台北榮總神經腫瘤診療指引
惡性腦瘤

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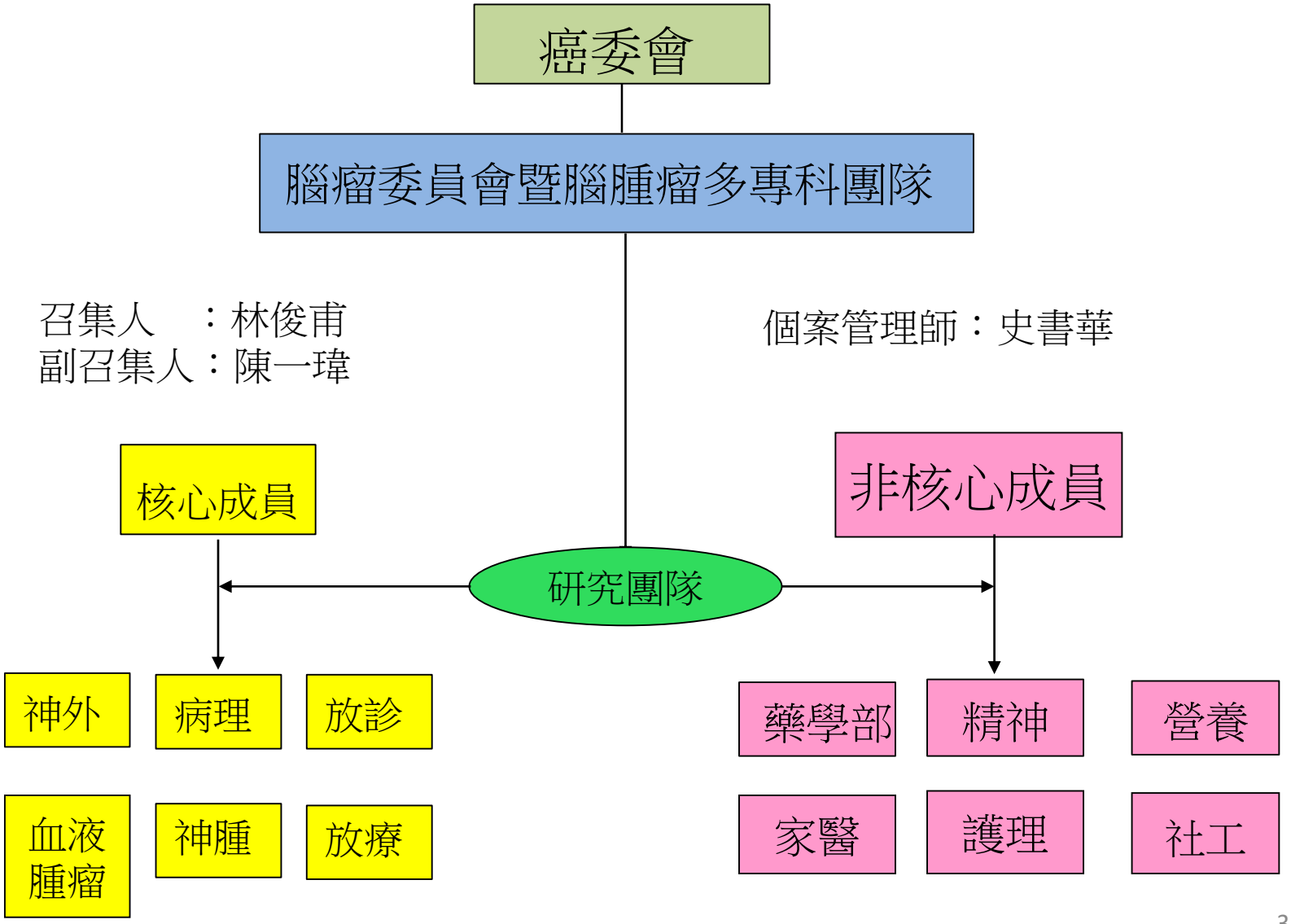
修訂日期：2019.09.16
修訂日期：2020.09.21
修訂日期：2021.10.25
修訂日期：2022.10.17

Multidisciplinary Team

- Neurosurgeon (Adult & Pediatric)
- Radiation Oncologist
- Neuro-Oncologist & Medical Oncologist
- Pathologist
- Neuro-radiologist (Adult & Pediatric)
- Nurses (Adult & Pediatric)
- Case Manager (Adult & Pediatric)
- Social Workers (Adult & Pediatric)
- Pharmacist
- Psychiatry
- Dietitian
- Researchers

臺北榮總腦神經腫瘤多專科醫療團隊



腦神經腫瘤多專科醫療團隊		
團隊召集人：林俊甫主治醫師		
團隊副召集人：陳一瑋主治醫師		
（核心成員）		
神經外科	許秉權	主任
	林俊甫	主治醫師
	王瑞鐸	主治醫師
病理檢驗部	林士傑	主治醫師
放射線部	吳嘉紘	主治醫師
	游鎧蔚	主治醫師
腫瘤醫學部	陳一瑋	主治醫師
	吳元宏	主治醫師
	康鈺玫	主治醫師
神經腫瘤	李宜燕	主治醫師
個案管理師	史書華	護理師
（非核心成員）		
家醫部（安寧共照）	林明慧	主治醫師
	黃茱楹	護理師
護理部	林美玲	督導長
	相關護理師	
精神部	劉英杰	主治醫師
藥學部	林家潔	藥師
營養部	舒宜芳	營養師
社工室	朱敏蓮	社工師
更新日期：2022/07/18		

Glioblastoma (GBM)

- Glioma 27% of all tumors
- 80% of malig. tumors
- Two variants: giant cell glioblastoma, gliosarcoma
- Treatment:
  - Surgery: maximal resection without deficit
  - Radiation therapy
  - Chemotherapy: Stupp Protocol: CCRT+Adjuvant Temozolomide or combine Avastin
  - Clinical trial
- Prognosis: survival 1-2 yrs with aggressive treatment

Pre-treatment

- Clinical history, physical and neurological exam
- CBC+D/C, PT/aPTT, blood chemistry
- MRI of brain (with/without MR Spectroscopy, Perfusion study)
- Optional studies
  - CT of brain
  - FDG PET
  - Visual Field
  - Neuropsychological test
  - Electroencephalography
  - Electromyography, somatosensory evoked potential, motor evoked potential

PRINCIPLES OF BRAIN TUMOR SURGERY

Guiding Principles
- Gross total resection (GTR) when appropriate
- Minimal surgical morbidity
- Accurate diagnosis

Factors
- Age
- Performance status (PS)
- Feasibility of decreasing the mass effect with surgery
- Resectability, including number of lesions, location of lesions, time since last surgery (recurrent patients)
- New versus recurrent tumor
- Suspected pathology – benign vs. malignant, possibility of other non-cancer diagnoses, projected natural history
- For patients with *IDH1* mutations, there is evidence to suggest that a supramarginal resection is most appropriate, which would include not only enhancing areas but also T2/flair areas when appropriate in terms of a safe surgical approach, with the use of any and all surgical adjuncts possible.[1]

Options
- GTR where feasible
- Stereotactic biopsy[2]
- MRI-guided laser interstitial thermal therapy (LITT)[3-8](category 2B)
  - LITT may be considered for patients who are poor surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases, radiation necrosis, and recurrent glioblastoma.
- Open biopsy/debulking followed by planned observation or adjuvant therapy
- Systemc therapy implants, when indicated (See footnote cc on GLIO-5)
- Carmustine polymer wafer may be placed in the tumor resection cavity of patients.[1,9]

Tissue
- Sufficient tissue to pathologist for neuropathology evaluation and molecular correlates
- Frozen section analysis when possible to help with intraoperative decision-making
- Review by experienced neuropathologist
- Postoperative brain MRI should be performed within 48 hours for gliomas and other brain tumors to determine the extent of resection. Postoperative spine MRI should be delayed by at least 2–3 weeks to avoid post-surgical artifacts.
- The extent of resection should be judged on the postoperative study and used as a baseline to assess further therapeutic efficacy or tumor progression.

Surgical Adjuncts
- A number of surgical adjuncts can be considered to facilitate safe brain tumor surgery, including use of an intraoperative microscope, frameless stereotactic image guidance, preoperative functional MRI and/or diffusion tensor imaging (DTI) fiber tracking, awake craniotomy, motor and/or speech mapping, intraoperative MRI, and intraoperative fluorescence-guided surgery with 5-ALA.

See refererences on next page

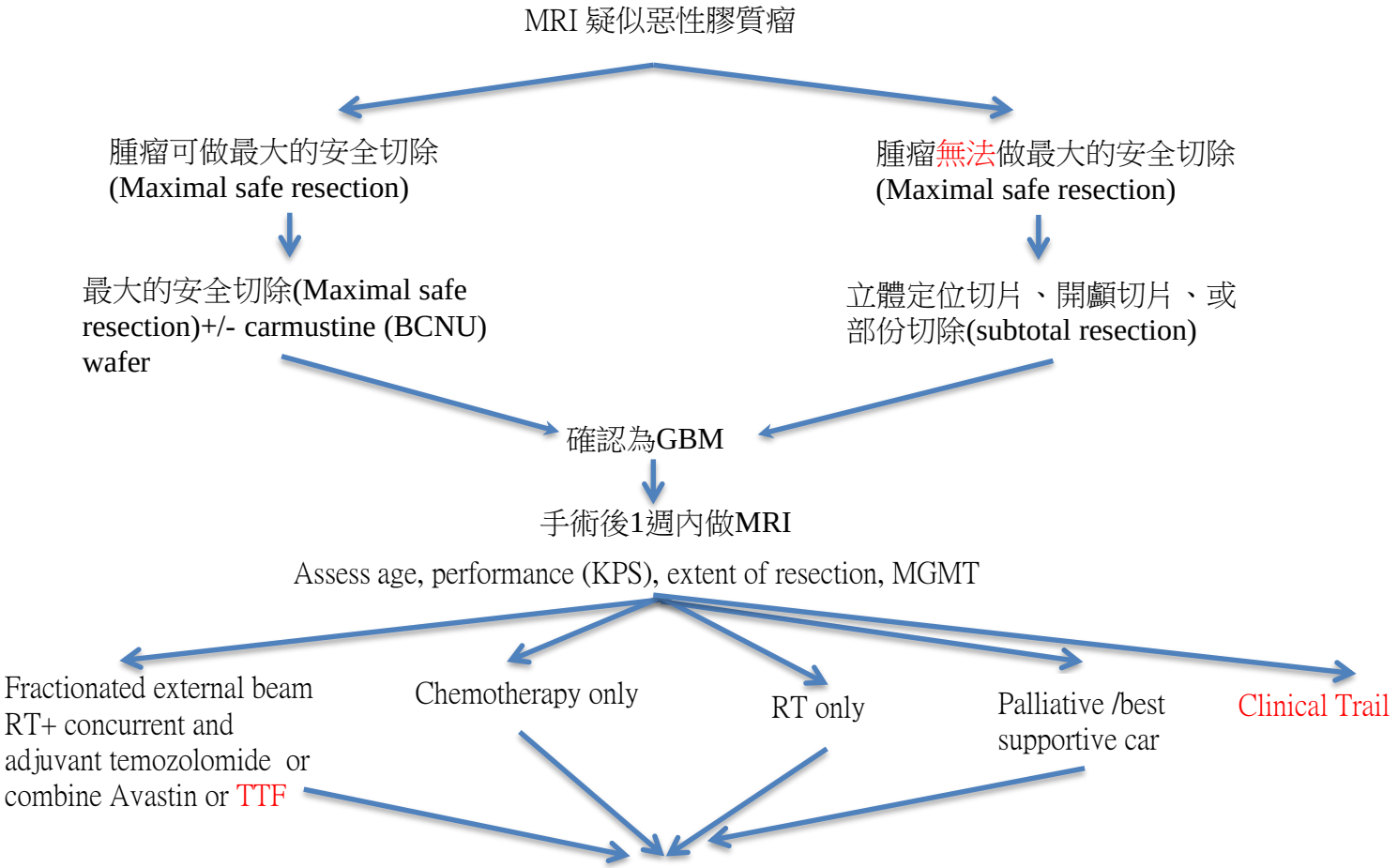
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

REFERENCES

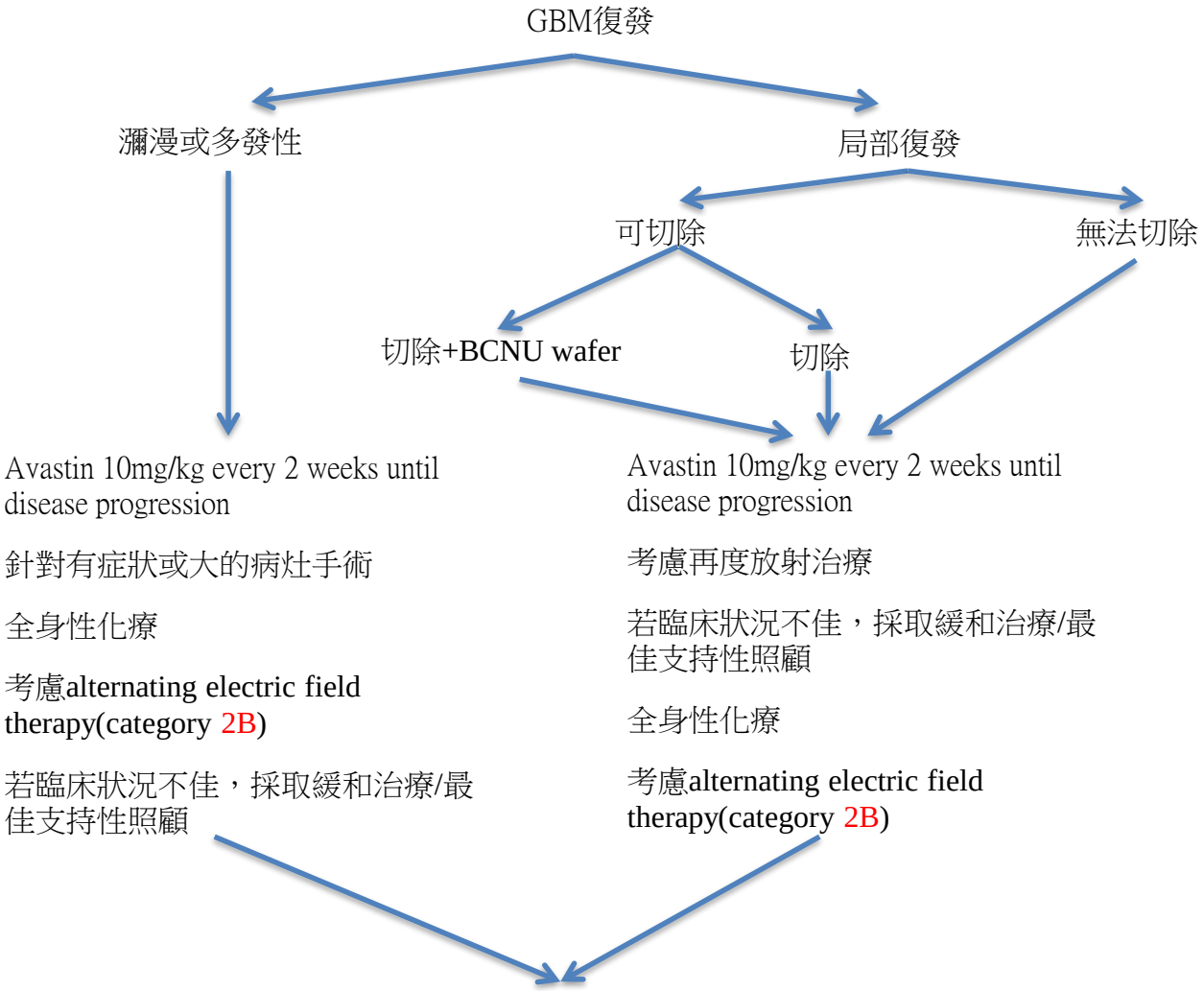
[1] Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. Clin Cancer Res 2007;13:3637-3641.
[2] Mohammadi AM, Sharma M, Beaumont TL, et al. Upfront magnetic resonance imaging-guided stereotactic laser-ablation in newly diagnosed glioblastoma: A multicenter review of survival outcomes compared to a matched cohort of biopsy-only patients. Neurosurgery 2019;85:762-772.
[3] Kim AH, Tatter S, Rao G, et al. Laser ablation of abnormal neurological tissue using robotic neuroblate system (laantern): 12-month outcomes and quality of life after brain tumor ablation. Neurosurgery 2020;87:E338-E346.
[4] Shah AH, Semonche A, Eichberg DG, et al. The role of laser interstitial thermal therapy in surgical neuro-oncology: Series of 100 consecutive patients. Neurosurgery 2020;87:266-275.
[5] Bastos DCA, Rao G, Oliva ICG, et al. Predictors of local control of brain metastasis treated with laser interstitial thermal therapy. Neurosurgery 2020;87:112-122.
[6] Sujijantarat N, Hong CS, Owusu KA, et al. Laser interstitial thermal therapy (LITT) vs. bevacizumab for radiation necrosis in previously irradiated brain metastases. J Neurooncol 2020;148:641-649.
[7] Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: A multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. J Neurosurg 2018;130:804-811.
[8] Kamath AA, Friedman DD, Akbari SHA, et al. Glioblastoma treated with magnetic resonance imaging-guided laser interstitial thermal therapy: safety, efficacy, and outcomes. Neurosurgery 2019;84:836-843.
[9] Brandes AA, Tosoni A, Amista P, et al. How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. Neurology 2004;63:1281-1284.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment Guideline for GBM



Treatment Guideline for Recurrent GBM



Principle of Surgery

- Extent of Resection
  - Maximal safe microsurgical resection
  - Intraoperative neuromonitoring may be used to reduce morbidity
  - 5-ALA, intra-op sonography or MRI may be used to facilitate adequate resection

Surgical management of newly diagnosed glioblastoma in adults: role of cytoreductive surgery

Timothy C. Ryken · Bruce Frankel · Terrance Julien · Jeffrey J. Olson

J Neurooncol (2008) 89:255–258

Level II recommendation

Based on the prospective data available and a general consensus in the retrospective data it is recommended that for newly diagnosed supratentorial malignant glioma in adults that the "maximal safe resection" be undertaken (i.e. the maximal cytoreductive procedure provided that post-operative neurological deficit can be minimized).

Kaplan-Meier Survival Plots for Patients Diagnosed With GBM

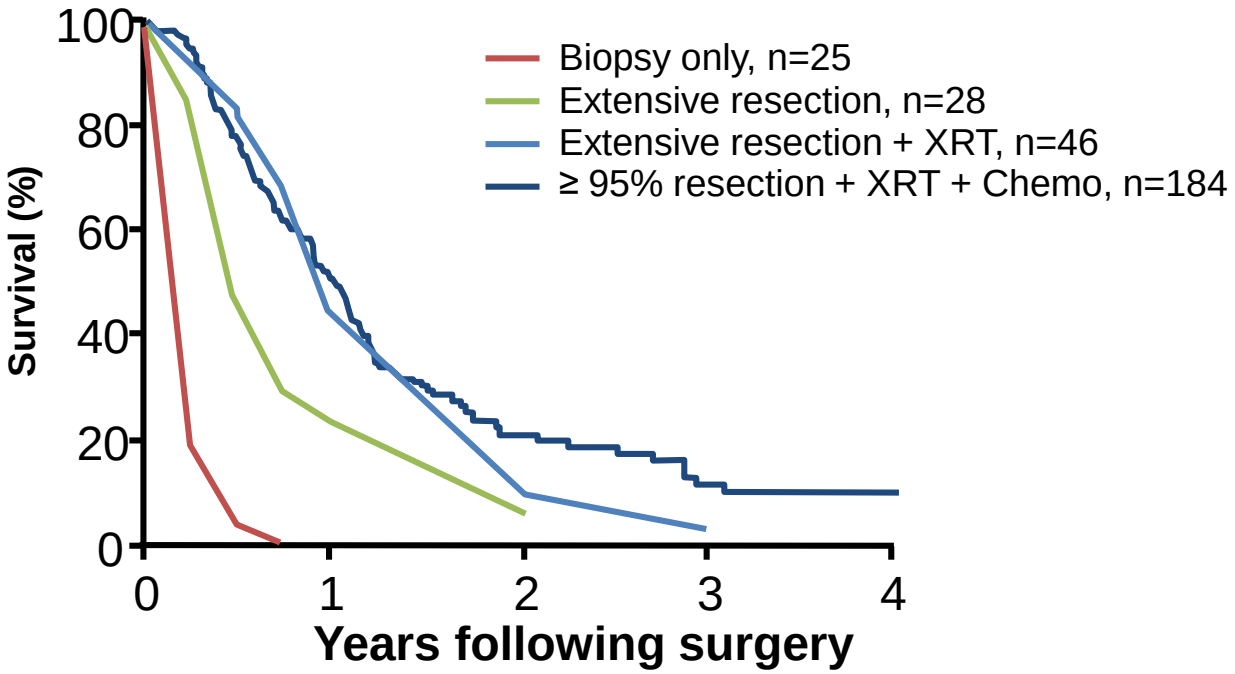
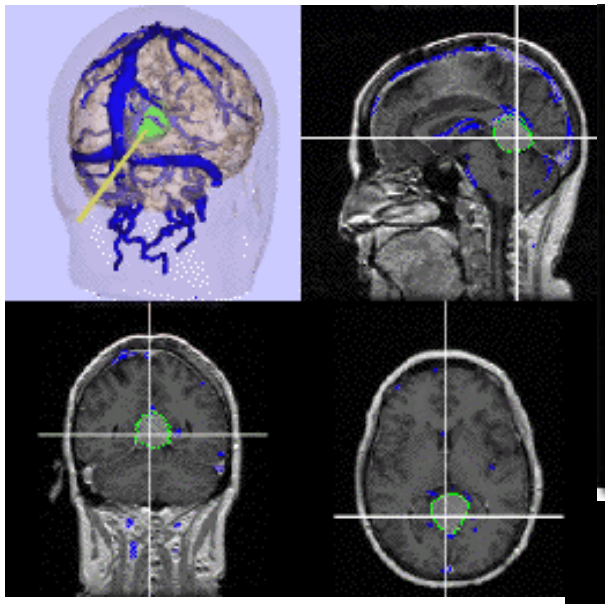
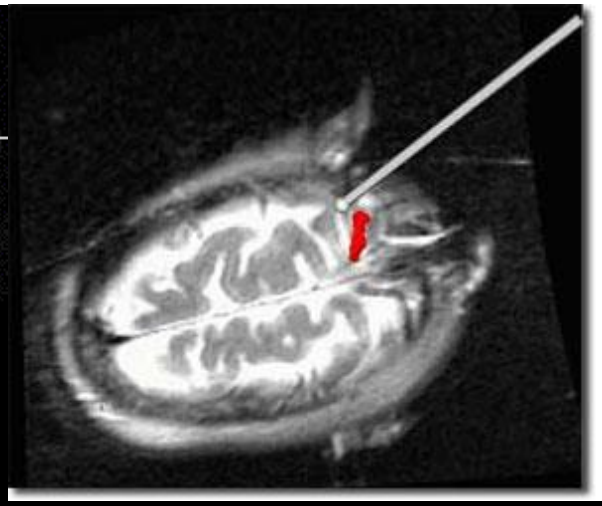


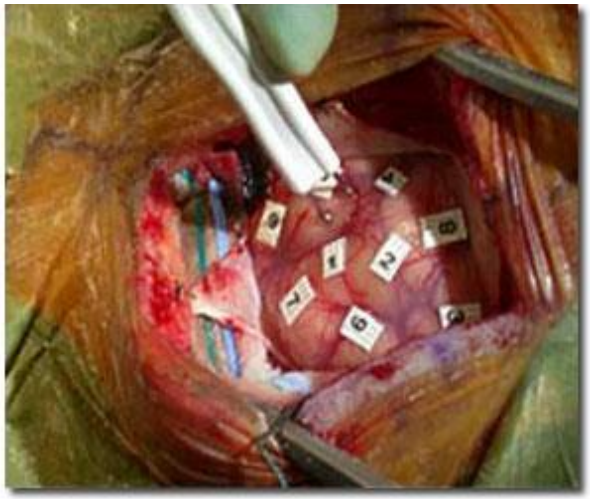
Fig. 3. Kaplan-Meier survival plots for patients diagnosed with GBM. Curves *A, B,* and *C* are historical data from Jelsma and Bucy published in 1967 before the availability of MRI scans: biopsy only (*A*), extensive resection (undefined) (*B*), and extensive resection followed by radiation therapy (*C*). Curve D is current data from the M.D. Anderson Cancer Center on patients with >95% resection (by volumetric MRI measurements) followed by both radiation therapy and chemotherapy. Although there are essentially no long-term survivors, removal of tumor mass clearly increases longevity.

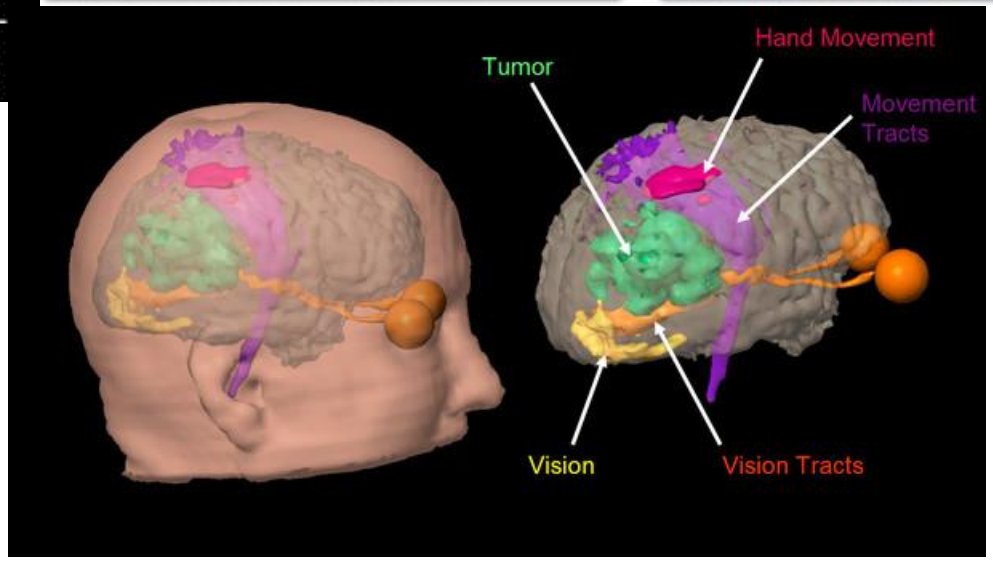
Holland EC. Proc Natl Acad Sci U S A. 2000;97:6242-6244.

Achieving maximally safe resection

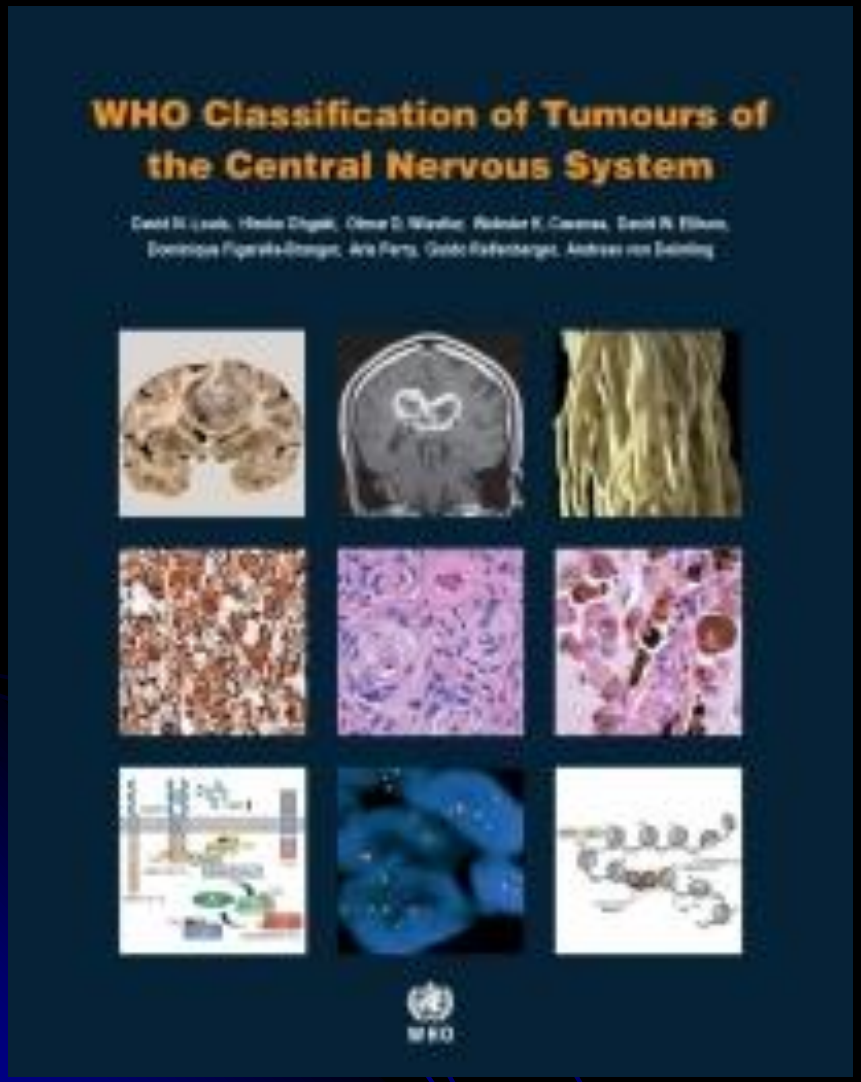




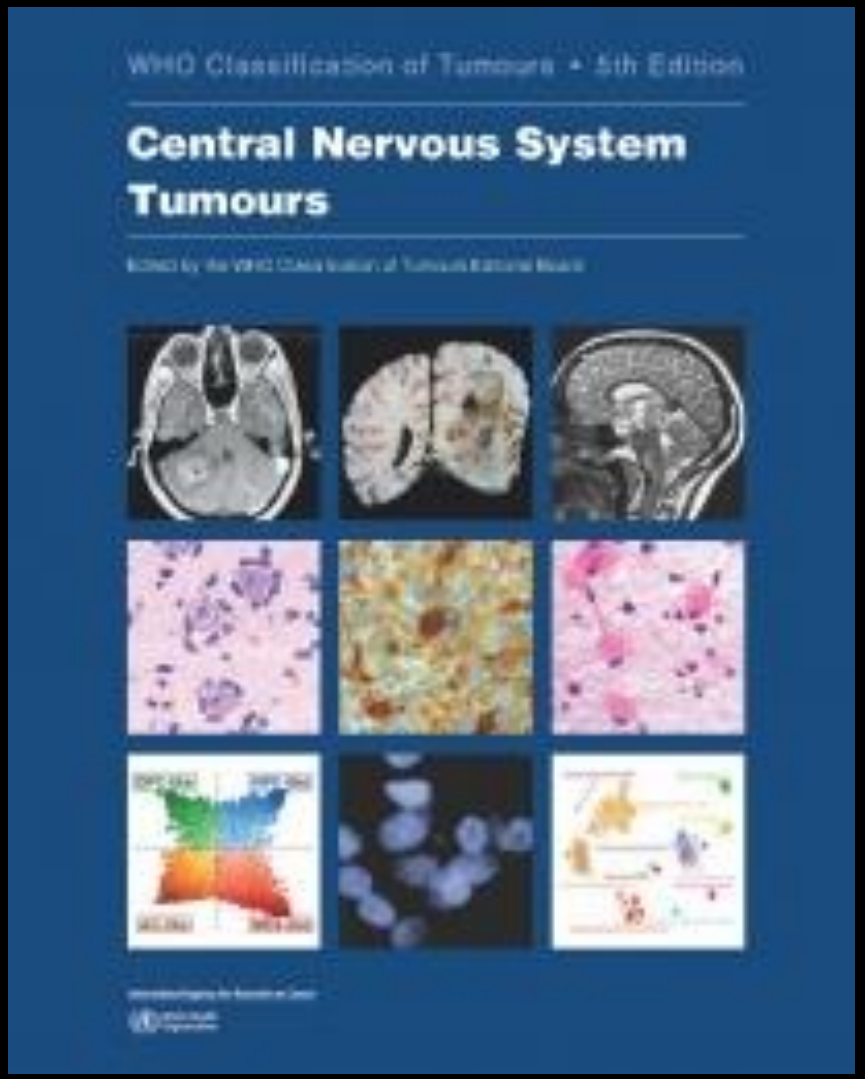




Revised 4th ed. 2016



5th ed. 2021



Brain Tumor Pathol. 2022 Mar 22.

Brain Tumor Pathology
https://doi.org/10.1007/s10014-022-00428-3

EDITORIAL

The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: the 10 basic principles

Takashi Komori[1]

第36回日本脳腫瘍病理学会学術集会
会長 小森隆司
東京都立神経病院 検査科部長

The 10 basic principles

- Histogenetic vs. molecular classification
- Integrated diagnosis
- Essential and desirable diagnostic criteria
- NOS and NEC diagnoses
- Grading across vs. grading within types
- Combined histological and molecular grading
- Pediatric-type vs. adult-type diffuse gliomas
- Use of type/subtype instead of entity/variant
- Gene and protein nomenclature
- DNA methylation profiling and newly recognized tumor types

Table 1 2021 WHO Classification of Tumors of the Central Nervous System. Provisional Entities are in Italics

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition	
Gliomas, glioneuronal tumors, and neuronal tumors	Glioneuronal and neuronal tumors
Adult-type diffuse gliomas	Ganglioglioma
Astrocytoma, IDH-mutant	Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	Dysembryoplastic neuroepithelial tumor
Glioblastoma, IDH-wildtype	*Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters*
Pediatric-type diffuse low-grade gliomas	Papillary glioneuronal tumor
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	Rosette-forming glioneuronal tumor
Angiocentric glioma	Myxoid glioneuronal tumor
Polymorphous low-grade neuroepithelial tumor of the young	Diffuse leptomeningeal glioneuronal tumor
Diffuse low-grade glioma, MAPK pathway-altered	Gangliocytoma
Pediatric-type diffuse high-grade gliomas	Multinodular and vacuolating neuronal tumor
Diffuse midline glioma, H3 K27-altered	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Diffuse hemispheric glioma, H3 G34-mutant	Central neurocytoma
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	Extraventricular neurocytoma
Infant-type hemispheric glioma	Cerebellar liponeurocytoma
Circumscribed astrocytic gliomas	Ependymal tumors
Pilocytic astrocytoma	Supratentorial ependymoma
High-grade astrocytoma with piloid features	Supratentorial ependymoma, *ZFTA* fusion-positive
Pleomorphic xanthoastrocytoma	Supratentorial ependymoma, *YAP1* fusion-positive
Subependymal giant cell astrocytoma	Posterior fossa ependymoma
Chordoid glioma	Posterior fossa ependymoma, group PFA
Astroblastoma, *MN1*-altered	Posterior fossa ependymoma, group PFB
	Spinal ependymoma
	Spinal ependymoma, *MYCN*-amplified
	Myxopapillary ependymoma
	Subependymoma

Table 1 Diffuse gliomas in WHO CNS 5

	CNS WHO grade
Adult-type diffuse gliomas	
Astrocytoma, IDH-mutant	2/3/4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2/3
Glioblastoma, IDH-wildtype	4
Pediatric-type diffuse low-grade gliomas	
Diffuse astrocytoma, *MYB*-or *MYBL1*-altered	1
Angiocentric glioma	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffuse low-grade glioma, MAPK pathway-altered	NA
Pediatric-type diffuse high-grade gliomas	
Diffuse midline glioma, H3 K27-altered	4
Diffuse hemispheric glioma, H3 G34-mutant	4
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4
Infant-type hemispheric glioma	NA

NA not assigned

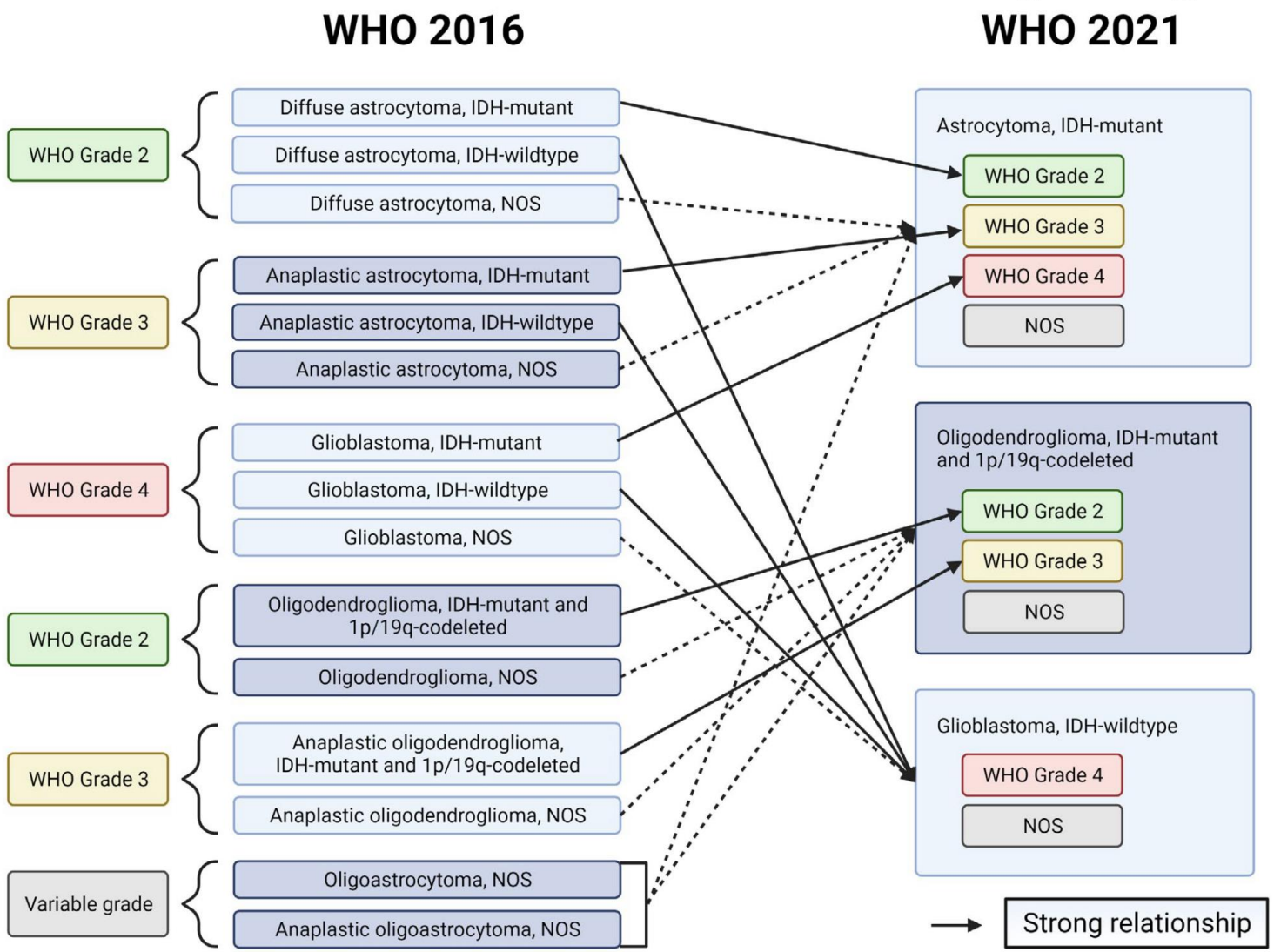


FIGURE 1 Schematic showing how the disease entities from WHO 2016 is now defined in WHO 2021. Solid lines denote strong correlations between the two classifications, while dotted lines denote how a WHO 2016 disease entity would likely, but not definitively, be defined

Brain Pathology. 2022;00:e13062.
https://doi.org/10.1111/bpa.13062

Box 2.01 Diagnostic criteria for astrocytoma, IDH-mutant

Essential:

A diffusely infiltrating glioma

AND

IDH1 codon 132 or *IDH2* codon 172 missense mutation

AND

Loss of nuclear ATRX expression or *ATRX* mutation

OR

Exclusion of combined whole-arm deletions of 1p and 19q

Desirable:

TP53 mutation or strong nuclear expression of p53 in > 10% of tumour cells

Methylation profile of astrocytoma, IDH-mutant

Astrocytic differentiation by morphology

Box 2.02 Diagnostic criteria for oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Essential:

A diffusely infiltrating glioma

AND

IDH1 codon 132 or *IDH2* codon 172 missense mutation[a]

AND

Combined whole-arm deletions of 1p and 19q

Desirable:

DNA methylome profile of oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Retained nuclear expression of ATRX

TERT promoter mutation

[a]IDH mutation analysis may not be required when DNA methylome profiling is performed and unequivocally assigns the tumour to the methylation class oligodendro-

Box 2.03 Diagnostic criteria for glioblastoma, IDH-wildtype

Essential:

An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma

AND

One or more of the following:

- Microvascular proliferation
- Necrosis
- *TERT* promoter mutation
- *EGFR* gene amplification
- +7/−10 chromosome copy-number alterations

Desirable:

DNA methylation profile of glioblastoma, IDH-wildtype

Box 2.01 Diagnostic criteria for astrocytoma, IDH-mutant

Essential:

A diffusely infiltrating glioma

AND

IDH1 codon 132 or *IDH2* codon 172 missense mutation

AND

Loss of nuclear ATRX expression or *ATRX* mutation

OR

Exclusion of combined whole-arm deletions of 1p and 19q

Desirable:

TP53 mutation or strong nuclear expression of p53 in > 10% of tumour cells

Methylation profile of astrocytoma, IDH-mutant

Astrocytic differentiation by morphology

Table 2. The definition of astrocytoma, IDH-mutant.

• Astrocytoma, IDH-mutant, grade 2
A diffusely infiltrative astrocytic glioma that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or low. Microvascular proliferation, necrosis, and CDKN2A/B homozygous deletions are absent
• Astrocytoma, IDH-mutant, grade 3
A diffusely infiltrative astrocytic glioma that exhibits focal or dispersed anaplasia and displays significant mitotic activity. Microvascular proliferation, necrosis and CDKN2A/B homozygous deletions are absent
• Astrocytoma, IDH-mutant, grade 4
A diffusely infiltrative astrocytic glioma that exhibits microvascular proliferation or necrosis or CDKN2A/B homozygous deletion or any combination of these features

Laboratory Investigation (2022) 102:126–133

COLLEGE of AMERICAN PATHOLOGISTS
Laboratory Quality Solutions

Molecular Biomarker Testing for the Diagnosis of Diffuse Gliomas

Statements and Strengths of Recommendations

SUMMARY OF RECOMMENDATIONS

Guideline Statement	Strength of Recommendation
1. Isocitrate dehydrogenase (IDH) mutational testing must be performed on all diffuse gliomas (DG).	Strong Recommendation
2. ATRX chromatin remodeler (ATRX) status should be assessed in all IDH-mutant DG unless they show 1p/19q codeletion.	Strong Recommendation
3. Tumor protein p53 (TP53) status should be assessed in all IDH-mutant DG unless they show 1p/9q codeletion.	Conditional Recommendation
4. 1p/19q codeletion must be assessed in IDH-mutant DG unless they show ATRX loss or *TP53* mutations.	Strong Recommendation
5. *Cyclin-dependent kinase inhibitor 2A (CDKN2A)/cyclindependent kinase inhibitor 2B (CDKN2B)* homozygous deletion testing should be performed on IDH-mutant astrocytomas.	Conditional Recommendation
6. *O-6-methylguanine-DNA methyltransferase (MGMT)* promoter methylation testing should be performed on all glioblastoma (GBM), IDH-wild type (WT).	Strong Recommendation
7. For IDH-mutant DG, *MGMT* promoter methylation testing may not be necessary.	Conditional Recommendation
8. *TERT* promoter mutation testing may be used to provide further support for the diagnosis of oligodendroglioma and IDH-WT GBM.	Conditional Recommendation
9. For histologic grade 2-3 DG that are IDH-WT, testing should be performed for whole chromosome 7 gain/whole chromosome 10 loss, *epidermal growth factor (EGFR)* amplification, and *telomerase reverse transcriptase (TERT)* promoter mutation to establish the molecular diagnosis of glioblastoma (GBM), IDH-WT, grade 4.	Strong Recommendation
10. Histone 3 (H3) K27M testing must be performed in DG that involve the midline in the appropriate clinical and pathologic setting.	Strong Recommendation
11. H3 G34 testing may be performed in pediatric and young adult patients with IDH-WT DG.	Conditional Recommendation
12. *B-Raf proto-oncogene (BRAF)* mutation testing (V600) may be performed in DG that are IDH-WT and H3-WT.	Conditional Recommendation
13. *MYB proto-oncogene (MYB)/ MYB-like (MYBL1)* and *fibroblast growth factor receptor 1 (FGFR1)* testing may be performed in children and young adults with DG that are histologic grade 2-3 and are IDH-WT and H3-WT.	Conditional Recommendation

Brat DJ, Aldape K, Bridge JA, et al. Molecular biomarker testing for the diagnosis of diffuse gliomas: Guideline from the College of American Pathologists in collaboration with the American Association of Neuropathologists, Association of Molecular Pathology, and Society for Neuro-Oncology. Arch Pathol Lab Med. Published online February 17, 2022. doi:10.5858/arpa.2021-0295-CP

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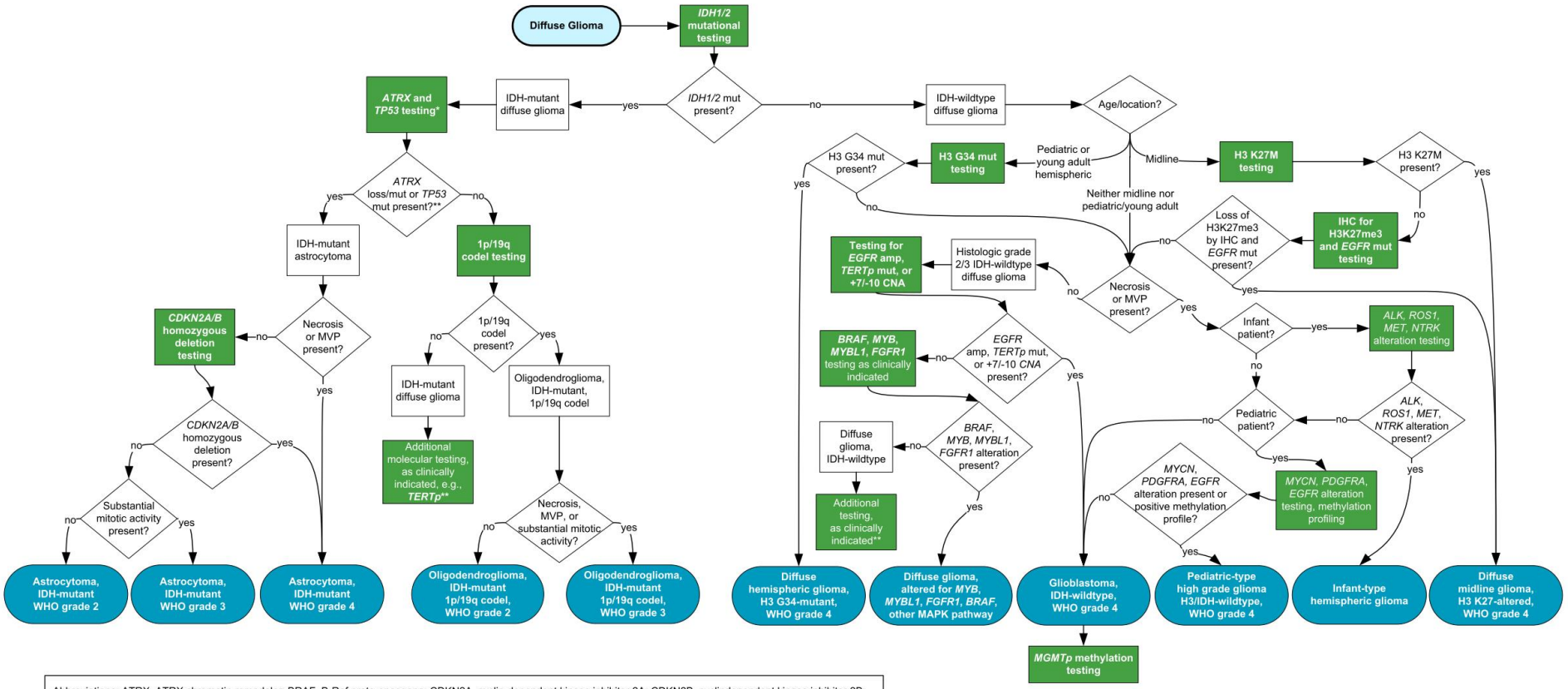
Molecular Biomarker Testing for the Diagnosis of Diffuse Gliomas: Algorithm



Abbreviations: ATRX, ATRX chromatin remodeler; BRAF, B-Raf proto-oncogene; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDKN2B, cyclindependent kinase inhibitor 2B; DGs, diffuse gliomas; EGFR, epidermal growth factor; FGFR1, fibroblast growth factor receptor 1; GBM, glioblastoma; H3, histone 3; IDH, isocitrate dehydrogenase; MGMT, O-6-methylguanine-DNA methlytransferase; MYB, MYB proto-oncogene; MYBL1, MYB-like; TERT, telomerase reverse transcriptase; TP53, tumor protein p53; WT, wild-type; Microvascular proliferation (MVP); Amplification (Amp); Mutation (mut); copy number alteration (CNA); MGMT promoter (MGMTp); Codeletion (Codel); TERT Promoter (TERTp)

Blue indicates WHO defined entities; Green indicates recommended tests; Italic indicates good practice statements
*Some institutions/laboratories may prefer to perform 1p/19q codeletion as the initial step for IDH-mutant gliomas. See recommendations 2-4 in the guideline manuscript.
**Additional molecular biomarker testing and DNA methylation profiling maybe helpful in establishing a diagnosis for challenging cases

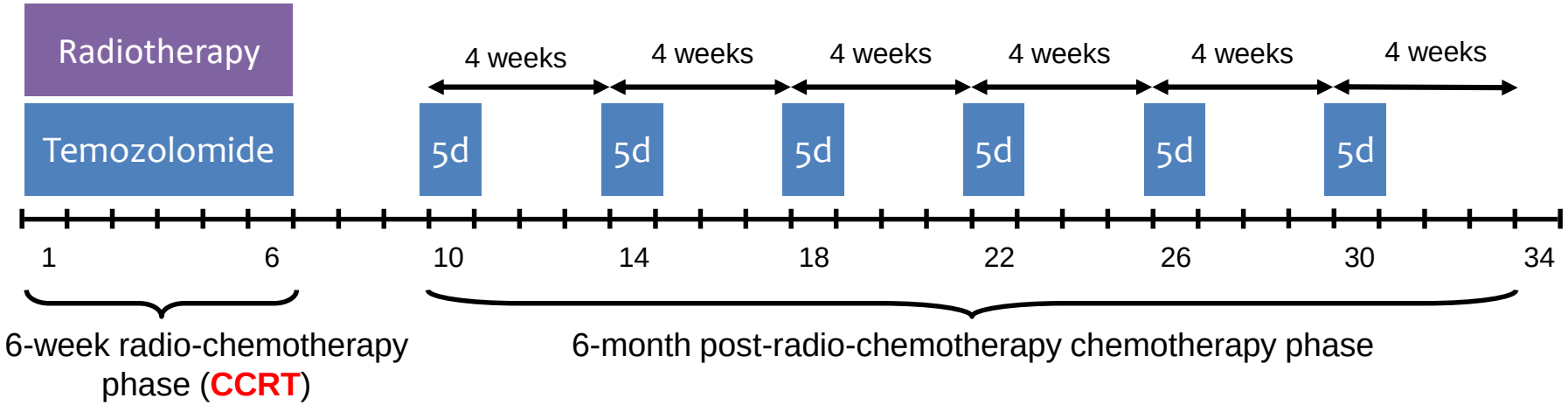
Brat DJ, Aldape K, Bridge JA, et al. Molecular biomarker testing for the diagnosis of diffuse gliomas: Guideline from the College of American Pathologists in collaboration with the American Association of Neuropathologists, Association of Molecular Pathology, and Society for Neuro-Oncology. Arch Pathol Lab Med. Published online February 17, 2022. doi:10.5858/arpa.2021-0295-CP

Systemic adjuvant chemotherapy with temozolomide

Systemic adjuvant chemotherapy with temozolomide is standard care for patients with newly-diagnosed glioblastoma

Oral alkylating agent that readily crosses the blood-brain barrier

Treatment involves a postoperative radio-chemotherapy phase and a subsequent chemotherapy phase[1]



Radio-chemotherapy phase
Radiation therapy: 60Gy to tumour volume plus 2–3cm margin
Temozolomide: 75mg/m^2/day for up to 42 days

Post-radio-chemotherapy chemotherapy phase
Temozolomide: 150–200mg/m^2/day on days 1–5 for of six 4-week cycles

1. Stupp, et al. N Engl J Med 2005

Systemic adjuvant chemotherapy with temozolomide

Radiation therapy plus temozolomide improves survival versus radiation therapy alone[1]

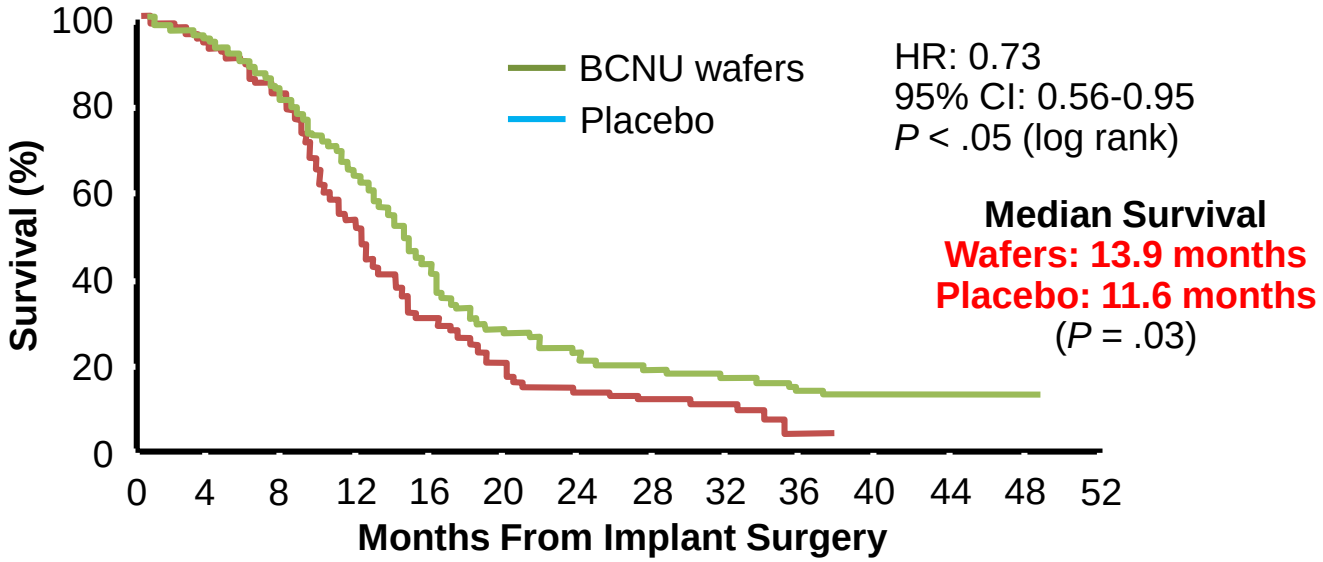
Unadjusted HR for death in radiation therapy + temozolomide group versus radiation therapy group: 0.63 (95% CI: 0.52–0.75)

Variable	Radiation therapy alone (n=286)	Radiation therapy plus temozolomide (n=287)
Median OS, months (95% CI)	**12.1 (11.2–13.0)**	**14.6 (13.2–16.8)**
OS, % (95% CI)		
6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median PFS, months (95% CI)	**5.0 (4.2–5.5)**	**6.9 (5.8–8.2)**
PFS, % (95% CI)		
6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

1. Stupp, et al. N Engl J Med 2005

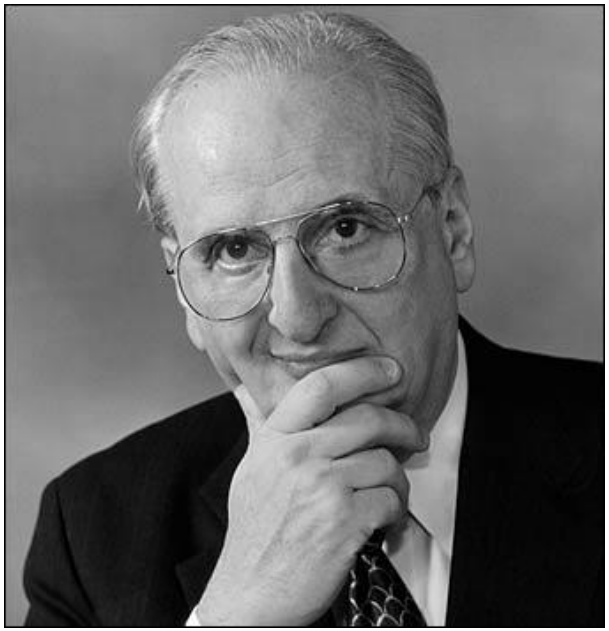
Adjuvant Treatment With BCNU Wafers (Gliadel Wafers®)

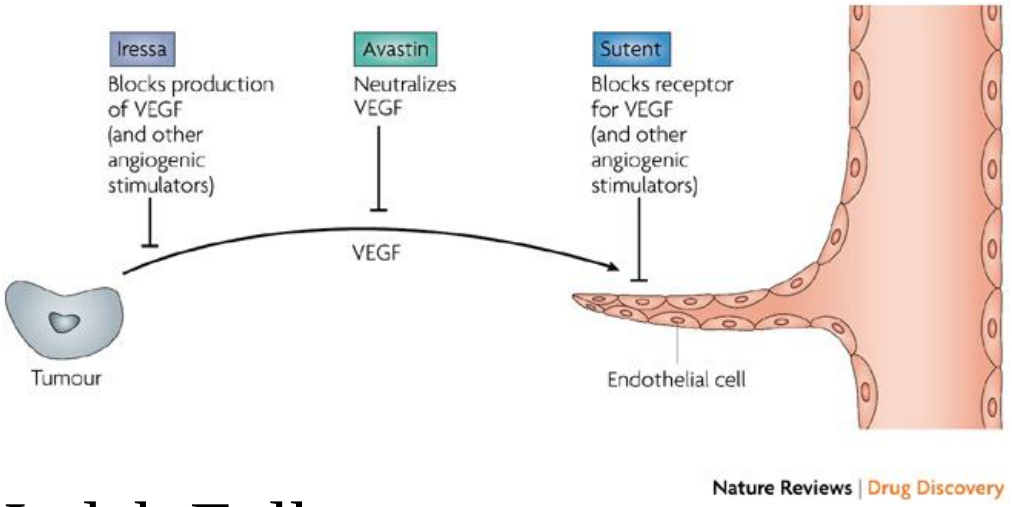
- BCNU (carmustine)-impregnated biodegradable wafers are implanted in the site of resection to deliver chemotherapy locally
  - Approved for treatment of newly diagnosed and recurrent GBM
- Significantly improved survival seen in phase III study (N = 240) of patients with newly diagnosed malignant gliomas



Westphal M, et al. Neuro Oncol. 2003;5:79-88.

The emergence of anti-angiogenesis therapy



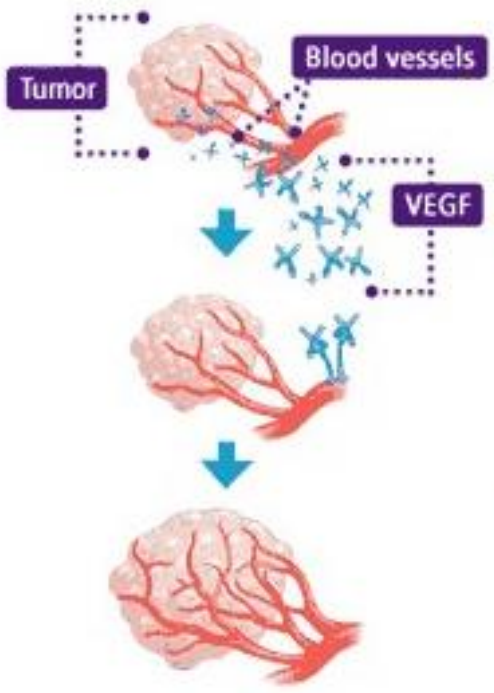


Judah Folkman.

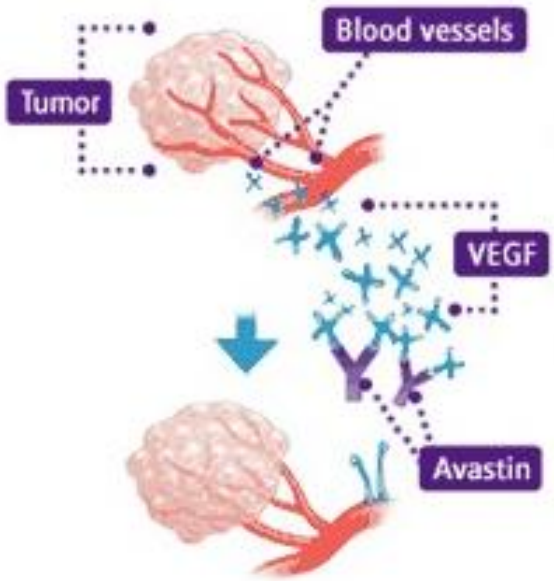
- In the 1970s, proposed that a cancer could be kept in check by cutting off its blood supply. Encountered significant opposition from the scientific community. It was widely believed that tumors grew along preexisting blood vessels.

- Subsequently identified tumor secreted factors that induce angiogenesis. Therapy developed against these factors. Topic of research in over 1,000 labs.

Bevacizumab (Avastin)



- Tumor continuously produces a protein, VEGF
- VEGF binds to receptors on nearby blood vessels
- Binding to receptors creates new blood vessels, which help the tumor grow and spread



- Tumor continuously produces a protein, VEGF
- Avastin attaches to VEGF, preventing it from binding to receptors

With Avastin:

- Existing blood vessels may shrink away from the tumor
- New blood vessels may be kept from forming, potentially helping to keep the tumor from growing and spreading

Clinical Application of Bevacizumab

- Avastin (Bevacizumab) 100mg / 4ml
  17600 NTD /amp
- For relapsed GBM: bevacizumab 10mg per Kg in NS 100ml IV for 90mins ST D1
  q2wks until disease progression or unacceptable toxicity
- no increased risk of intracranial hemorrhage with the concurrent use of bevacizumab and anticoagulants
- suspended within 4 to 6 wk of surgery.
- Monitor BP, proteinuria, creatinine every cycle or every other cycle.
- duration? combination? optimal dosage? patient selection? Radiographic/Lab response criteria?

Chamberlain M, Cancer, 116:3988-99(2010)

Noninvasive Application of Alternating Electric Fields in Glioblastoma: A Fourth Cancer Treatment Modality

By Philip H. Gutin, MD, and Eric T. Wong, MD

Overview: **Tumor treating fields (TTF) therapy is a novel antimitotic, electric field–based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is now a U.S. Food and Drug Administration (FDA)–approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.**

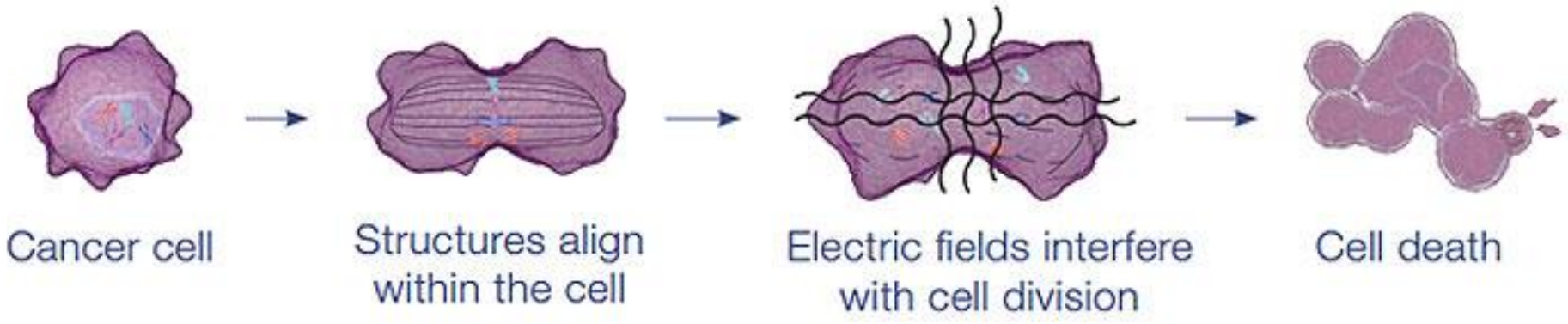


Table 3. Clinical Evidence Overview

Indication (Analysis Group)	Trial Phase (# of Subjects) Analysis	Overall Survival (Months) TTF	Overall Survival (Months) Chemo	Hazard Ratio (p)	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) TTF	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) Chemo	P value	References
Recurrent GBM (at first relapse)	Phase I-II (n = 10) *ITT Analysis*	14.5 m	6.0 m*	Non-randomized	50%	15%*	NA	*Proc Natl Acad Sci U S A*, 2007[5]
Recurrent GBM (at second and fourth relapse)	Phase III (n = 237) *ITT analysis*	6.6 m	6.0 m	HR = 0.86 (p = 0.26)	21.4%	15.2%	p = 0.24	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (treated patients only)	Phase III (n = 210) *PP Analysis*	7.8 m	6.0 m	HR = 0.67 (p = 0.012)	26.2%	15.2%	p = 0.03	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (KPS ≥ 80, age < 61)	Phase III (n = 110) *Subgroup analysis*	8.8 m	6.6 m	HR = NA (p < 0.01)	25.6%	7.7%	NA	*Neuro Oncol*, 2010[19]
Recurrent GBM (after bevacizumab failure)	Phase III (n = 43) *Subgroup analysis*	4.4 m	3.1 m	(p = 0.02)	NA	NA	NA	*Neuro Oncol*, 2010[20]
Recurrent GBM (TTF versus bevacizumab)	Phase III (n = 156) *Subgroup analysis*	6.6 m	5.0 m	HR = 0.65 (p = 0.048)	21%	21%	p > 0.05	*Neuro Oncol*, 2011[21]
Newly diagnosed GBM (together with temozolomide)	I-II (n = 10) *ITT Analysis*	39+ m	14.7 m*	(p = 0.002)	90% 155 w	50%* 26 w	NA	*BMC Med Phys*, 2009[9]
Relapsed advanced NSCLC (together with pemetrexed)	I-II (n = 42) *ITT Analysis*	13.8 m	8.2 m*	NA	28 w	12 w*		*ESMO*, 2010[25] *ERS*, 2010[8] *Expert Opin Investig Drugs*, 2010[11]

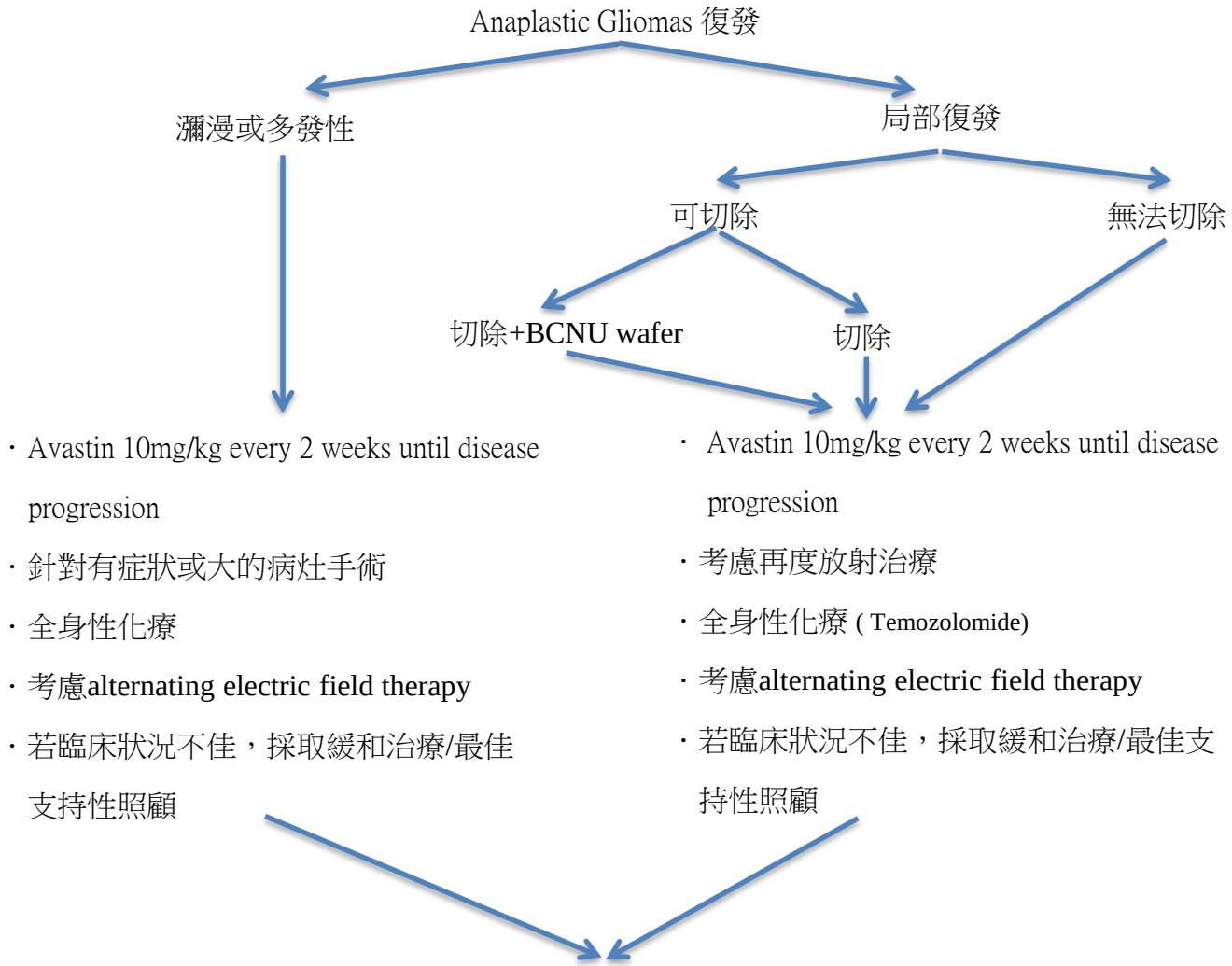
Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the authors); HR, hazard ratio; PP, per protocol; KPS, Karnofsky performance status; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.

* Single-arm trials with literature control

Reference

1. NCCN Guidelines(R) Updates. Journal of the National Comprehensive Cancer Network : JNCCN. 2019 version 1.
2. Stupp R et al., Lancet Oncol. 2009;10(5):459-66.
3. Stupp R et al., Ann Oncol. 2005;16(6):949-.
4. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.J Clin Oncol. 2009 Oct 1;27(28):4733-40. J Clin Oncol. 2009 Oct 1;27(28):4733-40.

Treatment Guideline for Recurrent Anaplastic Gliomas



Anti-cancer Drugs for High Grade Gliomas

- **CCRT**
- **Therapeutic class**: Alkylating agent
- **Generic Name**: Temozolomide
- **Brand Names**: Temodal, Tamos
- **Supply**:
- Temodal: 20mg; 100mg
- Tamos: 20mg; 100mg
- **Administration**: (Oral route)
- Newly Diagnosed Glioblastoma
- **Initial:** 75mg/m^2 daily x 42 days with focal radiotherapy
- **Cycle 1:** 150mg/m^2 qd x 5 days followed by 23 days without treatment
  Cycles 2-6: May increase to 200mg/m^2 at start of Cycle 2,
- [if nonhematologic toxicity for Cycle 1 is Grade ≤2 (excluding alopecia, N/V), absolute neutrophil count (ANC) ≥1.5 x 10^9/L, and platelet count ≥100 x 10^9/L]

- **Adjuvant**
- **Therapeutic class**: Alkylating agent
- **Generic Name**: Temozolomide
- **Brand Names**: Temodal, Tamos
- **Supply**:
- Temodal: 20mg; 100mg
- Tamos: 100mg
- **Administration**: (Oral route)
- Recurrent Anaplastic Astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma
- **Initial:** 200mg/m^2 qd x 5 consecutive days/28-day cycle until disease progression

- **References**:
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987-96.

- Roger Stupp, Monika E Hegi, Warren P Mason, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10: 459–66

- Perry JR, Bélanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol. 2010 Apr 20;28(12):2051-7.

- **Palliative treat**
- **Therapeutic class**: Nitrosourea alkylating agent
- **Generic Name**: Carmustine
- **Brand Names**: GLIADEL® Wafer
- **Supply**:
- Wafer: 7.7mg carmustine [8^{s}=61.6mg]
- **Administration**:
- Intracranial implantation

- **References**:

- Barr JG, Grundy PL. The effects of the NICE Technology Appraisal 121 (Gliadel and Temozolomide) on survival in high-grade glioma. Br J Neurosurg. 2012 Dec;26(6):818-22

- Duntze J, Litre CF, Eap C, et al. Implanted Carmustine Wafers Followed by Concomitant Radiochemotherapy to Treat Newly Diagnosed Malignant Gliomas: Prospective, Observational, Multicenter Study on 92 Cases. Ann Surg Oncol. 2013 Jun;20(6):2065-72.

- Gutenberg A, Lumenta CB, Braunsdorf WEK, et al. The combination of carmustine wafers and temozolomide for the treatment of malignant gliomas. A comprehensive review of the rationale and clinical experience. J Neurooncol. 2013 Jun;113(2):163-74.

- **Palliative Vascular endothelial growth factor (VEGF) inhibitor**

  Bevacizumab (Avastin) 100mg/4ml/Vial

  Dosage:

  10mg/kg, every two weeks

  Administration:

  Intravenous infusion with 100ml 0.9% NaCl

  First infusion: Administer infusion over 90 minutes.

  Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated.

  Administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

- **Reference**:
- Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.J Clin Oncol. 2009 Oct 1;27(28):4733-40. J Clin Oncol. 2009 Oct 1;27(28):4733-40.

- Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014 Feb 20;370(8):709-22.

Palliative chemotherapy of Glioma

Regimens (1)

Vinblastine 6 mg/ m^2 in NS 100ML IVD for 2hrs on D1

Etoposide 100-150 mg/ m^2 in NS 500 ML IVD for 4 hrs onD1,2,3

Cisplatin 90 mg/ m^2 in NS 500ML IVD for 6 hrs on D2 or

Carboplatin(AUC=4-5) 300-450 mg/ m^2 in NS 250 ML ivd for 2 hrs on D2 every 28 days

Regimens (2)

bevacizumab 10mg per Kg in NS 100ml IV for 90mins ST D1

irinotecan 125mg per BSA in D5W 250ml IV for 2hrs ST D1

Regimens (3)

Temozolomide 150-200 mg/m2 oral D1-5 q28days

Regimens(4)

Lomustine(CCNU) BSAX110mg Q6W

Vincristine 1mg in NS 30ml IVD QW

- References:

- 1. Thompson EM, Dosa E, Kraemer DF, Neuwelt EA. Treatment with bevacizumab plus carboplatin for recurrent malignant glioma. Neurosurgery. 2010;67(1):87-93.
- 2. Chamberlain MC, Tsao-Wei DD. Salvage chemotherapy with cyclophosphamide for recurrent, temozolomide-refractory glioblastoma multiforme. Cancer. 2004;100(6):1213-20.
- 3. Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with cyclophosphamide for recurrent temozolomide-refractory anaplastic astrocytoma. Cancer. 2006;106(1):172-9.
- 4. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(28):4733-40.
- 5. Vredenburgh JJ, Desjardins A, Reardon DA, Friedman HS. Experience with irinotecan for the treatment of malignant glioma. Neuro-oncology. 2009;11(1):80-91.

Treatment Principles of Central Nervous System Germ Cell Tumor

Germ Cell Tumor Evaluations

- Blood sample of alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (B-HCG).
  - It is very important for diagnosis and prognosis.
- Neuroimaging study requires brain and whole-spine MRI examination.
- The above study needs be done pre- and post-operatively and regularly during follow-up period.
- The team work between pediatric neurosurgeons, pediatric neurologist, radiologist, therapeutic radiologist, and pathologist is very important.

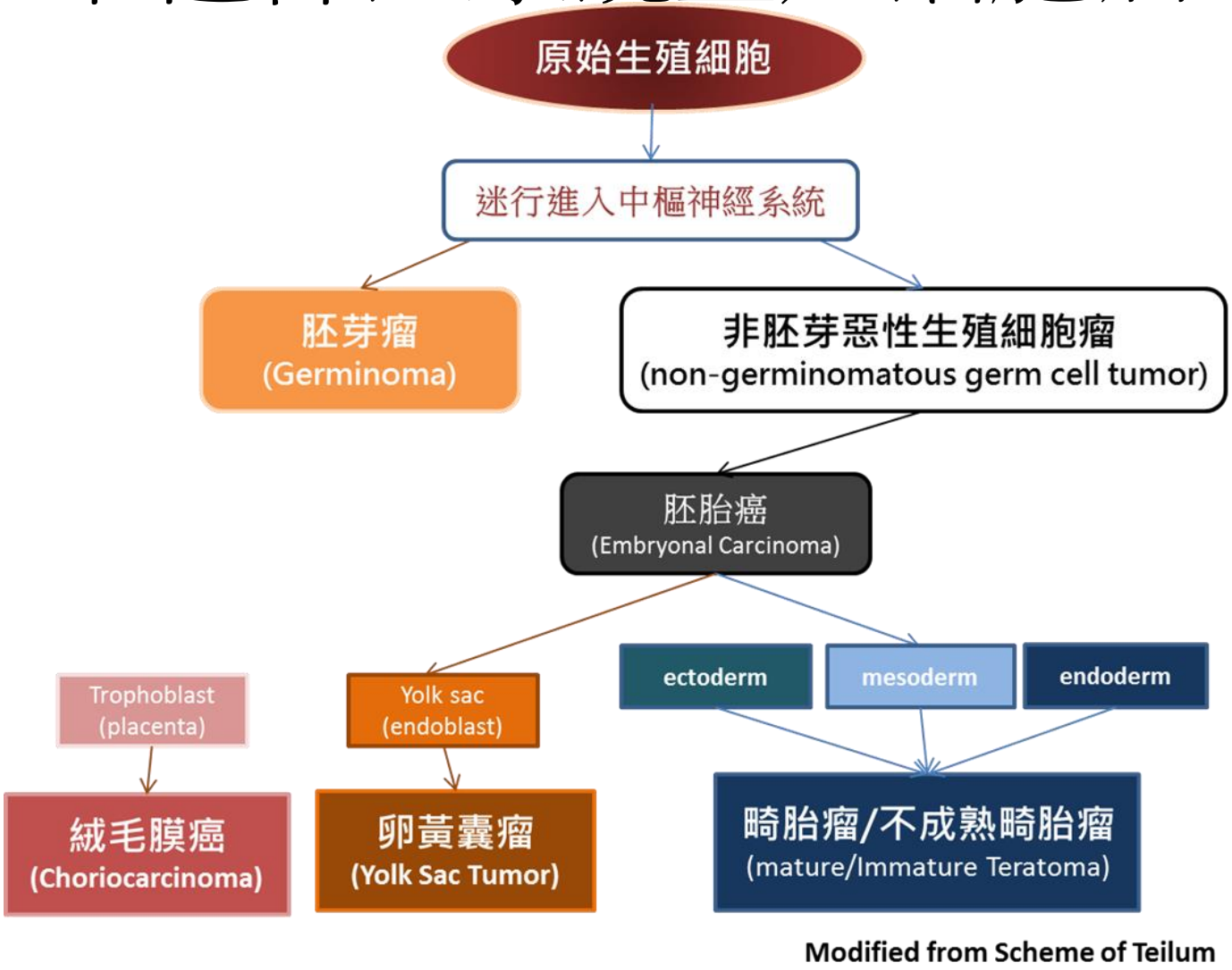
Germ Cell Tumor
Principles of Surgery

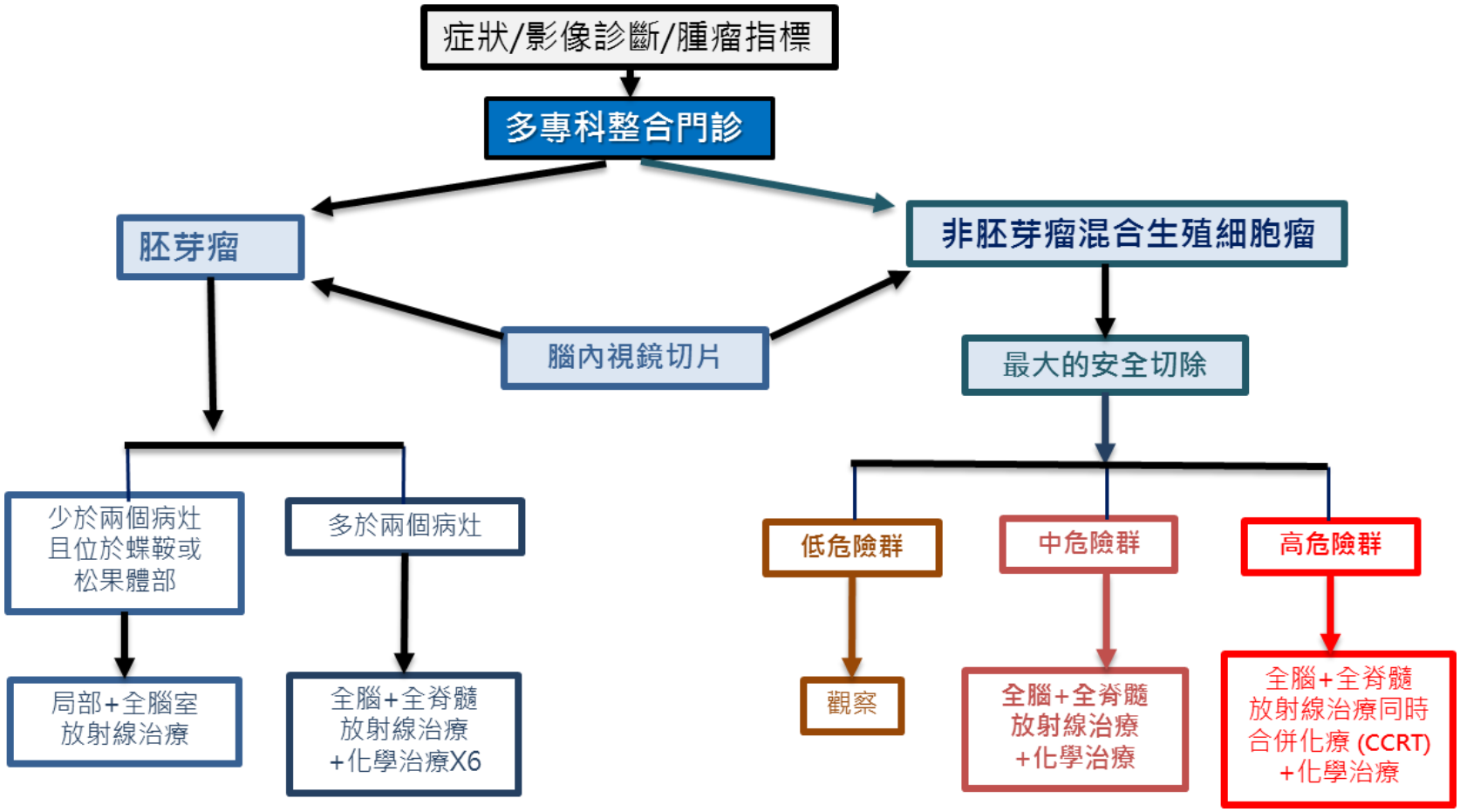
- Biopsy for definite diagnosis is necessary.
- The proper location for biopsy should be confirmed after discussion of pediatric neuro-oncology team. The surgery will be performed under stereotactic guidance.
  - Pineal region tumor will easily complicate with obstructive hydrocephalus. The tumor biopsy and endoscopic 3rd ventriculostomy should be done in one session.
  - If presumptive diagnosis is established by typical appearance in MRI and elevation of serum B-HCG (> 10 mIU/ml) with normal serum AFP (< 10 ng/ml), it is straightforward to perform radiotherapy.
- Radical or gross total removal of intracranial pure germinoma is usually neither indicated nor necessary.
  - Especially if the serum level of AFP and B-HCG is normal.

Therapeutic Classification of Central Nervous System Germ Cell Tumor

Low risk group Pure germinoma “Benign” teratoma (with AFP < 10 ng/ml)
Average risk group “Malignant” teratoma (with AFP > 10 ng/ml) Mixed tumors mainly composed of germinoma or teratoma
High risk group Choriocarcinoma Yolk sac tumor Embryonal carcinoma Mixed tumors of mainly choriocarcinoma, yolk sac tumor, or embryonal carcinoma

中樞神經系統生殖細胞瘤





追蹤計畫

1. 腦部（或含脊髓）的磁振攝影RT完成後4週,完成治療後前二年：每三個月一次、第三年後每半年一次、滿五年：每年一次
2. 每次追蹤時抽血作ＡＦＰ及β- ＨＣＧ檢查。若有需要可能實行其他檢查如視力檢查，內分泌檢查，智能評估、問卷調查等

Germ Cell Tumor (Germinoma) Principle of Radiotherapy I

- Treatment volume:

Volume option:

1. Whole ventricle irradiation (WVI) plus focal boost (FB).
2. Whole brain irradiation (WBI) plus FB.
3. Craniospinal irradiation (CSI) plus FB to primary tumor or metastatic sites.
4. Because focal (primary only) irradiation has highest relapse rate, focal irradiation is not recommended as first line treatment choice.

- Irradiation Volume definition:

GTV: image enhancement (MR or CT)

CTV (encompassing microscopic region): whole ventricle or whole neuraxis

PTV: consider organ motion or daily setup error, usually 3-5 mm is recommended.

- Radiation dose recommendation:

1. WVI: 2400 cGy to 3000 cGy (daily fraction size: 180 to 200 cGy).
2. CSI: 1980 cGy to 3600 cGy (Daily fraction size: 150 to 180 cGy).
3. FB: 3000 cGy to 4500 cGy (Daily fraction size: 180 to 200 cGy).

Germ Cell Tumor (Germinoma) Principle of Radiotherapy II

- Radiotherapy recommendation:

1. In VGHTPE, radiotherapy is the first choice for CNS germinoma because of its high radiosensitivity.
2. For solitary lesion or lesion number less than two (bifocal; double midline), WVI plus FB is the first choice. After radiotherapy persistent follow-up is recommended. Systemic chemotherapy is not standard treatment for this group of patients.
3. For initial dissemination CNS germinoma, CSI plus FB (primary and metastasis) is recommended as first treatment strategy. Followed systemic chemotherapy is highly recommended after radiotherapy.
4. For germinoma arising from basal ganglion, WVI plus FB is the first recommended protocol. Whole brain irradiation is not routinely recommended unless there is sufficient evidence of brain seeding.

- The primary therapy is whole-ventricle radiotherapy.
  - Craniospinal irradiation is reserved for cases with spinal dissemination.

Germ Cell Tumor
Principle of Chemotherapy

- Chemotherapy for germinoma is indicated in either of the following condition
  - Multiple lesions (≥ 3).
  - AFP > 10 ng/ml.
  - Spinal dissemination.
- Regimen for germ cell tumor is according to “risk stratification” :

Low risk:

Carboplatin 450mg/m^2 D1+ etoposide 100mg /m^2 D1-3 (CARE); or Vinblastine 6.5mg/m^2 D1, bleomycin 7.5mg /m^2D1-2, Etoposide 150mg/m^2 D3-5, Cisplatin 90mg /m^2D4(VBPE)

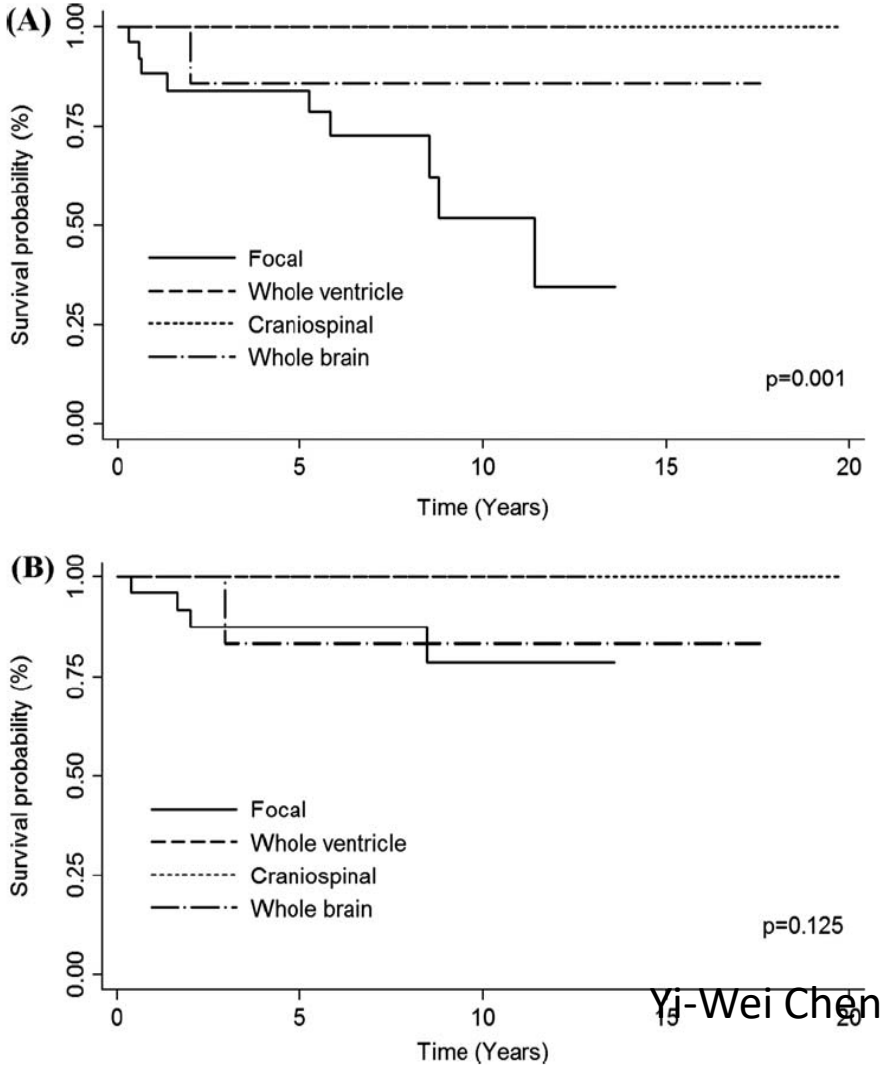
Average/high risk:

Ifosphamide/Cyclophosphamide+Cisplatin/Carboplatin+ Etoposide(ICE) or VBPE

Germ Cell Tumor
References of Chemotherapy

1. Afzal S, Wherrett D, Bartels U, Tabori U, Huang A, Stephens D, et al. Challenges in management of patients with intracranial germ cell tumor and diabetes insipidus treated with cisplatin and/or ifosfamide based chemotherapy. Journal of neuro-oncology. 2010;97(3):393-9.
2. Nakamura H, Makino K, Kochi M, Ushio Y, Kuratsu J. Evaluation of neoadjuvant therapy in patients with nongerminomatous malignant germ cell tumors. Journal of neurosurgery Pediatrics. 2011;7(4):431-8.
3. Kim JW, Kim WC, Cho JH, Kim DS, Shim KW, Lyu CJ, et al. A multimodal approach including craniospinal irradiation improves the treatment outcome of high-risk intracranial nongerminomatous germ cell tumors. International journal of radiation oncology, biology, physics. 2012;84(3):625-31.
4. McCarthy BJ, Shibui S, Kayama T, Miyaoka E, Narita Y, Murakami M, et al. Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. Neuro-oncology. 2012;14(9):1194-200.
5. Odagiri K, Omura M, Hata M, Aida N, Niwa T, Ogino I, et al. Treatment outcomes, growth height, and neuroendocrine functions in patients with intracranial germ cell tumors treated with chemoradiation therapy. International journal of radiation oncology, biology, physics. 2012;84(3):632-8.

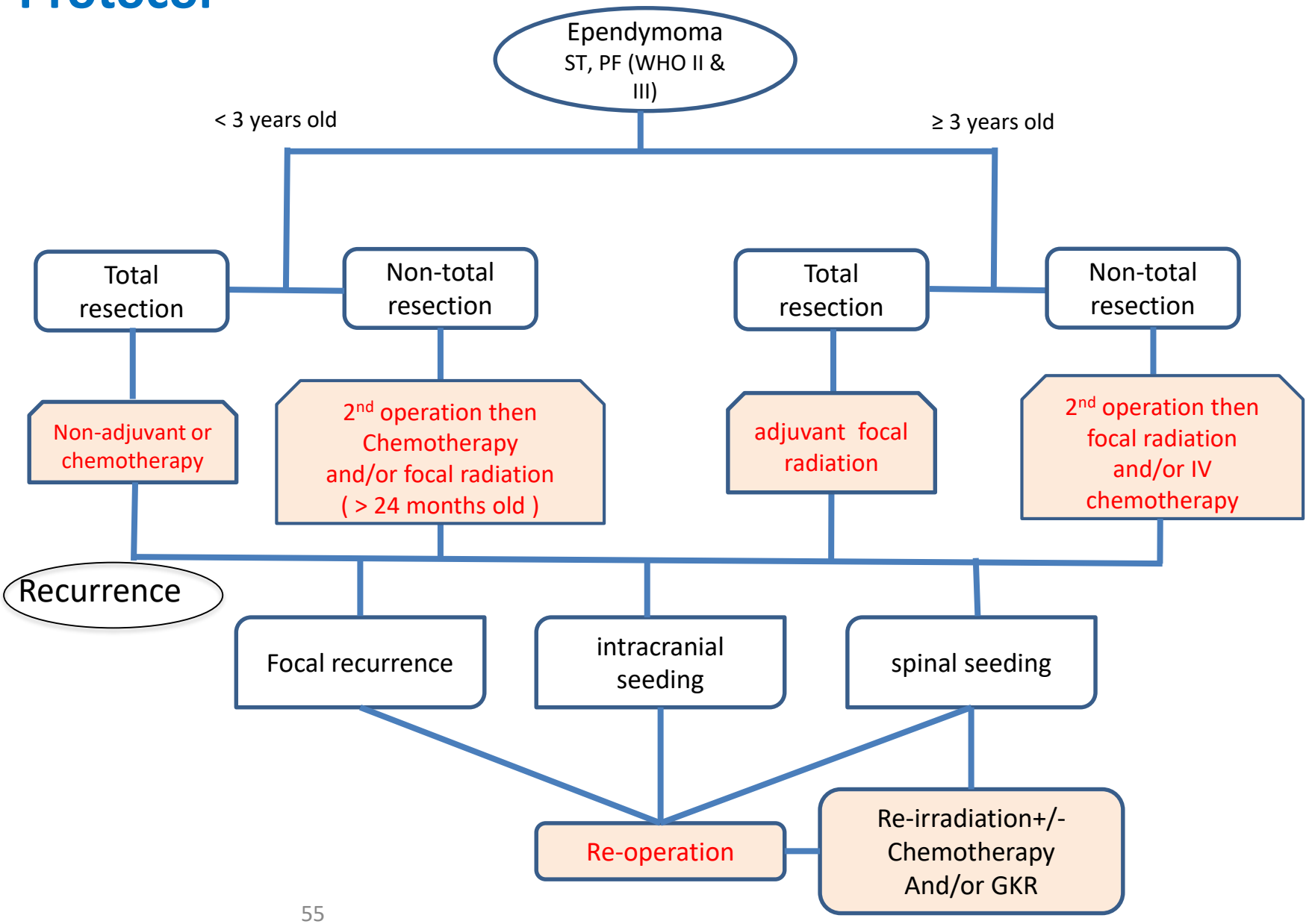
Germ Cell Tumor (Germinoma) Surveillance



Yi-Wei Chen et al., Cancer 2011

Treatment Principles of Central Nervous System Ependymomas

Protocol


Ependymoma
ST, PF (WHO II & III)
< 3 years old
≥ 3 years old
Total resection
Non-total resection
Total resection
Non-total resection
Non-adjuvant or chemotherapy
2nd operation then Chemotherapy and/or focal radiation (> 24 months old)
adjuvant focal radiation
2nd operation then focal radiation and/or IV chemotherapy
Recurrence
Focal recurrence
intracranial seeding
spinal seeding
Re-operation
Re-irradiation+/- Chemotherapy And/or GKR

Ependymoma
Principle of Radiotherapy

- Focal irradiation with volume-modulated technique is sufficient for radiotherapy dose coverage. Craniospinal irradiation is not treatment principal unless initial spinal dissemination is observed.
- The recommended dose is ranging from 50 to 60 Gy in brain area (both definitive and post-operative) with daily fraction size of 1.6 to 2.0 Gy. In spinal region, radiation dosage is limited from 45 Gy to 50 Gy with daily fraction size of 1.6 to 2.0 Gy.
- The dose is prescribed according to the limitation of adjacent critical organs (including brainstem, optic nerve, optic chiasma and etc.)

追 蹤時程

- 腦部（或含脊髓）的磁振攝影(MRI)評估分別於：術前、術後、放射治療後一個月(化療前); 完成治療後前二年：每三個月一次、第三年後每半年一次、滿五年：每年一次。
- 聽力檢查、牙科及24小時尿液檢查(腎臟功能)於每三次化療後檢查。
- 若是生殖細胞瘤患者，則需於每次追蹤時抽血作ＡＦＰ及β-ＨＣＧ檢查。
- 若有需要可能實行其他檢查如視力檢查，內分泌檢查，智能評估、問卷調查等。

References of Ependymoma

- 1. Liu AP, Shing MM, Yuen HL et al. Timing of adjuvant radiotherapy and treatment outcome in childhood ependymoma. Pediatr Blood Cancer. 2014 Apr;61(4):606-11.
- 2. Landau E, Boop FA, Conklin HM, et al. Supratentorial ependymoma: disease control, complications, and functional outcomes after irradiation. Int J Radiat Oncol Biol Phys. 2013 Mar 15;85(4):e193-9.
- 3. Merchant TE, Haida T, Wang MH, et al. Anaplastic ependymoma: treatment of pediatric patients with or without craniospinal radiation therapy. J Neurosurg. 1997 Jun;86(6):943-9.

Treatment Principles of Meningiomas

- Meningiomas are the most common benign intracranial tumor. They originate from arachnoid cap cells, which are cells within the thin, spider web-like membrane that covers the brain and spinal cord. The arachnoid is one of three protective layers, collectively known as the meninges, which surround the brain and the spinal cord. The other two layers of the meninges are the dura mater and pia mater. Although the majority of meningiomas are benign, these tumors can grow slowly until they are very large, if left undiscovered, and, in some locations, can be severely disabling and life-threatening. Other forms of meningioma may be more aggressive.

World Health Organization (WHO) Meningioma Classifications

WHO Grade I Benign	WHO Grade II Atypical	WHO Grade III Malignant
Meningiothelial	Chordoid	Papillary
Fibrous (fibroblastic)	Clear Cell	Rhabdoid
Transitional (mixed)	Atypical	Anaplastic
Psammomatous		
Angiomatous		
Microcystic		
Secretory		
Lymphoplasmacyte-rich		
Metaplastic		

- Atypical meningiomas (WHO grade II, which account for 18% of meningioma cases) exhibit increased tissue and cell abnormalities. These tumors grow at a faster rate than benign meningiomas and are often characterized by brain invasion. Atypical meningiomas have a higher likelihood of recurrence than benign meningiomas (WHO grade I).

- Malignant meningiomas (WHO grade III) show increased cellular abnormalities and grow at a faster rate than benign and atypical meningiomas. Malignant meningiomas are the most likely to invade the brain and recur more frequently than the other two subtypes.

Treatment Guideline for *Meningioma*

MRI :Dural based mass
Homogeneously contrast-enhancing
Dural tail
CSF cleft

Oberve
(small asymptomatic tumors)

Surgery
(Maximal safe resection)

RT or
GKRS

Meningioma, postoperative management depends on grade,extent of resection,and symptoms,as follows:

Grade1:observation or consider RT

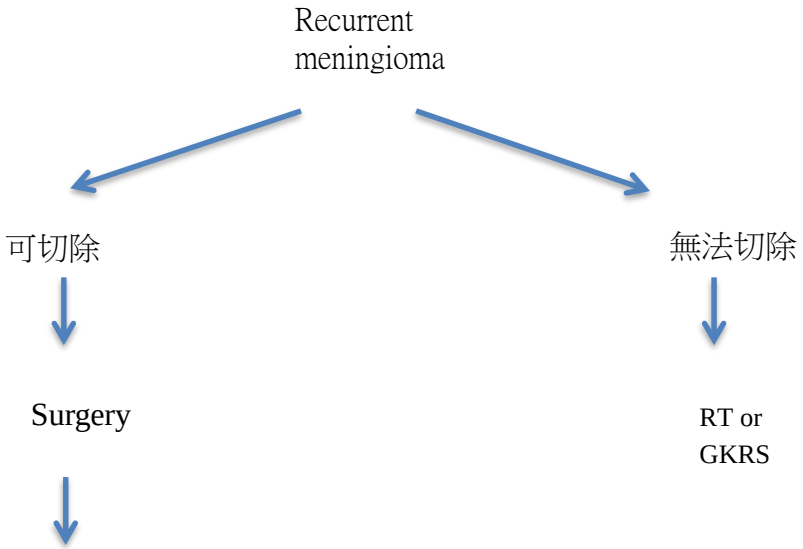
Grade2 with complete resection: observation or consider RT

Grade 2 with incomplete resection :RT

Grade 3 :RT

MRI追蹤:每2-4個月做一次 (或因病情需要)，持續2-3年之後可減少頻率

Treatment Guideline for Recurrent Meningioma



Meningioma, postoperative management depends on grade,extent of resection,and symptoms,as follows:

Grade1:observation or consider RT

Grade2 with complete resection: observation or consider RT

Grade 2 with incomplete resection :RT

Grade 3 :RT

References of Meningiomas

1. AANS 2020 Annual Report: The Science of Practice

2.NCCN Guidelines(R) Updates. Journal of the National Comprehensive Cancer Network : JNCCN. 2021 version 2.