

RT in Patients with CNS Germ Cell Tumors

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Detroit and Warren MI



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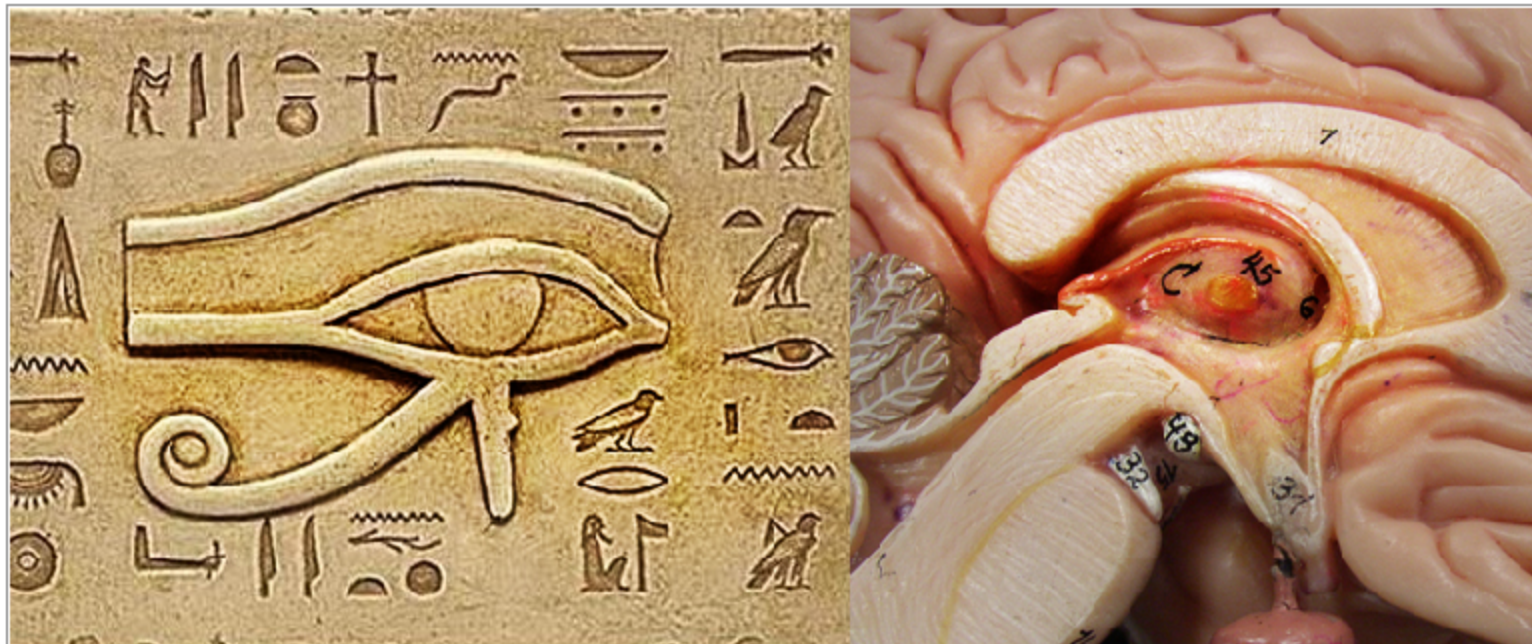
| Believe in better |

Surreal Magicalism

RSS ARCHIVE

* Light. Nature. Magic. Photography. Skateboarding. Film. Music. Animation. Installation + Street Art. Illustration + Painting. Anatomy. Laughter. Spirit. * Query

SEPTEMBER 3, 2012



The ancient Egyptian symbol Wadjet (the Eye of Horus) means god/goddess and bears a striking resemblance to the anatomy of the pineal gland and brainstem. It has been postulated that “near-death experiences” are caused by a massive release of dimethyltryptamine (DMT) from the pineal gland. The French philosopher René Descartes studied the pineal gland extensively and referred to it as “the principal seat of the soul.” (Source)

Germ Cell Tumors

- Variety of Histologies
- Common Origin: Primordial Germ Cell
- Gonadal and Non-Gonadal Presentation
 - Testis, Ovary
 - Mediastinum
 - Retroperitoneum
 - Pineal/Suprasellar

Definitions

- **Dysgerminoma:** A malignant neoplasm of the ovary (counterpart of seminoma of the testis) composed of undifferentiated gonadal germinal cells
- **Seminoma:** A malignant neoplasm of the testis of young males
- **Germinoma:** A neoplasm of the germinal tissue of the gonads, mediastinum, or pineal region

Malignant CNS Germ Cell Tumors

- Germ cell tumors (GCTs) make up about 3% of childhood malignancies.
- Germ cell neoplasia :
 - Requires formation of a transformed pluri-potential cell from a toti-potential precursor germ cell which would otherwise be destined to gametogenesis.
 - Differentiation into embryonal-like (somatically differentiated) tumors, as well as extra-embryonally differentiated (choroid and yolk sac) tumors.
 - Occurs without fertilization and requires “erasing” of imprinting.
 - Overexpression of cyclin D2 cell cycle G1/S checkpoint regulator.

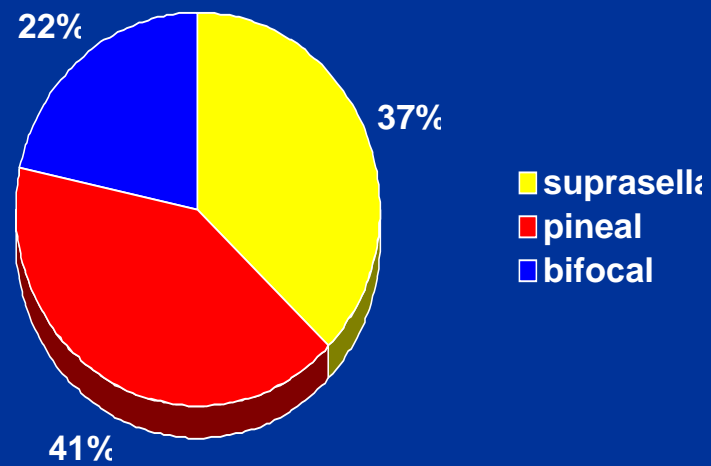
Overview

- What we have learned
 - Background GCT and NGGCT
- Some Results of Trials
 - Europe and Japan
 - POG and Single Institutions
 - ACNS0122 for NGGCT
 - ACNS0232 for GCT
- Where we are going
 - Newly opened COG trial
 - ACNS1123 response adapted RT for NGGCT and pure GCT

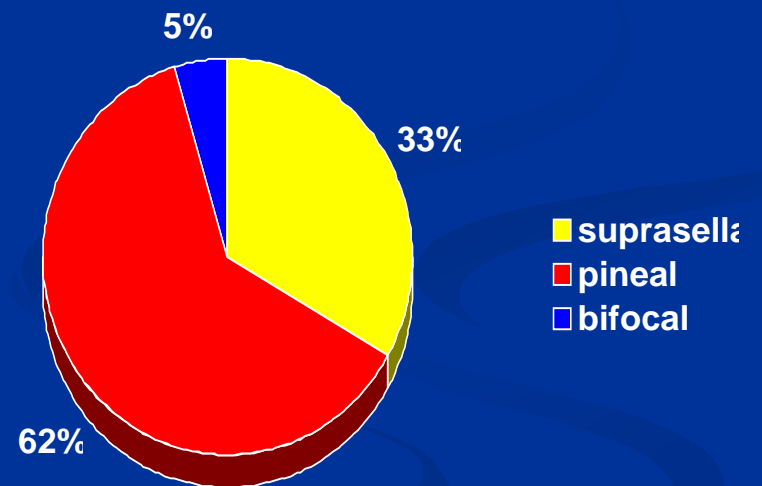
CNS GCT

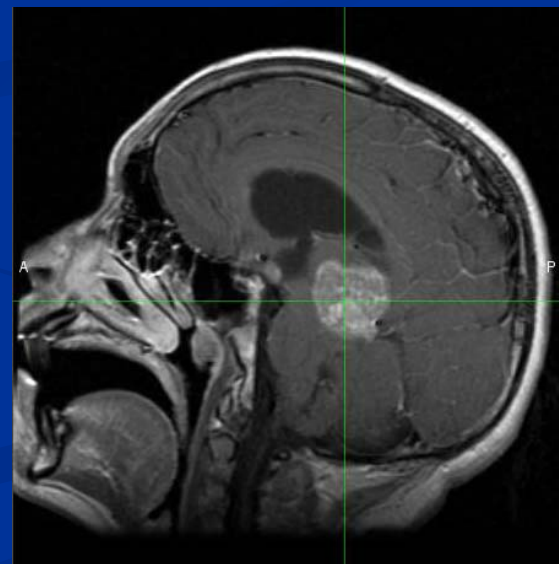
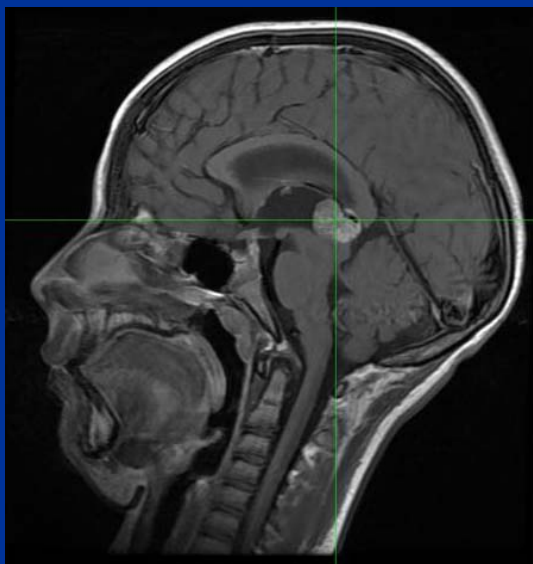
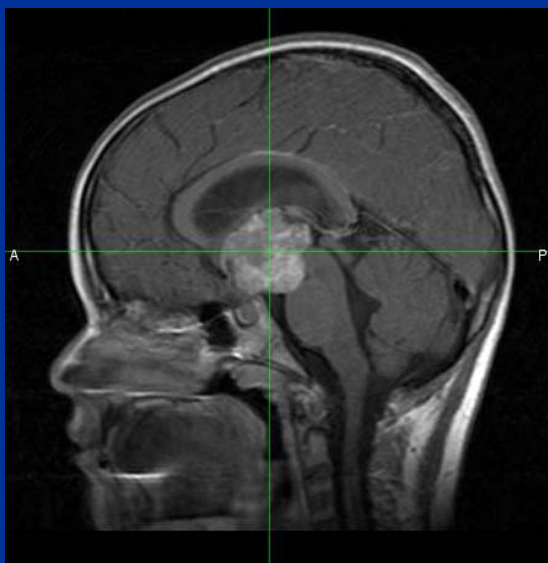
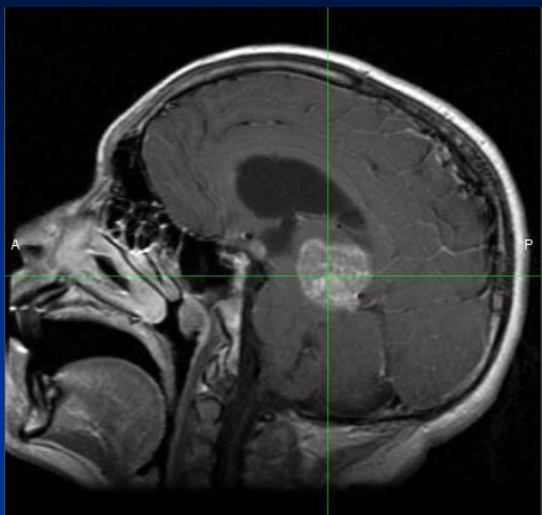
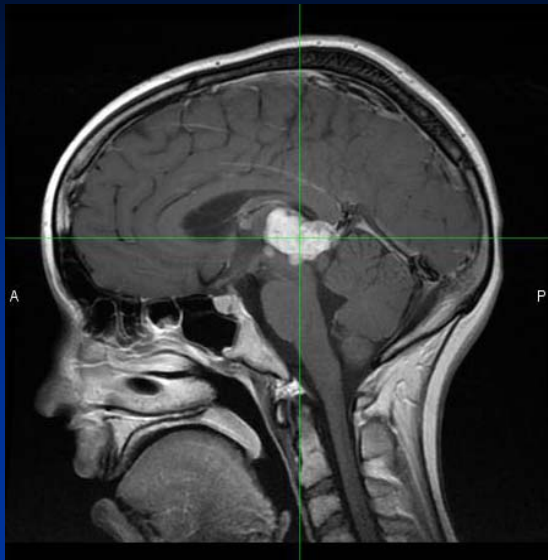
Location

GCT



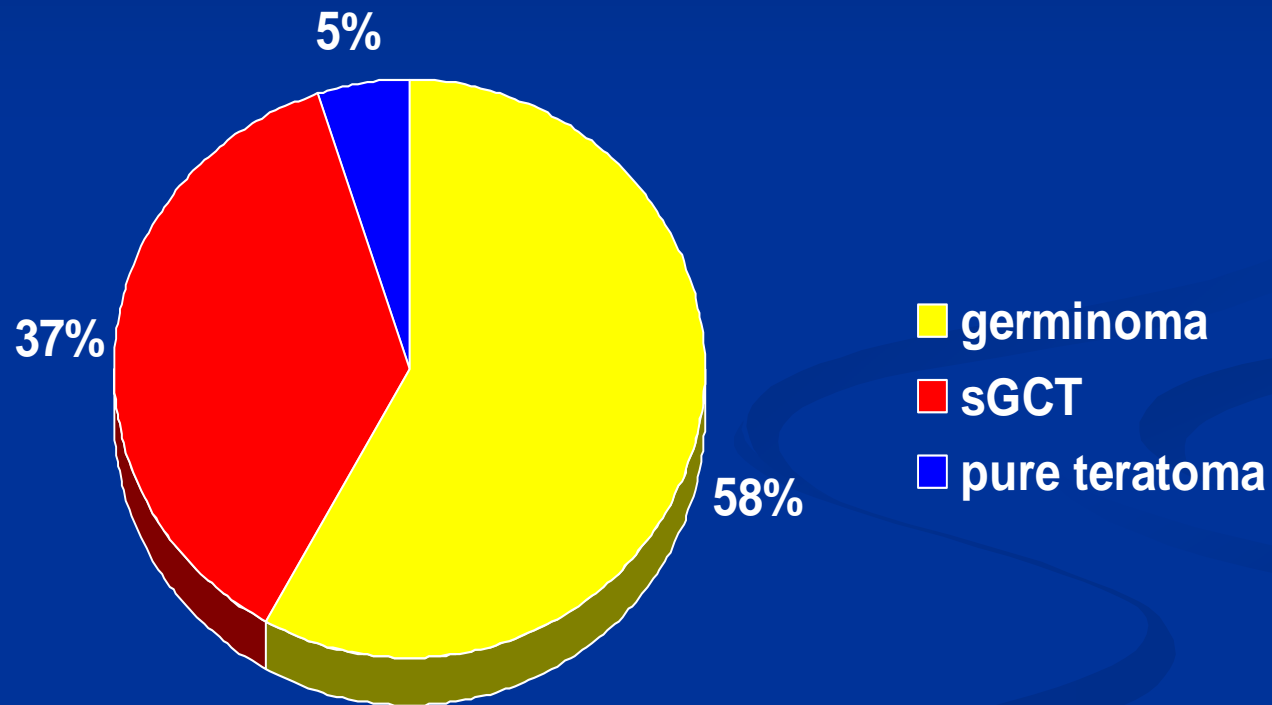
Secreting GCT





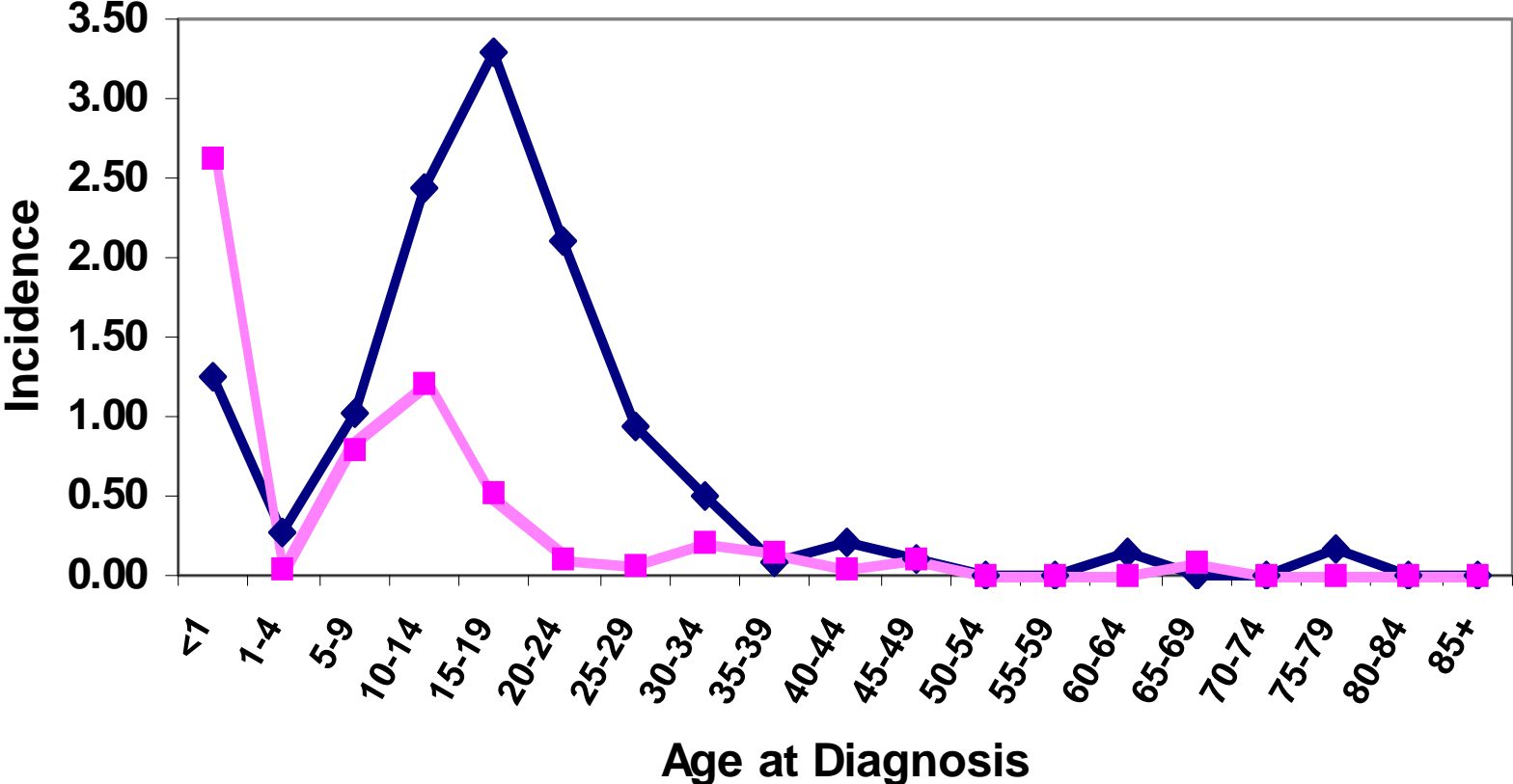
PRIMARY CNS GCT

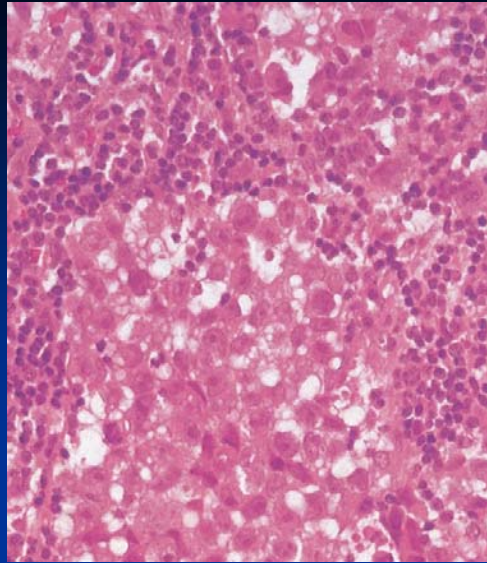
Histopathology (SIOP)



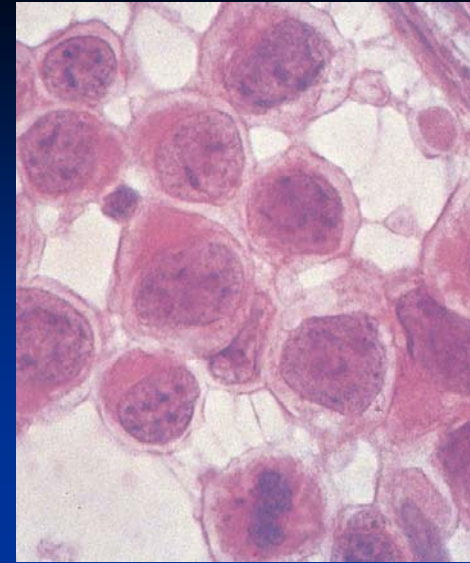
CNS Germ Cell Tumors

Incidence (per million)

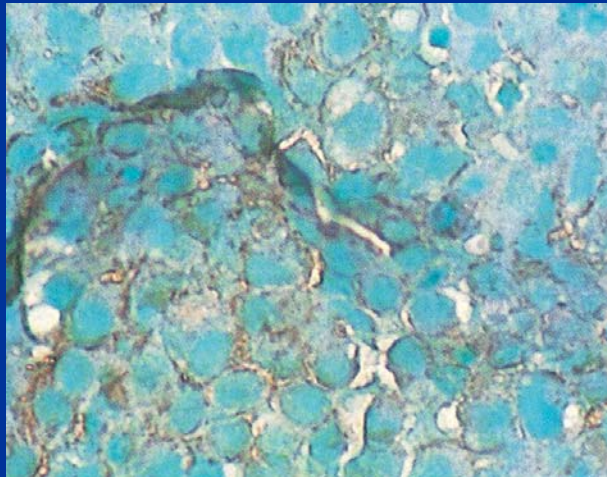




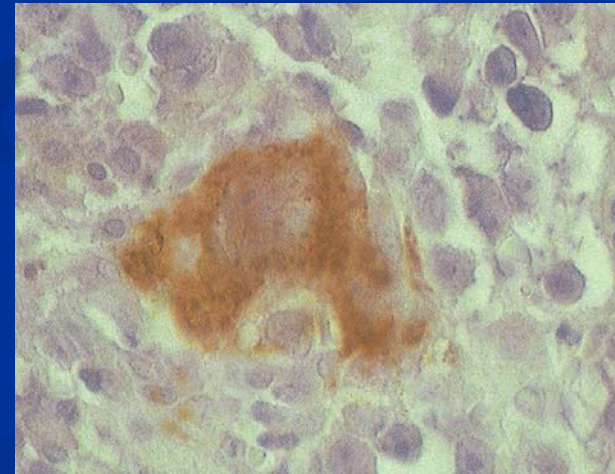
Germinoma



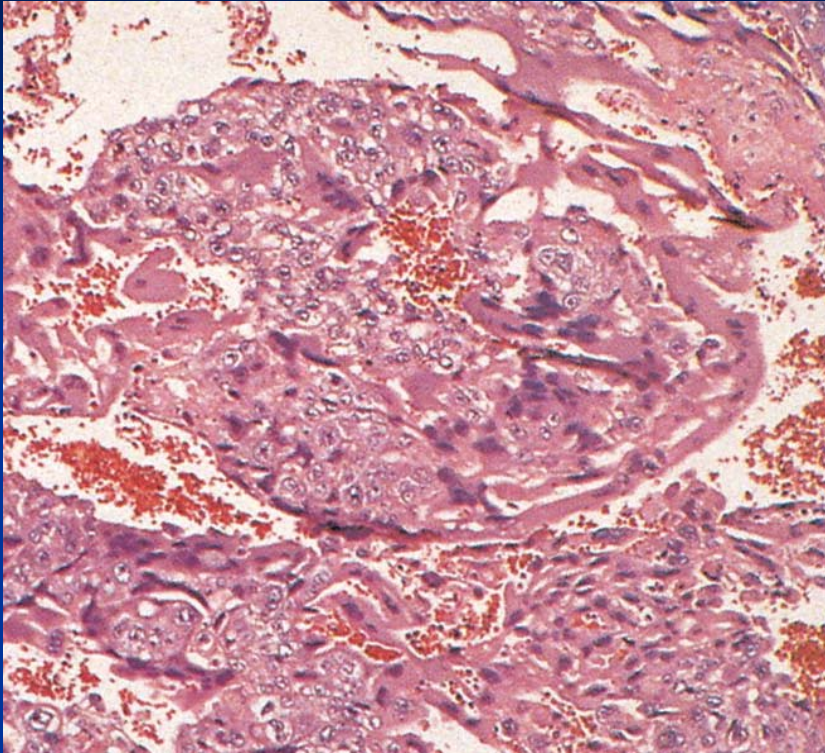
Touch Prep: High N/C Ratio



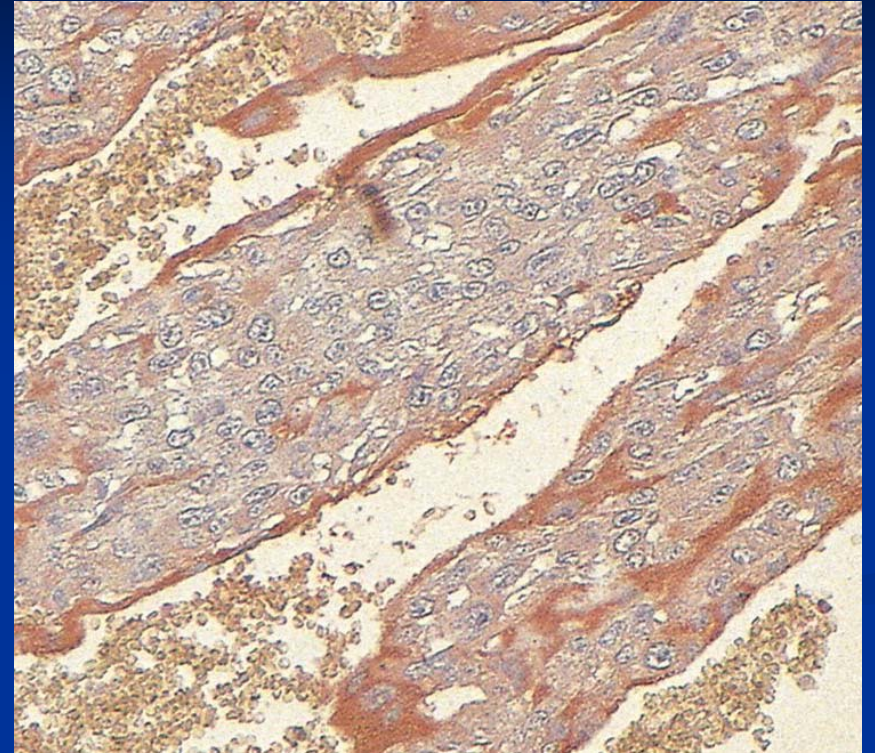
PAP



Beta-HCG



Tendency to Hemorrhage

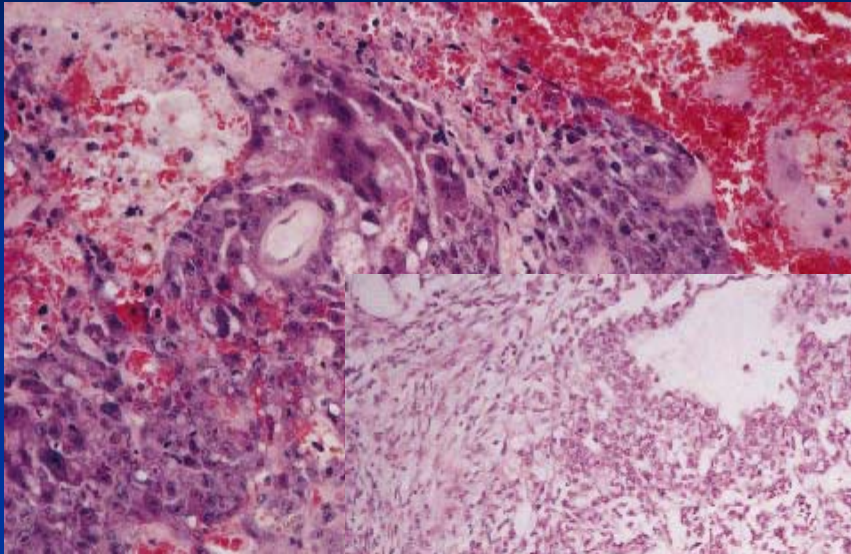


HCG Reactivity

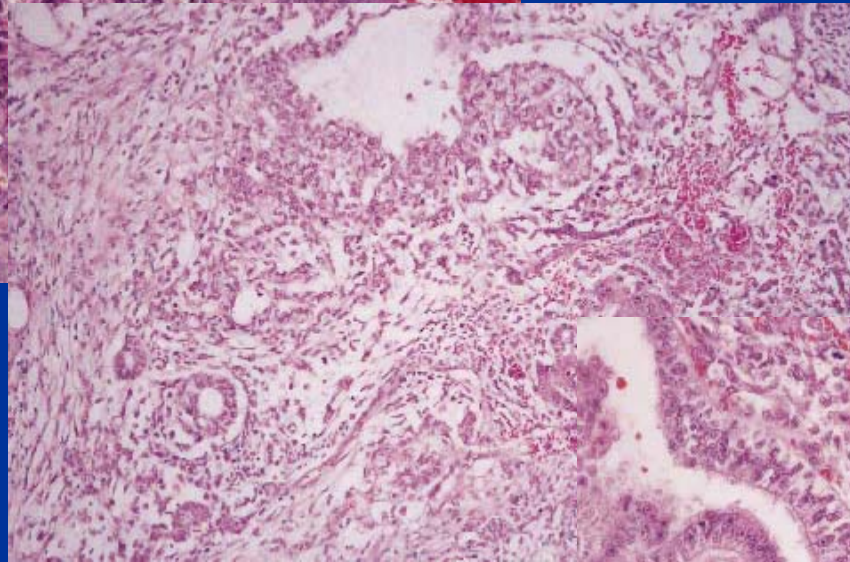
Pineal Choriocarcinoma from 12 yo Female

PRIMARY CNS GCT

NGGCTs

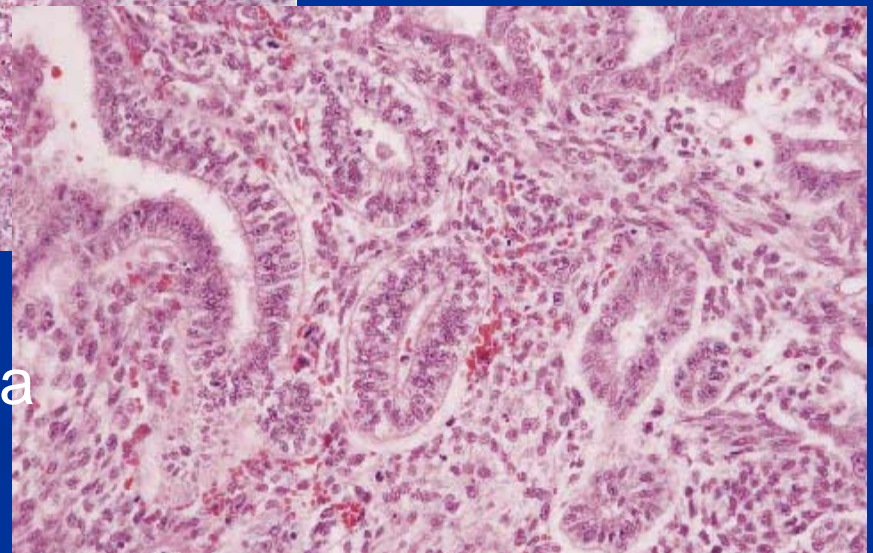


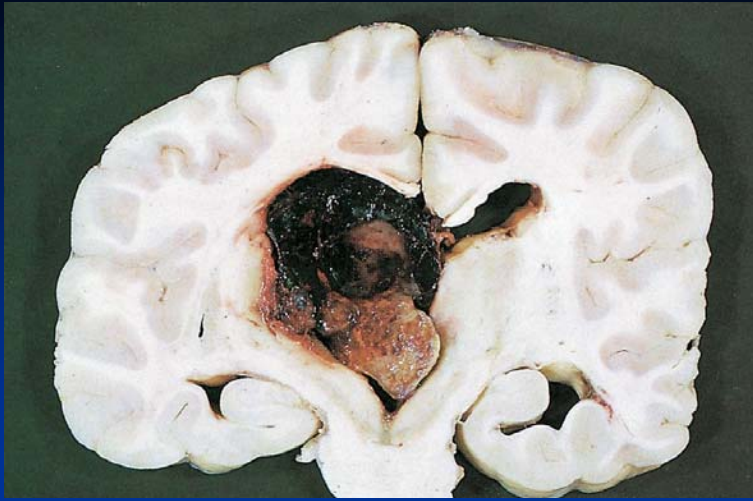
Choriocarcinoma (β HCG)



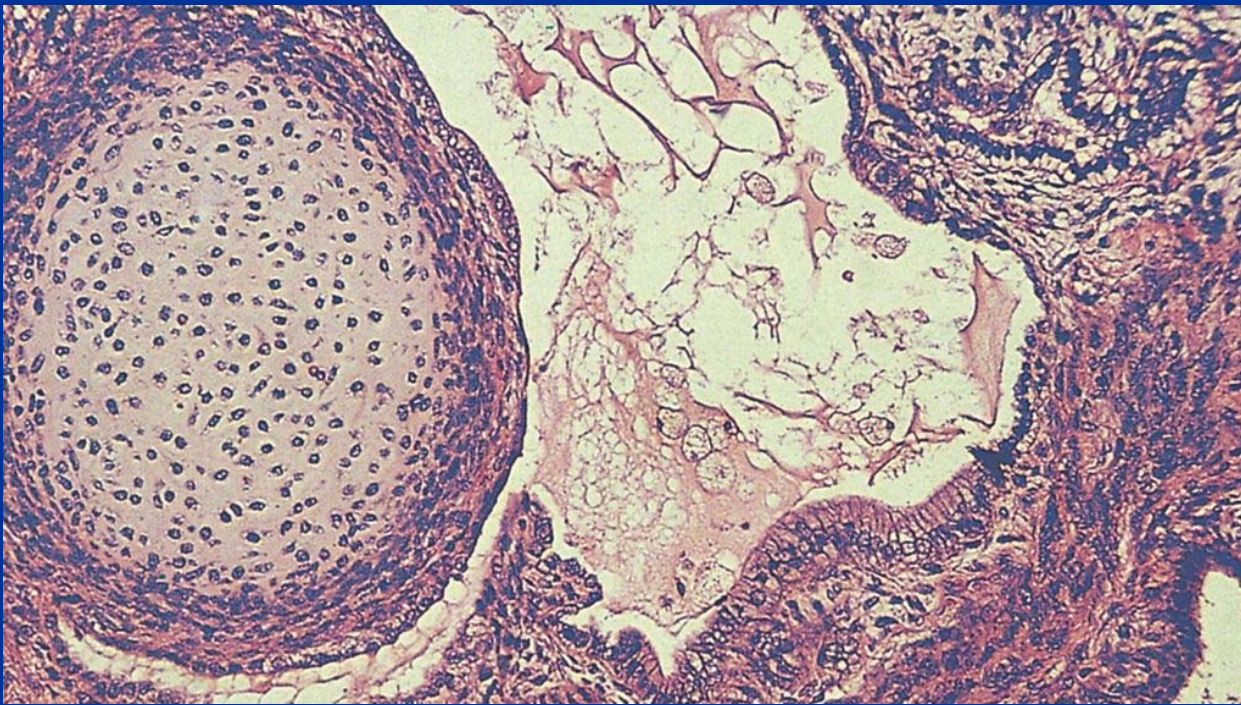
Yolk sac tumour (α FP)

embryonal carcinoma
(α FP + β HCG)

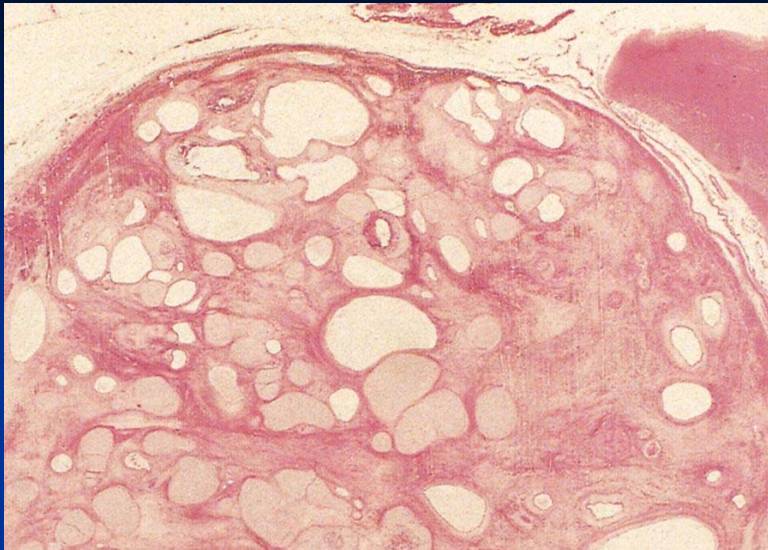




Immature Pineal Teratoma 12 yo Male



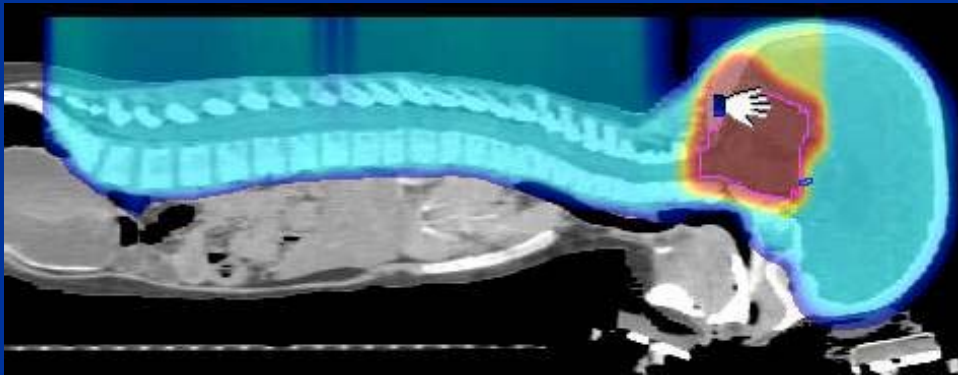
Cartilage,
Mucin Producing
Columnar Epithelium.,
Spindle Cell Stroma



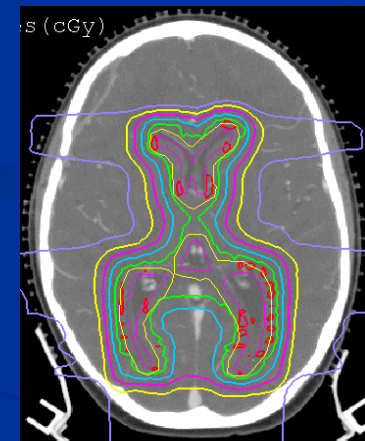
Mature Teratoma
Resembles Benign
Adult Cartilage,
Respiratory Epithelium,
Loose Fibrous Stroma



High Tech Radiation?



CSI



WVRT



The Eye of Horus: Symbol of Power and Good Health
Horus Was Ancient Sky God Depicted as A Falcon
(Mirror Image or Left Eye Sometime Represented the Moon)

Table 1: Incidence of CNS NGGCT
 Projected in the U.S. Population per year
 Based on SEER 1997

Age	STD US Pop'n	Brain (C71.x)	Other CNS (C72.x)	Pituitary (C75.1)	Pineal (C75.3)	TOTAL
0 to 4	18.90	15.5	1.1	0	0	16.6
5 to 9	19.70	1.2	1.2	0	2.5	4.9
10 to 14	19.90	6.5	0	5.2	10.4	22.1
15 to 19	19.90	2.7	0	0	10.7	13.4
20 to 24	18.50	1.2	0	0	1.2	2.4
	TOTAL	27.1	2.3	5.2	24.8	59.4

Author Year (ref)	Chemotherapy	Germinomas	NG-GCTs
Rustin 1986 (34)	PBVcrMTX/ECyActD; IT Mtx		1/2 CR
Matsutani 1987 (35)	VPB for 2 years	71%	
Allen 1987 (3)	Cy (1.8-2.4 g/m ²) VPB/Cy (.9 g/m ²)	7 CR, 1 PR 3/3 CR	2 PR, 1 PD
Miyamachi 1988 (36)	VcrPB	3 CR/ 2 PR	
Demeocq 1988 (37)	VPB / CyAct D	6/7: >75% PR	
Mizuno 1989 (38)	EP	2/2 CR	
Hayashida 1989 (39)	EP	1 CR	
Pinkerton 1990 (40)	EBCb		1 CR
Jereb 1990 (41)	Cy (80 mg/kg)	3/3 CR	
Baumgarten 1992 (42)	VPBE	6/10 CR's (GCT's and NG-GCT's)	
Plowman 1993 (24)	VcrE/Cb	4/5 CR / 1 PR	1 CR/ 1 PR/ 1 SD
Elyan 1993 (19)	P/Cb	5/7 Cr	2/4 alive
Skinner 1993 (20)	EP/VcrMtxB/ECb/VCRMt xB/IT Mtx		2 CR / 1 PR*
Herrman 1993 (21)	EPB/VPIfos		3/3 responses
Yoshida 1993 (43)	EP	7 CR / 9 PR of 30 patients (GCT's and NG-GCT's)	
Calaminus 1993 (44)	VBP pre-XRT Ifos/E post; or HDP/VB pre Ifos / E post		5/12 PFS*; 14/16 PFS *
Finlay 1993 (25)	BECb (1g/m ²) ± Cy (3.9 g/m ²)	21/23 CR	16 CR/13 PR
Allen 1994 (24)	Cb (150 mg/m ² /wk x 4)	7 CR / 3 PR / 1 NE	

A Phase II Consortium

Robertson et al 2005 (U of M, Beth Israel, CHOP, Vancouver)

- CNS NGGCT or Secretor (n=27)
 - CDDP, IFOS, VP-16
 - RT 36 Gy CSI Except Localized Disease With CR After Surgery or CHT (WV RT + Boost)
 - For Less than CR, 2nd Look Sx plus Carbo/CTX x 2 with PBSC Support
- Better PFS in Cases Achieving Initial CR
- 9/27 Relapsed
- 3/6 Relapsed Outside RT Field
 - “Emphasizes Need for CSI”

Amulets



POG 9530

Wharam/Kretschmar et al

- **A Phase II Study of Chemotherapy/XRT for Primary Malignant Germ Cell Tumors of the Central Nervous System (i.e. both GCT and NGGCT)**
- **Rationale**
 - Safer Biopsy Available to Identify Histologic Subtype
 - Platinum Based Chemotherapy Found to Be Effective
- **Objectives**
 - Reduce Radiotherapy Dose by Using Chemo for Good Risk Patients (i.e. GCT)
 - Improve Prognosis for Poor Risk Patients
(i.e. Non-germinoma histology, elevated AFP, HCG >50)
- **Four Courses CDDP/VP-16 alternating with Cytosin/VCR followed by Radiation**
 - CDDP 40 mg/m²/d IV and VP-16 100 mg/m²/d IV x 5 days alternating with Cyt 2g/m² for 2 days and VCR 1.5 mg/m² IV days 1,8,15.

POG 9530 Schema

	Neuraxis	Spine Gross Disease	Brain Gross Disease
low risk, CR not disseminated	0	0	3060 cGy
low risk, <CR not disseminated	0	0	5040 cGy
low risk, CR disseminated*	2340 cGy	3060 cGy	3060 cGy
low risk < CR disseminated*	3600 cGy	4500 cGy	5040 cGy
high risk, CR	3060 cGy	4500 cGy	5040 cGy
high risk, <CR	3600 cGy	4500 cGy	5400cGy

*Any patient with more than one site of disease is considered to have dissemination.

POG 9530 Results

- 11 of 14 NGGCT Patients Were Progression Free at Median 58 Mos (Range 42-71 Mos).
 - One Inevaluable Patient Received Only One Course of Chemo and Died During RT
 - One Patient With SD Died at 21 Mos of a Seizure at Home
 - One Patient With Mixed Yolk-sac Tumor Developed PD Before RT and Died of Disease 9 Months Later
- EFS Was 79% +/-11 % for High-risk or NGGCT (N=14).
- Accrual
- Response Rate (5 of 9) and PFS Comparable to Previous Reports

POG 9530: Results for NGGCT

no	sex	age	path	site	hcg	hcg csf	afp	afp csf	sx	Matsut. Class	rr	status
1	m	12.5	terato-choriocarcioma	pineal	2424	220	10.5	4.5	gtr	Poor	not eval.	PFS 67 mos
2	f	13.9	germinoma	pituitary	5496	nd	nl	nd	pr	interm	PR 96%	PFS 71 mos
3	m	16.3	none	pineal	nl	nl	286	314	shunt only	?int/poor	PR	PFS 61 mos
4	m	16.9	yolk-sac teratoma	pineal	13	nl	5190	26	75%	poor	early death	DOD 2 mos
5	m	18.1	mixed yolk-sac teratoma	pineal	13	nd	274	nd	pr	poor	PD	DOD 15 mos
6	f	11.2	germinoma met	ineal/frontal	9990	9800	1141	153	biopsy	interm	PR	PFS 64 mos
7	m	10.4	adenoca-teratoma	pineal	nl	nl	nl	nl	gtr	interm	not eval.	PFS 61 mos
8	m	11.6	germinoma met	pineal/csf	74	59	nl	nl	biopsy	interm?	CR	PFS 58 mos
9	m	7.1	none	pineal	165	1550	14	8	none	interm?	SD	PFS 43 mos
10	m	10.7	germ-chorio	pineal	nl	471	nl	nl	gtr	poor	not eval.	PFS 52 mos
11	f	6.5	germ-chorio	suprasellar	nl	2392	nl	nl	pr	poor	SD	died of sz 21 mos
12	m	16.2	none	pineal	200	74	80	12	none	poor?	SD	PFS 51 mos
13	f	14	mixed	suprasellar	719		3247		pr	interm	CR	PFS 50 mos
14	m	10.4	mixed yolk sac teratoma	pineal	4		156	nl	gtr	poor	not eval.	PFS 50 mos

SFOP without RT

Baranzelli et al J Neurooncol 37 229-39. 1998

- 18 Secretors 10 AFP, 2 HCG, 6 Both
 - 6 Cycles of Chemotherapy
 - Vinblastine-bleomycin - Carboplatin or Etoposide - Carboplatin/ifosfamide – Etoposide
- Fifteen Patients Were Treated According to the Protocol By:
 - Chemotherapy Alone (N=13)
 - Or Chemotherapy and Radiation of Residue (2).
- Twelve of the 13 Non Irradiated Patients Relapsed
 - 8 in Local And/or Regional Area, 3 in Cerebrospinal Area and 1 Undetermined
- 12/18 Patients Alive With a Median Follow up of 68 Months.
 - All but One Had Focal Radiation As Part of Treatment.
- Six Patients in 2nd CR
 - Chemotherapy And/or Surgery, Then Consolidation With Radiation And/or High Dose Chemotherapy or Craniospinal Radiation
- ‘Focal Radiotherapy Should Be Part of the Treatment’

SFOP with Focal RT

Barenzelli et al

- 27 Secreting GCT
 - 15 AFP, 7 HCG, 5 Both
 - Rx Carbo/VP Alt. IFOS (6-8 Courses)
 - Focal RT 55 Gy, CSI for Mets (n=3)
 - 14/27 Had Sx for Residual
- Median F/U 53 Mos
 - 20/27 Alive, 8/27 Relapsed

SIOP CNS GCT Study 96

SIOP 2005 Report

- 13 CNS NGGCT CDDP, VP-16, Ifos x 4
 - Local Disease IF RT 54 Gy
 - Met Disease 30 Gy CSI + 24 Gy Boost
- Median F/U 39 Mos
 - PFS 67% for Localized
 - 72% for Metastatic
- Residual After Induction and AFP >1000 Poor Prognosticators
- Spinal Failure Rate?

SIOP CNS GCT

Perilongo PROS 2007 Report

- 26 Of 123 NGGCT Were Metastatic
 - Metastatic divided into CSF positive and Macroscopic.
 - Non-metastatic includes Bifocal
- Relapses “Mostly Ventricular”
- Survival
 - 77% at 72 months for localized
 - 66% at 72 months for metastatic
- Residual disease at end of therapy?
 - EFS 82% vs 45%

Matstutani

Matsutani et al J. Neurosurg 86:446 1997

- “Pure” Malignant Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma
 - 5 year OS of Less than 10 percent
 - Greater than 70% OS for Mixed Tumors

Concluded:

- Treat Germinoma With Combination Chemotherapy and Reduced Dose Radiation Therapy
- Intermediate risk NGGCT Cis or Carbo Combination with Radiation
- Poor Risk: Need More Aggressive Chemotherapy

Matsutani

12th Peds Neuro-Onc Symposium

- 38 HCG Secreting Germinoma (Treated As Pure Germinoma)
 - CARE followed by local RT 24 Gy
 - 5/38 Recurrences
 - 5 yr OS 100%
- 40 NGGCT
 - Intermediate Prognosis Group (n=40)
 - Malignant Teratoma and Mixed Tumor Mainly composed of germinoma or Teratoma
 - CARE (Carbo/VP-16) Followed by Local RT 50 Gy
 - 5 Yr OS 97%
 - Poor Prognosis Group (n=27):
 - Choriocarcinoma, Yolk Sac, Embryonal, Mixed
 - ICE followed by CSI then ICE x 5
 - 5 Yr OS 56%

Matsutani et al 1997

J. Neurosurg 86:446 1997

Histology	n=	1-yr	3-yr	5-yr	10 yr	15 yr
Germinoma	50	100	95.4	95.4	92.7	87.9
Germinoma with STGC	7	100	100	83.3	83.3	NC
Mature Teratoma	16	100	92.9	92.9	92.9	NC
Malignant Teratoma	11	100	70.7	70.7	70.7	NC
Pure Malignant Germ Cell Tumor	11	45.5	27.3	27.3	NC	NC
Mixed Tumor	39	87.2	61	57.1	40.1	NC
Germinoma and Teratoma (MGT)	17	94.1	94.1	84.7	70.6	NC
Germinoma or Teratoma (MXB)	10	80	70	52.5	35	NC
Mainly Pure Elements (MXM)	12	83.3	9.3	9.3	NC	NC

NC= not calculable

The Questions?

- Is Chemotherapy Effective and Are Responses Durable? YES
 - cf Testicular Tumors
- Is RT Needed? YES
 - SFOP: 6 Cycles of Chemotherapy (with Surgery and Focal Radiation for Viable Residual. 12 of 13 non-irradiated patients relapsed
 - Kellie et al: Intensive chemo w/o RT effective in about 1/3 of patients
- If RT then how much? Dose and Field Size
 - CSI
 - Popularity
 - Neurocognitive Function and Bone Growth Delay
 - Second Malignancy? Endocrine ?
 - What Are the Spinal failure Rates?
 - Predilection to Involve CNS

A Phase II Study to Assess the Ability Neoadjuvant Chemotherapy and Second Look Surgery to Eliminate All Measurable Disease Prior to Radiotherapy for NGGCT

3.2.2 Histologic Diagnosis

3.2.2.1 Eligible Histological Diagnosis (See Section 15.0)

- a) Endodermal sinus tumor (yolk sac tumor)
- b) Embryonal carcinoma
- c) Choriocarcinoma
- d) Immature teratoma and teratoma with malignant transformation
- e) Mixed germ cell tumor

Any histologically confirmed germinoma tumor with elevation of serum and/or CSF beta HCG >50 IU/dl or any elevation of serum and/or CSF alpha fetoprotein >10 IU/L (ng/mL) or institutional norm.

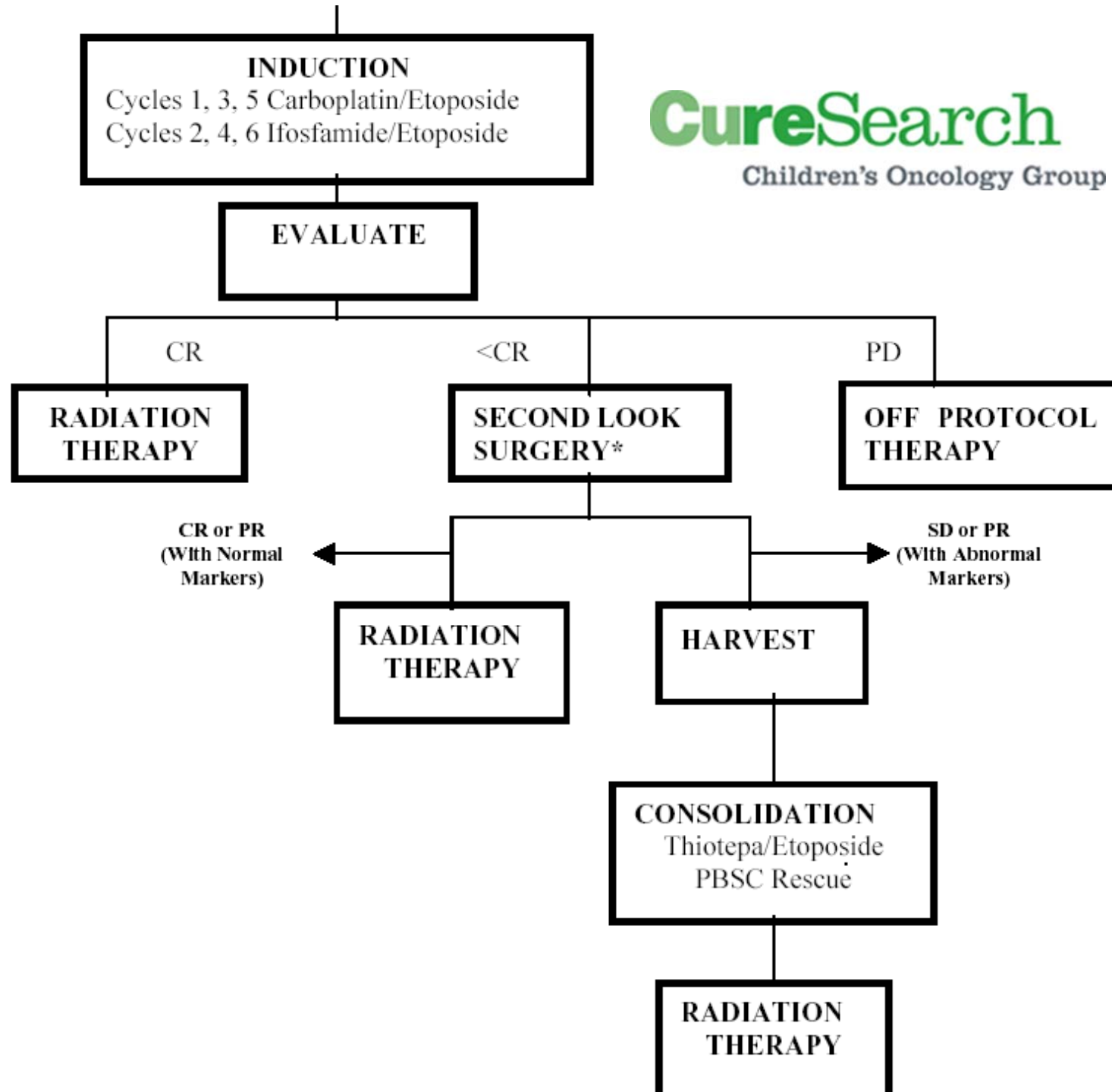
Histologically unconfirmed pineal and/or suprasellar tumors with serum and/or CSF tumor markers of beta HCG >50IU/dl or any elevation of alpha fetoprotein >10 IU/L (ng/mL) or institutional norm.

Patients with normal AFP and B-HCG < 50IU/dl without histologic diagnosis of a NGGCT are ineligible and patients with pure germinoma without elevation of tumor marker are ineligible.

ACNS0122 Eligibility

- Age 3 to <25 yrs
- Histological Diagnosis
 - Yolk Sac
 - Embryonal Carcinoma
 - Choriocarcinoma
 - Immature Teratoma & Teratoma With Malignant Transformation
 - Mixed Germ Cell tumor
- Histologically confirmed Germinoma with serum &/or CSF β -HCG >50lu/l
- Pineal &/or suprasellar tumors with serum &/or CSF β -HCG >50lu/l; or AFP > 10



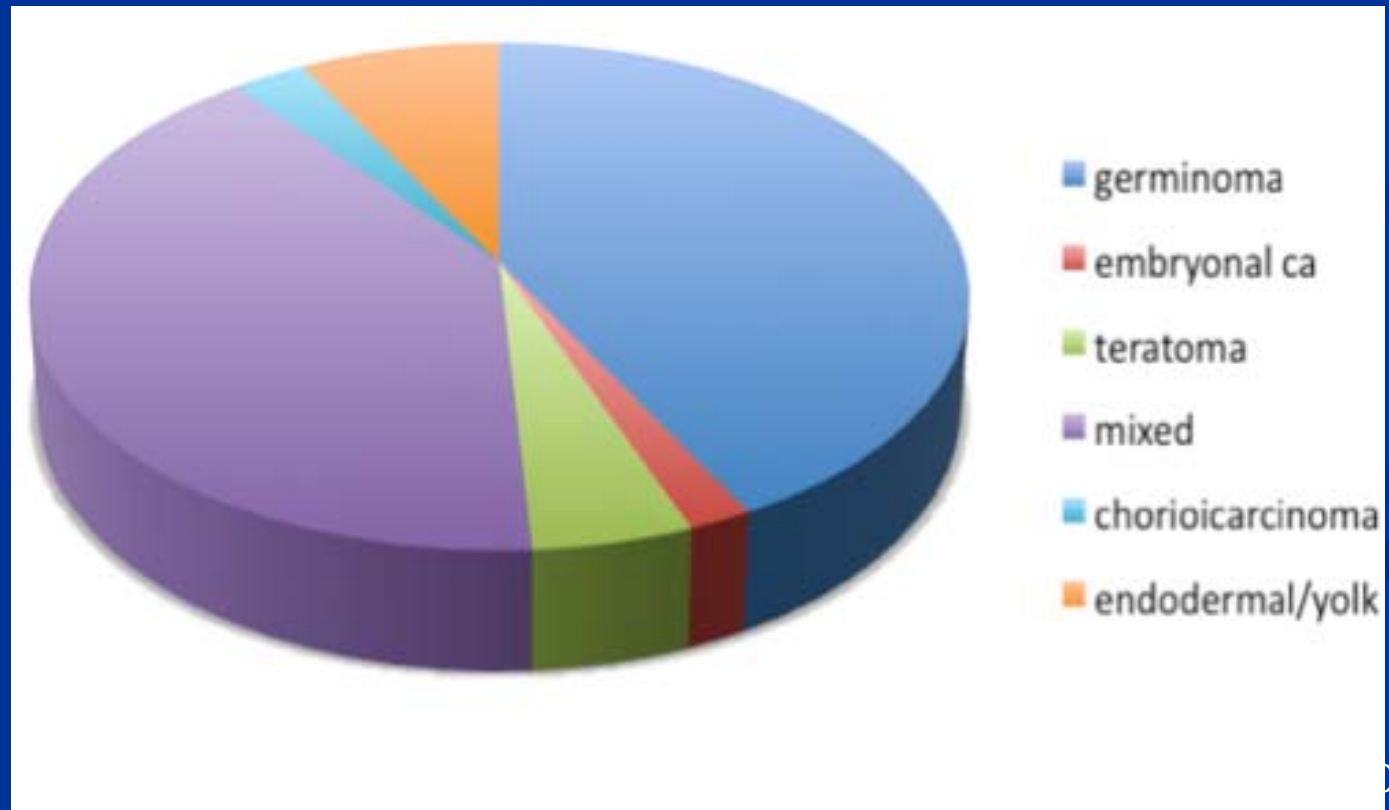


ACNS0122 NGGCT

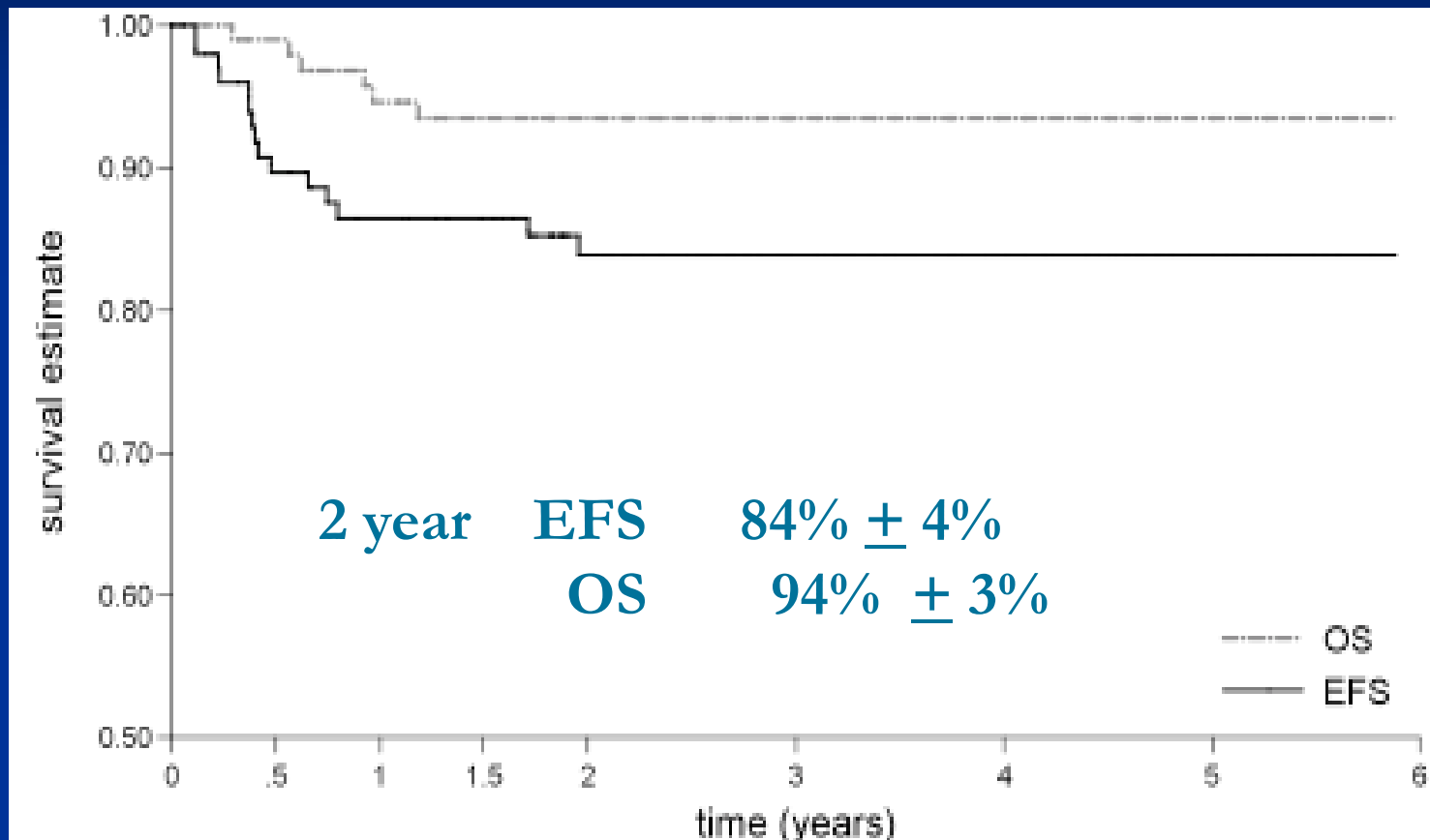
- All patients received 6 cycles of chemotherapy (alternating Carboplatin/Etoposide & Ifosfamide/Etoposide)
- Patients with radiographic response and marker normalization treated with CSI 36 Gy f/b IFRT to primary tumor to total dose of 54 Gy
- Second look surgery was encouraged for residual disease
- Thiotepa/Etoposide f/b PBSC rescue was encouraged for patients with viable disease

ACNS0122 NGGCT

- 104 patients enrolled
- 15 recurrences, 6 deaths
- Median f/u 2.8 years



ACNS0122



Median TTP 0.4 years
Median TTD 0.77 years

Courtesy of Stewart Goldman, MD

ACNS0122



- Relapses mainly local
 - 9 local recurrences
 - 4 distant
 - 2 spinal
 - 1 spine and distant brain
 - 1 abdominal carcinomatosis
 - 2 markers only

ACNS0122

- Second look surgery for poor response (15)
 - Teratoma (6)
 - Malignant teratoma (3)
 - Fibrosis (4)
 - NGGCT (2)
- Second look surgery for progressive disease (6)
 - Growing Teratoma Syndrome (4)
 - Embryonal (2)

Too few patients went on to HD chemotherapy f/b
PBSC to assess efficacy

Pure Germinoma/ACNS 0232

- ACNS0232 randomized trial comparing:
 - 1) RT alone (WVRT 24 Gy f/b IFRT to total 45 Gy) – STANDARD ARM
 - 2) Chemotherapy followed by response-based RT (2-4 cycles* f/b IFRT to 30 Gy).

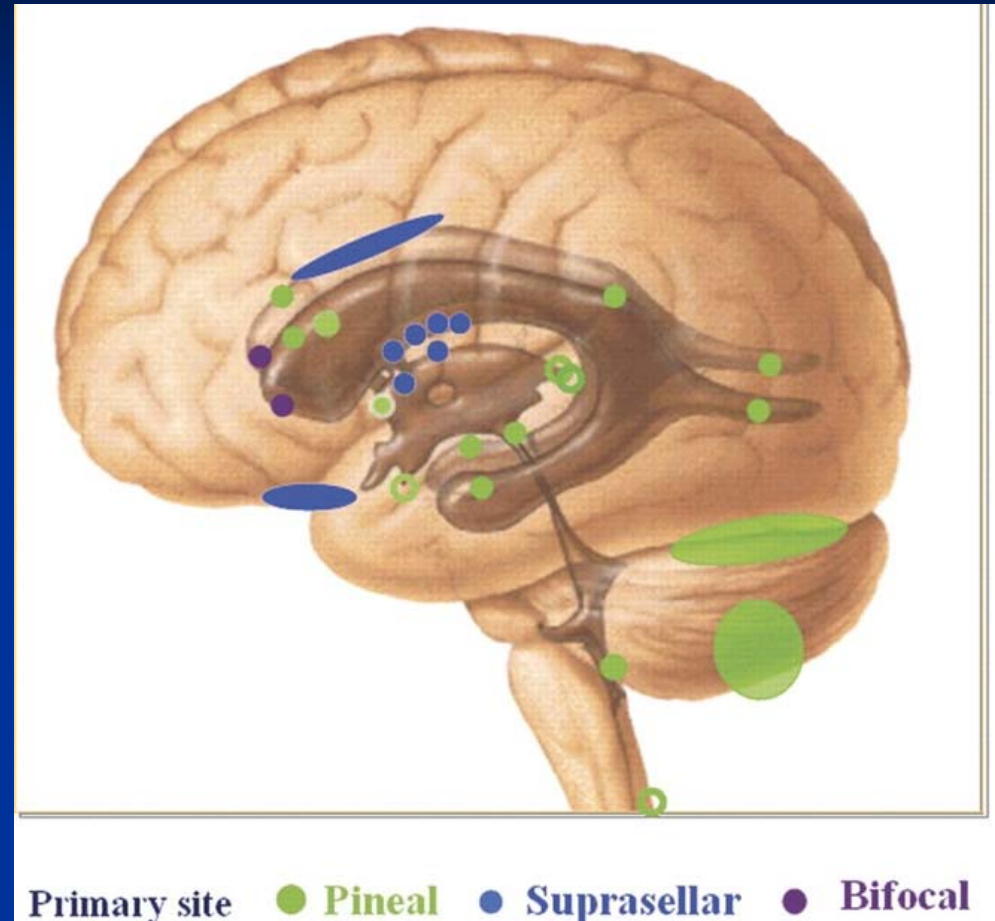


*carboplatin/etoposide x2 f/b response assessment;
If CR no further therapy & if < CR cisplatin/cyclophosphamide x 2

Ventricular Relapse

Reports of high rates of ventricular relapse led several cooperative groups to abandon IFRT as a treatment option

ACNS0232 closed to poor accrual

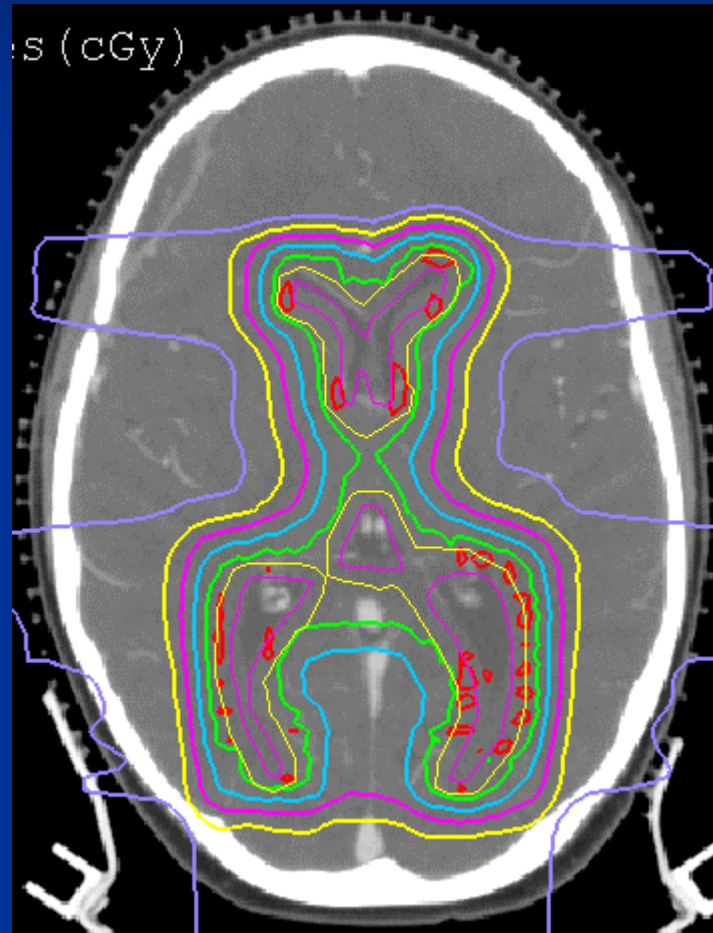


Conclusions

- 1 Increased risk of relapse with chemotherapy followed by IFRT
- 2 Radiation volume cannot be reduced from WVRT to IFRT

Can we reduce radiation dose for patients who are responding to chemotherapy?

WVRT



PLANNED STRATEGY IN SIOP CNS GCT 2003

- SECRETING GCTs -

AFP > 25 ng/ml or β HCG > 50 IU/l in serum or CSF

standard risk

AFP \leq 1000 ng/ml
and age > 5 years
and complete
workup

3 x PEI

E
V
A
L
U
A
T
I
O
N

CR

PR

Res

1 x PEI

non-metast.
TU 54 Gy
metastatic
CSI 30 Gy
+TU 24 Gy

high risk

AFP > 1000 ng/ml
or age \leq 5 years
or incomplete workup

3 x PEI

E
V
A
L
U
A
T
I
O
N

CR

PR

Res

HD PEI

only if
age > 5 y.
else
STOP

non-metast.
TU 54 Gy
metastatic
CSI 30 Gy
+TU 24 Gy



NGGCT



Germinoma

ACNS1123

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized
Central Nervous System
Germ Cell Tumors

ACNS1123

- Combines NRGCT and pure GCT (2 strata)
- Primary objectives:
 - 1 To determine, as measured by 3 year PFS if volume/dose of RT can be reduced for NRGCT and if chemotherapy f/b low dose WVRT plus IF RT is effective for pure GCT
 - 2 To prospectively evaluate the cognitive, social, and behavioral functioning of children and young adults who are treated with reduced RT dose/volume

Eligibility

- Only for patients with localized disease
 - Bifocal tumors eligible
 - Patients with disease found on endoscopic examination of ventricles eligible

Eligibility

- Stratum 1 (NGGCT)
 - Patients with identified levels:
 - Serum and/or CSF β -HCG >100 mIU/mL, or,
 - Any elevation of serum and CSF AFP > 10 ng/mL, or, institutional norm
 - Biopsy not required
 - Patients with any of the following elements on biopsy/resection, irrespective of serum and/or CSF β -HCG and AFP levels:
 - endodermal sinus tumor (yolk sac), embryonal carcinoma, choriocarcinoma, malignant/immature teratoma, mixed GCT with malignant GCT elements.

Eligibility

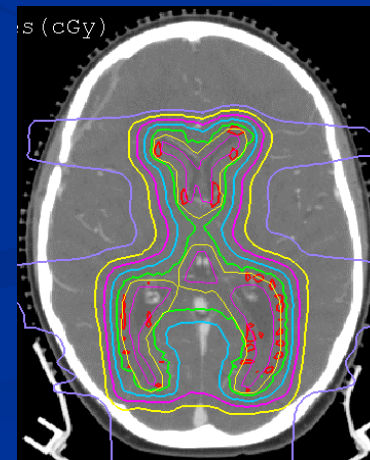
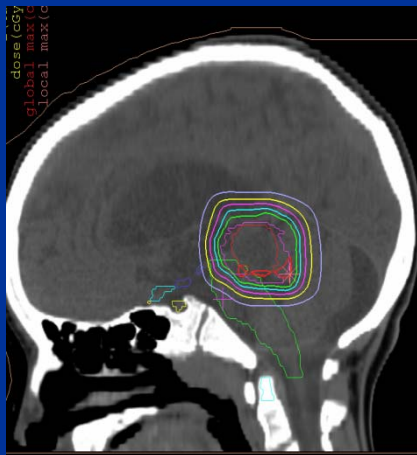
■ Stratum 2 (Germinoma)

- Patients with institutional normal AFP and β -HCG $5 - \leq 50$ mIU/mL in serum and/or CSF (biopsy not required)
- Patients with bifocal involvement or pineal lesion with DI and β -HCG ≤ 100 mIU/mL and institutional normal AFP in serum/CSF (biopsy not required)
- Patients with histologically confirmed germinoma or germinoma mixed with mature teratoma and β -HCG ≤ 100 mIU/mL and institutional normal AFP in serum/CSF

ACNS1123- pure GCT



- Chemotherapy
 - 4 cycles of Carboplatin/Etoposide
- Radiation
 - WVRT to 18 Gy
 - IFRT to bring primary disease to total 30 Gy



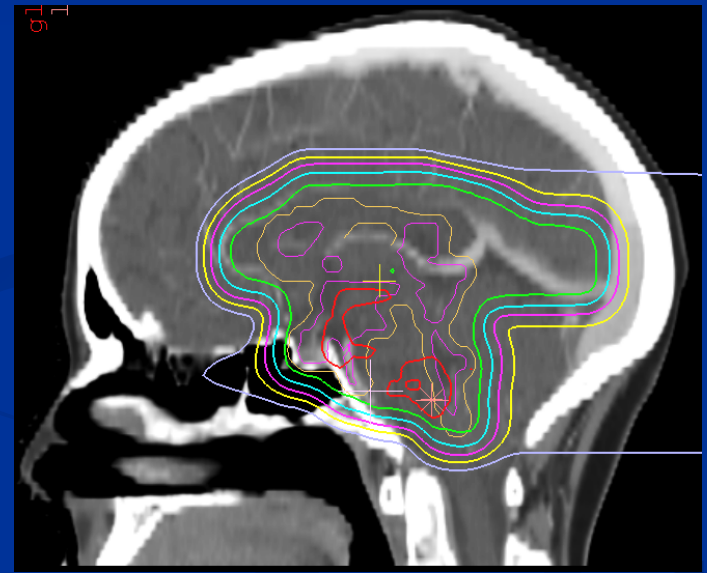
RT Guidelines



- 3D planning required
- 3D photons, IMRT, protons allowed
- 2 CTV's
 - Whole Ventricles
 - Involved Field
- Involved field CTV must be contoured upfront and added to whole ventricle volume to ensure full coverage

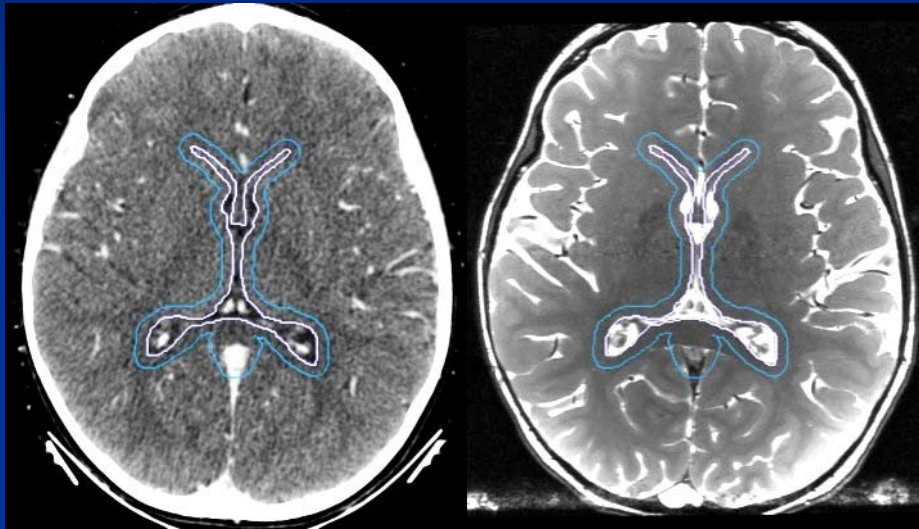
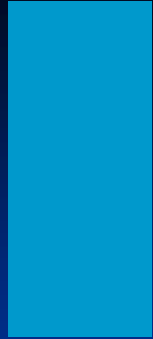
WVRT

- While few patients were treated with WVRT on prior studies, all patients enrolled on ACN1123 will receive WVRT
- Difficult volume to contour with variability among clinicians
- Review of volumes from ACNS0232 demonstrated need for clear guidelines
- ACNS1123 will allow for smaller margins and more conformal techniques



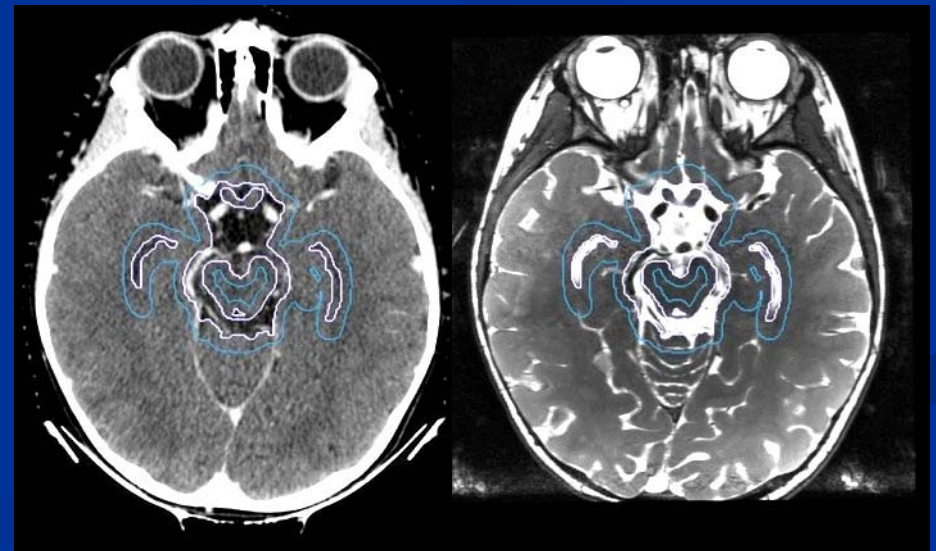


Whole ventricle atlas



- To improve consistency
- Provide a visual guide
- Decrease protocol violations

- Will be available on QARC website



Stem Cell Research Points The Way To The Cell of Origin For Intracranial Germ Cell Tumors

Tan C, Scotting P. J. Pathol. 229:4-11 2013.

- Neural Stem Cell leads to GCT?
- Parental Chromosome Duplications
Implies Possible Pre-Meiotic Event
- Proposed Cell of Origin, the Germ Cell Progenitor, Would Not Normally Be Found In The Brain
- No Other Class Of Primary Cancer Arises From A Cell From A Distant Organ
- Evidence For Model Of Transformation Of Endogenous Brain Cells

Conclusions:

North American Approach to CNS GCTs

- Incremental Progress?
- Different Strategies Compared
 - Europe
 - Japan
- ACNS 0122, ACNS 1123
- Goal: Define Risk – Tailor Treatment
- Future:
 - Radiation Questions?
 - Achieve Consensus?