Primary Intracranial Germ Cell Tumor (GCT)

Bryce Beard MD, Margaret Soper, MD, and

Ricardo Wang, MD

Kaiser Permanente Los Angeles Medical Center

Los Angeles, California

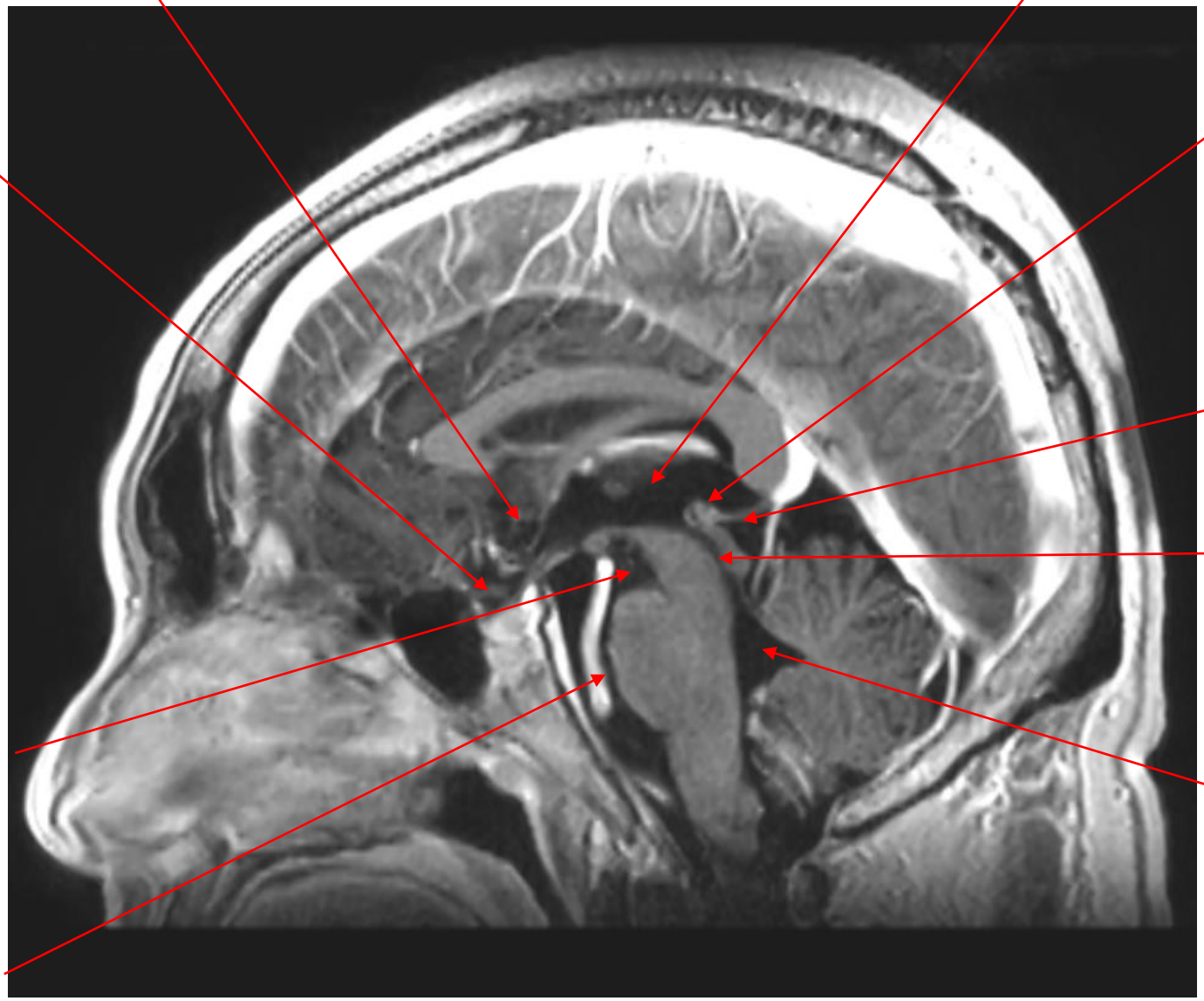
Case

- 10 year-old boy presents with headache x 2 weeks.
- Associated symptoms include nausea, vomiting, and fatigue
- PMH/PSH: none
- Soc: Lives with mom and dad. 4^{th} grader. Does well in school.
- PE: WN/WD. Lethargic. No CN deficits. Normal strength. Dysmetria with finger-to-nose testing on left.

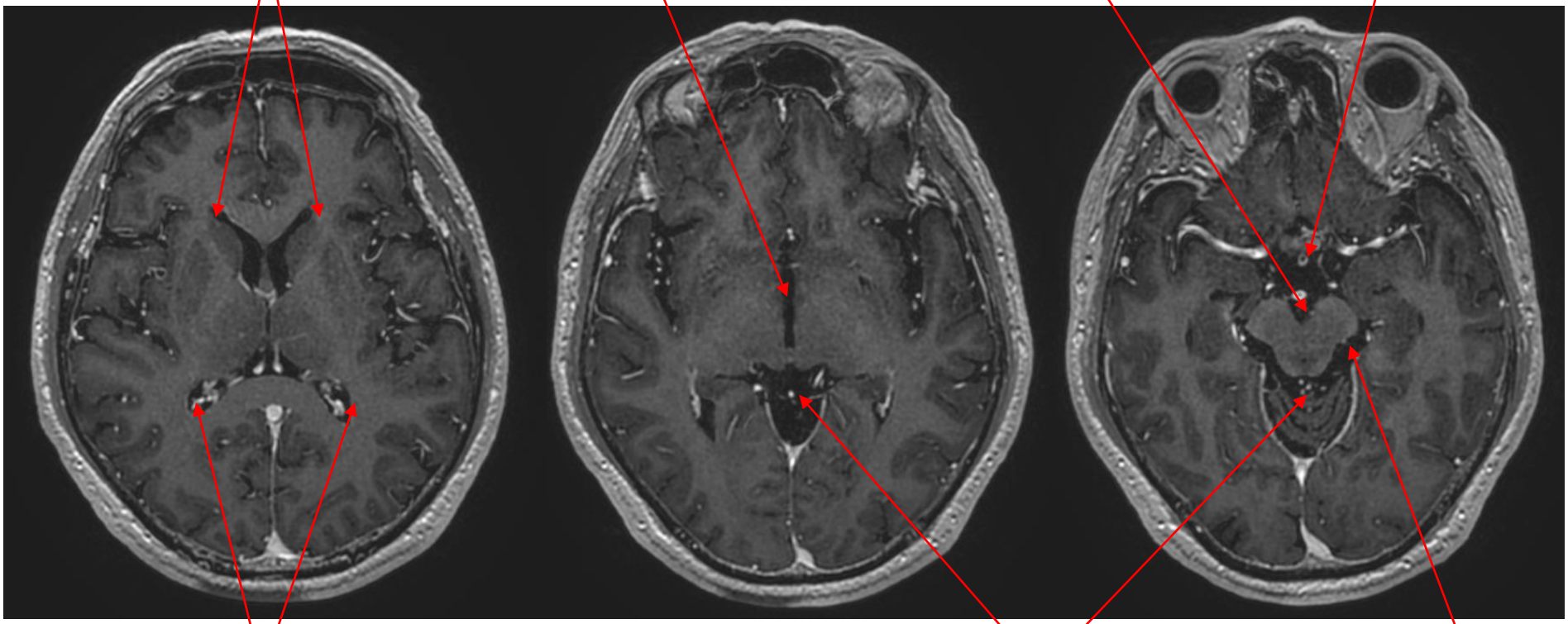
Presentation of Intracranial GCTs

- Symptoms depend on location of tumor.
  - Pineal location
    - Acute onset of symptoms
    - Symptoms of increased ICP due to obstructive hydrocephalus (nausea, vomiting, headache, lethargy)
    - Parinaud's syndrome: Upward gaze and convergence palsy
  - Suprasellar location:
    - Indolent onset of symptoms
    - Endocrinopathies
    - Visual field deficits (i.e. bitemporal hemianopsia)
  - Diabetes insipidus can present due to tumor involvement of either location.
  - 2:1 pineal:suprasellar involvement. 5-10% will present with both ("bifocal germinoma").

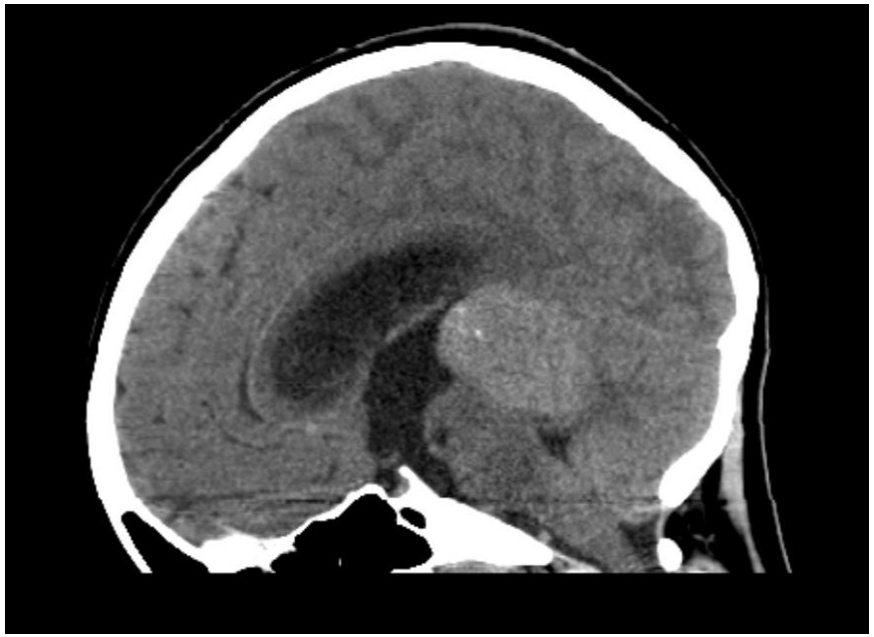
Anatomy

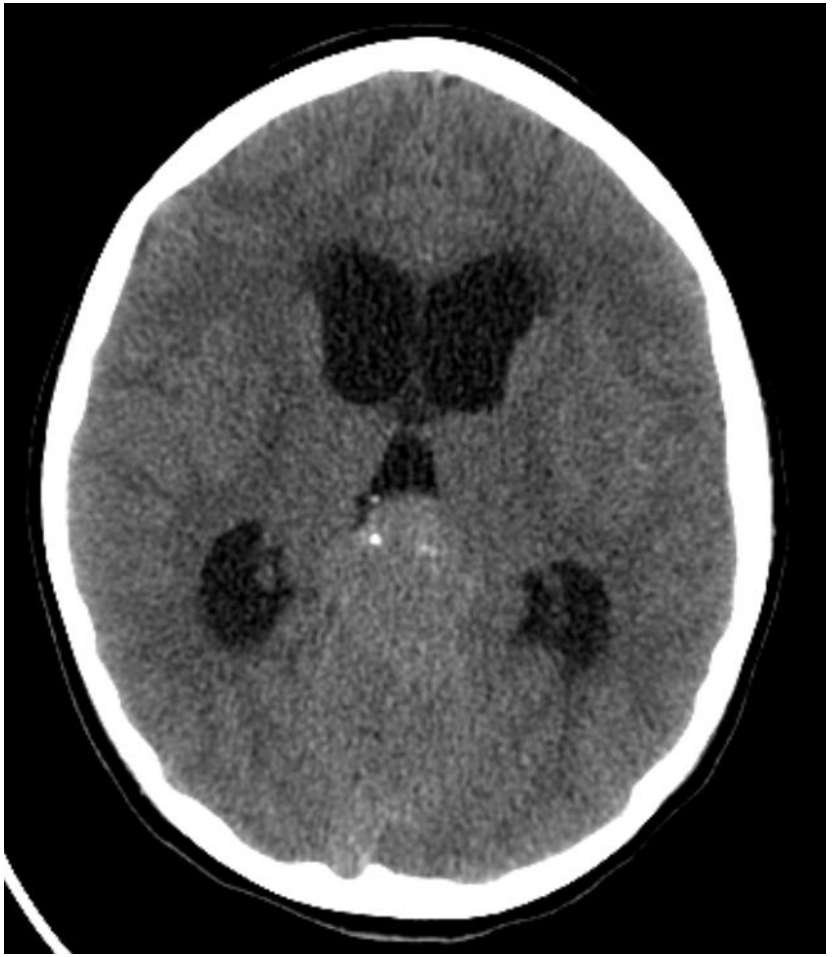

Suprasellar cistern
3rd ventricle
Optic chiasm
Pineal gland
Quadrigeminal Cistern
Cerebral (Sylvian) aquaduct
Interpeduncular Cistern
4th ventricle
Prepontine Cistern

Anatomy


Frontal horn of lateral ventricle
3rd ventricle
Interpeduncular cistern
Suprasellar cistern
Occipital horn of lateral ventricle
Quadrigeminal cistern
Ambient cistern

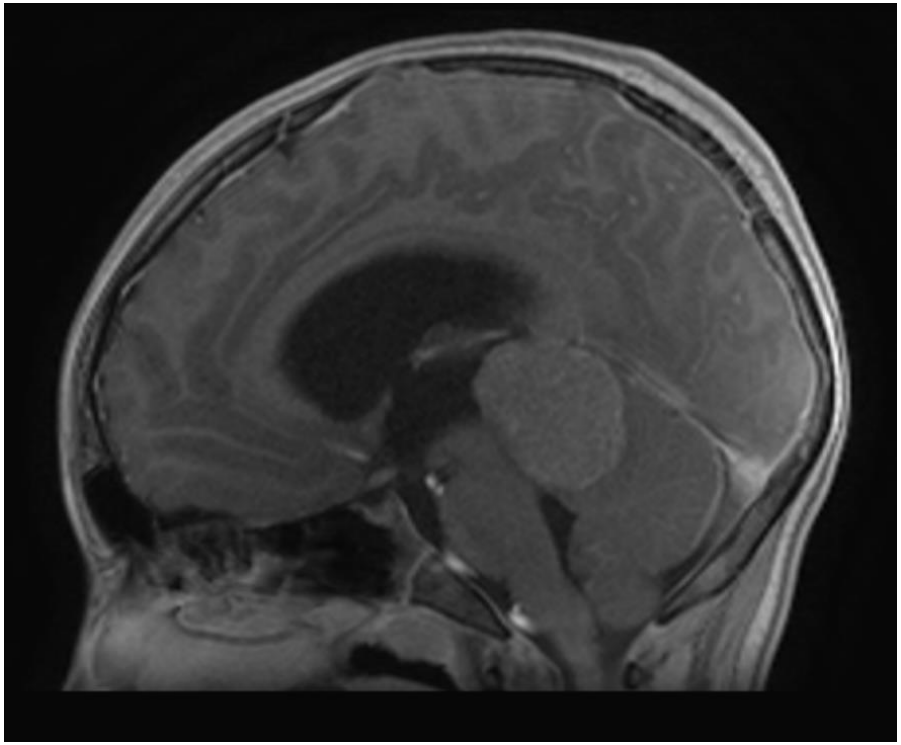
Case

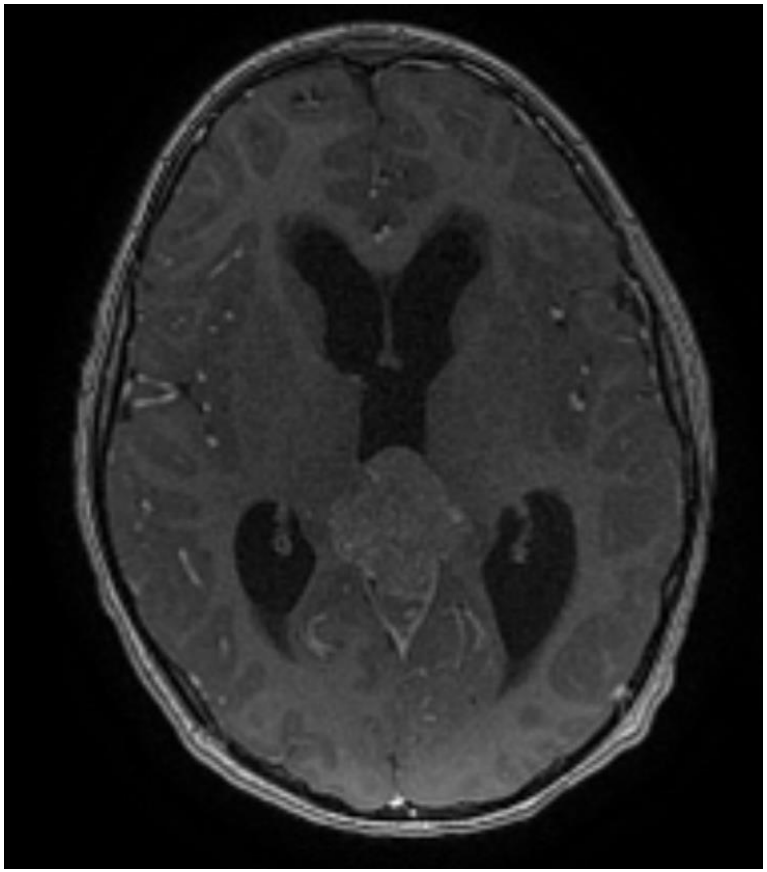




CT head: Hydrocephalus with enlargement of lateral and 3rd ventricles. 4.4 x 3.3 x 3.3 cm midline mass isodense to grey matter with calcifications.

Case





MRI brain: Intermediate- to hyper-intense 3rd ventricle/aqueduct mass with heterogenous enhancement.

Imaging Characteristics

- Imaging cannot reliably distinguish different types of GCTs, however non-germinomatous germ cell tumors (NGGCTs) tend to have more heterogenous imaging characteristics compared to germinomas.
- **CT**: hyperdense compared to normal brain, vivid contrast enhancement, calcifications due to normal pineal gland component or due to tumor
- **MRI**: T1 & T2 isointense to grey matter, vivid contrast enhancement

Differential Diagnosis

Pineal region tumor

- Germ cell tumor
  - (most common)
- Pineoblastoma
- Pineocytoma
- Pineal parenchymal tumor of intermediate differentiation
- Meningioma
- Ependymoma
- Central neurocytoma
- Metastasis
- Benign cyst

Suprasellar region tumor

- Pituitary adenoma
  - (most common)
- Germ cell tumor
- Craniopharyngioma
- Glioma
- Meningioma
- Metastasis
- Vascular lesion
- Infectious
- Granulomatous

What additional work-up is necessary when GCT is suspected?

- Basic labs
- MRI total spine
- Serum/CSF tumor markers (bHCG, AFP)
- CSF cytology
- Biopsy*

* Biopsy may not be required when tumor markers are characteristically elevated, however patients will often require surgical intervention due to hydrocephalus (pineal tumors) or visual field deficits (suprasellar tumors).

Case

- CBC, metabolic panel normal.
- No evidence of drop metastases on MRI total spine.
- Serum AFP: < 2.0 ng/mL (nl <= 8.8 ng/mL)
- Serum bHCG: 5.9 ng/mL (nl <= 2.5 ng/mL)

If CNS GCT is suspected, when is biopsy indicated?

- Tissue biopsy is required in the absence of tumor marker elevation.
- When tumor markers suggest NGGCT (AFP abnormal, bHCG > 50 ng/dL) , biopsy is not required.
- When imaging suggests bifocal germinoma (pineal and pituitary involvement) with moderately elevated bHCG and normal AFP, biopsy is not required.

Case

- Pt underwent endoscopic third ventriculostomy with biopsy.
- CSF AFP: < 0.5 (nl < 0.5 ng/mL)
- CSF bHCG: 45.1 (nl < 5.0 mIU/mL)
- CSF cytology: No malignant cells
- Final pathologic diagnosis: Germinoma (CD117+, OCT3/4+, CD30-)

Epidemiology

- In US & Europe, GCTs represent 0.5 to 3% of pediatric CNS tumors.
- In Asian countries, GCTs represent up to 11% of pediatric CNS tumors
- Peak incidence: 10-12 years old
  - Germinomas: Older patients
  - NGGCTs: Younger patients
- Male predominance
  - Germinomas: 1.8:1 (male: female)
  - NGGCTs: 3:1

Pathogenesis

- There are multiple theories regarding pathogenesis. Most hold that multiple histologic subtypes share a common cell of origin. For example:
  - "Germ cell theory": Primordial germ cells mismigrate during embryonic development and subsequently undergo malignant transformation.
  - "Embryonic cell theory": Pluripotent embryonic cells mismigrate and give rise to GCTs.

Extragonadal GCTs

- GCT with no evidence of primary in the testes or ovaries.
- Typically occur in midline structures
- Location varies with age:
  - Adults: mediastinum > retroperitoneum
  - Pediatric: sacrococcygeal > intracranial

WHO Classification of Intracranial GCTs

- Broadly categorized as germinoma (~2/3) and NGGCT (~1/3)
- NGGCT types include:
  - Endodermal sinus tumor (aka yolk sac tumor)
  - Choriocarcinoma
  - Embryonal carcinoma
  - Mixed malignant germ cell
  - Teratoma (immature, mature, malignant transformation)

Tumor Markers

Type of GCT	Beta-HCG	Alpha-fetoprotein
Teratoma	-	-
Germinoma (pure)	+/-	-
Germinoma (syncytriotrophoblastic)	+	-
Choriocarcinoma	++	-
Mixed germ cell	++	++
Endodermal sinus (Yolk Sac Tumor)	+/-	++
Embryonal carcinoma	+/-	+/-

Table adapted from Packer *et al*. The Oncologist. 2000.

AFP > 10 ng/mL excludes pure germinoma
Beta-HCG typically < 50 ng/mL in pure germinoma

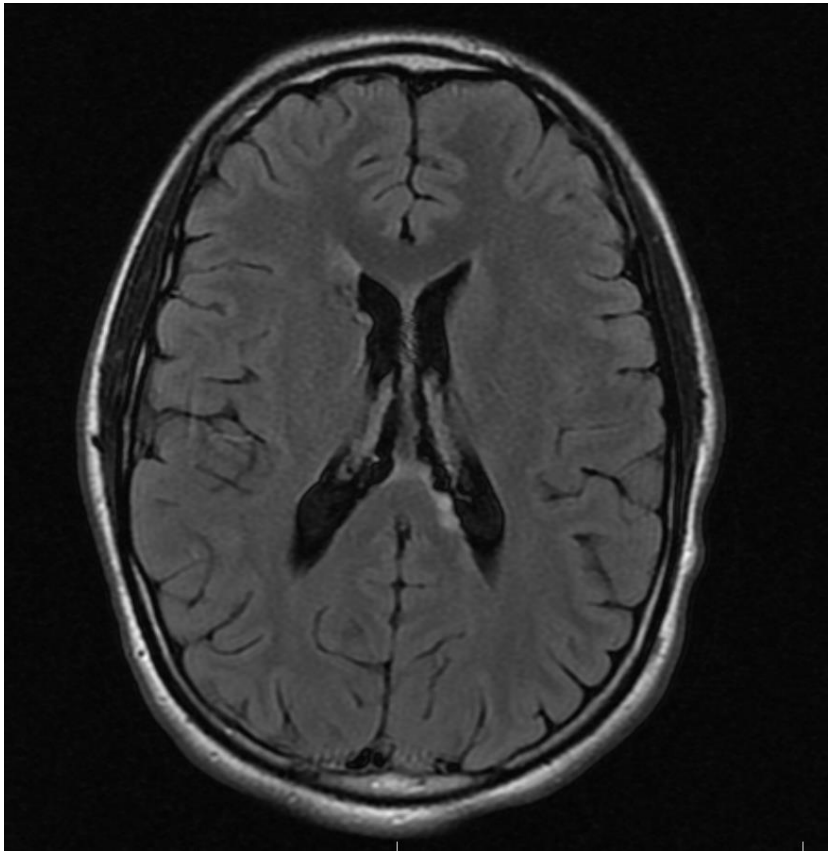
Staging

- No formal staging system
- Modified Chang system (from medulloblastoma) has been used to characterize M-stage
  - M0: No neuro-axial or extra-CNS metastases
  - M1: + CSF cytology
  - M2: Nodular intracranial seeding
  - M3: Nodular spinal seeding
  - M4: Extra-neural spread

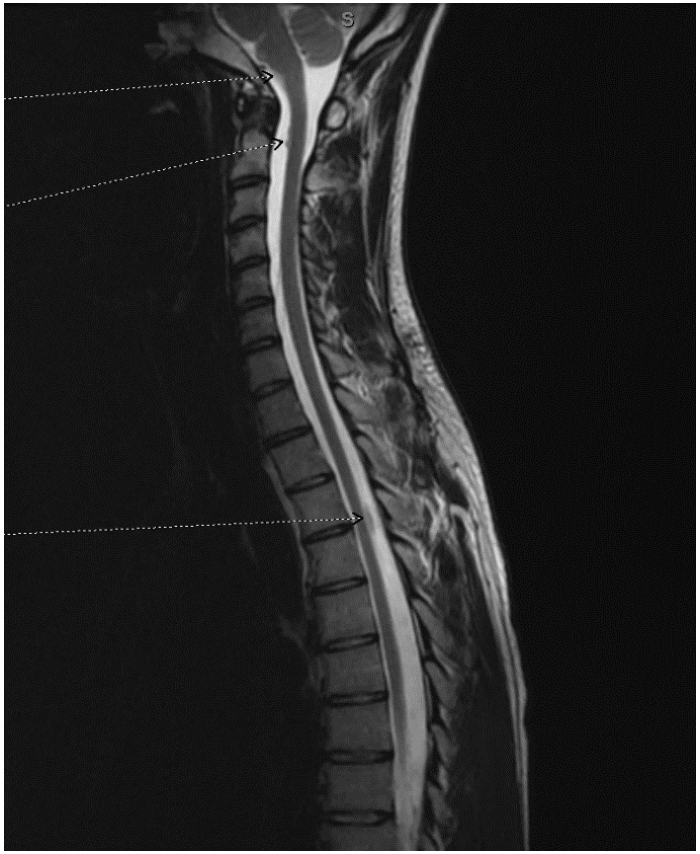
Staging

- Pragmatically, disease extent is categorized as M0 (localized) or M+ (disseminated)
- 10-15% will have leptomeningeal dissemination at time of diagnosis

Staging – Disseminated Disease

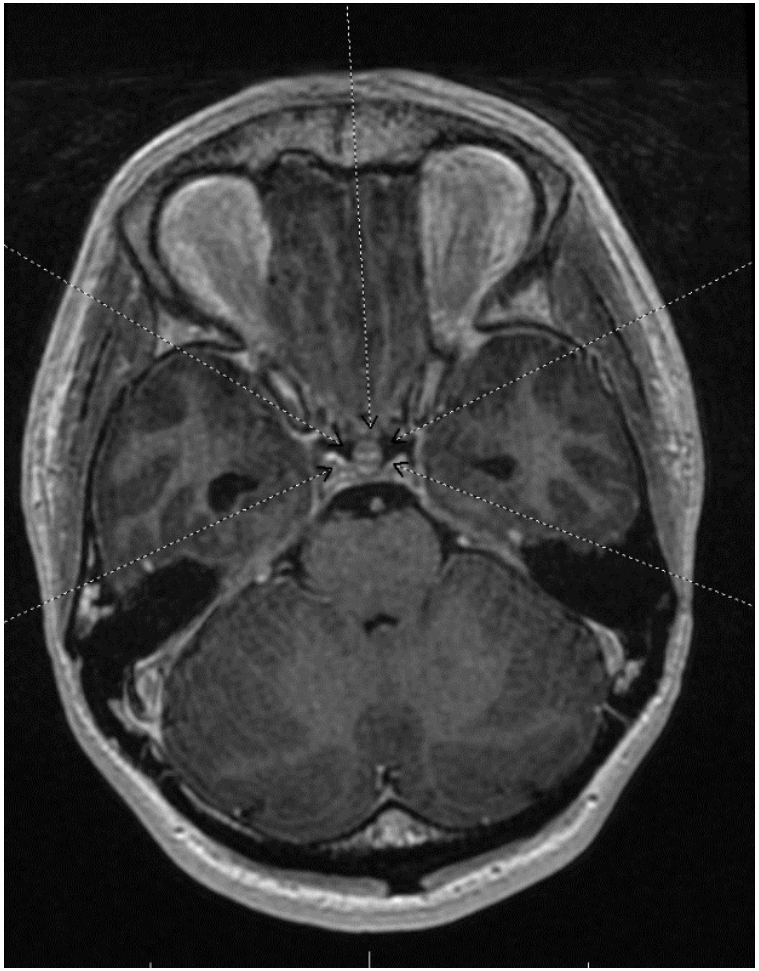


Example of subependymal spread in a patient with a pineal germinoma and no evidence of spine metastases. Treated as disseminated disease.



Example of disseminated disease with drop metastases in a patient with a pineal mixed germ cell tumor.

Staging – Bifocal disease (Localized)



Example of pituitary stalk thickening in a patient with a pineal germinoma and no other signs of spread of disease. Treated as localized disease.

Treatment Overview

- Histology (germinoma versus NGGCT) is most important prognostic factor

Histology	5-year PFS	5-year OS
Germinoma	>90%	>90%
NGGCT	40-70%	60-70%

- Histology and M-stage are major determinants of treatment approach.

Treatment Overview

- Target volumes reflect tendency for subependymal/CSF spread.
- Historical standard treatment for GCTs was single modality radiotherapy with 36 Gy craniospinal irradiation (CSI) + primary boost to 50-54 Gy.
- Given the overall excellent prognosis (particularly for germinomas) and recognition of late effects of radiation (endocrine, neurocognitive, secondary malignancy, musculoskeletal, auditory/visual), practice has evolved towards combined-modality treatment (CMT) with chemotherapy, lower RT doses, and smaller RT volumes.

Treatment Overview

- Pure germinoma:
  - Localized
    - Single modality: Whole ventricle radiotherapy (WVRT)(21-24 Gy) + tumor boost (40-45 Gy total)
    - Combined-modality: chemotherapy → reduced dose WVRT + tumor boost. For example, ACNS 1123 is an ongoing trial looking at response-based RT doses after chemotherapy
      - CR: 18 Gy WVRT + primary boost (30 Gy total)
      - PR/SD: 24 Gy WVRT + primary boost (36 Gy total)
  - Disseminated
    - Single modality: 30 Gy CSI + tumor boost (45 Gy total)
    - Combined modality: chemotherapy → 24 Gy CSI + tumor boost (40 Gy total)
- NGGCTs:
  - Typical approach: 4-6 cycles platinum-based chemotherapy → CSI (30-36 Gy) + tumor boost (50.4-54 Gy total)
  - CSI is the current standard regardless of M-stage
  - Chemotherapy is mandatory and improves survival (OS 20-40% RT alone → 60-70% CMT)
  - Consider "second-look" surgery if residual disease after chemoradiation.

Reducing Dose: MAKEI 83/86/89

- Series of German prospective, nonrandomized trials enrolling from 1983 to 1993
- Assessing dose reduction in CNS germinomas
- MAKEI 83/86 (pilot studies)
  - 11 patients
  - 36 Gy CSI + 14 Gy boost (1.8-2.0 Gy fx)
  - No relapses
- MAKEI 89
  - 49 patients
  - 30 Gy CSI + 15 Gy boost (1.5 Gy fx)
  - 5 relapses (4 outside of CNS)
- Conclusion: CSI dose can be reduced to 30 Gy in germinomas

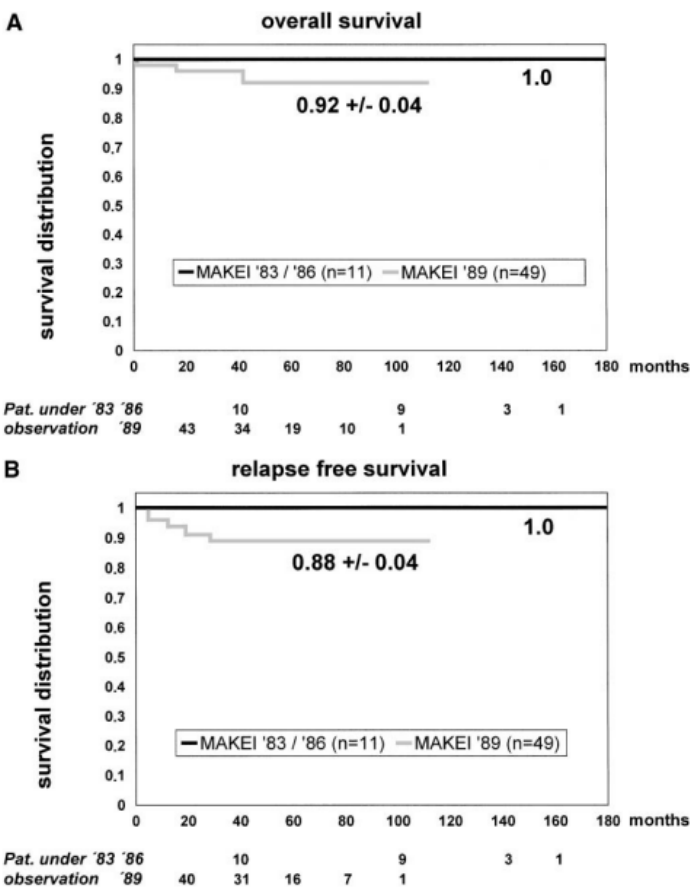
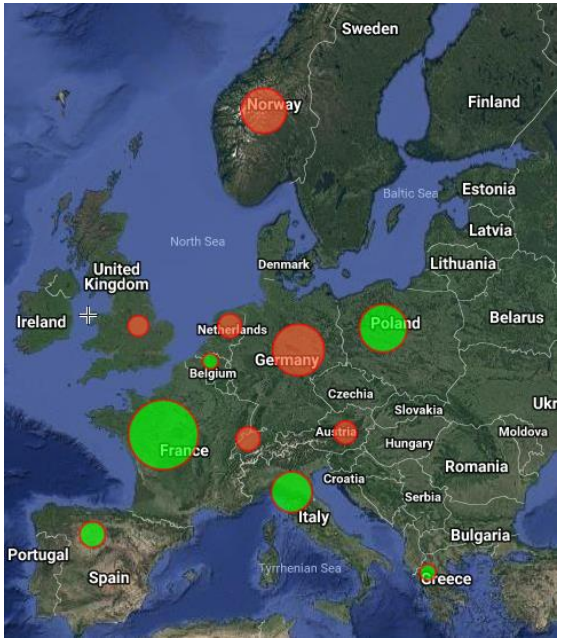


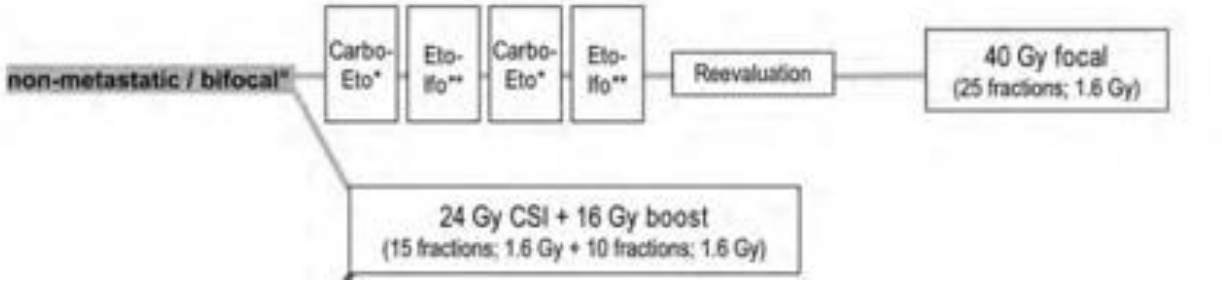
Fig 1. Actuarial (A) overall and (B) relapse-free survival rates after treatment with radiotherapy alone in patients (Pat.) with intracranial germinoma (MAKEI 83/86/89) (Kaplan-Meier survival distribution function).

Bamberg *et al*. JCO. 1999.

Reducing Volume: SIOP GCT 96

- Prospective, nonrandomized, international trial enrolling from 1996 to 2005.
- Included germinomas and NGGCTs.
- Comparing CMT with involved-field radiation (IFRT) versus radiotherapy alone with CSI.
- Treatment was assigned according to national practice





Red = IFRT
Green = CSI

Calaminus *et al*. *Neuro oncol*. 2013.

Reducing Volume: SIOP GCT 96

Table 1. Chacteristics of 11 patients with relapses, by age, site, dissemination, tumor markers, radiological response, time to relapse, tumor markers at relapse, site of relapse, and pathology at relapse

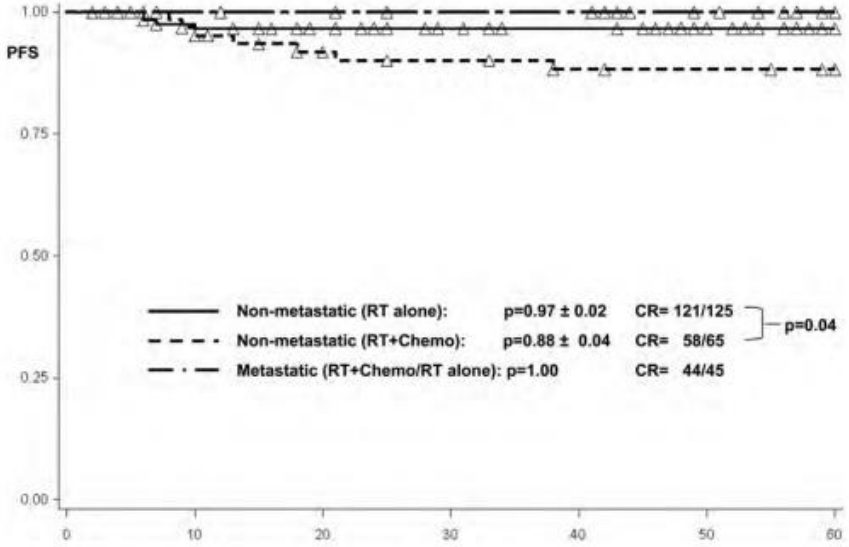
Variable	Patient Sex	1 Male	2 Female	3 Male	4 Female	5 Male	6 Female	7 Male	8 Male	9 Male	10 Male	11 Male
primary diagnosis	age (years/ months)	11;2	10;6	15;9	4;10	7;3	15;7	9;0	16;4	12;10	14;11	10;4
	tumour site	Pineal	suprasellar	basal ganglia	bifocal	pineal	corpus callosum/ epiphysis/ hypothal	pineal	pineal	pineal	pineal + suprasellar	suprasellar
	metastases	no	no	no	no	no	no	no	no	no	no	no
	AFP serum	3 ng/mL	5 ng/mL	n.d.	3 kU/L	2,3 ng/mL	1 ng/mL	2,9 ng/mL	3,3 ng/mL	2 kU/L	2 ng/mL	1 ng/mL
	AFP CSF	1 ng/mL	n.d	n.d.	<1 kU/L	n.d.	1 ng/mL	<4 ng/mL	1,3 ng/mL	<2 kU/L	n.d.	n.d.
	HCG serum	4 U/L	38 U/L	n.d.	6 IU/L	29,3 mIU/mL	2 U/L	2 U/L	<2 U/L	<2 kU/L	2 U/L	2 U/L
	HCG CSF	1 U/L	n.d.	n.d.	8 IU/L	n.d.	5 U/L	10 U/L	3,7 U/L	2 kU/L	n.d.	n.d.
	therapy group	chemo + focal irradiation	chemo + focal irradiation	chemo + focal irradiation	chemo + focal irradiation	chemo + focal irradiation	chemo + focal irradiation	chemo + focal irradiation	CSI	CSI	CSI	CSI
	radiological response	CR	CR	PR	PR	CR	CR	CR	CR	no information available	CR	CR
At relapse	Time to relapse from original diagnosis	10 months	19 months	9 months	34 months	13 months	21 months	9 months	8 months	4 months	10 months	8 months
	AFP serum	2,5 U/mL	normal	2 kU/L	2 kU/	0,99 ng/mL	2 kU/l	<4 ng/mL	1272 ng/ mL	n.d.	1483 kU/L	2 ng/mL
	AFP CSF	n.d.	n.d.	1 kU/L	0.2 kU/L	0,38 ng/mL	n.d.	n.d.	109 ng/ mL	n.d.	n.d.	n.d.
	HCG serum	7,7 mU/mL	123 U/L	<2 U/L	22 IU/L	14,8 U/L	<2 kU/L	<1 U/L	negativ	n.d.	not done	<1 U/L
	HCG CSF	n.d.	734 U/L	HCG 3 U/L	27 IU/L	231 U/L	n.d.	n.d.	negativ	n.d.	n.d.	n.d.
	pathology	nekrotic tissue	not done	teratoma (after chemo)	no information available	not done	not done	not done	YST	TD immature	necrotic and reactive tissue (after chemo)	not done
	Site of relapse	right frontal horn	leptomeningeal at bottom of 4th ventricle	Local ventricles	no information available	lateral ventricles, CSF-cytology positive	frontal horn/ corpus callosum	spinal C1–5 3. Ventricle	pineal	right parietal lobe incl. Pineal area	pineal	local

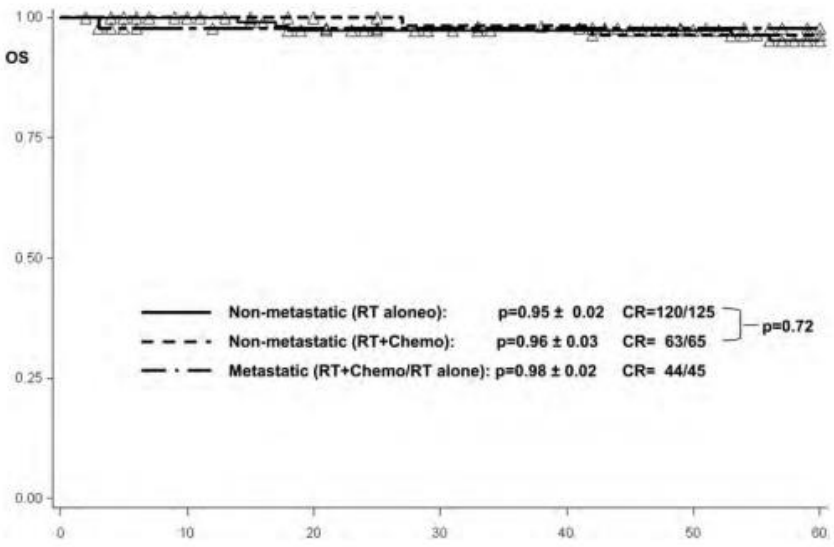
In CSI group, all failures were at primary site.

In IFRT group, majority of failures were outside of the primary site within ventricles.

Calaminus *et al*. *Neuro oncol*. 2013.

Reducing Volume: SIOP GCT 96





- **Conclusion**: Combined modality treatment with reduced dose is a treatment options. When combined modality treatment is used, volume should cover at least ventricles.

- See also Rogers *et al*. Lancet Oncol 2005.
  - Individual patient data meta-analysis
  - Compared recurrence rates using WB/WVRT versus CSI in localized germinoma.
  - Found there was no notable increased risk of isolated spinal relapse (2.9% v 1.2%).

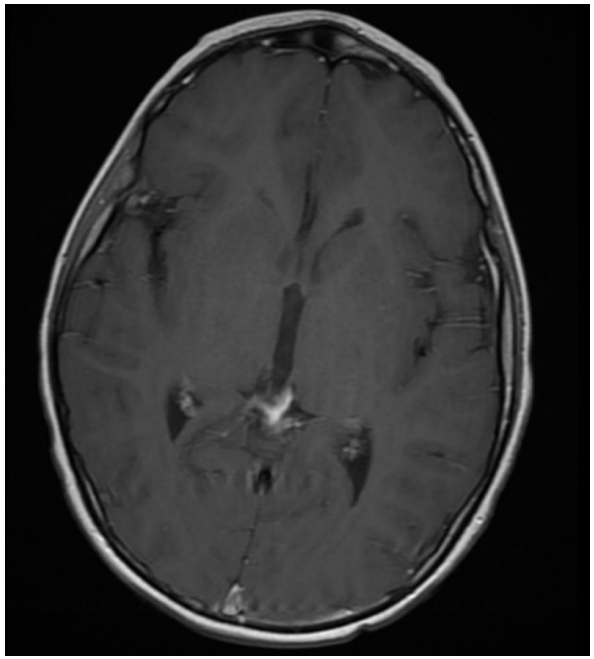
Calaminus *et al*. *Neuro oncol*. 2013.

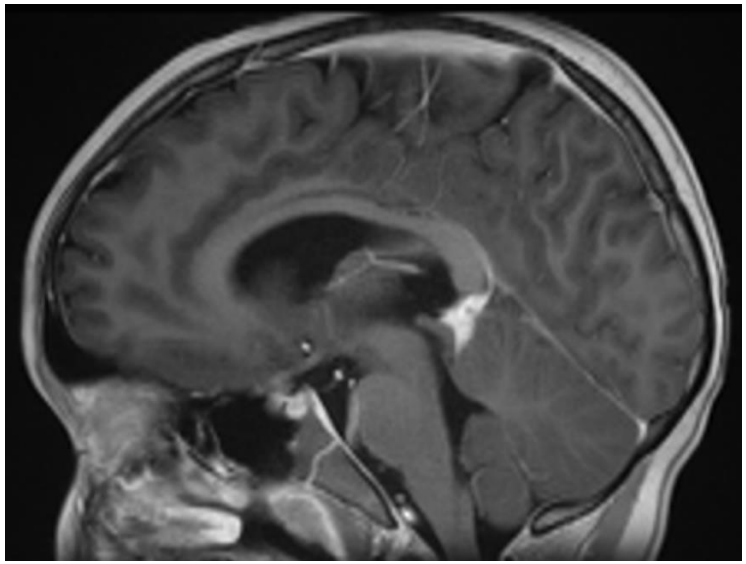
Case

- **Clinical diagnosis:** Localized germinoma
- **Treatment recommendation:** Neoadjuvant chemotherapy followed by whole ventricle radiotherapy (WVRT) + tumor boost.

Case

- Pt underwent 4 cycles carboplatin + etoposide
- MRI brain following chemotherapy showed good response.
- Repeat serum and CSF tumor markers within normal limits.
- Repeat spinal imaging & CSF cytology showed no evidence of dissemination.
- Recommended to proceed with radiotherapy.





Radiotherapy Planning

- Simulate supine with mask
- Technique: IMRT
- Dose and volume
  - WVRT: 21 Gy in 1.5 Gy fractions
  - Sequential IFRT boost: 9 Gy in 1.5 Gy fractions
- Fuse imaging
  - Pre-chemo post-contrast T1 & T2 MRI brain
  - Post-chemo post-contrast T1 & T2 MRI brain

Target Volume Delineation

- See ACNS 1123 protocol atlas for details (https://www.qarc.org/cog/ACNS1123_Atlas.pdf)
- Generate Involved Field PTV
  - Contour pre-chemotherapy GTV
  - Expand 5mm to CTV
  - Expand 3-5mm to PTV

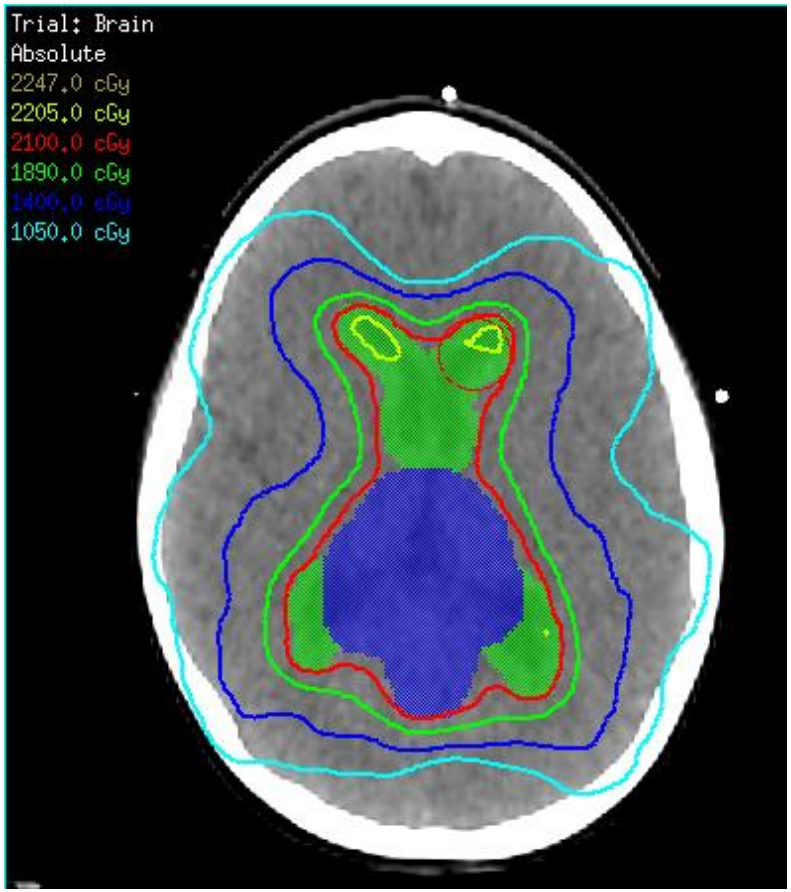
Target Volume Delineation

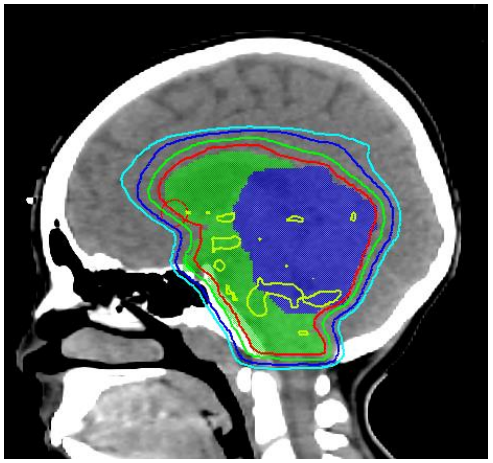
- Generate whole ventricle PTV
  - Generate whole ventricular volume (WVV). Includes
    - Pre-chemotherapy GTV
    - Lateral, 3rd, 4th ventricles
    - Suprasellar cistern, pineal cistern
    - If large sellar tumor or s/p endoscopic third ventriculostomy, then include prepontine cistern
  - Expand 5mm to CTV
  - Expand 3-5mm to PTV

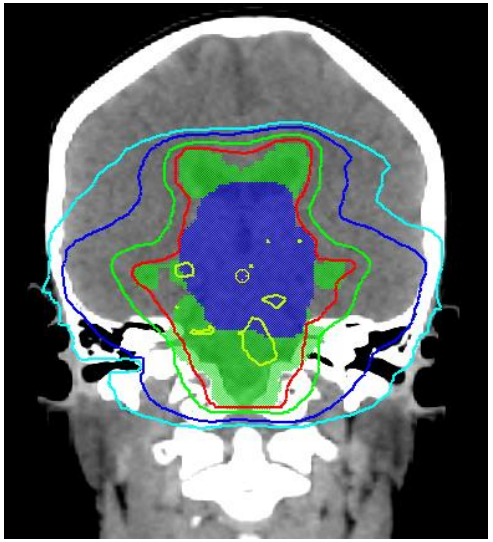
ACNS 1123 Dose Constraints

- Optic chiasm/nerve/tract: Max 54 Gy
- Single cochlea:
  - Goal: D50% < 3000 cGy
  - Preferred: D50% < 2000 cGy
- Brainstem/spinal cord: Max 54 Gy
- Optic globes: Max 45 Gy

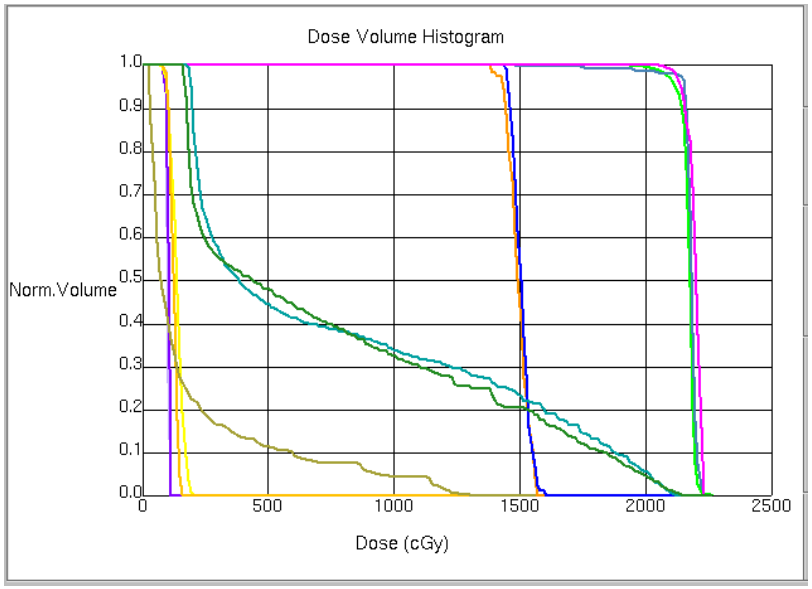
Whole Ventricle RT (21 Gy)







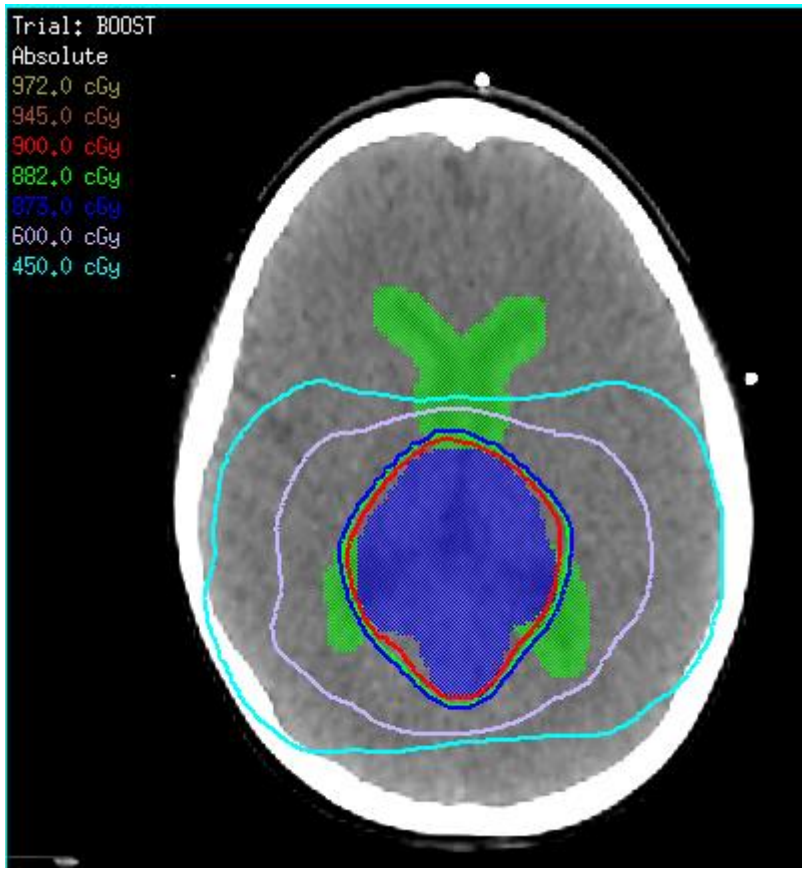
Whole Ventricle RT (21 Gy)

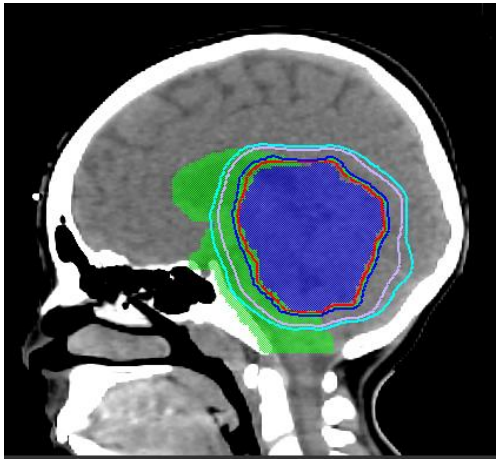


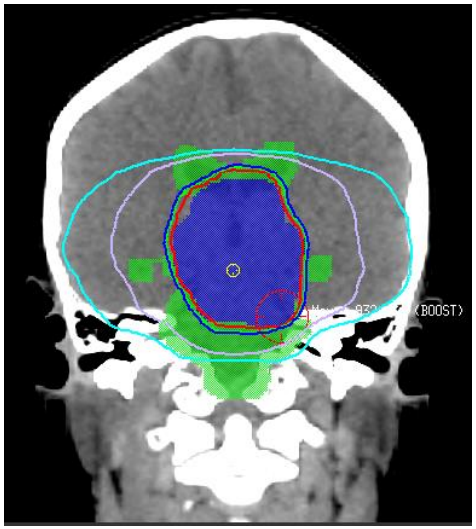
ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	PTV2100	Brain	1484.4	2256.9	2169.0	33.6	0.00 %	0.00 %
	Left Lens	Brain	90.1	111.0	99.3	4.3	0.00 %	0.00 %
	Right Lens	Brain	83.3	111.4	102.5	5.9	0.00 %	0.00 %
	Eye_L	Brain	74.0	214.4	135.4	25.1	0.00 %	0.00 %
	Eye_R	Brain	76.1	162.5	122.1	15.0	0.00 %	0.00 %
	cord	Brain	27.1	1302.0	178.9	276.4	6.65 %	0.00 %
	BrainStem	Brain	1435.2	2242.1	2175.3	63.8	0.00 %	0.00 %
	right cochlea	Brain	1382.4	1569.2	1492.6	39.7	0.00 %	0.00 %
	left cochlea	Brain	1445.5	1603.5	1504.7	33.2	0.00 %	0.00 %
	Optical Chiasm	Brain	2045.0	2233.0	2195.1	28.4	0.00 %	0.00 %
	Left Optical Nerve	Brain	179.6	2122.3	779.0	670.0	0.00 %	0.00 %
	Right Optical Nerve	Brain	159.2	2142.2	749.8	649.2	0.00 %	0.00 %

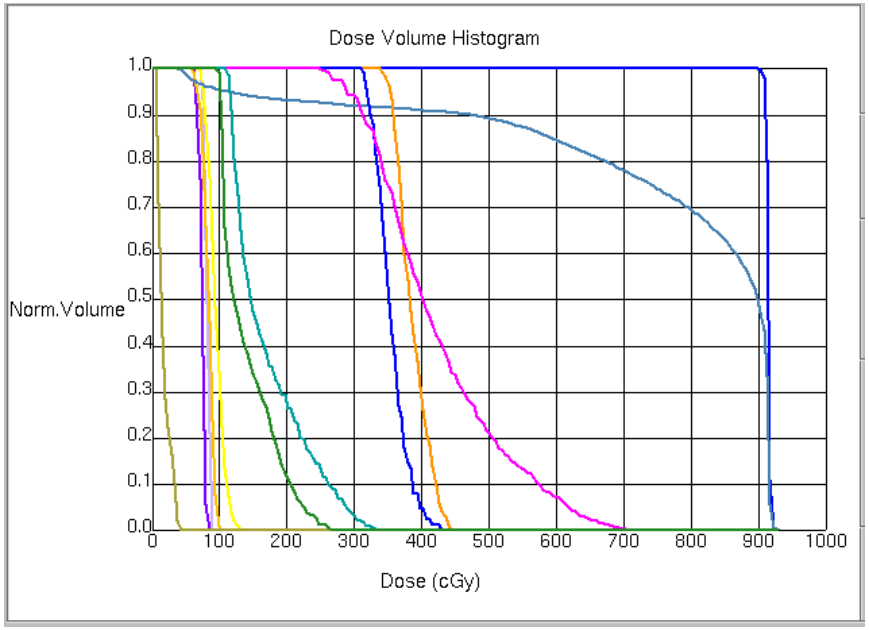
Sequential IFRT boost (9 Gy)







Sequential IFRT boost (9 Gy)



ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	PTV900	BOOST	884.0	930.0	914.7	2.7	0.00 %	0.00 %
	Left Lens	BOOST	71.6	87.6	80.8	3.7	0.00 %	0.00 %
	Right Lens	BOOST	61.0	81.6	73.1	4.6	0.00 %	0.00 %
	Eye_L	BOOST	64.9	134.9	93.8	12.1	0.00 %	0.00 %
	Eye_R	BOOST	57.0	101.3	82.4	8.3	0.00 %	0.00 %
	cord	BOOST	7.0	39.6	15.0	9.8	6.65 %	0.00 %
	right cochlea	BOOST	340.8	442.2	385.9	23.8	0.00 %	0.00 %
	left cochlea	BOOST	311.5	426.2	354.1	23.8	0.00 %	0.00 %
	Optical Chiasm	BOOST	246.4	704.9	422.4	98.2	0.00 %	0.00 %
	Left Optical Nerve	BOOST	110.0	332.5	170.0	56.5	0.00 %	0.00 %
	Right Optical Nerve	BOOST	96.7	263.5	139.6	42.0	0.00 %	0.00 %

References

Bamberg, M., R. D. Kortmann, G. Calaminus, G. Becker, C. Meisner, D. Harms, and U. Göbel. 1999. "Radiation Therapy for Intracranial Germinoma: Results of the German Cooperative Prospective Trials MAKEI 83/86/89." Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 17 (8): 2585–92.

Borja, Maria J., Michael J. Plaza, Nolan Altman, and Gaurav Saigal. 2013. "Conventional and Advanced MRI Features of Pediatric Intracranial Tumors: Supratentorial Tumors." AJR. American Journal of Roentgenology 200 (5): W483–503.

Calaminus, Gabriele, Rolf Kortmann, Jennifer Worch, James C. Nicholson, Claire Alapetite, Maria Luisa Garrè, Catherine Patte, Umberto Ricardi, Frank Saran, and Didier Frappaz. 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." Neuro-Oncology 15 (6): 788–96.

Chang, T., M. M. Teng, W. Y. Guo, and W. C. Sheng. 1989. "CT of Pineal Tumors and Intracranial Germ-Cell Tumors." American Journal of Roentgenology. https://doi.org/10.2214/ajr.153.6.1269.

Echevarria, M. E., J. Fangusaro, and S. Goldman. 2008. "Pediatric Central Nervous System Germ Cell Tumors: A Review." The Oncologist. https://doi.org/10.1634/theoncologist.2008-0037.

Freda, Pamela U., and Kalmon D. Post. 1999. "DIFFERENTIAL DIAGNOSIS OF SELLAR MASSES." Endocrinology and Metabolism Clinics of North America. https://doi.org/10.1016/s0889-8529(05)70058-x.

Fujimaki, Takamitsu. 2012. "Diagnostic Imaging of Intracranial Germ Cell Tumors. Review." Germ Cell Tumor. https://doi.org/10.5772/35588.

Jennings, Mark T., Rebecca Gelman, and Fred Hochberg. 1985. "Intracranial Germ-Cell Tumors: Natural History and Pathogenesis." Journal of Neurosurgery. https://doi.org/10.3171/jns.1985.63.2.0155.

Louis, David N., Arie Perry, Guido Reifenberger, Andreas von Deimling, Dominique Figarella-Branger, Webster K. Cavenee, Hiroko Ohgaki, Otmar D. Wiestler, Paul Kleihues, and David W. Ellison. 2016. "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary." Acta Neuropathologica. https://doi.org/10.1007/s00401-016-1545-1.

Murphy, E. S., J. Fangusaro, G. Dhall, U. Bartels, M. Fouladi, D. Shaw, S. Khatua, et al. 2018. "A Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors (CNS GCT): A Children's Oncology Group (COG) Study. Patterns of Failure and Radiation Dosimetry for Nongerminomatous Germ Cell Tumors." International Journal of Radiation Oncology*Biology*Physics. https://doi.org/10.1016/j.ijrobp.2018.06.099.

Packer, R. J., B. H. Cohen, and K. Cooney. 2000. "Intracranial Germ Cell Tumors." The Oncologist 5 (4): 312–20.

Rogers, S. J., M. A. Mosleh-Shirazi, and F. H. Saran. 2005. "Radiotherapy of Localised Intracranial Germinoma: Time to Sever Historical Ties?" The Lancet Oncology 6 (7): 509–19.

Smith, Alice Boyd, Elisabeth J. Rushing, and James G. Smirniotopoulos. 2010. "From the Archives of the AFIP: Lesions of the Pineal Region: Radiologic-Pathologic Correlation." Radiographics: A Review Publication of the Radiological Society of North America, Inc 30 (7): 2001–20.

Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com