

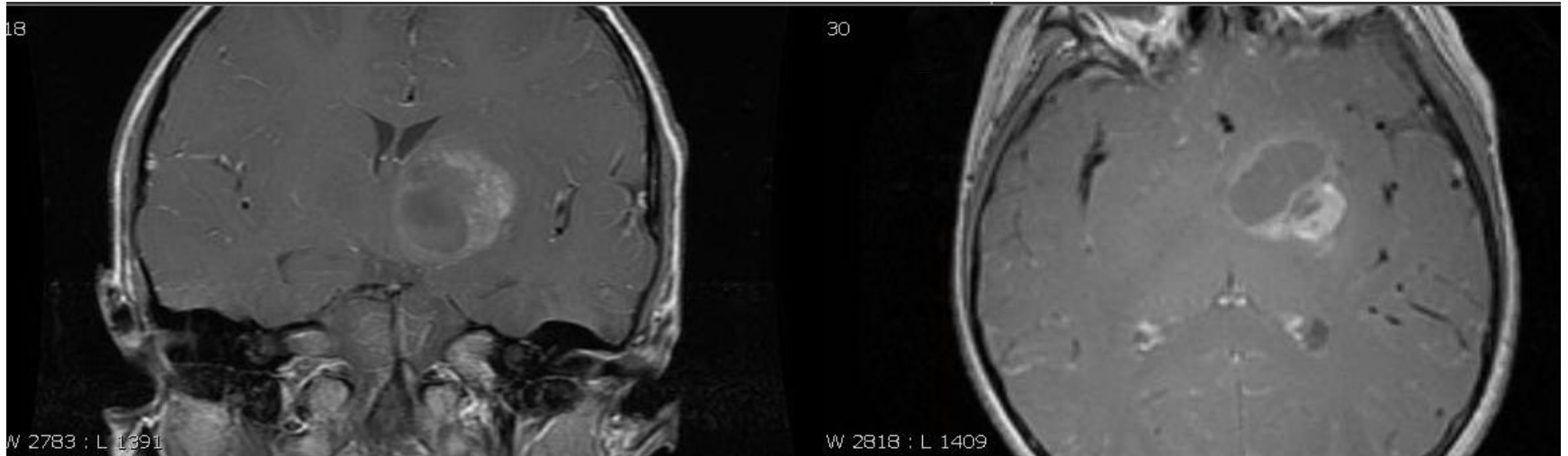
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CNS Germinoma: An evolution in radiation therapy

Patient Presentation

- JL is a 8 year old boy who presented with coordination problems in using his right hand (difficulty tying his shoes) in January 2011.
- Imaging revealed a 3 x 4.5 cm mass in the left basal ganglia with a cystic component.
- Biopsy revealed germinoma. Additional work up showed no metastatic disease in the spine.
- He ultimately came to DCH for treatment with chemotherapy and radiation therapy.

Imaging

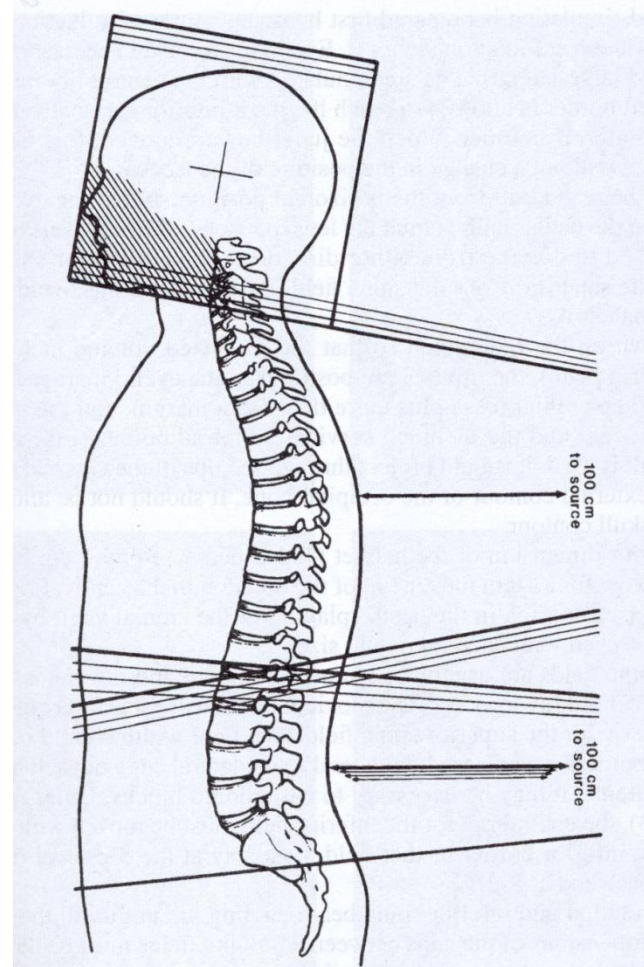


Goals of discussion

- Review the historical results of treating germinoma with radiation alone.
- Describe the rationale for the current recommendations of radiation fields.
- Discuss the use of chemotherapy in localized germinoma to decrease dose.
- Postulate what potential decrease in toxicity may be seen with the current management strategies.

Radiation therapy alone

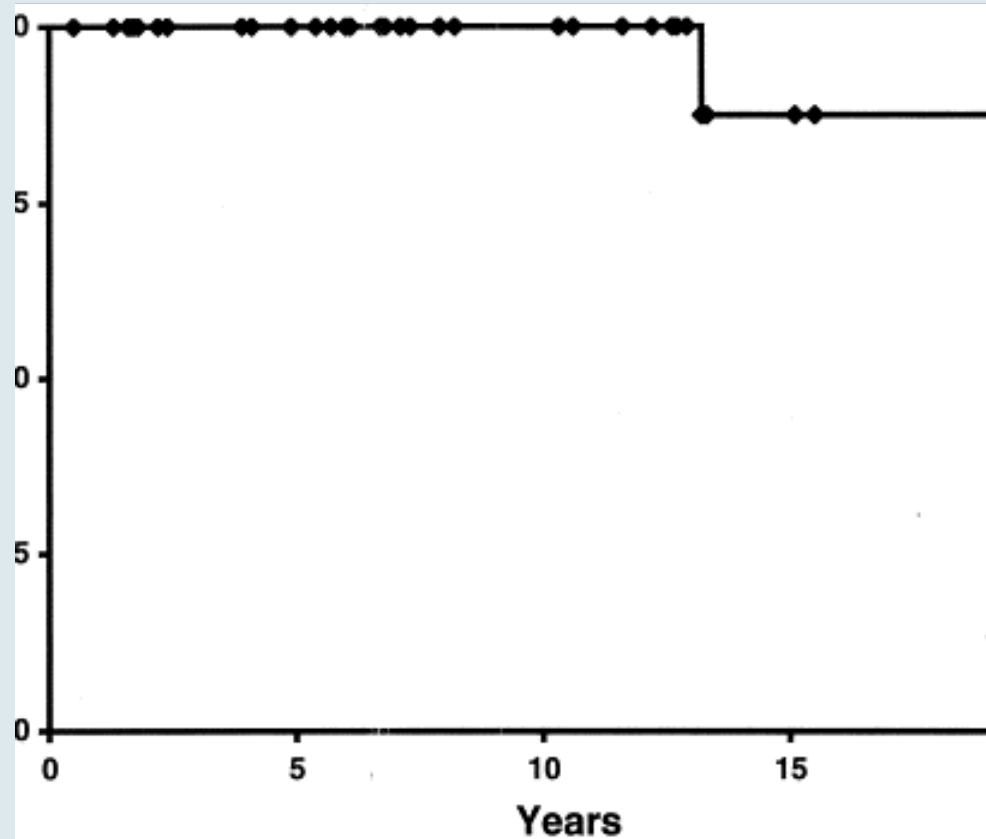
- Craniospinal (CSI) fields were used to prevent the development of spinal metastases.
- In localized disease, this risk was reported in up to 36% of cases.
- Survival with craniospinal radiation was excellent, >90% .



Survival with CSI

Kaplan-Meier plot for overall survival of patients with germinoma treated with craniospinal radiation.

“Craniospinal radiation in the treatment of biopsy-proven intracranial germinomas: twenty-five years’ experience in a single center” Maity et al., *Int J Rad Oncol Biol Phy* 58:1165-70, 2004.



Dose reductions

- While craniospinal fields were felt to be necessary, risk of long term sequelae also acknowledged.
- To decrease that risk, dose given to the field was gradually reduced in non-metastatic cases from 30-36 Gy before 1990 to 18-23.4 Gy.

Results with decreased dose

“INTRACRANIAL GERMINOMA: THE CASE FOR LOWER DOSE RADIATION THERAPY”

NO DIFFERENCE IN RELAPSE BASED ON DOSE

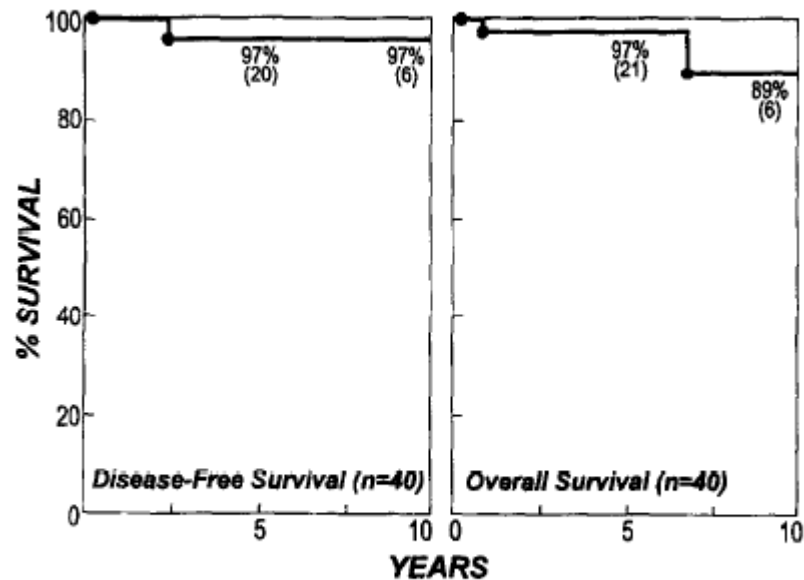


Fig. 1. Five- to 10-year disease-free and actuarial overall survival of presumed germinomas.

Table 3. Local failure by radiation dose (no chemotherapy)

Dose	WB	TV	Spine	
			<22 Gy	0 Gy
Low failures	≤25.5 Gy 0/9	<50 Gy 0/14	0/9	0/5
High failures	>25.5 Gy 0/26	≥50 Gy 0/21	>22 Gy 0/21	

Hardenbergh et al. Int J Rad Oncol Biol Phy 39:419-426, 1997.

Prospective trial of dose reduction: MAKEI '83 and '89

MAKEI '83: patients received 36 Gy to the craniospinal axis and 14 Gy boost to the tumor.

MAKEI '89: patients received 30 Gy to the craniospinal axis and 15 Gy boost to the tumor.

Conclusion: decreased dose level is effective and further attempts to decrease total doses are justified.

Bamberg et al. JCO, 17:2585-2592, 1999.

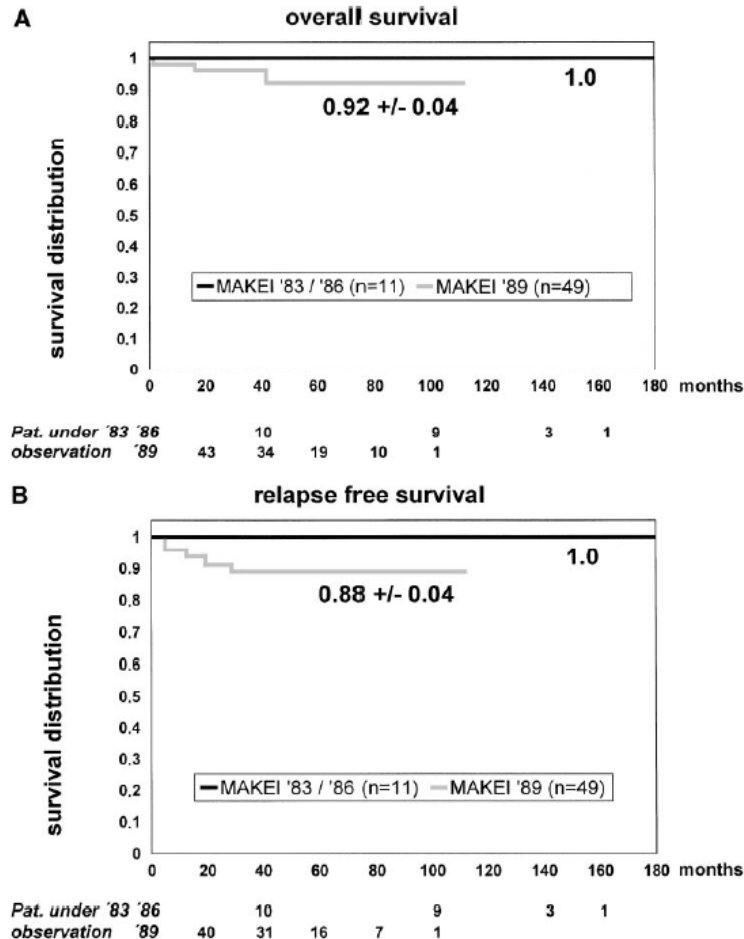


Fig 1. Actuarial (A) overall and (B) relapse-free survival rates after treatment with radiotherapy alone in patients (Pat.) with intracranial germinoma (MAKEI 83/86/89) (Kaplan-Meier survival distribution function).

Field reductions

- With improvements in staging including separating out non-germinomatous tumors, rates of spinal metastases were lower.
- Move was to eliminate the spinal field and treat the whole brain or whole ventricular system.
- No randomised data comparing CSI, whole brain (WBI) or whole ventricular (WVI) have been completed.

Review of changing volumes

- Review of 788 patients from selected series.
- Looked at dose and volume.
- Found no substantial difference in rates of isolated spinal relapse between patients treated with CSI and those treated with either WBI or WVI.

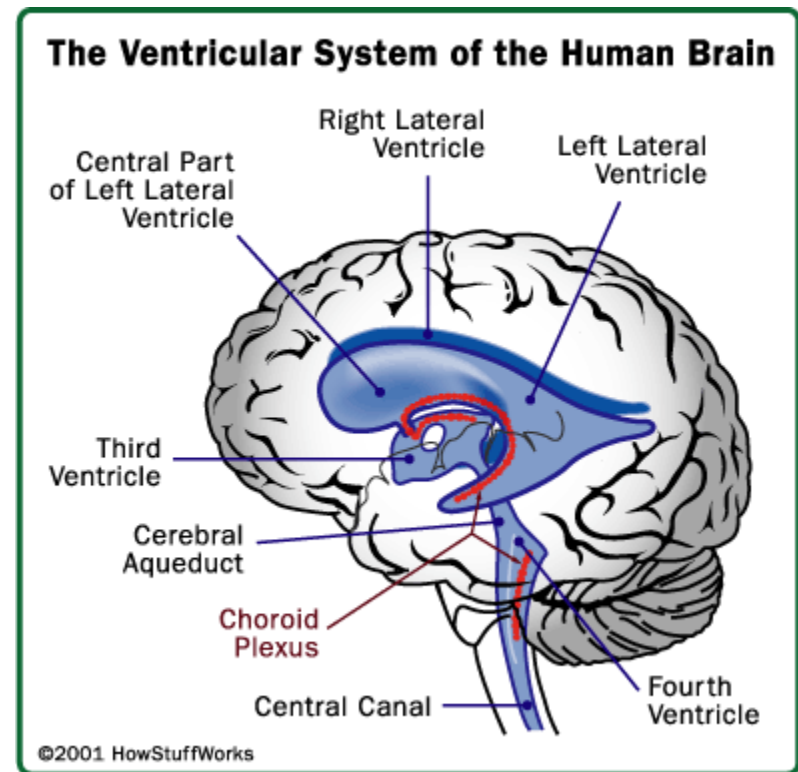
	Patients	Relapses		
		Total	Local	Isolated spinal
Craniospinal plus boost	343	13 (4%)	1 (<1%)	4 (1%)
Whole brain or whole-ventricle plus boost	278	21 (8%)	7 (3%)	8 (3%)
Focal	133	31 (23%)	9 (7%)	15 (11%)

Table 3: Relapses in patients with localised intracranial germinomas given reducing irradiation volumes as definitive therapy

“Radiotherapy of localised intracranial germinoma: time to sever historical ties?” Rogers SJ, Mosleh-Shirazi MA, Saran FH, Lancet Oncol 6:509-519, 2005.

Challenge of WVI

- In WVI, the entire ventricular system must be treated.
- Prior to 3D treatment planning, this volume was challenging to contour.
- Difficulty in delineating target volume may have resulted in some marginal misses.



What is the advantage of WVI over WBI?

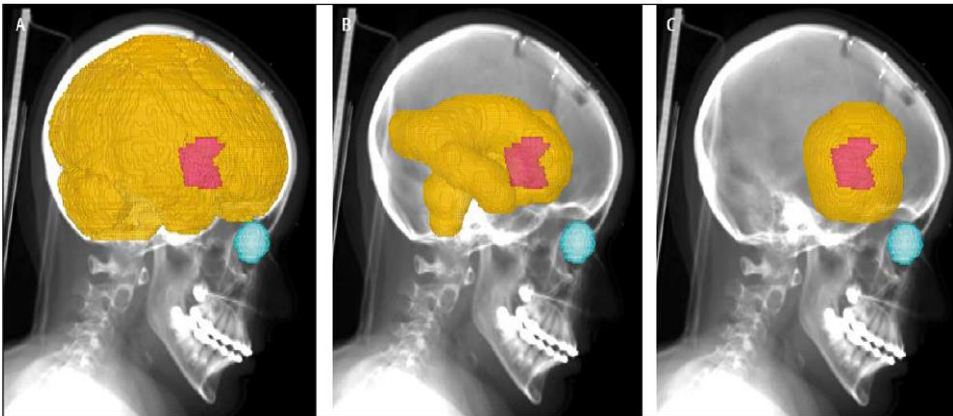


Figure 3: Whole-brain radiotherapy (A), whole-ventricular radiotherapy (B), or focal radiotherapy (C) of localised suprasellar germinoma as part of a limited-volume irradiation approach

Orange=whole brain (A), cerebral ventricles plus a 1 cm margin (B), or primary tumour plus a 2 cm margin (C), as outlined on the planning CT scan. Pink=primary tumour. Blue=eyes.

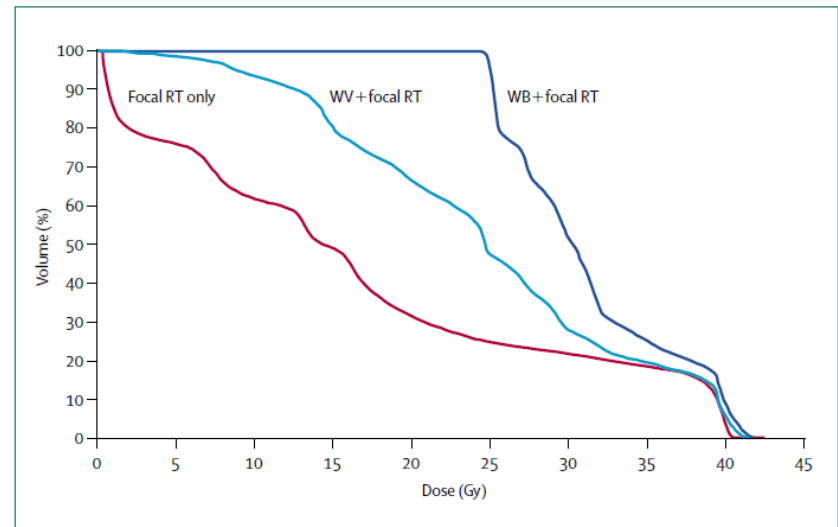


Figure 5: Cumulative dose-volume histograms of entire brain tissue for three limited-volume radiotherapy regimens for localised germinomas

The whole-brain (WB) and whole-ventricular (WV) treatments are prescribed to total dose of 24 Gy followed by 16-Gy phase-2 focal radiotherapy boost. Focal radiotherapy approach is single-phase 40-Gy treatment. Planning target volume for whole-ventricular approach was restricted to all ventricles as clinical target volume plus a three-dimensional safety margin of 1 cm. Focal approach was planned with tumour visible on the planning CT scan as well as the tumour bed after initial partial tumour debulking as gross tumour volume plus 2-cm margin in all dimensions. All therapeutic approaches covered planning target volumes with prescribed dose within -5% to 7% according to international guidelines (International Commission on Radiation Units and Measurements 50/62). Depending on the treatment approach chosen, the volume of normal brain exposed to higher irradiation doses differs substantially.

Functional outcome with CSI

- Investigators at St. Jude's examined 12 patients treated with CSI for germinoma. They received a median dose of 25.6 Gy (23.4-32 Gy) with a boost to the primary of 50.4 Gy (45-54 Gy).
- After a median follow up of 69 months, all patients were alive and there were no significant differences between pre- and post-irradiation full-scale, verbal and performance IQ scores.
- Proposed that lack of change may be secondary to older age of patient (median age= 12 years, range 9-16 years) and may have substantial preexisting morbidity.

"CNS Germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation"
Merchant et al. Int J Rad Oncol Biol Phys 46:1171-1176, 2000.

Differences in neurocognitive outcome with CSI vs. WVI

- Review of 35 patients with germinoma treated with either CSI or WVI and followed with neurocognitive testing.
- Found no significant change in full-scale, verbal comprehension, and perceptual reasoning IQ scores.
- Found decline in working memory, processing speed, and immediate and delayed visual memory.
- Found that patients treated with CSI performed “poorly” relative to those treated with WVI.

“Longitudinal evaluation of neurocognitive function after treatment for central nervous system germ cell tumors in childhood”, Mabbott DJ et al, Cancer 2011

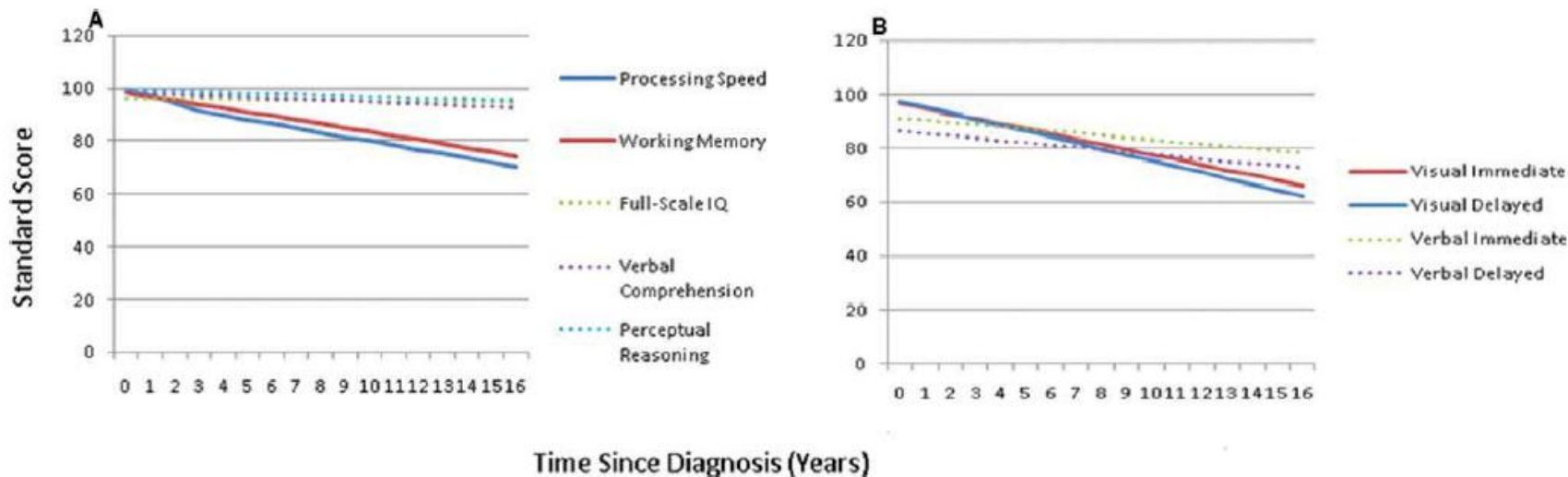


Figure 1. Estimated change over time based on linear models for the entire sample are shown for full-scale IQ, verbal comprehension, perceptual reasoning, working memory, and processing speed indices from the Wechsler Intelligence Scales for Children/Wechsler Adult Intelligence Scales (A) and visual and verbal memory scores (B).

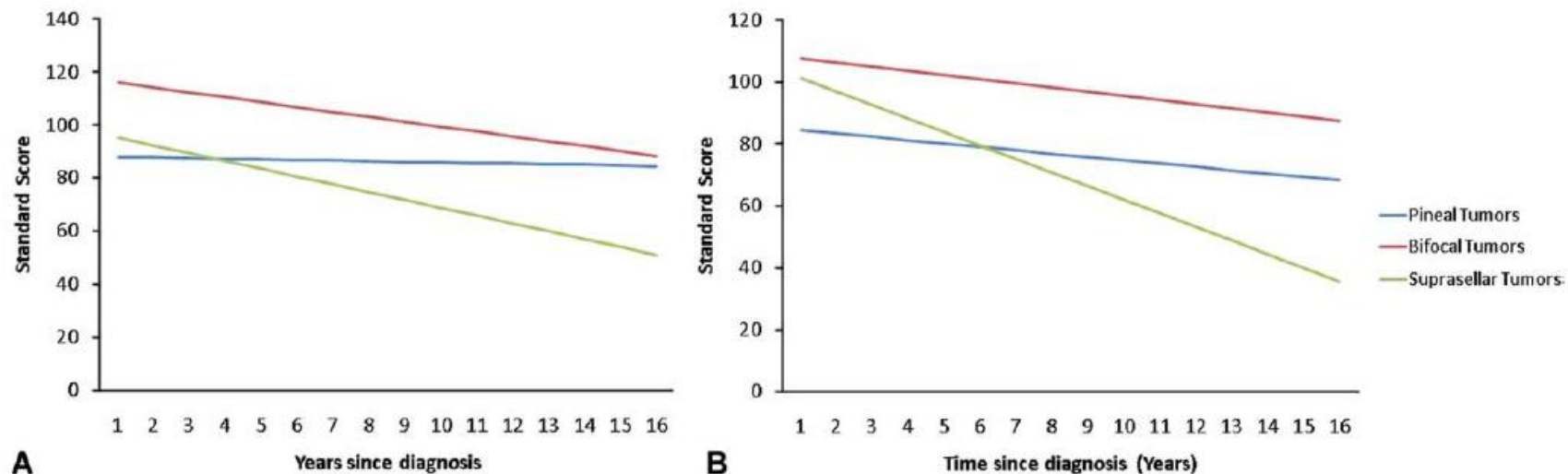
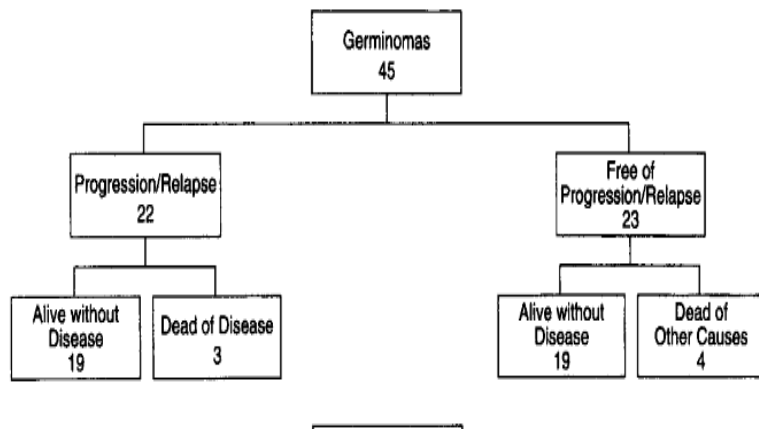


Figure 2. Estimated change over time based on linear models considering the impact of tumor location is shown for processing speed (A) and visual delayed memory (B).

Chemotherapy alone?

- Collaborative trial of 31 institutions enrolled 71 patients with primary CNS germ cell tumors, 45 germinomas and 26 NGGCT.
- Patients were treated with 4 cycles of carboplatin, etoposide and bleomycin.
- Patients with CR after 4 cycles received an additional 2 cycles.
- Radiation or second look surgery was allowed if unable to achieve CR.

Able to avoid radiation but poorer survival



CHEMOTHERAPY WITHOUT IRRADIATION FOR CNS GCT

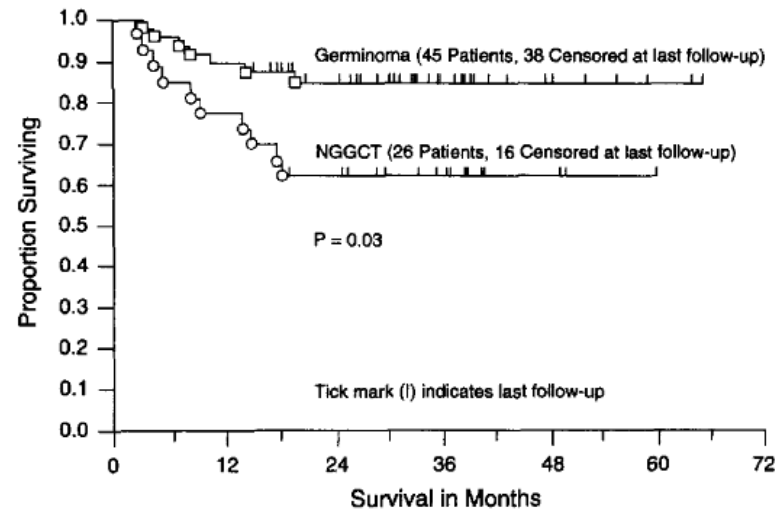


Fig 5. Overall survival by pathology.

“Chemotherapy without irradiation- a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial” JCO 14: 2908-2915, 1996.

ACNS 0232: volume reduction with chemotherapy

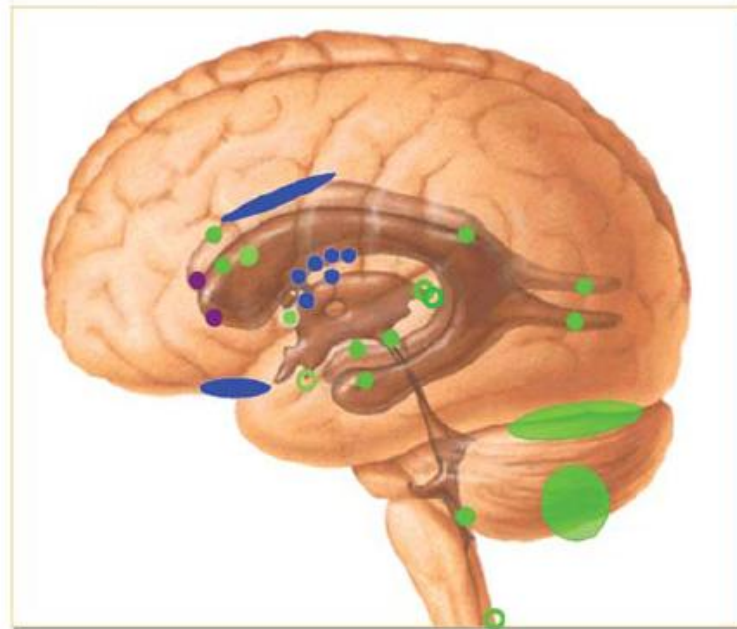
- RCT comparing standard radiation to carboplat and etoposide x 2 cycles followed by reduced radiotherapy for those in CR; for those in MRD/PR/SD, 2 cycles of cisplat and cytoxan followed by reduced radiation.
- Standard radiation for localized disease= 24 Gy WVI plus boost to 45 Gy.
- Reduced radiation for localized disease= 30 Gy involved field only.
- Trial closed to accrual in May 2009

Concern with focal field only

- SFOP prospective protocol, TGM-90, using 4 cycles of carbo, ifosphamide, and etoposide followed by 40 Gy to initial tumor volume.
- Found a 5 year event-free survival of 84.2% with 10 year event-free survival of 81.8%; 10 year overall survival of 96%.
- Concluded that there is a risk of relapse outside of radiation field when a focal field is used, possibly because of subclinical disease existing in the subependymal space.

Pattern of relapses

Site of relapses following combined treatment



Ventricular system		8/10
V only	5/8	
V + Post Fossa	1/8	
V + T. bed	2/8	
positive CSF	1/8	
Subfrontal (optic nerve encasement)		1/10
Spinal leptomeningeal		1/10

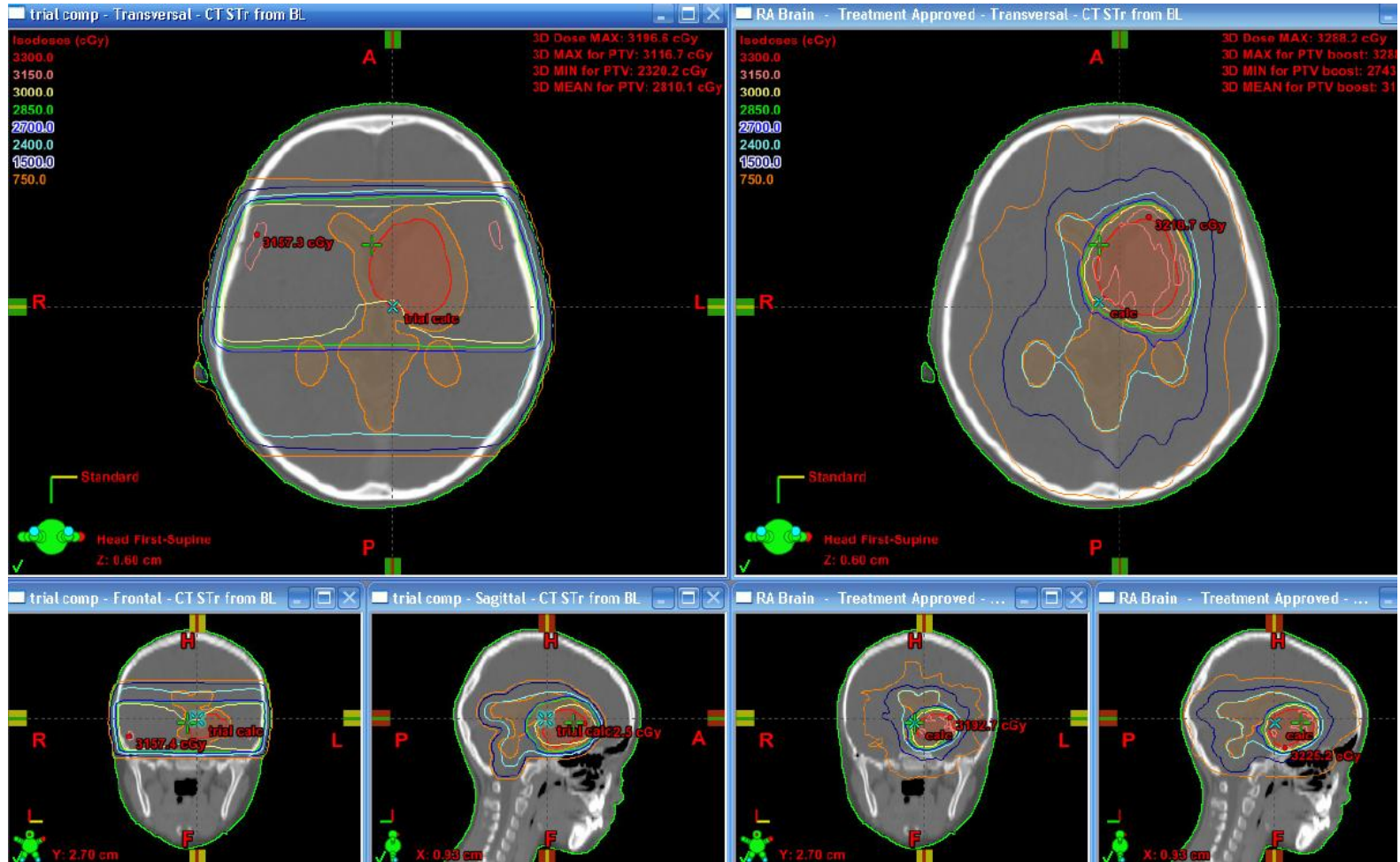
Primary site ● Pineal ● Suprasellar ● Bifocal

Fig. 2. Distribution of all sites of first relapse: several patients had more than 1 site of failure; 2 sites in patients 2, 4, and 5; 4 sites in patient 6; multiple sites in patients 8 and 9; and continuous spread along the wall of lateral ventricles in patient 10.

How are we treating JL?

- He is being treated following a CHLA (Finlay) protocol. He received 4 cycles of carboplatin and etoposide followed by WVI plus boost to the primary site.
- Dose for the WVI is 23.4 Gy with a simultaneous integrated boost to 30.6 Gy.
- The margins are very “tight”: 3 mm margin on ventricles and 4 mm margin on the pre-biopsy tumor volume.

Further normal tissue reduction with IMRT



What have we gained?

- By eliminating the spinal field, we have stopped the decreased growth seen in vertebral bodies and decreased secondary dose to other organs.
- By moving to WVI, we have decreased dose to frontal lobes and parietal lobes but dose to temporal lobes persist.
- By decreasing dose, we have decreased the risk for neurocognitive effects and second malignancies.

What is the current “standard”?

- Standard for localized germinoma is WVI to 23.4 Gy followed by a boost to the primary site of 45-50 Gy.
- In patients treated with chemotherapy off protocol, radiation should still be given to the WVI with a boost to the primary site.