ARROCase: Neuroblastoma

Resident: Clayton B. Hess, MD (Radiation Oncology)
Staff: Ruben C. Fragoso, MD, PhD (Radiation Oncology)
Jonathon M. Ducore, MD, MPH (Pediatric Oncology)
Regina F. Gandour-Edwards, MD (Pathology)
Cameron Foster, MD (Nuclear Medicine)

University of California Davis Comprehensive Cancer Center

Outline

- Case Presentation
- Overview
- Etiology
- Epidemiology/Presentation
- Work-up
- Risk Stratification
- General Management
  - Low Risk
  - Intermediate Risk
  - High Risk
- Radiation Treatment Planning

Case Presentation

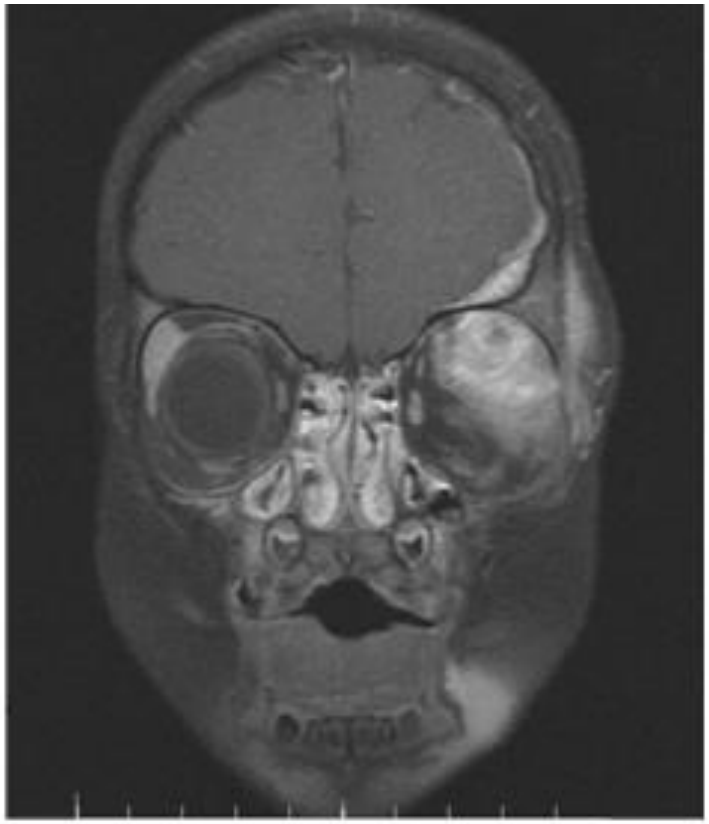
- CC: left eye swelling x 1 week
- HPI: 2 year old girl; concerns for child abuse
- PMH: unremarkable
- SH: Foster care
- Physical Exam:
  - Palpable soft tissue mass in lateral aspect of left orbit with fullness of upper lid. Significant (6-8mm) proptosis/exopthalmos of left globe. Some restriction in upward gaze in left eye. Full motility in right eye. Fixes and follows with each eye. No pupillary defects.

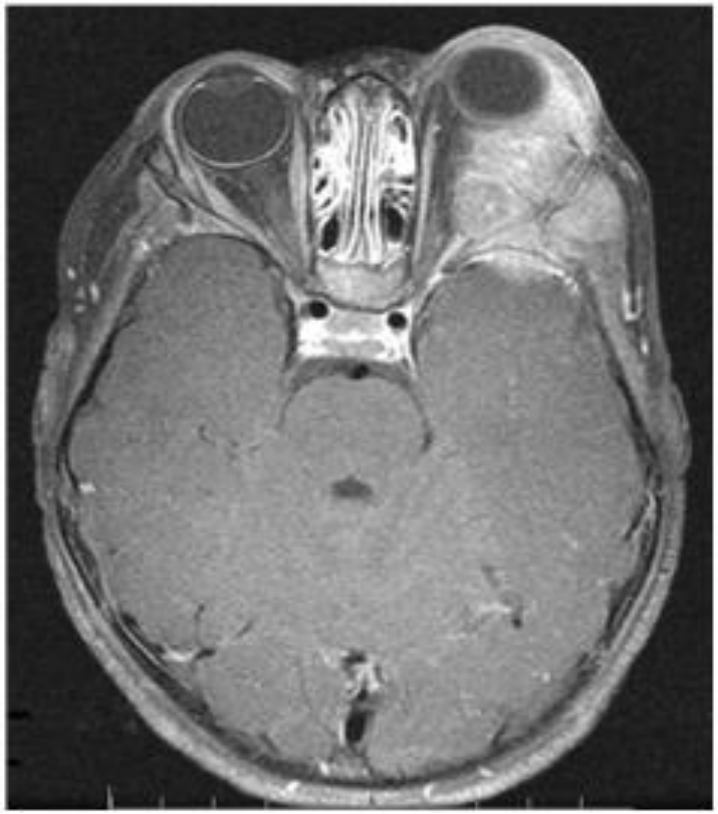
Work up

- Head CT
  - Soft tissue mass in the left periorbital region with intracranial extension, adjacent small subdural hematomas in left frontal and temporal lobes.
- Bone Survey (due to concern for trauma/child abuse)
  - Indistinct irregular left orbital roof and frontal bone, concerning for focal bony lesion.
  - No other abnormalities

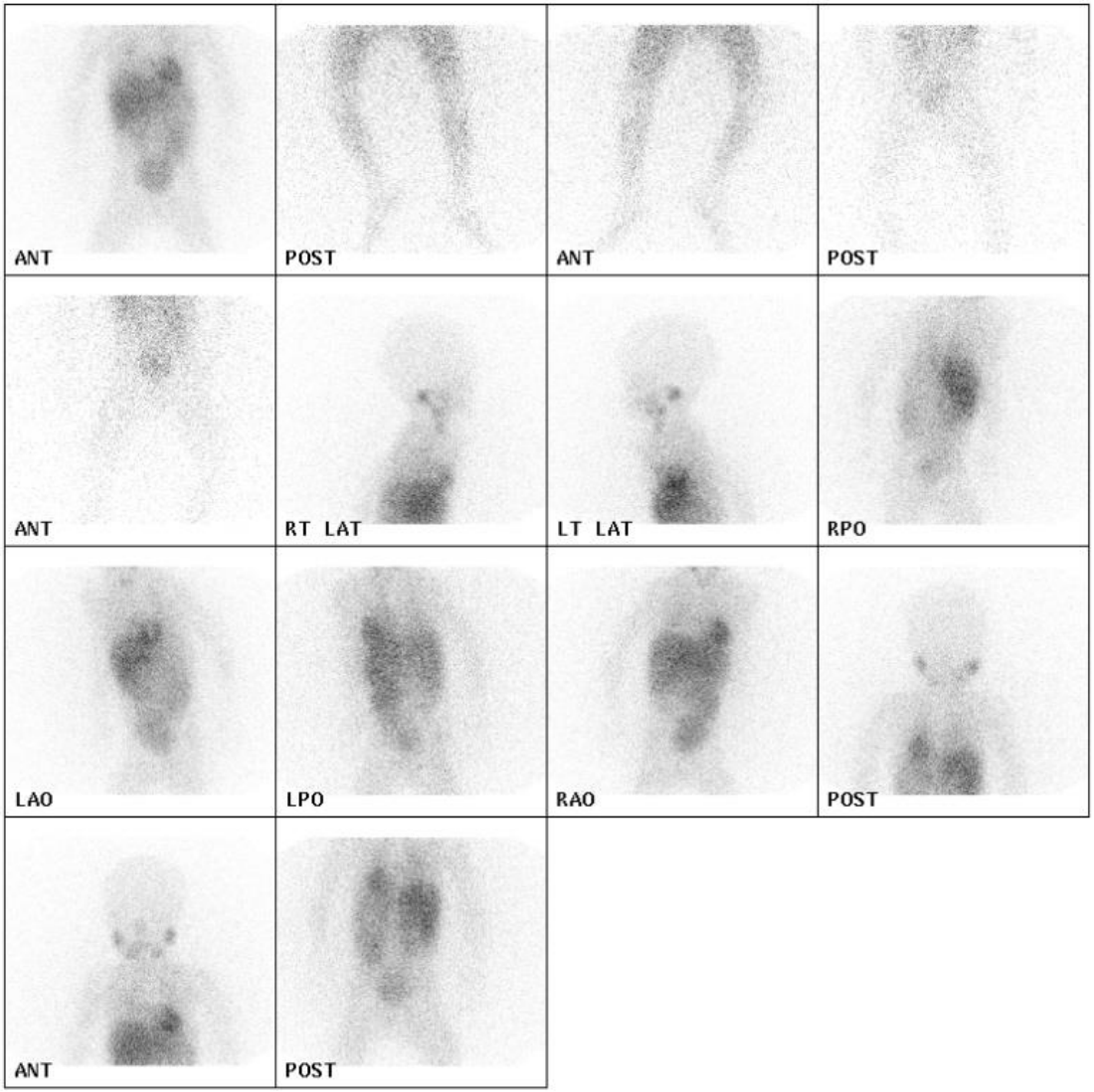
Work up

- MRI of brain and orbit
  - Enhancing lesion of the left sphenoid with intraorbital, left lateral extraorbital, transphenoidal, and intracranial components.
  - Findings concerning for neuroblatoma vs. rhabdomyosarcoma





Work up



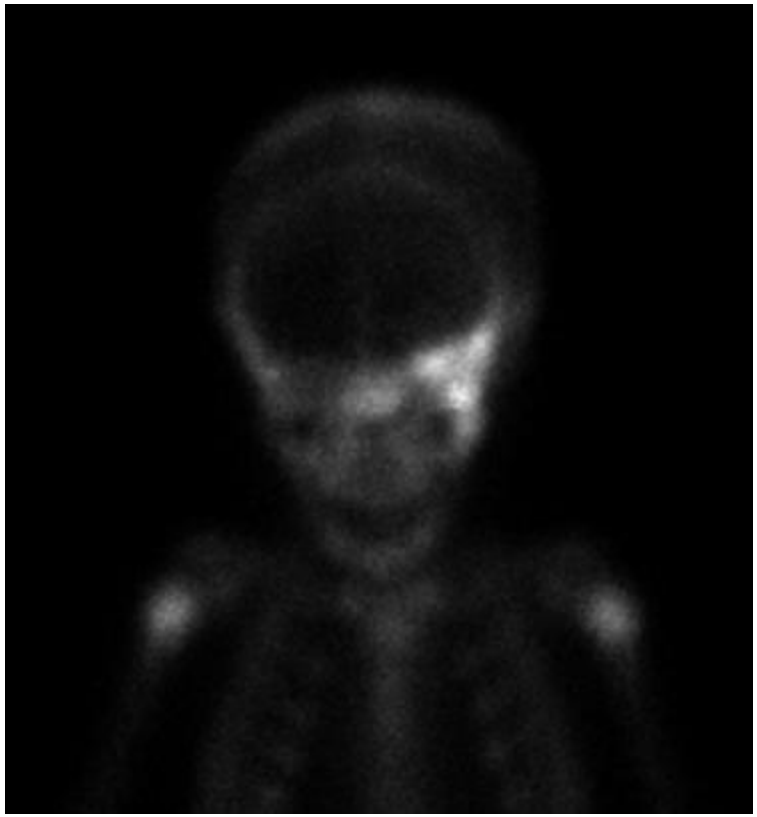
CT of the chest, abdomen, and pelvis showed no evidence of metastatic disease

MIBG* Scan: shown left, only minimal radiotracer activity is noted in the left orbit corresponding to the left orbital mass seen on MRI.

* MIBG = I-123 metaiodobenzylguanidine

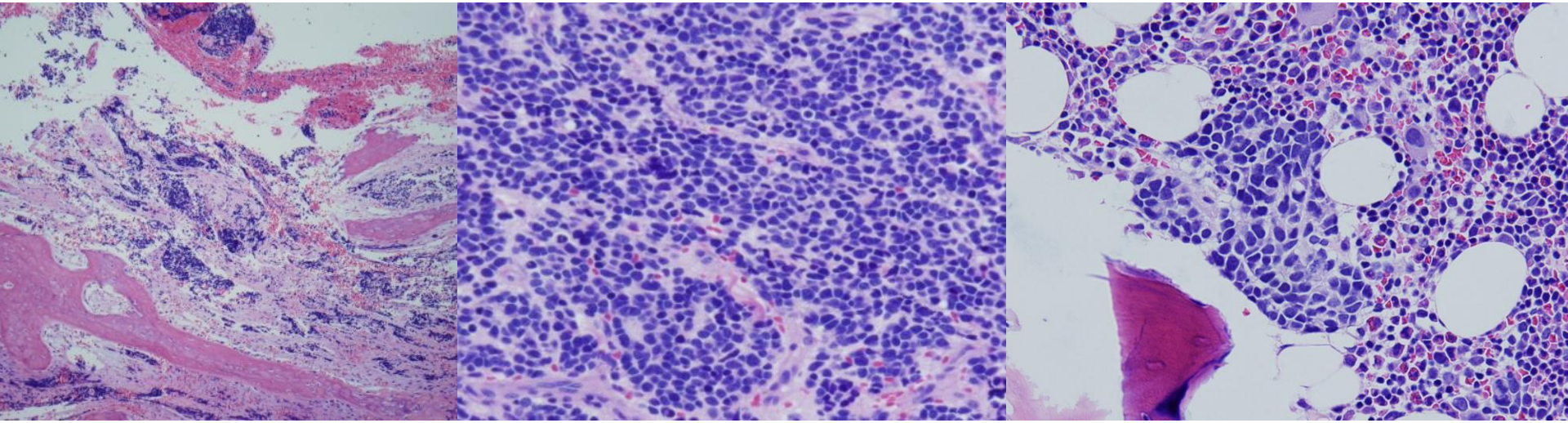
Work up

- Bone Scan: Increased tracer activity in left sphenoid sinus and left lateral orbit
- No evidence for distant osseous metastases



Work up

- Urine catecholamines:
  - VMA-to-creatinine ratio: 28 mg/g (elevated)
  - HVA-to-creatinine ratio: 20 mg/g (within normal limit)
- Bone marrow biopsy (BMB)
  - 50% clusters of foreign cells
  - CONSISTENT WITH METASTATIC NEUROBLASTOMA



Work up

- Excisional biopsy with orbitotomy.
- Pathology:
  - Unfavorable histology
  - Poorly differentiated subtype
  - MYCN oncogene was not amplified by FISH
  - Mitotic-Karyorrhexis Index (MKI) < 100
  - Invading into adjacent skeletal muscle, no necrosis, no calcifications, no ganglion cells
  - 46XX

Treatment

- Induction Chemo (per COG ANBL00P1)

  C1: cisplatin/etoposide

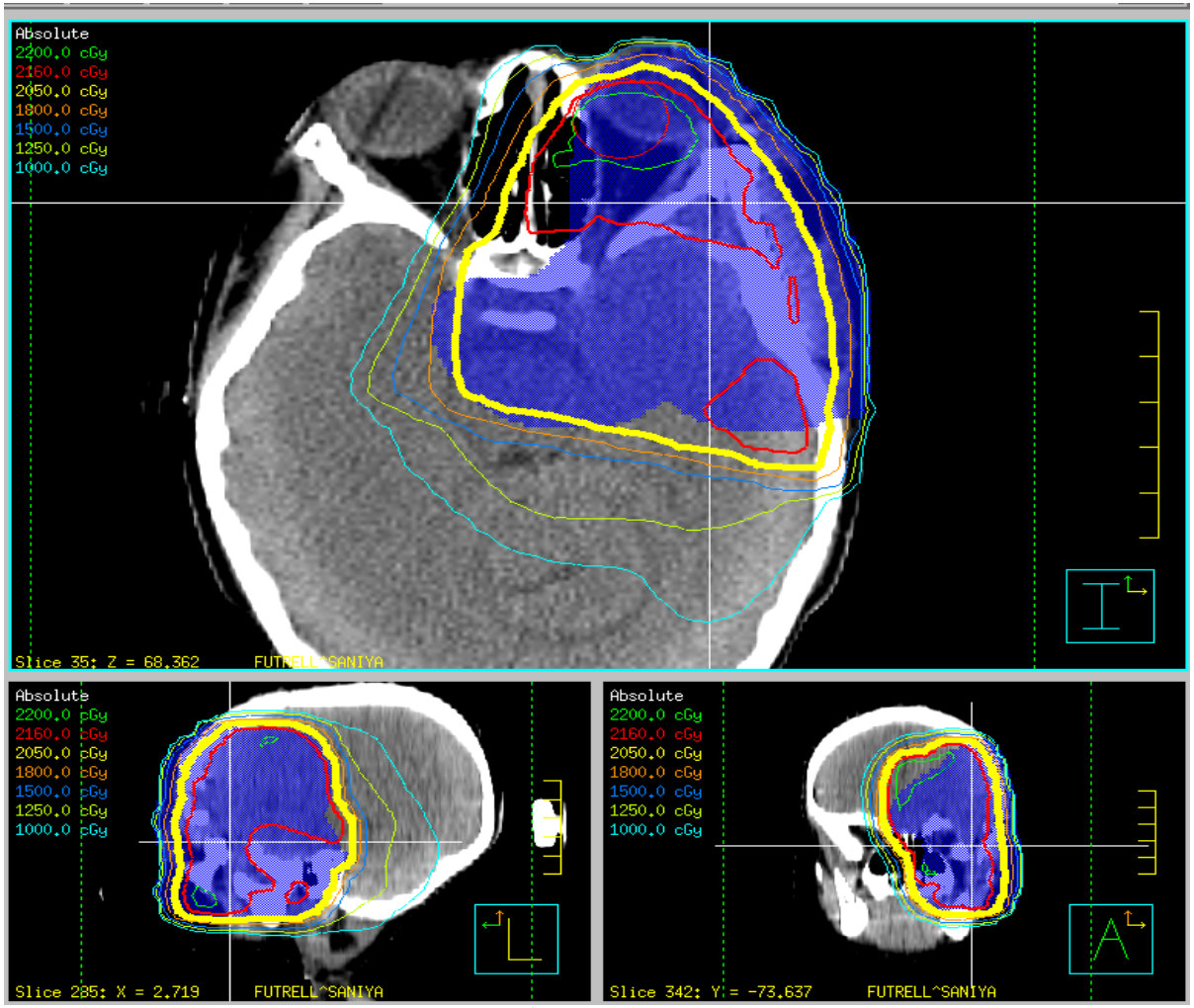
  - Residual disease on BMB

  C2-5: Vin/cisplatin/doxo/mesna/cyclophos/carbo /ifos

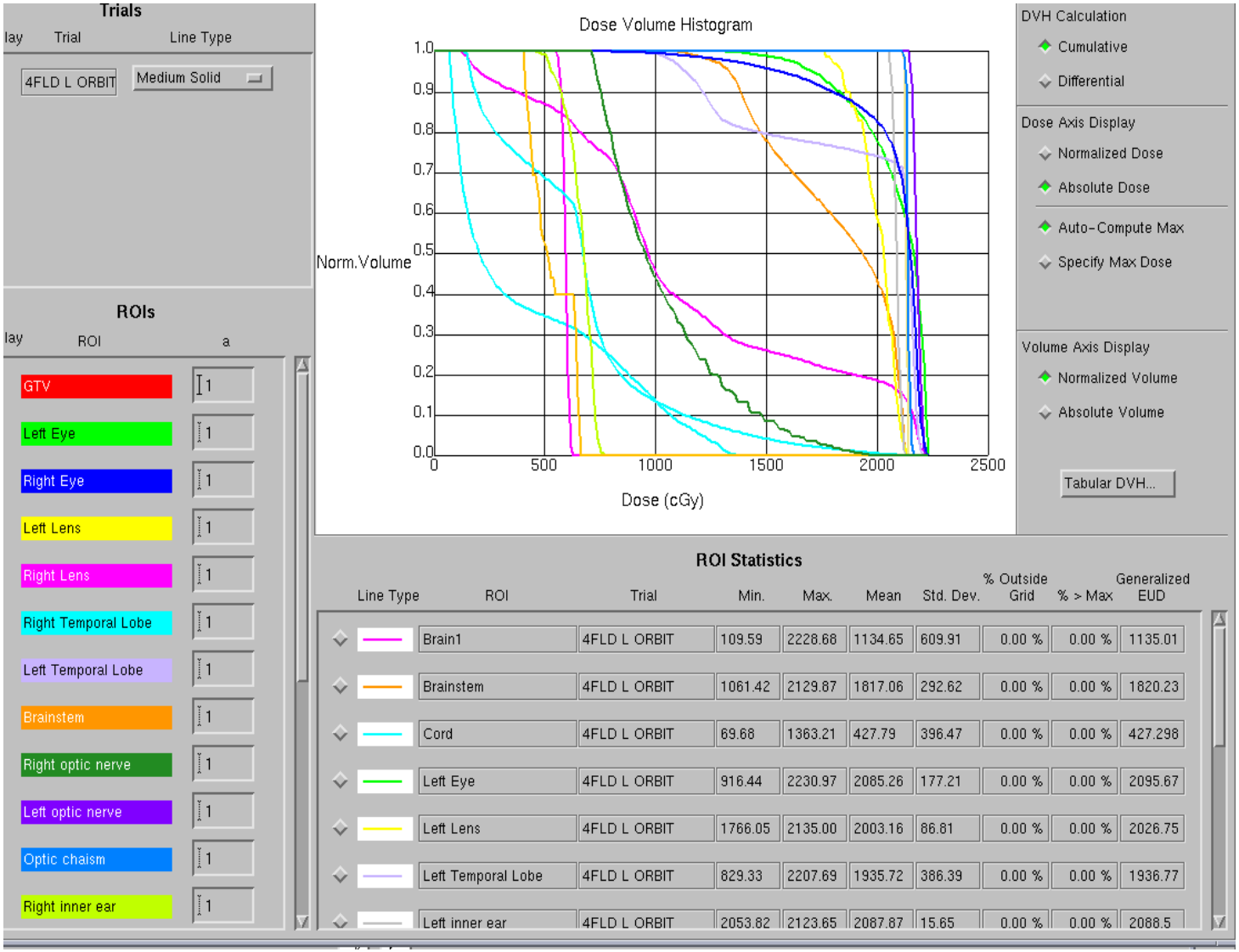
  - Residual disease on BMB b/w cycles 4 and 5
- Orbitozygomatic craniotomy with resection of orbital roof, sphenoid bone, tumor involving orbit and temporalis muscle
  - Intra-operative: Extending through peri-orbita, frontal bone, orbit, zygoma, sphenoid bone, maxillary bone and temporalis muscle.
  - Gross Total Resection
  - Final Pathology: Residual neuroblastoma with bone invasion
- Post-op consolidative RT (next slide)
- Six cycles of Accutane (isotretinoin)
- Autologous stem cell transplant
  - Preparative regimen: Melphalan/etoposide/carbo (no TBI)

Post-op Consolidative RT

- 2160 cGy in 180s to primary site with 2cm margin
- Four-field, 3DCRT
- Mixed energies, 6 and 15 MV
- MLC and dynamic wedge to improve dose homogeneity



Post-op Consolidative RT



Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD
	Brain1	4FLD L ORBIT	109.59	2228.68	1134.65	609.91	0.00 %	0.00 %	1135.01
	Brainstem	4FLD L ORBIT	1061.42	2129.87	1817.06	292.62	0.00 %	0.00 %	1820.23
	Cord	4FLD L ORBIT	69.68	1363.21	427.79	396.47	0.00 %	0.00 %	427.298
	Left Eye	4FLD L ORBIT	916.44	2230.97	2085.26	177.21	0.00 %	0.00 %	2095.67
	Left Lens	4FLD L ORBIT	1766.05	2135.00	2003.16	86.81	0.00 %	0.00 %	2026.75
	Left Temporal Lobe	4FLD L ORBIT	829.33	2207.69	1935.72	386.39	0.00 %	0.00 %	1936.77
	Left inner ear	4FLD L ORBIT	2053.82	2123.65	2087.87	15.65	0.00 %	0.00 %	2088.5

STRUCTURES

(Right to left on 1.0 line)

- Left Optic Nerve
- Optic Chiasm
- Left Middle Ear
- Left Inner Ear
- Left Lens
- Left Eye
- Right Eye
- Brainstem
- Left Temporal Lobe
- Right Optic Nerve
- Right Lens
- Right Inner Ear
- Right Middle Ear
- Right Temporal Lobe
- Brain
- Cord

Case Summary

- 2 year old girl with IPSS high-risk, unfavorable histology, NMYC non-amplified, orbital neuroblastoma (versus unknown primary with orbital rim metastasis), stage 4 by virtue of extensive marrow involvement.
- Treated in 4 phases
  (1) Intensive induction chemotherapy
  (2) Local therapy: surgical resection of the primary followed by consolidative orbital radiation
  (3) Adjuvant cis-RA
  (4) Autologous stem cell transplant
- 3 years later she remains without evidence of disease
- Treatment side effects
  - Growth delay (requiring supplemental growth hormone)
  - Bilateral sensorineural hearing loss
  - Headaches of unclear etiology

Overview

- Neuroblastoma is an enigmatic pediatric malignancy
- Early stages can be cured with surgery alone; some cases spontaneously regress or even mature to a benign ganglioneuroma
- Advanced stage disease is more common and may be fatal

Etiology

- Fetal adrenergic neuroblasts of neural crest tissues
- May arise from any site in the sympathetic nervous system
- Most common sites of origin:
  - Adrenal medulla (30-40%)
  - Paraspinal ganglia in abdomen or pelvis (25%)
  - Thoracic (15%)
  - Head and neck (5%)

Epidemiology

- Most common extra-cranial solid pediatric tumor
- Most common malignancy of infancy
- Median age: 17 months
- 75% < 2 years; 90% < 5 years

Presentation

- 60% are metastatic at presentation with mets mostly to bone, liver, skin
- Pain is most common presenting symptom
- Symptoms depend on location; paraneoplastic syndromes not uncommon
  - Cord compression (so-called “dumbbell shaped tumor”)
  - Catecholamine-induced HTN or diarrhea (Kerner-Morrison syndrome)
  - Cervical sympathetic involvement with Horner’s syndrome (ptosis, miosis, anhidrosis)
  - Orbital rim mets (Racoon eyes)
  - Skin mets (Blueberry muffin sign)
  - Random eye muscle jerks due to anti-neural antibodies (Opsoclonus-myoclonus syndrome)
  - Hepatomegaly from liver mets (Pepper syndrome)
  - Limping due to bone metastases (Hutchinson syndrome)

Screening is not recommended

- Urinary catecholamine screening
  - Results in overdiagnosis and false positives
  - No improvement in overall survival
  - Screening only identifies tumors likely to spontaneously regress anyway.

Work up

- Labs
  - Urine catecholamines (VMA, HVA)
- Imaging
  - Abdominal ultrasound
  - CT/MRI (calcification on imaging is a favorable sign)
  - Bone Scan
  - MIBG scan
- Bilateral bone marrow biopsy

I-123 MIBG Scan

- MIBG (metaiodobenzylguanidine) is a derivative of norepinephrine and epinephrine that is concentrated in secretory granules of both normal and neoplastic neural crest
- It is labeled with radioactive iodine (I-123 metaiodobenzylguanidine) and administered to assess for metastases
- MIBG scan sensitivity and specificity are both ~ 90%. Cannot distinguish between cortical bone involvement and marrow involvement; bone scan is still recommended for standard workup.
- Normal activity in adrenal medulla
- Activity in ectopic neuroendocrine tumors: Pheochromocytoma , Neuroblastoma, Carcinoid, Medullary thyroid carcinoma, Paraganglioma
- Biodistribution: liver (diffuse homogeneous), spleen, kidney (primary route of elimination), heart, salivary glands, and to a lesser extent bowel and lung.

Histology

- A small round blue cell tumor
  - Other small round blue cell tumors: lymphoma, Ewings/PNET, rhabdomyosarcoma, medulloblastoma, and retinoblastoma
- Homer-Wright Pseudo-Rosettes
- Stains for NSE or synaptophysin

Prognostic Factors

- Age and stage at initial presentation remain two most important factors that influence outcome.
- **Risk Groups**
  - Two systems for determining Risk Group are available:
    - Children's Oncology Group (COG) (most commonly used)
    - International Neuroblastoma Risk Group (INRG)
  - Both take into account the following prognostic factors:
    - Pathology
    - Biology
    - Stage
    - Age

Prognostic Factors

- **Pathology**
  - Shimada system (old)
  - International Neuroblastoma Pathology Committee (new, updated Shimada)
- **Biology**
  - MYCN gene (most prognostic)
  - 1p and 11q deletion
  - 17q gains
  - DNA ploidy
- **Staging**
  - Multiple older surgical staging systems have fallen out of favor
  - Current (1993) Post-op INSS: Stages 1, 2A, 2B, 3, 4, 4S
  - Pre-op INRG: Stages L1, L2, M, MS
- **Age**
  - <18 mo = favorable
  - > 5 years = unfavorable

Pathology

International Neuroblastoma Pathology Committee System (1999, i.e. revised Shimada)

- **NEUROBLASTOMA**
  - Favorable
    - < 1.5 years
      - intermediate differentiation OR
      - poor differentiation and low/intermediate MKI (mitosis-karyorrhexis index = # mitoses/5,000 cells)
    - 1.5 – 5 years
      - well differentiated with low MKI
  - Unfavorable
    - <1.5 years
      - poor differentiation and high MKI
    - 1.5 – 5 years
      - poor differentiation OR
      - intermediate or high MKI
    - > 5 years
- **GANGLIONEUROBLASTOMA** – favorable if no nodular component
- **GANGLIONEUROMA** – favorable if no nodular component

Biology

- **N-MYC (MYCN) amplification**
  - Occurs in 30-40% of advanced stage NB
  - Portends unfavorable outcome, even in disease settings that would otherwise be favorable
- **Chromosomal deletions 1p (23%) and 11q (35%)**
  - Both associated with worse prognosis
- **Chromosomal gains in 17q (around 50%)**
  - Most common genetic alteration in NB; occurs in 50% of cases
  - Associated with worse prognosis
- **DNA ploidy**
  - Hyperdiploid outcomes superior to diploid
  - Ploidy is an important discriminator of response to chemo

Neuroblastoma Staging Systems

- Most commonly used system is the International Neuroblastoma Staging System (INSS) based on clinical, radiographic, and surgical findings.
- Others staging systems include:
  - Evans and D'Angio (1971)
  - St. Jude/Pediatric Oncology Group (POG)

Current INSS Surgical Staging (1993)

Stage 1: Localized

Complete resection +/- microscopic residual, LN negative

Stage 2A: Localized

Incomplete gross resection, LN negative

Stage 2B:

+/- complete resection, regional LN positive

Stage 3:

Unresectable unilateral tumor, crosses midline +/- regional LN

OR localized with contralateral LN positive

OR midline tumor with bilateral extension or LN positive

Stage 4:

Distant LN positive OR non-stage 4S distant mets

Stage 4S:

Stage 1, 2A, 2B < 1 year of age with mets limited to skin, liver, marrow (cells <10% of total nucleated cells)

Pre-op Staging

- Used in INRG risk group definitions
  - L1: localized, not involving vital structures
  - L2: locoregional with one or more image-defined risk factors (e.g. encasement of vasculature)
  - M: distant mets (not stage MS)
  - MS: mets AND age < 18 months with mets to skin, liver, and bone marrow only (<10% involvement)

COG Risk Groups (uses INSS surgical staging)

- Low Risk (12 yr OS > 90%)
  - Any path, any bio, INSS stage 1, any age
  - Any path, non-amplified MYCN, INSS stage 2A/2B, any age
  - Favorable path, hyperdiploidy & non-amplified MYCN, INSS stage 4S, < 12 months
- Intermediate Risk (12 yr OS >80%)
  - Any path, non-amplified MYCN, INSS stage 3, and < 18 mo
  - Favorable path, non-amplified MYCN, INSS stage 3, and > 18 mo
  - Any path, non-amplified MYCN, INSS stage 4, and < 18 mo
  - Favorable path, diploid AND non-amplified MYCN, INSS stage 4S, and < 12 mo
  - Unfavorable path, non-amplified MYCN, INSS stage 4S, and < 12 mo
- High Risk (12 yr OS 30-40%)
  - Unfavorable path, non-amplified MYCN, INSS stage 3, and > 18 mo
  - Any path, MYCN amplified, stage 2A-4S and any age.

General Management

- Low Risk (4 yr OS 99%)
  - Surgery alone; RT reserved for residual/recurrent disease
- Intermediate Risk (3 yr OS 75-98%)
  - Resectable: surgery +/- chemo
  - Unresectable: neoadjuvant chemo → surgery
  - Role of RT controversial in intermediate risk disease

General Management

- High risk (10 yr OS 59%)
  - Four phases
    - Induction chemotherapy
    - Maximal surgical resection and management of residual disease with consolidative RT to primary and metastatic sites of disease
      - Improvement in local control with RT: 21-81% vs. 10-52%
      - Typical doses: 12 – 37.5 Gy (21 Gy standard, higher for gross residual tumor may be beneficial)
    - Cis-retinoic acid (cis-RA)
    - Autologous bone marrow transplant

General Management

SUMMARY

Risk group	*management*	*5Yr EFS*	*Note*	*Note*
Low Risk			Chemo:	
1) resected +/- microscopic residual	**surgery alone**	> 90%	6-12 weeks	
2) unresectable or STR or Recurrence	chemo → surgery	60 – 90%	Carbo/VP 16 alternate with	
3) symptomatic (Cord comp, resp distress)	immediate chemo→surgery		Carbo/CP/Dox	
4) If no resp to Chemo	RT 21 Gy/1.5 Gy			
Intermediate Risk			Chemo:	Indx for RT: controversial
1) Resectable	**Resection/LND → chemo** +/- RT	90% FH	12—24 weeks	Reserved for refractory
2) Unresectable	Chemo→2nd look surgery +/- RT	50 – 80% UH	Carbo/VP 16 alternate with Carbo/CP/Dox	disease despite Sx and Chemo
High Risk	**Dose Intensive CT →surgery → +/- TBI+ABMT→ RT 21.6/1.8 → cisRA for 6 m**	30-50 %	Chemo: Add Ifosfamide and CDDP	
Stage 4S with respir distress	Supportive RT 4.5 Gy/1.5 Gy	75-90%		

CDDP: cisplatin. cisRA: cis-retinoic acid. Comp: compression. Dox: Doxorubicin. FH: favorable histology. Indx: indication. VP16: etoposide. Carbo: carboplatin. CP: cyclophosphamide. Resp: Respiratory/response. STR: subtotal resection. Sx: surgery. UH: unfavorable histology

Contribution from Baoqing Li, MD, PhD
Weill Cornell Medical College, NY, NY

Indications for RT in Neuroblastoma

- No role for RT in low risk disease
- RT is controversial in intermediate risk disease
- RT to primary site in high risk, residual, or recurrent NB
- RT for hepatomegaly in 4S disease or palliation of other mets

RT for Hepatomegaly

- Liver irradiation for symptomatic stage 4S disease
- Dose: 450-600cGy in 2-4 fractions (450cGy in 3 fractions)
- Volume: opposed lateral fields to avoid renal and ovarian exposure
- Borders
  - Anterior: 2 cm anterior to liver
  - Posterior: anterior vertebral body
  - Superior: 2 cm superior to liver
  - Inferior: superior iliac crest to avoid ovarian exposure

RT to primary site or residual MIBG-positive metastatic site

- Most abdominal and pelvic sites are best treated with AP fields
- Dose: 21.6 Gy in 1.8 Gy daily fractions
- If entire peritoneum needs to be irradiated, dose should be < 15 Gy
- If major portion of both lungs are irradiated, dose should be < 15 Gy
- GTV
  - primary tumor volume = pre-surgery CT/MIGB scans
  - Bone met site = volume positive on MIGB/bone scan after induction chemo
- PTV = GTV + 2cm
- Dose constraints:
  - Liver: < 50% to receive 9 Gy and < 25% to receive > 18 Gy
  - Contralateral kidney: < 50% to receive > 8 Gy and < 20% to receive > 12 Gy

References

1. Baker DL, Schmidt ML, Cohn SL, Maris JM, London WB, Buxton A, Stram D, Castleberry RP, Shimada H, Sandler A, Shamberger RC, Look AT, Reynolds CP, Seeger RC, Matthay KK; Children's Oncology Group. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1313-23.
2. Berthold, Lancet Oncology 2005 GERMAN NB97
3. CCG 3881 (Perez. JCO 18, 18-26. 2000)
4. Children's Cancer Study Group (CCSG);1971 (Evans, 1971, PMID 5100400; Evans, 1980, PMID 7370930)
5. COG-ANBL00P1: Seif, et al. Bone Marrow Transplant. 2013 Jul;48(7):947-52.
6. Comprehensive Clinical Psychiatry. Stern: Massachusetts General Hospital. Textbook
7. De Bernardi, et al. Excellent Outcome with Reduced Treatment for Infants with Disseminated Neuroblastoma without MYCN Gene Amplification. J Clin Oncol. 2009 Mar 1;27(7):1034-40.
8. Guglielmi M, et al. Resection of primary tumor at diagnosis in stage IV-S neuroblastoma: Does it affect the clinical course? J Clin Oncol 1996;14(5):1537–1544.
9. Halperin, Pediatric Radiation Oncology. Textbook
10. Hero, et al. Localized Infant Neuroblastomas Often Show Spontaneous Regression: Results of Prospective Trial NB95-S and NB97. JCO. 26:15-4-1510 (2008)
11. Matthay KK, et al. Excellent Outcome of Stage II Neuroblastoma Is Independent of Residual Disease and Radiation Therapy JCO 7: 236. 1989
12. Matthay KK, et al. Successful treatment of stage III neuroblastoma based on prospective biologic staging: a Children's Cancer Group study. J Clin Oncol. 1998 Apr;16(4):1256-64.
13. Matthay et al., JCO 2009, 27:1007-103
14. POG 8104 (Castleberry. JCO 10:1299. 1992). Infants with Neuroblastoma and regional lymph node metastases have a favorable outlook after limited postoperative chemotherapy: a Pediatric Oncology Group study
15. POG 8104 (Nitschke. JCO 6:1271. 1988)
16. POG 8104 (Strother et al, J Ped Hem Oncol 1995; 17: 254-259)
17. POG 8742/9244 (Strother. Euro J Cancer 12:2121. 1997) Event-free Survival of children with biologically favorable neuroblastoma based on the degree of initial tumor resection: Results from the Pediatric Oncology Group
18. Schilling FH et al. Cancer Lett. (2003) Children may not benefit from neuroblastoma screening at 1 year of age. Updated results of the population based controlled trial in Germany.
19. Schmidt M, Simon T, Hero B, Schicha H, Berthold F. The prognostic impact of functional imaging with (123)I-mIBG in patients with stage 4 neuroblastoma >1 year of age on a high-risk treatment protocol: results of the German Neuroblastoma Trial NB97. Eur J Cancer. 2008 Jul;44(11):1552-8.
20. Shimada H, et al. The International Neuroblastoma Pathology Classification (the Shimada system). Cancer 1999;86(2);364-372
21. Shimada; J Natl Cancer Inst 1984; 73: 405-416
22. Successful management of stage 4S neuroblastoma and severe hepatomegaly using absorbable mesh in an infant. McGahren ED, Rodgers BM, Waldron PE. J Pediatr Surg. 1998 Oct;33(10):1554-7
23. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. Susan L. Cohn, Andrew D.J. Pearson, Wendy B. London, Tom Monclair, Peter F. Ambros, Garrett. J Clin Oncol 27:289-297
24. Wein: Campbell-Wash. Urology, 10th ed. Textbook
25. Yalcin B, Kremer LCM, Caron HN, Van Calen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma (Review). The Cochrane Collaboration.