of CNS metastases to cytotoxic chemotherapy (ChT) are not uncommon and there is a high correlation between extra- and intracranial response, thus systemic therapy is a feasible treatment option.



CNS, Central nervous system.



For selected patients with CNS metastases, therapy with targeted agents should be considered, ideally within a multidisciplinary tumour board.

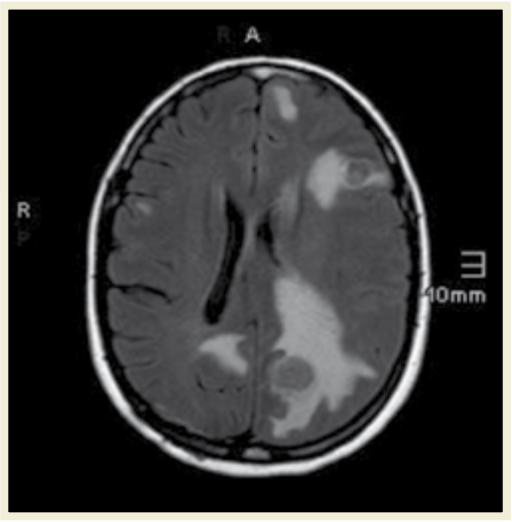
Responses of CNS metastases have been documented to *HER2* blockers, BRAF inhibitors, epidermal growth factor receptor (EGFR) inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, bevacizumab and immune checkpoint inhibitors.

Combination of targeted agents with RT may have synergistic effects, but for some drugs also carries the risk of excess toxicity.

Peritumoural brain oedema is a common finding in CNS metastases and may cause significant symptoms such as raised intracranial pressure and seizures.

Dexamethasone is the drug of choice to treat symptomatic brain oedema, but prolonged administration has multiple and severe adverse effects.

The initial daily dexamethasone dose is usually 12–16 mg and should be rapidly tapered to individual need ("as much as needed, as little as possible").



REVISION QUESTIONS

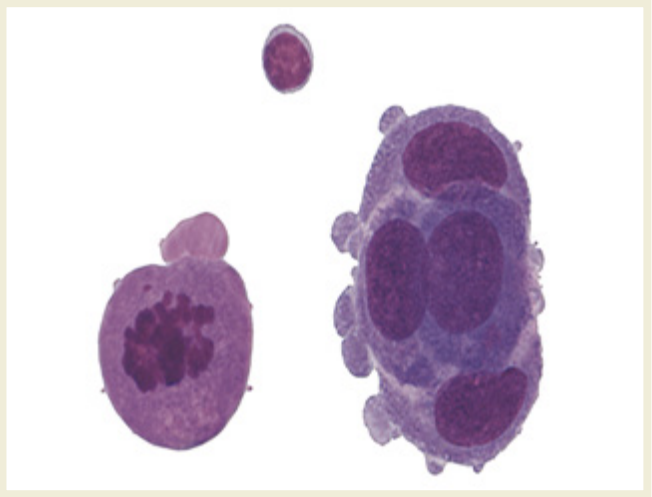
1. Are CNS metastases a contraindication for systemic cytotoxic ChT?
2. Name three biologicals for which therapeutic responses of CNS metastases have been seen.
3. Which drug is indicated for the treatment of symptomatic brain oedema in patients with CNS metastases?

Leptomeningeal metastasis

In patients with suspected neoplastic meningiosis, a cerebrospinal fluid (CSF) puncture (spinal tap) should be performed to detect tumour cells.

Neoplastic meningiosis may present with headache, neck or back pain, confusion, cranial nerve palsy or radicular symptoms like paraesthesia or paresis.

Neoplastic meningiosis is most common in patients with breast cancer, lung cancer, melanoma or haematological neoplasms (lymphoma, leukaemia).



Main therapy options for neoplastic meningitis:

- Radiotherapy
  - Whole brain RT (WBRT)
  - Focal RT
  - Cranio-spinal irradiation
- Chemotherapy/biological
  - Intravenous
  - Intrathecal
- Supportive therapy
  - Corticosteroids
  - Anticonvulsants
  - Antiemetics
  - Analgesics

RT, Radiotherapy.

There is a lack of controlled clinical trials guiding clinical decision-making, and treatment should be discussed in a multidisciplinary setting (tumour board).

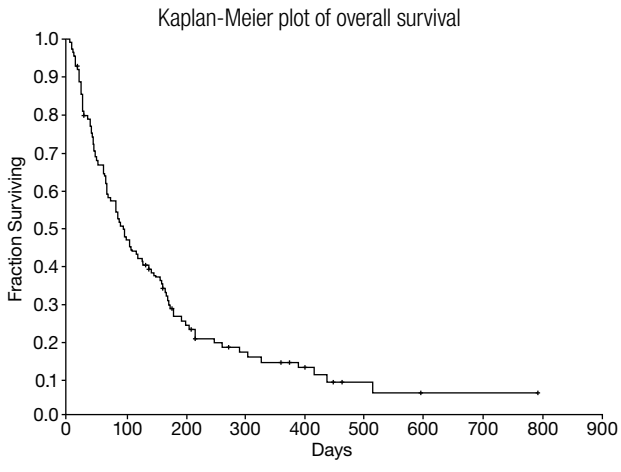
The main treatment options for neoplastic meningioses comprise supportive therapy, RT and systemic or intrathecal ChT.

RT is most commonly applied as WBRT or focal irradiation of solid meningeal tumour nodules.

The efficacy of systemic therapy including ChT and targeted agents against neoplastic meningiosis is unclear.

Intrathecal therapy may be applied via an intraventricular catheter system (Ommaya or Rickham reservoir) or repeated lumbar punctures.

For intrathecal therapy, methotrexate and (liposomal) cytarabine are most commonly used. Other drugs include thiotepa, etoposide and trastuzumab.



REVISION QUESTIONS

1. Which tumour types most commonly cause meningeal spread?
2. Discuss the different modes of intrathecal therapy.
3. What are the main treatment options for leptomeningeal metastasis?

Summary: Management of CNS metastases

- CNS metastases are frequent and associated with high morbidity and mortality
- CNS metastases are most common in lung cancer, breast cancer and melanoma patients
- The incidence of CNS metastases is increasing
- The prognosis of CNS metastasis patients is limited, but long-term survivors exist
- The main prognostic factors are patient age, Karnofsky Performance Status, number of brain metastases and status of extracranial disease
- Established treatments include neurosurgical resection, RT (including stereotactic radiosurgery and WBRT), and supportive care measures
- Targeted therapies are emerging as useful treatment options in selected CNS metastasis patients
- Neoplastic meningiosis is most common in patients with lung cancer, breast cancer and haematological neoplasms
- The main treatment options for neoplastic meningiosis are RT, systemic or intrathecal ChT and supportive care

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B

More advanced knowledge

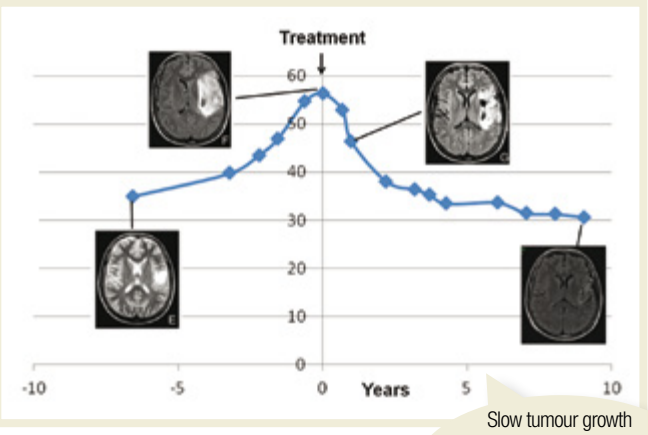
9 Treatment of oligodendroglioma (IDHmt, *1p/19q* codeleted)

Low-grade (Grade 2) oligodendroglioma

Low-grade oligodendrogliomas (IDHmt, *1p/19q* codeleted) are radio- and chemosensitive, slow-growing tumours. With the WHO 2016 classification, the diagnosis of an (anaplastic) oligodendroglioma now requires the presence of both an IDH mutation and combined loss of 1p and 19q. When feasible, maximal safe resection is indicated.

After surgery (whether complete or not), a careful wait and see policy is possible in young patients without neurological deficits and with well-controlled seizures.

Adjuvant treatment is indicated in patients with poor prognostic factors (age >40–45 years, large tumours), neurological deficits or intractable seizures.



PCV, Procarbazine/lomustine/vincristine.

Slow tumour growth before treatment and slow tumour decrease after treatment (here PCV chemotherapy) in a low-grade oligodendroglioma patient

In this population, initial treatment with either radiotherapy (RT) alone or temozolomide (TMZ) alone is similarly effective in terms of progression-free survival (PFS) (EORTC 22033-26033 study).

PFS and OS in EORTC 22033-26033 and RTOG 9802 studies

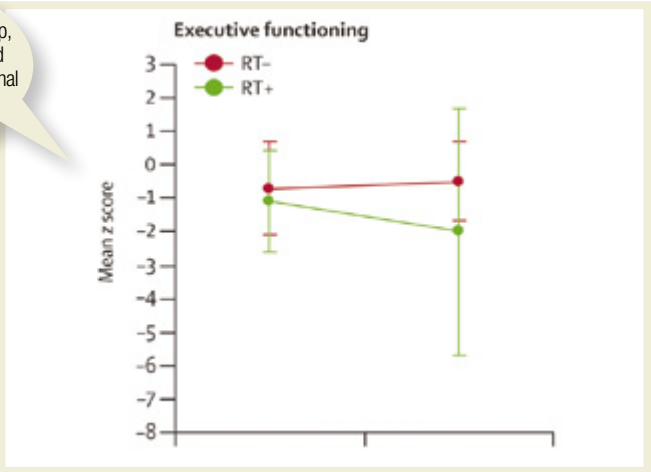
	Progression-free survival (years)	Overall survival (years)
EORTC 22033-26033		
RT only (*1p/19q* codeleted)	5	Not yet reached
TMZ only (*1p/19q* codeleted)	4.5	Not yet reached
RTOG 9802		
RT only (all LGG)	4	7.8
RT+PCV (all LGG)	10.4	13.3

LGG, Low-grade glioma; PCV, procarbazine/lomustine/vincristine; PFS, progression-free survival; OS, overall survival; RT, radiotherapy; TMZ, temozolomide.

In contrast, in low-grade glioma (LGG) patients, initial treatment with RT plus PCV (procarbazine, lomustine and vincristine) is superior to RT alone in terms of PFS and overall survival (OS) (RTOG 9802 study).

Based on the European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) studies, the standard of care of low-grade oligodendrogliomas requiring treatment other than surgery is RT plus PCV.

In a prospective study, at a mean of 12 years of follow-up, LGG patients treated with RT had more deficits that affected attentional functioning than those who did not receive RT



LGG, Low-grade glioma; RT, radiotherapy.

PCV is more toxic than TMZ. However, it remains to be determined whether PCV can be replaced by TMZ without impairing OS.

Long-term survivors after RT seem at risk of decline in attentional functioning.

However, whether first-line PCV alone could defer RT and its potential neurotoxicity without impairing OS also remains to be determined.

REVISION QUESTIONS

1. Is a wait and see policy possible in low-grade oligodendrogliomas?
2. Which treatment should be given to patients who require treatment other than surgery?
3. Can PCV be replaced by TMZ?

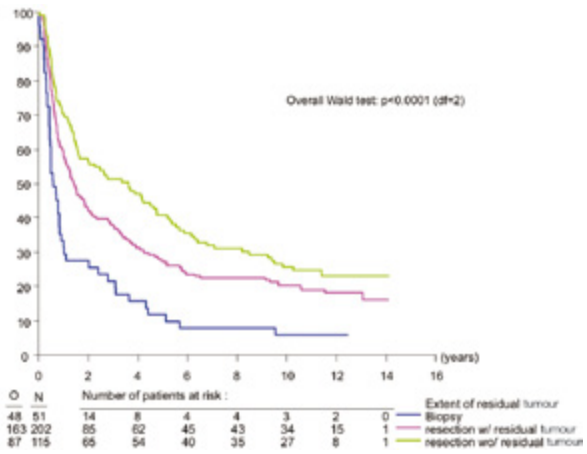
Anaplastic (Grade 3) oligodendroglioma

IDHmt, *1p/19q* codeleted anaplastic oligodendrogliomas have a better prognosis compared with anaplastic astrocytomas. Maximal safe resection is indicated, when feasible.

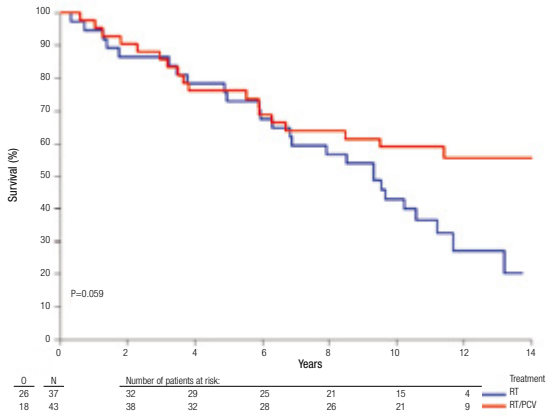
Median survival in IDHmt, *1p/19q* codeleted oligodendrogliomas treated with RT followed by chemotherapy (ChT) is approximately 14 years.

In anaplastic oligodendroglial tumours, maximum resection is associated with improved survival, especially if imaging shows no residual tumour.

Survival according to resection in anaplastic oligodendrogliomas



Survival according to treatment (RT or RT plus PCV) in anaplastic oligodendrogliomas with a *1p/19q* codeletion (EORTC 26951 study)



PCV, Procarbazine/lomustine/vincristine; RT, radiotherapy.

The morphological distinction between low-grade and anaplastic oligodendroglioma is subjective, but in anaplastic tumours further treatment is indicated after surgery.

Outcome in IDHmt, *1p/19q* codeleted anaplastic oligodendroglioma is improved if ChT is added to RT (compared to RT alone).

The studies on adjuvant ChT have investigated PCV ChT; similar studies on TMZ in oligodendroglioma have not been performed.

The German NOA-04 trial suggests that RT alone is as effective as ChT alone. This suggests that survival in patients treated with ChT alone will be poorer compared with survival in patients treated with RT plus ChT.

ChT can be given either before or after RT.

RT may have an impact on quality of survival because of effects on cognitive function (memory, attention), interfering with independent living in some patients.

EORTC 26951 Quality of survival in a cohort with long-term follow-up
Evaluation of cognitive functioning:

• Progression-free patients (n=27): highly variable
  • 44% no cognitive impairments
  • 30% severe cognitive impairments

• Treatment (small subgroups): additional PCV not associated with worse cognition
• 41% were employed and 81% could live independently
• Progressive disease (n=5): more severe cognitive impairments
• **Does this warrant postponement of RT?**

PCV, Procarbazine/lomustine/vincristine; RT, radiotherapy.

REVISION QUESTIONS

1. Following surgery, is adjuvant treatment indicated in anaplastic IDHmt, *1p/19q* codeleted tumours?
2. In anaplastic glioma, is ChT alone more effective than RT alone?
3. What is the median survival in *1p/19q* codeleted anaplastic oligodendroglioma treated with RT and PCV ChT?

Options at progression/recurrence

There are no randomised phase III studies guiding treatment of recurrent oligodendroglioma at this stage.

Depending on initial treatment, options at progression include repeated surgery, RT and/or ChT (TMZ or PCV).

In patients with recurrent low-grade oligodendroglioma, a careful wait and see policy after subtotal re-resection is an option.

Treatment options at recurrence according to initial treatment

Initial treatment	Options at progression
Resection and wait and see	Re-resection and wait and see or RT + PCV
RT + PCV	Re-resection, TMZ
RT alone	Re-resection, PCV, TMZ
TMZ alone	Re-resection, RT +/- PCV
PCV alone	Re-resection, RT +/- TMZ

PCV, Procarbazine/lomustine/vincristine; RT, radiotherapy; TMZ, temozolomide.

Response rates and PFS with PCV, TMZ and bevacizumab at recurrence

	Response rate	Progression-free survival (months)
First-line PCV or TMZ (after RT only)	≈ 60% to 100%	≈14 to 24
Second-line PCV or TMZ (after TMZ or PCV)	≈ 25%	≈ 6
Bevacizumab	≈ 70%	≈ 6

PCV, Procarbazine/lomustine/vincristine; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

Recurrent oligodendrogliomas after RT alone are usually chemosensitive. At this time, PCV and TMZ seem equally effective.

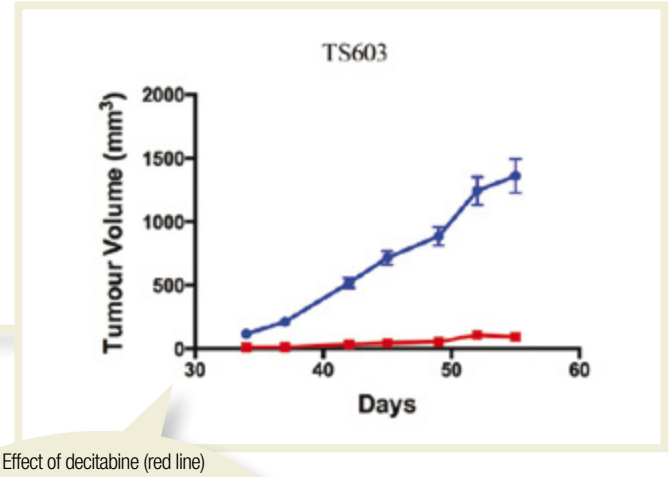
Patients who progress after previous treatment with PCV can still respond to TMZ and vice versa; however, with inferior rates and duration of response.

Patients who progress after initial treatment with ChT alone should receive RT (probably associated with ChT).

Retrospective studies suggest that recurrent oligodendrogliomas can also respond to bevacizumab-containing regimens; any survival benefit, however, remains to be established.

Similarly, the optimal treatment at recurrence after initial treatment with RT plus PCV remains to be determined.

Strategies (hypomethylating agents, specific inhibitors, vaccination) directed against the IDH mutation might help treat recurrent oligodendrogliomas in the future.



Effect of decitabine (red line) versus control (blue line) on the growth of an IDH mutated xenograft. IDH mutated gliomas display a hypermethylated phenotype. Hypomethylating agents such as decitabine could help inhibit tumour growth and promote tumour differentiation

REVISION QUESTIONS

1. Is there a standard treatment for oligodendrogliomas?
2. Can patients who progress after RT plus PCV respond to TMZ?
3. In the future, which strategy might help in treating recurrent oligodendrogliomas?

Summary: Treatment of oligodendroglioma (IDHmt, *1p/19q* codeleted)

- Oligodendrogliomas, defined by the IDHmt, *1p/19q* codeletion, are gliomas associated with the best prognosis (median survival ≈10 to 15 years)
- Maximal safe surgical resection is recommended, when possible
- After surgery (whether complete or not), low-grade oligodendrogliomas can be managed with a careful wait and see policy
- In low-grade oligodendrogliomas needing treatment other than surgery, RT plus PCV is the standard of care
- In anaplastic oligodendrogliomas, initial treatment with RT plus PCV is the standard of care
- In both low-grade and anaplastic oligodendrogliomas, RT plus PCV improves OS compared with RT alone
- Whether oligodendrogliomas can be treated with first-line ChT alone in order to defer RT and its potential neurotoxicity remains to be determined
- At recurrence/progression, there is no standard of care
- Patients previously treated with RT plus PCV can benefit from second-line TMZ or bevacizumab
- Strategies directed against the IDH mutation might help in treating recurrent oligodendrogliomas in the future

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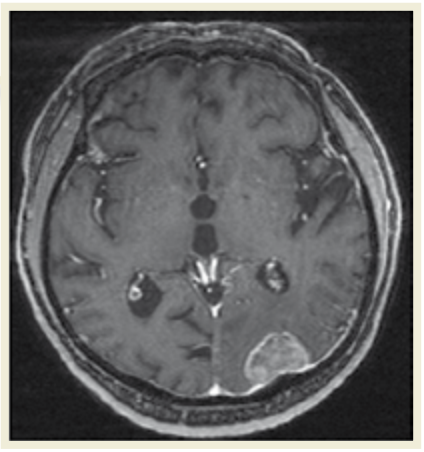
10 Classification and treatment strategies of meningiomas

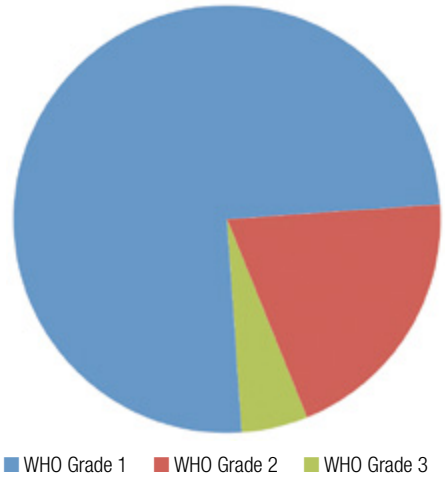
Epidemiology, diagnosis, histopathological grading, key molecular features

Meningiomas are tumours derived from arachnoidal cells and are typically attached to the inner surface of the dura mater. Diagnosis is usually done by cranial magnetic resonance imaging (MRI).



Meningiomas represent the most common primary intracranial/intraspinal tumours in adults. Meninigiomas preferentially affect women. Paediatric meningiomas are exceptionally rare.

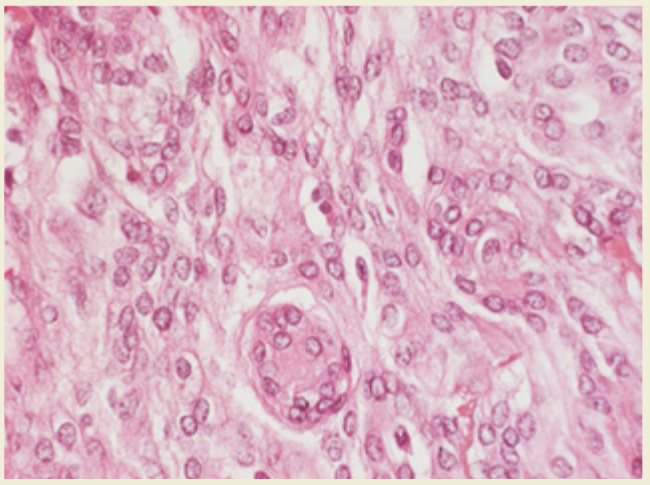
Risk factors include higher age, female gender, prior cranial irradiation and hereditary tumour syndromes such as neurofibromatosis Type 2 (NF2).



WHO, World Health Organization.

Common intracranial locations are the cerebral convexities, olfactory grooves, sphenoid wings, tentorium and posterior fossa. Spinal meningiomas are less common and are mainly found in the thoracic region.

Histopathology distinguishes 9 benign WHO Grade 1 forms, with meningothelial and fibroblastic/transitional meningiomas covering the majority of these tumours. About 20% represent aggressive Grade 2 meningiomas, while anaplastic Grade 3 tumours are rare, with 1%–5% of all tumours.



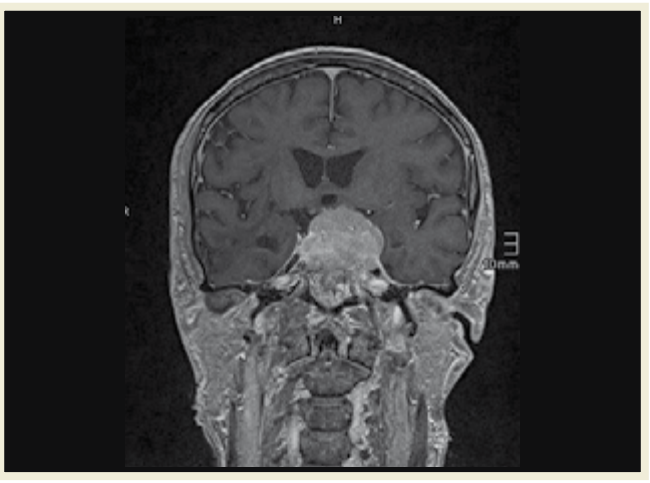
About 50% of meningiomas have molecular alterations in the *NF2* gene. In *NF2* wildtype tumours, mutations in *Smo, Akt,* or *KLF4/TRAF7* genes occur in a small number of tumours. Patients suffering from germline *NF2* alterations are prone to develop (multiple) meningiomas.

REVISION QUESTIONS

1. What are the main risk factors for meningioma development?
2. Where do meningiomas preferentially grow?
3. Are the majority of meningiomas benign or malignant?

Therapy: surgery, radiotherapy, drug treatment

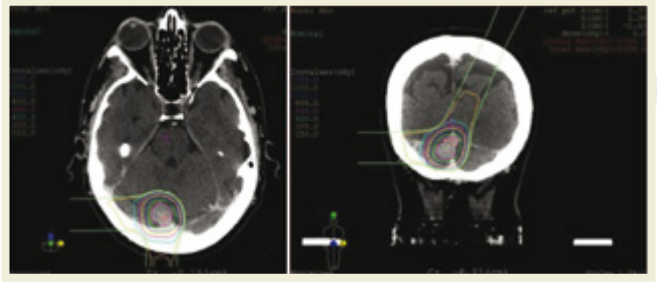
Neurosurgical resection is the treatment of choice for newly diagnosed meningiomas and is curative in most cases. However, meningiomas in inaccessible locations (e.g. skull base) may not be completely resectable.



Incompletely resected meningiomas and meningiomas with histopathological signs of increased malignancy (WHO Grade 2 or 3 meningiomas, tumours with brain infiltration) have a tendency to progress or recur and often require salvage therapies.

If feasible, neurosurgical resection is an important treatment option for progressive or recurrent meningioma.

Radiosurgery dosimetry: dosimetry map for proton radiosurgical treatment of a torcular meningioma



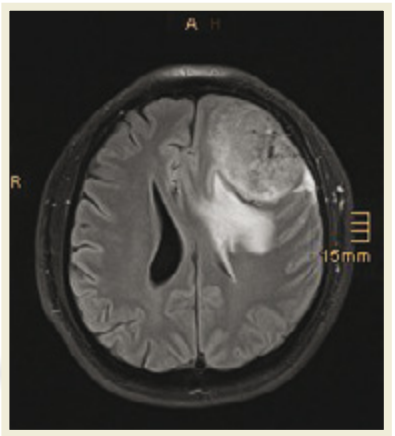
In the newly diagnosed setting, adjuvant radiotherapy (RT) is commonly applied after resection of WHO Grade 3 meningiomas, and after incomplete resection of WHO Grade 2 meningiomas.

In the recurrent setting, fractionated RT or radiosurgery are important treatment options, depending on meningioma size, localisation and prior therapies.

Drug therapy is commonly considered in meningiomas recurring after the exhaustion of all surgical and radiotherapeutic options. However, the lack of clinical trials with systemic agents in this patient population precludes recommendation of specific drugs. Cytotoxic therapies such as hydroxyurea seem to be of very limited value.

Antiangiogenic agents such as bevacizumab and sunitinib have shown signs of anti-meningioma activity in small and uncontrolled studies that require confirmation in further investigations.

Some meningiomas are associated with significant and symptomatic brain oedema that may require anti-oedematous therapy, e.g. with dexamethasone.



REVISION QUESTIONS

1. What is the treatment of first choice for newly diagnosed convexity meningioma?
2. Discuss treatment options for recurrent Grade 2 meningioma.
3. What is the role for cytotoxic chemotherapy in recurrent meningioma?

Summary: Classification and treatment strategies of meningiomas

- Meningiomas are the most common primary intracranial/intraspinal tumours in adults
- Meningiomas are more common in women than in men
- Risk factors include higher age, female gender, prior cranial irradiation and hereditary tumour syndromes (e.g. NF2)
- Patients with germline *NF2* mutations typically present with multiple meningiomas and bilateral vestibular schwannomas
- Radiological assessment is preferentially done by cranial MRI
- Common intracranial locations are the cerebral convexities, olfactory grooves, sphenoid wings, tentorium and posterior fossa
- Histopathologically, approximately 75% of cases correspond to WHO Grade 1 (benign meningioma), 20% to WHO Grade 2 (atypical meningioma) and 5% to WHO Grade 3 (malignant meningioma)
- Neurosurgical resection is the treatment of choice for newly diagnosed meningiomas
- Adjuvant RT is commonly applied after resection of WHO Grade 3 meningiomas, and after incomplete resection of WHO Grade 2 meningiomas
- In the recurrent setting, surgical resection, fractionated RT, radiosurgery or systemic therapy are commonly applied, but evidence from clinical trials is lacking

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Classification and treatment of paediatric brain tumours

11

General aspects

Epidemiology

Brain tumours are the most frequent solid tumours in children, accounting for approximately 20% of paediatric cancers.

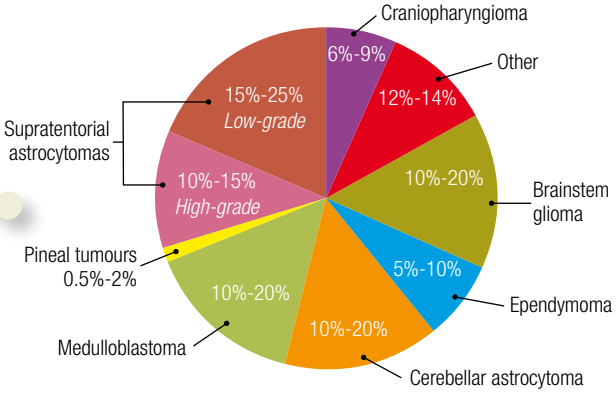
Embryonal tumours and low-grade gliomas (LGGs) are more common in children, followed by high-grade glioma (HGG), brainstem glioma and ependymoma.

Specific inherited disorders lead to an increased risk of developing a brain tumour.

Syndrome	CNS tumour type
Cowden	Dysplastic gangliocytoma of the cerebellum
Li-Fraumeni	Multiple brain tumours, more frequently supratentorial primitive neuroectodermal tumour (PNET), medulloblastoma, astrocytoma
NF1	Neurofibromas, optic glioma
NF2	Schwannoma, meningioma, spinal ependymoma
Gorlin syndrome	Medulloblastoma, meningioma
Rubinstein-Taybi	Medulloblastoma, oligodendroglioma, meningioma
Tuberous sclerosis	Subependymal giant-cell astrocytoma
Turcot	Medulloblastoma
Von Hippel-Lindau	Haemangioblastoma

CNS, Central nervous system.

Approximate incidence of common brain tumours in children



Clinical presentation

Symptoms are related to age and tumour location:

- Infants: Irritability, anorexia, open cranial sutures, failure to thrive, macrocephaly
- Children: Headache especially upon awakening in the morning, decerebrate rigidity, head tilt, stiff neck, behavioural changes, irritability, vomiting, decreased social interactions

REVISION QUESTIONS

1. What percentage of paediatric cancers are brain tumours?
2. To which parameters are paediatric brain tumour symptoms related?
3. Cite three inherited disorders associated with brain tumours.

Medulloblastomas

Medulloblastoma (MB) is an embryonal tumour of the cerebellum and the most common malignant brain tumour in children (15%–20% of primary central nervous system [CNS] neoplasms).

Peak age of incidence for MB is between 3 and 5 years, with 80% of cases diagnosed in the first 15 years of life. In 30% of patients the disease is metastatic at diagnosis.

This kind of tumour is biologically more aggressive in children, with a higher surgical risk and a poorer long-term survival than in adults.

Medulloblastoma in children and adults	
Children	**Adults**
Peak age of incidence: 3-5 years	Median age: 24-30 years
Shorter clinical history: about 2 months	Longer clinical history: about 5 months
Classical MB is more common	Desmoplastic MB is more common
Biologically more aggressive	Biologically less aggressive
Usually median location	Usually lateral location
Higher surgical morbidity and mortality	Lower surgical morbidity and mortality
Poor RT tolerance	Better RT tolerance
Poor long-term survival	Better long-term survival

MB, Medulloblastoma; RT, radiotherapy.

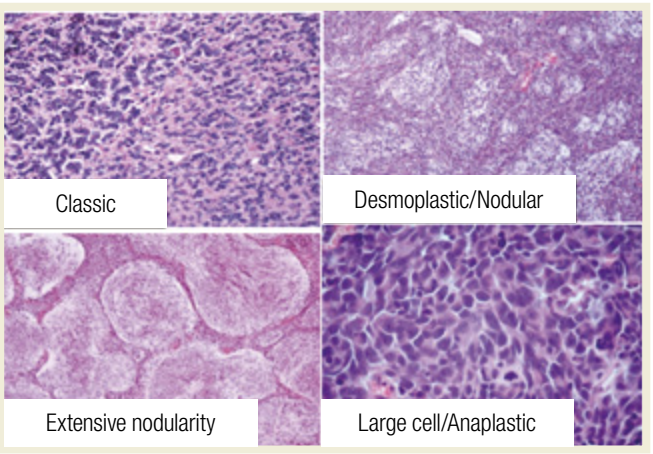
Medulloblastomas (continued)

The diagnostic work-up includes: brain and spine magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination for tumour cells before surgery, molecular analysis (important for molecular subgroups) and risk stratification of patients with MB.

In the 2016 World Health Organization (WHO) classification of CNS tumours, MBs are separated into the classic tumour and four variants: desmoplastic/nodular (D/N), medulloblastoma with extensive nodularity (MBEN), anaplastic MB and large cell MB.

Infants with MBENs and D/N MBs have a better outcome than those with classic tumours, while large cell and anaplastic MBs behave aggressively.

2016 WHO classification of medulloblastoma



WHO, World Health Organization.

Molecular subgroups of medulloblastoma

WNT (10%)	SHH (30%)	Group 3 (25%)	Group 4 (35%)
CTNB1 mutation Monosomy 6	*PTCH1/SMO/SUFU* mutation *MYCCN* amplification	*MYCN* amplification *PVT1-MYC* fusion	*CDK6* amplification Isochromosome 1*7q* *SNCAIP* duplication
WNT signalling	SHH signalling P13K signalling	Photoreceptor/ GABAergic signalling TGF-β signalling	Neuronal/ glutamatergic signalling NF-κB signalling
MYC+	MYCN+	MYC+++	
Rare M+	Uncommon M+	Very frequent M+	Frequent M+
5y OS 94 %	5y OS 87%	5y OS 32%	5y OS 76%

GABA, Gamma-aminobutyric acid; OS, overall survival; TBF-β, transforming growth factor beta.

Four molecular subgroups have been identified:

1. WNT: Activation of WNT/beta-catenin signalling, overexpression of genes of the WNT pathway, with frequent mutations of the *CNNTB1* gene, loss of chromosome 6 and accumulation of nuclear beta-catenin (favourable marker).

2. Activation of the Sonic Hedgehog (SHH) pathway: For most desmoplastic MBs, which arise in a context of inactivating mutations in *PTCH1* and *SUFU* genes, loss of 9q.

3. Group 3 tumours: High incidence of large cell/ anaplastic histology, very frequently metastatic, frequent *MYC* amplification.

4. Tumours of Group 4: Identified by isochromosome *17q* as a frequent chromosomal alteration, mostly histologically of the classic variant.

Treatment (according to molecular classification): multimodal treatment including surgical resection, radiotherapy (RT) and chemotherapy (ChT) has led to an improvement in long-term survival (66%), but also to a major related toxicity.

In conclusion: standard-risk MB is a curable disease, unlike high-risk MB, thanks to better therapy and a reduction of side effects.

Risk stratification for medulloblastoma

Risk Stratification	
Low	Desmoplastic MB, beta-catenin
Standard	Total or near total resection, no metastasis
High	Post-surgical residual disease >1.5 cm^2, metastasis, CSF involvement
Very high	Large cell/anaplastic MB, *C-MYC/N-MYC* amplification

CSF, Cerebrospinal fluid; MB, medulloblastoma.

REVISION QUESTIONS

1. In MBs, what should be part of the diagnostic work-up?
2. Which of the MB molecular subgroups has the better prognosis?
3. Is MB a rare malignant brain tumour in children?

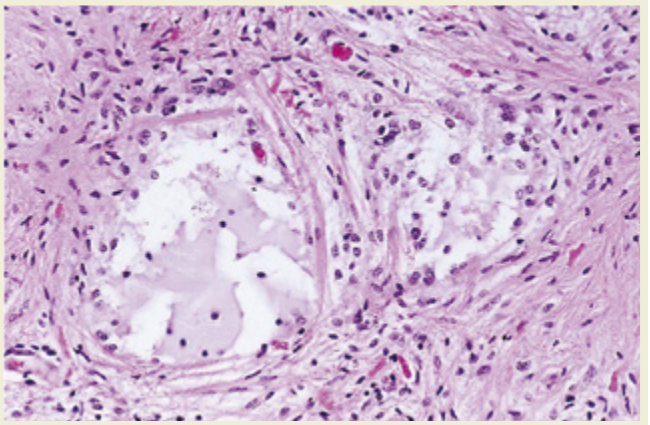
Low-grade gliomas

General aspects

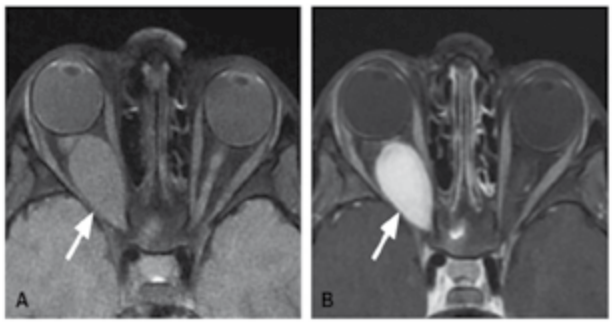
LGGs are slow-growing tumours, with a relatively benign histology. They include pilocytic astrocytoma, diffuse astrocytoma, ganglioglioma, glio-neuronal tumours and mixed neuronal-glial tumours.

Average age at diagnosis ranges from 6 to 9 years. Spine metastases in LGG are rare, affecting 5% of children.

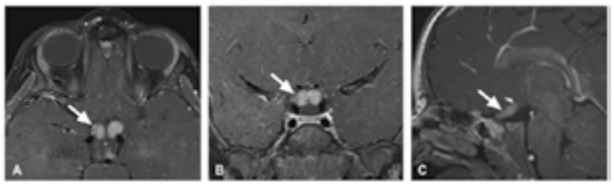
Pilocytic astrocytoma



Optic pathway glioma: right optic nerve involvement



Optic pathway glioma: chiasmal involvement



Optic pathway glioma

The term "optic pathway gliomas" (OPGs) indicates pilocytic astrocytomas arising in the optic nerves, chiasm and hypothalamus. They account for 3%–5% of paediatric intracranial tumours.

Children with Type 1 neurofibromatosis (NF1) have an approximately 20% risk of developing an optic glioma. Patients with NF1 have a less aggressive clinical course than children without NF1.

Treatment

Gross total excision is the goal. This is possible in the majority of hemispheric tumours, but in only a minority of diencephalic tumours. Carboplatin-containing ChT and/or RT are reserved for recurrent or progressive tumours and/or symptomatic patients. Treatment decisions are based largely on the tumour location and the patient's age at diagnosis.

The most frequent genomic alteration in paediatric LGGs are *KIAA-BRAF* fusion genes or BRAF V600 mutations, which activate the mitogen-activated protein kinase (MAPK) pathway.

Vemurafenib and dabrafenib are competitive small molecules that bind and inhibit the ATP-binding domain of mutant BRAF V600E.

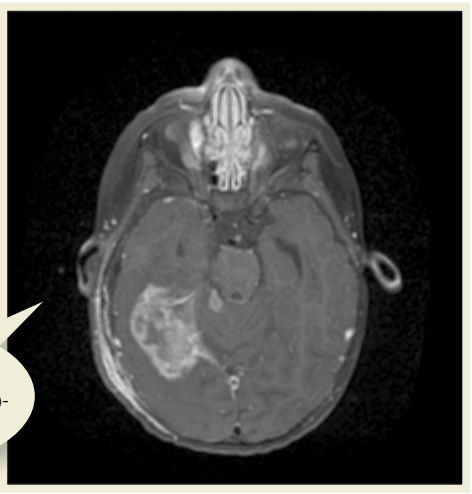
REVISION QUESTIONS

1. What can you say about the histology of LGGs?
2. Which syndrome is often associated with OPG?
3. What is the main prognostic factor in children with LGG?

Supratentorial high-grade gliomas

Supratentorial HGGs represent 7%–11% of childhood CNS tumours. The median age at diagnosis is 9–10 years.

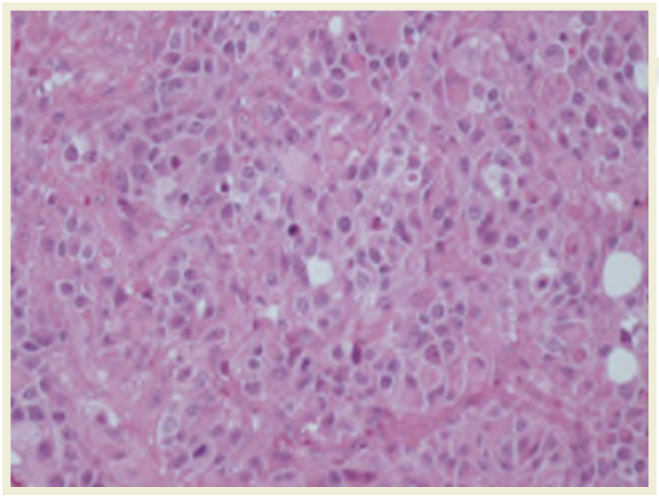
HGGs occur most frequently in the cerebral hemisphere, in contrast to LGGs, which occur in cerebellar and deep midline locations. These tumours are clinically aggressive and regionally invasive.



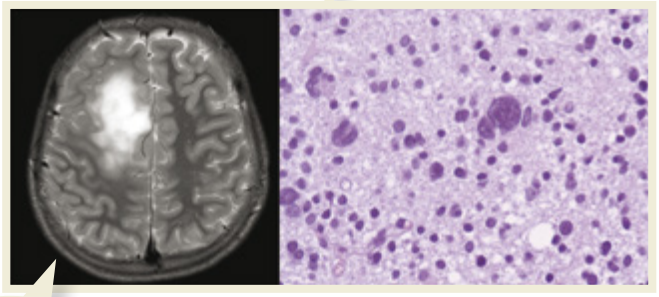
Female, 2 years old. Cranial MRI: axial T1+ gadolinium. Right parieto-temporal glioblastoma, WHO Grade 4

MRI, Magnetic resonance imaging; WHO, World Health Organization.

High-grade glioma



Paediatric high-grade diffuse gliomas, i.e. glioblastoma and anaplastic astrocytoma (WHO Grade 3/4) represent a single category.



Male, 13 years old. Anaplastic astrocytoma (WHO Grade 3)

WHO, World Health Organization.

Although histologically similar to their adult equivalents, the two groups present distinct genetic alterations. Commonly altered genes in hemispheric high-grade astrocytomas of childhood are *TP53* (in 30%–50% of cases), *ATRX* (in ~25%), *SETD2* (in ~15%), *CDKN2A* (deletion; in ~30%), and *PDGFRA* (amplification and/or mutation; in ~30%)

Mutations of the histone genes *H3 (H3.1/H3.3) K27M* are found exclusively in midline tumours as diffuse intrinsic pontine gliomas (DIPG) or thalamic lesions, whereas *H3.3 G34* mutations are found exclusively in tumours of the cerebral hemispheres, more frequently seen in teenagers and young adults. In contrast, hemispheric glioblastomas in infants harbour *NTRK* fusions in approximately 40% of cases, and histone mutations have not been reported.

Surgery followed by RT is the standard treatment of patients with HGG. Surgery has prognostic significance in patients with near-total resection and is at present the strongest indicator of prognosis in paediatric HGG. Focal RT is used as first-line therapy except in children <3 years. The role of ChT is evolving.

REVISION QUESTIONS

1. What is the median age at diagnosis for HGG?
2. What is the standard treatment of children with HGG?
3. In which paediatric tumour can the *H3.3 K27* mutation be observed?

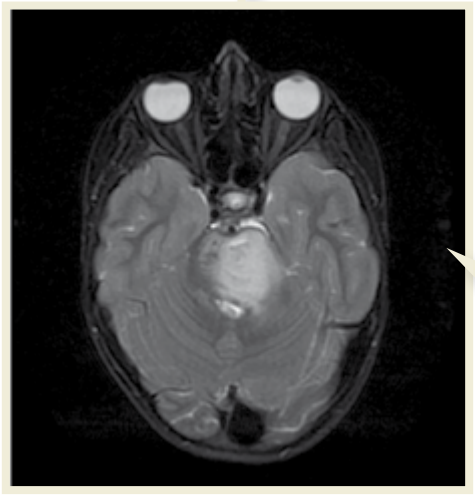
Brainstem gliomas

Brainstem gliomas account for 20% of all CNS tumours in children and are characterised by heterogeneous biological behaviour.

DIPG account for 80% of paediatric brainstem tumours and the prognosis is worse than in focal brainstem glioma.

Usually the diagnosis is performed by MRI. Median age at presentation is 5–7 years.

Diffuse and focal brainstem glioma	
Diffuse tumours	**Focal tumours**
Majority (75%–80%)	20% remainder
Pons epicentre Diffuse growing with medulla-midbrain infiltration	Midbrain Pons: exophytic or intrinsic focal Medullary junction
Not surgically amenable	Possible surgery
Usually high grade	Usually low grade (not all)
2-year survival is less than 10%	Much better prognosis



Male, 7 years old. Cranial MRI: axial T2 FSE. Pontine infiltrative mass

FSE, Fast spin echo; MRI, magnetic resonance imaging.

To date, the prognosis for children with brainstem glioma remains poor.

RT is the standard care, leading to temporary clinical improvement in a substantial proportion of patients. Until now, a number of trials with conventional ChT failed to demonstrate an advantage over RT alone.

REVISION QUESTIONS

1. What percentage of paediatric CNS tumours are brainstem gliomas?
2. How is the diagnosis of brainstem gliomas in children generally obtained?
3. What is the median age of occurrence for paediatric brainstem gliomas?

Ependymomas

Ependymomas account for 10% of all primary CNS tumours in children. The highest incidence in children occurs in the first 7 years of life.

According to the 2016 WHO classification of brain tumours, ependymal tumours are classified into five main subtypes:

WHO Grade	Corresponding tumour
1	Subependymoma
1	Myxopapillary ependymoma
2	Ependymoma
2 or 3	Ependymoma, *RELA* fusion-positive
3	Anaplastic ependymoma

WHO, World Health Organization.

Ependymomas (continued)

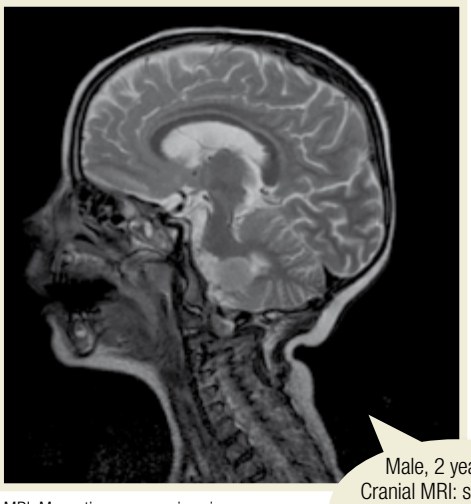
Clinical presentation

The clinical presentation depends on tumour location:

Infratentorial (posterior fossa) ependymoma:
In children, approximately 65%–75% of ependymomas arise in the posterior fossa. Children may present with signs and symptoms of obstructive hydrocephalus due to obstruction at the level of the fourth ventricle. They may also present with ataxia, neck pain or cranial nerve palsies.

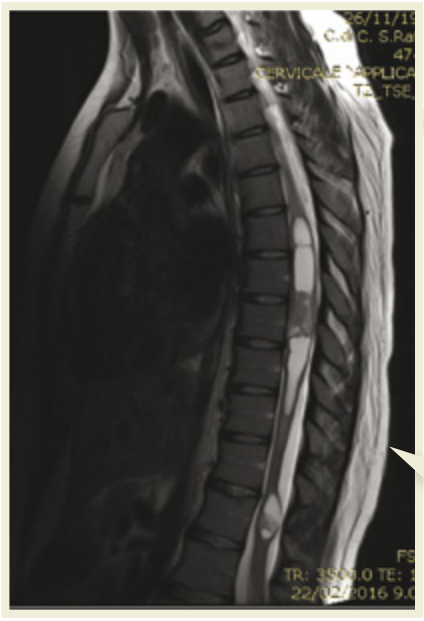
Supratentorial ependymoma: May result in headache, seizures or location-dependent focal neurological deficits.

Spinal cord ependymoma: Often the myxopapillary variant, tends to cause back pain, lower extremity weakness and/or bowel and bladder dysfunction.



MRI, Magnetic resonance imaging; WHO, World Health Organization.

Male, 2 years old. Cranial MRI: sagittal T2. Left pontocerebellar angle ependymoma, WHO Grade 3



MRI, Magnetic resonance imaging; WHO, World Health Organization.

Female, 21 years old. Dorsal spinal cord MRI: sagittal T2. Spinal ependymoma, WHO Grade 2. Lesions at levels D7-D8 and D12 associated with syringomyelia

Treatment

The primary treatment remains surgical resection followed by RT, with gross total resection frequently reported as the most important prognostic factor.

Although postoperative RT may induce stabilisation and occasionally disease regression, most incompletely resected tumours ultimately progress.

Adjuvant ChT has yet to predictably affect outcome, possibly due to the molecular heterogeneity of histologically similar tumours.

Prognosis

Five-year progression-free survival for children with ependymoma ranges from 30% to 50%, with a worse prognosis for patients with residual disease after surgery.

Survivors often experience serious physical and neurocognitive disabilities secondary to the disease and its treatment.

Unfavourable factors:
• Gain of chromosome 1q25, present in approximately 20% of paediatric intracranial ependymomas
• Tumour location. Cranial variants of ependymomas have a less favourable outcome than primary spinal cord ependymomas
• Younger age at diagnosis
• Anaplastic histology
• Subtotal resection
• Lower doses of radiation at diagnosis

REVISION QUESTIONS

1. What is the most common location for ependymomas in children?
2. What is the 5-year progression-free survival for children with ependymoma?
3. What is the main prognostic factor in paediatric ependymoma?

Summary: Classification and treatment of paediatric brain tumours

- Brain tumours are the most frequent solid tumours in children, with embryonal tumours and LGGs representing the largest fraction of these cancers
- Symptoms are related to age and tumour location
- Approximately 10% of brain tumours occur in children with genetic syndromes, such as NF1 and NF2, Li-Fraumeni, Cowden, Gorlin and Turcot syndromes, tuberous sclerosis complex and Von Hippel-Lindau syndrome
- Biopsy is very important to define diagnosis and individualised treatment based on molecular biology
- In MB, four molecular subgroups have recently been identified, which are important for prognosis, risk stratification and treatment
- LGGs are slow-growing tumours, with a relatively benign histology, and gross total excision is the main treatment. The most frequent genomic alterations in paediatric LGGs are *KIAA-BRAF* fusion genes or BRAF V600 mutations
- OPGs account for 3%–5% of paediatric intracranial tumours, and children with NF1 have an approximately 20% risk of developing an optic glioma
- HGGs are clinically aggressive and regionally invasive. Current treatment consists of maximal resection and RT. The role of ChT is evolving
- The prognosis in children with brainstem glioma remains poor. RT is the standard care, leading to temporary clinical improvement. Chemotherapeutic strategies, including multiagent neoadjuvant ChT, concurrent ChT with RT, and adjuvant ChT, have not provided any survival advantage
- Two-thirds of ependymomas occur in the posterior fossa. The primary treatment remains surgical resection followed by RT, with gross total resection frequently reported as the most important prognostic factor

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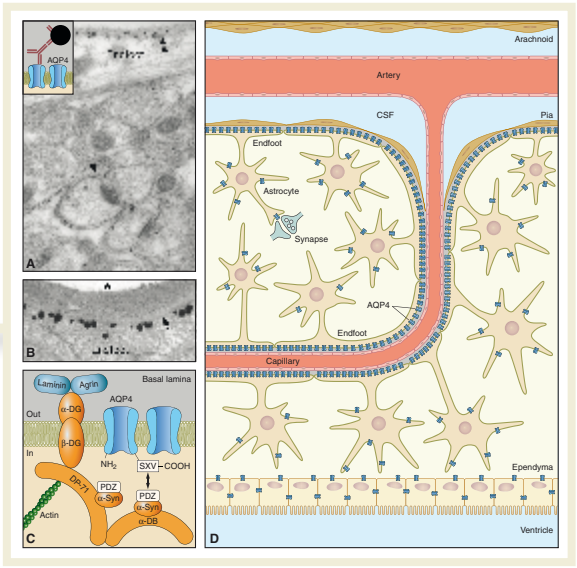
12 Anticoagulation and management of seizures and brain oedema in brain tumour patients

Brain oedema

The breakdown of the healthy blood–brain barrier (BBB) is one of the key diagnostic findings in malignant gliomas, and contributes substantially to symptoms related to increased intracranial pressure.

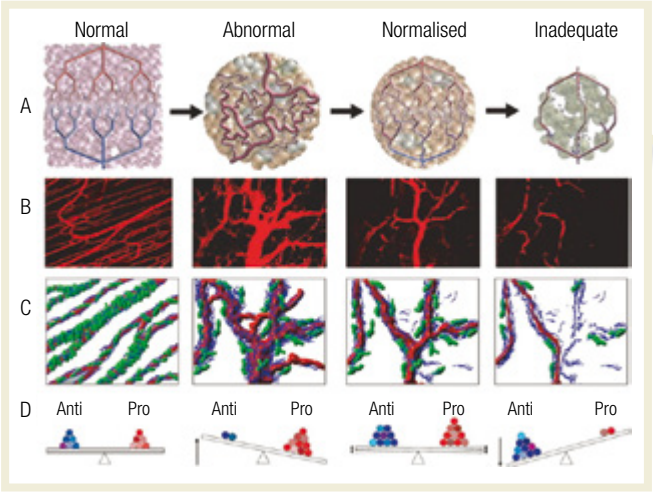
Brain oedema in glioblastoma has several causes:

1. Glioma cells differ from normal astrocytes by loss of polarity, due to expression of aquaporin 4 (AQP4) molecules mainly in the endfeet of normal astrocytes, contacting pericytes or endothelial cells. AQP4 is involved in regulation of extracellular space volume, K^+ buffering, interstitial fluid resorption, waste clearance and neuronal excitability. Redistribution of AQP4 over glioma cells severely impairs functionality of the BBB.



AQP4, Aquaporin 4; CSF, cerebrospinal fluid.

Changes in (A) tumour vasculature, (B) vessel structural patterns, (C) pericyte coverage (green) and basement membrane thickness (blue), and (D) balance of pro- and antiangiogenic factors before, during and with sustained VEGFR2 blockade.



VEGRF2, Vascular endothelial growth factor receptor 2.

2. Accelerated cell division and increased metabolic demands in high-grade gliomas cause hypoxia, triggering increased expression of vascular endothelial growth factor (VEGF), leading to neoangiogenesis and formation of abnormal vessels with dysfunctional BBB and increased permeability.

Current therapeutic options to treat symptomatic brain oedema and restore BBB function consist mainly of treatment with glucocorticoids or, experimentally, molecules targeting VEGF. There are currently no evidence-based dosing or tapering regimens; both options are effective, but efficacy is transient and side effect burden has to be considered carefully. Osmotic treatment with mannitol shows only a short-lived response.

Comparison between corticosteroids and bevacizumab to treat brain oedema

	Corticosteroids (dexamethasone)	Bevacizumab
Type	Hormone	Humanised antibody
(Usual) starting dose	12 mg, best in the morning	10 mg/kg every two weeks
Route of administration	Oral	Intravenous
Time to effect	Less than one hour	Hours
Recommended duration of therapy	As short as possible, Immediate tapering after clinical response is recommended	No recommendation
Approval in Europe for this use	Yes	No
Medication cost	Low	High
Mode of action	Anti-inflammatory	Blocks VEGF
Main side effects	Iatrogenic diabetes, iatrogenic Cushing syndrome, myopathy, osteoporosis, avascular necrosis, psychiatric disorders	Hypertension, proteinuria, hand-foot syndrome, arthralgias, bleeding, cardiovascular events, gastrointestinal perforation

VEGF, Vascular endothelial growth factor.

REVISION QUESTIONS

1. Describe the mechanisms of brain oedema in patients with gliomas.
2. How does bevacizumab decrease brain oedema?
3. List the side effects of dexamethasone used to prevent/alleviate brain oedema in patients with gliomas.

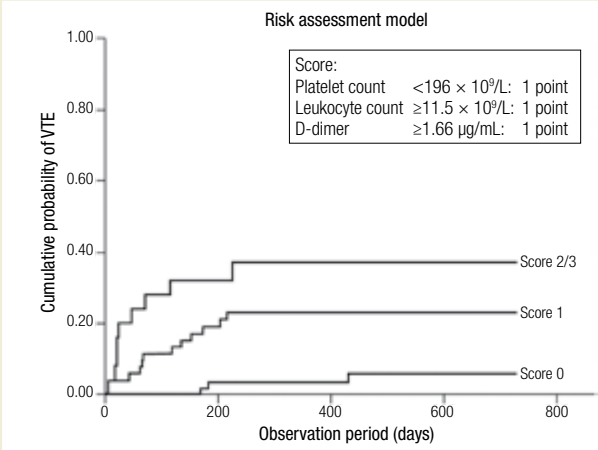
Thromboembolic complications

Risk of venous thromboembolic (VTE) complications such as deep vein thrombosis and pulmonary embolism in patients with primary brain tumours, especially high-grade gliomas, is high, reaching up to 18% per year. It depends on patient factors, glioma-associated factors and treatment-related factors.

Biomarker	Hazard ratio in multivariate analysis	p-value
Platelet count per 50x10^9 L increase	0.73	0.019
Soluble P selectin per doubling	2.71	0.006
D-dimer per doubling	1.33	0.020

Patient factors
Age (especially >75)
ABO blood type (A, AB)
Prior deep vein thrombosis or pulmonary embolism
Leg paresis, prolonged immobility
Multiple medical comorbidities
Obesity
Glioma-associated factors
Tumour grade (high > low-grade glioma)
Intraluminal thrombosis in surgical specimen
Recurrent disease
Tumour size (>5 cm)
Postoperative residual disease (biopsy>partial>gross total resection)
Treatment-associated factors
Postoperative period
Chemotherapy
VEGF-targeted treatment
Hormonal therapy
Venous access devices
Possible biomarkers

VEGF, Vascular endothelial growth factor.



VTE, Venous thromboembolism.

Proposed risk model for VTE in brain tumour patients:

Risk for VTE is unevenly distributed among glioma patients. This risk assessment model uses only routine laboratory parameters;

1. Leukocyte count (cutoff ≥11.5 × 10^9/L)
2. Platelet count (cutoff <196 × 10^9/L)
3. D-dimer (cutoff ≥1.66 µg/mL).

One point was assigned, respectively, according to these cutoffs.

Recommendations for VTE prophylaxis and therapy in brain tumour patients:

Therapeutic efficacy as well as substantially increased risk of intracranial bleeding have to be considered.

As yet, there are no studies on the use of novel oral anticoagulants in brain tumour patients.

Time point	Measure
Perisurgical	• Antithrombotic stockings • LMWH at prophylactic dose
During treatment and follow up	• No general recommendation
VTE	• LMWH at therapeutic dose, switched to prophylactic dose after 6 months

LMWH, Low molecular weight heparin; VTE, venous thromboembolism.

REVISION QUESTIONS

1. Is the risk of VTE in patients with primary brain tumours high or low?
2. Define suitable routine laboratory parameters for individual risk assessment of VTE in glioma patients.
3. What kind of drug therapy is currently used in patients with primary brain tumours with VTE?

Management of seizures in brain tumour patients

Seizures are a common neurological complication in brain tumour patients. They may be the initial sign of a brain tumour or occur during the course of disease. Frequency of seizures varies between 30% and 100%, depending on the histology and site of the brain tumour.

Frequency of seizures in different brain tumours	
Primary brain tumours	**Frequency**
Malignant glioma	30%–60%
Low-grade glioma	70%–90%
Dysembrioblastic neuroepithelial tumours	90%–100%
Brain metastases	
Melanoma	60%–70%
Lung cancer	30%–40%
Breast cancer	10%–20%
Gastrointestinal	10%–20%
Total	20%–40%

Epileptogenesis in brain tumour patients is multifactorial. Site of the tumour, destruction of neuronal tissue and networks, haemosiderin deposition, necrosis, oedema, tumour-induced neurochemical changes, as well as treatment-related complications are the major contributing factors.

Selected anticonvulsants recommended for brain tumour-associated epilepsy	
Drug	**Mean dose**
Levetiracetam	1000–2000 mg/day
Valproic acid	600–2000 mg/day
Lacosamide	200–400 mg/day
Zonisamide	300–500 mg/day
Lamotrigine	100–200 mg/day

Seizures as well as possible side effects from anticonvulsants may affect the patient's neurological function and quality of life. Moreover, anticonvulsant-related adverse events are more frequent in patients with brain tumours versus patients with epilepsy due to other causes.

Treatment recommendations for antiepileptic drugs in brain tumour patients are in line with general guidelines for treating epilepsy. However, antiepileptic drugs with low potential for side effects, without hepatic enzyme induction, low plasma protein binding, and predominant renal excretion should primarily be considered.

Recommendations for antiepileptic treatment in different clinical settings of tumour-associated epilepsy	
Acute treatment	Follow the general guidelines for epilepsy
Prophylactic treatment	Not indicated, but may be considered in selected patients
Chronic administration	Avoid enzyme-inducing anticonvulsants. First choice is levetiracetam, valproic acid and others (see table above).

Up to 70% of patients can achieve seizure freedom by using anticonvulsants, at least in gliomas. The efficacy of treatment strongly depends on the type and location of the tumour, as well as on antitumour treatment, anticonvulsants used and type of seizure (simple partial seizures are associated with less favourable control). Accordingly, multiple treatment strategies have to be considered. Surgery, radiotherapy and chemotherapy may contribute to seizure control.

Recommendations for diagnostic procedures and follow-up of brain tumour patients with seizures are: a seizure-tracking calendar and interviewing patients and their relatives for possible seizure equivalents. An electroencephalogram (EEG) might be helpful in some cases to detect or monitor seizure activity. In case of an increase in the seizure frequency or a change in the type of seizures, tumour recurrence or progression must be ruled out.

Stopping anticonvulsant therapy may be considered in patients with stable brain tumour disease over time, without seizure activity in the EEG and seizure freedom. A slow tapering of anticonvulsants is required.

REVISION QUESTIONS

1. Brain tumour patients frequently suffer from seizures. The probability of having seizures depends on what factors?
2. What are the treatment options for tumour-associated seizures?
3. Which drugs are recommended for anticonvulsant treatment?

Summary: Anticoagulation and management of seizures and brain oedema in brain tumour patients

- Adequate symptom palliation is beneficial for the quality of life of patients and their caregivers
- The most frequent brain tumour symptoms besides neurological deficits are brain oedema, epileptic seizures and thromboembolic events
- Effective anti-tumoural treatment is the best defence against tumour-related complications, but is not always achievable
- Only patients with symptomatic oedema require treatment
- Oral dexamethasone is still the most used treatment against symptomatic brain oedema, given prophylactically during the perisurgical period and at initiation of radiotherapy (starting dose 8–16 mg/day)
- Due to its heavy side effect burden, as soon as no further symptomatic improvement is reached, dexamethasone dose should be reduced by half and further tapering should be tried
- Thromboembolic events: general prophylaxis is not recommended outside the perisurgical period
- Treatment of symptomatic thromboses can be safely done using LMWH; after six months an individual decision for further prophylaxis must be made. However, as the risk for recurrence in brain tumour patients is high, lifelong prophylaxis has to be considered
- Seizures are a frequent complication in patients with primary brain tumours. Prophylactic treatment is not recommended
- For symptomatic treatment of patients with seizures, antiepileptic drugs with low potential for side effects, without hepatic enzyme induction, low plasma protein binding, and predominant renal excretion (levetiracetam, lamotrigine, valproic acid, lacosamide, zonisamide, etc.) should primarily be considered

Further Reading

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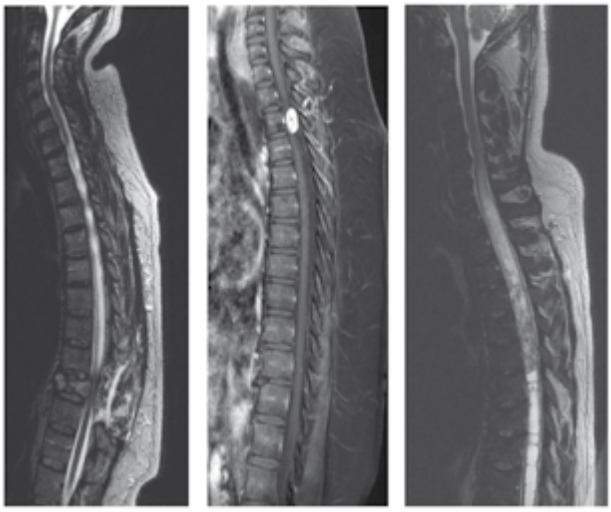
13 Management of spinal tumours

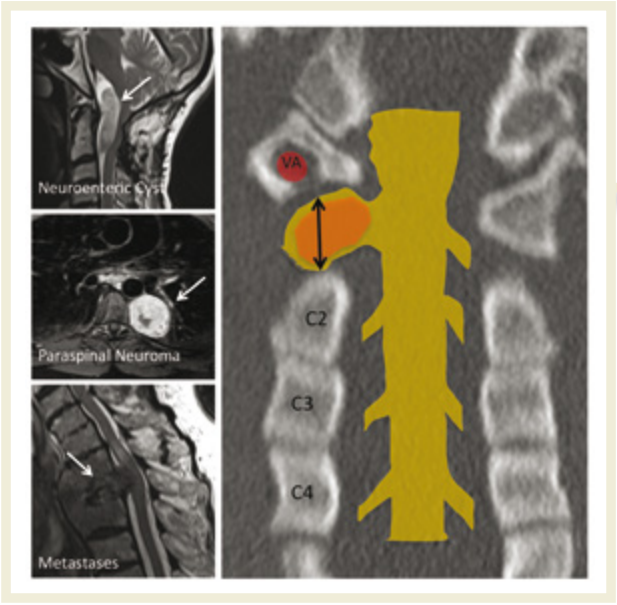
Compartments, diagnosis and presentation

Compartments of spinal tumour occurrence: 50% extradural, 40% intradural–extramedullary and 10% intramedullary manifestation.



Ninety-five percent of extradural tumours are metastases and the remaining 5% are primary bone tumours.

Intradural neuromas, ependymomas and meningiomas are most frequently found. Intra-axial ependymomas, astrocytomas and haemangiomas are also diagnosed.



Magnetic resonance imaging (MRI) is the first choice diagnostic procedure in spinal tumour disease. X-ray and computed tomography (CT) are used in diagnosing intramedullary lesions but not in extramedullary.

Clinical differential diagnoses of intramedullary tumours are: infectious diseases, degeneration of dorsal column, vitamin B12 or folic acid deficit or vascular lesions.

Positron emission tomography (PET)-CT or PET-MRI and scintigraphy with additional SPECT may be helpful to evaluate the tumour extent within the staging process of extradural lesions.

Most patients with spinal tumours pass through the same diagnostic setting as patients with degenerative spinal diseases, due to similar clinical presentation.

Extramedullary pain with subsequent radicular symptoms and more or less prominent paraparesis are common. But acute deterioration due to pathological fracture or bleeding can also occur.

Sensory deficits, proprioception deficits and pain are the leading symptoms in patients with intramedullary tumours.

Tumour	Axial pain	Lumbar pain	Radicular symptoms	Ataxia	Myelopathy	Vegetative dysfunction	Intracranial pressure
Extradural	++	+	+	–	–	+	–
Intradural–extramedullary	–	+	++	+	+	+	(+)
Intramedullary	–	–	++	++	++	+	+

REVISION QUESTIONS

1. What are the three typical compartments of spinal tumour occurrence?
2. Which differential diagnoses have to be kept in mind in intramedullary spinal tumours?
3. Which symptoms occur primarily in extradural (bone) tumours or metastases?

Treatment options

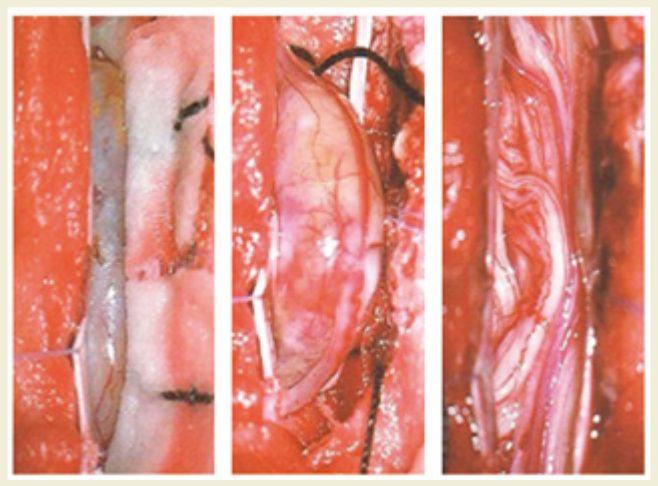
Skeleton tumours of the spine have an incidence of only 0.4% of all neoplasms. Benign lesions occur in younger patients. Malignancy is associated with older age.

The origin, biological behaviour and preferred treatment options of common primary extradural tumours of the spine are shown in the table.

Medical treatment, radiotherapy, radiosurgery, vertebral augmentation, decompression and spinal fusion alone or in combination are the treatment options.

Common extradural spine tumours

Origin	Tumour	Biological behaviour	Preferred therapy
Bone	Osteoidosteoma	Benign	Intralesional curettage
	Osteoblastoma	Benign	Marginal en-bloc resection
Cartilage	Osteochondroma	Benign	En-bloc resection
Blood vessels	Aneurysmal bone cyst	Semi-malignant	Interventional embolisation, intralesional curettage
Notochordal	Chordoma	Malignant	Aggressive en-bloc resection + radiotherapy
Haematopoietic system	Multiple myeloma	Malignant	Radiotherapy + chemotherapy
	Ewing sarcoma	Malignant	



Intradural-extramedullary tumours (mostly neuroma or meningioma) have to be treated surgically in case of neurological deficit or documented growth.

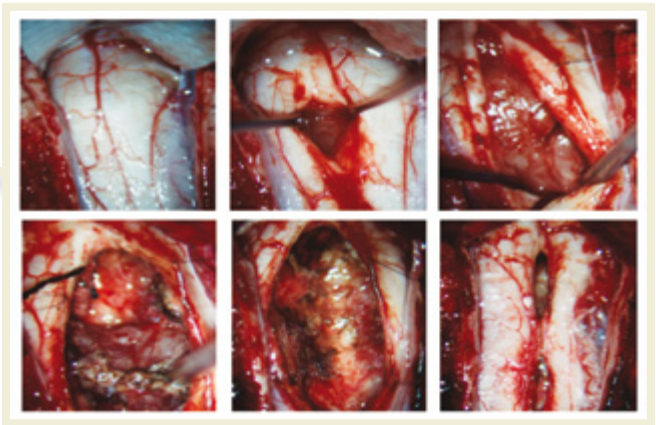
Surgical steps: Complete extirpation of a spinal neuroma, which is mostly possible.

Adjuvant treatment is generally not required.

Intramedullary tumours have to be treated in case of manifest or imminent neurological impairment, which is mostly the case.

Surgical steps: Identifying the dorsal spinal cord midline, myelotomy, preparing the lesion and identifying the borders to healthy tissue, removing the prepared lesion and pial suturing of spinal cord.

Incompletely resected tumours are treated by dural extension plastic and adjuvant expansion therapies, adapted from intrinsic cerebral gliomas.



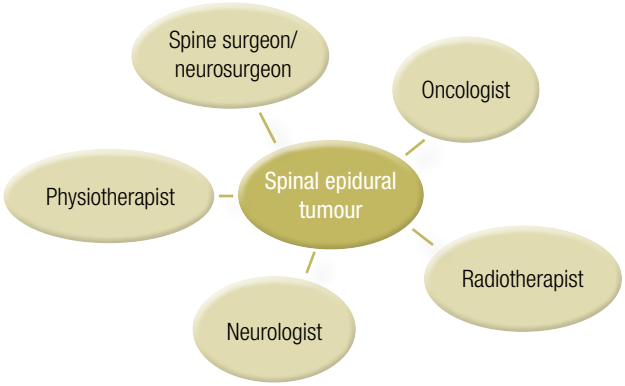
REVISION QUESTIONS

1. What is the incidence of skeleton tumours of the spine?
2. What is the indication to treat intradural-extramedullary spinal cord lesions?
3. Where is the typical dorsal myelotomy approach located?

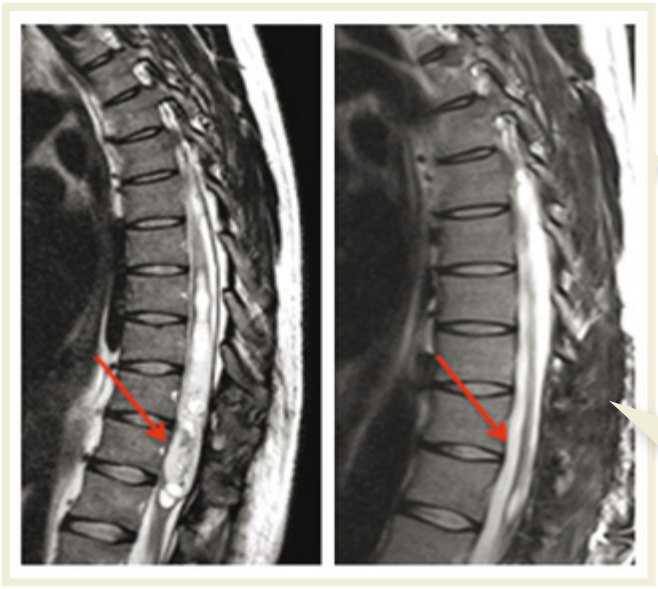
Interdisciplinarity, follow-up and rehabilitation

Treatment of intramedullary and intradural–extramedullary tumours is a surgical domain with superior long-term results. Radiotherapy must be considered in malignant tumours.

Patients with spinal metastasis (all compartments) and primary spinal bone tumours have to be included in an interdisciplinary decision-finding process.



As a general rule, extradural spinal tumours can be treated with radiation or have to be irradiated after primary decompression and stabilisation (photons or protons [e.g. chordomas]). Oncological treatment of primary cancer is mandatory.



Recurrent pilocytic spinal astrocytoma after 13 years with complete resection and excellent neurological results

The follow-up of metastatic spinal tumour diseases relates to the follow-up algorithm of the primary cancer.

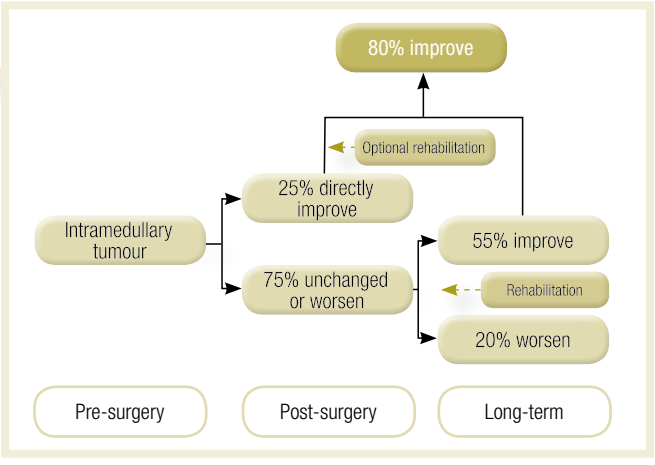
Benign intradural pathologies show recurrence in a low percentage. Therefore MRI control has to be performed initially on a yearly basis, with extended intervals in the long-term follow-up.

In terms of recurrent tumour manifestations, all potential treatment options should be discussed in an interdisciplinary setting.

Neurological deficits from benign intradural lesions (i.e. meningiomas) often improve after surgery, without need for special rehabilitation programmes.

Patients with malignant diseases and reduced life expectancy benefit from a short (one-month) rehabilitation programme to adapt to their new functional status.

Patients with better oncological prognosis benefit from a short intensive rehabilitation programme, followed by physical therapy and occupational therapy, potentially lifelong.



REVISION QUESTIONS

1. On which algorithm does the follow-up of spinal metastasis depend?
2. Which diagnostic method is the first choice in the follow-up of intradural tumours?
3. What proportion of patients improve directly post surgery after resection of spinal intramedullary tumours?

Summary: Management of spinal tumours

- Spinal oncology division compartments with 50% extradural, 40% intradural–extramedullary and 10% intramedullary manifestation
- Spinal neuro-oncology is very similar to cranial neuro-oncology
- Surgical management of spinal cord tumours requires a high degree of specialisation
- Progressive neurological symptoms warrant immediate intervention to prevent progressive to irreversible deficits
- Surgery is recommended in all symptomatic intradural-extramedullary tumours
- Surgery of intramedullary tumours can be performed with minimal morbidity
- Interdisciplinary decision-finding processes are recommended in primary and secondary spinal tumours
- Indications for surgery of primary and secondary spinal tumours are isolated tumour manifestations and/or threatening paraplegia or instability
- Surgery combined with radiotherapy is superior to radiotherapy alone
- Spinal decompression and stabilisation is effective in reduction of pain

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Appendix 1: 2016 WHO Classification and Grading of Tumours of the Central Nervous System

Diffuse astrocytic and oligodendroglial tumours

- Diffuse astrocytoma, IDH-mutant
  - Gemistocytic astrocytoma, IDH-mutant
- Diffuse astrocytoma, IDH-wildtype
- Diffuse astrocytoma, NOS
- Anaplastic astrocytoma, IDH-mutant
- Anaplastic astrocytoma, IDH-wildtype
- Anaplastic astrocytoma, NOS
- Glioblastoma, IDH-wildtype
  - Giant cell glioblastoma
  - Gliosarcoma
  - Epithelioid glioblastoma
- Glioblastoma, IDH-mutant
- Glioblastoma, NOS
- Diffuse midline glioma, H3 K27M–mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Oligodendroglioma, NOS
- Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Anaplastic oligodendroglioma, NOS
- Oligoastrocytoma, NOS
- Anaplastic oligoastrocytoma, NOS

Other astrocytic tumours

- Pilocytic astrocytoma
  - Pilomyxoid astrocytoma
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma
- Anaplastic pleomorphic xanthoastrocytoma

Ependymal tumours

- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
  - Papillary ependymoma
  - Clear cell ependymoma
  - Tanycytic ependymoma
- Ependymoma, *RELA* fusion–positive
- Anaplastic ependymoma

Other gliomas

- Chordoid glioma of the third ventricle
- Angiocentric glioma
- Astroblastoma

Choroid plexus tumours

- Choroid plexus papilloma
- Atypical choroid plexus papilloma
- Choroid plexus carcinoma

Neuronal and mixed neuronal–glial tumours

- Dysembryoplastic neuroepithelial tumour
- Gangliocytoma
- Ganglioglioma
- Anaplastic ganglioglioma
- Dysplastic cerebellar gangliocytoma
  (Lhermitte–Duclos disease)
- Desmoplastic infantile astrocytoma and ganglioglioma
- Papillary glioneuronal tumour
- Rosette-forming glioneuronal tumour
- Diffuse leptomeningeal glioneuronal tumour
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma
- Paraganglioma

Tumours of the pineal region

- Pineocytoma
- Pineal parenchymal tumour of intermediate differentiation
- Pineoblastoma
- Papillary tumour of the pineal region

Embryonal tumours

- Medulloblastoma
- Medulloblastoma, NOS
- *Medulloblastomas, genetically defined*
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH
- *Medulloblastomas, histologically defined*
- Medulloblastoma, classic
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large cell / anaplastic medulloblastoma
- Embryonal tumour with multilayered rosettes, C19MC-altered
- Embryonal tumour with multilayered rosettes, NOS
- Other CNS embryonal tumours
- Medulloepithelioma
- CNS neuroblastoma
- CNS ganglioneuroblastoma
- CNS embryonal tumour, NOS
- Atypical teratoid/rhabdoid tumour
- CNS embryonal tumour with rhabdoid features

Tumours of the cranial and paraspinal nerves

- Schwannoma
- Cellular schwannoma
- Plexiform schwannoma
- Melanotic schwannoma
- Neurofibroma
- Atypical neurofibroma
- Plexiform neurofibroma
- Perineurioma
- Hybrid nerve sheath tumours
- Malignant peripheral nerve sheath tumour (MPNST)
- MPNST with divergent differentiation
- Epithelioid MPNST
- MPNST with perineurial differentiation

Meningiomas

- Meningioma
- Meningioma variants
- Meningothelial meningioma
- Fibrous meningioma
- Transitional meningioma
- Psammomatous meningioma
- Angiomatous meningioma
- Microcystic meningioma
- Secretory meningioma
- Lymphoplasmacyte-rich meningioma
- Metaplastic meningioma
- Chordoid meningioma
- Clear cell meningioma
- Atypical meningioma
- Papillary meningioma
- Rhabdoid meningioma
- Anaplastic (malignant) meningioma

Mesenchymal, non-meningothelial tumours

- Solitary fibrous tumour / haemangiopericytoma
- Haemangioblastoma
- Haemangioma 25
- Epithelioid haemangioendothelioma
- Angiosarcoma
- Kaposi sarcoma
- Ewing sarcoma / peripheral primitive neuroectodermal tumour
- Lipoma
- Angiolipoma
- Hibernoma
- Liposarcoma
- Desmoid-type fibromatosis
- Myofibroblastoma
- Inflammatory myofibroblastic tumour
- Benign fibrous histiocytoma
- Fibrosarcoma
- Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma
- Leiomyoma
- Leiomyosarcoma
- Rhabdomyoma

- Rhabdomyosarcoma
- Chondroma
- Chondrosarcoma
- Osteoma
- Osteochondroma
- Osteosarcoma

Melanocytic tumours

- Meningeal melanocytosis
- Meningeal melanomatosis
- Meningeal melanocytoma
- Meningeal melanoma

Lymphomas

- Diffuse large B-cell lymphoma of the CNS
  - Corticoid-mitigated lymphoma
  - Sentinel lesions
- Immunodeficiency-associated CNS lymphomas
  - AIDS-related diffuse large B-cell lymphoma
  - EBV+ diffuse large B-cell lymphoma, NOS
  - Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- Miscellaneous rare lymphomas in the CNS
  - Low-grade B-cell lymphomas
  - T-cell and NK/T-cell lymphomas
  - Anaplastic large cell lymphoma (ALK+/ALK–)
- MALT lymphoma of the dura

Histiocytic tumours

- Langerhans cell histiocytosis
- Erdheim–Chester disease
- Rosai–Dorfman disease
- Juvenile xanthogranuloma
- Histiocytic sarcoma

Germ cell tumours

- Germinoma
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma
  - Mature teratoma
  - Immature teratoma
- Teratoma with malignant transformation
- Mixed germ cell tumour

Familial tumour syndromes

- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Schwannomatosis
- Von Hippel–Lindau disease
- Tuberous sclerosis
- Li–Fraumeni syndrome
- Cowden syndrome
- Turcot syndrome
  - Mismatch repair cancer syndrome
  - Familial adenomatous polyposis
- Naevoid basal cell carcinoma syndrome
- Rhabdoid tumour predisposition syndrome

Tumours of the sellar region

- Craniopharyngioma
  - Adamantinomatous craniopharyngioma
  - Papillary craniopharyngioma
- Granular cell tumour of the sellar region
- Pituicytoma
- Spindle cell oncocytoma

Metastatic tumours

Appendix 2: Selected treatment schedules

Regimen	Chemotherapy	Dose	Route	Schedule
RT/TMZ->TMZ [1]	Temozolomide, concomitant with radiotherapy	75 mg/m^2	p.o.	7 days per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 days
	Temozolomide, maintenance therapy	150 mg/m^2 for cycle 1, 200 mg/m^2 for subsequent cycles	p.o.	5/28 days, start 4 weeks after end of chemoradiotherapy, for up to 6 cycles
PCV [2,3]	Procarbazine	60 mg/m^2	p.o.	Daily on Days 8–21 of every 6–8-week cycle
	CCNU (lomustine)	110 mg/m^2	p.o.	Day 1 of every 6–8-week cycle
	Vincristine	1.4 mg/m^2 (maximal 2 mg)	i.v.	Days 8 and 29 of every 6–8-week cycle
CCNU [4]	CCNU (lomustine)	110 mg/m^2	p.o.	Day 1 of every 6-week cycle

Abbreviations: i.v., intravenous; p.o., oral.

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Image sources

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Figure 11. Adapted from Ostrom QT, et al. Neuro Oncol 2014;16:896-913.

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Chapter 10
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Chapter 11
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Index

Note: Abbreviations used in the index are listed on page ix

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NEURO-ONCOLOGY

ESSENTIALS *for* CLINICIANS

edited by Matthias Preusser & Michael Weller

Neuro-Oncology is part of the "Essentials for Clinicians" series produced by the European Society for Medical Oncology (ESMO). Although primary brain tumours are relatively infrequent and are not encountered on an everyday basis outside of specialised oncology units, basic knowledge of the classification and management standards of gliomas are important to ensure adequate patient care in every clinical setting. Importantly, this book also covers secondary central nervous system (CNS) affections of cancers and provides a clearly structured and concise overview of management strategies for brain metastases and leptomeningeal carcinomatosis, which are critical manifestations of advanced cancer and require competent care. *Neuro-Oncology: Essentials for Clinicians* is structured into a section covering the basics of what every oncologist should know and a section providing more advanced information and novel developments. The high quality illustrations and clear structure make the book an easy-to-use and accessible source of knowledge, and provide a balanced and up-to-date knowledge of the current state of the art for students and physicians interested in cancers of the CNS.

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