台北榮總兒童神經腫瘤診療指引

台北榮兒童總神經腫瘤團隊

Version 202110

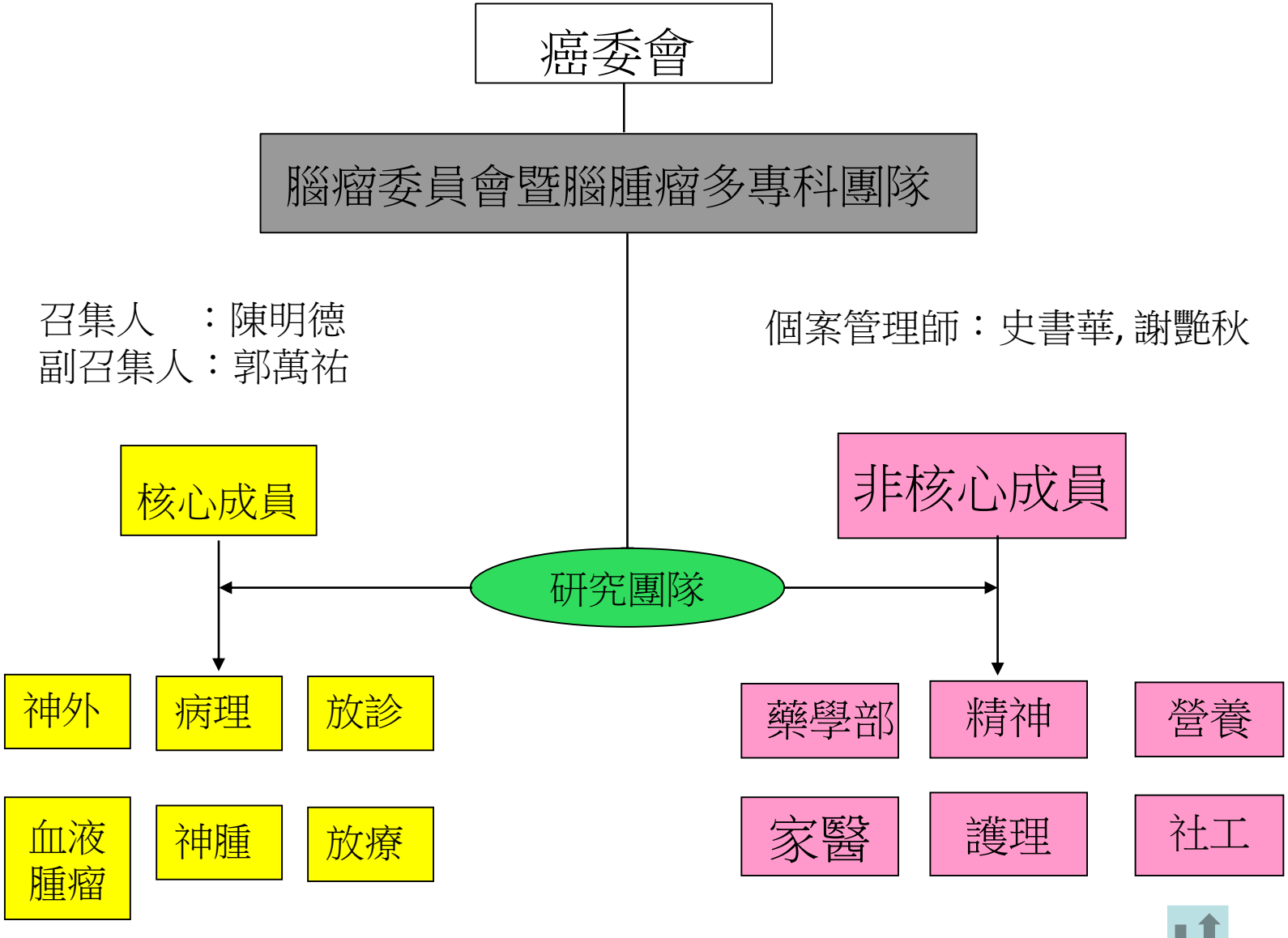
制定日期：2021年10月7日

Table of Content

Multidisciplinary Team

- Neurosurgeon (Adult & Pediatric)
- Radiation Oncologist
- Neuro-Oncologist & Medical Oncologist
- Neuro-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



兒童神經腫瘤多專科醫療團隊		
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團隊副召集人：郭萬佑		
（核心成員）		
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	陳信宏	主治醫師
	李宜燕	主治醫師
	郭懿萱	主治醫師
	柯金柱	主治醫師
一般兒科	許庭榕	科主任
	顏秀如	主治醫師
	林為聖	主治醫師
放射線部	張豐基	科主任
	吳智君	主治醫師
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	康鈺玫	住院醫師
個案管理師	謝艷秋	護理師
（非核心成員）		
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護理部	柯識鴻	護理長
	鍾素珍	專科護理師
	趙芷麟	專科護理師
復健醫學部	黃婉如	心理師
營養部	徐嘉徽	營養師
社工室	古登儒	社工師
家醫部(安寧共照)	張曉婷	主治醫師
	黃茱楹	共照護理師
更新日期：2021/03/01		

Summary of Evaluation

- **History, physical and neurological examinations**
- **CBC, DC, PT/APTT, BUN/Cr, ALT/AST, Na/K/Cl**
- **Brain CT: emergency situation, no need for every case**
- **Brain MRI: standard diagnostic tool**
- **Tumor markers: serum AFP and beta-HCG (suspected germ cell tumors), CSF study if indicated**
- **Spine MRI: all embryonal tumors, germ cell tumor at initial diagnosis, others are according to the location and symptoms**
- **CSF analysis: embryonal tumors, germ cell tumors, relapse tumors could consider**
- Optional Study: VA/VF, Endocrine, Neuropsychological test, Electroencephalography

Taipei Veterans General Hospital Practice Guidelines for

Glioblastoma (GBM)

Glioblastoma (GBM)
Table of Content

Glioblastoma (GBM)
Multidisciplinary Team

- **Neurosurgeon**
- **Radiation Oncologist**
- **Neuro/Medical Oncologist**
- **Neuro-pathologist**
- **Neuro-radiologist**
- **Nurses (for specialized)**
- **Social Workers**

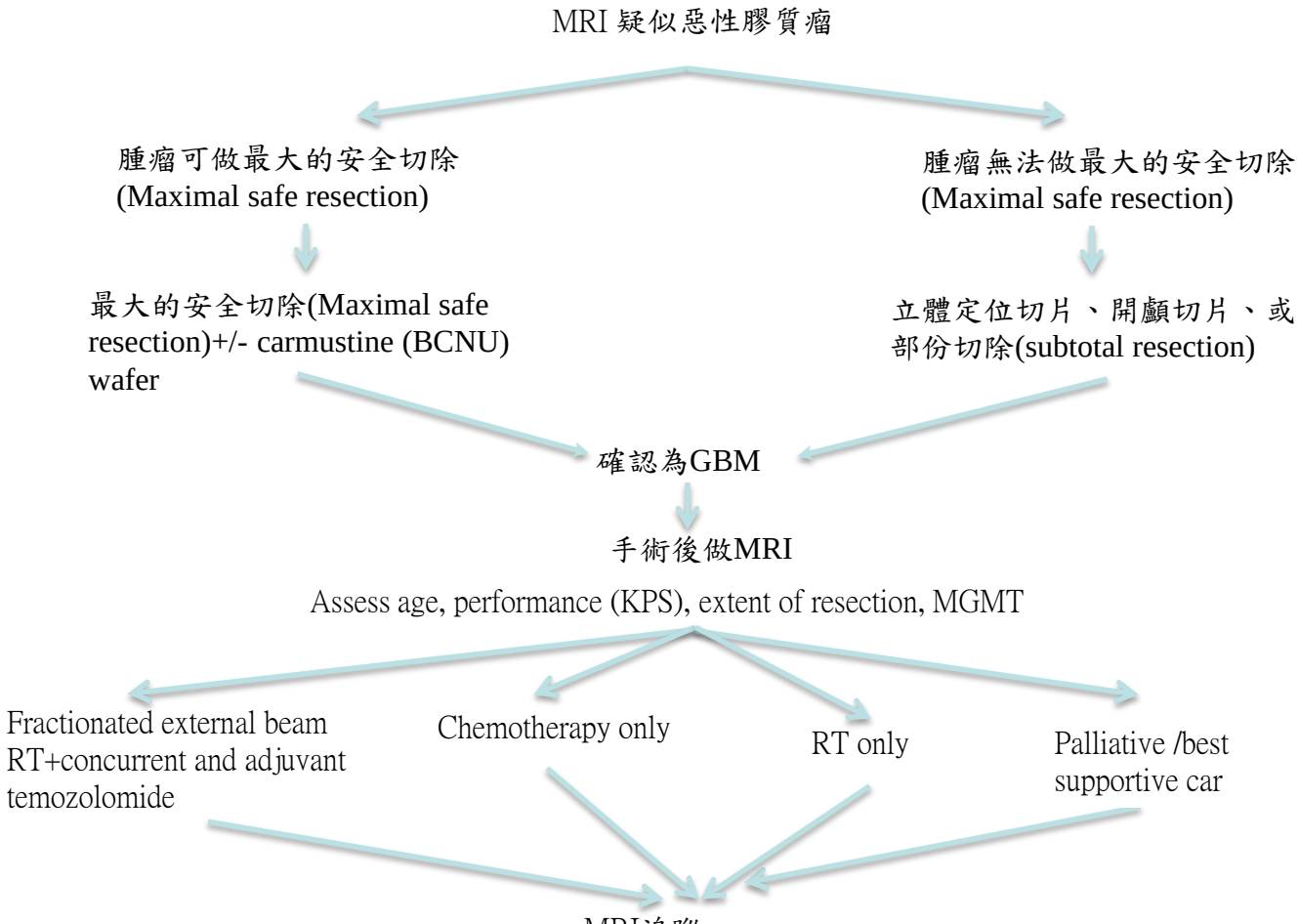
Glioblastoma (GBM)

- **20% of all intracranial tumors**
- **Two variants: giant cell glioblastoma, gliosarcoma**
- **Treatment:**
  - Surgery: maximal resection without deficit
  - Radiation therapy
  - Chemotherapy: Stupp Protocol: CCRT+Adjuvant Temozolomide
  - <=3 years old, consider chemotherapy first, hold radiotherapy if recurrent
- **Prognosis: survival 1-2 yrs with aggressive treatment**

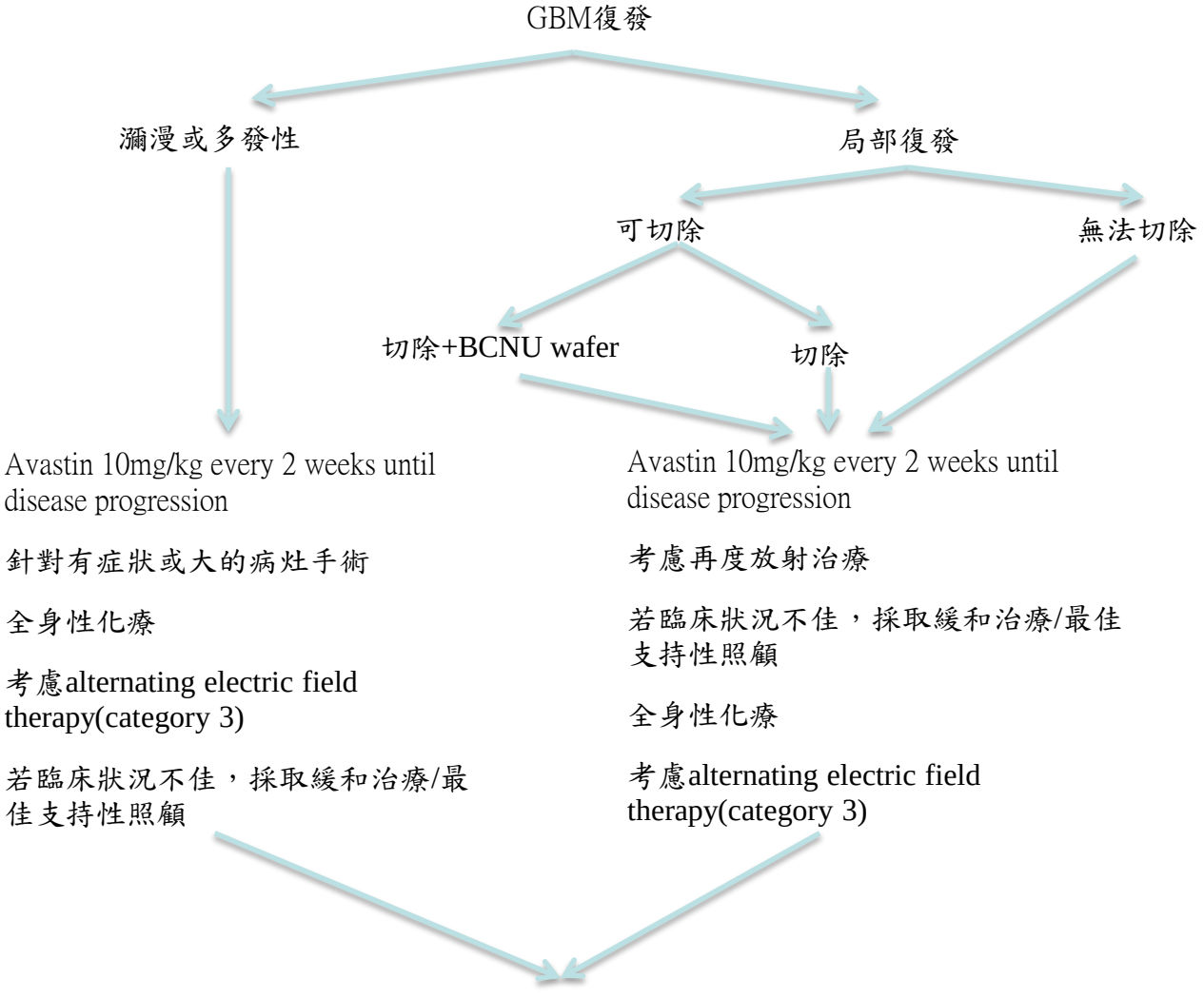
Glioblastoma (GBM)
Pretreatment

- **History, physical and neurological exam**
- **CBC+D/C, PT/aPTT, blood chemistry**
- **MRI of brain**
- **Optional studies**
  - CT of brain
  - Visual Field
  - Neuropsychological test
  - Electroencephalography

Treatment Guideline for GBM



Treatment Guideline for Recurrent GBM

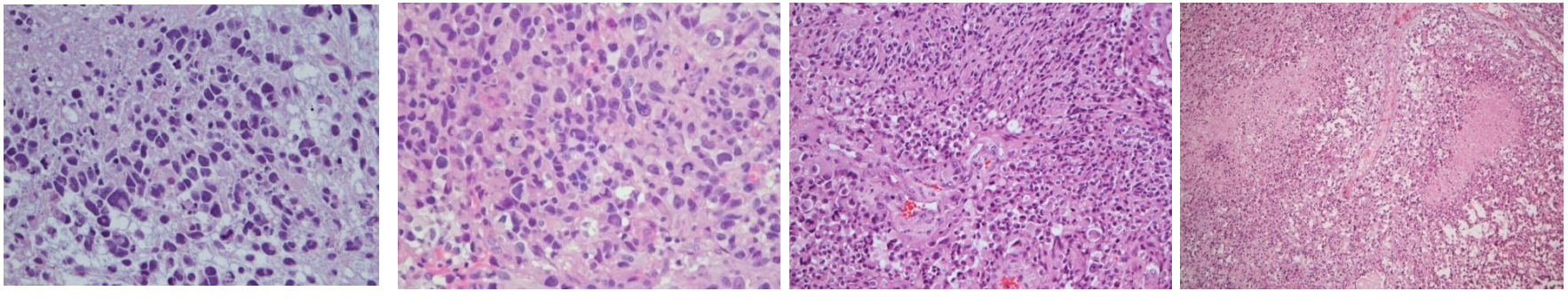


Glioblastoma (GBM)
Principle of Surgery

- **Extent of Resection**
  - Maximal safe microsurgical resection
  - Intraoperative neuromonitoring may be used to reduce morbidity
  - Intra-op MRI may be used to facilitate adequate resection

World Health Organization (WHO) grading of astorcytic tumours

Nuclear atypia | Mitoses | Endothelial proliferation | Necrosis



WHO Grade	WHO Designation	Histologic Criteria
II	Diffuse astrocytoma	1 criterion: usually nuclear atypia
III	Anaplastic astrocytoma	2 criteria: usually nuclear atypia and mitoses
IV	Glioblastoma	3 criteria: usually nuclear atypia, mitoses, and endothelial proliferation and/or necrosis

Glioblastoma (GBM)
Principle of Radiotherapy for Malignant Gliomas (Definitive or post-operative)

- Conventional fractionated X-ray radiotherapy (RT) is recommended for inoperable (definitive) or post-operative malignant gliomas.
- GTV (gross tumor volume) is defined according to (pre-op and post-operative) enhancement of T1 and FLAIR/T2 in MR image.
- CTV (Clinical target volume) is expanded from GTV by 2-3 cm and also includes peri-tumor edema (MR-T2).
- PTV (Planning target volume) encompasses daily setup error with 3-5 mm.
- Two stages of RT is arranged(reduce with boost).

Glioblastoma (GBM)

Principle of Radiotherapy for Malignant Gliomas (Dose)

- **The recommended dose is ranging from 50 to 60 Gy (both definitive and post-operative) 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.)**
- **Hypo-fractionated RT with daily dose higher than 2.5 Gy is not recommended unless for palliative intent or for patients with poor performance.**

Glioblastoma (GBM)
Principles of Chemotherapy

Glioblastoma & WHO Grade IV gliomas

- Adjuvant Therapy:

  Concurrent (with RT) Temozolomide 75 mg/m^2 daily; post RT 150-200 mg/m^2 for 5 days, every 28 days maintains at last 6 cycles.

  Stupp, et al. NEJM 2005

- Recurrence/Salvage:

1. Bevacizumab 10mg/kg in NS 100 ML IVD (over 90 minutes at first use), Q2week
2. Bevacizumab + chemotherapy (4 or 5 or 6),
3. Temozolomide re-challenge
4. Carboplatin 300-450 mg/m ^{2} on Day1 and Etoposide 100 mg/m^2 on Day 1-3 (CARE)
5. Vinblastine 6 mg/m^2 on Day 1, and Etoposide 100 mg/m^2 on Day1-3 and Cisplatin 75 mg/m^2 on Day 2(Cisplatin)
6. Cyclophosphamide 700-1000 mg/m^2 on Day 1,2 and Vinblastine 6 mg/m^2 on day 3, alternating with CARE

Glioblastoma (GBM)
Reference

1. NCCN Guidelines(R) Updates. Journal of the National Comprehensive Cancer Network : JNCCN. 2013;11(9):xxxii-xxxvi.

2. Stupp R et al., Lancet Oncol. 2009;10(5):459-66.

3. Stupp R et al., Ann Oncol. 2005;16(6):949-.

Treatment Principles of Diffuse Intrinsic Pontine Glioma (DIPG)

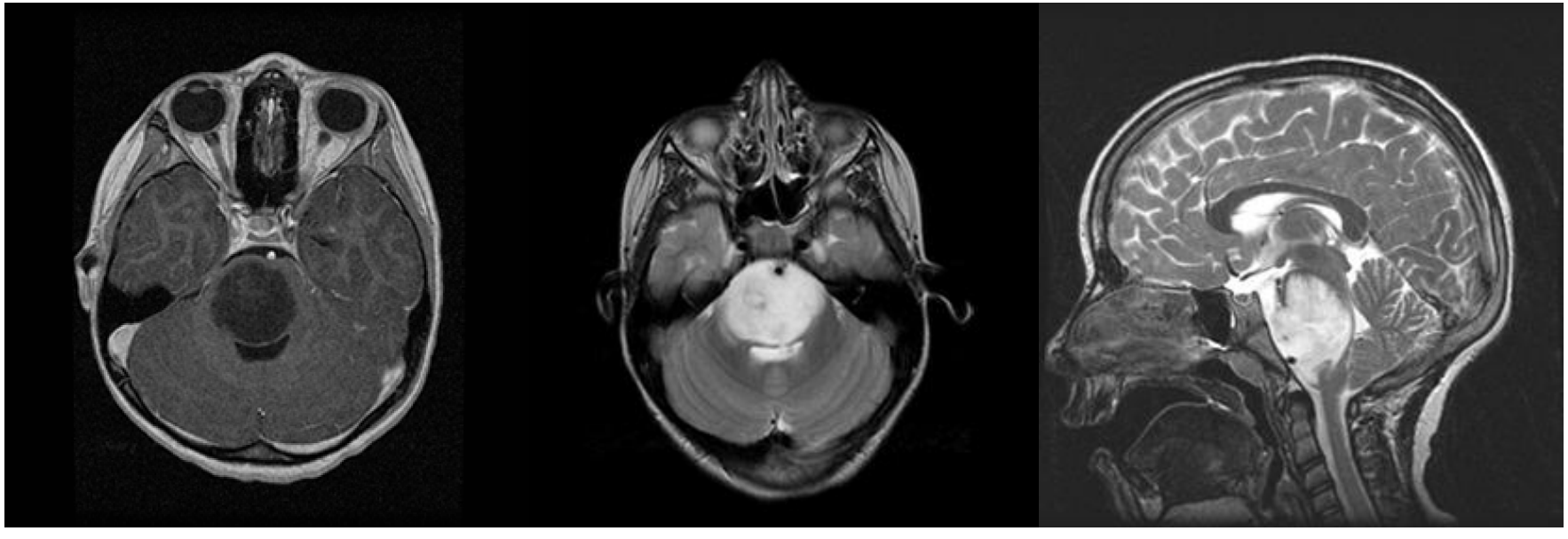
Diffuse Intrinsic Pontine Glioma (DIPG)

- **15-20% of all pediatric brain tumours**
- **Typical clinical presentation**
  - Short history (6 → 3 → 1 month)
  - At least 2 of the 3 signs/symptoms
    - Cranial nerve deficit
    - Long tracts signs
    - Ataxia
  - Not often reported, but nearly always present: behavioral changes
    - Laughter (night)
    - School phobia, etc.

Diffuse Intrinsic Pontine Glioma (DIPG)

Image Diagnosis

- More than 50% of the pons
- Hypodense
- Little/no enhancement



Diffuse Intrinsic Pontine Glioma (DIPG)
Treatment

- **Role of surgery**
  - For typical case: no role has been demonstrated
  - For atypical case (age, image, presentation): biopsy is indicated
- **Radiation**
  - The standard treatment (definitive management)
  - Aims: to improve symptoms (the best palliative treatment)
  - Dose: 50 -60 Gy in 30-33 fractions (daily fraction size ranges from 1.6 to 2.0 Gy)

Diffuse Intrinsic Pontine Glioma (DIPG)
Reference

- 1. M Ronghe, T Yanagisawa, E Bouffet. Diffuse intrinsic pontine gliomas. Oncology of CNS Tumors, 2010 – Springer.
- 2. D Hargrave, N Chuang, E Bouffet. Conventional MRI cannot predict survival in childhood diffuse intrinsic pontine gliom. Journal of neuro-oncology, 2008.
- 3. Kebudi R, Cakir FB. Management of diffuse pontine gliomas in children: recent developments. Paediatr Drugs. 2013 Oct;15(5):351-62.
- 4. Chiang KL, Chang KP, Lee YY, Huang PI, Hsu TR, Chen YW, Chang FC, Wong TT. Role of temozolomide in the treatment of newly diagnosed diffuse brainstem glioma in children: experience at a single institution. Childs Nerv Syst. 2010 Aug;26(8):1035-41.

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.

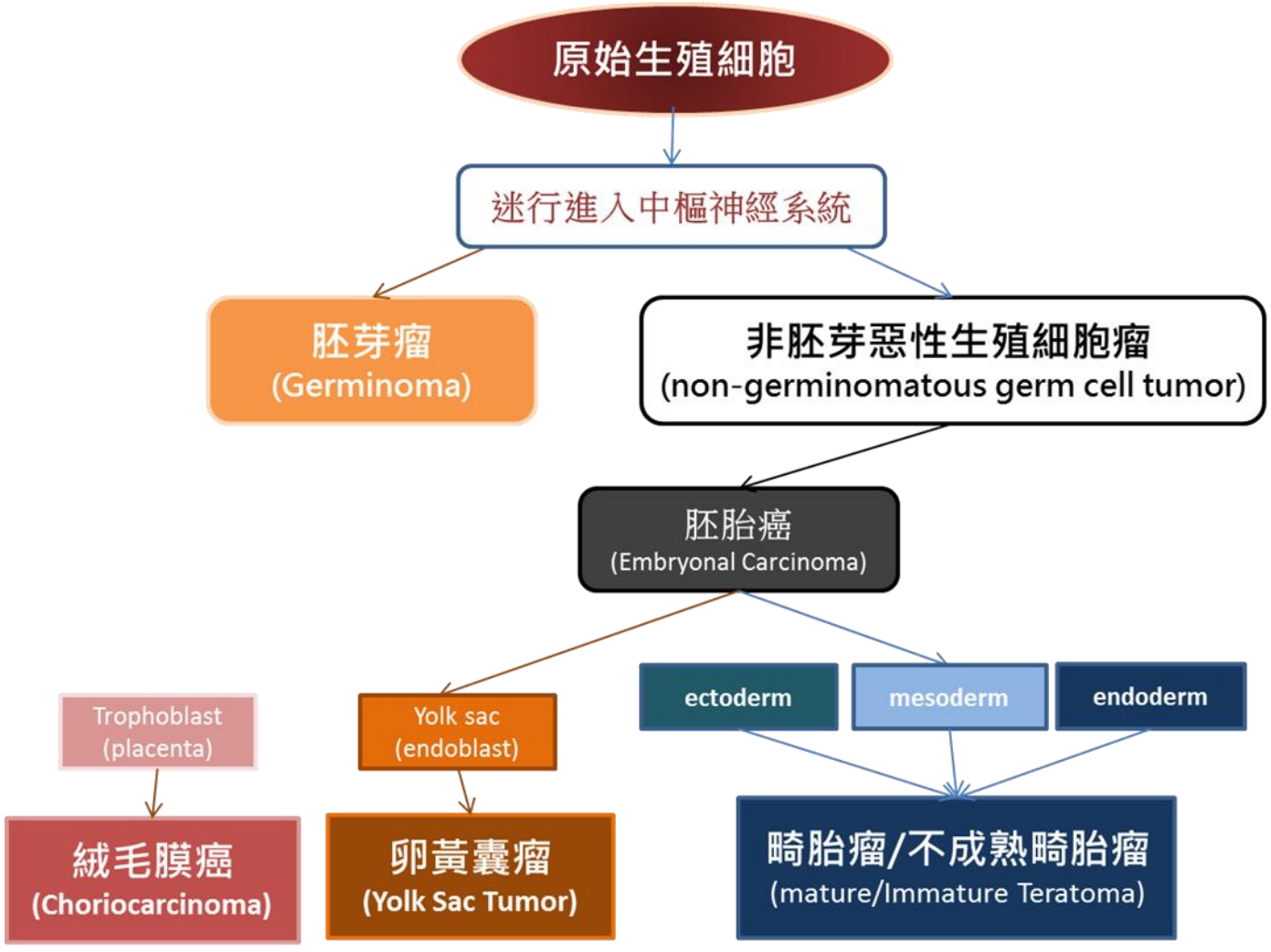
Therapeutic Classification of Central Nervous System Germ Cell Tumor

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

兒童中樞神經系統生殖細胞瘤



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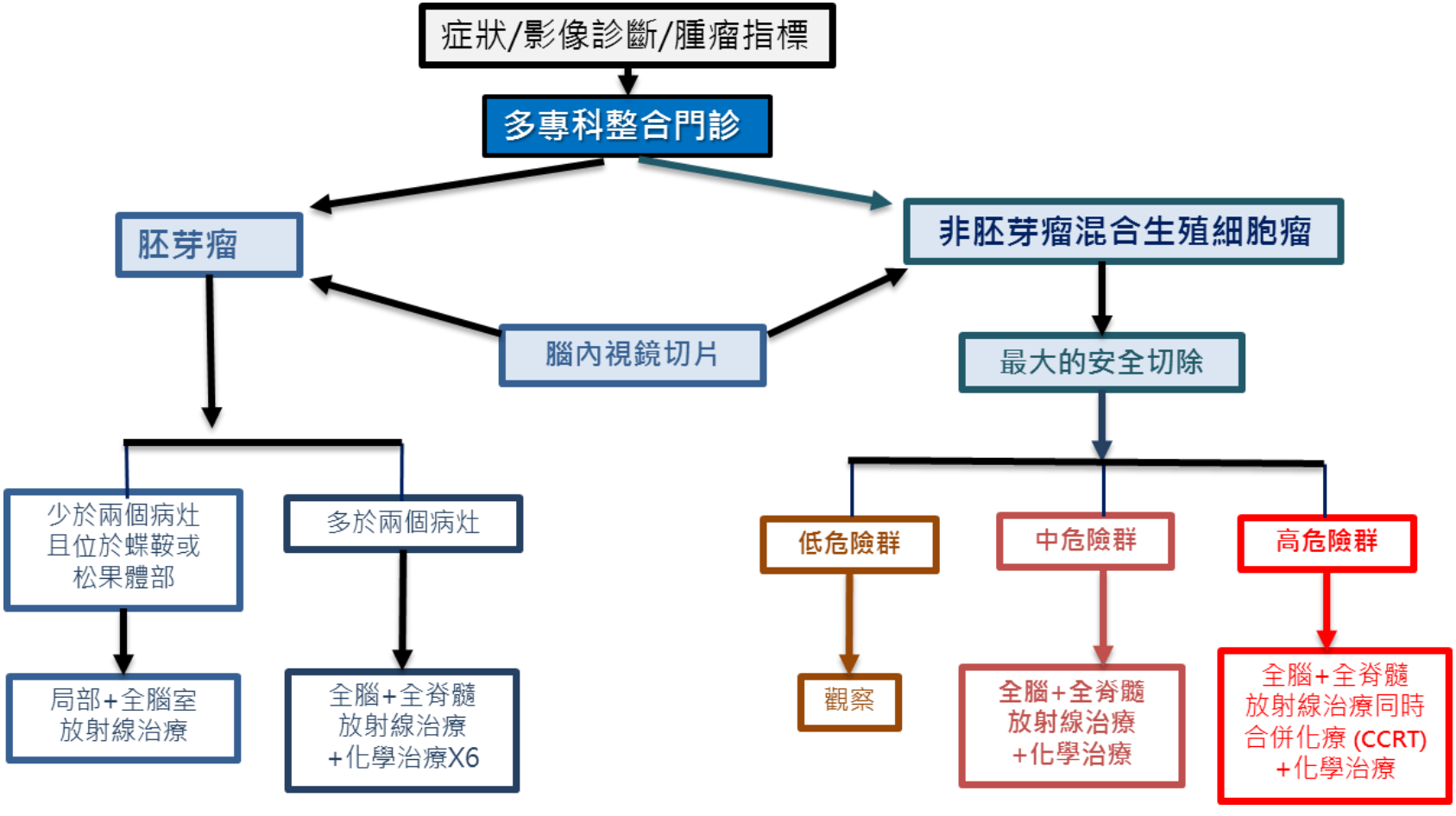


追蹤計畫

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 risk :

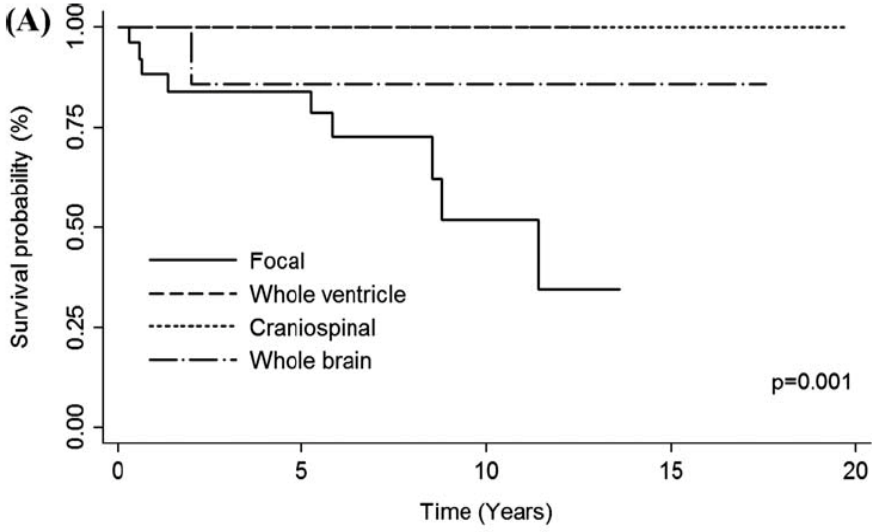
Ifosphamide/Cyclophosphamide+Cisplatin/Carboplatin+ Etoposide(ICE) or VBPE

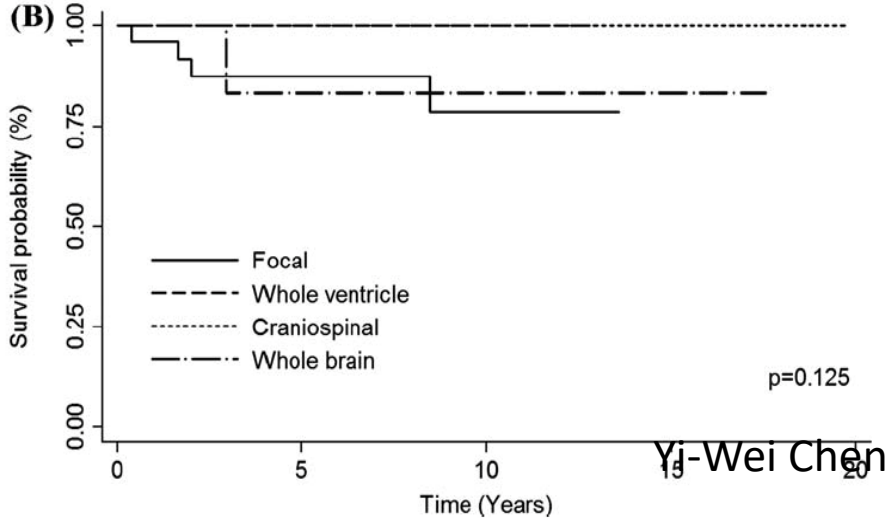
High risk: Concurrent radiotherapy and chemotherapy

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.
6. Yu-Mei Kang, Shih-Chieh Lin, Yi-Yen Lee, Feng-Chi Chang, Muh-Lii Liang, Hsin-Hung Chen, Tai-Tong Wong, Yi-Wei Chen, “A Single-Center Study of Treatment Outcomes of Pediatric Basal Ganglia Germinoma in Taiwan”, Child's Nervous System; 2020 Aug; 36(8): 1745-1753.

Germ Cell Tumor (Germinoma) Surveillance



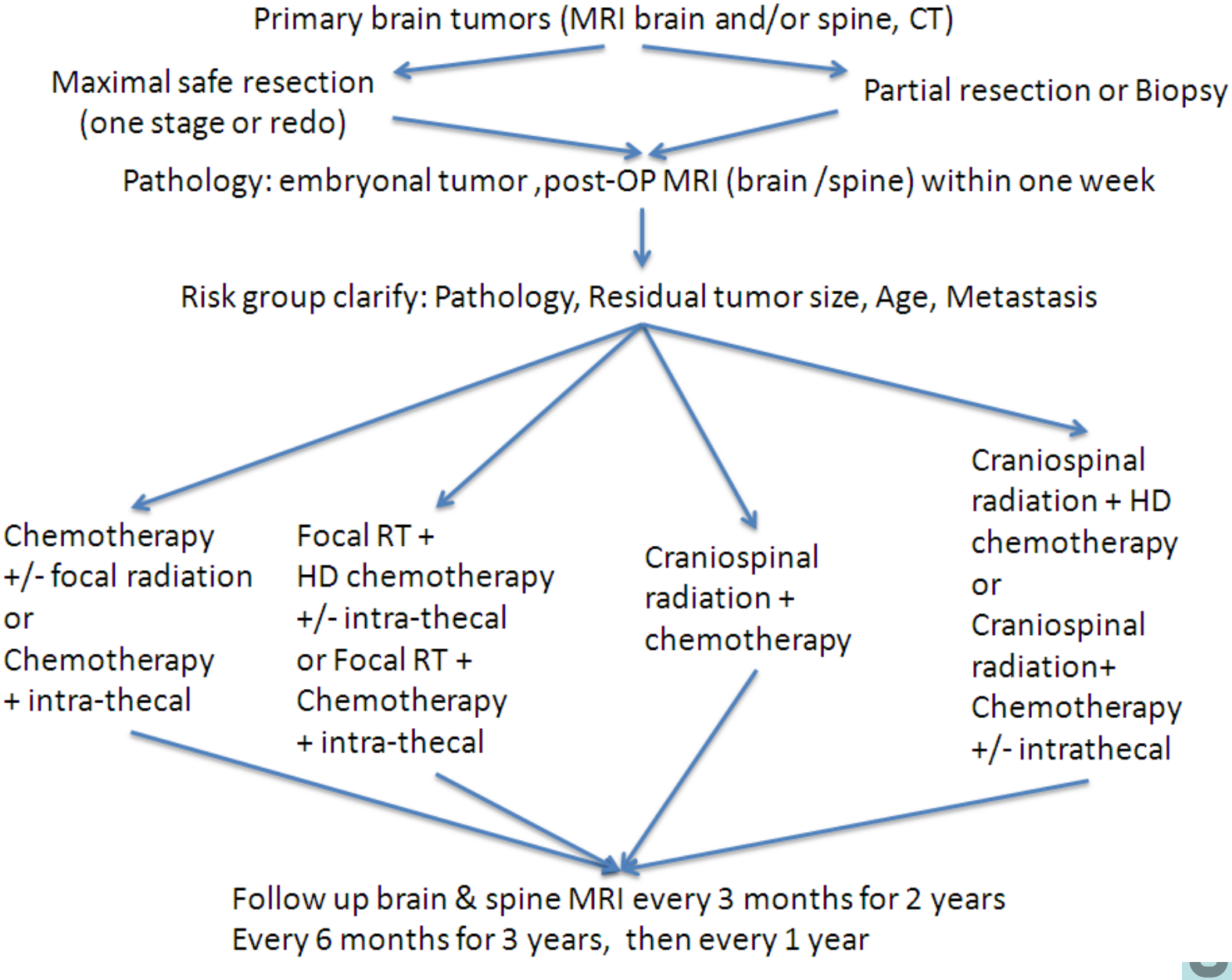


Yi-Wei Chen et al., Cancer 2011

Treatment Principles of Central Nervous System Embryonal Tumors and Pineoblastomas

Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*

CNS Embryonal Tumors



Principles of Radiotherapy

- **Craniospinal irradiation (CSI) plus primary and metastatic boost (PB & MB) is the mainstay treatment policy for embryonal tumors.**
- **Radiotherapy strategy for medulloblastoma depends most on risk groups.**
- **For "Average-risk group", CSI 2340-2400 cGy (1.5-1.8 Gy) is recommended and PB 5000-5580 cGy is recommend.**
- **For "High-risk group", CSI 3000-4000 cGy (1.5-1.8 Gy daily) is recommended and PB 5000-5580 cGy (1.5-2 Gy daily) is recommended and 4000-5000 cGy(1.5-2 Gy daily) boost is recommended for major spinal seeding.**
- **For patients whose age are less than three years, we recommend to arrange focal irradiation only with dose range from 4000-5000 cGy (1.8 to 2 Gy).**
- **GTV: primary enhancement lesion in MR image.**
- **CTV1 (Craniospinal axis): the volume encompasses whole brain and whole spinal canal (the lower level is at S2/3)**
- **CTV2: primary enhancement lesion (GTV) plus 1-1.5 cm margins (Usually locate in post fossa).**
- **PTV: CTV plus 0.3-0.5 cm margins.**
- **Only two dose level is recommended. (No posterior fossa boost is recommended)**
- **Other embryonal tumors, including PNET and AT/RT will follow the policy for medulloblastoma.**

CNS Embryonal Tumors
Principle of Chemotherapy

Average risk:

- Regimen A: Vinblastine 6 mg/m^2 on Day 1, and Etoposide 100 mg/m^2 on Day1-3 and Cisplatin 75 mg/m^2 on Day 2
- Regimen B: Cyclophosphamide 700-1000 mg/m^2 on Day 1,2 and Vinblastine 6 mg/m^2 on day 3, alternating with Regimen A

High risk:

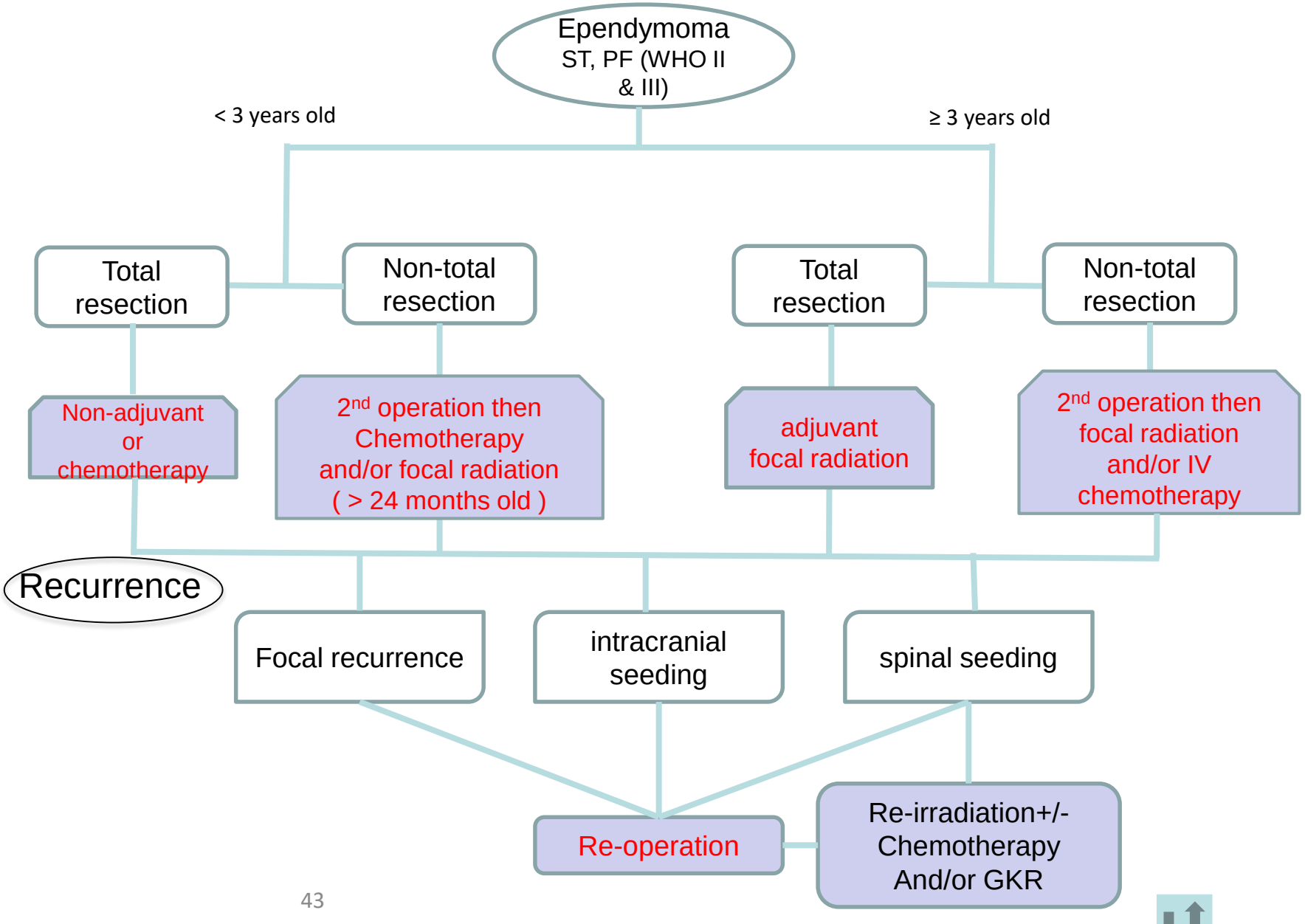
- ICE: Ifosfamide 2-2.4 g/m^2 on D1-3 and Etoposide 150 mg/m^2 on Day1-3 and Cisplatin 90 mg/m^2 on Day 2

CNS Embryonal Tumors
References of Chemotherapy

1. Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, et al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol. 2009;27(3):385-9.
2. Fangusaro J, Finlay J, Sposto R, Ji L, Saly M, Zacharoulis S, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): Report of the Head Start I and II experience. Pediatric Blood & Cancer. 2008;50(2):312-8.
3. Fangusaro J, Massimino M, Rutkowski S, Gururangan S. Non-cerebellar primitive neuroectodermal tumors (PNET): summary of the Milan consensus and state of the art workshop on marrow ablative chemotherapy with hematopoietic cell rescue for malignant brain tumors of childhood and adolescents. Pediatr Blood Cancer. 2010;54(4):638-40.
4. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. The Lancet Oncology. 2006;7(10):813-20.
5. Garre ML, Tekautz T. Role of high-dose chemotherapy (HDCT) in treatment of atypical teratoid/rhabdoid tumors (AT/RTs). Pediatr Blood Cancer. 2010;54(4):647-8.
6. Lafay-Cousin L, Strother D. Current treatment approaches for infants with malignant central nervous system tumors. Oncologist. 2009;14(4):433-44.
7. Rutkowski S, Cohen B, Finlay J, Luksch R, Ridola V, Valteau-Couanet D, et al. Medulloblastoma in young children. Pediatr Blood Cancer. 2010;54(4):635-7.

Treatment Principles of Central Nervous System Ependymomas

Central Nervous System Cancers



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.)**

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.

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。

Salvage BNCT for recurrent pediatric brain tumors (BNCT: Boron Neutron Capture Therapy)

- BNCT is an internal targeted particle therapy (Binary treatment: both boron drug injection and thermal neutron irradiation).
- Treatment location: National Tsing-Hua University Open Pool Reactor (THOR)
- Treatment indication: recurrent pediatric brain tumors (grade III, IV and intractable low grade gliomas).
- Treatment criteria: FBPA-PET T/N ratio >2.5 (performed in nuclear medicine department of VGHTPE)
- Treatment interval: one day only in THOR.
- Treatment fee: all self-paid.

2021修訂

p10修改 <=3 years old, consider chemotherapy first, hold radiotherapy if recurrent

- P18 Etoposide 100 mg/m^2