The ABCs of Peds

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Disclosures

Travel grant, Ion Beam Applications, 2018

Employer: University of Florida

Learning Objectives

1

Formulate treatment recommendations for common pediatric tumors.

2

Develop radiation treatment plans using appropriate dose, volume, and planning parameters.

3

Recognize the potential acute and late toxicity associated with radiotherapy in the pediatric population.

Outline

- Non-CNS
  - Rhabdomyosarcoma
  - Ewing sarcoma
  - Wilms tumor
  - Neuroblastoma
- CNS
  - Medulloblastoma
  - Ependymoma
  - Germinoma
  - Low grade glioma

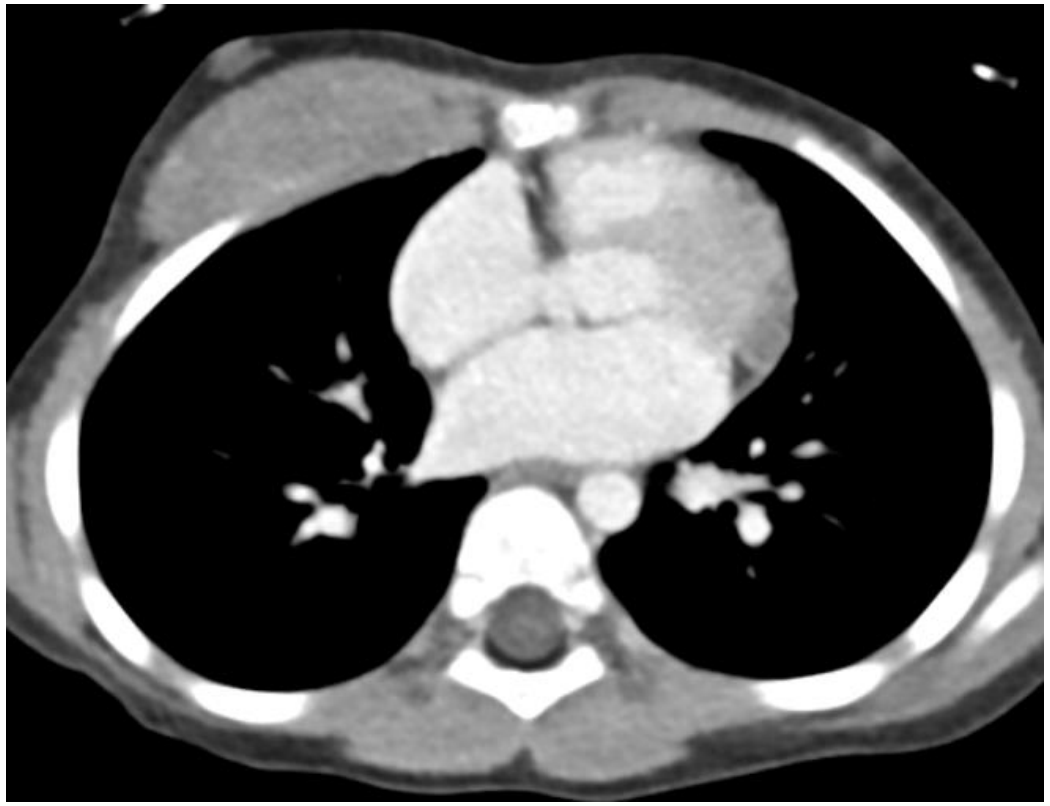
For all cases:

- Perform complete history and physical exam

- Fuse initial imaging (MRI preferred, and/or CT or PET) for treatment planning (both those at initial diagnosis and post-chemo or post-op)
  - Delineate tumor at initial presentation first

Case 1

- 3 yo girl with right chest wall mass, like a breast bud, rapidly increasing in size



US, then CT or MRI of primary site

Biopsy: RMS, FOX01 fusion positive

Favorable or Unfavorable Site?

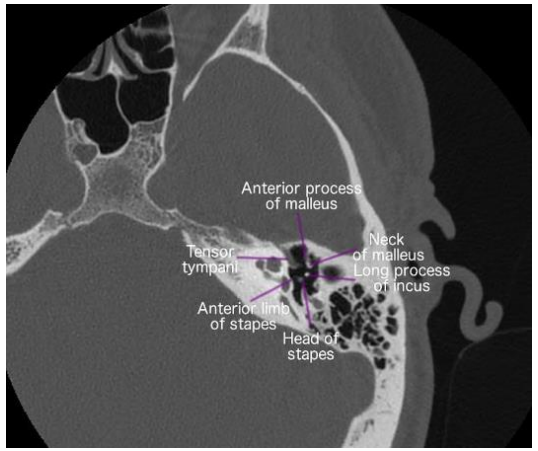
Favorable

- Orbit
- Head and neck (excluding parameningeal)
- Genitourinary (excluding bladder/prostate)
- Biliary tract/liver

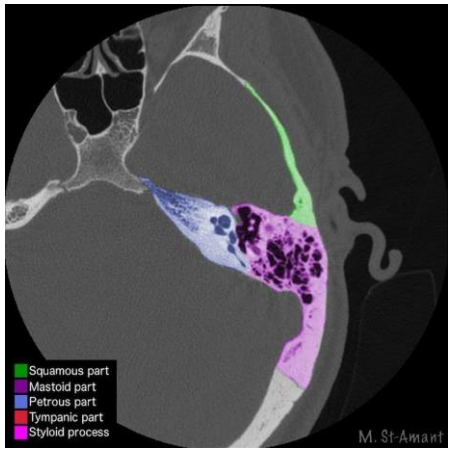
Unfavorable

- Bladder/prostrate
- Extremity
- Parameningeal (Mnemonic: MMNNOOPP)
- Trunk, intrathoracic
- Retroperitoneum
- Pelvis, perineal/perianal
- Gastrointestinal

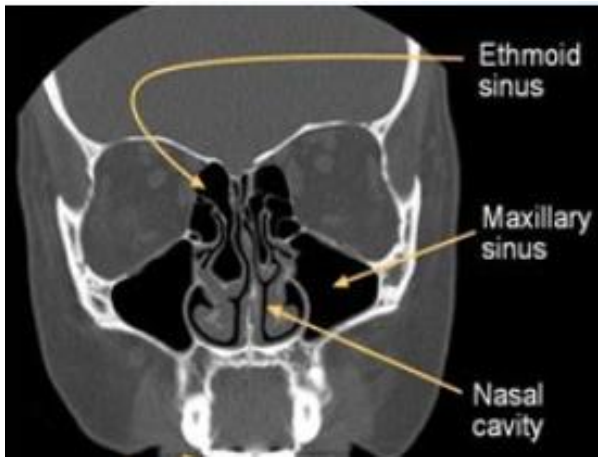
Middle ear



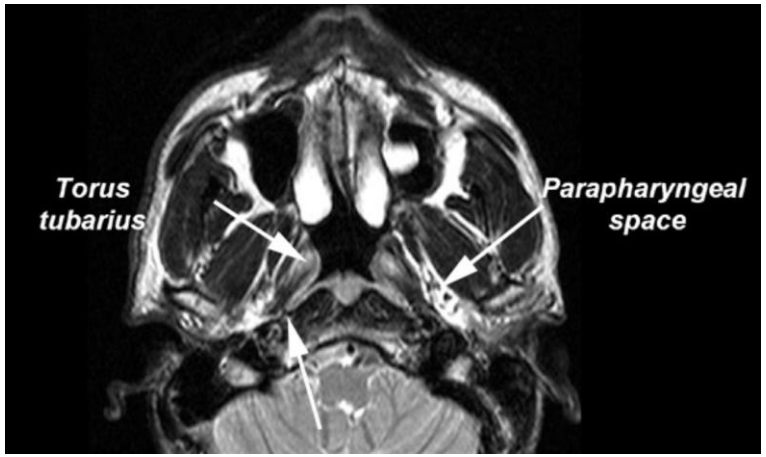
Mastoid region



Nasal cavity

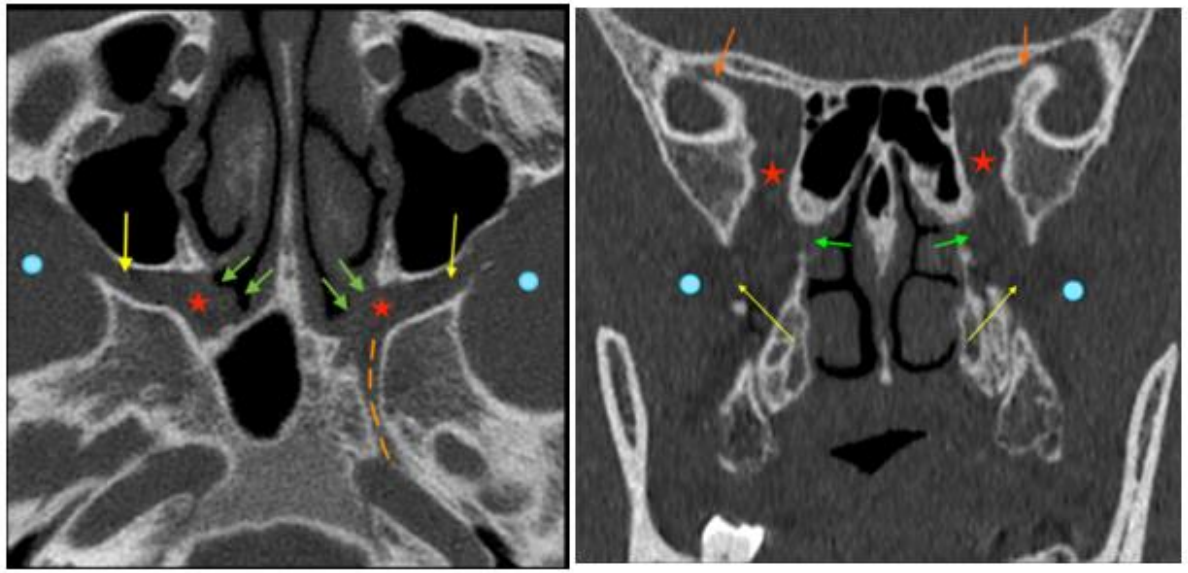


Nasopharynx

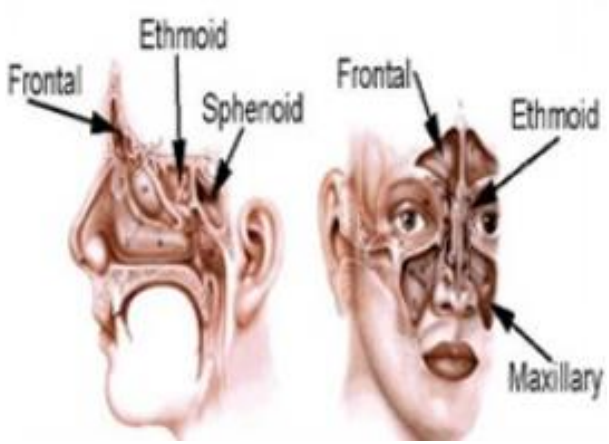


★ Pterygopalatine fossa

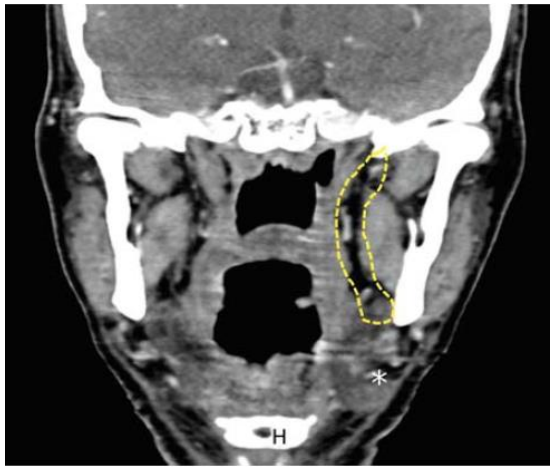
● Infratemporal fossa



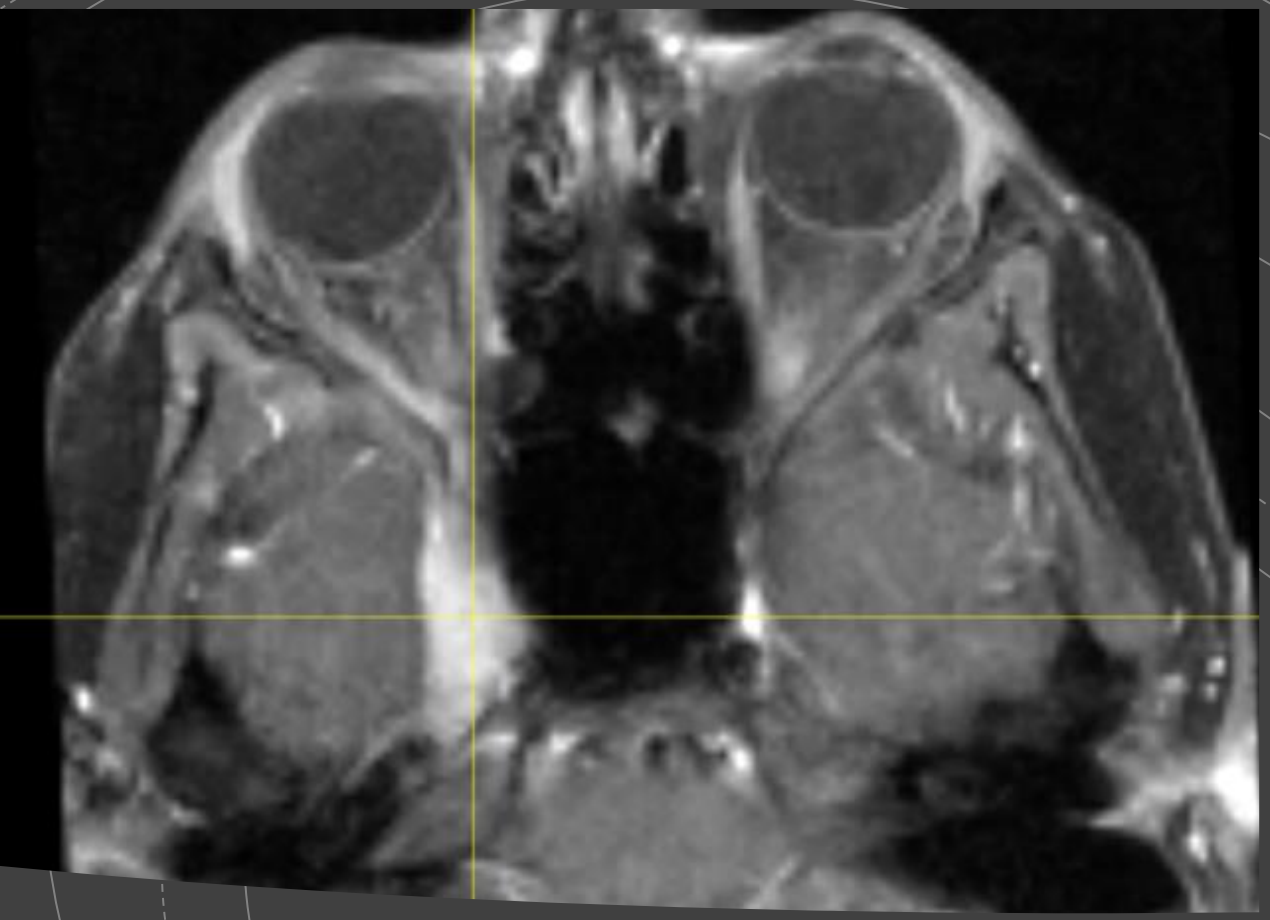
Paranasal sinus

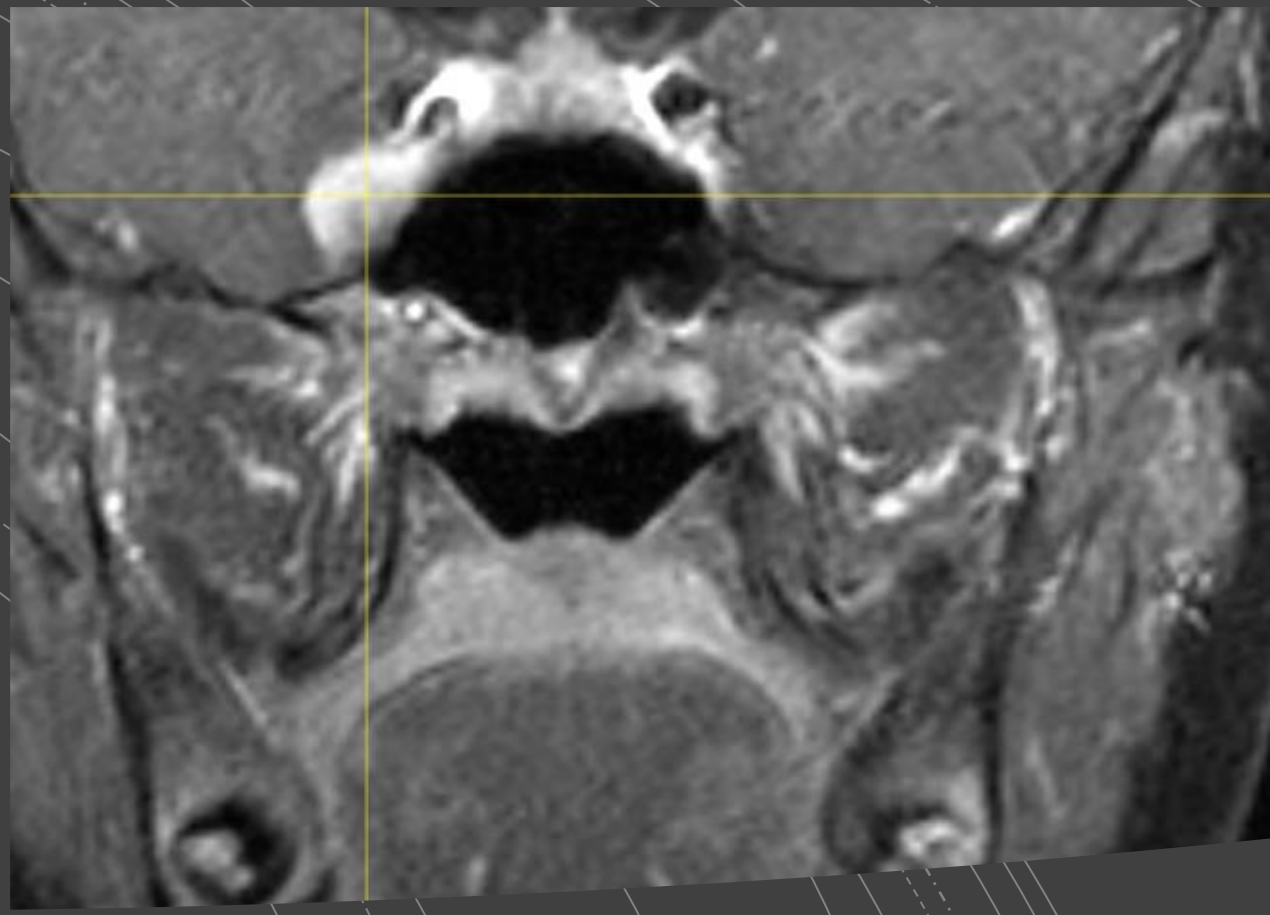


Parapharyngeal region



Allemeersch G, European Society of Radiology
Arya et al Int J Otorhinol Clin 2012; https://radiopaedia.org
https://radiopaedia.org
https://slideplayer.com/slide/6108058, 4556214





Intracranial extension (ICE)

Stage	Site*	Invasiveness	Size	Nodal status	Mets
I	Favorable	T1 or T2	a or b	N0 or N1	M0
II	Unfavorable	T1 or T2 a		N0	M0
III	Unfavorable	T1 or T2 b		N0	M0
			a or b	N1	M0
IV	Any site	T1 or T2		N0 or N1	M1

Group I	**Localized disease, completely resected**
A	Confined to organ or muscle of origin
B	Infiltration outside organ or muscle of origin; regional nodes not involved
Group II	**Compromised or regional resection**
A	Grossly resected tumor with microscopic residual disease
B	Regional disease, completely resected, in which nodes may be involved or extension of tumor into adjacent organ may exist
C	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease
Group III	**Incomplete resection or biopsy with gross residual disease**
Group IV	**Distant metastases at diagnosis**

REGIONAL NODAL BASINS FOR RHABDOMYOSARCOMA

Extremity
Lower Extremity –inguinal, femoral, popliteal nodes (rarely involved)
Upper extremity – axillary, brachial, epitrochlear, infraclavicular nodes (infraclavicular)

Genitourinary
Bladder/Prostate – pelvic, retroperitoneal nodes at renal artery level or below
Cervix and Uterus– pelvic, retroperitoneal nodes at renal artery level or below
Paratesticular – pelvic, retroperitoneal nodes at renal artery level or below
Vagina – retroperitoneal, pelvic nodes at or below common iliacs inguinal nodes
Vulva – inguinal nodes

Head and Neck
Head/Neck – ipsilateral cervical, jugular, preauricular, occipital, supraclavicular nodes for laterally placed tumors (excluding scalp); may have bilateral adenopathy with centrally placed tumors
Orbit/Eyelid – ipsilateral jugular, preauricular, cervical nodes

Intrathoracic
Internal mammary, mediastinal nodes

Retroperitoneum/Pelvis –
Pelvic, retroperitoneal nodes

Trunk
Abdominal Wall – inguinal, femoral nodes
Chest Wall – axillary, internal mammary, infraclavicular nodes

OTHER
Biliary/Liver – liver hilar nodes
Perianal/Perineal – inguinal, pelvic nodes; may be bilateral

RMS: General Treatment Paradigm

Biopsy
- Core needle biopsy
- Histology, PAX-FOX fusion

WorkUp
- Bone marrow bx, PET or bone scan, CT C/A, CBC/CMP, Echo
- If parameningeal, MRI brain and LP
- Determine Stage

Surgery
- *IF* resectable while maintaining form and function
- Determine Group and Risk group

Chemo
- Vincristine, Actinomycin +/- Cyclophosphamide or VAC/VI
- 12 weeks for low and int risk, 20 weeks high risk (induction)

RT or DPE + RT
- *IF* indicated. Doses 36, 41.4 or 50.4 Gy at 1.8 Gy/fx
- Starts at week 12, given concurrent with chemo (hold actinomycin)

Chemo
- Vincristine, Actinomycin +/- Cyclophosphamide or VAC/VI
- For 24-66 weeks (consolidation and maintenance)

This Case

Small round blue cell tumor, rhabdomyosarcoma, FOX-01 positive

Negative
Stage III T2b N0 M0, unfavorable site

Op Note: "…removing it from the chest wall completely."
Group I; Intermediate Risk

VAC x 12 weeks

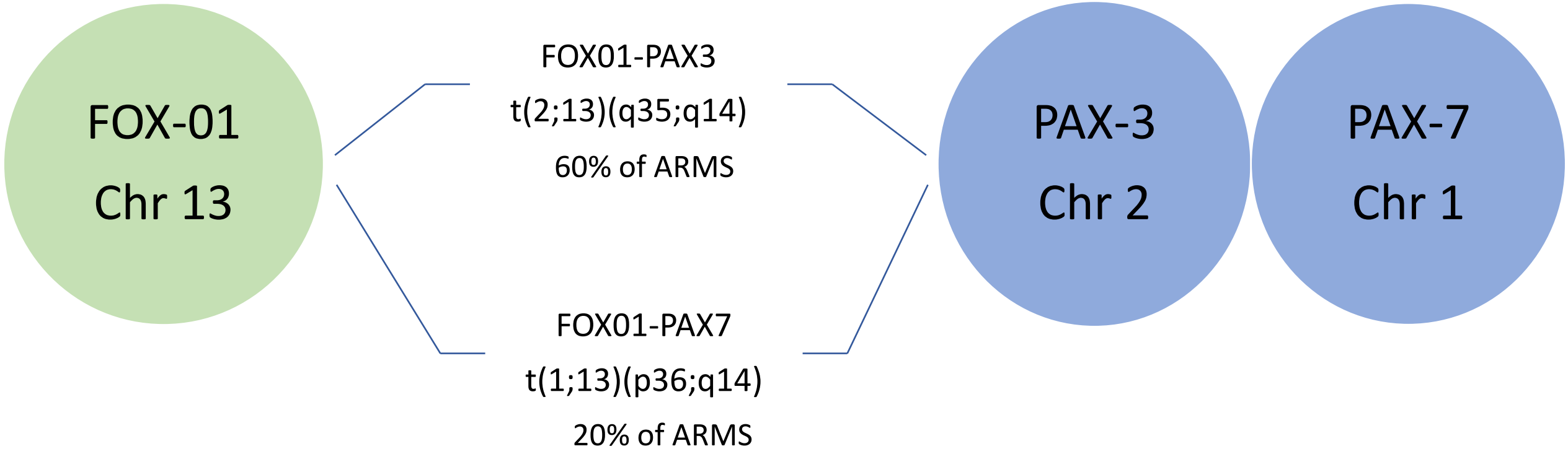
36 Gy in 30 fxs at week 12 to tumor bed (GTV) + 1cm margin edited for barriers to spread (CTV) + 0.5cm PTV

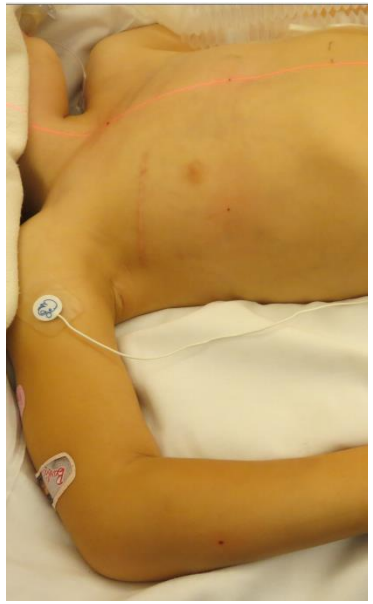
VAC x 14 cycles/42 weeks total

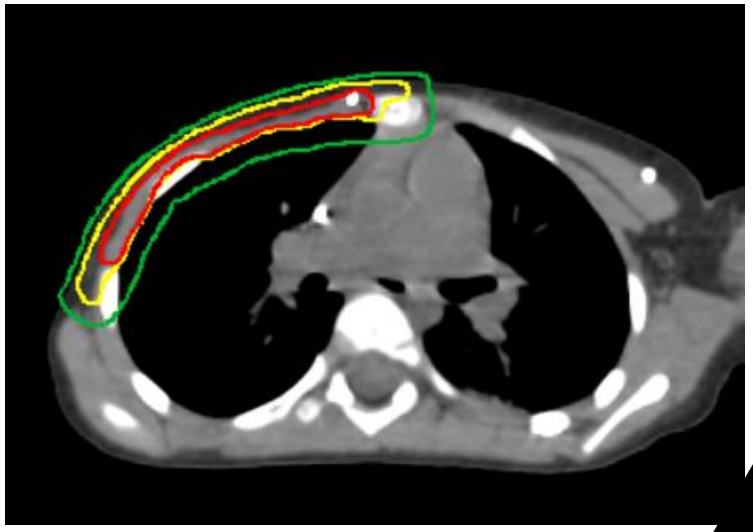
Translocations in RMS

Encode fusion proteins with oncogenic activity

>95% of embryonal RMS (ERMS) do NOT contain a FOXO1 fusion







GTV1: tumor extent at diagnosis

CTV: 1cm expansion, edited to barriers of spread (+draining lymphatics for N+)

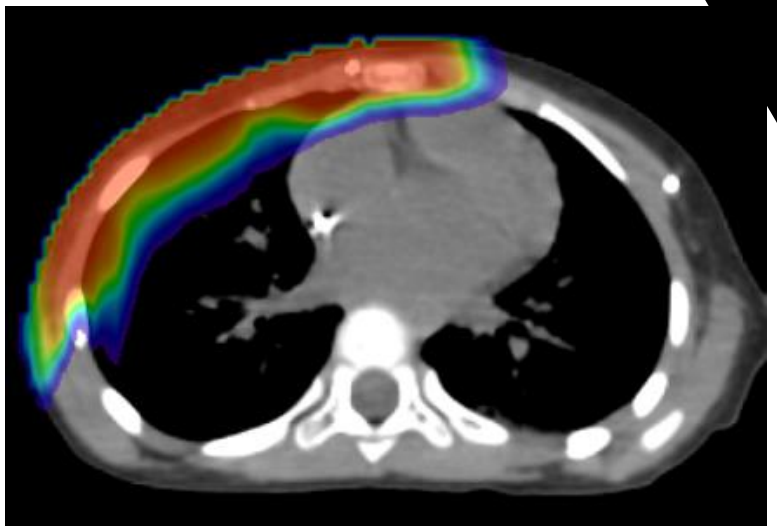
PTV: 0.5cm expansion

GTV2: residual gross induction chemo

CTV2: 1cm expansion, edited to barriers of spread

PTV2: 0.5cm expansion

	1	100.00 (%)	36.00 (Gy)
	1	95.00 (%)	34.20 (Gy)
	1	80.00 (%)	28.80 (Gy)
	1	65.00 (%)	23.40 (Gy)
	1	50.00 (%)	18.00 (Gy)
	1	10.00 (%)	3.60 (Gy)



*PTV can be 0.3cm in skull base/head and neck sites

Radiation Dose for RMS

	Fusion negative	Fusion positive
Group I	No RT	36 Gy
Group II	36 Gy	36 Gy
Group III	50.4 Gy*	50.4 Gy*

- Node positive
- Draining lymphatic chain: 36 Gy
- Resected nodes: 41.4 Gy
- Unresected nodes: 50.4 Gy

ARST1431 doses for metastases

17.7.5 Standard (Non-SBRT) Radiation Dose Guidelines for Individual Metastatic Lesions (all non-bone sites, all non-lung sites and bone sites > 5 cm)

	Dose (Gy)
Sites of initial metastases in CR	40 in 20 fractions
Lesions which are SD or PR	50 in 25 fractions

17.7.6 SBRT Dose Guidelines for Lesions that are SD or PR at Completion of VAC/VI Chemotherapy

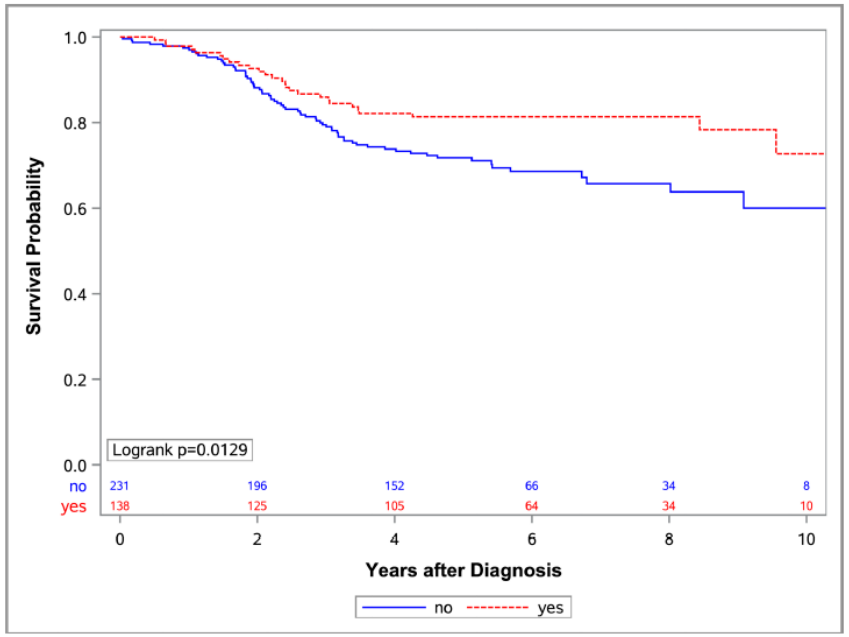
	Dose/fraction (Gy)	Dose (Gy)
PTV2 = GTV2	7.0	35
PTV1= CTV2 + 2mm	6.0	30
After 15Gy whole lung		
PTV2 = GTV2	6.0	30
PTV1 = CTV2+2mm	5.0	25

17.7.7 SBRT Dose Guidelines for Lesions that are CR at Completion of VAC/VI Chemotherapy

PTV2 = GTV2	6.0	30
PTV1= CTV2 + 2mm	5.0	25
After 15Gy whole lung		
PTV2 = GTV2	5.0	30
PTV1 = CTV2+2mm	4.0	20

*59.4 Gy being investigated for tumors > 5cm at diagnosis on ARST1431

Delayed primary excision (DPE)



81% had reduction in RT dose after DPE

22% with DPE had loss of organ or function

For initial Group III disease

Sites: bladder/prostate, extremity, retroperitoneal, trunk, intrathoracic and perineal tumors

If disease becomes resectable after induction chemotherapy

Weigh likelihood of R0/R1 resection and surgical morbidity vs RT dose.

No benefit to debulking

Do not omit RT after DPE even if R0 or R1 resection, but can decrease dose based on extent of resection

R0: 36 Gy; R1: 41.4 Gy; R2: 50.4 Gy

For RT after DPE, GTV = initial extent of tumor + post-op surgical bed

Lautz et al Cancer. 2021 Jan 15;127(2):275-283

Outcomes

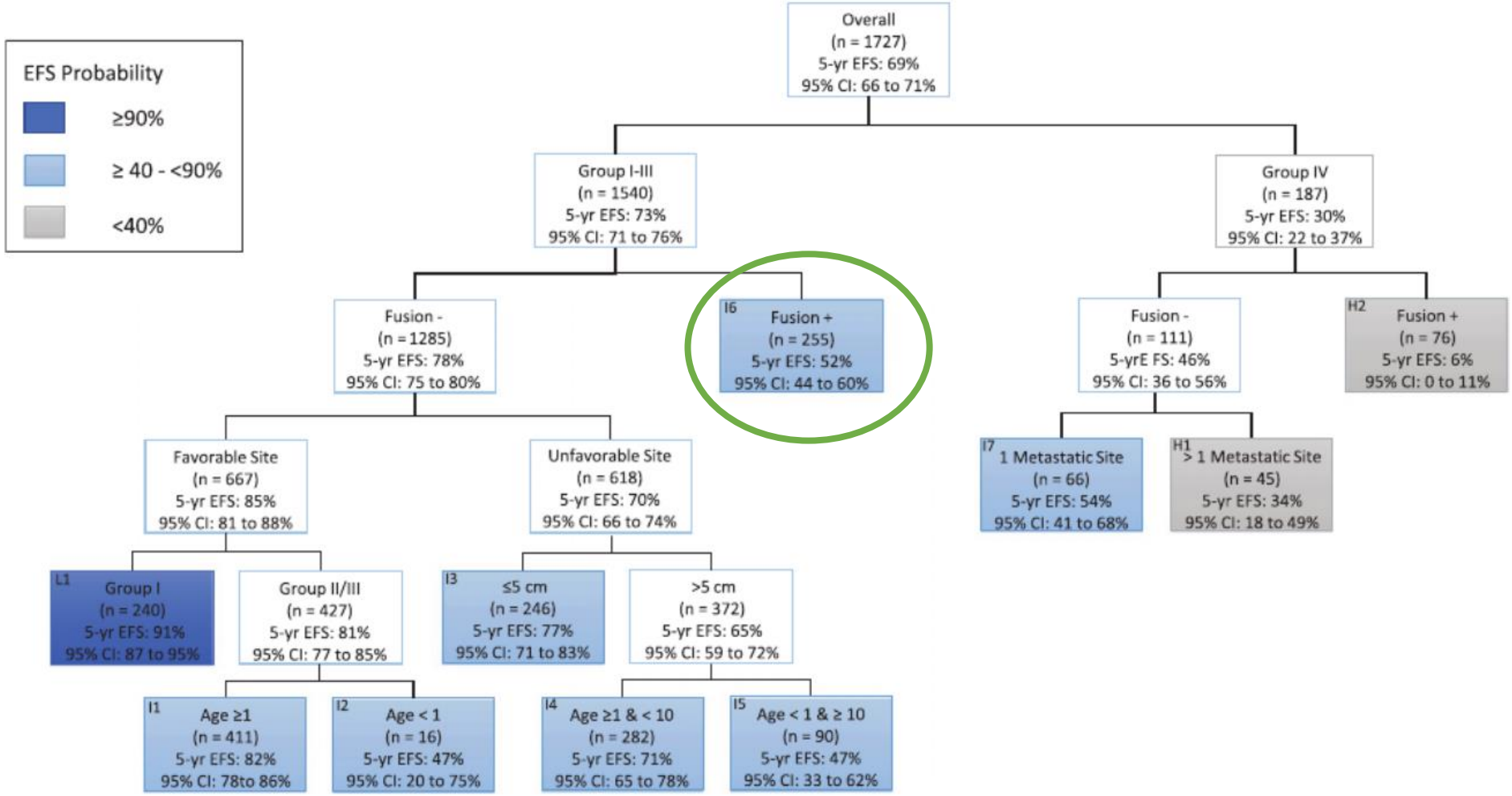


FIGURE 1 Event-free survival (EFS) tree of analytic cohort with terminal leaves labeled by risk groups. EFS, event-free survival; Fusion, FOXO1 fusion status

Hibbitts et al Cancer. 2019 Oct;8(14):6437-6448

Toxicity

- Acute
  - Dermatitis
  - Fatigue
- Late
  - Pneumonitis
  - Pulmonary fibrosis
  - Cardiac disease
  - Bone and soft tissue hypoplasia
  - Breast hypoplasia
  - Second malignancy
- Echo annually

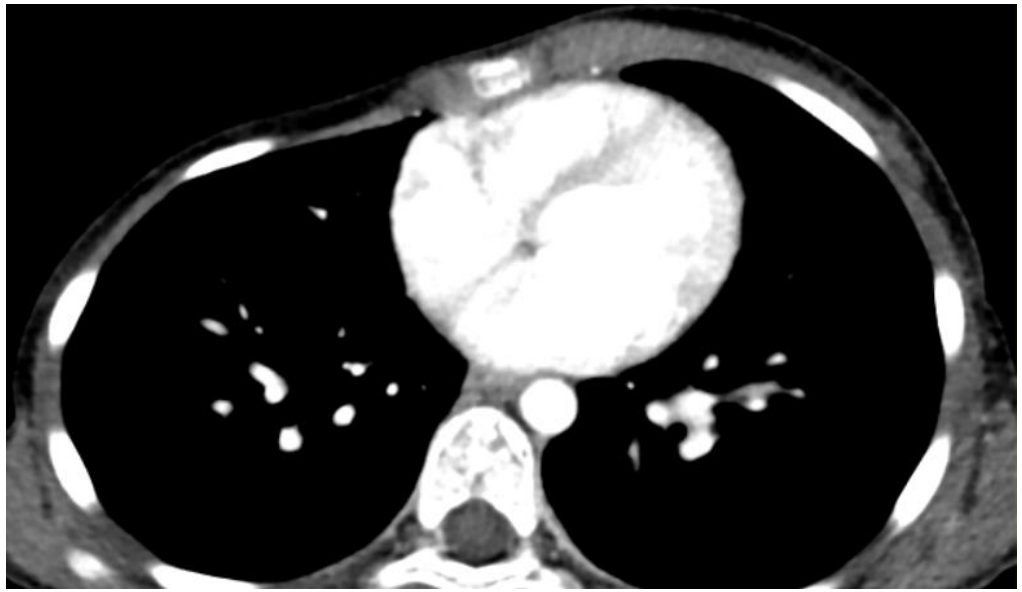


Table 3
Late toxicities observed in 83 RMS patients treated with PBS proton therapy.

Type of toxicity	PM RMS ($n = 46$) Any grade/(grade 3) *	Orbital RMS: ($n = 17$) Any grade/(grade 3) *	UG RMS ($n = 10$) Any grade/(grade 3) *	Others RMS ($n = 10$) Any grade/(grade 3) *
Localised alopecia	8/(N/A) **	1/(N/A) **	0/(N/A) **	1/(N/A) **
Growth Hormone deficiency	11/(N/A) **	3/(N/A) **	0/(N/A) **	0/(N/A) **
Other endocrinopathies	6/(0)	2/(0)	0/(0)	1/(0)
Facial hypoplasia	9/(0)	5/(0)	0/(0)	0/(0)
Visual complications	9/(3)	13/(10)	0/(0)	0/(0)
Hearing impairment	7/(2)	0/(0)	1/(0)	0/(0)
Dental growth impairment	3/(0)	0/(0)	0/(0)	0/(0)
Chronic nasal and sinus congestion	2/(0)	0/(0)	0/(0)	0/(0)
Urinary complication	0/(0)	0/(0)	3/(0)	0/(0)
Defecation problems	0/(0)	0/(0)	2/(0)	0/(0)
Secondary cancer (radiation induced)	0/(0)	0/(0)	0/(0)	1/(1)

Leiser et al. Radiother and Oncol. 2016. 120:163-68

RMS: Ongoing considerations

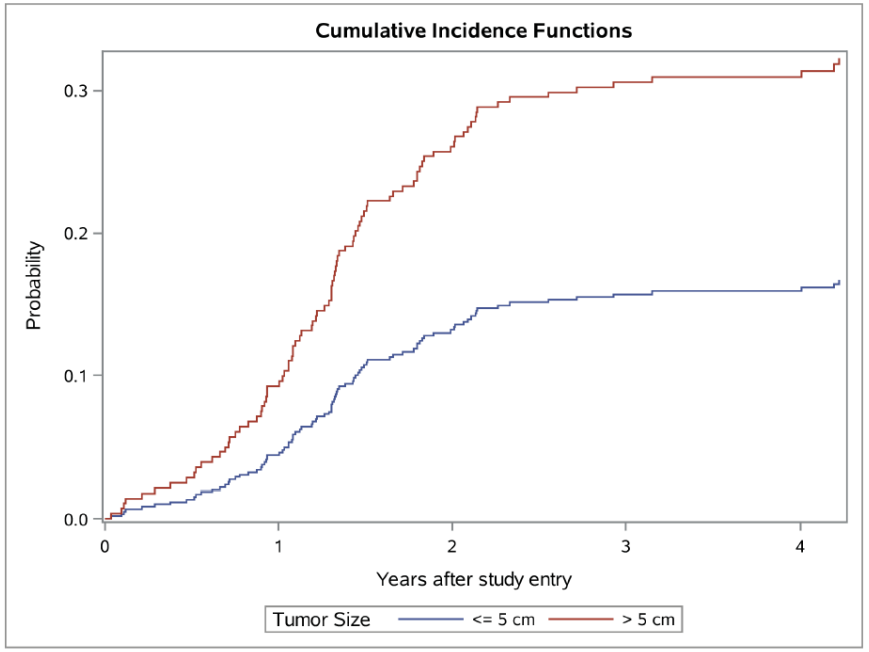


Figure 2.
Local failure on ARST0531 for group III patients with tumors ≤ 5cm (n=161) >5cm (n=205)

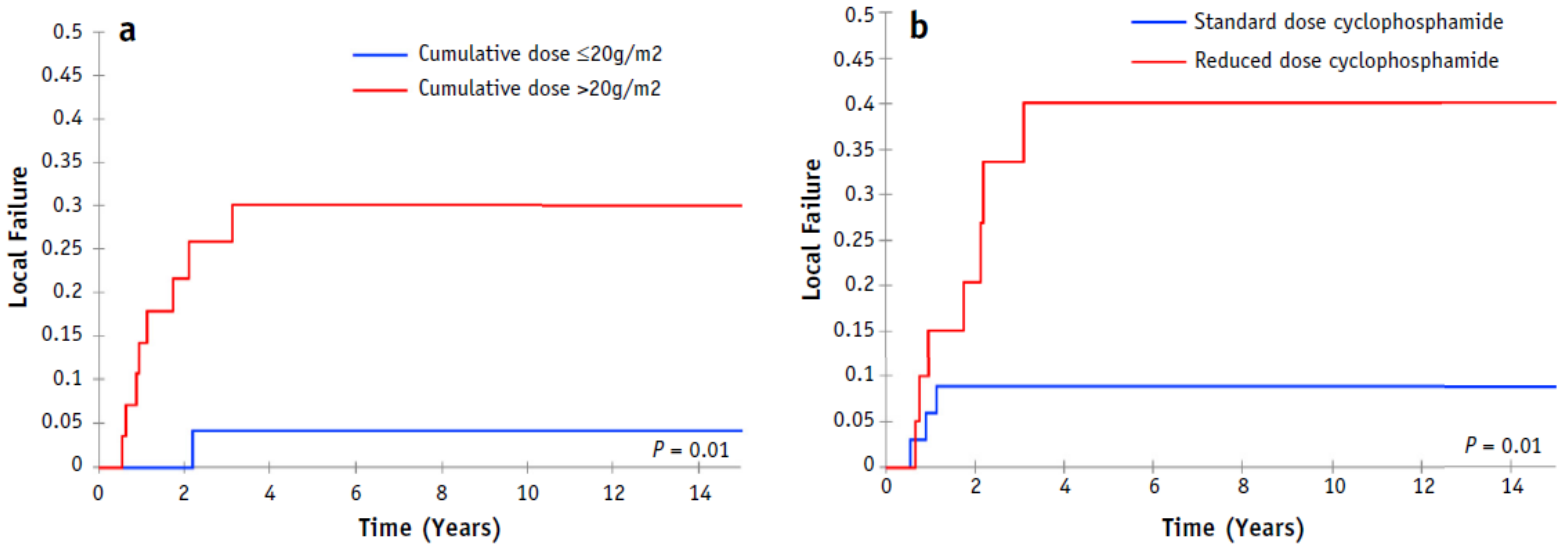


Fig. 3. Local failure in patients with parameningeal rhabdomyosarcoma by (a) cumulative cyclophosphamide dose and (b) cyclophosphamide dose intensity.

Orbital Dose? 45 vs 50.4 Gy
Timing of RT for parameningeal RMS with ICE?

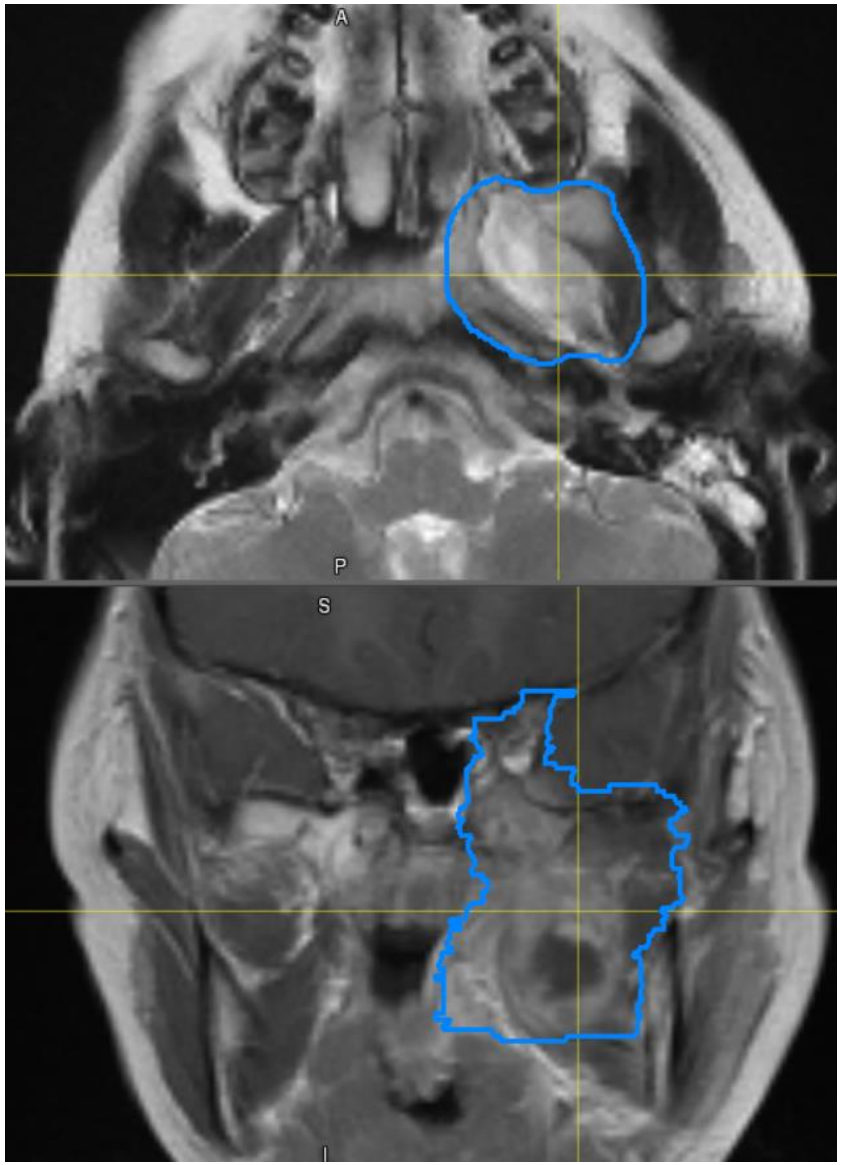
Casey et al. Cancer. 2019 September 15; 125(18): 3242–3248

Casey et al. IJROBP 2019 Apr 1;103(5):1151-1157

Case 2

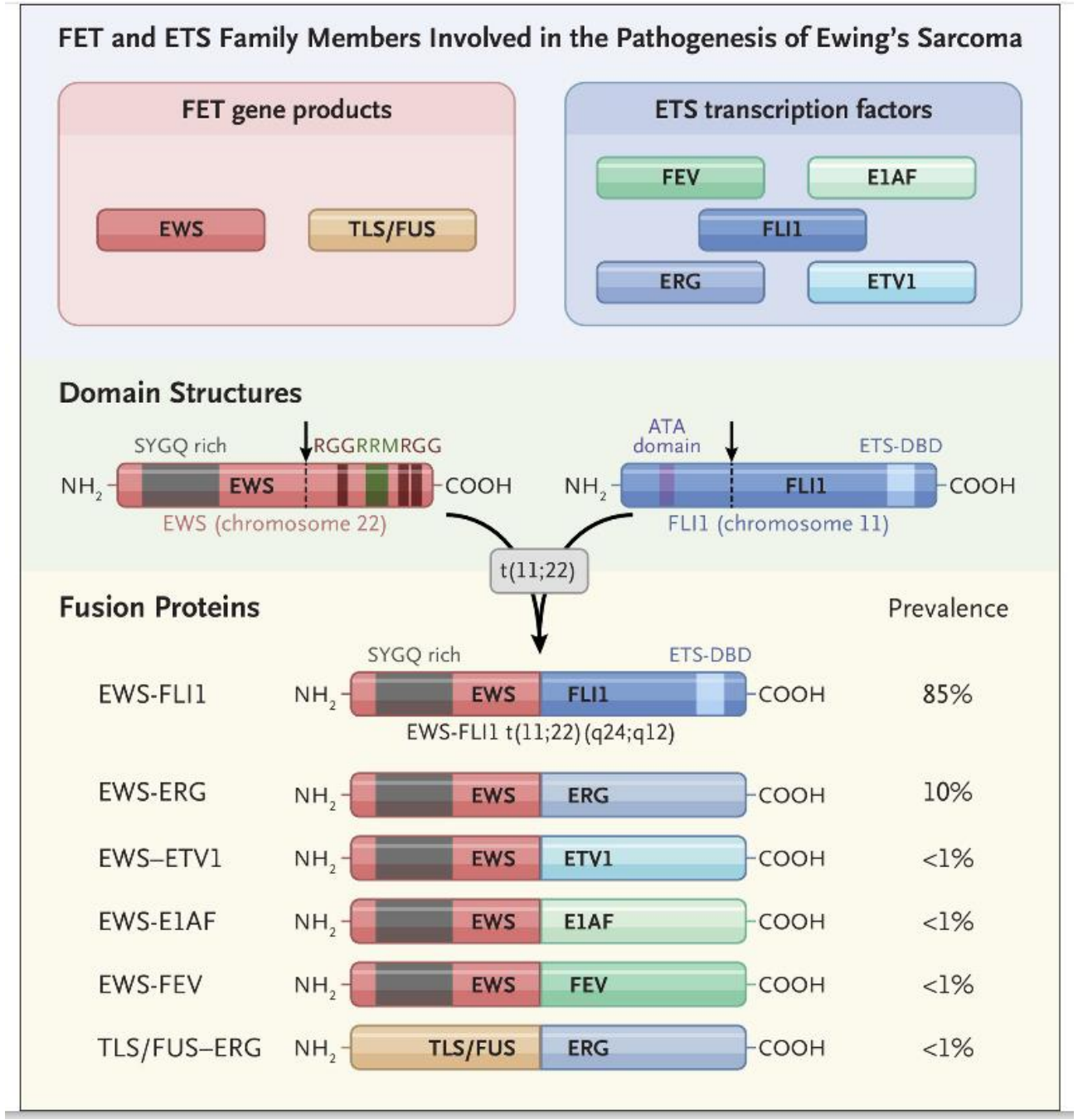
- 12 yo girl in 5th grade who loves Monopoly had left otitis media x 2 treated with antibiotics, then onset of left facial pain and numbness

5 x 3 x 2 cm mass extending from left paraparyngeal space to the inferior margin of the left orbit. Intracranial extemsion along the left anterior cavernous sinus and anterior left temporal dura. Focal destruction left maxillary antrum. Tumor involvement of the left nasopharynx and left retromolar trigone. Left eustachian canal obstruction and associated left osteomastoiditis.



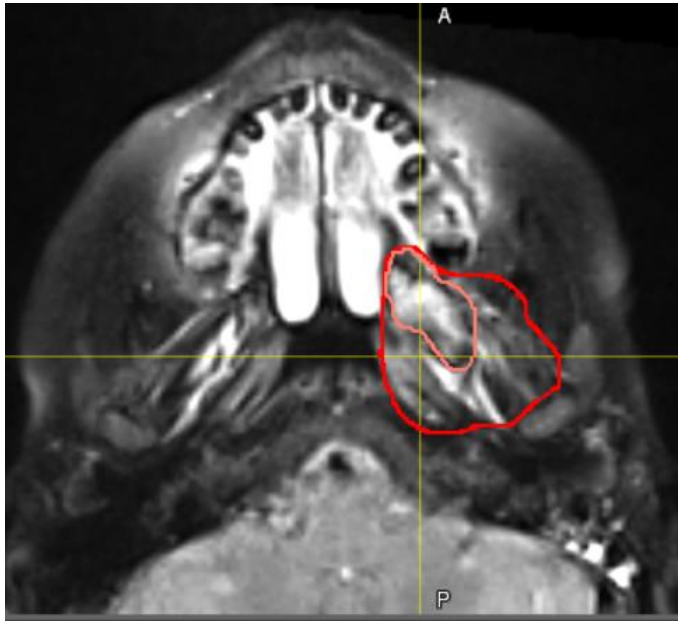
Ewing: General Treatment Paradigm

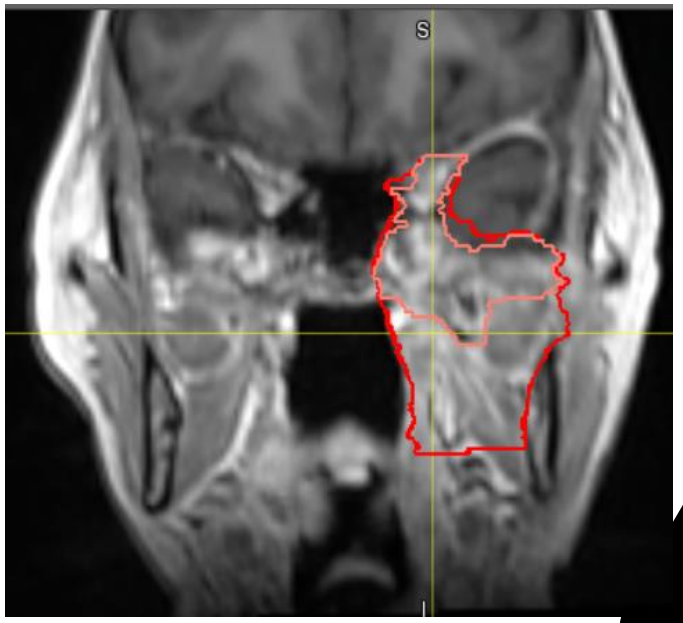
		This Case
Biopsy	• Core needle biopsy • Histology, t(11;22)(q24;q12) translocation (present in 85%)	Small round blue cell tumor, Ewing, 11;22 translocation present
WorkUp	• PET, Bone marrow biopsy, CT chest, CBC/CMP; Echo • Determine Stage	Negative AJCC bone tumor staging (includes grade): Stage IIA T1 N0 M0
Chemo	• Vincristine, Adriamycin, Cyclophosphamide/Ifosofamide + Etoposide • q 2 weeks x 6 cycles	VAC/IE x 12 weeks
Local Therapy	• Radiation (PreOp, PostOp, or Definitive; 45-55.8 Gy) with concurrent chemo (VC/IE) • Surgery	Definitive RT: 45 Gy to PTV1, total dose 55.8 Gy in 31 fxs at week 13
Chemo	• Vincristine, Adriamycin, Cyclophosphamide/Ifosofamide + Etoposide • q 2 weeks x 11 cycles	VAC/IE x 34 weeks total

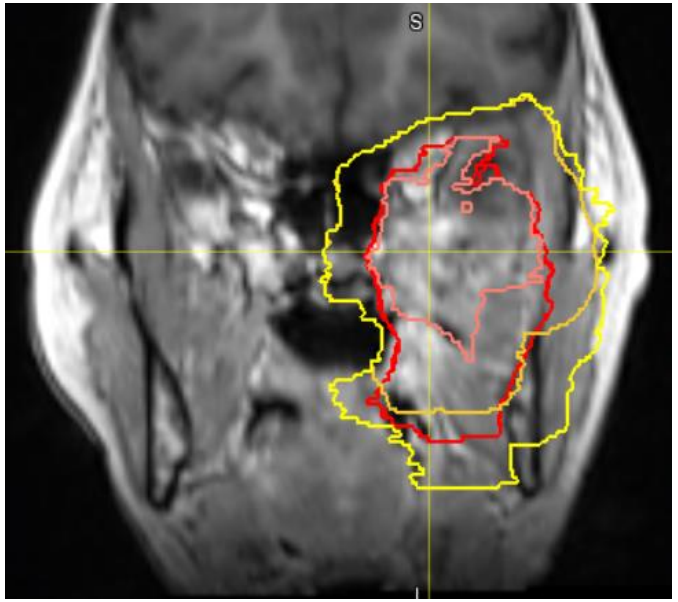


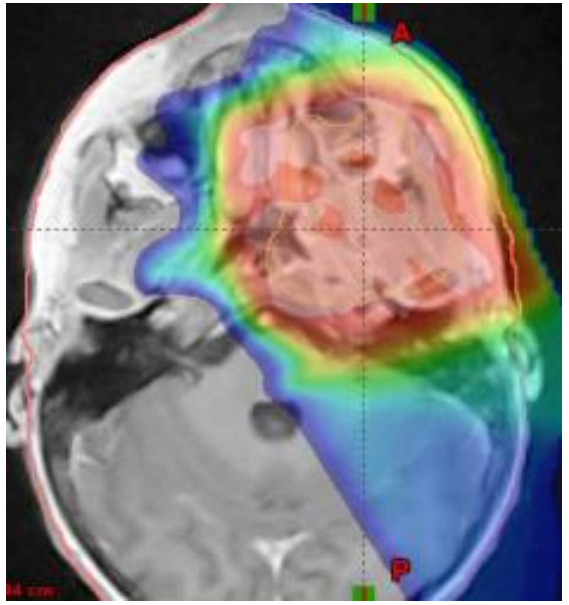
- Treatment strategy: direct inhibition of the FET-ETS fusion protein
  - lack of enzymatic activity and disordered structure make it difficult to target
- Alternative mechanism-based approaches:
  - inhibition of effector molecules of the FET-ETS fusion protein
  - reversion of the FET-ETS–induced epigenetic modifications
  - targeting of molecules and signaling pathways that support and cooperate with fusion protein function

Riggi et al N Engl J Med. 2021 Jan 14;384(2):154-164









- GTV1: disease prior to any surgical debulking or chemotherapy.
- CTV1 = GTV1 + 1cm
- PTV1: 0.3cm expansion
- GTV2: residual tumor after induction chemo with or without surgery.
  For unresected tumors, include *pre-treatment abnormalities in bone and the gross residual tumor in soft tissue* after induction chemotherapy.
- CTV2 = GV2 + 1cm
- PTV: 0.3 cm expansion

Radiation Dose for Ewing sarcoma

17.7.2.1 Radiation dose guidelines for all targeted volumes, excluding lymph nodes, and chest wall tumors with malignant pleural effusion or pleural nodules

Tumor Site and Presentation	PTV1	PTV2
Definitive RT	45 Gy	10.8 Gy
Definitive RT – vertebral bony lesion	45 Gy	5.4 Gy
Definitive RT – extraosseous ESFT without bony involvement with CR to Chemotherapy	50.4 Gy	N/A
Preop RT	36 Gy	N/A
Postop RT after pre-op RT: microscopic residual, >90% necrosis	N/A	14.4 Gy
Postop RT after pre-op RT: microscopic residual, <90% necrosis	14.4 Gy	N/A
Postop RT after pre-op RT: gross residual	19.8 Gy	
Postop RT –microscopic residual, >90% necrosis	N/A	50.4 Gy
Postop RT – microscopic residual, <90% necrosis	50.4 Gy	N/A
Postop RT – gross residual	45 Gy	10.8 Gy

experimental

17.7.2.2 Radiation dose guidelines for pathologically involved lymph nodes

Involved Lymph Nodes Doses	PTV1	PTV2
LN resected – separate from primary site	50.4 Gy	
LN resected – contiguous with primary site	50.4 Gy	
LN unresected - primary adequately resected	45 Gy	10.8 Gy
LN unresected - primary inadequately resected (microscopic residual)	45 Gy	10.8 Gy
Whole abdomen RT for malignant ascites or diffuse peritoneal involvement	24 Gy*	

* Whole abdomen RT will be administered at 1.5 Gy per fraction

17.7.2.3 Radiation dose guidelines for pathologically involved pleural fluid

Chest wall tumors with positive fluid cytology			
Age	PTV1*	PTV2*	PTV3^
≤ 6	32.4 Gy	10.8 Gy	12 Gy
> 6	30.6 Gy	9 Gy	15 Gy

*PTV1 and PTV2 - 1.8 Gy per fraction
^PTV3 - 1.5 Gy per fraction
Note: Heterogeneity correction must be used for lung irradiation

17.7.2.4 Radiation dose guidelines for pleural nodules

Chest wall tumor with secondary soft tissue only pleural nodules, radiographic PR			
Age	PTV1*	PTV2*	PTV3^
≤ 6	23.4 Gy	19.8 Gy	12 Gy
> 6	21.6 Gy	19.8 Gy	15 Gy
Chest wall tumor with secondary soft tissue only pleural nodules, radiographic CR			
Age	PTV1*	PTV2*	PTV3^
≤ 6	37.8 Gy		12 Gy
> 6	36 Gy		15 Gy

*PTV1 and PTV2 - 1.8 Gy per fraction
^PTV3 - 1.5 Gy per fraction
Note: Heterogeneity correction must be used for lung irradiation

AEWS1031

Radiation dose affects local control

Ahmed et al 2017 (retrospective)

- 100% of cohort pelvic primary
- 5 year local control 72% with dose < 56 Gy vs. 83% with dose ≥ 56 Gy (p=0.61)

Paulino et al 2007 (retrospective)

- 25% of cohort with pelvic primary
- For tumors > 8cm, dose > 54 Gy achieved higher local control (86% vs 27%, p=0.006)

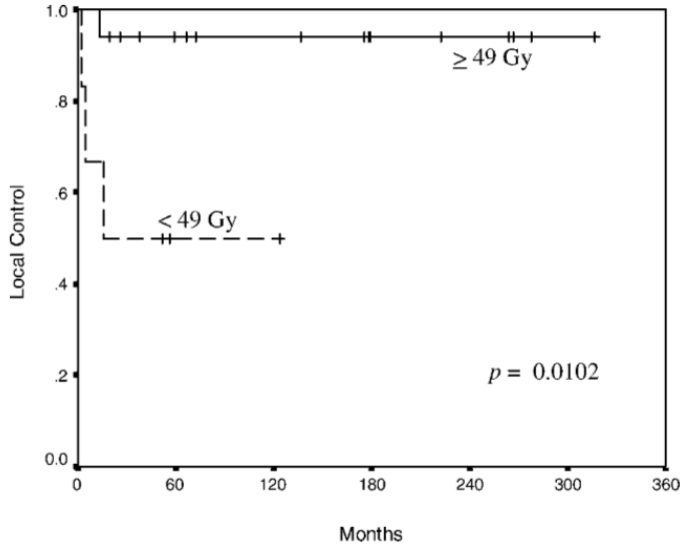


Fig. 1. Local control in tumors ≤8 cm (n = 23) according to radiotherapy dose.

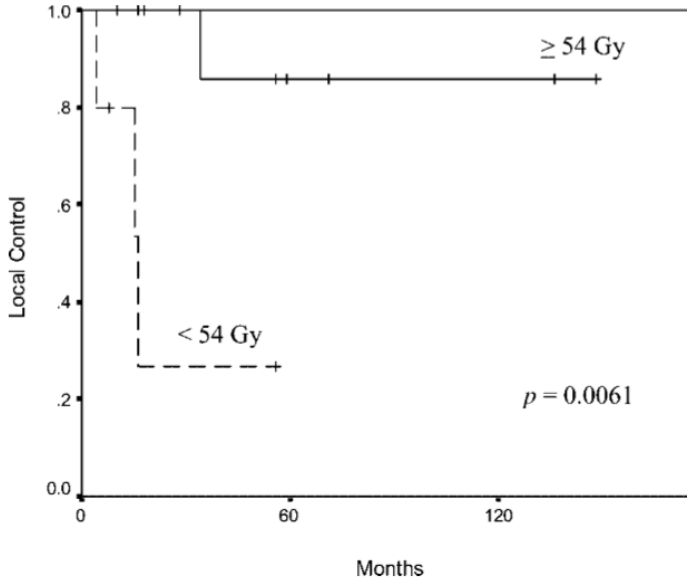
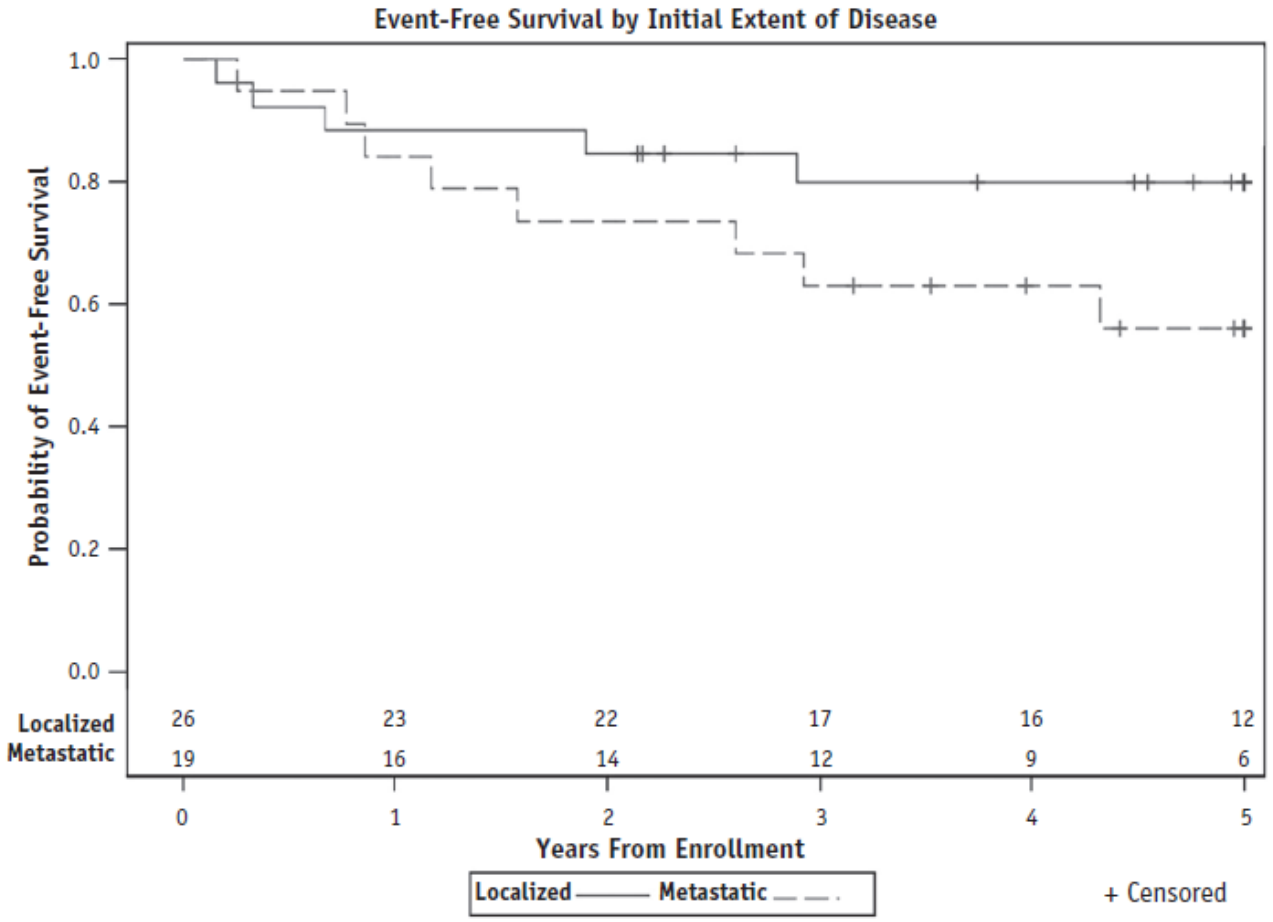


Fig. 2. Local control in tumors >8 cm (n = 17) according radiotherapy dose.

Improved local control with dose escalation

- Talleur et al 2016 (phase II)
  - 36% of cohort with pelvic primary
  - Tumor <8cm treated to 55.8 Gy
  - Tumor ≥ 8cm treated to 64.8 Gy
- 10 year local failure 4.4%
- No local failures in tumors ≥8 cm treated to 64.8 Gy



IJROBP 2016 Sep 1;96(1):119-26.

Toxicity

Acute: dermatitis, mucositis, odynophagia, xerostomia

Late: dental hypoplasia, dental caries, xerostomia, trismus, facial hypoplasia, skin pigmentation, hearing loss, dry eye, cataract, neurocognitive dysfunction, endocrinopathy, decreased vision, second malignancy

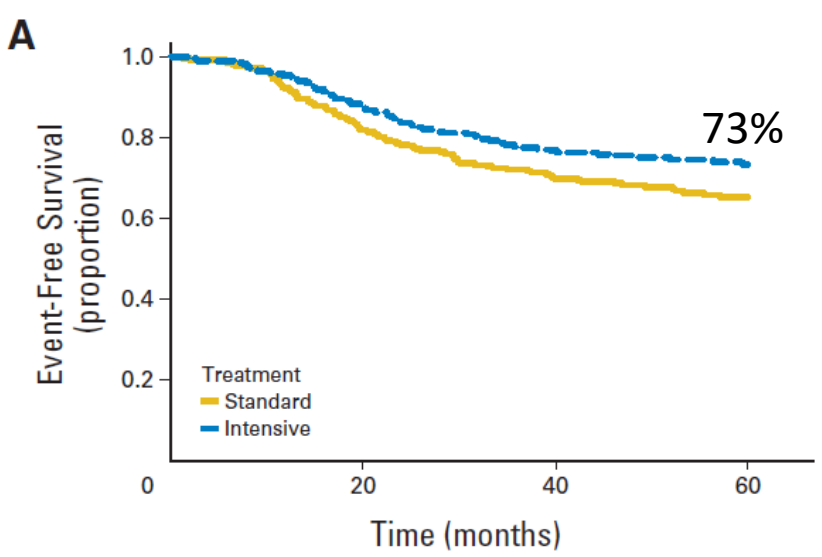
Table 17.9: Organs at risk dose recommendations

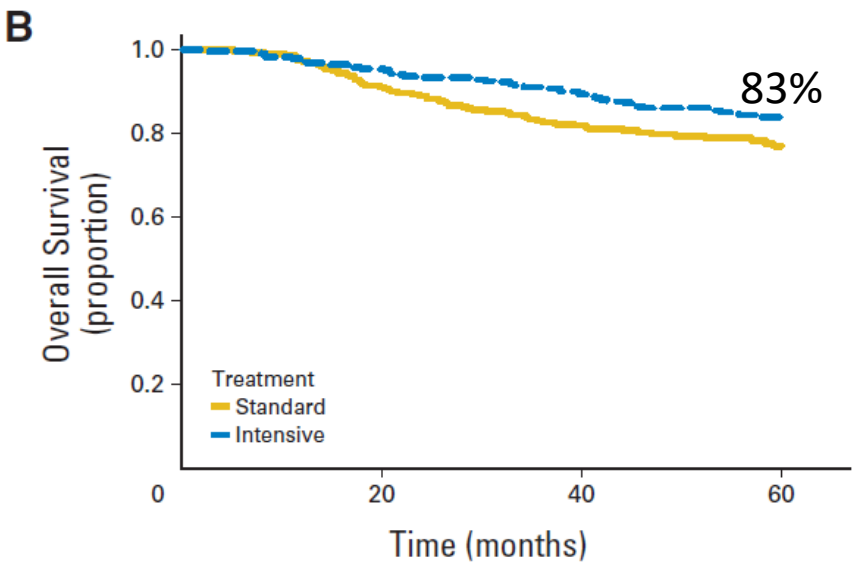
Organ	Volume (%)	Dose (cGy)
Single organs		
Bladder	100%	4500
Esophagus	50%	4000
Heart	100%	3000
Liver	100%	2340
	50%	3000
Rectum	100%	4500
Optic chiasm	100%	5400
Small Bowel	75%	4500
Spinal Cord	Any volume	5040
Paired organs		
Kidney (bilateral)	50%	2400
Kidney (bilateral)	100%	1440
Lung (bilateral)^	20%	2000
Lung (bilateral) ‡	35%	2000
Lung (bilateral)	100%	1500
Optic nerve	100%	5400
Eye	100%	4500
Lens	100%	600
Cochlea	100%	4000

AEWS1031

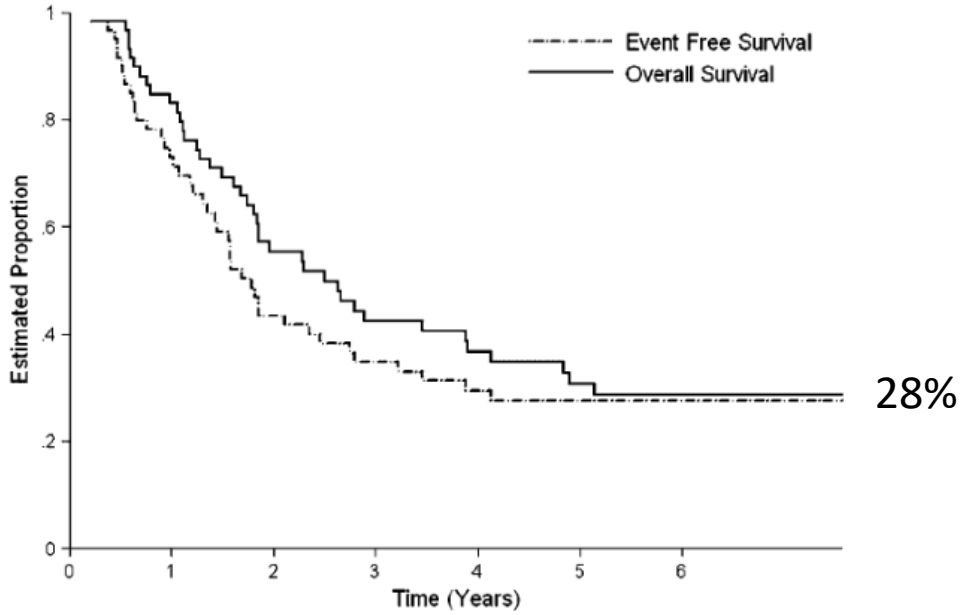
Outcomes: Ewing sarcoma

Localized





Metastatic

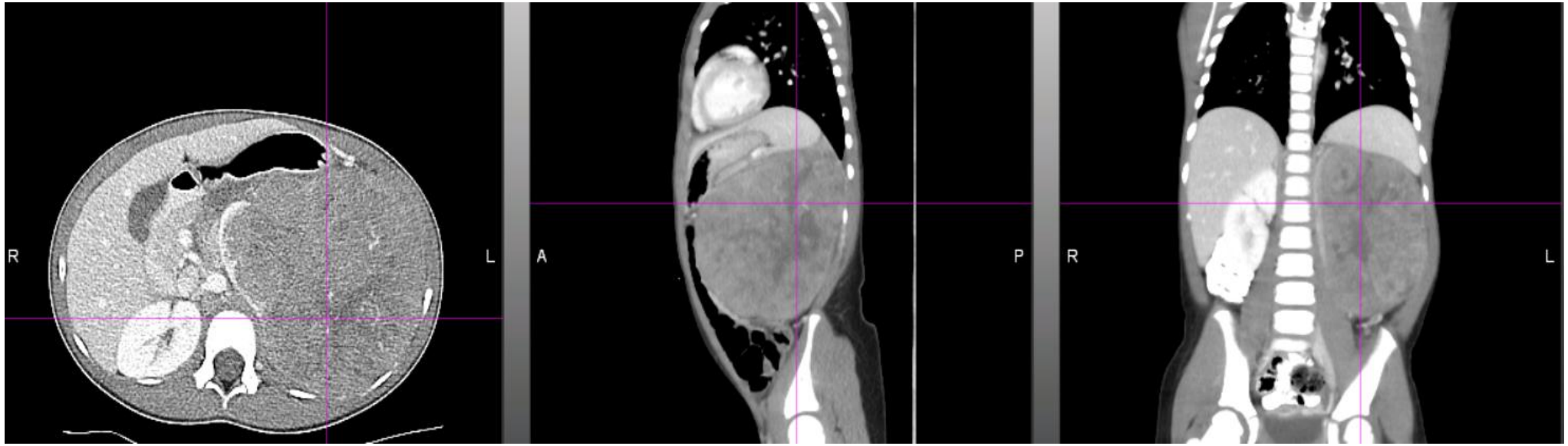


Womer et al. J Clin Oncol. 2012 Nov 20;30(33):4148-54.

Miser et al. Pediatr Blood Cancer 2007;49:894–900

Case 3

- 4 yo girl who enjoys dance and gymnastics presents with abdominal pain and distension



Wilms: General Treatment Paradigm

Surgery
- No biopsy
- Histology (favorable vs unfavorable), 1q and LOH 1p/16q testing; margins, nodes

WorkUp
- CT C/A/P (80% of metastatic disease is to the lungs); bone scan for clear cell variant and brain MRI for rhabdoid variant
- Determine Stage

RT
- *IF* indicated. Flank vs whole abdomen. Concurrent chemo
- Stage 3, high risk histology, sites of mets for Stage 4

Chemo
- Vincristine, Actinomycin +/- doxorubicin +/- cyclo, carbo, etop
- 25-28 weeks total

Note: SIOP approach is chemo first
Advantages: reduced risk of tumor rupture, assess responsiveness, potential for downstaging and treatment deintensification (~20%)

This Case

Small round blue cell tumor, Wilms, FH with no anaplasia

Op Note: "… renal vein margin positive. 4 of 7 lymph nodes…"

Negative
Stage III

10.8 Gy flank RT by day 10 to tumor bed (GTV) + 0.5 cm CTV + para-aortics T10-L5 + 0.5cm PTV

VAD total of 25 weeks

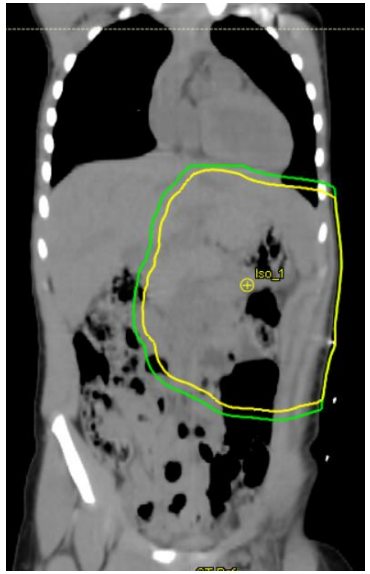
Surgical staging

I	Tumor limited to kidney and completely excised. No penetration of capsule of involvement of renal sinus vessels
II	Tumor extends beyond kidney but is not completely excised. There is penetration of capsule of involvement of renal sinus vessels.
III	Residual/unresectable tumor after surgery, positive nodes, local spillage or needle biopsy, R1/R2 resection, transected tumor thrombus, piecemeal resection, diffuse peritoneal contamination, peritoneal implants
IV	Hematogenous metastases to lung, liver, bone, brain or LNs outside of abdomen
V	Bilateral Wilms tumor (then stage each kidney separately)

Flank RT

Whole abdomen RT

- pre-op tumor rupture
- Intraop tumor spill beyond tumor bed



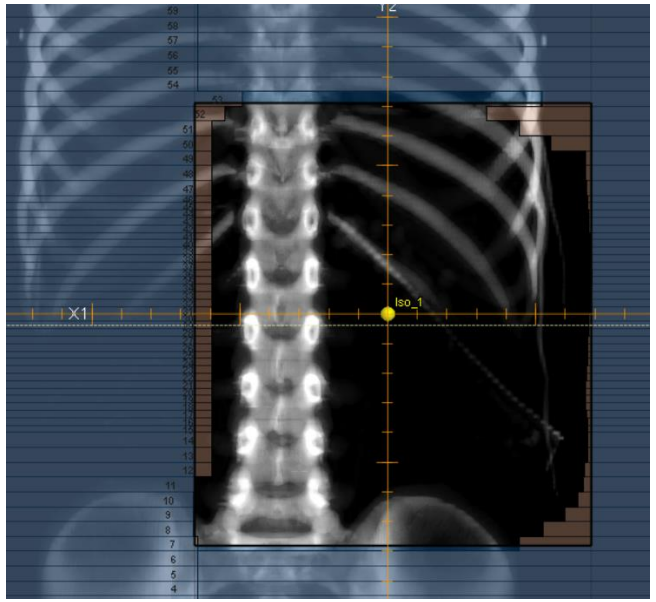
4D CT recommended

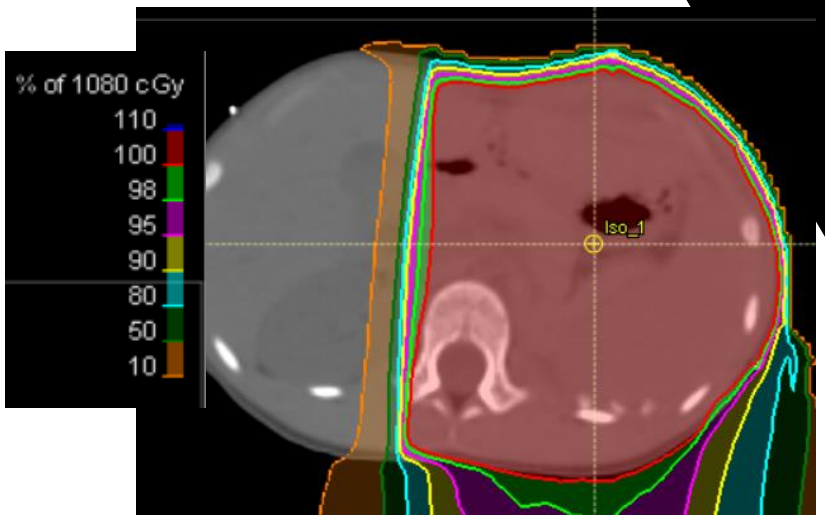
AREN1921 Contouring Atlases

- General Instructions
- Whole Lung Contouring Guidelines (young adult male)
- Cardiac Contouring Guidelines (young adult male)
- Whole Lung IMRT contours (pediatric female)
- Cardiac Contouring Atlas (pediatric female)
- Contouring Steps for combined IMRT Lung and Whole Abdomen (pediatric female)
- Contouring Steps for combined IMRT Lung and Flank (pediatric female)

https://www.qarc.org/cog_protocol_resources.htm

- GTV1: tumor extent at diagnosis before any therapy
- CTV1: 0.5cm + para-aortic LNs from top of T10 – bottom of L5
- PTV1: 0.5-1cm + entire vertebral bodies
- GTV2: residual disease if > 1cm
- CTV2: GTV2 + 0.5cm
- PTV2: 0.5-1cm

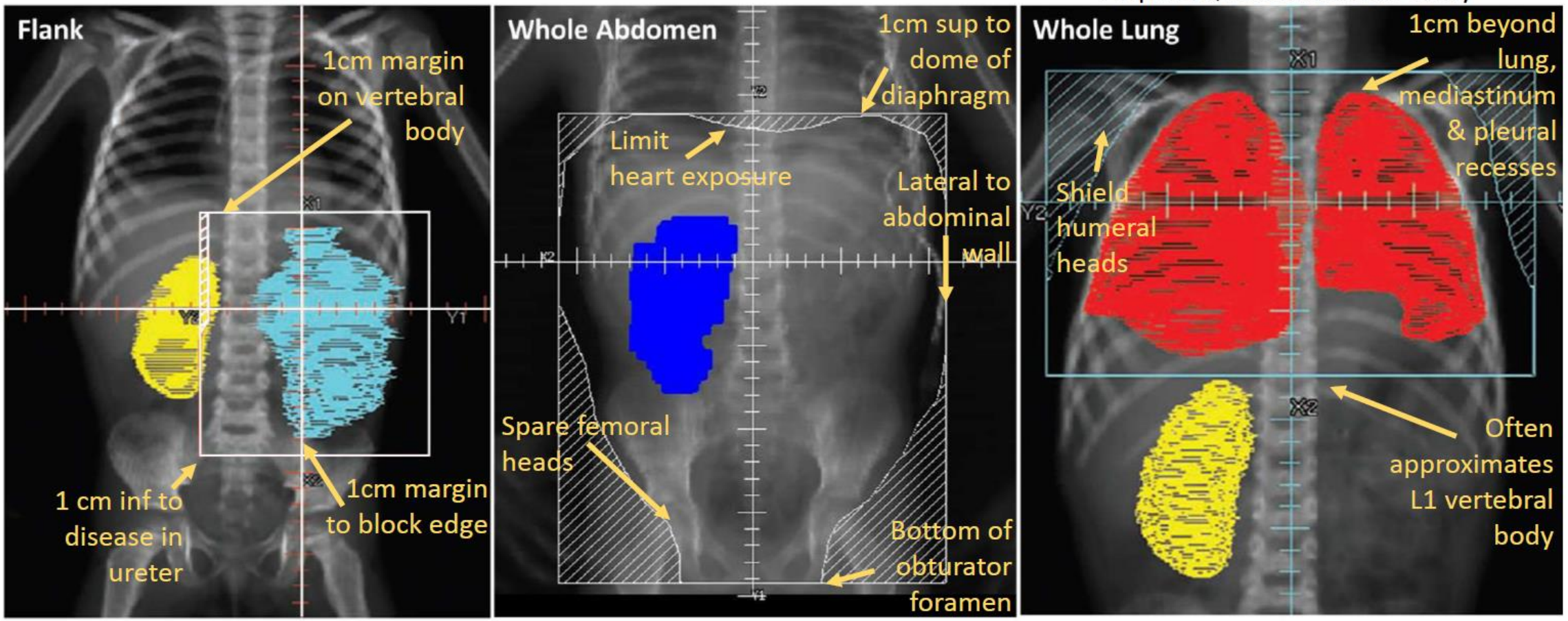




Field Design

Field design is based on initial presentation volumes on CT/MR scan

Timing: If WLI & Flank/WART required, treat concurrently



Slide courtesy of Dr John Lucas

Radiation Dose for Wilms Tumor

No radiation	10.5 Gy at 1.5	10.8 Gy at 1.8 Flank
Stage I-II FH	Whole WLI for age < 12 months	Stage III FH Stage I-III FA Stage I-II DA Stage III DA Infants Also, resected LNs age < 12 months

12 Gy at 1.5 WLI	19.5 Gy at 1.5 Whole abdomen	19.8 Gy at 1.8
Stage IV with lung metastases For all UH For FH if no CR at week 6	Stage III DA age > 12 months with diffuse unresectable peritoneal implants	Unresected LN mets or resected LNs age > 12 months Stage III DA Liver mets (focal or whole liver)

21.6 Gy at 1.8	25.2 Gy at 1.8	30.6 Gy at 1.8
Whole brain if < 5 lesions (+ 10.8 Gy focal boost)	Bone mets for age < 16	Whole brain if > 5 lesions (no boost) Bone mets for age 16+

Boost dose to unresected primary disease > 1cm: 10.8 Gy

Renal dose should be limited to 14.4 Gy by using renal shielding.

AREN1921

Molecular classification

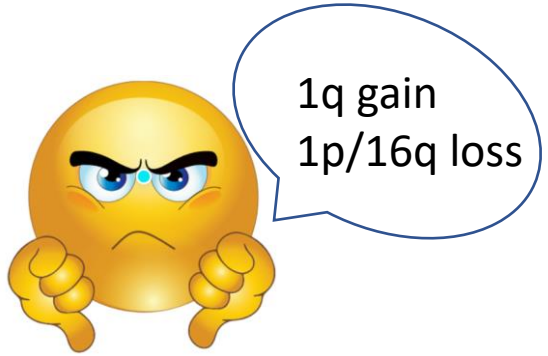
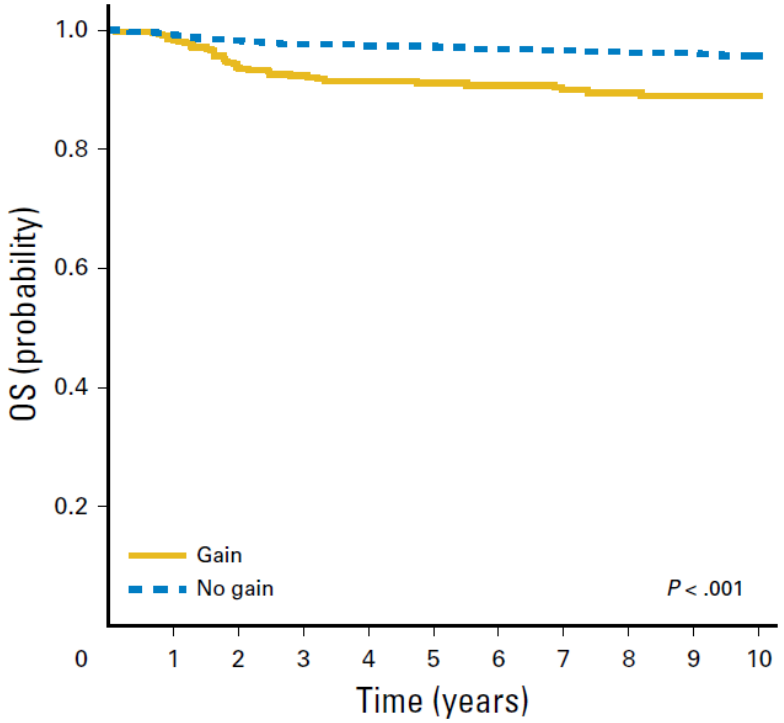
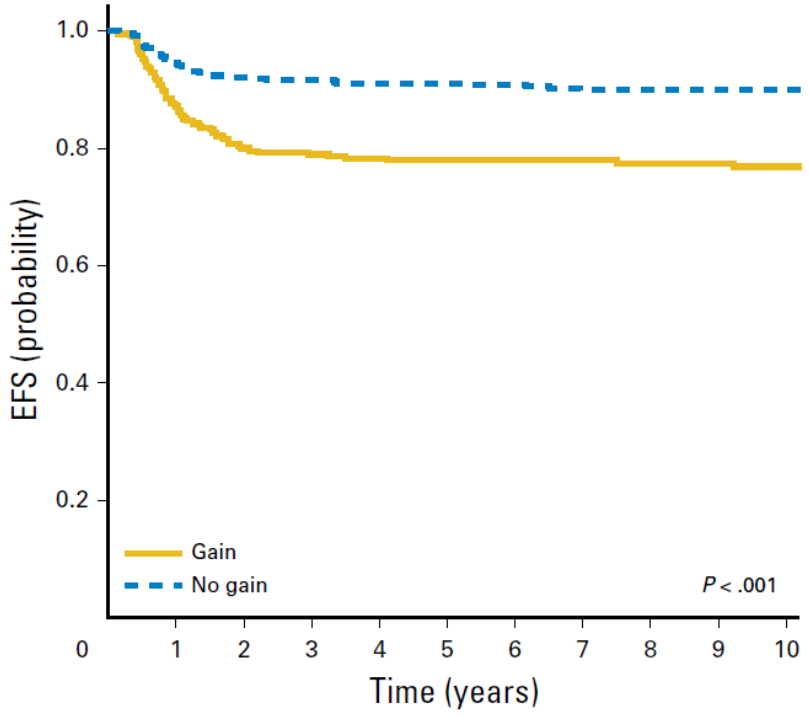


Table 2. Eight-Year EFS Stratified by 1q Status and LOH 1p/16q Status

1q Status	1p or 16q Call	No. of Patients	8-Year EFS (95% CI)
No gain	No loss	715	91 (88 to 93)
No gain	Loss	82	84 (74 to 93)
Gain	No loss	174	77 (69 to 84)
Gain	Loss	143	78 (70 to 87)

Abbreviation: EFS, event-free survival; LOH, loss of heterozygosity.





Gratias et al. J Clin Oncol. 2016 Sep 10;34(26):3189-94.

Children's Oncology Group (COG) Renal Protocols	
Tumor Risk Classification	Multimodality treatment
Very Low Risk FH WT <2 years, stage I FH, <550 g	Surgery, NO therapy if central path review & LN sampling
Low Risk FH WT ≥2 years, Stage I FH, ≥ 550g or Stage II FH without LOH	Surgery, No RT, Regimen EE4A
Standard Risk FH WT Stage I and II FH with LOH or Stage III FH without LOH	Surgery, Regimen DD4A Surgery, RT, Regimen DD4A

Children's Oncology Group (COG) Renal Protocols	
Tumor Risk Classification	Multimodality treatment
High Risk FH WT Stage III/IV FH with LOH Stage IV FH slow/incomplete responders	Surgery, RT, Regimen M, WLI
Stage IV FH: CR of lung metastases at wk 6/DD4A (rapid early responders)	Surgery, RT, Regimen DD4A. No WLI*
Stages I-III FA Stage I DA	Surgery, RT, Regimen DD4A
Stage IV FA Stage II-IV DA	Surgery, RT, Regimen UH1
Stage V	PreOp Chemo; eval @ week 6 for bx, sx, or continued chemo if CR; eval @ week 12 for sx vs chemo if CR; If sx, postop chemo/RT based on sx/path findings

*do not omit WLI in patients with 1q gain

Regimen	Agents
EE4A	Vincristine, dactinomycin (VA)
DD4A	Vincristine, dactinomycin, doxorubicin (VAD)
M	Vincristine, dactinomycin, doxorubicin, cyclophosphamide, etoposide (VADCyE)
UH1	alternating VDCy/CyC [carboplatin] E

Slide courtesy of Dr John Lucas

Outcomes: Wilms Tumor

24% of survivors are affected by *severe* chronic health conditions:

Cardiac toxicity

Pulmonary toxicity

Infertility

Second malignancies

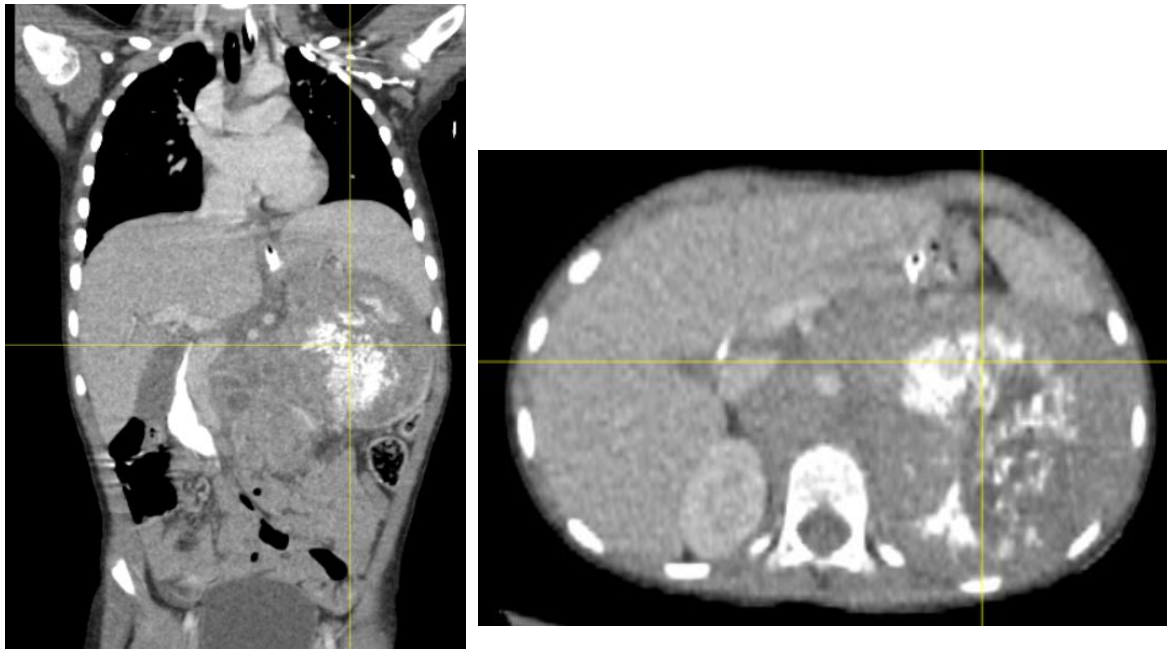
	4 Year	
Stage	RFS/EFS (%)	OS (%)
I (age <24months, tumor weight <550g)	84	98
I/II, no LOH	91	98
I/II, LOH 1p and 16q	75	91
III/IV, no LOH	83	92
III/IV, LOH 1p and 16q	66	78
V, any LOH	61	81
I, diffuse anaplasia	68	79
II, diffuse anaplasia	83	82
III, diffuse anaplasia	65	67
IV, diffuse anaplasia	33	33
V, diffuse anaplasia	25	42

Termuhlen et al. Pediatr Blooc Cancer. 2011 Dec 15;57(7):1210-6

Table courtesy of Dr John Lucas

Case 4

- 2 yo presents with abdominal distension and pain and persistent low grade fever. On exam, palpable mass LUQ abdomen
- Abdominal US and xray showed large mass
- Urine assay: elevated HVA/Crt ratio of 193.8 [normal range 0.0 – 22/0 ug/mg]; elevated VMA/Cr ratio of 147.2 [normal range 0.0 – 11.0 mg/g]
- US guided biopsy: poorly differentiated neuroblastoma with unfavorable histology and MKI >4%. **N-MYC not amplified**
- BM biopsy: negative



Calcified multilobulated retroperitoneal abdominal mass, likely arising from the left adrenal gland. 13.3 x 9.5 x 13.2cm. **Encasesment** of the abdominal aorta, superior mesenteric artery, inferior mesenteric artery, and bilateral renal arteries. The tumor **crossed midline** to the right side of the abdomen. **Osseous metastasis** was demonstrated at T9, L5, and S1.

I-123 MIBG: abnormal uptake within the left abdomen and right paramidline abdomen, corresponding to the retroperitoneal tumor on CT. Additional foci of activity was demonstrated at the skull vertex, skull base, L5, and S1.

Staging

Table 1. International Neuroblastoma Staging System (INSS).

INSS Stage	Description
1	Localized tumor, grossly resected, no lymph node involvement
2A	Unilateral tumor, incomplete gross excision, negative lymph nodes
2B	Unilateral tumor with positive ipsilateral lymph nodes
3	Tumor infiltrating across midline or unilateral tumor with contralateral lymph nodes or midline tumor with bilateral lymph nodes
4	Distant metastatic disease
4S	Localized primary tumor as defined by stage 1 or 2 in patient under 12 months with dissemination limited to the liver, skin, and/or bone marrow (<10% involvement)

Table 2. International Neuroblastoma Risk Group Staging Sysem (INRGSS).

INRG Stage	Description
L1	Localized tumor with no image-defined risk factors [13]
L2	Localized tumor with one or more image-defined risk factors [13]
M	Distant metastatic disease
MS	Metastatic disease in children under 18 months with metastases limited to skin, liver, and/or bone marrow (<10% involvement)

Table 3. International Neuroblastoma Pathology Classificaiton (INPC) histology definitions.

Favorable Histology	Unfavorable Histology
Ganglioneuroma mature (stroma-dominant)	Ganglioneuroblastoma, nodular (composite; stroma-rich/stroma-dominat and stroma-poor)
Ganglioneuroma maturing (stroma-dominant)	Neuroblastoma (stroma-poor)—all else not in favorable histology category
Ganglioneuroblastoma, intermixed (stroma-rich)	
Neuroblastoma (stroma-poor), differentiating or poorly differentiated with low/intermediate MKI in patients <1.5 years at diagnosis	
Neuroblastoma (stroma-poor), differentiating with low MKI in patients 1.5–5 years at diagnosis	

Risk Categories

INSS Stage	Age	MYCN Status	Shimada Histology	DNA Ploidy	Risk Group
1	0- 21 yrs	Any	Any	Any	low
2A/2B	<1 y ≥ 1-21 y ≥ 1-21 y ≥ 1-21 y	Any Non-Amp Amp Amp	Any Any Fav Unfav	Any - - -	Low Low Low High
3	<1yr <1yr ≥ 1-21 y ≥ 1-21 y ≥ 1-21 y	Non-Amp Amp Non-Amp Non-Amp Amp	Any Any Fav Unfav Any	Any Any - - -	Intermediate High Intermediate High High
4	<1y <1y ≥ 1-21 y	Non-Amp Amp Any	Any Any Any	Any Any -	Intermediate High High
4S →	<1 y <1 y <1 y <1 y	Non-Amp Non-amp Non-amp Amp	Fav Any Unfav Any	> 1 = 1 Any Any	Low Intermediate Intermediate High

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS →	< 18			NA	No		C Very low
					Yes		Q High
				Amp			R High

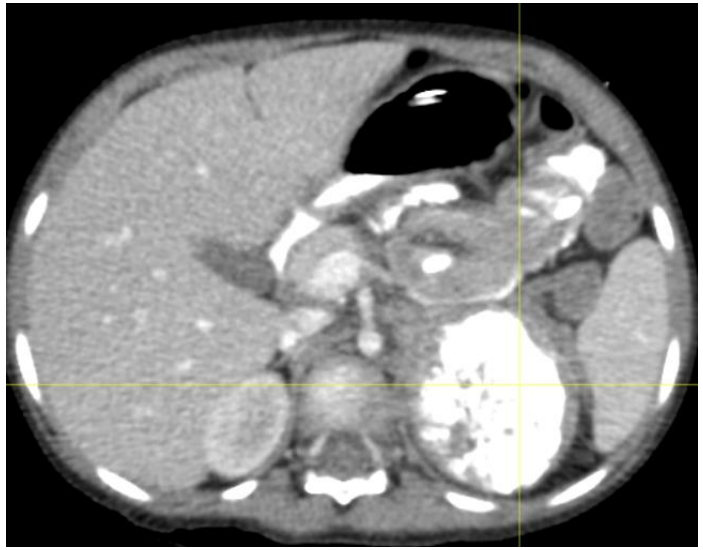
Sokol et al. Children (Basel). 2019 Feb 11;6(2):27

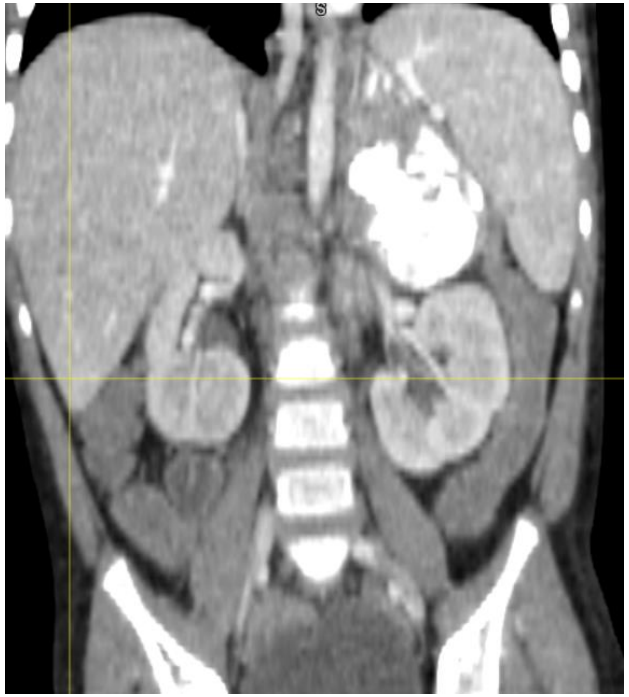
Neuroblastoma: Treatment paradigm

RISK GROUP	TREATMENT
Very low risk	Observation
Low risk	Surgery alone
Intermediate risk	Surgery + chemotherapy (doxorubicin, cyclophosphamide, cisplatin) 4-8 cycles RT for liver mets causing respiratory distress (4.5 Gy at 1.5 GY/fx) or spinal cord compression (9 Gy for < 3yo and 21.6Gy for > 3 yo @ 1.8/fx)
High risk	Induction chemo (5 cycles) + surgery + high dose chemo with stem cell rescue (tandem) + **RT** + consolidation isotretinoin or immunotherapy

Treatment course

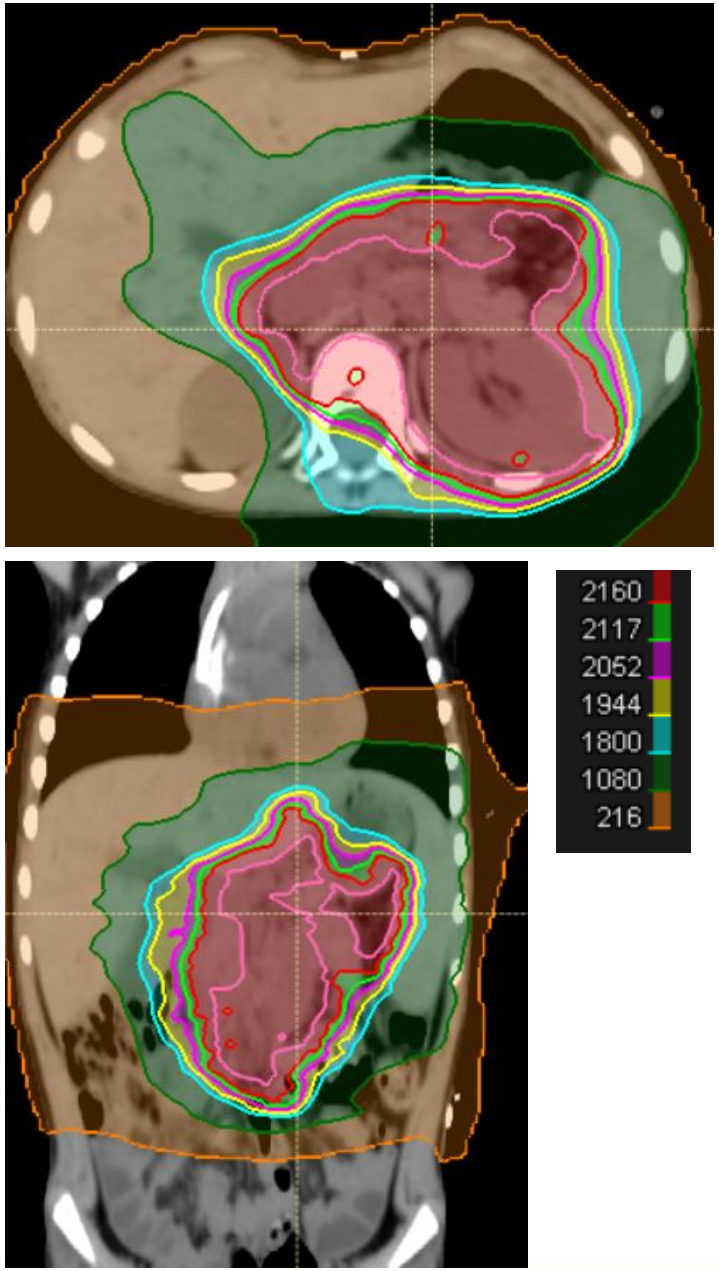
- Induction chemo x 5 cycles (TOPO/CPM; CDDP/ETOP; VCR/DOXO/CPM)
- CT C/A/P: decreased tumor size to 7.9 x 6.2 x 4.8cm
- STR: The main tumor was resected completely but residual adenopathy could not be completely resected due to the risk of vascular injury. Pathologic examination demonstrated **maturing ganglioneuroma (favorable histology)**.
- CT C/A/P: Residual tumor was in LUQ of the abdomen interposed between the superior mesenteric artery and portal vein and extending inferiorly in the left periaortic region, with some degree of encasement of the left renal artery and vein. This corresponded to the radiotracer activity seen on the MIBG scan.
- I-123 MIBG scan: increased uptake in the left mid-abdomen just left of the midline. No bone disease.
- Tandem ASCT
- Radiation to residual disease + tumor bed 21.6 Gy
- No radiation to bony mets given complete response to induction chemo





Radiation planning (high risk disease)

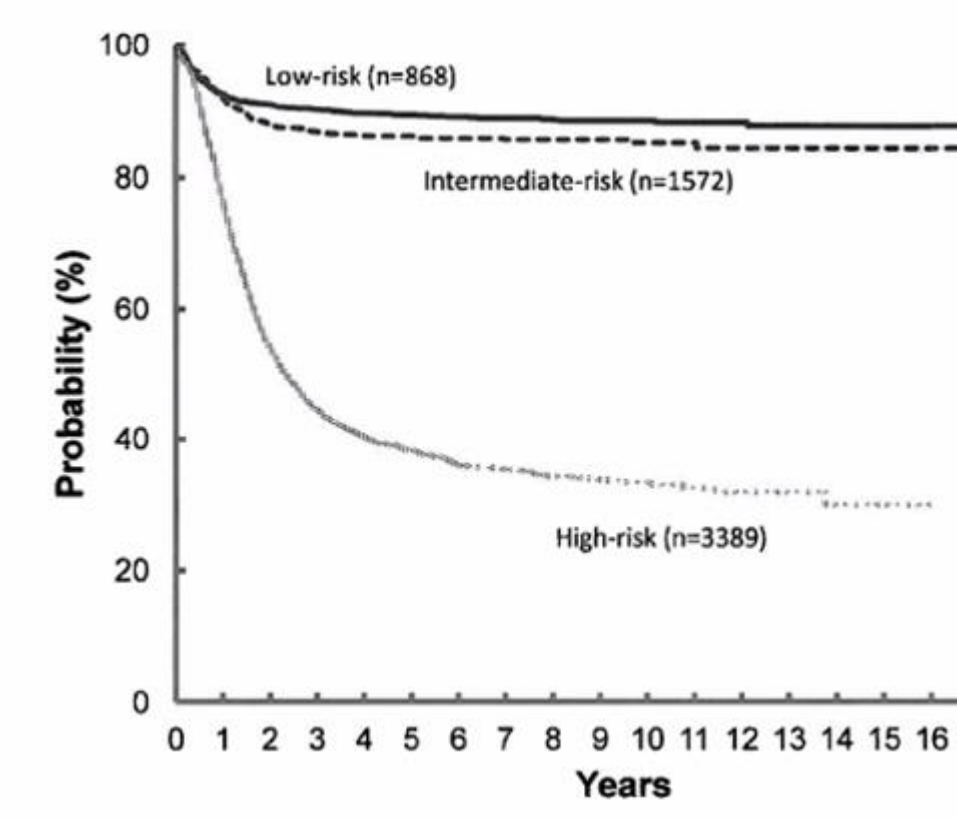
Dose	21.6 Gy at 1.8 Gy/fx
Target	Postchemo/PreOp tumor + involved nodal regions 1cm CTV 0.5cm PTV
Boost	No (per ANBL0532; JCO 2020)
Elective nodal radiation	No (per COG A3973; Braunstein et al 2018)
Metastatic sites	21.6 Gy at 1.8 Gy/fx to disease positive on MIBG pre-HSCT (< 5 mets) or positive after HSCT for > 5 mets
RT timing	4-6 weeks post-transplant



Outcomes: Neuroblastoma

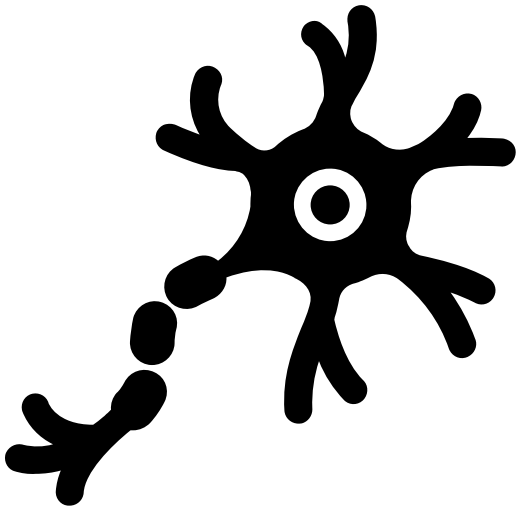
Acute: nausea, emesis, diarrhea, cytopenia

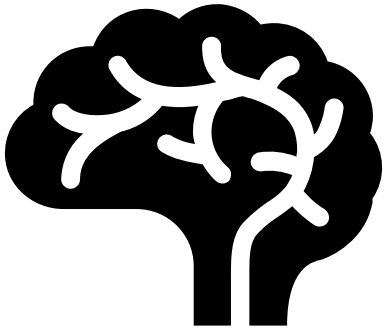
Late: bone hypoplasia/curvature, heart injury, lung injury, second malignancy, hearing loss, infertility



Park et al. Pediatr Blood Cancer. 2013 Jun;60(6):985-93

	Wilms Tumor	Neuroblastoma
Age	Peak 3-4 years	< 2 years
Clinical presentation	Painless abdominal mass Rarely constitutional symptoms	Painful abdominal mass Often constitutional symptoms
Origin	Kidney	Retroperitoneal neural crest
Renal mass effect	Intrinsic	Extrinsic
Calcifications	< 15%	> 85%
Crosses midline	Rarely	Frequently
Vessel involvement	Invasive	Encases
Metastatic spread	Lung Liver Lymphatics	Bone/bone marrow Liver Skin
Staging work-up	CT/MRI abdomen, CT chest	CT/MRI abdomen, MIBG, bone scan, urine VMA and HVA
Prognostic factors	Stage, histology, age, 1q gain, LOH 1p/16q	Stage, histology, age, mycn status
Special stages	V (bilateral)	IVS (< 1 year old with spread to skin, liver, bone marrow)





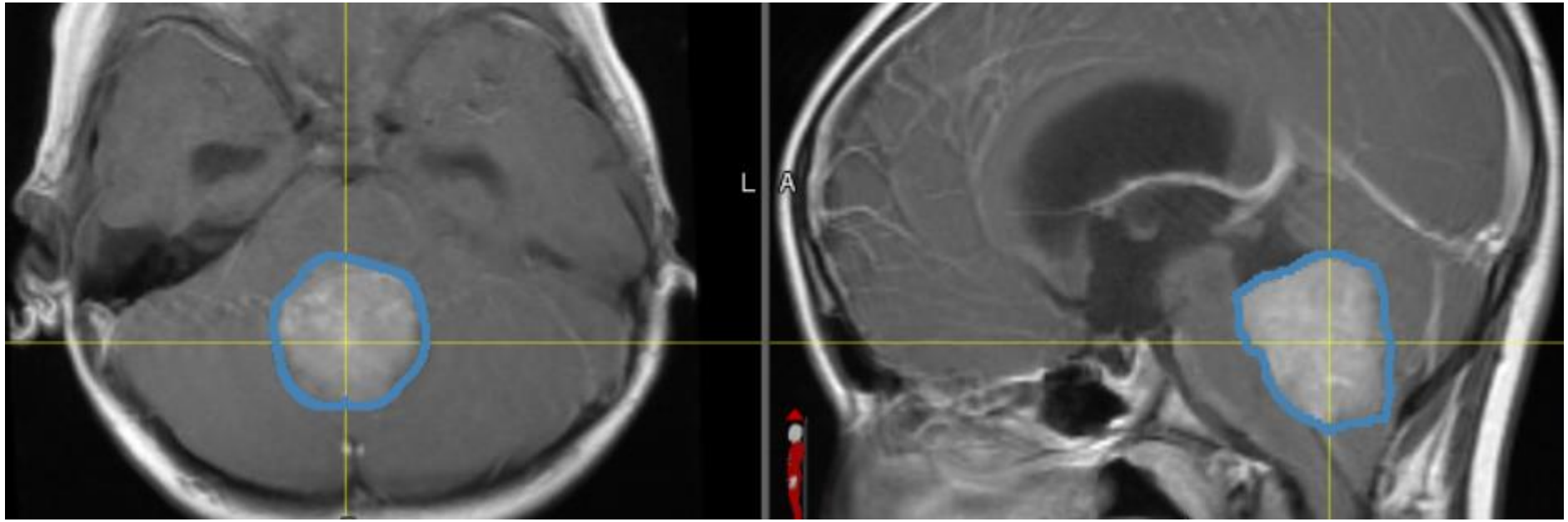
CNS Tumors

Normal structures for intracranial cases

- Brain
- Cerebellum
- Brainstem
- Brainstem core and surface
- Cochlea
- Cornea
- Globe
- Hippocampus
- Hypothalamus
- Lacrimal glands
- Lens
- Optic nerves and chiasm
- Pituitary
- Mastoids
- Scalp
- Spinal cord
- Supratentorial brain
- Temporal lobes

Case 5:

- 12 yo girl presents with headache, emesis and fatigue



Medulloblastoma: General Treatment Paradigm

Surgery
- Aim for GTR
- Histology, molecular subtype

WorkUp
- MRI spine, post-op MRI brain within 1-2 days, LP post-op (10-14 days), CBC (weekly during RT)
- Determine Stage

RT
- CSI 23.4 – 36 Gy; boost to tumor bed to total dose 54 Gy.
- Aim for 1 month post-op. Avoid treatment breaks (↓outcomes if > 45 day RT course)

Chemo
- +/- weekly Vincristine concurrent
- Adjuvant x 4-6 cycles, Cis/VCR & CPM/VCR

CSI **not** recommended for children < 3 years (Instead, intensive chemo such as HeadStart protocol +/- focal RT)

Additional work-up: Ophthalmology exam, audiology exam, baseline endocrine labs (baseline and yearly), neurocognitive testing (baseline and q2-3 years)

This Case

Histological classification:	Medulloblastoma, classic variant
WHO grade:	Grade IV
Molecular information:	Non-WNT/non-SHH molecular subgroup (IHC) p53 wild type pattern (IHC) No significant gain or amplification of *MYC* No significant gain or amplification of *MYCN* Monosomy chromosome 6 not detected

Op Note: "…The tumor was noted to be adherent to the midportion of the floor of the 4th ventricle. This portion was shaved down to a very thin rind…"

Negative work-up
Chang stage T2 N0 M0

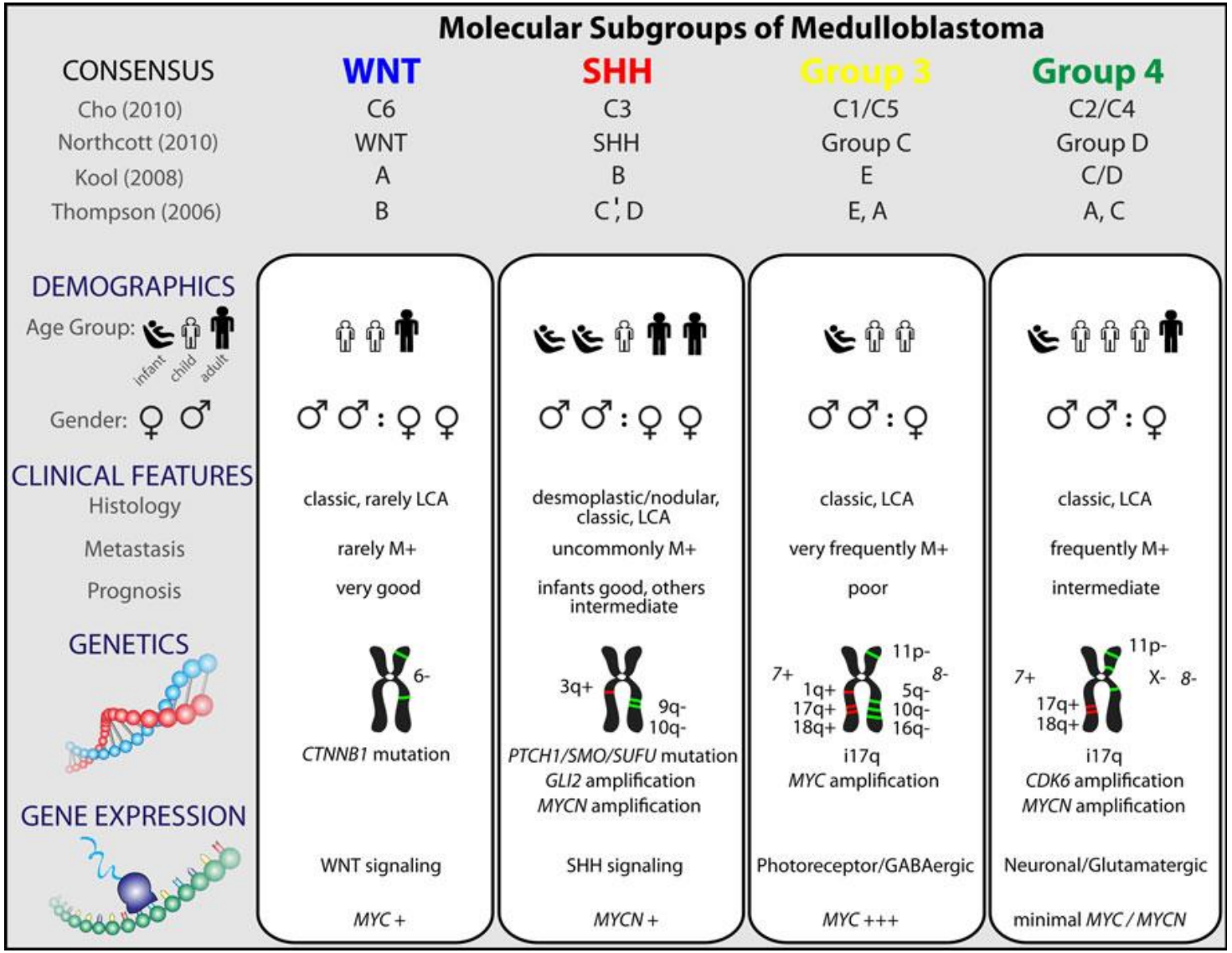
23.4 Gy in 20 fxs CSI + 30.6 Gy in 17 fxs to tumor bed = 54 Gy

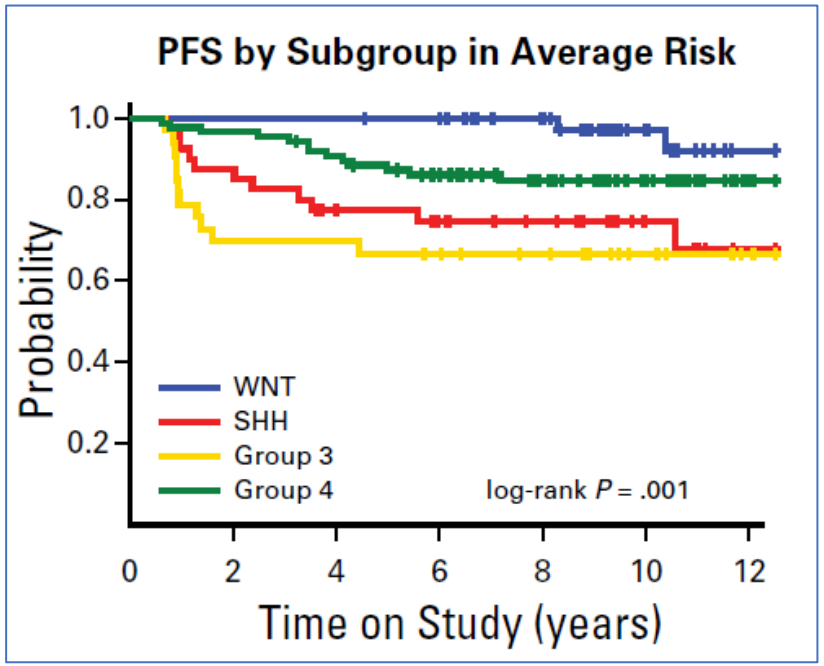
9 cycles adjuvant chemo

Risk Group: Traditional

	Standard Risk	High Risk
Residual gross disease	<1.5cm^2	> 1.5cm^2
Metastatic spread	M0	M1-4
Patient age	≥ 3 years	< 3 years
Histology	Classic, desmoplastic	

“Other than average risk” large cell anaplastic histology, M0, GTR





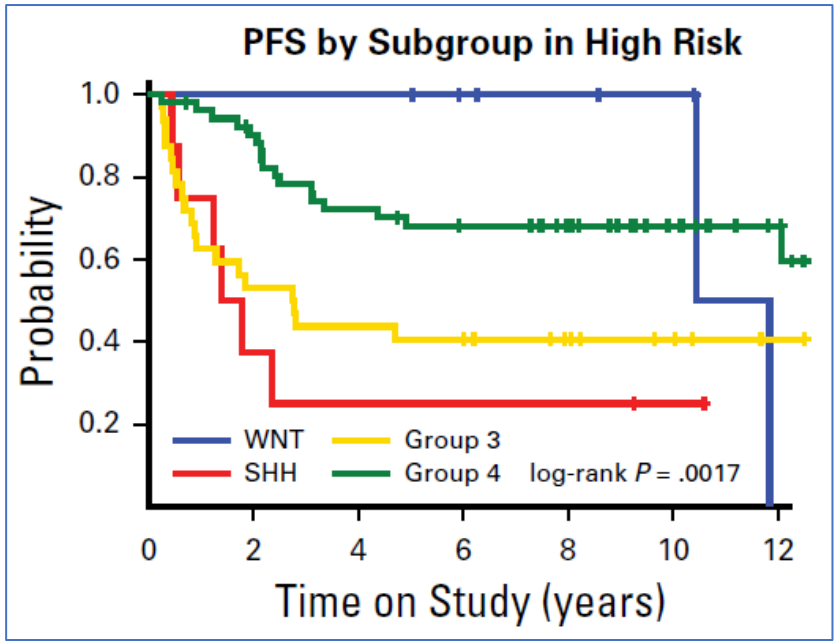
5 year

100%

87%

78%

67%



100%

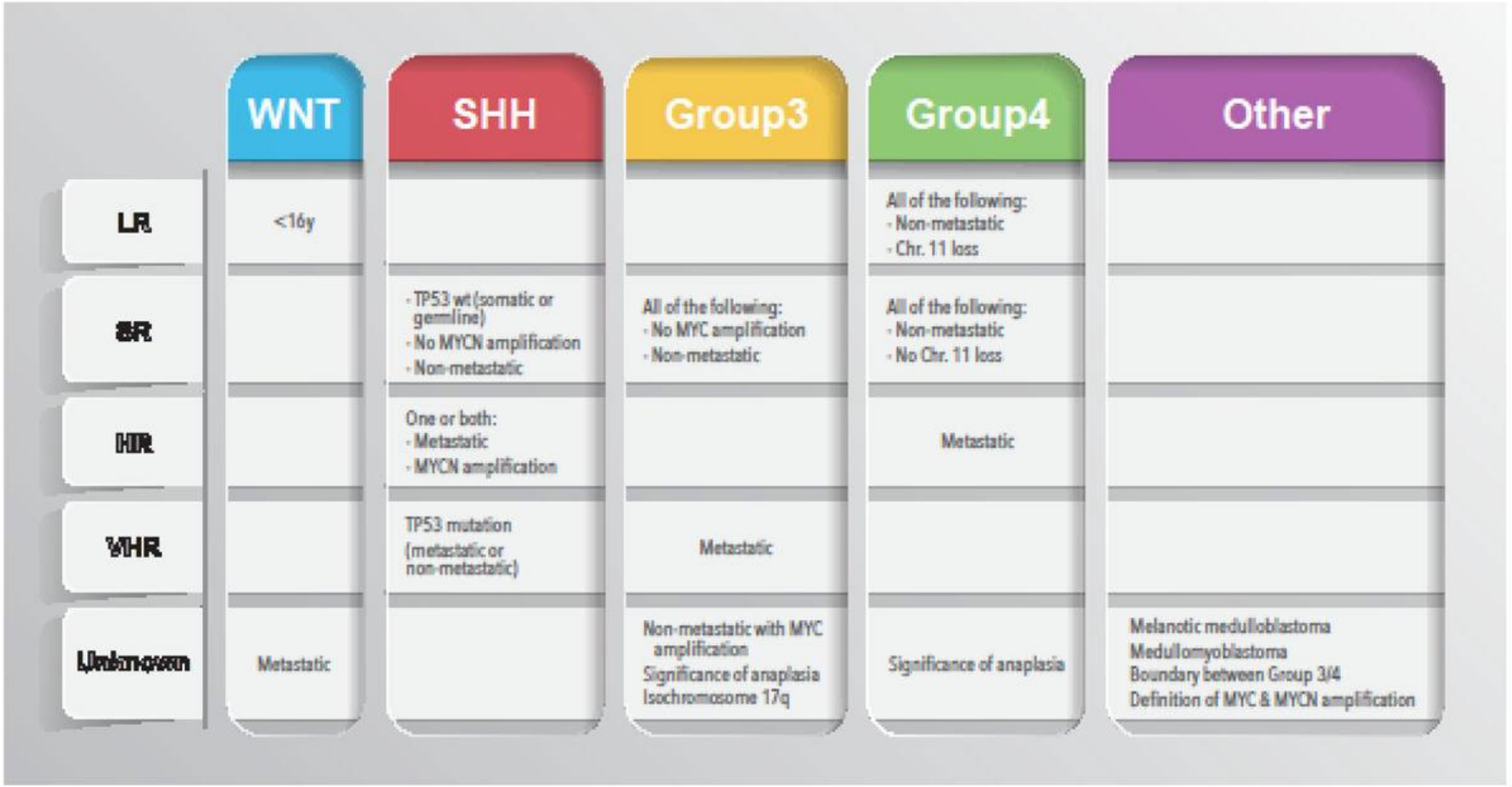
68%

41%

25%

Taylor et al. Acta Neuropathol. 2012. 123:465-72.
Gajjar et al. J Clin Oncol. 2021 Mar 1;39(7):822-835

Molecular Based Risk Groups

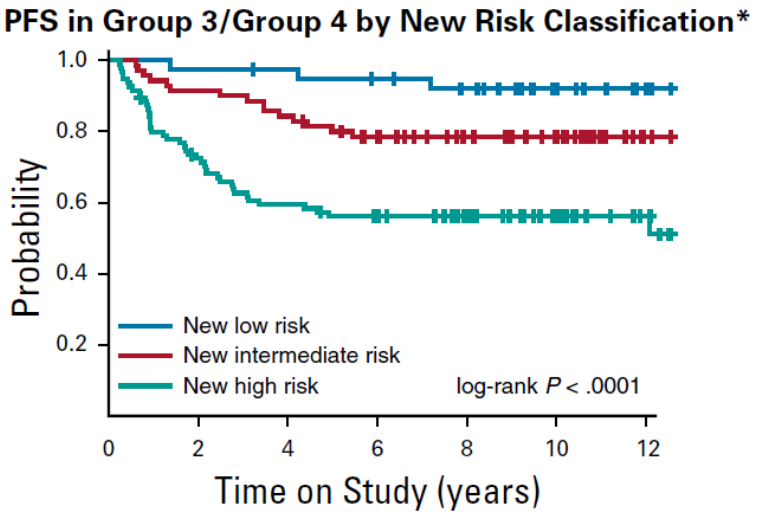


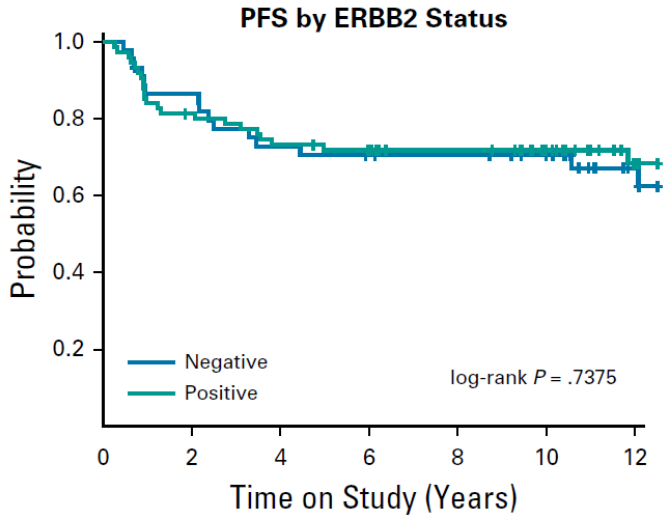
	WNT	SHH	Group3	Group4	Other
LR	<16y			All of the following: · Non-metastatic · Chr. 11 loss	
IR		· TP53 wt (somatic or germline) · No MYCN amplification · Non-metastatic	All of the following: · No MYC amplification · Non-metastatic	All of the following: · Non-metastatic · No Chr. 11 loss	
HR		One or both: · Metastatic · MYCN amplification		Metastatic	
VHR		TP53 mutation (metastatic or non-metastatic)	Metastatic		
Unknown	Metastatic		Non-metastatic with MYC amplification Significance of anaplasia Isochromosome 17q	Significance of anaplasia	Melanotic medulloblastoma Medullomyoblastoma Boundary between Group 3/4 Definition of MYC & MYCN amplification

Ramaswamy et al. Acta Neuropathol. 2016 Jun;131(6):821-31

Clinicomolecular risk factor analysis identified:

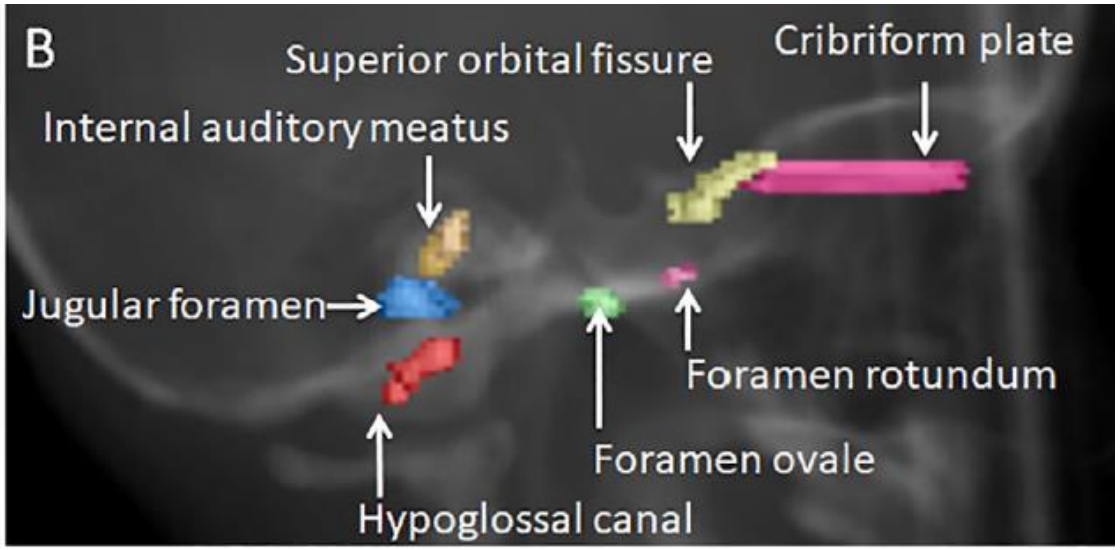
- 3 low-risk groups
  - WNT, low-risk SHH, and low-risk combined groups 3 and 4
  - Excellent survival, 5-year PFS > 90%
- 2 very high-risk groups
  - high-risk SHH and high-risk combined groups 3 and 4
  - Poor survival; 5-year PFS < 60%

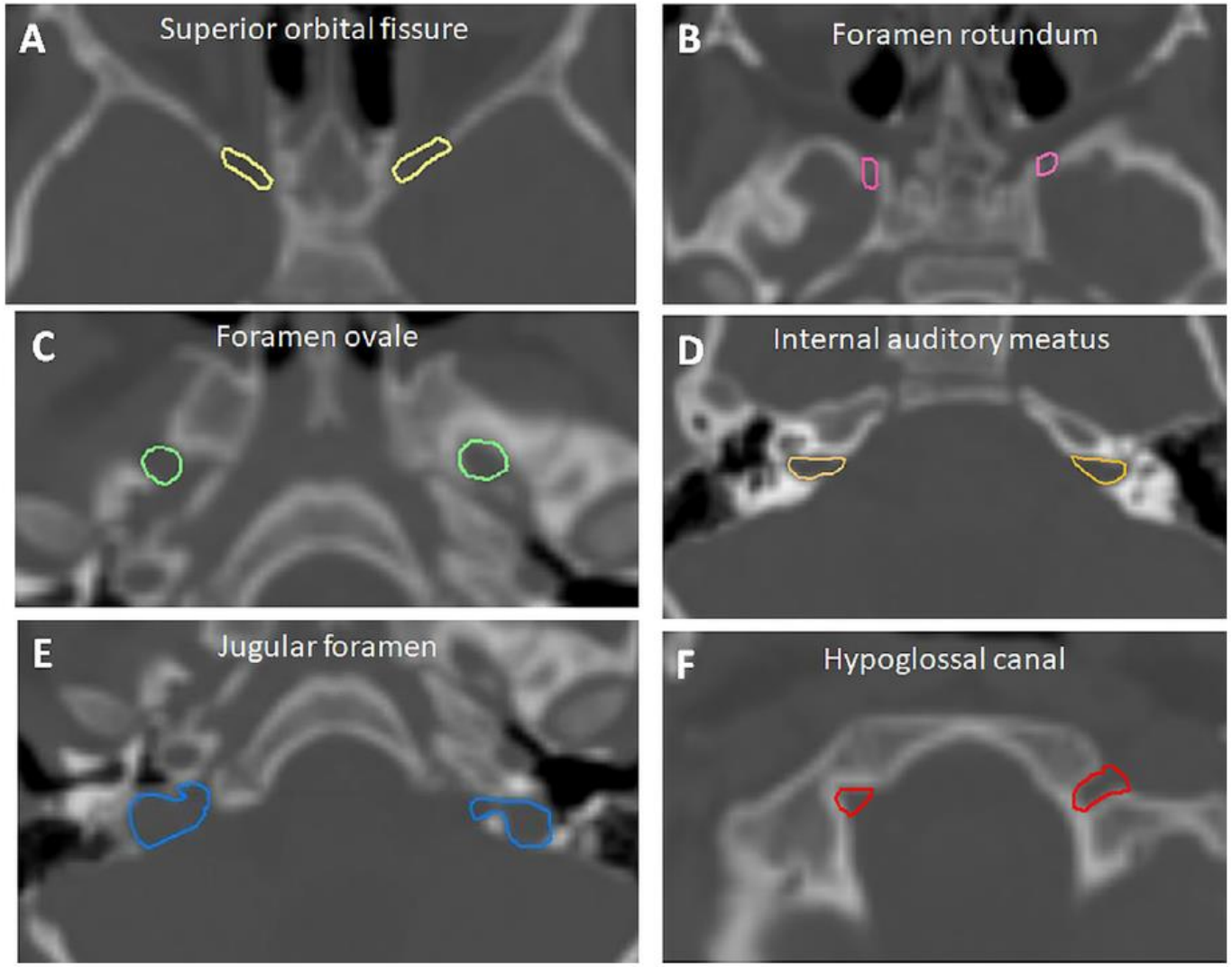




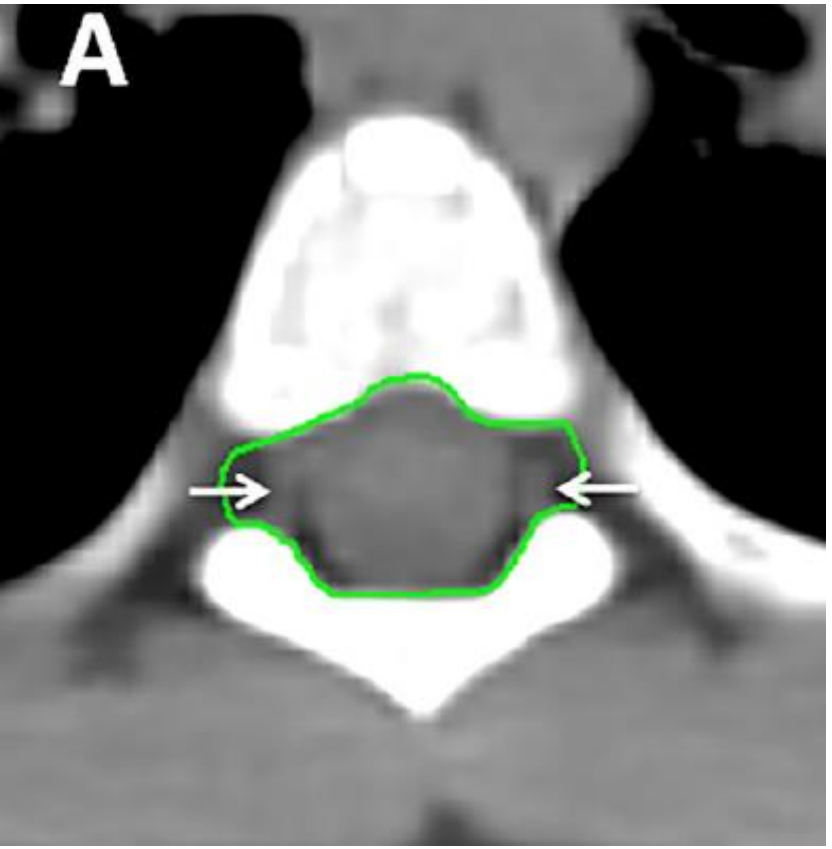
Gajjar et al. J Clin Oncol. 2021 Mar 1;39(7):822-835

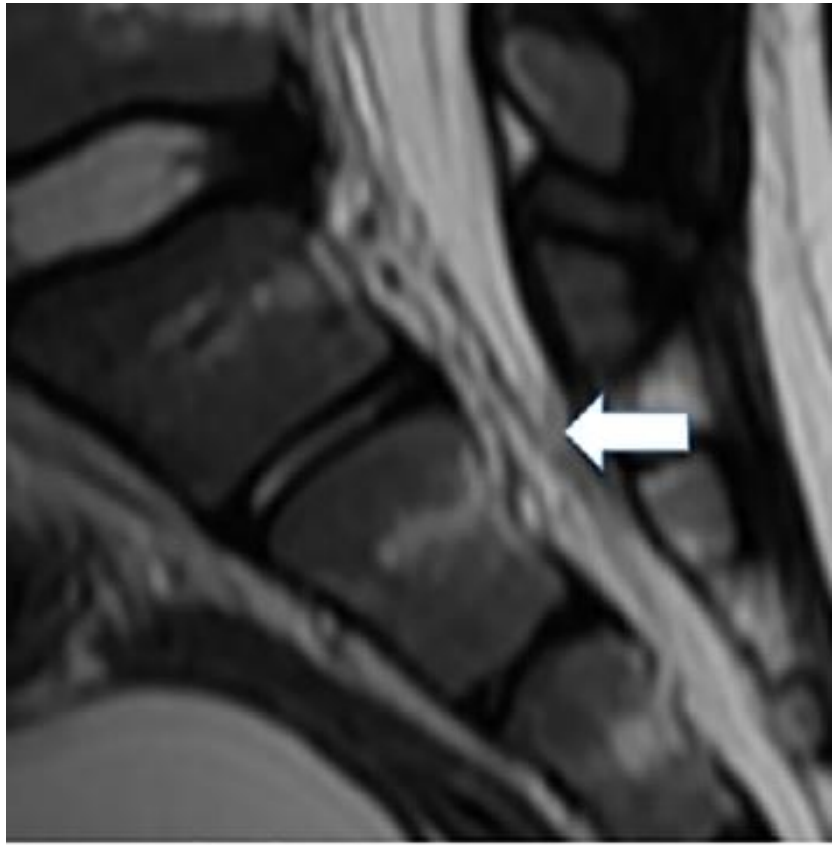
Skull base canals/foramen

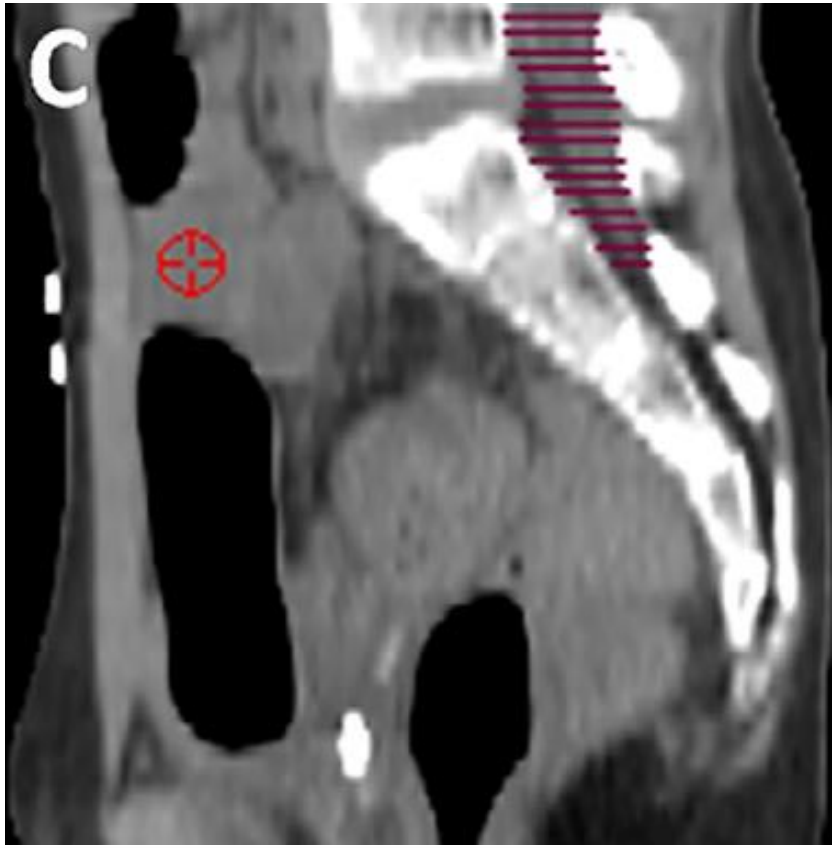




Ajithkumar T et al. Radiother Oncol Actions. 2018 Aug;128(2):192-197.



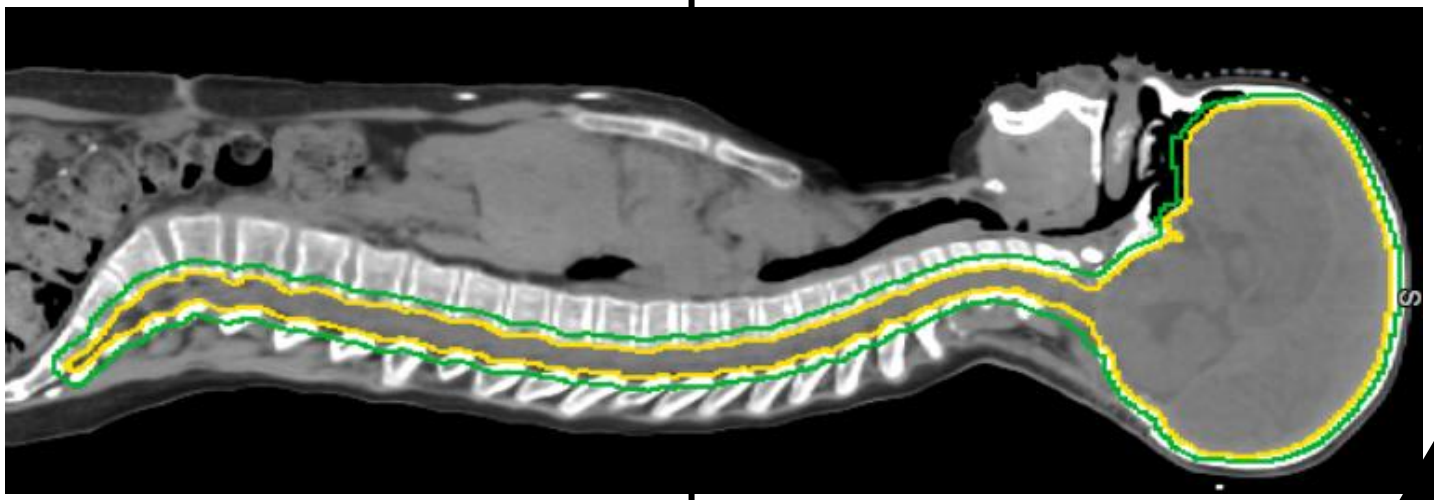




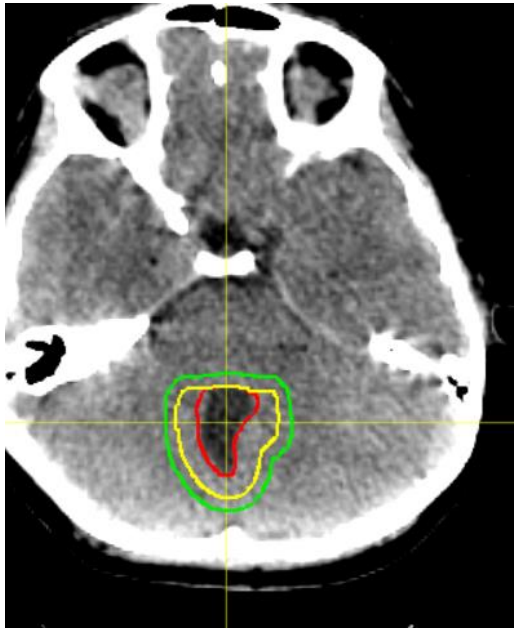
Spine CTV

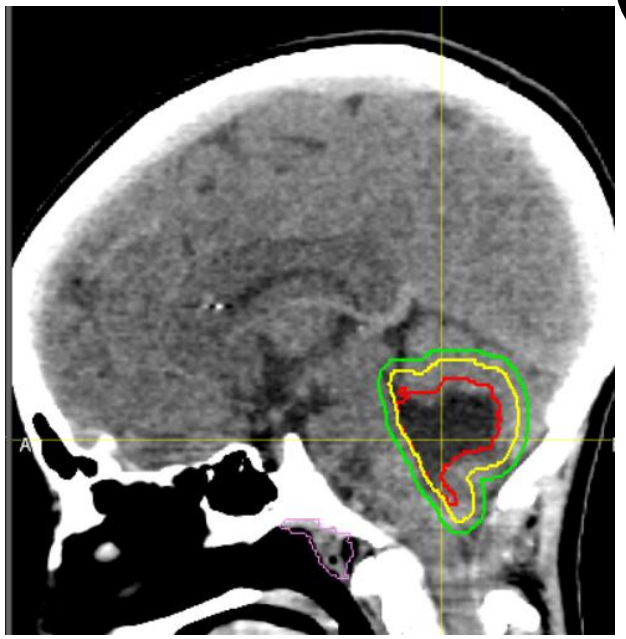
- Include extensions along the nerve roots laterally (A)
- Include thecal sac as identified by MRI - usually the bottom of S1 as an obvious CSF space but there is often elongation which is less obvious extending down to the bottom of S2 or even further inferiorly" (B-C)

Ajithkumar T et al. Radiother Oncol Actions. 2018 Aug;128(2):192-197.



- CTV Brain + CTV Spine = CTV CSI
- PTV Brain = + 3mm
- PTV Spine = + 5mm
- PTV Brain + PTV Spine = PTV CSI





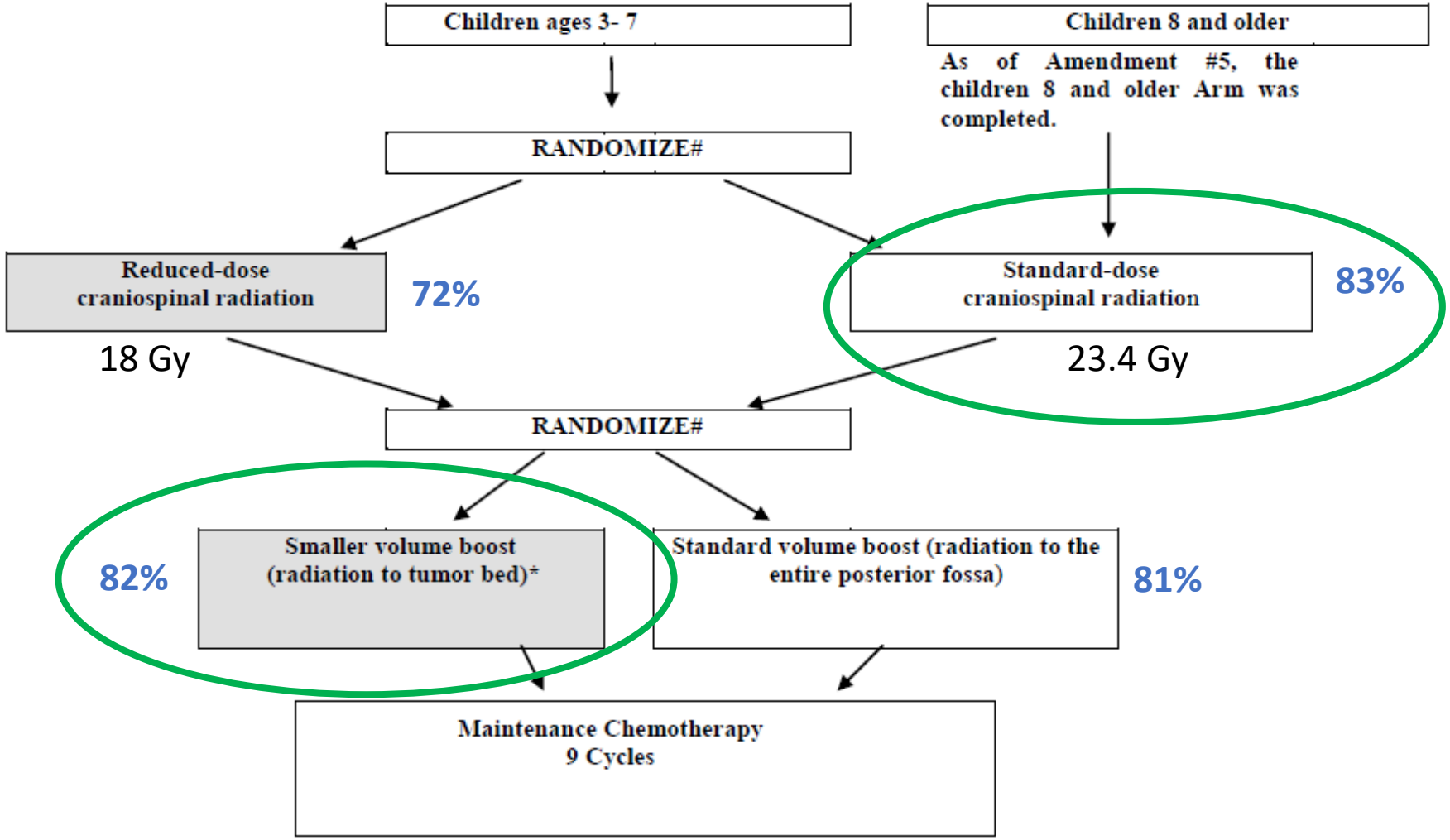
- GTV: residual disease + tumor bed
- CTV: + 5-10mm
- PTV: + 3mm

Include pseduomeningocele if present

Variability across institutions on extending CTV in brainstem

5 year Event Free Survival

ACNS0331



Michalski et al. ASTRO 2016

Toxicity

Acute: dermatitis, alopecia, fatigue, headache, nausea, emesis, diarrhea, cytopenia

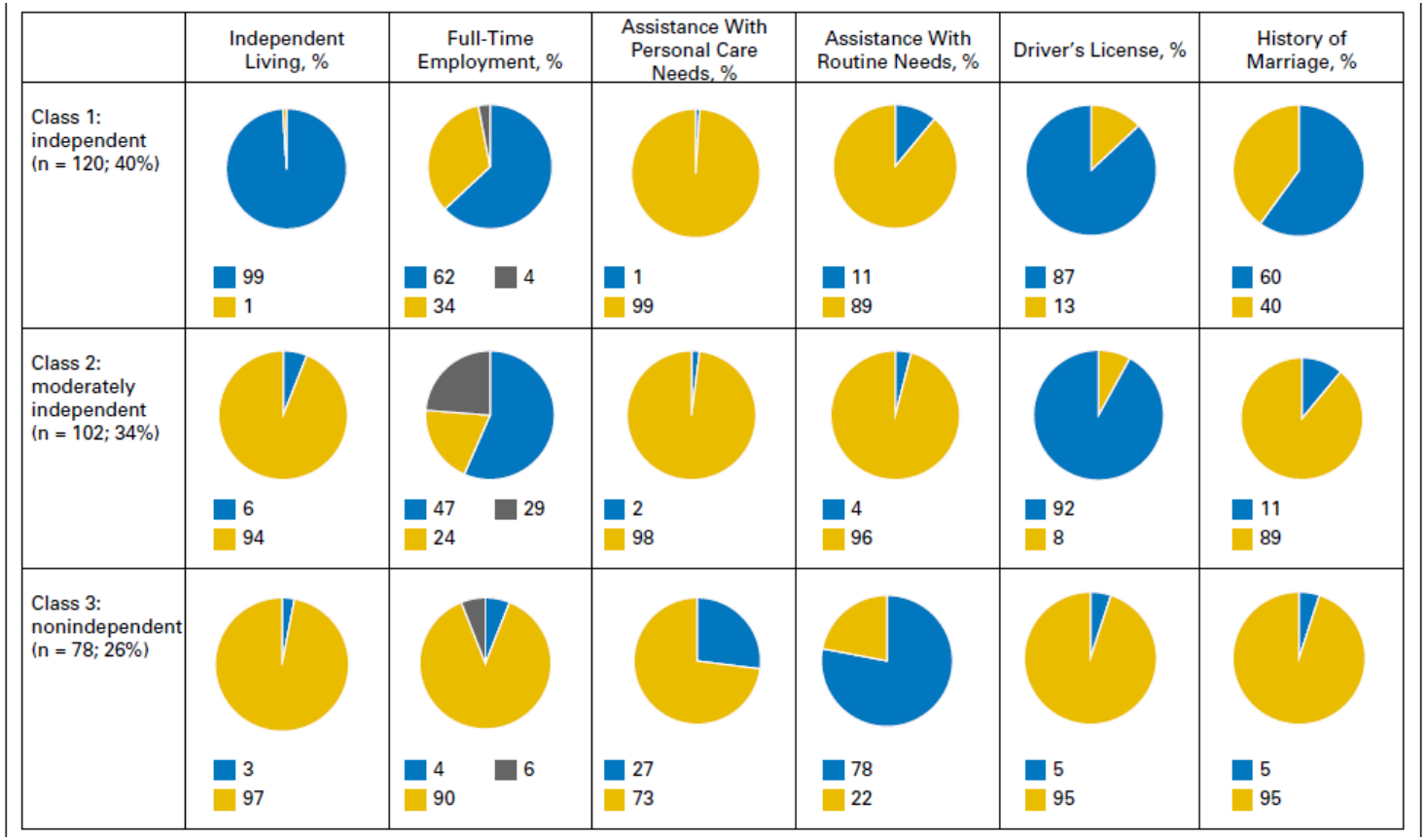
Late: cataracts, hearing loss, neurocognitive dysfunction, endocrinopathy, decreased truncal height, fracture, stroke, necrosis, second malignancy

Table IV. Time from initial surgery to occurrence of serious toxicity.

Deficit	No. of patients	Median time to occurrence from completion of treatment (years)	Range (years)
Serious edema/ herniation	1	0.7	–
Radionecrosis	3	2.81	1.5–10.11
Visual disturbance	1	2.81	–
Cognitive disturbance	7	3.6	0.7–7.2
Hearing deficit	8	8.1	0.5–23
Secondary malignancy	5	12.0	6.4–13.7
Seizures	1	19.5	–
Ataxia	1	20.5	–
Stroke	1	24	–
Basilar aneurysm	1	34.5	–

Christopherson et al. Acta Oncol. . 2014 Apr;53(4):471-80

Toxicity

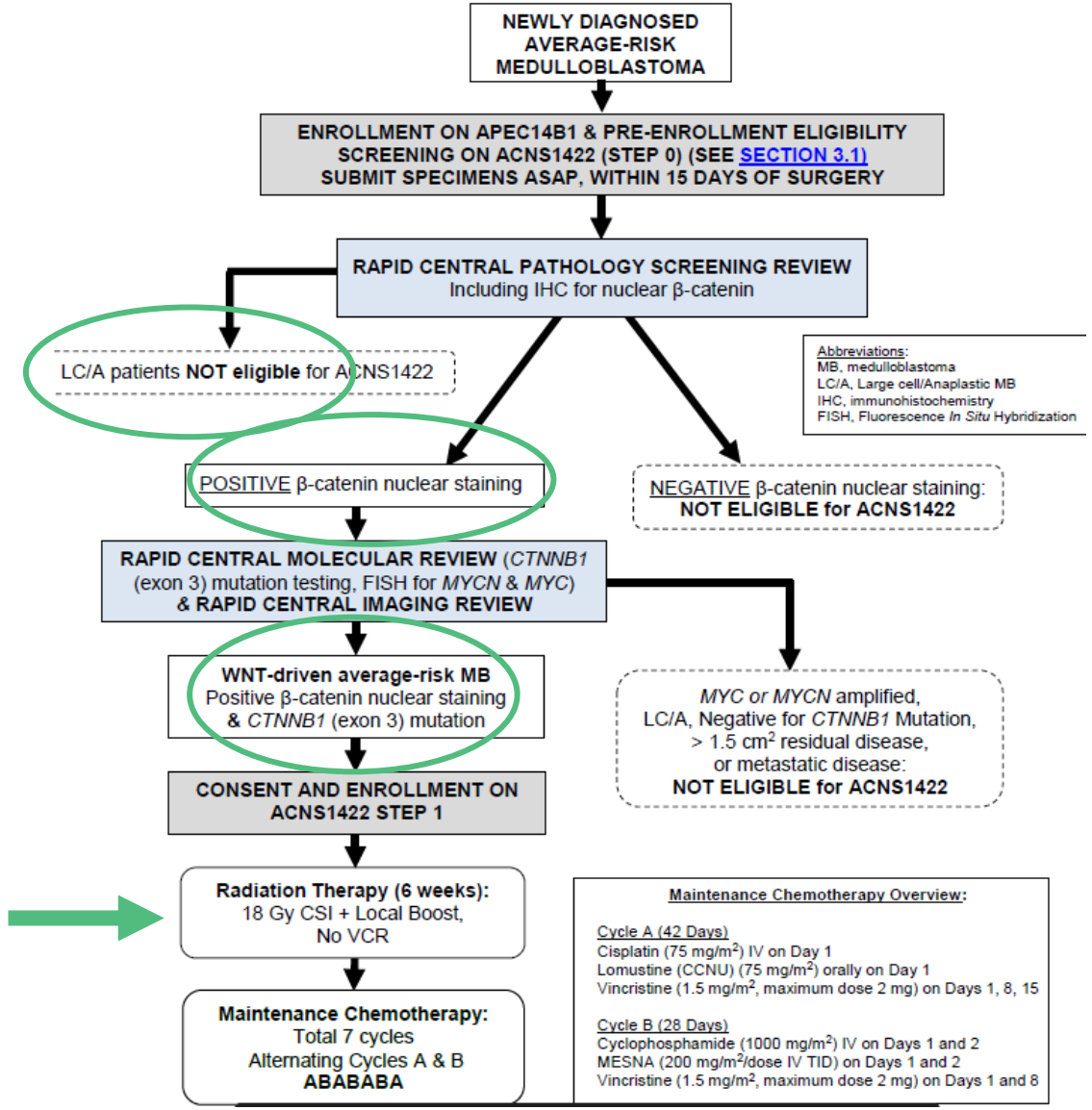


On MVA, decreased likelihood of independence with:

- CSI (OR 4.2)
- Hydrocephalus with shunting (OR 2.6)
- Younger age at diagnosis (OR 1.2)

Brinkman et al. J Clin Oncol. 2018 Sep 20;36(27):2762-2769

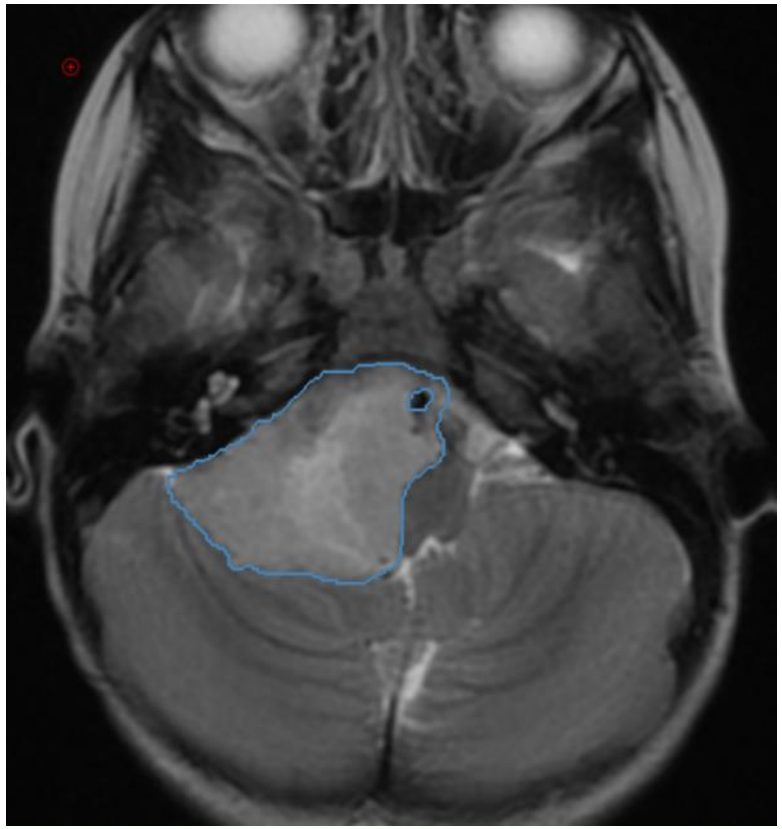
Medulloblastoma: Ongoing considerations



ACNS 1422, phase II

Case 6

- 3 yo boy with ataxia, torticollis, neck pain, and emesis



Intracranial Ependymoma: General Treatment Paradigm

Surgery
- Aim for GTR (*extent of resection strong prognostic factor)
- Histology

WorkUp
- MRI spine, post-op MRI brain within 1-2 days, LP post-op (10-14 days)

RT
- Tumor bed 54-59.4 Gy (CSI to 36 Gy if M+)
- Aim for 1 month post-op

Chemo
- To convert STR to resectable disease or on trial (VCR, Carbo, CPM, Etop)
- Pre or post-RT, not concurrent

*Radiation recommended for all ages with posterior fossa tumors (dose 54 Gy for < 18 months if GTR/NTR) and for all grade 3

Additional work-up: Ophthalmology exam, audiology exam, baseline endocrine labs (baseline and yearly); neurocognitive testing (baseline and q2-3 years

This Case

anaplastic ependymoma, WHO grade III

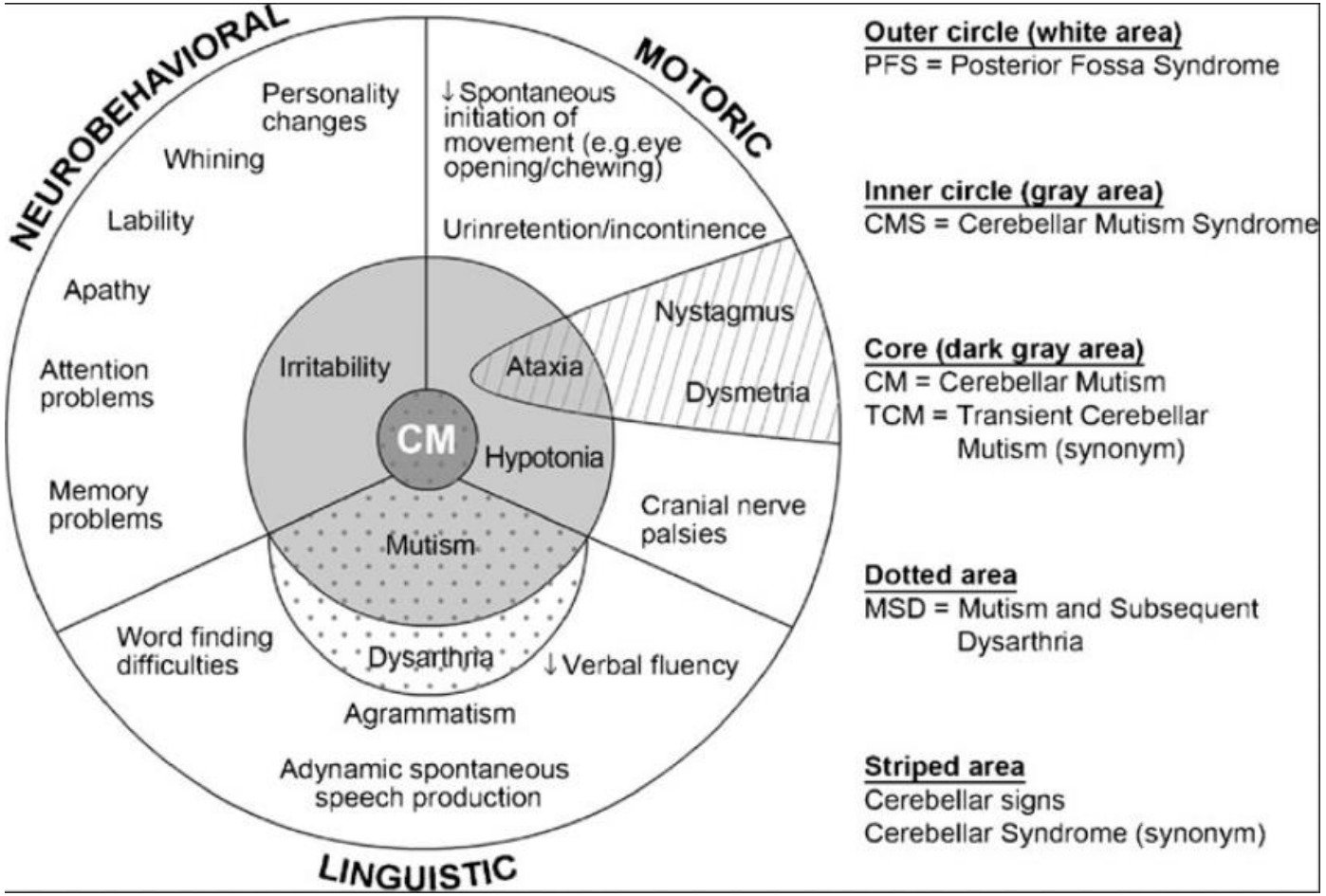
Op Note: "…a small amount of tumor densely adherent to cranial nerves and vascular structures and therefore not safe to remove and was left behind. The tumor was dissected from CN V- XI, vertebral artery, and PICA…"

Negative work-up, M0

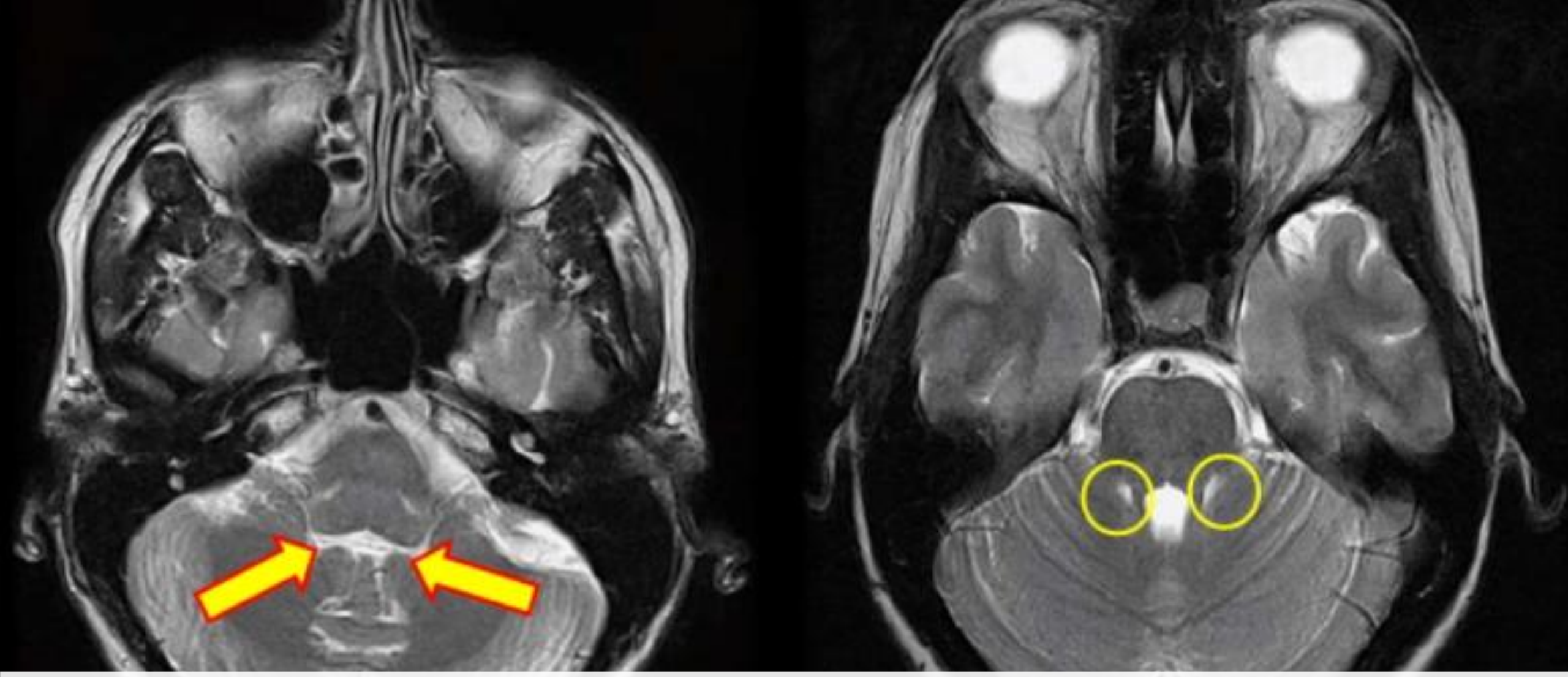
54 Gy in 30 fxs tumor bed + 5mm + 5.4 Gy in 3 fxs to tumor bed = 59.4 Gy

Posterior Fossa Syndrome

- Postop, the child had difficulty swallowing, was unable to speak, and had truncal ataxia
- Should radiation be delayed until these symptoms improve?
- No

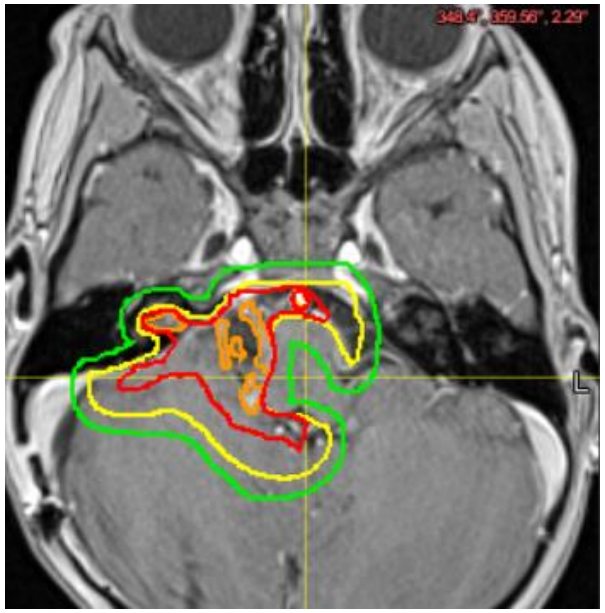


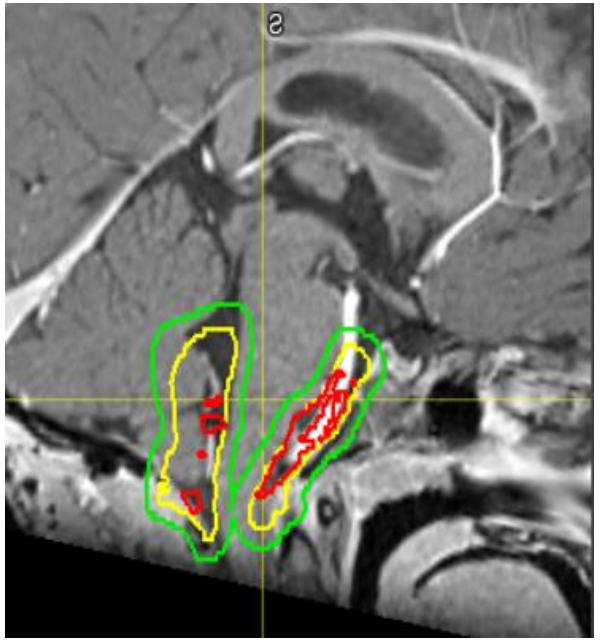
Gudrunardottir et al. Childs Nerv Sys. 2011

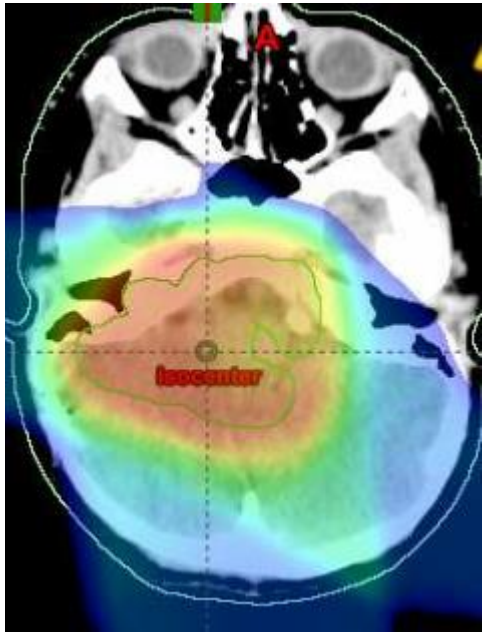


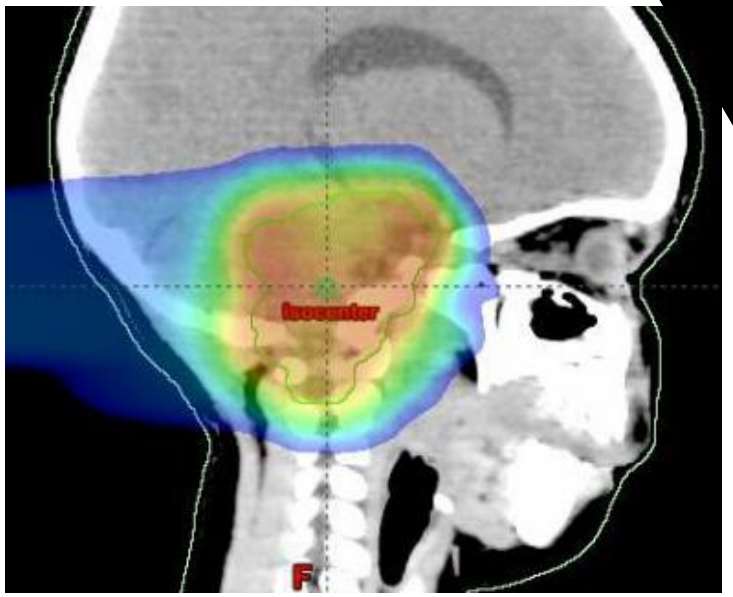
Foramen of Luschka and lateral recess

Brain Sections (slideshare.net)









Initial phase

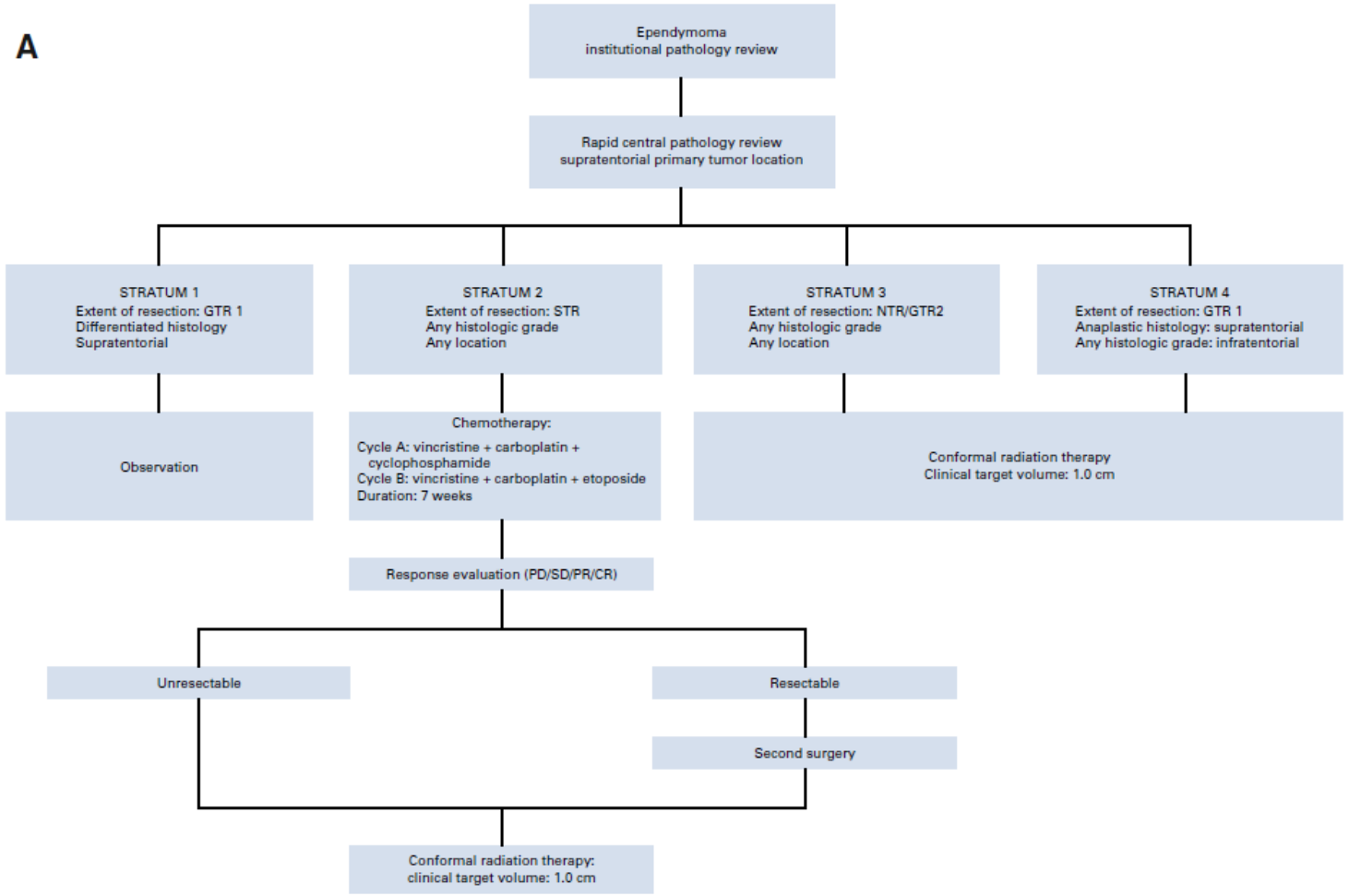
- GTV1: residual disease + tumor bed
- CTV1: + 5-10mm
- PTV1: + 3mm

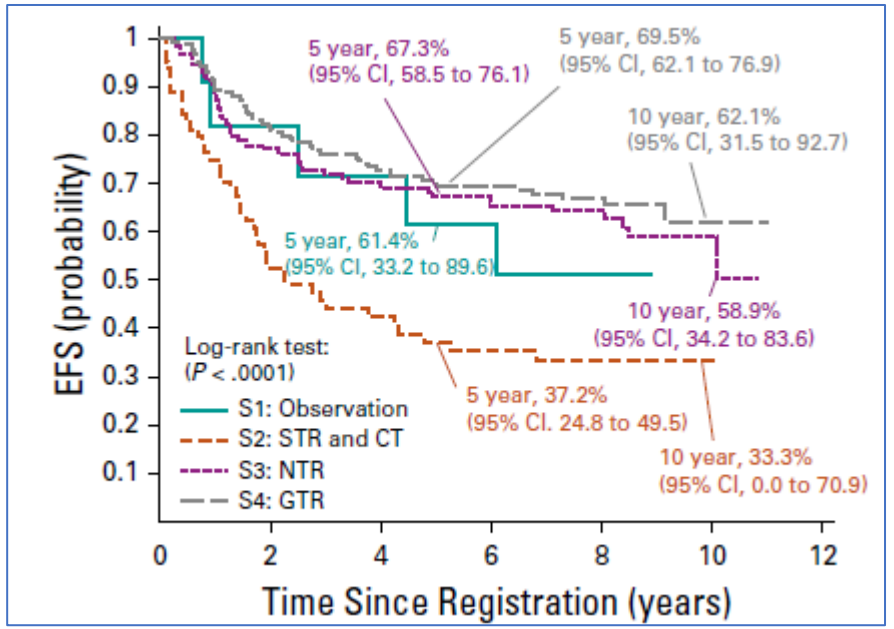
Boost phase

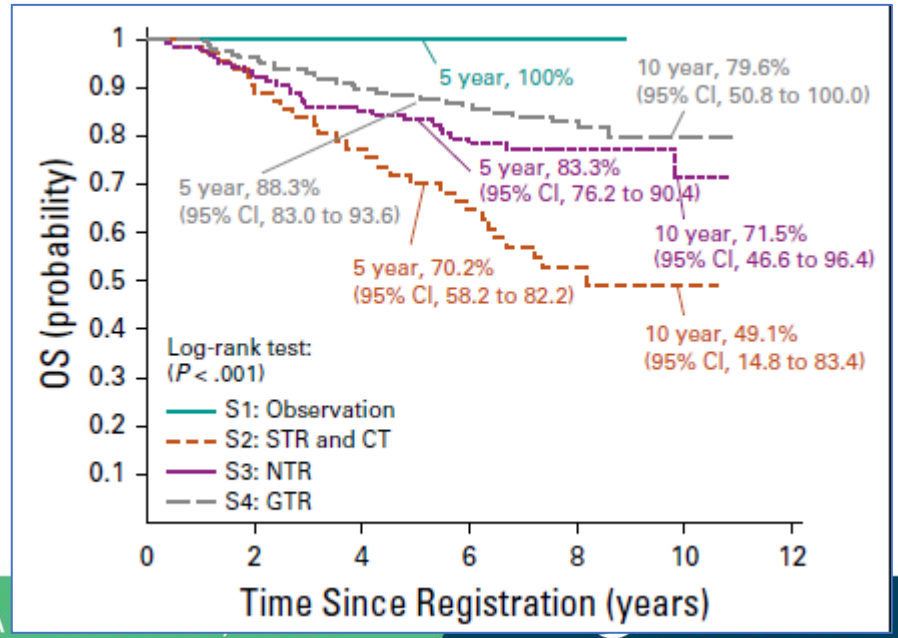
- GTV1 = GTV2 = CTV2
- PTV2: + 3mm

Variability across institutions on extending CTV in brainstem

ACNS0121







29% ≤ 3 years old

Merchant et al J Clin Oncol. 2019 Apr 20;37(12):974-983

Ependymoma: Molecular subtyping

- Outcomes not affected by RELA fusion status or PF-A/PF-B subgrouping by methylation status in ACNS0121
- Inferior outcomes with presence of 1q gain

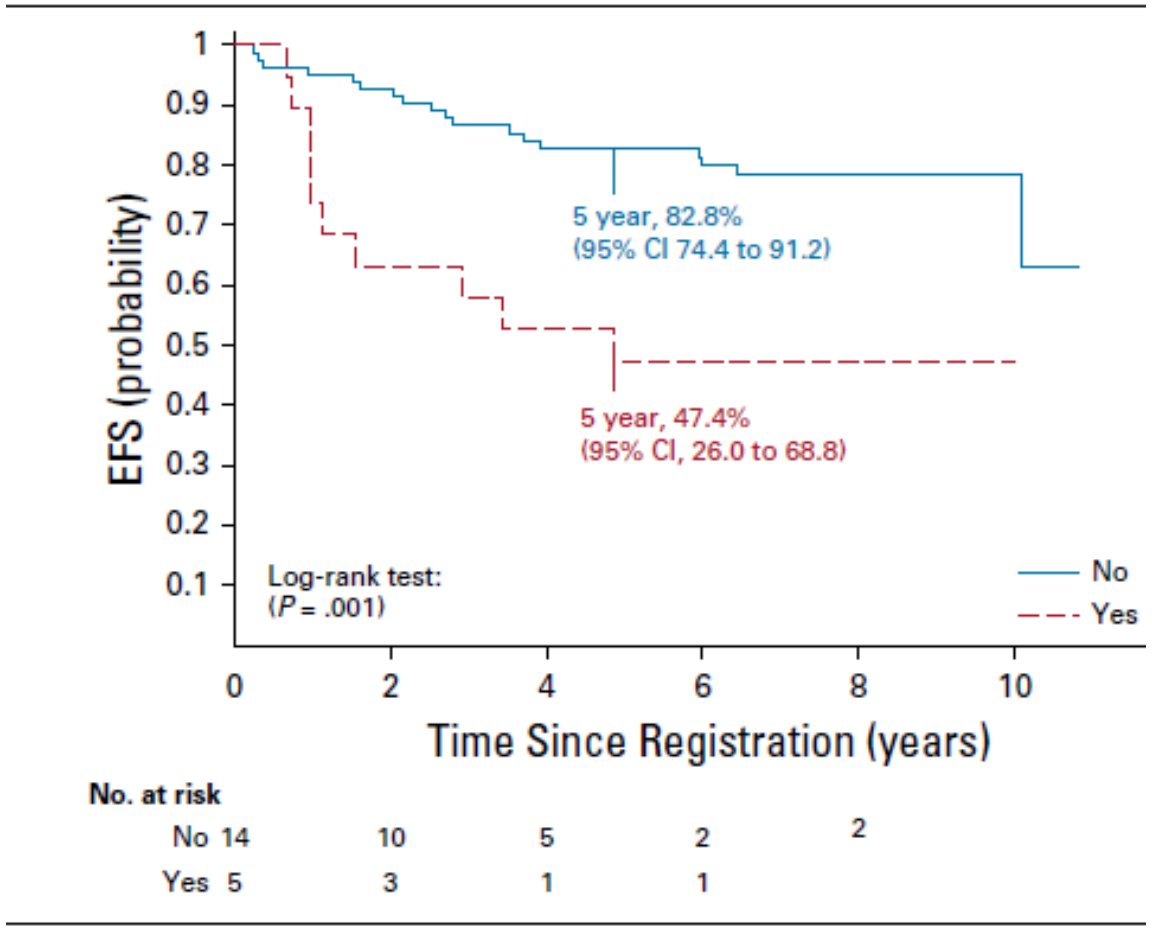
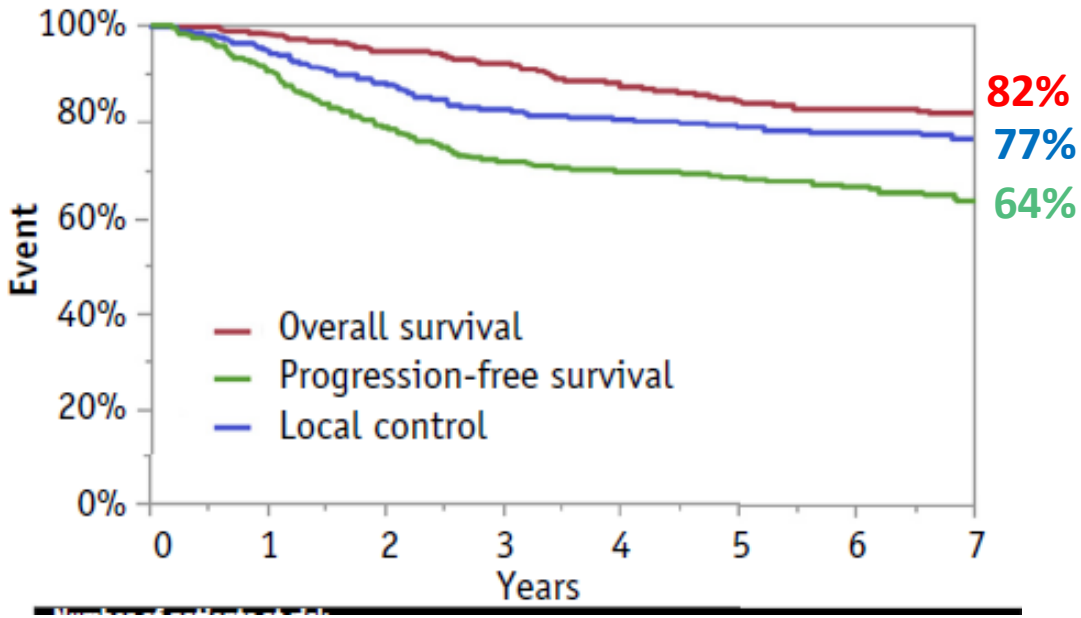


FIG 4. Event-free survival (EFS) for patients treated with immediate postoper radiation therapy (strata 3 and 4) according to 1q gain status.

Merchant et al J Clin Oncol. 2019 Apr 20;37(12):974-983



Toxicity	Incidence	Duration to onset Median (range)	Radiation dose Median (range)	% of those affected < 5 years old
Brainstem necrosis	4%	4 months (3-7)	55.8GyRBE (52.2-59.4)	86%
Symptomatic non-brainstem CNS toxicity*	3.4%	36 months (5-132)	54 GyRBE (52.2-59.4)	100%
Second malignancy	1.3%	8 years (4-14)	Within high dose volume	80%

*vascular events, non-brainstem necrosis

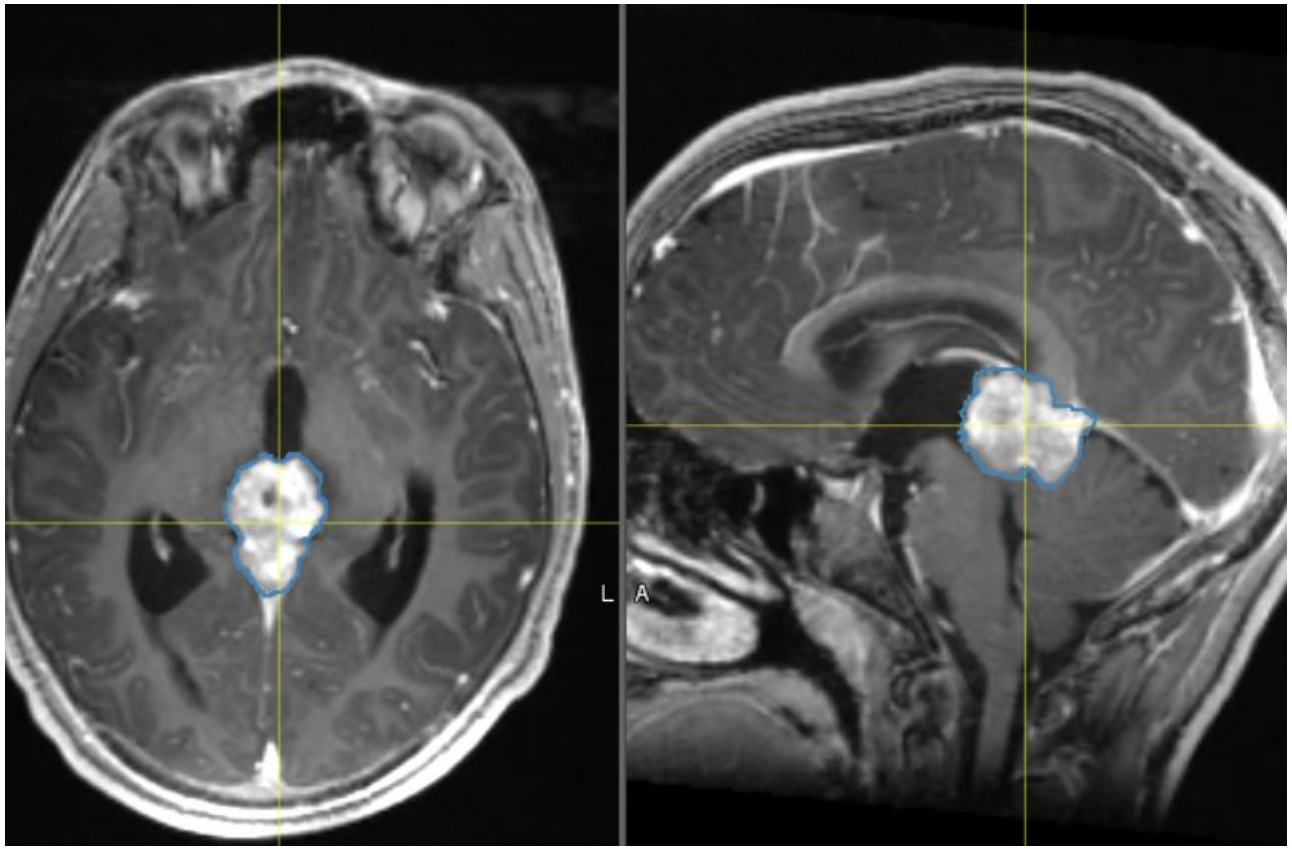
Outcomes: Intracranial Ependymoma

- Acute: dermatitis, alopecia, fatigue, headache, nausea, emesis
- Late: hearing loss, neurocognitive dysfunction, endocrinopathy, brainstem necrosis, second malignancy

Indelicato et al. Int J Radiat Oncol Biol Phys. 2021 Jan 27;S0360-3016(21)

Case 7

- 12 yo boy who enjoys riding his hoverboard presents with progressive headaches x 4 months



	GERMINOMA	NON-GERMINOMA
Tumor markers (serum & CSF)	AFP normal, βHCG normal to mild ↑	↑ AFP or ↑ βHCG possible
Biopsy	Required	Not required if tumor markers elevated but helpful to know histologic subtype
MRI spine and LP	Yes	Yes
Treatment paradigm	Chemo → Sx if incomplete response → RT Alternative: RT alone	Maximal safe resection → chemo → RT
Chemo drugs	Carboplatin & etoposide x 4 cycles Q 3 weeks	Carboplatin, etoposide, ifosfamide x 6 cycles induction, Q 3 weeks
Radiation volume for M0 disease	Whole ventricle + primary site boost	CSI + primary site boost
Radiation dose	PostChemo: 18 or 24 Gy WVV, 12 Gy boost to primary site @ 1.5 Gy/fx RT alone: WVV 25 Gy, 20-25.4 Gy boost	36 Gy CSI, 18 Gy boost to primary site @ 1.8 Gy/fx
Prognosis (5 yr PFS/OS)	88%/93%	60%/68%

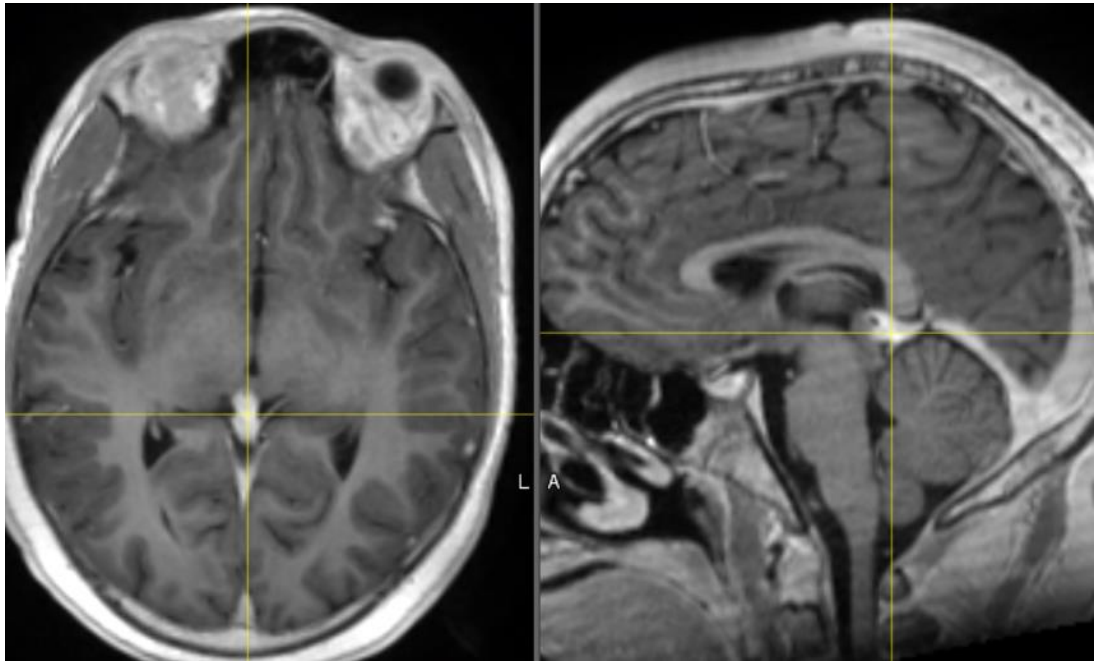
Treatment course

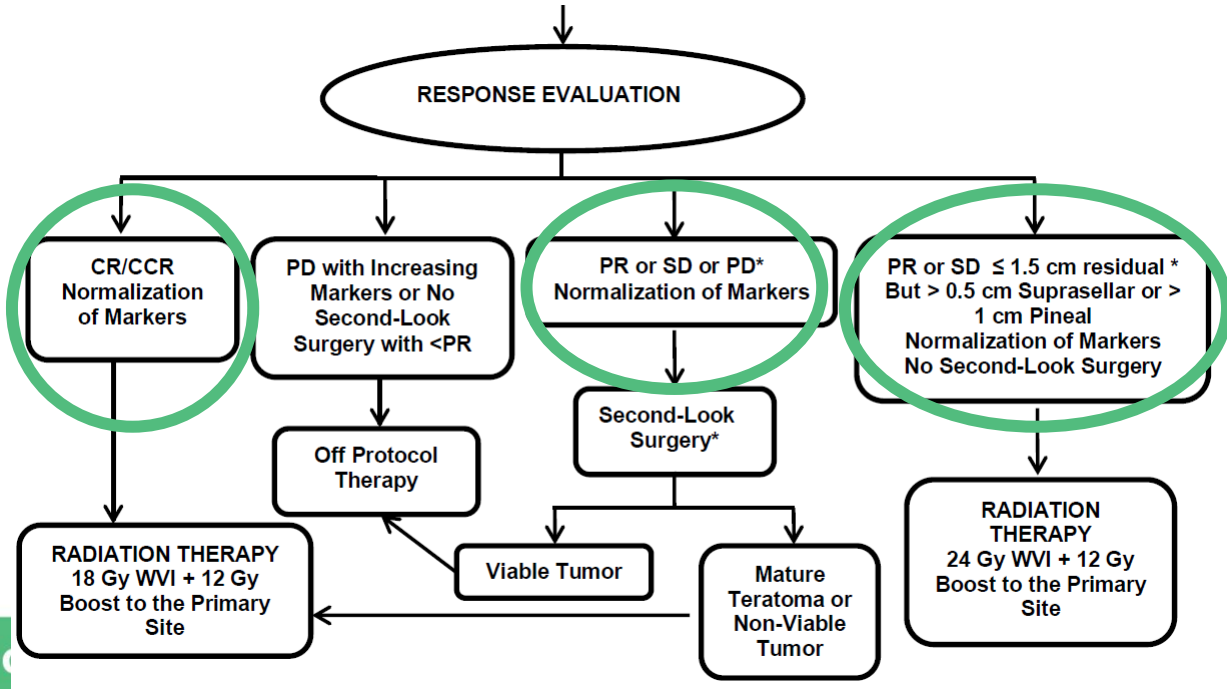
3rd ventriculostomy with biopsy: germinoma

Carboplatin/etoposide x 4 cycles

Post-chemo MRI brain: 14 x 7 x 6mm

24 Gy WVV; 12 Gy boost

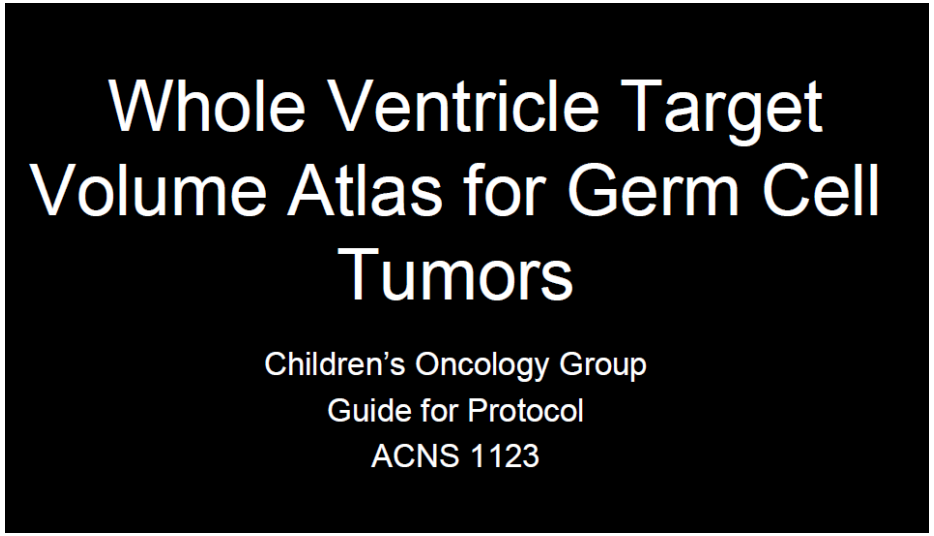


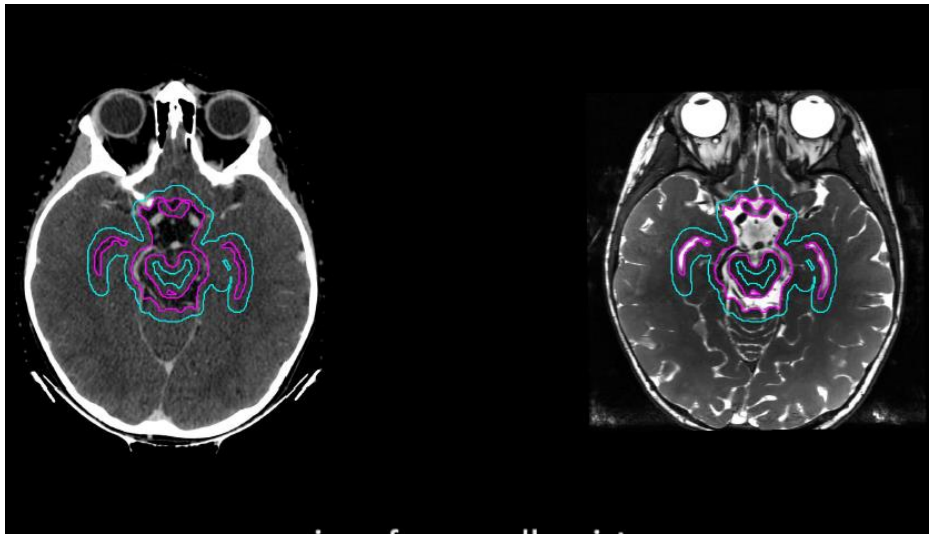


ACNS1123

Tips for whole ventricular delineation

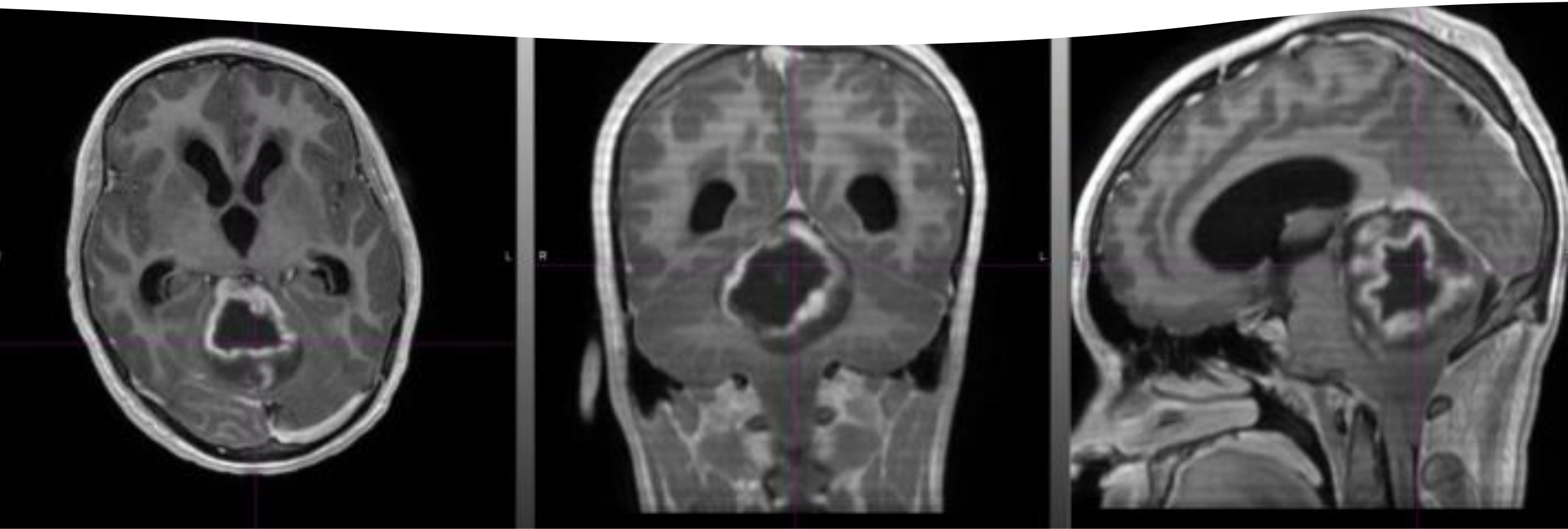
- Encompass the lateral, 3rd and 4th ventricles suprasellar and pineal cisterns
- Include prepontine cistern in WVV CTV if 3rd ventriculostomy or large suprasellar tumor
- Ensure that initial WVV CTV encompasses the entire primary site boost CTV
- WVV contouring atlas @ https://www.qarc.org/cog/ACNS1123_Atlas.pdf
- Need thin slice MRI (1-2mm); fuse and use T1 and **T2** sequences

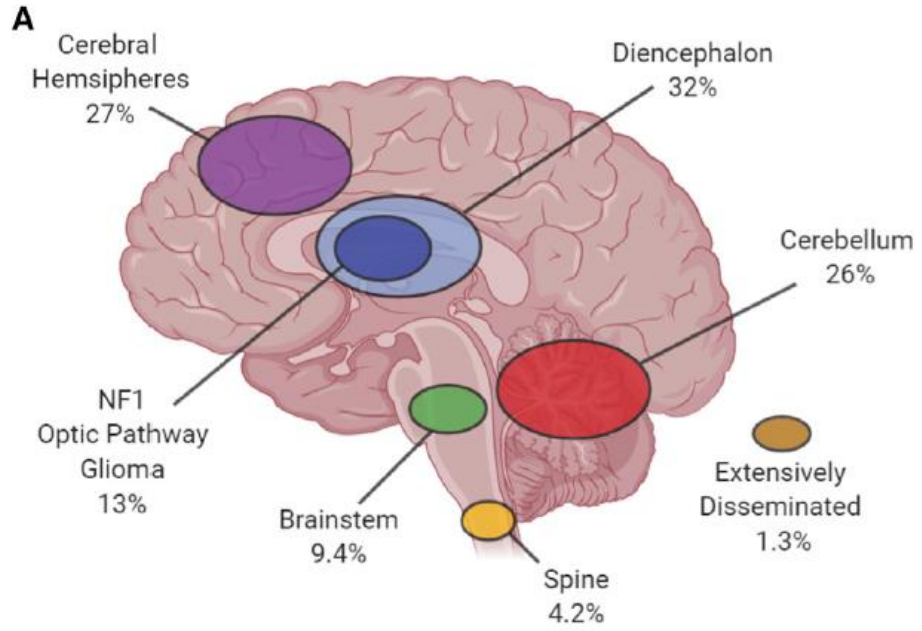


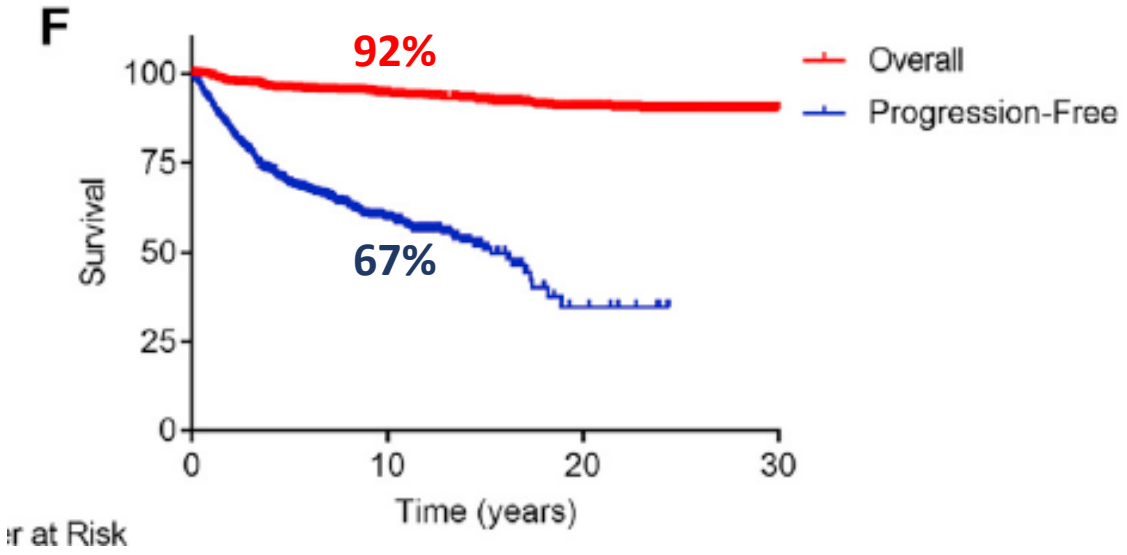


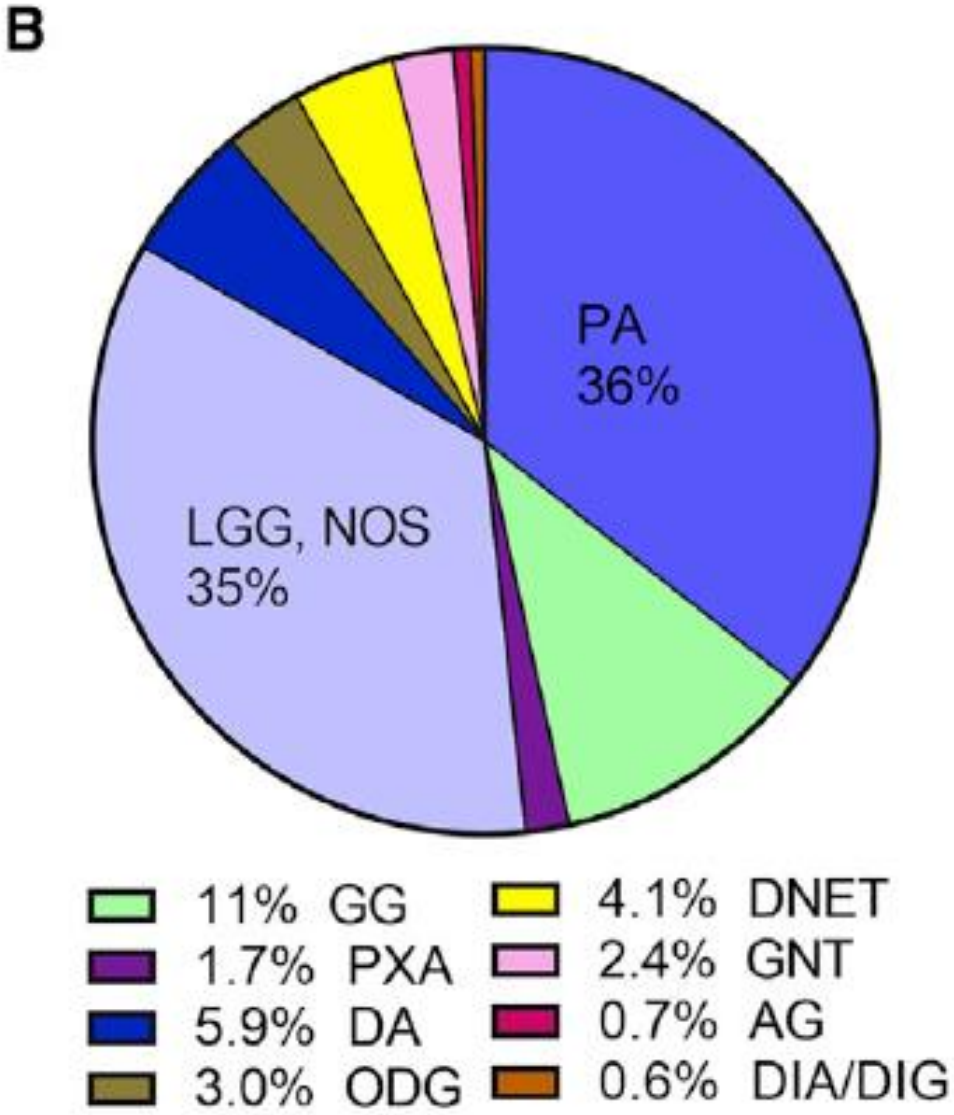
Case 8

- 16 yo boy presented with headaches, sluggishness, left facial droop and shaking
- MRI brain
- EVD placement and STR
- Pathology: WHO Grade I pilocytoic astrocytoma, IDH-1 equivocal, +GFAP, Ki-67 <1%, BRAF V600E negative, BRAF rearranged by FISH
- 2.7cm residual tumor on post-op MRI

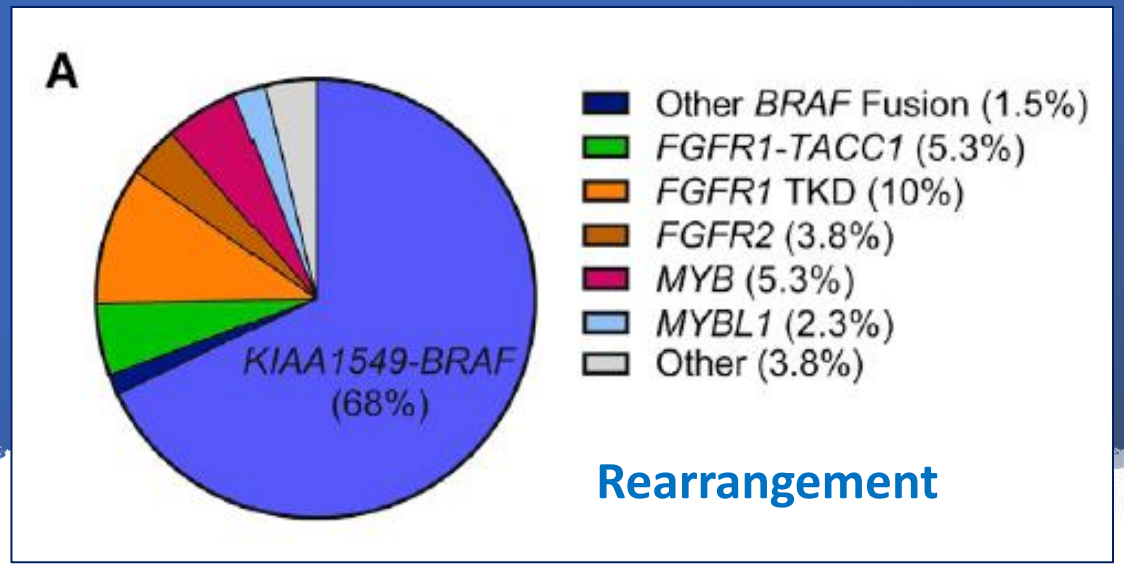


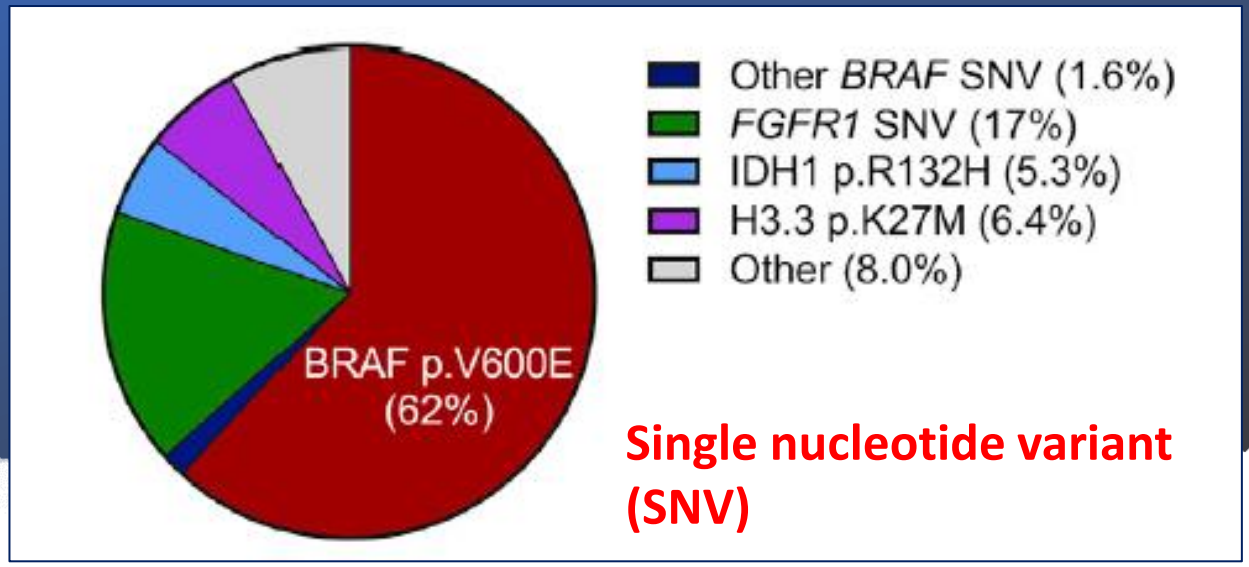


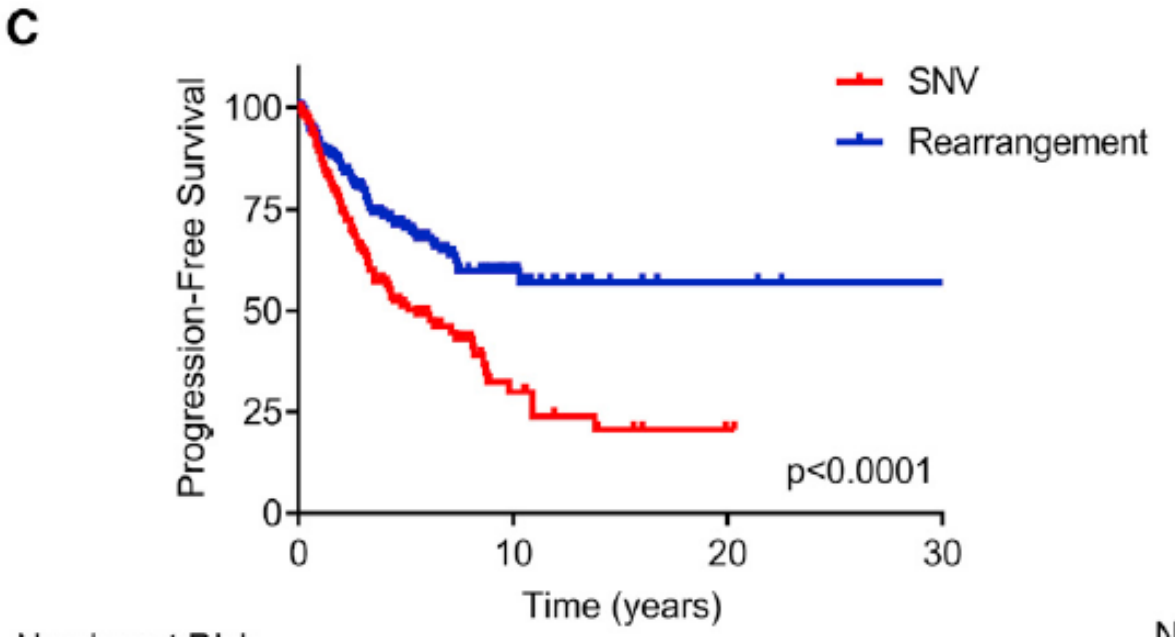


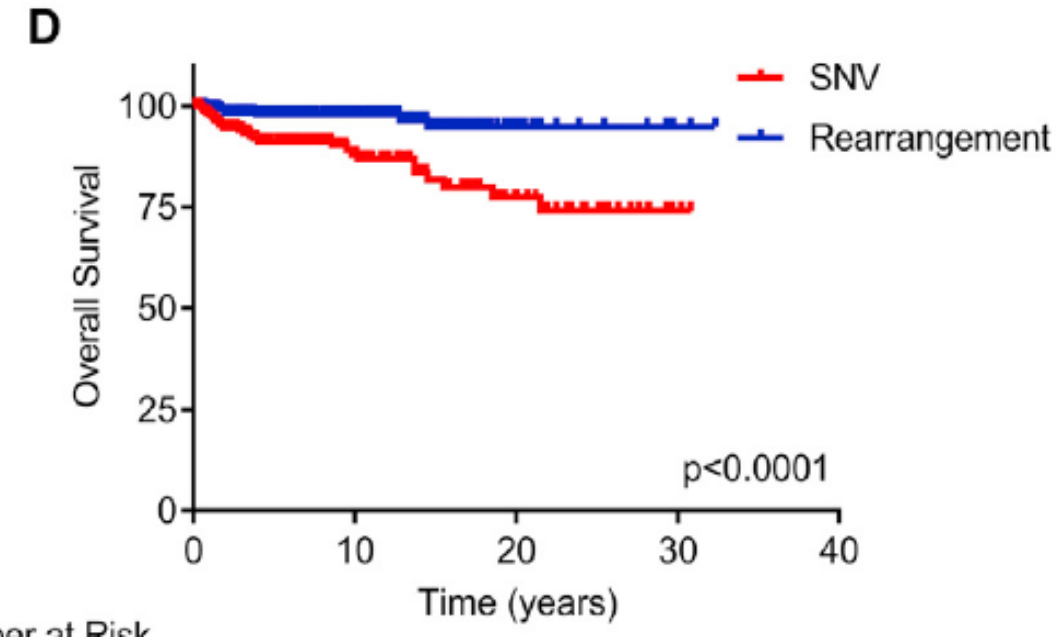


Ryall et al. Cancer Cell. 2020 Apr 13;37(4):569-583.e5



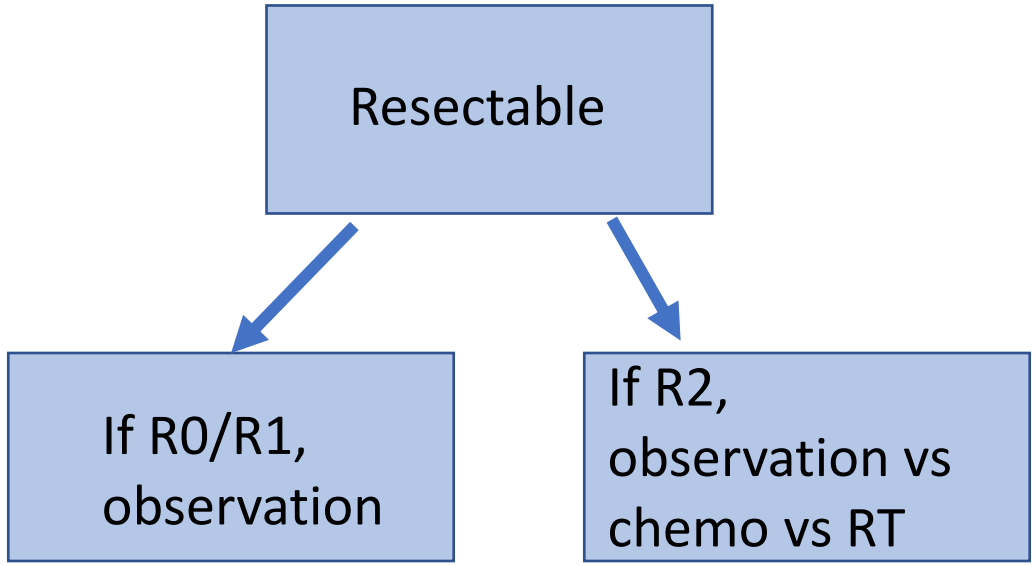


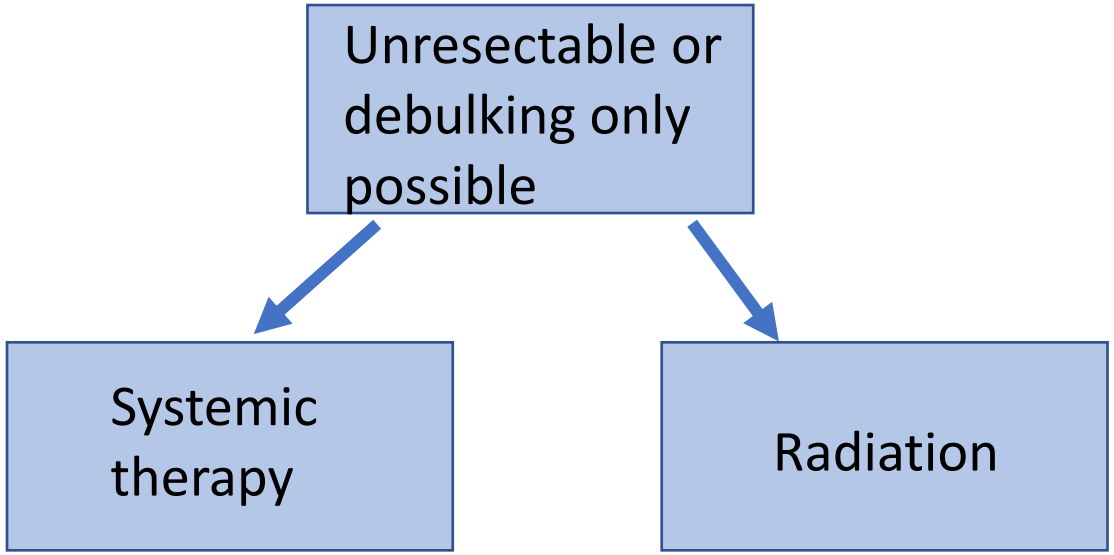




Ryall et al. Cancer Cell. 2020 Apr 13;37(4):569-583.e5

LGG: Treatment paradigm



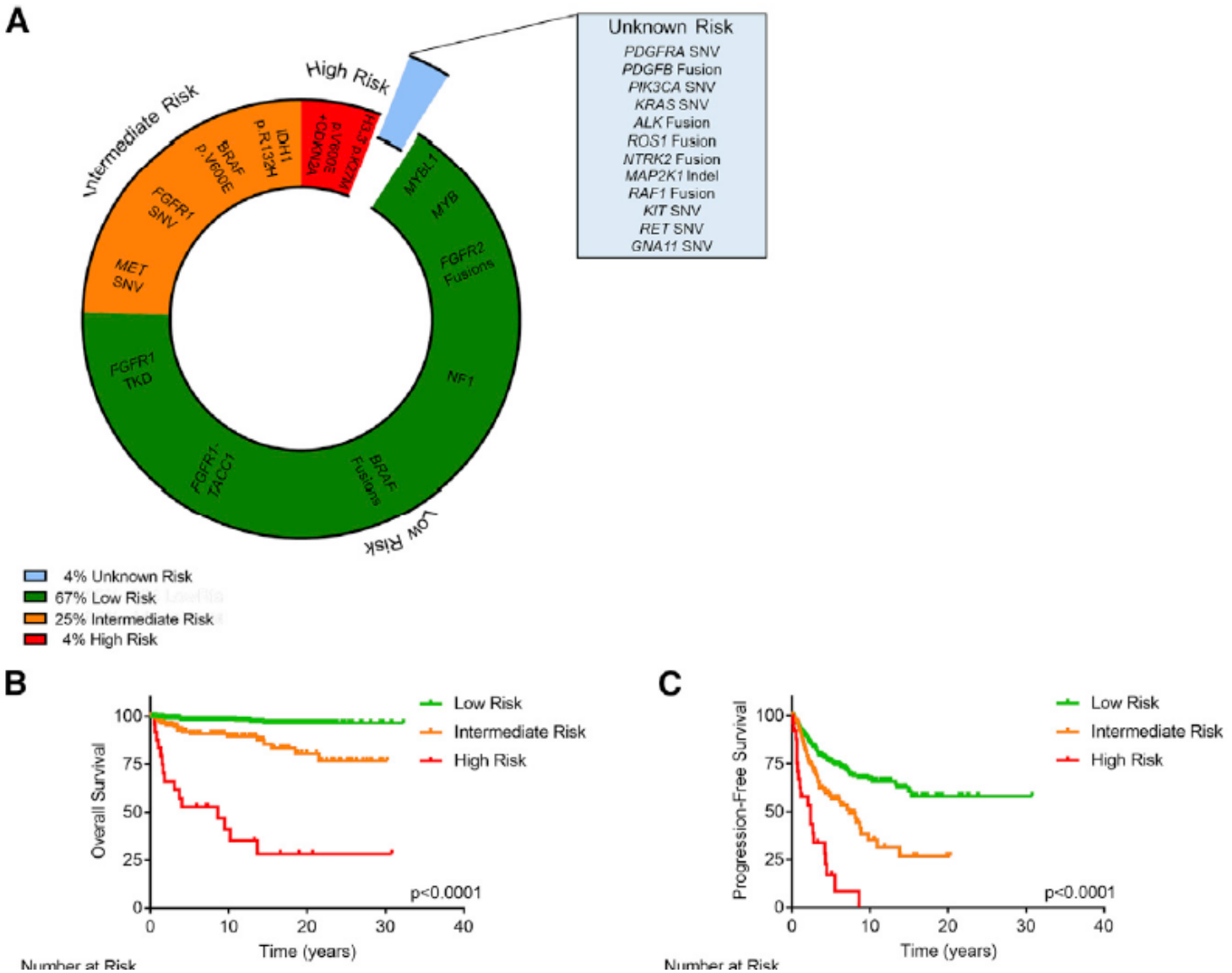


3 yr PFS 52-83%
Younger children
NF-1
Common regimens: carbo/Vcr, TPCV, vinblastine alone
Novel agents, eg Dabrafenib (BRAF inhibitor), Selumetnib (MEK inhibition)

5 yr PFS > 80%
Older children
Dose 50.4-54 Gy at 1.8 Gy/fx
0.5cm CTV margin
0.3mm PTV margin

de Blank et al. Curr Opin Pediatr. 2019 Feb;31(1):21-27

LGG: Ongoing considerations



Ryall et al. Cancer Cell. 2020 Apr 13;37(4):569-583.e5

Pseudoprogression

Definition: increase in tumor size by ≥10% in at least two dimensions between two and three consecutive MR imaging studies

10-year cumulative incidence of **29.0%**

Median time to pseudoprogression**: 6 months after RT.**

More common in **pilocytic astrocytoma** (43%)

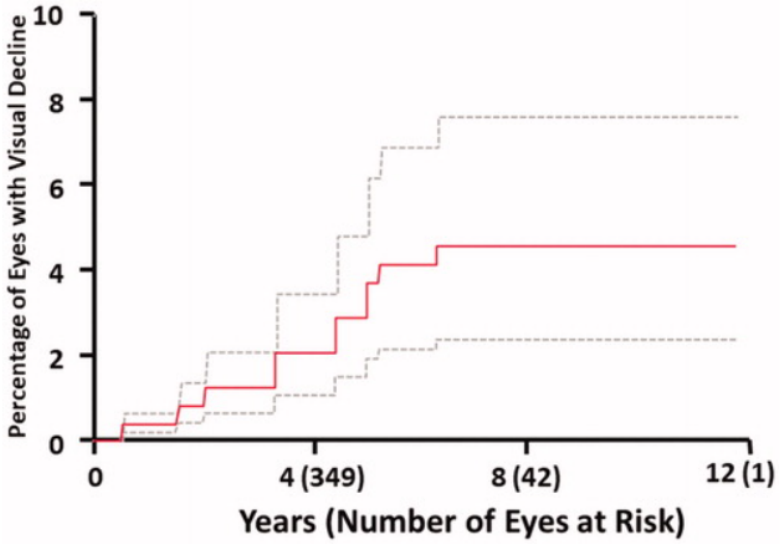
For those with PA, improved 10-year EFS (84.5% vs. 58.5%, P = 0.008) and OS (98.0% vs. 91.2%, P = 0.03) if pseudoprogression

Indelicato et al. Int J Radiat Oncol Biol Phys 2019 May 1;104(1):149-156

Tsang et al. J Neurooncol. 2017 Nov;135(2):371-379

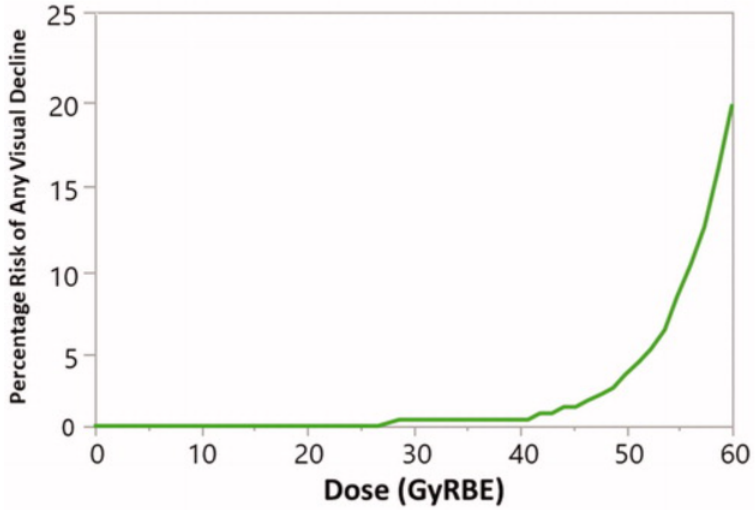
Visual toxicity

Figure 1. Cumulative incidence of visual acuity decline in the eyes of children treated with radiotherapy for intracranial tumors and at high risk of acuity decline.



- All visual decline occurred in children with primary tumors of the optic pathway or suprasellar region.

Figure 2. Logistic regression model of the risk of visual acuity decline by radiotherapy dose to 0.1 cm^3 of the ipsilateral optic nerve or optic chiasm.



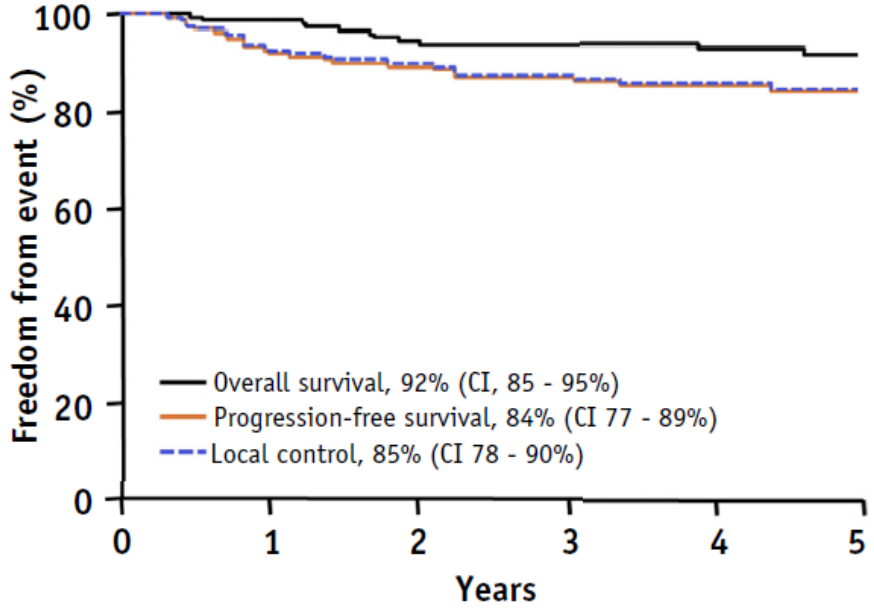
Risk of decline in visual acuity	Dose to 0.1 cm^3 ipsilateral optic nerve or chiasm
1%	52.7 GyRBE
5%	56.6 GyRBE
10%	58.3 GyRBE

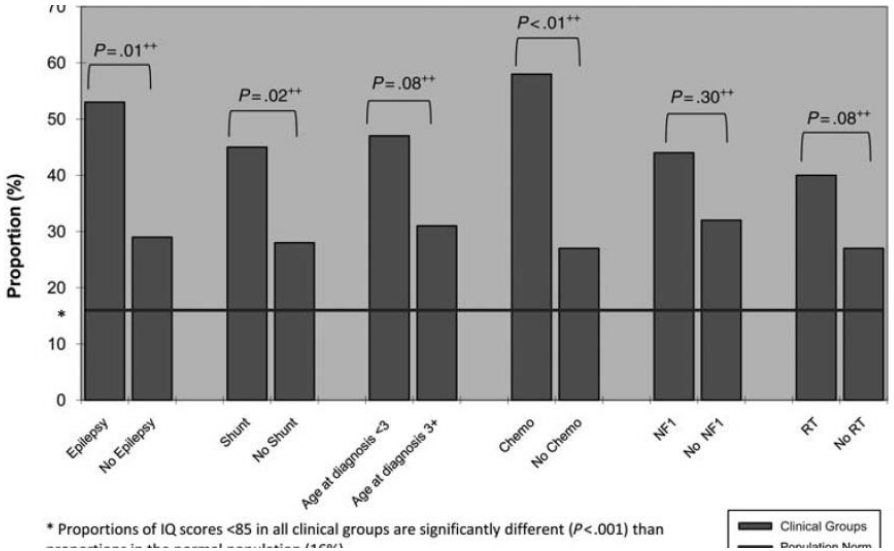
Bates et al. Acta Oncol. 2020 Oct;59(10):1257-1262

Outcomes: LGG

Acute: dermatitis, alopecia, fatigue, headache, nausea, emesis

Late: retinopathy, hearing loss (2%), neurocognitive dysfunction, endocrinopathy (22%), stroke, vasculopathy (3%), necrosis, second malignancy

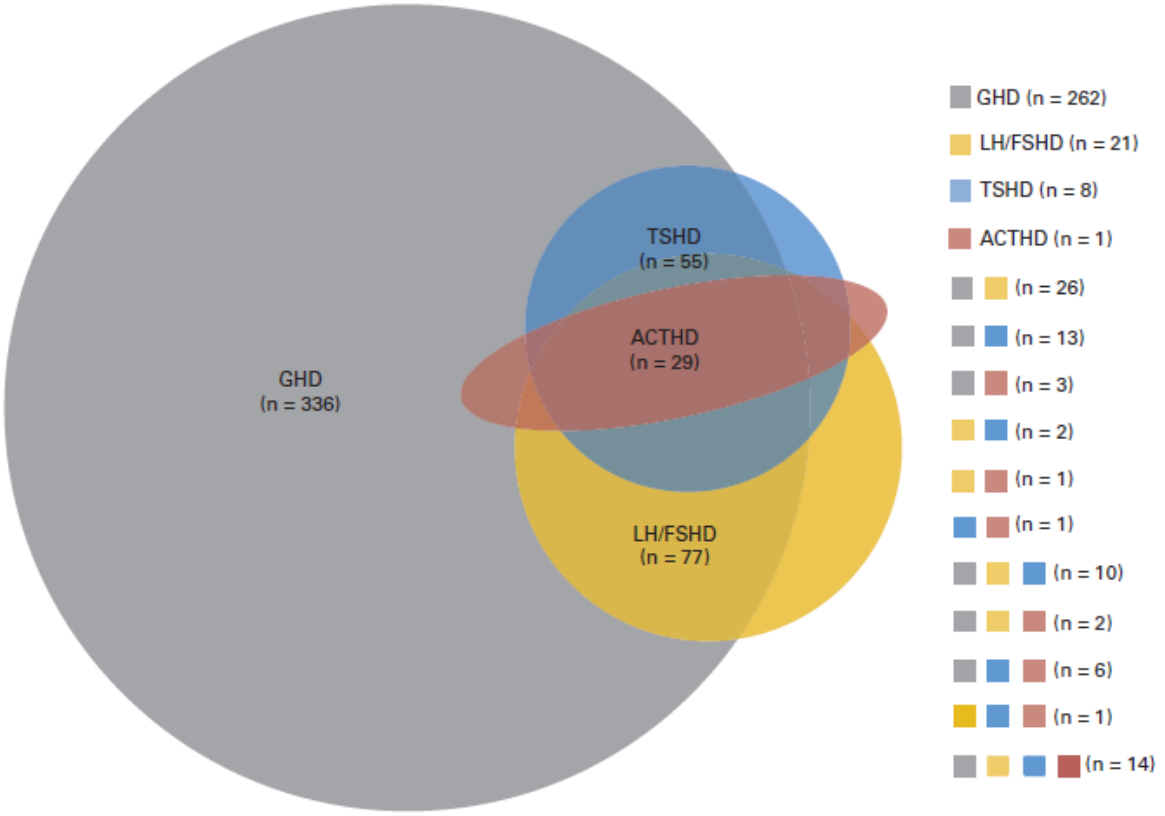




Indelicato et al. Int J Radiat Oncol Biol Phys. 2019 May 1;104(1):149-156

Armstrong et al. Neuro Oncol. 2011 Feb;13(2):223-34

Endocrinopathy after cranial irradiation



	Probability of GH Deficiency (peak GH <7ng/ml) by Mean Hypothalamus Dose and Time											
Time	5Gy	10Gy	15Gy	20Gy	25Gy	30Gy	35Gy	40Gy	45Gy	50Gy	55Gy	60Gy
12mo	12%	14%	17%	19%	22%	25%	28%	31%	34%	38%	42%	45%
36mo	11%	18%	26%	37%	48%	59%	70%	79%	86%	91%	95%	97%
60mo	11%	22%	39%	57%	75%	87%	95%	98%	99%	100%	100%	100%

Chemaitilly et al. JCO. 2015 Feb 10;33(5):492-500

Merchant, ASTRO 2009

General Takeaways

- Important to know overall management in addition to the details of radiotherapy
- Use of molecular markers for prognosis and to direct treatment is increasing
- When there is a choice of surgery vs RT for local therapy, consider risks to form and function with each approach
- Long-term follow-up with active monitoring for toxicity is critical