How to treat germ cell tumours

19 Dec 2015
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Disclosure

- Nil

Review

www.thelancet.com/oncology Vol 16 September 2015

Consensus on the management of intracranial germ-cell tumours

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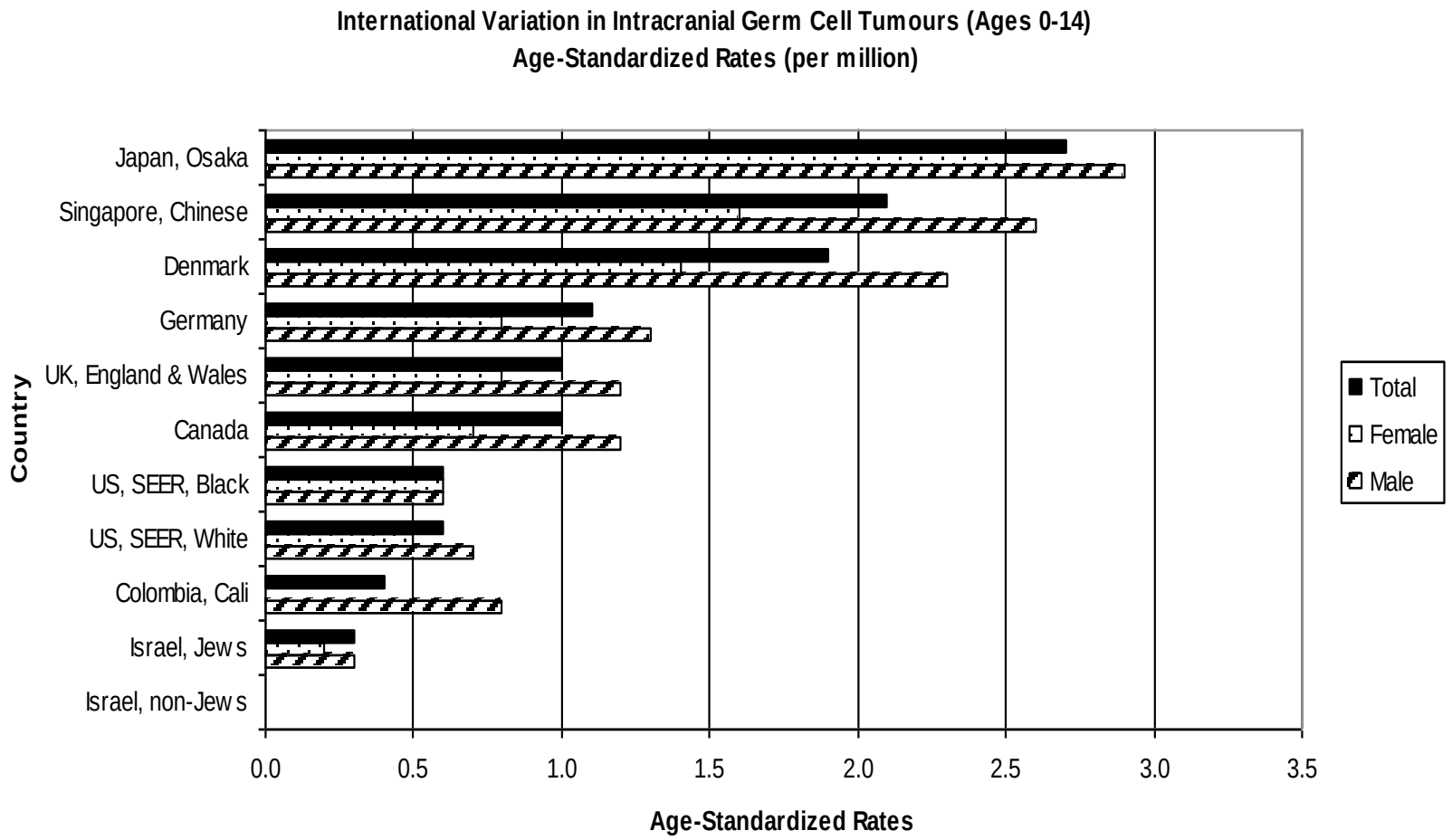
- Delphi Survey : 77 experts, 70% support with 60% respond

- Description / Diagnosis, radiological & cytological Staging /
- Management of hydrocephalus / Role of Surgery
- Role of histopathology
- Treatment of Germinoma / NGGCT, Focal/Metastatic disease
- Follow-up / Late effects

- 34 (89%) / 38 Consensus statements

IARC


International Variation in Intracranial Germ Cell Tumours (Ages 0-14)
Age-Standardized Rates (per million)
Country
Japan, Osaka
Singapore, Chinese
Denmark
Germany
UK, England & Wales
Canada
US, SEER, Black
US, SEER, White
Colombia, Cali
Israel, Jews
Israel, non-Jews
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Age-Standardized Rates
Total
Female
Male

Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries

Neuro-Oncology 14(9):1194–1200, 2012.

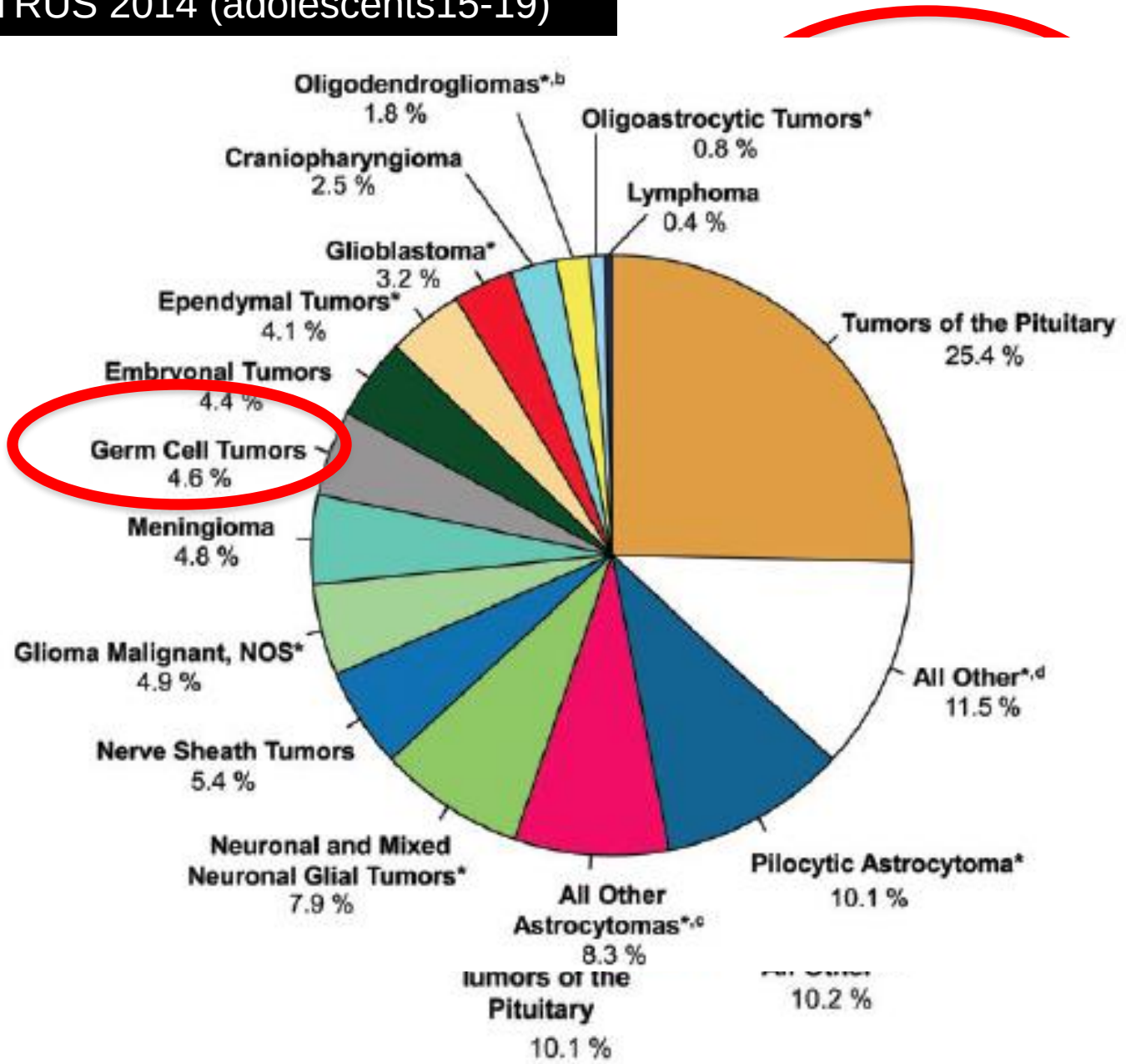
Japan – JCSRG / BTRJ	US – SEER / NCDB
0.096 / 100,000	**0.075** / 100,000
M = 0.143	M = 0.118
F = 0.046	F = 0.03

Incidence of Primary Central Nervous System Germ Cell Tumors in Childhood: A Regional Survey in Kumamoto Prefecture in Southern Japan

Pediatr Neurosurg 2013;49:155–158

	Age-adjusted / 100,000
Kumamoto (Japan)	**0.45** (1989-2013)
Taiwan	**0.221** (1996-2010)
Korea	**0.32** (2011)
Singapore	**0.359** (1997-2005)
USA (CBTRUS / SEER)	**0.18** / 0.15 (2004-2009)
Germany (Kaatsch)	**0.10** (1990-1999)

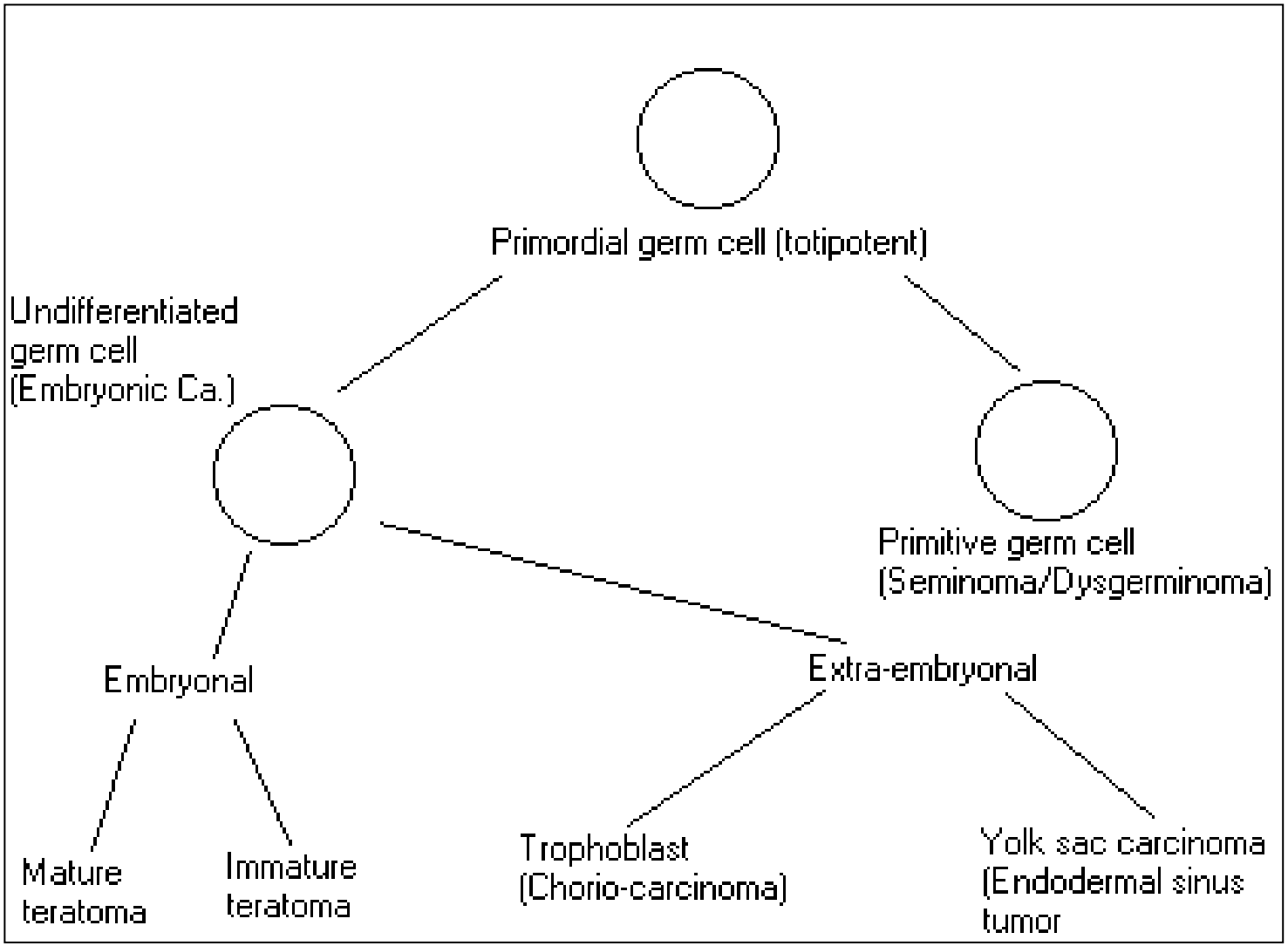
CBTRUS 2014 (adolescents15-19)



Sex / Age / Sites / Types

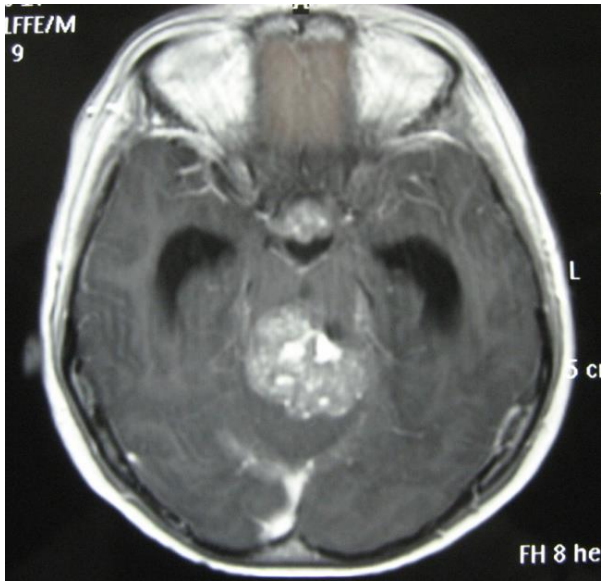
Characteristics	JCSRG (malignant)		SEER (malignant)	
	n (%)	Incidence (95% CI)	*n* (%)	Incidence (95% CI)
All malignant GCTs	122 (100.0)	0.096 (0.079–0.114)	289 (100.0)	0.075 (0.067–0.084)
Male	93 (76.2)	0.143 (0.113–0.172)	233 (80.6)	0.118 (0.103–0.134)
Female	29 (23.8)	0.046 (0.029–0.064)	56 (19.4)	0.030 (0.023–0.039)
00–14 y[a]	43 (35.3)	0.188 (0.132–0.244)	119 (41.2)	0.147 (0.122–0.176)
15–29 y[a]	65 (53.3)	0.224 (0.169–0.278)	141 (48.8)	0.175 (0.147–0.207)
30+ y[a]	14 (11.5)	0.013 (0.006–0.019)	29 (10.0)	0.014 (0.009–0.020)
Primary site				
Pineal (C75.3)	49 (40.2)	0.039 (0.028–0.049)	134 (46.4)	0.035 (0.029–0.041)
Nonpineal (C700–729, 751–752)	73 (59.8)	0.058 (0.044–0.071)	155 (53.6)	0.040 (0.034–0.047)
Suprasellar Region[b]	51	0.038 (0.027–0.049)	88	0.023 (0.018–0.028)
Ventricle	–	–	28	0.007 (0.005–0.010)
Brain, NOS	36	0.027 (0.018–0.036)	40	0.010 (0.007–0.014)
Pituitary gland	13	0.010 (0.004–0.015)	19	0.005 (0.003–0.008)
Cerebrum	16	0.014 (0.007–0.021)	29	0.007 (0.005–0.011)
All other sites	–	–	38	0.010 (0.007–0.014)
Selected histologies				
Germinoma	100 (82.0)	0.078 (0.062–0.093)	224 (77.5)	0.058 (0.051–0.066)
Teratoma	7 (5.7)	0.006 (0.002–0.011)	21 (7.3)	0.005 (0.003–0.008)
Mixed GCT	9 (7.4)	0.007 (0.002–0.012)	32 (11.1)	0.008 (0.006–0.012)

Classification

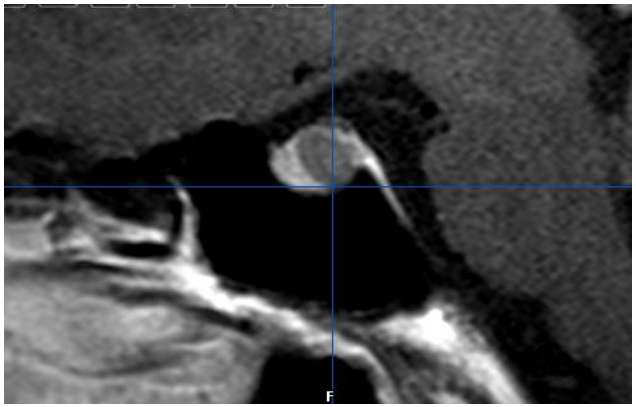


Locations

Pineal

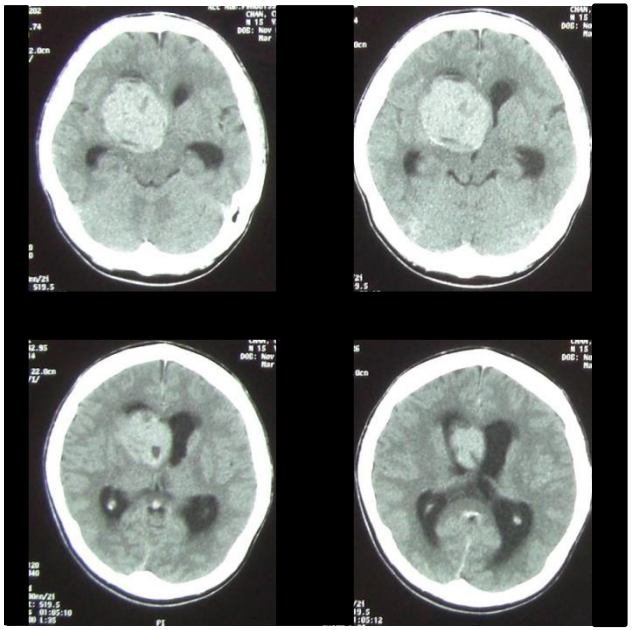


pituitary

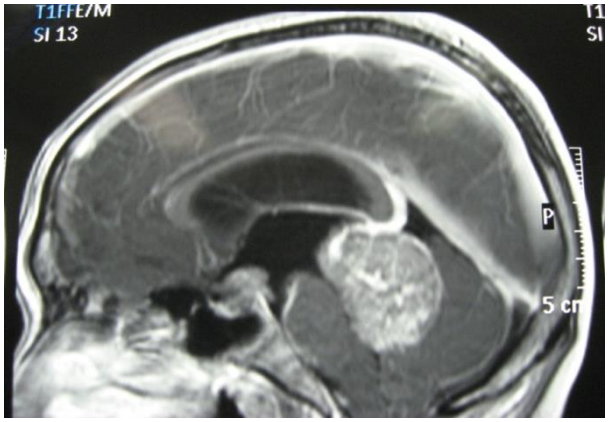


Bifocal

Basal ganglia



Suprasellar

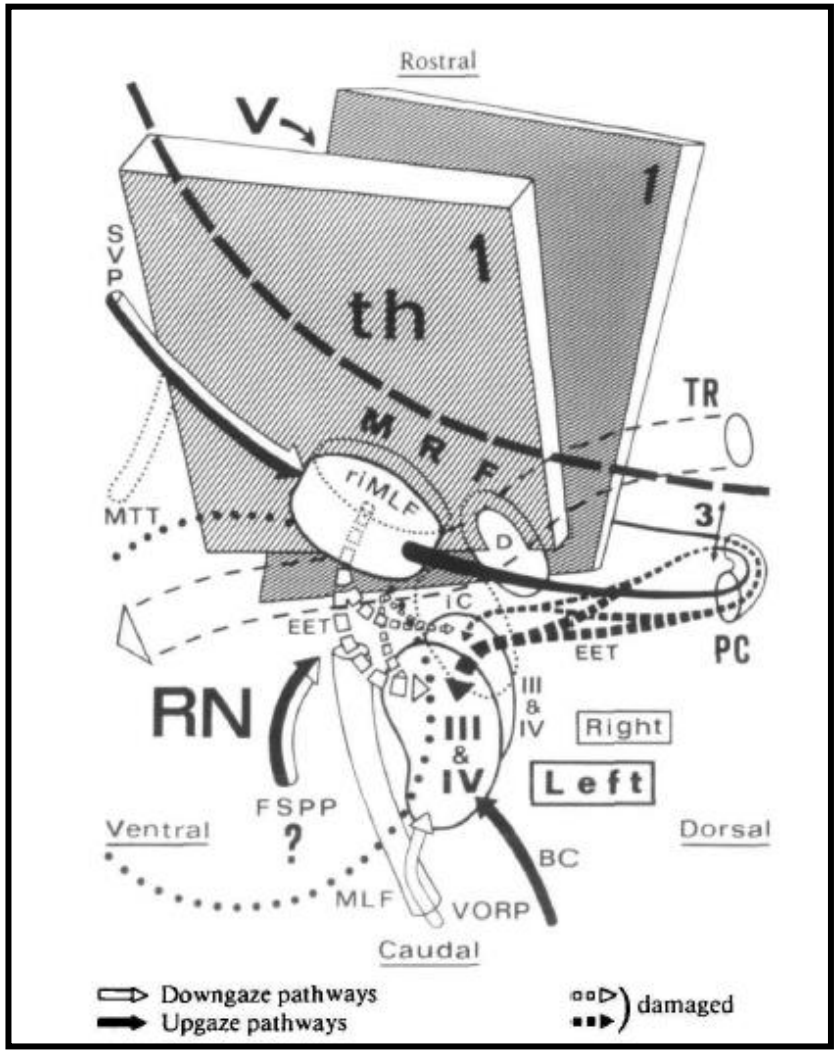


Clinical presentation

- Acute hydrocephalus (Ventricular)
- Parinaud's syndrome (Pineal region)
  - Upward gaze impairment
- Endocrine dysfunction (Suprasellar/sellar)
  - DI, hypothyroid, hypogonadism, panhypopituitarism
- Hemiparesis (basal ganglia)

Parinaud's syndrome

- Dorsal Midbrain Syndrome
  - rostral interstitial nuclei of the medial longitudinal fasciculus
- Upward gaze palsy
- Convergence retraction nystagmus
- Light-near dissociation
- Pathological lid retraction (Collier's sign)



Brain (1982), **105**, 667-696

Tumour markers : AFP / beta-HCG

- Serum
- CSF – Ventricular / LP-CSF
- NGGCT – elevated AFP / beta-HCG
  - AFP – Yolk sac tumour
  - Beta HCG – Choriocarcinoma
  - Both – Embryonal carcinoma
- Germinoma – normal AFP / ? beta-HCG
  - 50IU/L
  - 200IU/L

CSF Cytology

- 7 – Where treatment protocol decision are based on the result of CSF cytology, then CSF cytology examination is essential (after treatment for hydrocephalus but before treatment)

- 8 - Lumbar CSF cytology is prefered to ventricular CSF

Surgery

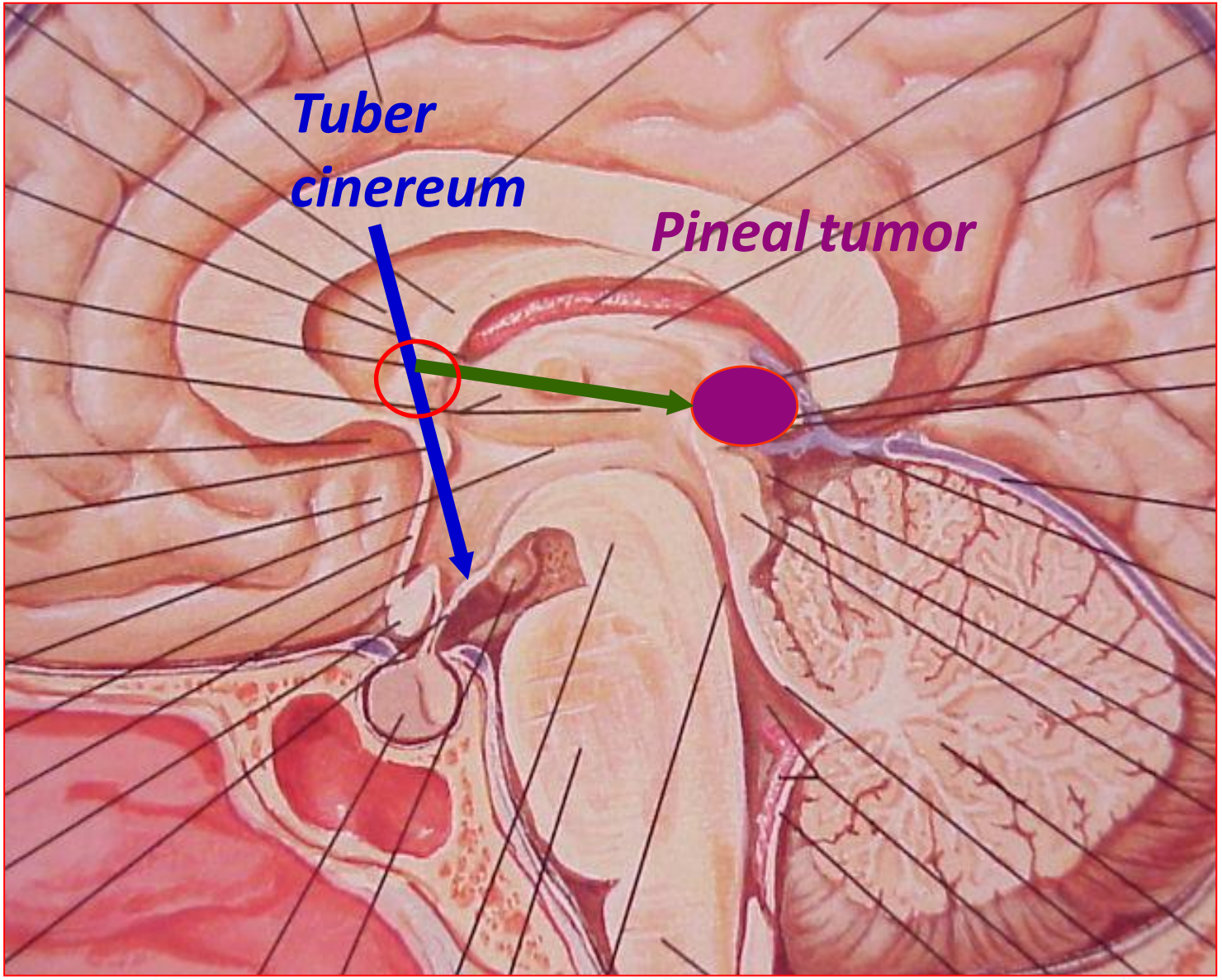
Goals of surgical treatments

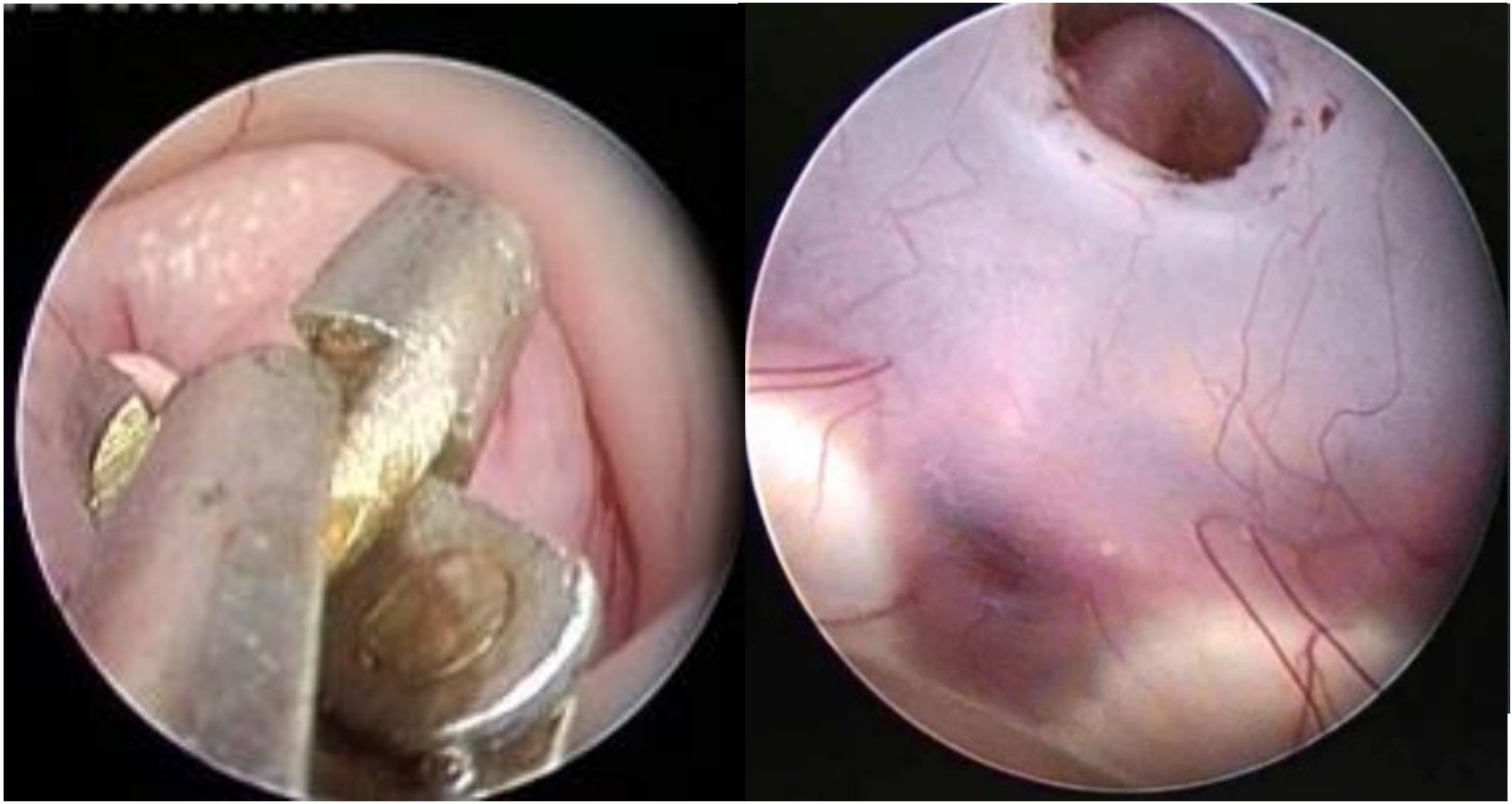
- Diagnosis
  - 1st presentation
  - 2nd look surgery
- Relief of hydrocephalus
- Excision and decompression

Surgical Options

- Endoscopic approach
  - Endoscopic biopsy
  - Endoscopic 3rd ventriculostomy
  - Sampling of ventricular CSF for tumour markers
- Stereotactic biopsy
- Transphenoidal approach
- Open surgery
  - Craniotomy for excision and decompression

Endoscopic tumour biopsy & 3rd ventriculostomy

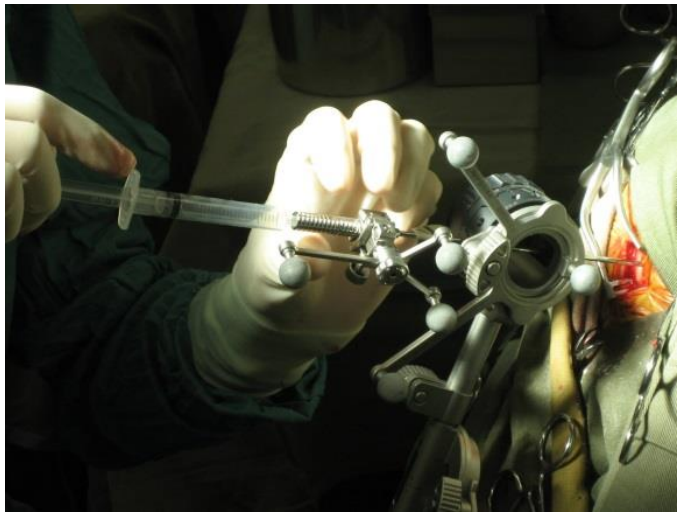


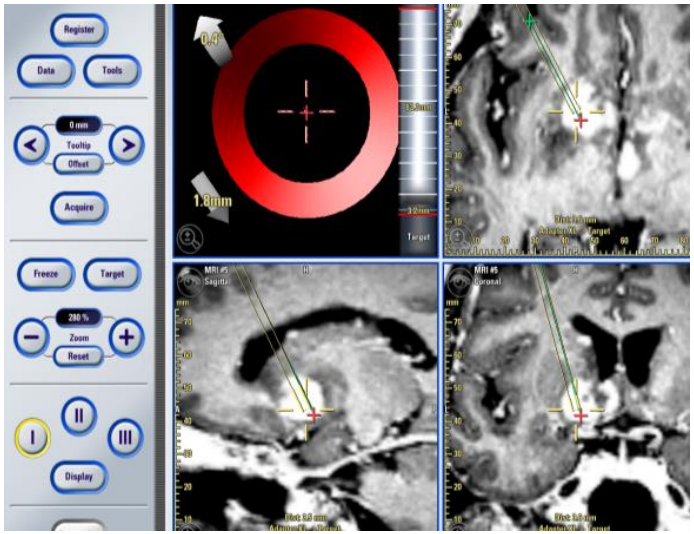


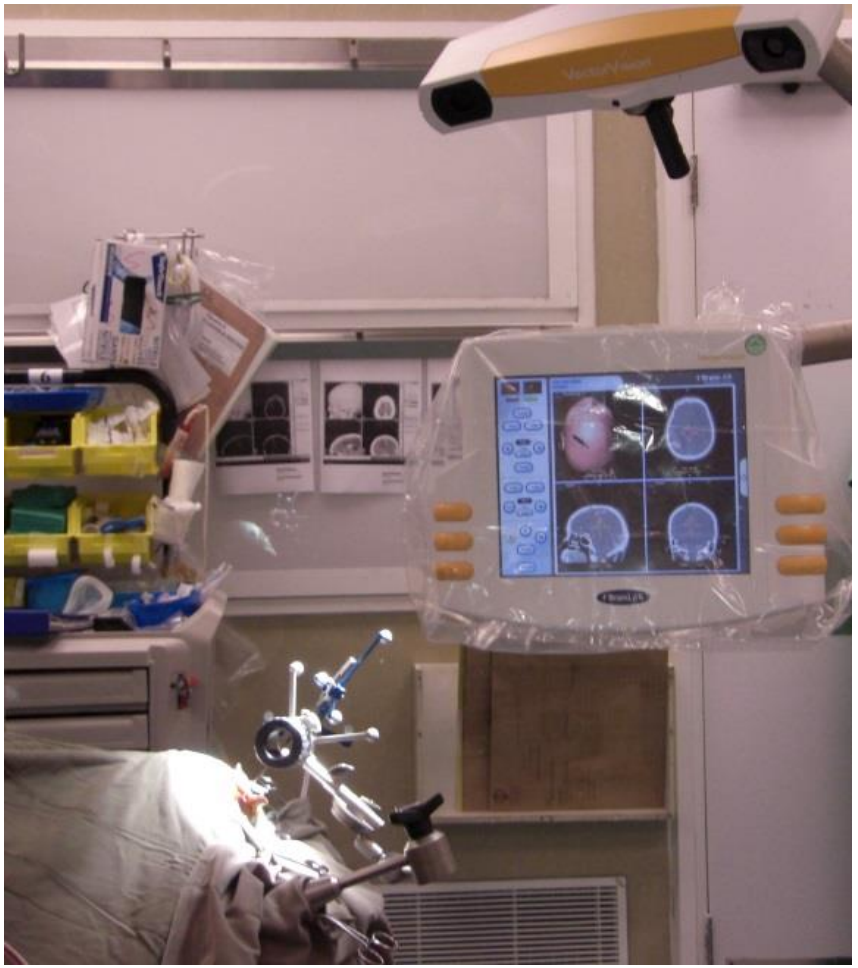
Endoscopic approach

- One surgery serves two purposes : diagnosis and relief of hydrocephalus
- Provide treatment for obstructive hydrocephalus without shunting.
- Can be safely performed by single burr hole for most of the cases (with navigation planning).
- **Pitfall:** quite often the peripheral part of the tumour is reached which may give rise to negative result, or sampling error.

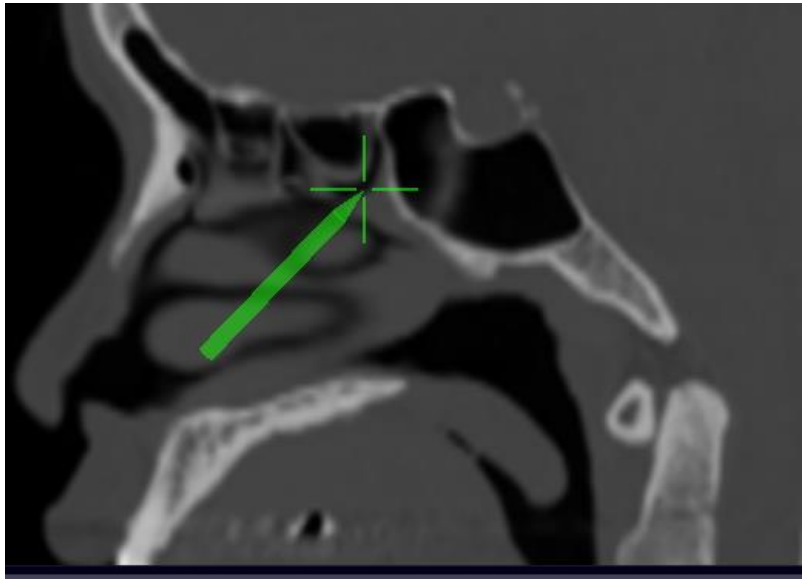
Stereotactic biopsy

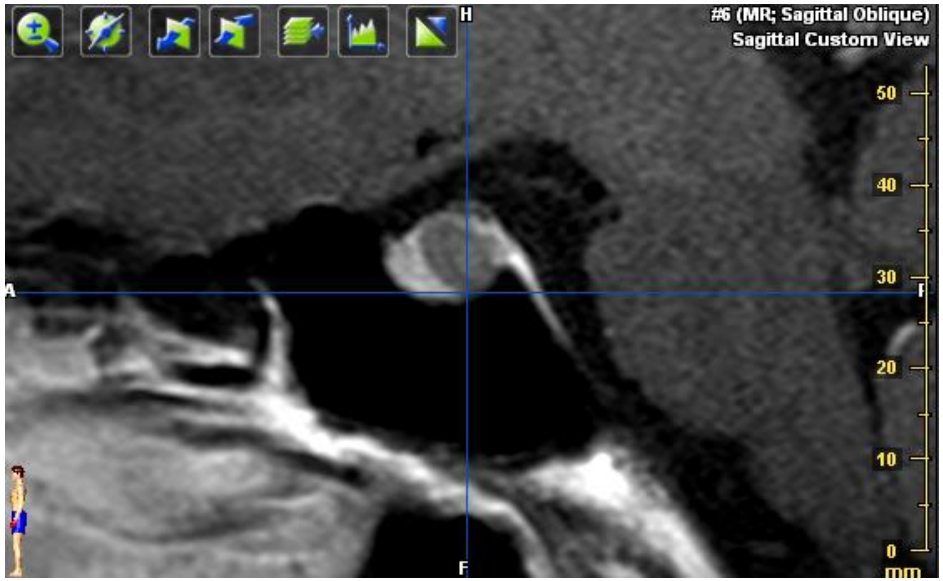






Transphenoidal approach



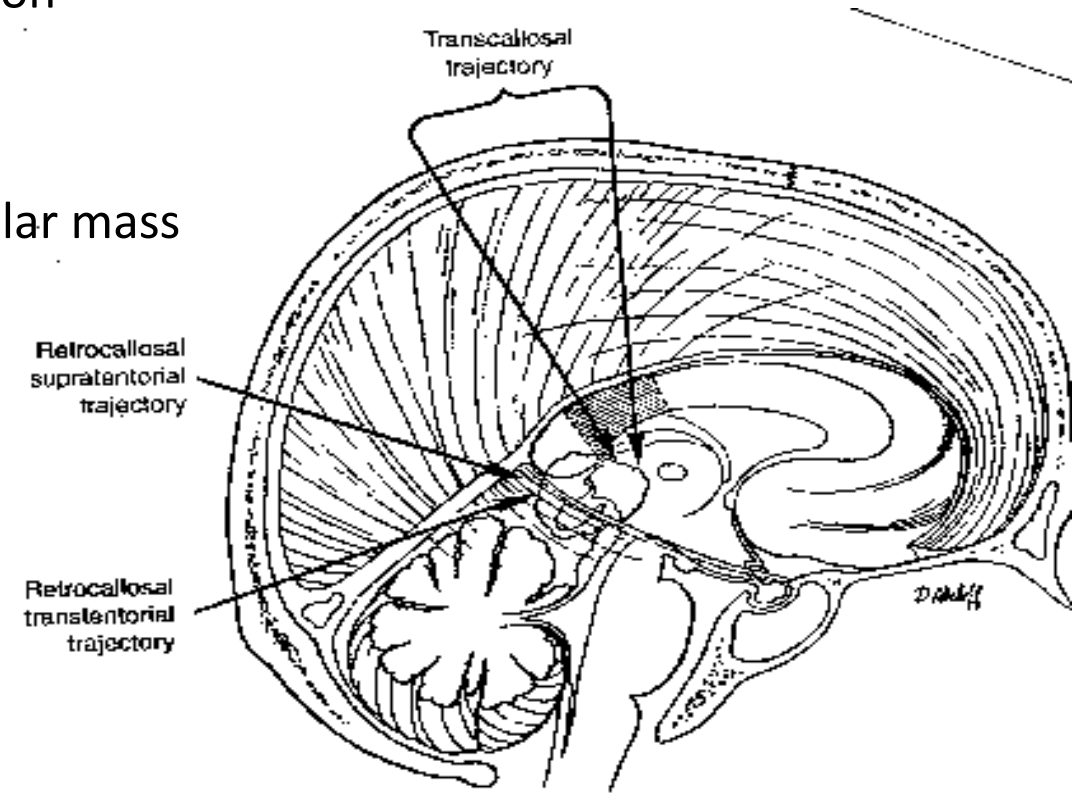


Open surgery - Craniotomy

- Primary or 2nd look Surgery
  - Diagnosis
  - Decompression
  - Excision

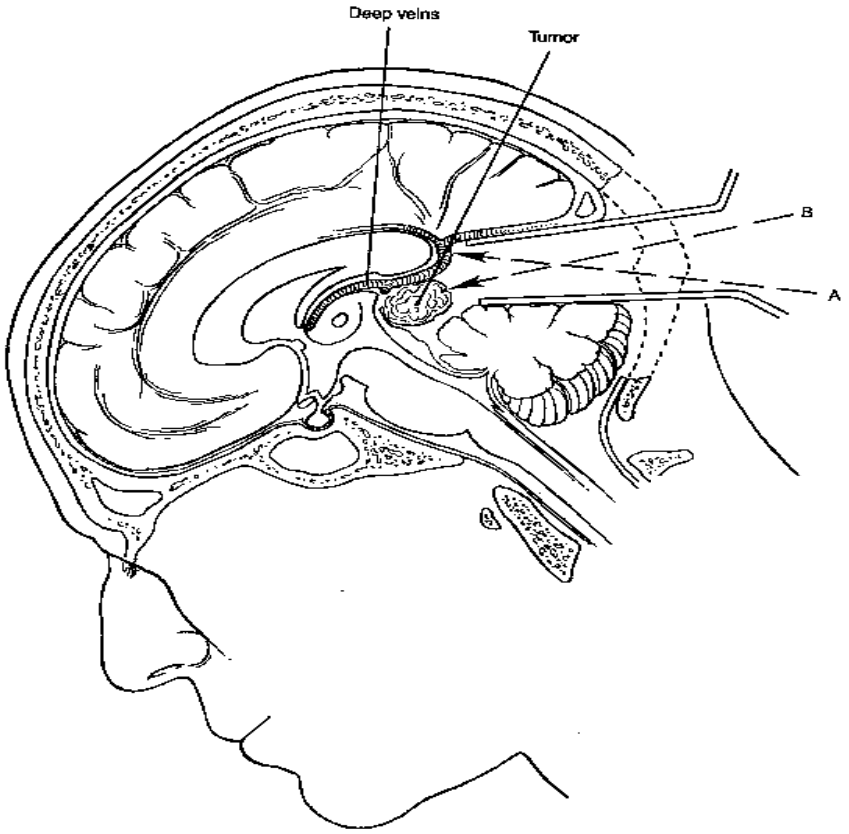
Supratentorial (occipital transtentorial)

- *Indications*
  - Predominant supratentorial extension
  - Corpus callosum extension
  - Lateral extension
  - Thalamic extension
  - Predominant III ventricular mass



Infratentorial supracerebellar appr.

- *Midline approach*
- *Tumor ventral to velum interpositum & deep venous system*
- *Sitting or concord position*



Overall therapeutic purpose

- Germinoma
  - To maintain excellent overall survival whilst attempting to minimize late-effects of treatment
- NGGCT
  - To improve overall survival

Pure germinoma

- Radiotherapy maximizes chance of cure
- Localised germinoma
  - Focal radiation fields alone are insufficient
  - Whole ventricular radiation
- Chemotherapy can reduce the dose of radiotherapy

Malignant NGGCT

- Combination of chemotherapy and radiotherapy
- Metastatic disease should be treated with craniospinal radiotherapy
- Residual tumour should be resected

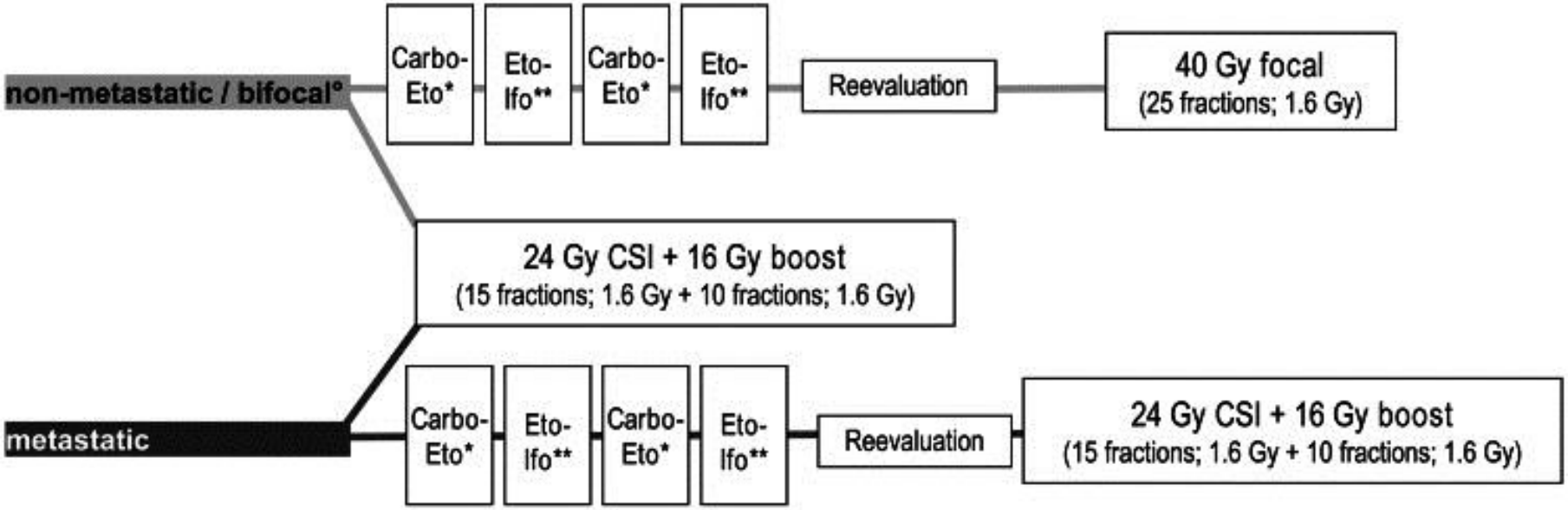
COMBINED TREATMENT WITH LOCAL IRRADIATION IS NOT SUFFICIENT TO CONTROL SUBCLINICAL DISEASE IN LOCALISED INTRACRANIAL GERMINOMA. FINAL RESULTS OF SIOP CNS GCT 96

- Gabriele Calaminus et al
- SIOP CNS GCT 96 standardised diagnostics/treatment for Germinoma on an international basis.
- Diagnosis was made by imaging and biopsy.
- Measurement of AFP/HCG in serum / CSF excludes nongerminomatous (secreting) elements.

Neuro-Oncology 15(6):788–796, 2013.
doi:10.1093/neuonc/not019
Advance Access publication March 3, 2013

SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease

Gabriele Calaminus, Rolf Kortmann, Jennifer Worch, James C. Nicholson, Claire Alapetite, Maria Luisa Garrè, Catherine Patte, Umberto Ricardi, Frank Saran, and Didier Frappaz



* Day 1 – 3; 43 – 45 **Carbo**platin 600 mg/m²/day / Etoposide 100 mg/m²/day
** Day 22 – 27; 64 - 69 Etoposide 100 mg/m²/day / Ifosfamide 1800 mg/m²/day

° For bifocal tumors radiotherapy includes both primaries

Treatment

- In case of no dissemination (negative CSF, negative imaging): two options were offered, either:
  - 1) two courses of Carboplatin/Etoposide alternating with Etoposide/Ifosfamide, followed by focal irradiation with 40 Gy (RT), or
  - 2) RT alone with 24 Gy to the craniospinal axis (CSI) and 16 Gy tumor boost.
- In metastatic disease, patients received 24 Gy CSI with 16 Gy boost to the primary site/ metastases.
- Time since international closure of SIOP CNS GCT 96 is > 3 years.

PATIENTS and Results

- N=284 protocol patients
- Age: 4-42 years (median 13 years)
- Boys = 217.
- 222 were localised (117 pineal, 58 suprasellar, 36 bifocal, 11 other sites) and
- 61 metastatic.

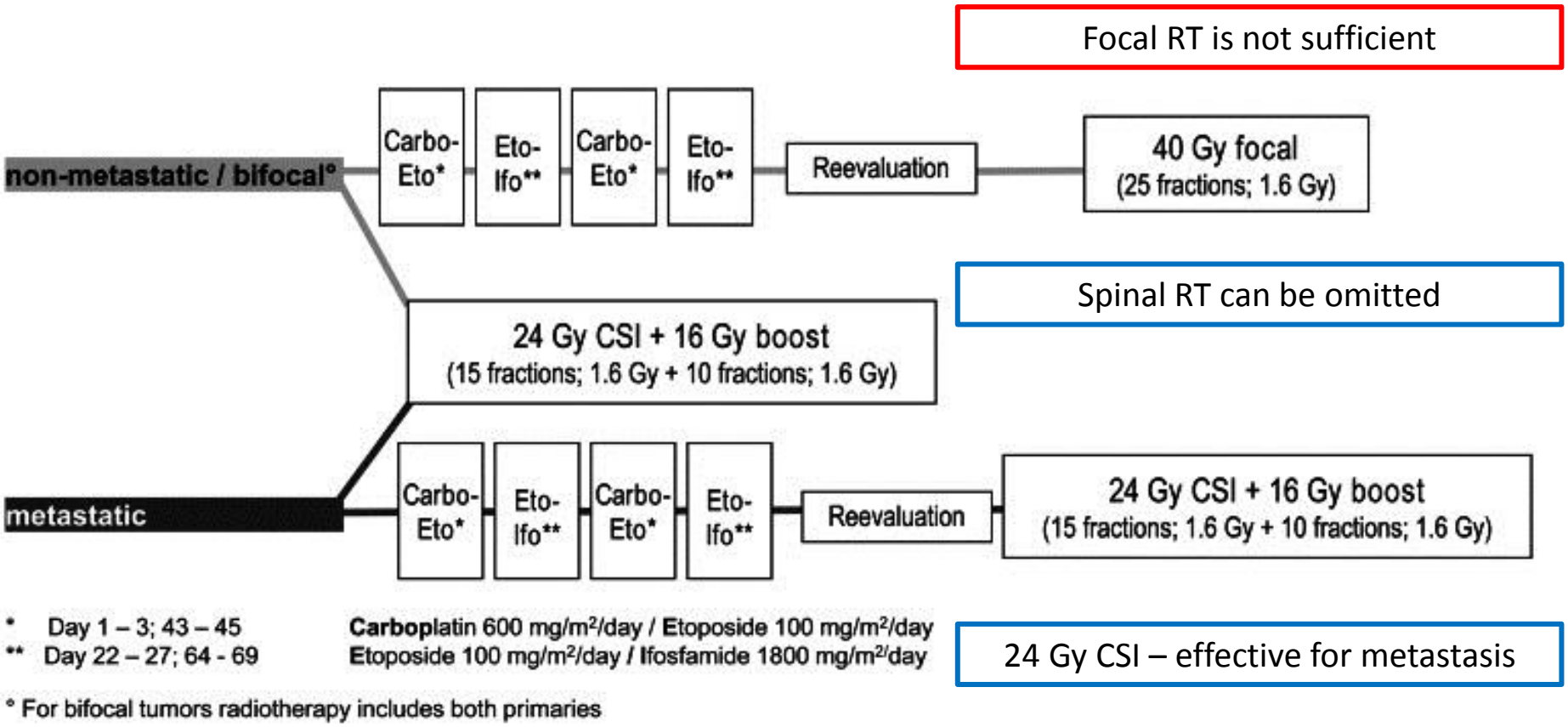
Results

- 1) Localised disease and chemo + focal RT (n= 81)
  - (median follow-up 75 months)
  - OS : 0.93 +PFS: 0.68 + 0.13 0.03 (median follow-up 70 months)
  - Events included 11 relapses, 6 where local and 5 combined relapses +ventricular area.
- 2) Localised disease and CSI radiotherapy (n =134):
  - PFS: 0.97 + 0.02: 0.97 + 0.01 (median follow-up 60 months)
  - OS: 0.97 + 0.01 (median follow-up 60 months):
  - Events included 4 relapses, all local.
- 3) 59 metastatic pts: all received CSI:
  - PFS: 0.96 + 0.03 (median follow-up 63 months)
  - OS: 0.98 + 0.02 (median follow-up 60 months).

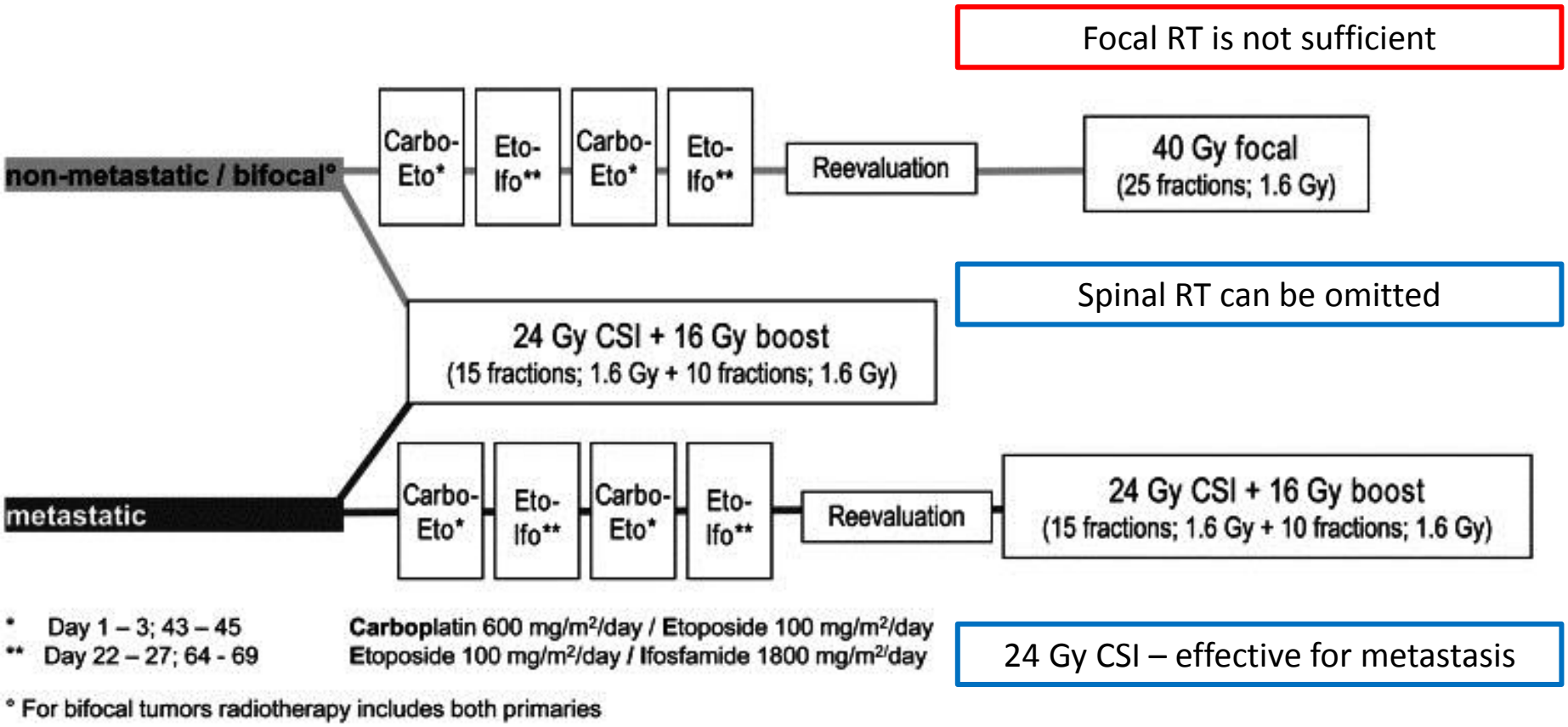
CONCLUSION:

- Reduced CSI (24 Gy) effectively controls metastatic disease.
- Spinal RT can be omitted in localised germinoma with chemotherapy,
- Focal RT after chemotherapy is not sufficient to prevent recurrences in the ventricles.
- In SIOP CNS GCT II trial, opened in October 2011, treatment for localised Germinoma includes ventricular irradiation (24 Gy) after chemotherapy, with additional tumour boost (16 Gy) in case of residual disease.

SIOP CNS GCT 96



SIOP CNS GCT 96



Non-germinomatous germ cell tumours (NGGCT) of the Central Nervous system

- A heterogeneous group:
  - embryonal carcinoma,
  - endodermal sinus tumor (yolk sac tumor),
  - choriocarcinoma,
  - malignant teratoma and
  - mixed tumors: one or more of these histologies and sometimes germinoma elements.
- Less radiosensitive than pure germinomas
- Prognosis following standard radiotherapy alone has been poor
  - (20-45% five-year survival)

RISK ADAPTED IRRADIATION IS FEASIBLE IN INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMOURS (NGGCT): FINAL RESULTS OF SIOP CNS GCT 96

- Gabriele Calaminus et
- The SIOP CNS GCT 96 protocol:
  - Standardised diagnostics and treatment of intracranial Non-Germinomatous Germ Cell Tumors (NGGCT).
  - Diagnosis was made by imaging/markers in serum and CSF (AFP and ß-HCG).
  - In cases of negative markers in both compartments histological diagnosis was necessary.
  - The trial was closed internationally as on 1.07.2008.

PATIENTS AND TREATMENT:

- N= 197 protocol patients,
- Age: 0-30 years (median 12 years) and
- 150 were boys.
- 154 were localised (86 pineal, 40 suprasellar, 13 bifocal, 15 other), and
- 43 metastatic.
- Localised disease: 4 courses of Cisplatin/Etoposide/Ifosfamide (PEI) followed by focal radiotherapy of 54 Gy.
- Patients with metastases: after chemo received 30 Gy *craniospinal radiotherapy (CSI) and 24 Gy boost to tumor* and macroscopic metastatic sites.

RESULTS:

- Localized disease:
  - PFS: chemo + focal radiotherapy: 0.69 + 0.04 (median follow-up 53 months),
  - OS: 0.78 + 0.04; (median follow-up 41 months)
- Those with dissemination and chemo and CSI:
  - PFS: 0.67 + 0.08 (median follow-up 55 months).
  - OS: 0.70 + 0.09; (median follow-up 36 months).
- 13 relapsed after CSI (n=43), including 7 local, 2 distant and 4 combined.
- There were 41 relapses after chemo + focal radiotherapy (n=146) : 23 local, 8 combined and 5 distant.

RISK PROFILES:

- 22 patients had AFP > 1000 ng/ml (serum and/or CSF):
  - 12 relapsed (PFS 0.38 + 0.11; median follow-up 11 months).
  - OS: 0.32 + 0.13 (median follow-up 15 months).
- After radiotherapy a residual tumor was found in 80 of the 197 patients, 25/80 patients relapsed.

CONCLUSION:

- SIOP CNS GCT 96 has proven:
  - local irradiation is sufficient for local disease control.
  - CSI is able to control micro dissemination.
  - With the applied regimen metastatic disease does not contribute to an inferior prognosis.
- In the consecutive SIOP CNS GCT II trial, opened since October 2011, treatment for standard risk NGGCTs will be continued. Patients with AFP > 1000ng/ml receive an intensified chemotherapy.

Relapse

- High dose chemotherapy + autologous PBSCT
- Radiotherapy

Long term complications

- Psychological / Cognitive consequence
  - IQ preserved
  - Working memory/visual memory/visual spatial perception – deteriorated
  - Site / Histology / Treatment
    - Basal ganglia > worse > Suprasellar / Pineal
    - WBRT / CSI > worse > WVRT
- Endocrine dysfunction
  - DI
  - Pan-hypopituitarism

Summary - Consensus

2. Germinoma – excellent survival, minimise late side-effects of treatments

3. NGGCT – to improve survival

4, 5. Multidisciplinary team and experience centres

6. MRI + C – brain, whole spine(sagittal)

7, 8. LP CSF for cytology

9, 10, 11, 12. Serum / CSF AFP, beta-HCG

13, 14, 15, 16. CSF diversion, Endoscopic 3rd ventriculostomy

17, 21. Surgical biopsy, excision of teratoma

Summary - Consensus

- 22, 23, 24. For lcoalised Germinoma, radiotherapy is essential for cure of disease. Focal radiation is insufficient. CSI is not needed. Chemotherapy can lower the radiation dose.

- 25,26,27. NGGCT – Localised disease combined chemotherapy and radiotherpay for chance of cure. For metastatic disease, CSI

- 28. Serum tumour markers should be monitored

- 29, 30, 31. For relapse, re-staging, no standardized regime. HD-ChemoRx + PBSCT+/-RT+/-Surgery

- 33,34. Late-effects of the disease & treatment. Neuro-cognitive, psychological and QoL follow-up

Thank You