# case presentation

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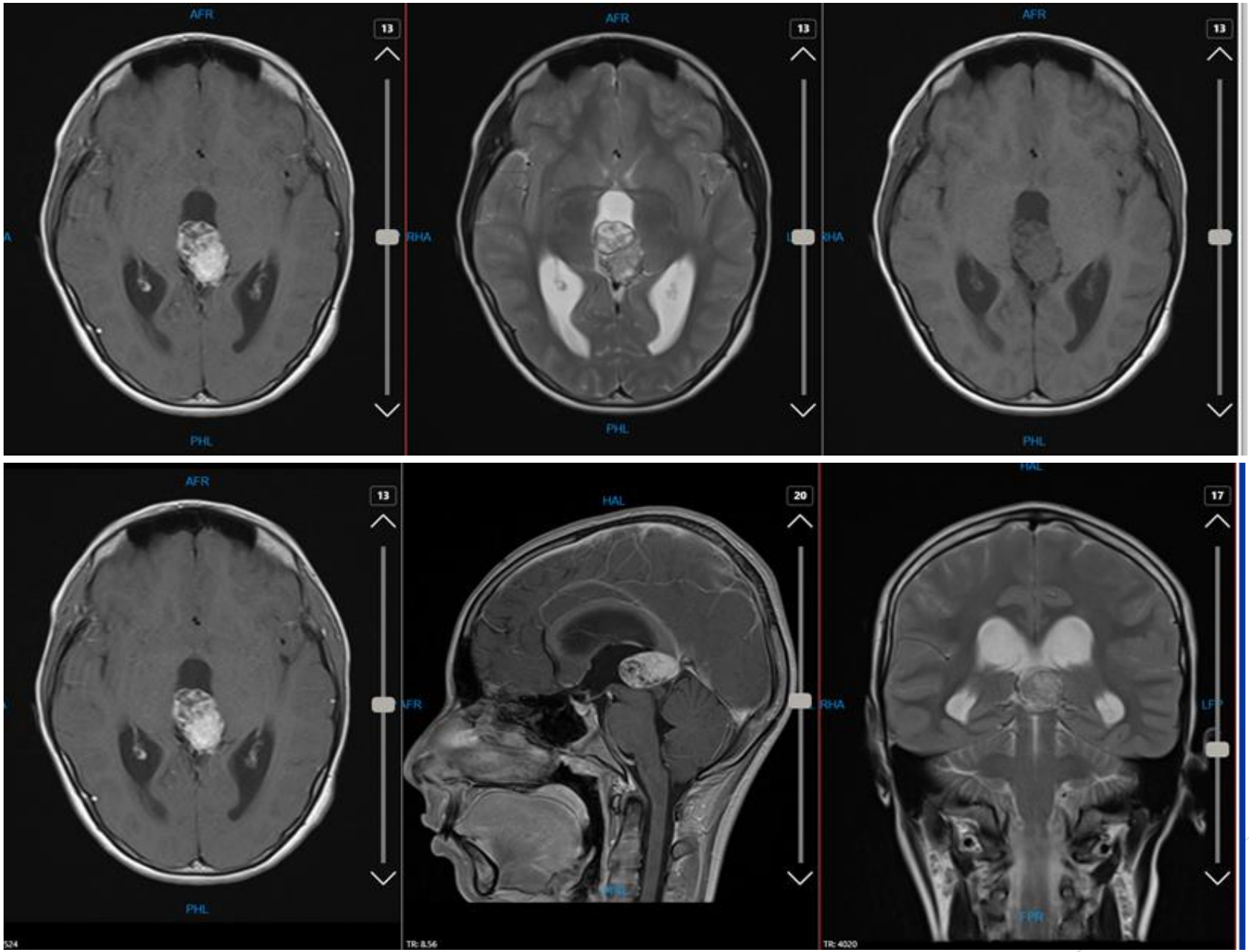
MAHAK

- 12 Y/O boy
- C.C : headache & N/V , from 20 days ago
- Brain MRI (1403.6.1) : pineal mass

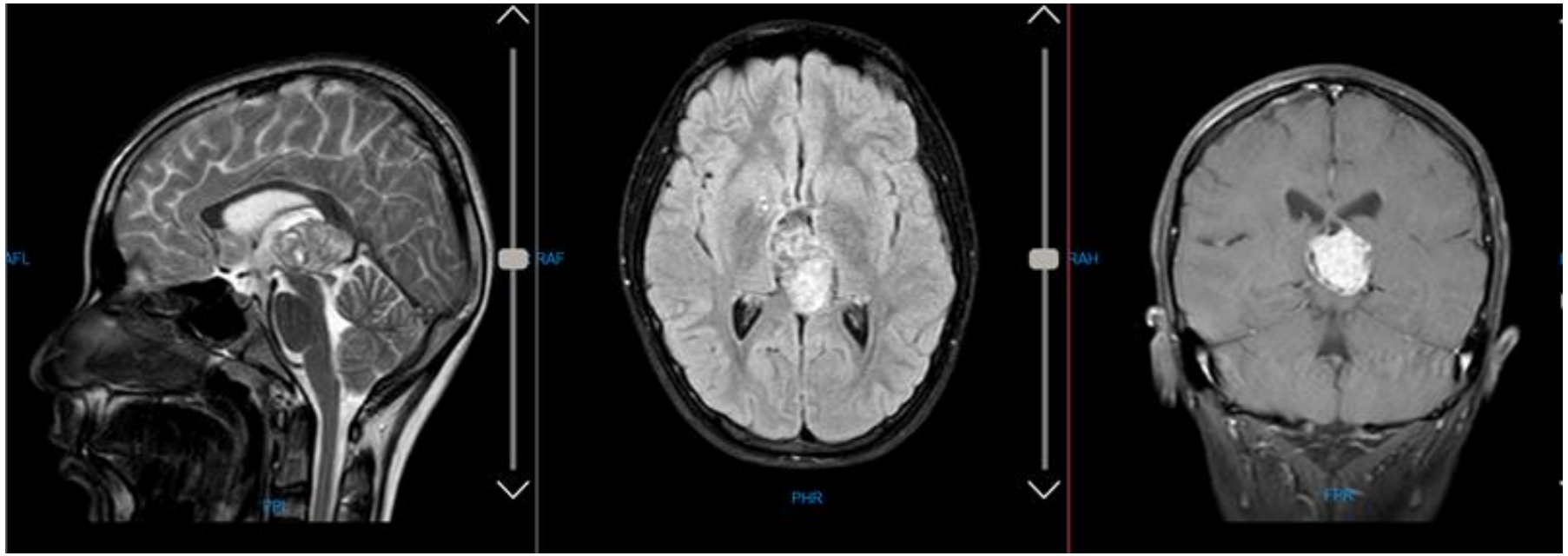


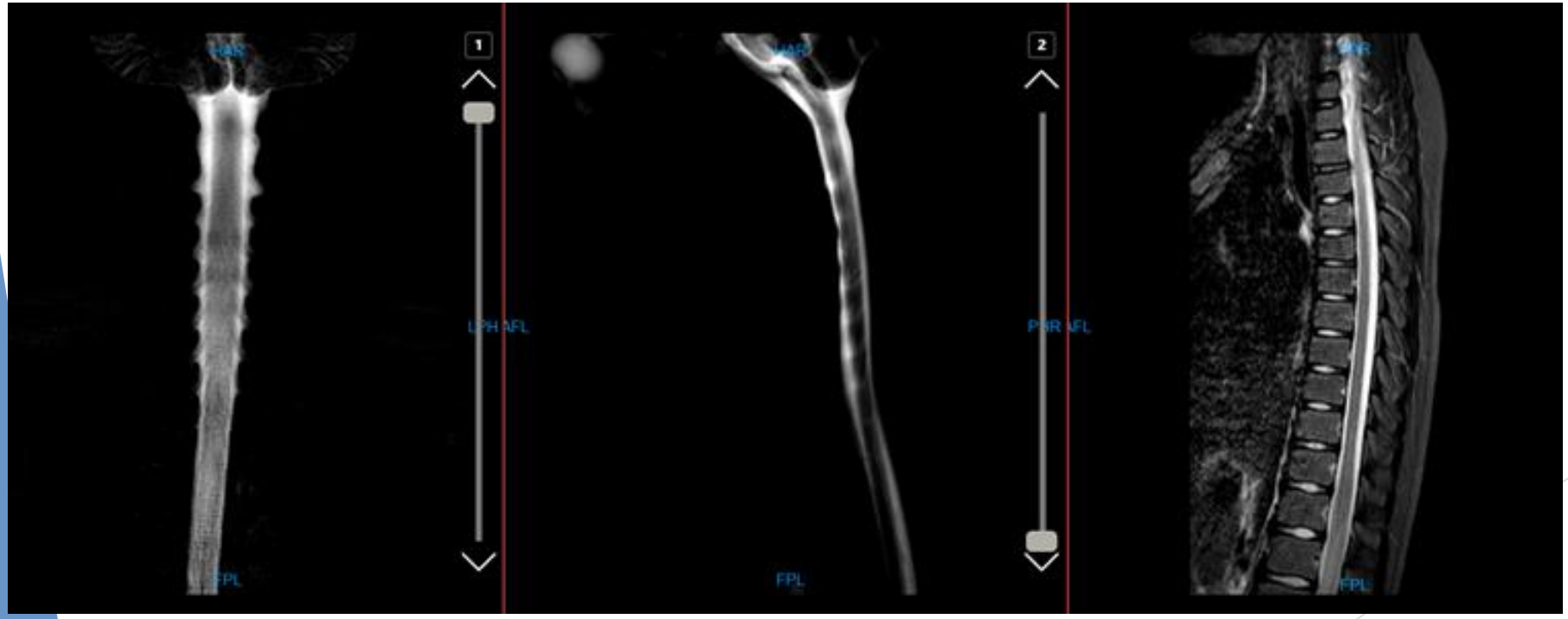

# Pre-op (1403.6.1)

# evaluations

- Serum ßHCG : < 1
- Serum αFP : 11.3

# After Shunt & Bx MRI (1403.7. )





# first pathology

Clinical Data : Pineal mass.

Macroscopic : SRIF consists of multiple fragments of tan white soft tissue, TM=0.3cm.
TS/1B.

Microscopic : Sections reveal a heterogeneous neoplasm composed of lobules of cartilage with some cytologic atypia, multiple glandular structures lined by flat to cuboidal ciliated epithelial cells. A spindle and also a small cell- like components are also noted.
IHC study result:

- SALL4: Negative
- Panck: Positive
- GFAP: Positive
- Synaptophysin: Focally positive
- Vimentin: Positive
- CD45: Negative
- CD3: Negative
- CD20: Negative
- Ki67: High in small cell component

**Diagnosis : Brain tumor, pineal, biopsy:**

- **Pineal anlage tumor.**

# Pineal anlage tumor (PAT)

- An extremely rare tumor of paediatric population.
- Subtype of pineoblastoma having ectomesenchymal/ rhabdomyoblastic and cartilaginous differentiation.
- Aggressive behaviour with propensity for (CSF) spread due to histologically resemblance with pineoblastoma.
- requiring intensive multimodality treatment with craniospinal irradiation and chemotherapy.

**Clinical information:** Not provided
MRI: There is an enhancing mass 30x20 mm in anatomic location of pineal gland which causes obstructive tissue ventricular hydrocephalus. White/gray matter signal is within normal limit. Sellar and suprasellar structures have normal appearance and signal.

**Specimen:** Paraffin block TP-03-12477

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**PROCEDURE**

Immunohistochemical studies were performed using antibodies against the following markers:

| MARKERS | RESULTS |
|---|---|
| **1** – SALL4 | Positive in undifferentiated/germinoma cells |
| **2** – CD117 | Positive in undifferentiated/germinoma cells |
| **3** – PLAP | Positive in undifferentiated/germinoma cells |
| **4** – Glypican 3 | Patchy positive in stromal cells |
| **5** – Synaptophysin | Patchy/focally positive in neuroepithelial elements |
| **6** – Pan-CK | Positive in epithelial/glandular elements |
| **7** – α-FP | Negative in tumor cells |
| **8** – CD30 | Negative in tumor cells |
| **9** – Ki67 | Positive in up to 25% tumor cells |

**INTERPRETATION**

Histology and results of immunophenotyping are that of "Mixed Germ Cell Tumor, comprising Germinoma (<10%) and immature teratoma (>90%)"

# Pathology revised

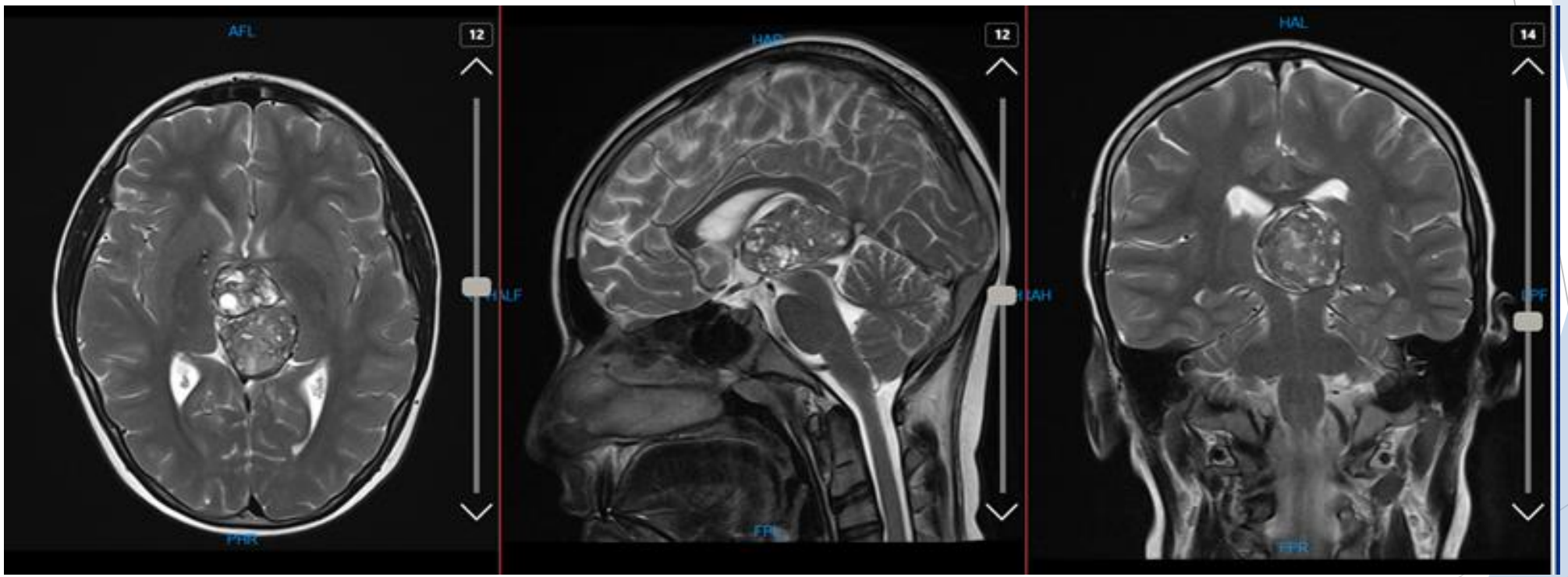
# CTx protocol

- ***ACNS1123***

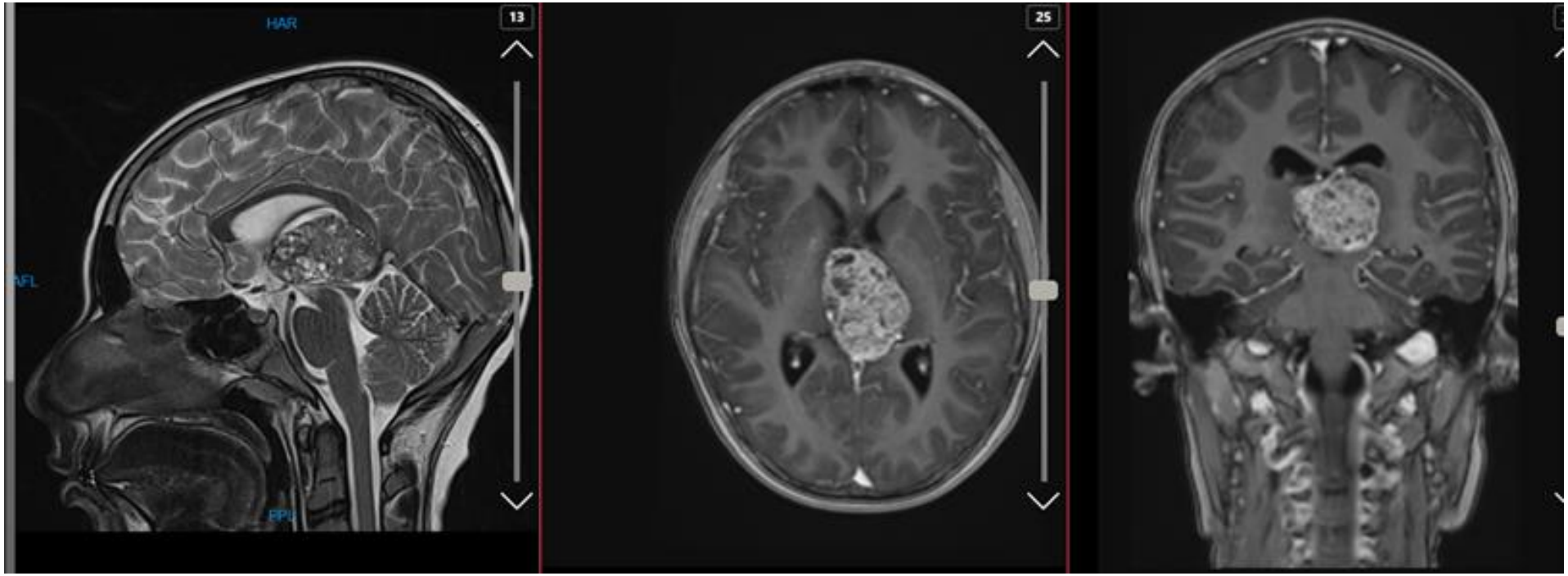
Chemotherapy A (weeks 0, 6, and 12)
Carboplatin 600 mg/m$^2$ on day 1
Etoposide 150 mg/m$^2$ on days 1-3

Chemotherapy B (weeks 3, 9, and 15)
Ifosfamide 1,800 mg/m$^2$ on days 1-5
Etoposide 100 mg/m$^2$ on days 1-5

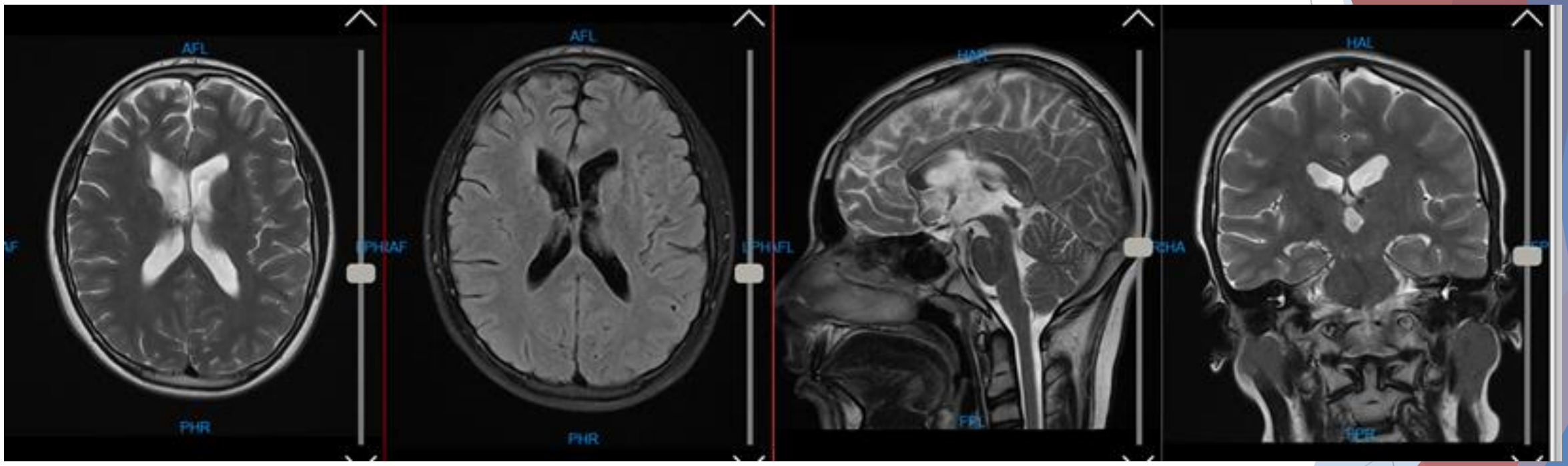
# MRI after 4th course (1403.10.)



# End of CTx MRI (1403.12.)



# Post 2nd N/S MRI (1404.1.)/ GTR



| MARKERS | RESULTS |
|---|---|
| 1 – GFAP: | Highlights mature and glial neuronal component |
| 2 – Synaptophysin: | Highlights mature and glial neuronal component |
| 3 – SALL4: | Negative |
| 4 – Ki-67: | Positive in <5% of cells |

**INTERPRETATION**

Histology and results of immunophenotyping are that of "Mature Teratoma" *See the note & comment*

**NOTE:**

Please also see the pathology report TP-04-623

**COMMENT:**

The case of this 12-year-old body, initially diagnosed with a mixed germ cell tumor predominantly composed of immature teratoma (>90%) and a minor germline component (<10%), presents an intriguing diagnostic challenge. The subsequent development of a large mass in the same region within six months, with histological review revealing a mature teratoma component, raises the possibility of Growing Teratoma Syndrome (GTS), a rare phenomenon occurring in approximately 5% of central nervous system germ cell tumors.

GTS is characterized by tumor growth during and after chemotherapy, consisting exclusively of mature teratomas without elevated tumor markers. The hypothesized mechanisms include chemotherapy-induced elimination of all but the mature teratoma component, uncontrolled proliferation of the mature teratoma, or chemotherapy-induced differentiation of the immature component into mature teratoma. However, the precise biological drivers of this rapid increase in mature benign tissue remain unclear.

Given the histological findings and clinical progression, further investigation is warranted to confirm the presence of GTS in this case. A comprehensive review of imaging studies, tumor marker trends, and histopathological assessments will be essential in guiding appropriate management strategies. Surgical resection remains the primary treatment for GTS, as chemotherapy is ineffective against mature teratomas.

**DISCLAIRMENT:**

The diagnosis provided in this report is based on the examination of the submitted FFPE block, which corresponds to the original pathology report number S-1403-7259, Toos Hospital pathology lab, Tehran. This diagnosis is intended for a second opinion and should be considered in conjunction with the patient's clinical history, other diagnostic tests, and the primary pathology report. The accuracy of the diagnosis is contingent upon the quality and integrity of the submitted sample. Any discrepancies or additional findings should be discussed with the referring laboratory and the patient's healthcare provider.

# 2nd pathology

# GTS

- Growing teratoma syndrome (GTS) led to PD .
- GTS was first reported by Logothetis et al in 1982 in six patients with systemic, nonseminomatous germ cell tumors and has been estimated to occur in 2% to 7% of systemic GCTs.
- GTS should be suspected in patients with:
  - (1) history of NSGCT,
  - (2) increasing size of metastatic lesions on serial imaging during or after systemic chemotherapy,
  - (3) normalized serum tumor markers or a physiological explanation for the presence of abnormal tumor markers.
- The diagnosis is confirmed by the presence of mature teratoma and the absence of any malignant germ cells on final surgical pathology.

# GTS

- The etiology of GTS is unclear.
- The two most-quoted theories are that:
  - (1) chemotherapy destroys only the immature malignant cells, leaving the mature benign teratomatous elements.
  - (2) chemotherapy alters the cell kinetics toward transformation from a totipotent malignant germ cell toward a benign mature teratoma.
- Complete surgical resection of GTS is often **curative.**

**Clinical information:** Known case of mixed germ cell tumor of pineal region
MRI: Large 36x34 mm intraventricular mass filling and expanding the body of the left lateral ventricle and extension to 3th ventricle. It has signal, low T1 signal and has multiple small cystic regions within it (bubble appearance). Following contrast administration only minimal heterogeneous enhancement is present.

**Specimen:** Mass of pineal and intraventricular region; seven FFPE blocks with the copy of corresponding pathology report reference No: S-1403-7259 from Toos Hospital pathology lab, Tehran, sent for second opinion.

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## MICROSCOPIC DESCRIPTION:

Histology sections show variable sized keratin-filled cystic structures which lined by mature stratified squamous epithelium. There are also islands of mature and immature cartilage as well as simple and complex glands which formed by mature endocervical, intestinal or respiratory epithelium. Stroma show desmoplastic fibrosis with patchy inflammation and foreign body giant cell reaction next to keratinized cyst. Islands of mature neuronal and glial tissue were also seen which are highlighted with Synaptophysin and GFAP.
SALL4 is negative. Ki-67 is estimated less than 5%.

## SECOND LOOK DIAGNOSIS:

**MASS OF PINEAL AND VENTRICULAR REGION (OUTSIDE FFPE BLOCK NO: S-1403-7259):**

- Mature teratoma-*See the note*

## NOTE:

Please see the IHC report TP-04-624

## COMMENT:

The case of this 12-year-old body, initially diagnosed with a mixed germ cell tumor predominantly composed of immature teratoma (>90%) and a minor germline component (<10%), presents an intriguing diagnostic challenge. The subsequent development of a large mass in the same region within six months, with histological review revealing a mature teratoma component, raises the possibility of Growing Teratoma Syndrome (GTS), a rare phenomenon occurring in approximately 5% of central nervous system germ cell tumors.
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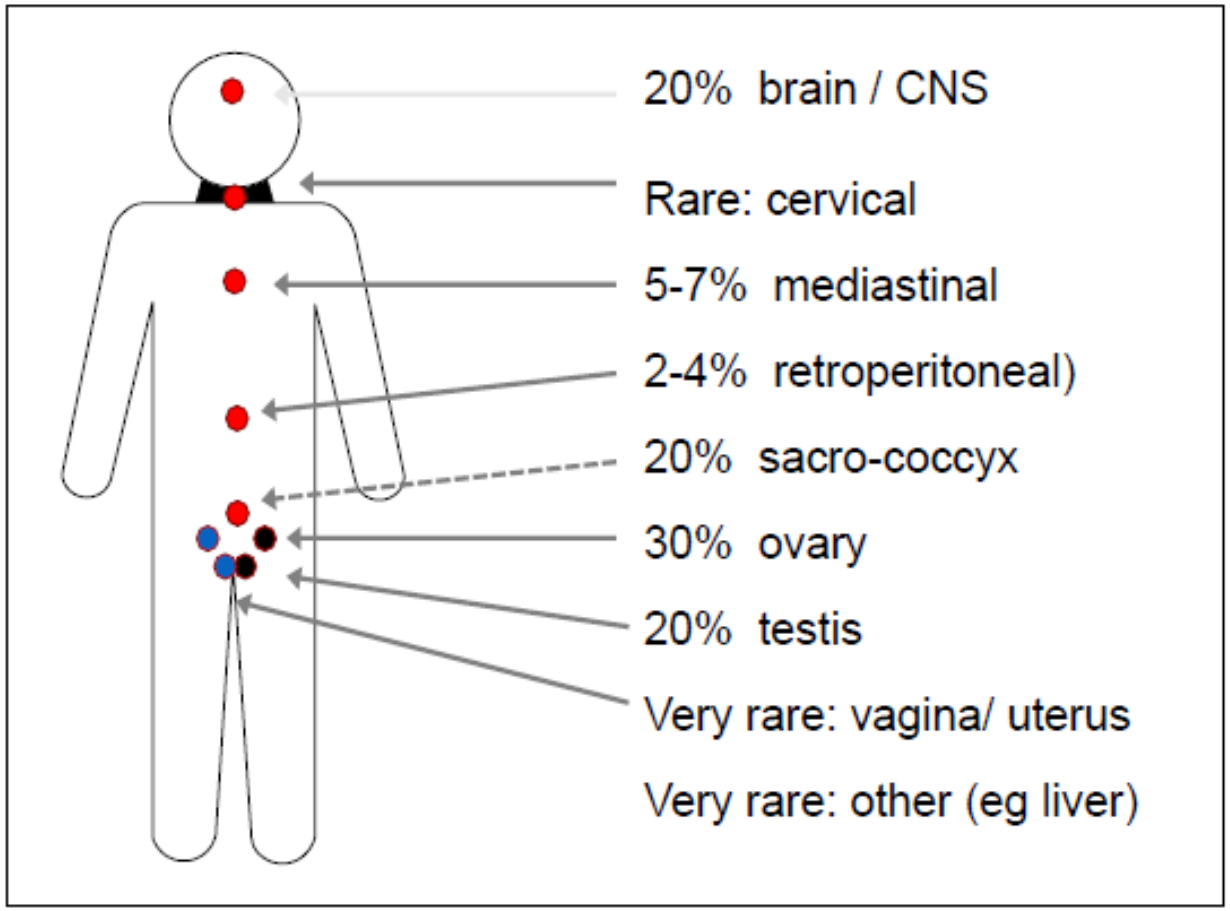
# RTx

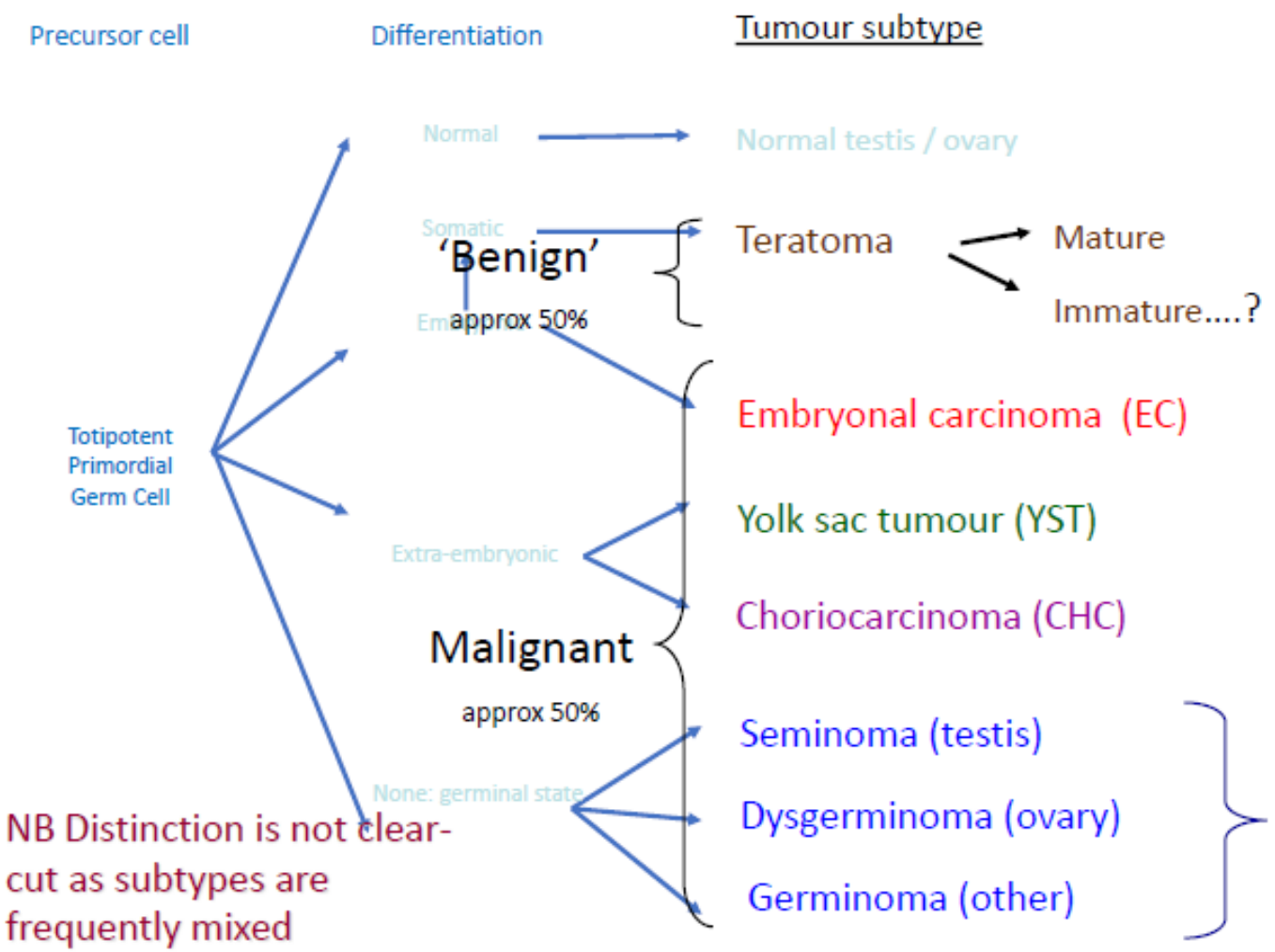
- CSI (36 Gy) + Boost (54 Gy)

# Childhood germ cell tumour sites




GCTs account for around 4% of childhood cancer

# GCT classification



# GCT classification

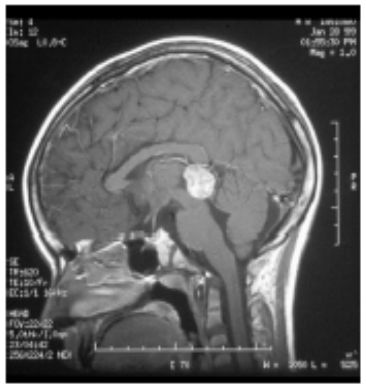
| Tumour markers | Tumour subtype | |
|---|---|---|
| ↑AFP ..... | Teratoma → Mature / Immature | |
| +-↑AFP ↑HCG ..... | Embryonal carcinoma (EC) | |
| ↑↑AFP..... | Yolk sac tumour (YST) | |
| ↑↑HCG..... | Choriocarcinoma (CHC) | *(rare)* |
| ↑HCG ..... | Seminoma (testis) | |
| | Dysgerminoma (ovary) | |
| | Germinoma (other) | |

# CNS GCT Classification – Europe / US

- Defined by most malignant component
  - Germinoma (account for ~2/3)
    - may also include teratoma component
  - Nongerminoma (NGGCT) - one or more of:
    - YST, CHC, EC
    - May also contain germinoma and/or teratoma
    - Most are therefore *mixed malignant GCT*
    - Majority can be diagnosed by markers alone; hence '*secreting GCTs*'
- Presence of teratoma in mixed tumour may only become apparent later, as resection not routinely performed at time of diagnosis

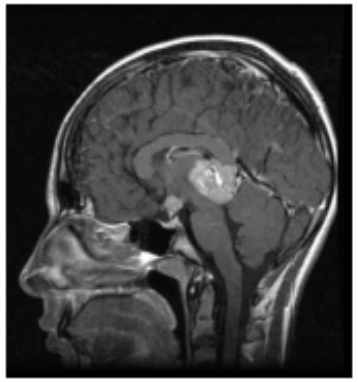
# Sites of CNS GCT and presenting features

- **Pineal (40-60%)**

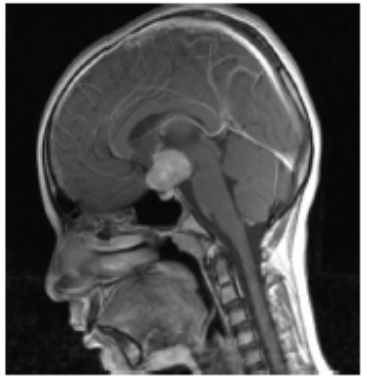


  - Raised ICP
  - Visual disturbance – Parinaud syndrome

- **Bifocal (2-26%)**



- **Suprasellar (30-40%)**
  - Diabetes Insipidus
  - Precocious or delayed puberty
  - Hypopituitarism / GH deficiency
  - Visual disturbance
  - Raised ICP



- **Other (e.g. basal ganglia) (10-15%)**
  - Behaviour and emotional changes
  - Pyramidal tract signs or ataxia
- **Diagnosis often delayed**
  - No change in OS
  - But metastatic disease more frequent, more treatment, more late-effects

# Diagnostic work-up

- MRI scan – head and spine
- CSF cytology

….for staging purposes

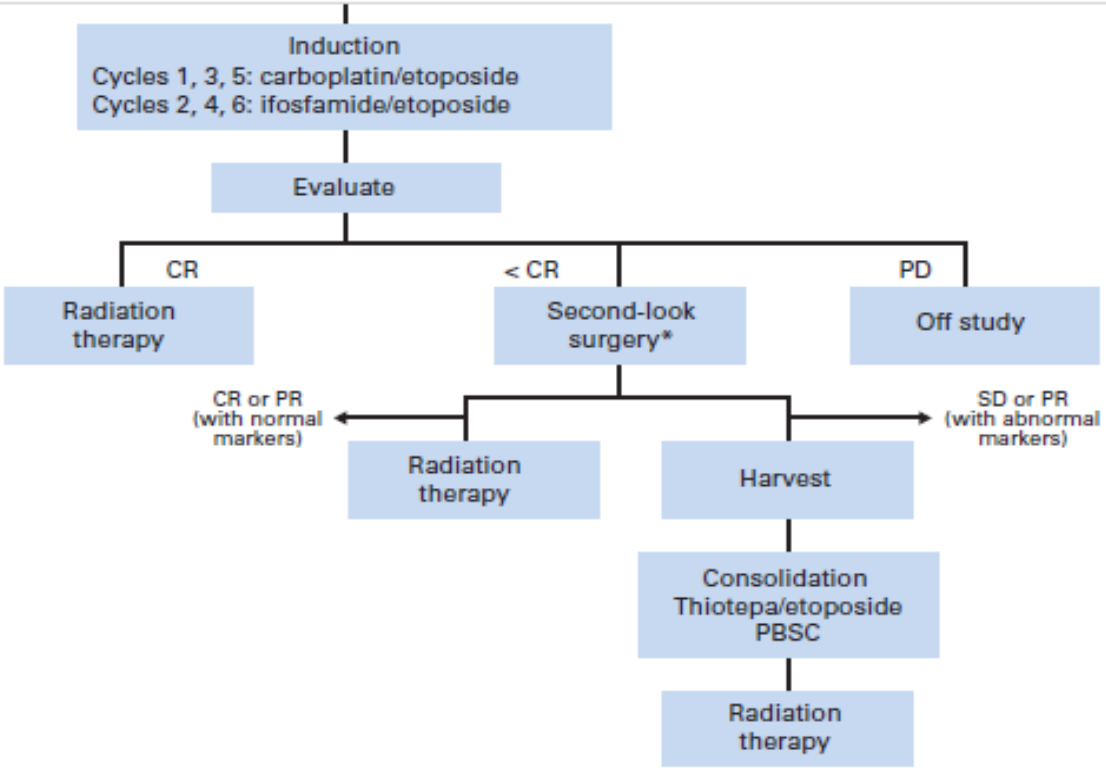

- CSF cytology

….for staging purposes


Marker Thresholds
(SIOP trials)
AFP>25 ng/ml
ß-HCG >50 IU/L

- Serum *and* CSF markers
- Histology – only if markers negative in *both serum and CSF*

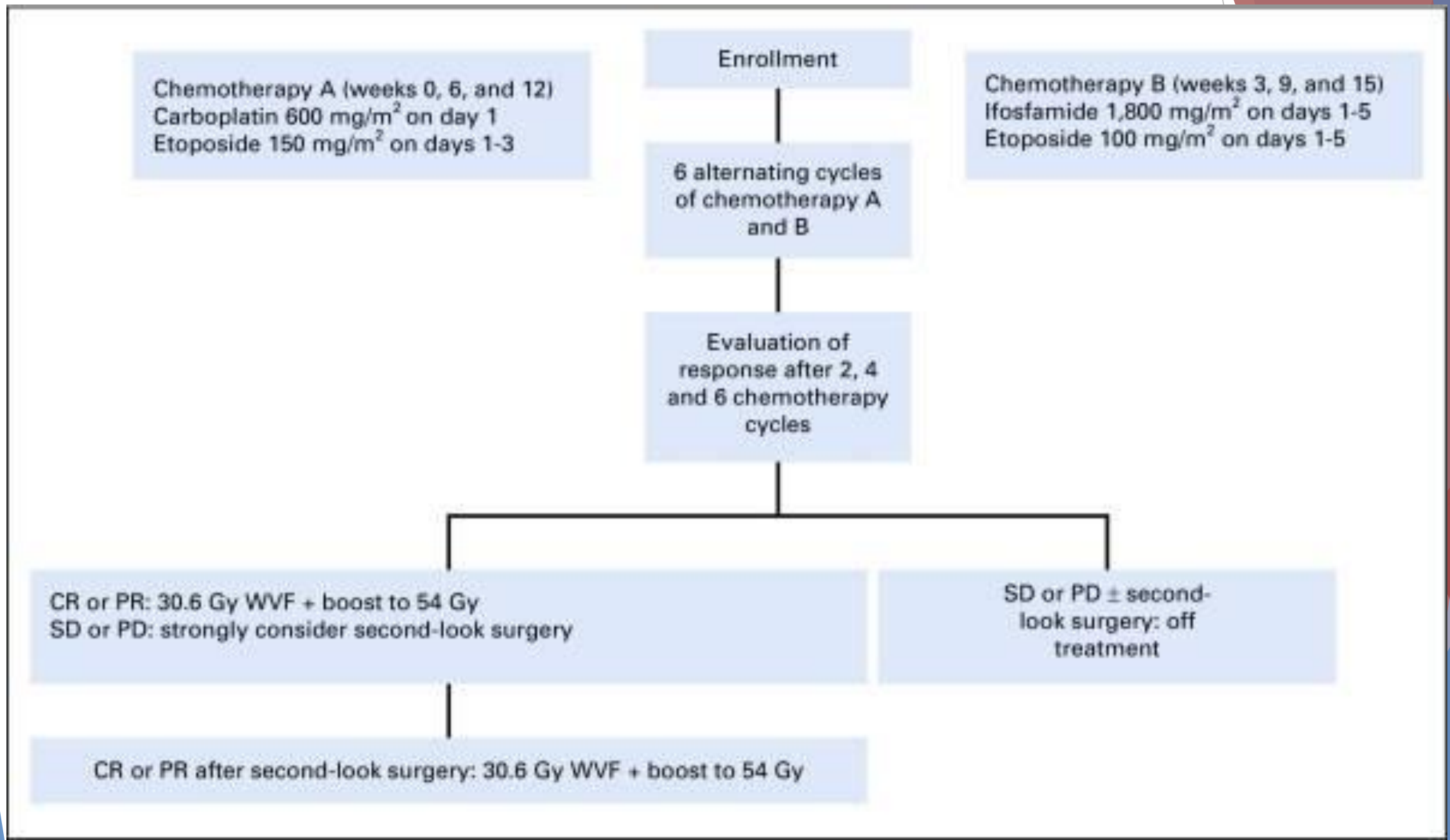
….to distinguish Germinoma from secreting tumour




| Induction | |
|---|---|
| Cycles 1, 3, 5<br>Carboplatin 600 mg/m² day 1<br>Etoposide 90 mg/m²/day days 1, 2, 3<br>G-CSF 5 μg/kg/day SQ/IV/day days 4-13 or until ANC > 1,500/μL | Cycles 2, 4, 6<br>Ifosfamide 1,800 mg/m²/day days 1-5<br>Etoposide 90 mg/m²/day days 1-5<br>G-CSF 5 μg/kg SQ/IV/day days 6-15 or until ANC > 1,500/μL<br>Mesna 360 mg/m²/dose days 1-5 |
| **Consolidation** | |
| Etoposide 500 mg/m²/day days -5 to -3 (1,500 mg/m²)<br>Thiotepa 300 mg/m²/day days -5 to -3 (900 mg/m²)<br>Rest day -2 and -1<br>Day 0 PBSC infusion<br>G-CSF 5-10 μg/kg SQ/IV/day starting day 1 until ANC > 10,000/μL | |
| **Radiation Therapy** | |
| 36 Gy CSI 54 Gy tumor bed with 45 Gy to bulky spinal metastasis | |

# ACNS0122

# ACNS1123


Enrollment
Chemotherapy A (weeks 0, 6, and 12)
Carboplatin 600 mg/m$^2$ on day 1
Etoposide 150 mg/m$^2$ on days 1-3
Chemotherapy B (weeks 3, 9, and 15)
Ifosfamide 1,800 mg/m$^2$ on days 1-5
Etoposide 100 mg/m$^2$ on days 1-5
6 alternating cycles of chemotherapy A and B
Evaluation of response after 2, 4 and 6 chemotherapy cycles
CR or PR: 30.6 Gy WVF + boost to 54 Gy
SD or PD: strongly consider second-look surgery
SD or PD ± second-look surgery: off treatment
CR or PR after second-look surgery: 30.6 Gy WVF + boost to 54 Gy

- **CR** was defined as a complete disappearance of disease on imaging, allowing for MRD or enhancement of not more than 0.5 cm in the suprasellar region or not more than 1 cm in the pineal region.

- **PR** was defined as greater than 0.5-cm residual in the suprasellar region or greater than 1 cm in the pineal region and at least a 65% decrease in the sum of the products of the three perpendicular diameters of the localized target lesion.

- The CR and PR definitions mandated normalization of serum and CSF AFP and b-HCG levels.

- **SD**(Stable disease) was defined as neither sufficient decrease to qualify for PR nor increase to qualify for progressive disease (PD).

- **PD** was defined as a 40% or more increase of the lesion, the appearance of new lesions, and/or increased tumor markers.

# Intracranial GCTs – Treatment rationale

Intracranial GCTs share chemosensitivity of extracranial GCTs
***BUT*** require radiotherapy for cure

- **Role of surgery limited**
  - Biopsy if markers negative; resection of residual in certain cases
- **Germinoma (OS ~95%)**
  - cured *either* with cranio-spinal radiotherapy *or* combined chemo-RT
  - focus has been on reducing toxicity
- **Non-germinoma (NGGCT; OS ~70%)**
  - need *both* chemo and RT for cure
  - majority diagnosed without biopsy
  - limit radiotherapy fields according to dissemination

# Thank you