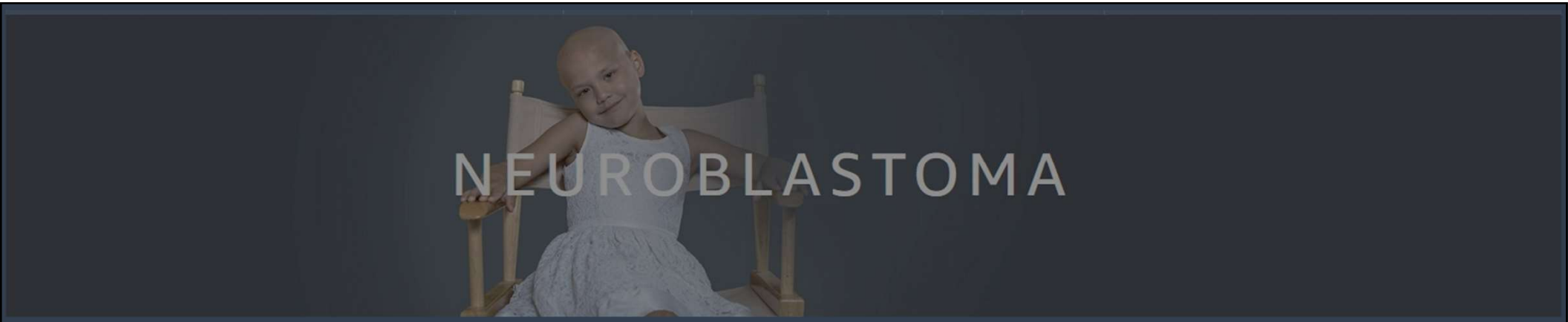
# NEUROBLASTOMA

Samuel Negash M.D.

Pediatric Surgery Resident

# Introduction

- Most common solid extracranial tumor
- Arise from Sympathetic nervous system
- It is a hetrogenous disease (location, pathology, biology)
- Therapy driven by COG research protocols




1. Epidemiology
2. Pathology and Cytogenetics
3. Clinical manifestation, Labs
4. Imaging
5. Treatment Protocols

# 1. Epidemiology

*subsaharan Africa

# Epidemiology

- 3rd most common childhood cancer
- 8% of pediatric cancer
- 15% of pediatric cancer deaths

# Epidemiology

- Most common malignancy in infants
- Incidence is 1 per 100,000 children
- 200x increase incidence in autopsy of infants

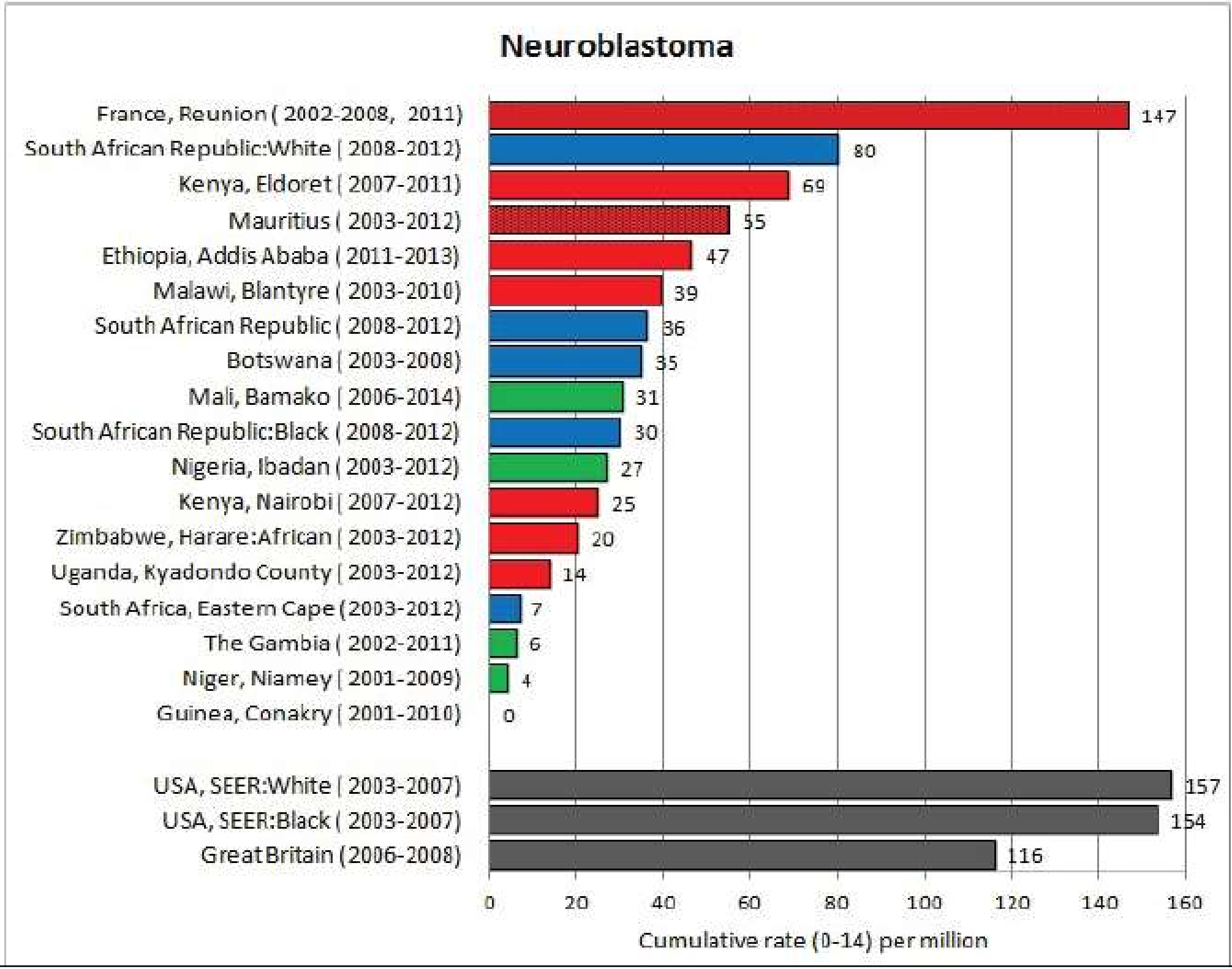
# Incidence

- Age: 40% are < 1 yr (Rare after 10 yrs)
- Race: whites > blacks (~ 1.8 x)
- Sex: boys > girls (~1.2 x)

# Cancer of childhood in sub-Saharan Africa

Cristina Stefan[1], Freddie Bray[2], Jacques Ferlay[2], Biying Liu[3] and D Maxwell Parkin[3, 4]

- Most extensive data on cancer in sub-Saharan Africa
- 16 population based registries from African Cancer Registry Network (ACRN)
- Most have higher incidence than HIC


Neuroblastoma
France, Reunion ( 2002-2008, 2011)
South African Republic:White ( 2008-2012)
Kenya, Eldoret ( 2007-2011)
Mauritius ( 2003-2012)
Ethiopia, Addis Ababa ( 2011-2013)
Malawi, Blantyre ( 2003-2010)
South African Republic ( 2008-2012)
Botswana ( 2003-2008)
Mali, Bamako ( 2006-2014)
South African Republic:Black ( 2008-2012)
Nigeria, Ibadan ( 2003-2012)
Kenya, Nairobi ( 2007-2012)
Zimbabwe, Harare:African ( 2003-2012)
Uganda, Kyadondo County ( 2003-2012)
South Africa, Eastern Cape (2003-2012)
The Gambia ( 2002-2011)
Niger, Niamey ( 2001-2009)
Guinea, Conakry ( 2001-2010)
USA, SEER:White ( 2003-2007)
USA, SEER:Black ( 2003-2007)
Great Britain (2006-2008)
147
80
69
55
47
39
36
35
31
30
27
25
20
14
7
6
4
0
157
154
116
0
20
40
60
80
100
120
140
160
Cumulative rate (0-14) per million

# Neuroblastoma in Africa: A Survey by the Franco-African Pediatric Oncology Group

- survey of 10 pediatric oncology centres
- relative frequency of neuroblastoma among cases seen in children's cancer services
- Sub-Saharan Africa 3-5%, North Afr 7-30%

# Subsaharan Africa

- very low relative frequency of NB ( < 1%) in early clinical series from tropical Africa
- ratio of neuroblastoma to Wilms was less than half of that in blacks in USA
- lack of facilities leading to under-diagnosis

# 2. Pathology and Genomics

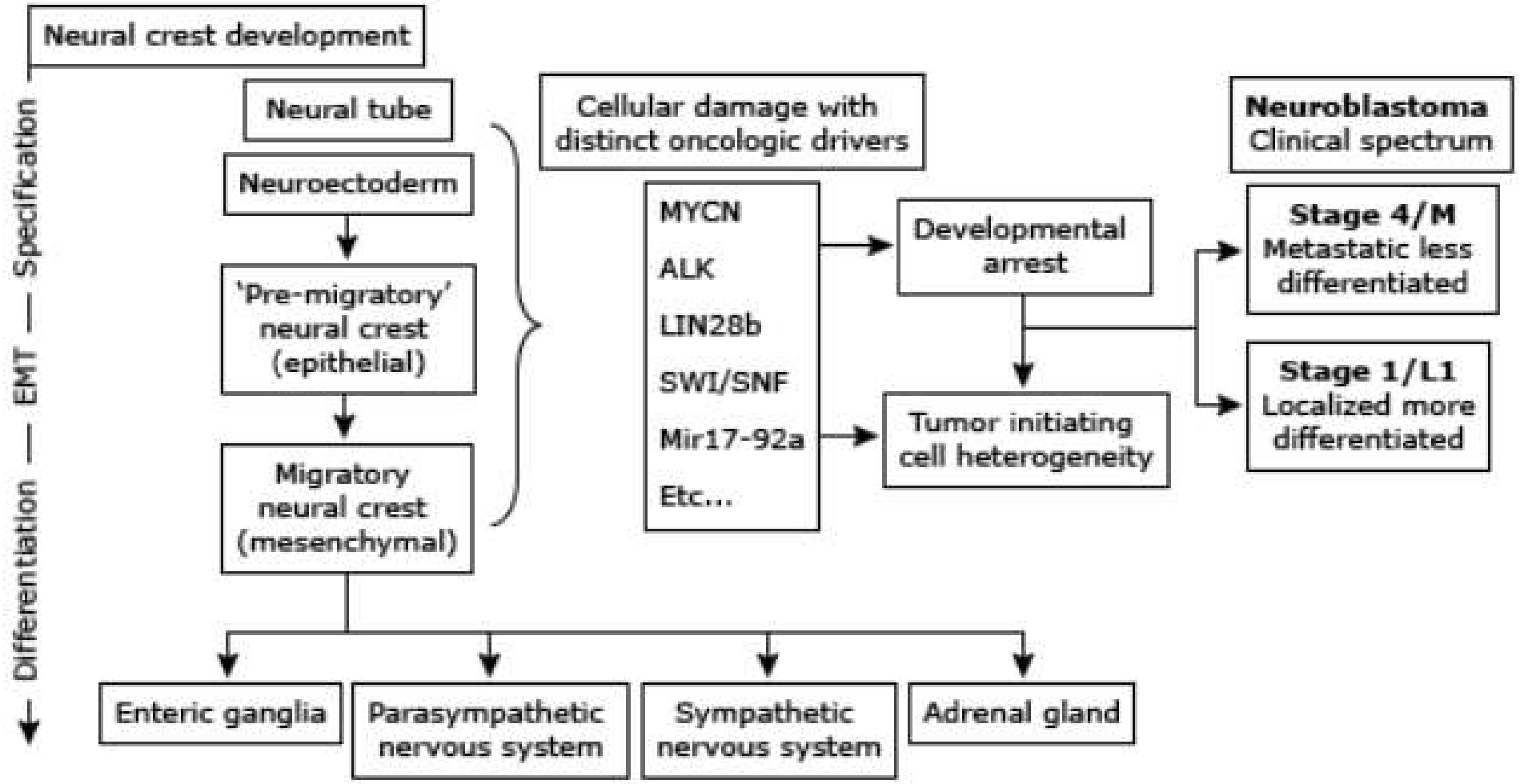
* embryology

# Embryology

- 5th wk – neural crests migrate along the spine
- 12 wk - adrenal medulla is well developed
- Fetal life - most chromaffin tissue is in extramedullary paraganglia
- After birth - paraganglia atrophy (2-3 yr)

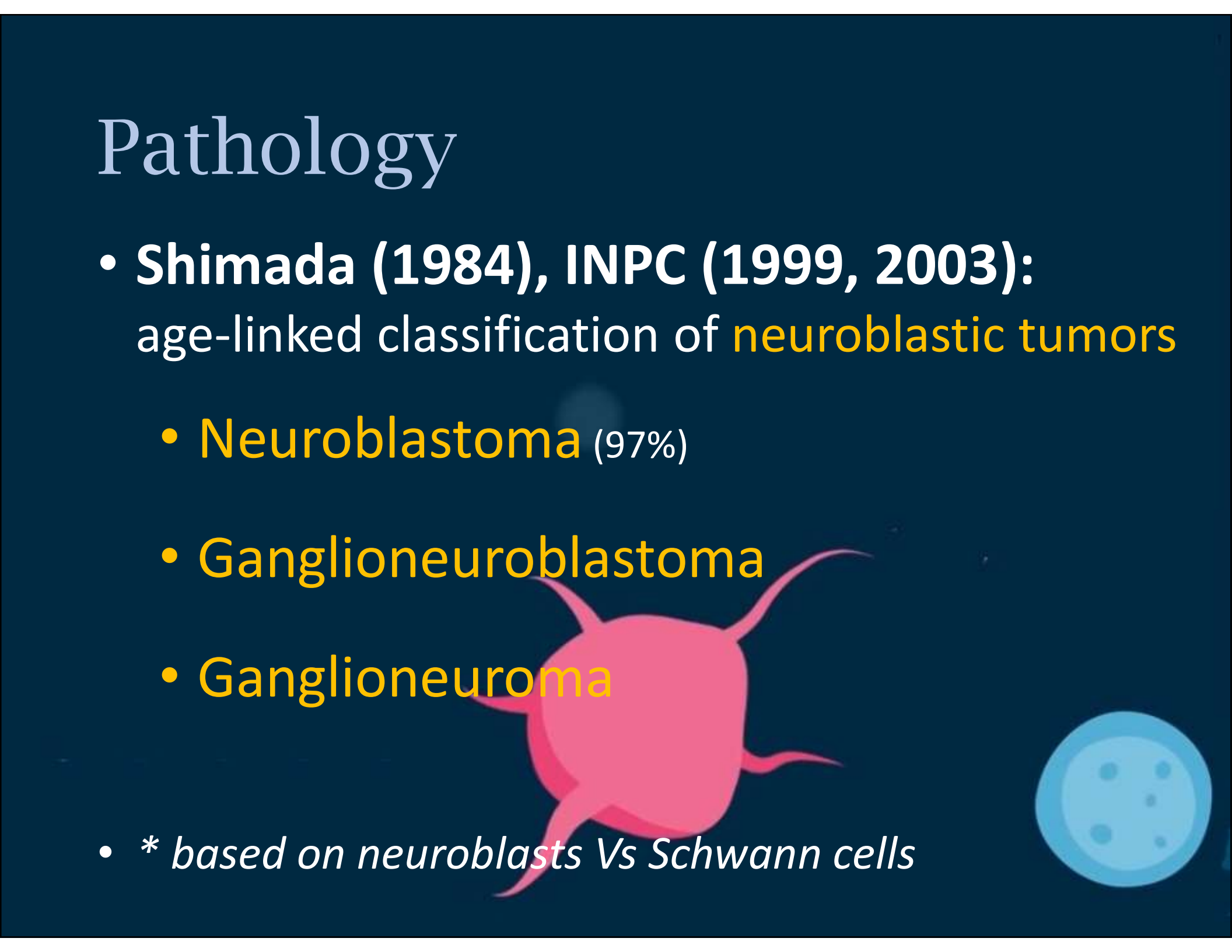
# Embryology

## Neural crest development and neuroblastoma tumorigenesis



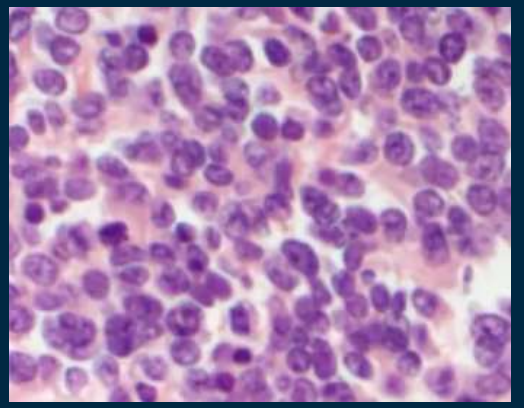
# Pathology

- **Shimada (1984), INPC (1999, 2003):** age-linked classification of neuroblastic tumors
  - Neuroblastoma (97%)
  - Ganglioneuroblastoma
  - Ganglioneuroma
- ** based on neuroblasts Vs Schwann cells*

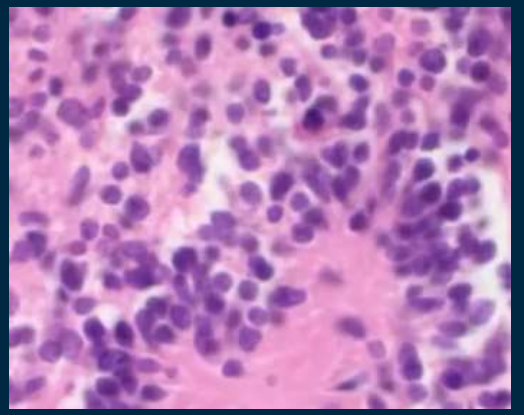


# Neuroblastoma subtypes

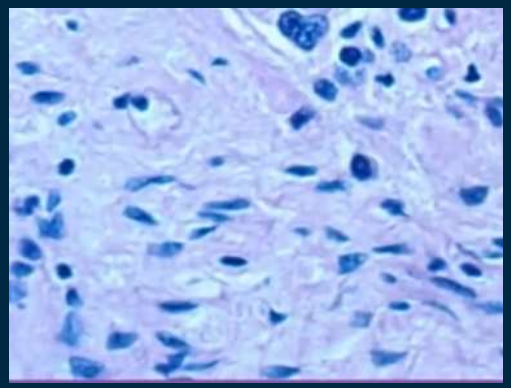
- Undifferentiated
  - **Small round blue cell** (neural crest)
  - *lack cytoplasm, large blue nuclei*



- Poorly differentiated
  - *Smaller nuclei, more cytoplasm*
  - **Neuropil** (nerve fibers)
  - * rosettes (cells around neuropil)



- Differentiating
  - *Lots of cytoplasm, (>5% of cells)*
  - **Schwannian stroma** (form myelin)

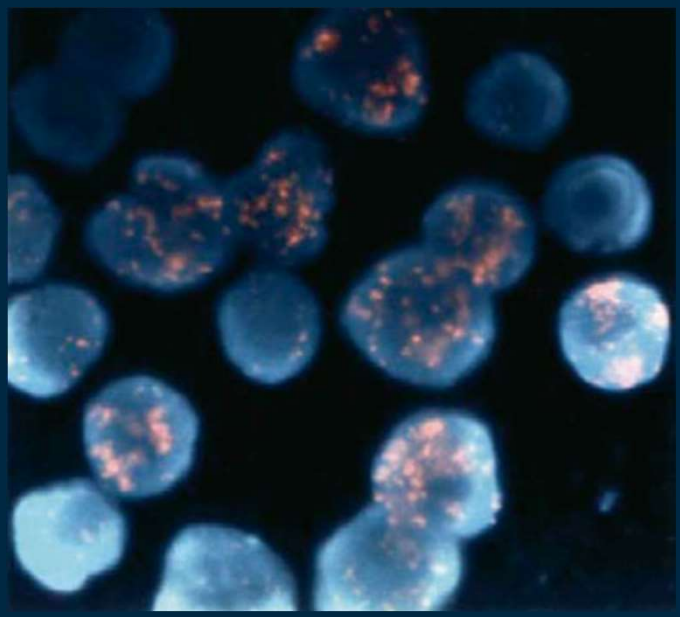


# International Neuroblastoma Pathology Classification

| Favorable | Unfavorable |
|---|---|
| - Poorly differentiated NB<br>- Low MKI<br>- <1.5 years | - Poorly differentiated NB<br>- 1.5 to 5 years |
| - Differentiating NB<br>- low MKI (<100)<br>- 1.5 to 5.0 years of age | Undifferentiated NB |
| | High MKI (>200) |
| Ganglioneuroblastoma intermixed | Nodular ganglioneuroblastoma |
| Ganglioneuroma | Age > 5 years |

# Cytogenetics

- Oncogens Amplification
  - MYCN (*n-Myc*) {25%}
  - ALK
- Tumor suppressor Deletion
  - PHOX2B
  - chromosome 1p & 11q
- DNA index (ploidy)
  - Diploid vs hyperploid



# Cytogenetics

NIH NATIONAL CANCER INSTITUTE

## New Drug for Pediatric Neuroblastoma Shows Promise in Preclinical Studies

Subscribe

December 17, 2015, by NCI Staff

An international team of scientists has identified a possible new treatment target for pediatric neuroblastoma. Based on promising findings in animal models, the team is planning an early-stage clinical trial of a drug that inhibits this target in children with neuroblastoma.

The findings were published November 4 in *Science Translational Medicine*.

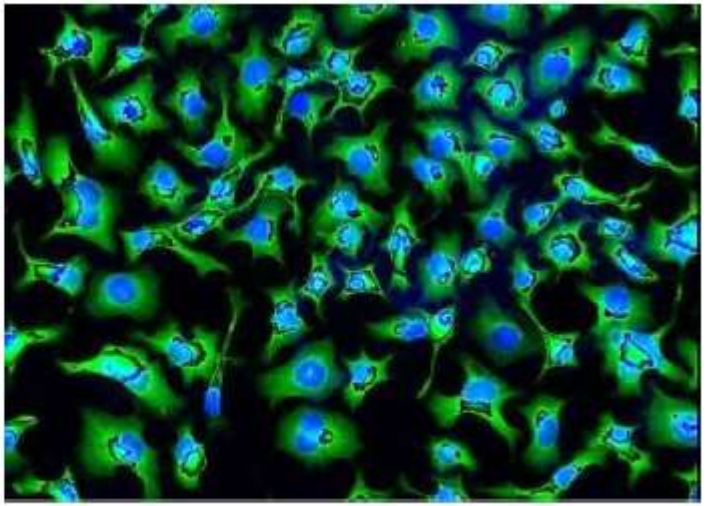
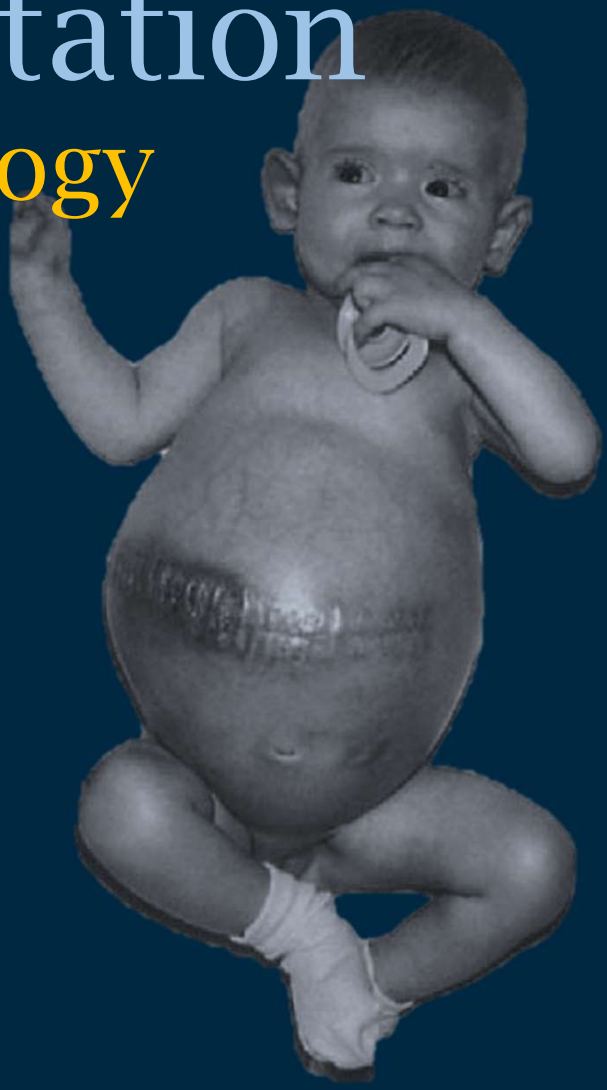


Image of neuroblastoma cells,

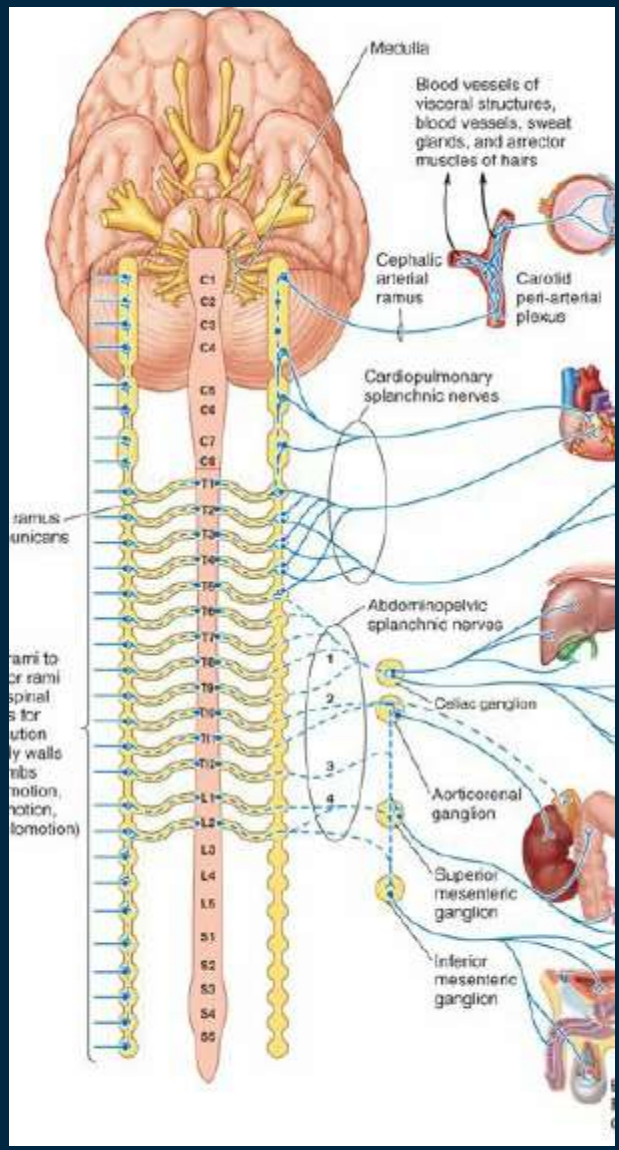
# 3. Clinical presentation

* Anatomy/physiology

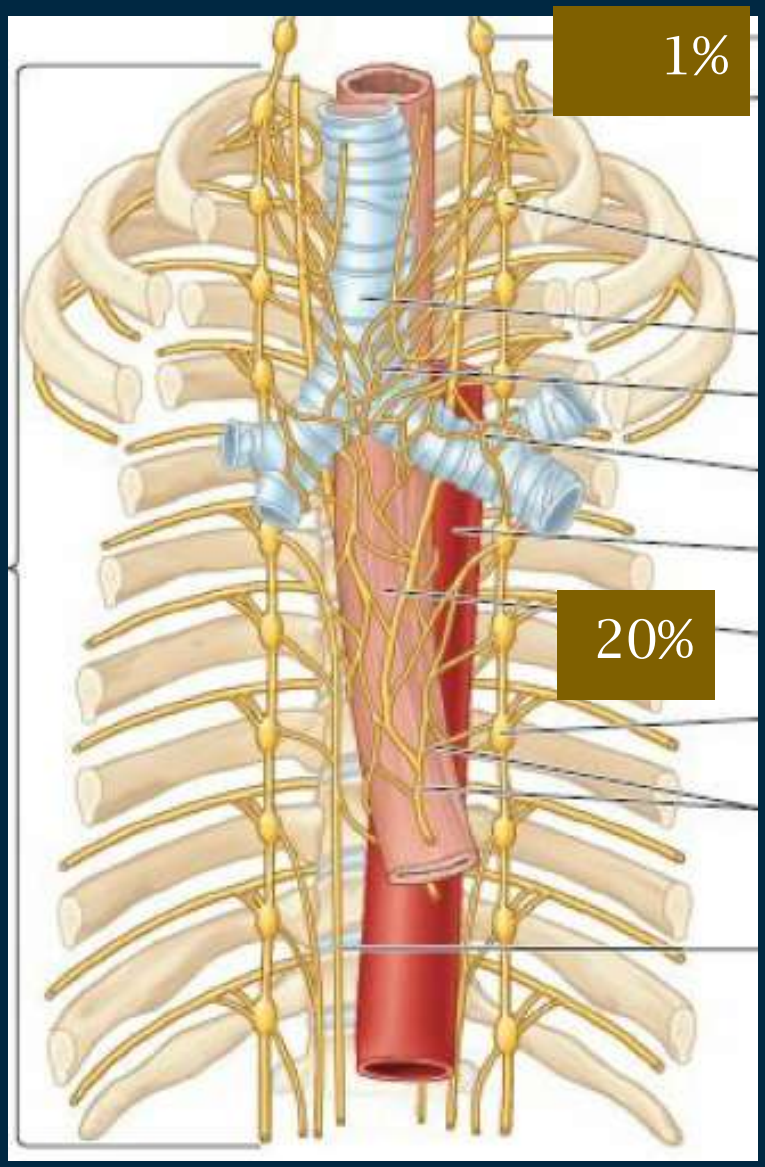


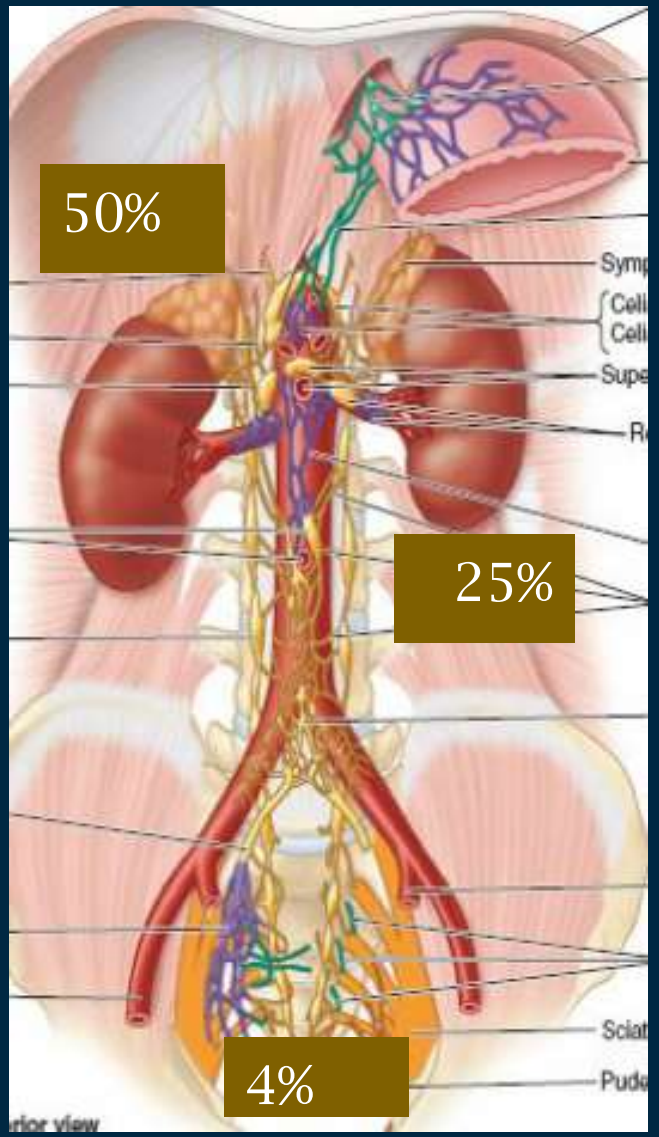
# Anatomy/physiology

- Sympathetic ganglia
  - Paraspinal (sympathetic chain)
  - Collateral (via Splanchnic)
- Adrenal medulla
- Sympathetic Paraganglia
  - Para-aortic body (pelvic organ of zukerkandl)



# Distribution

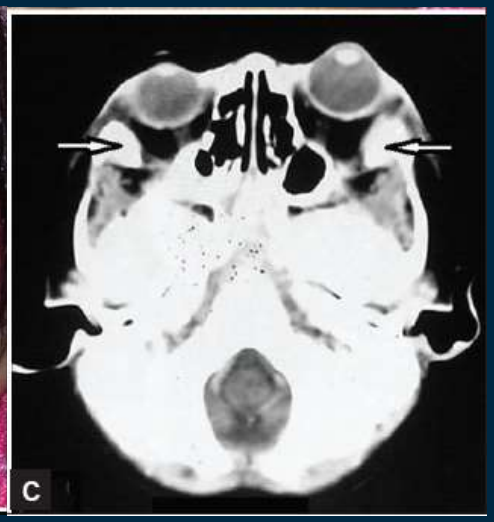


# Clinical presentation

- Age - Most are < 4 (peak 2 yrs)
- Constitutional symptoms (Chemokine release)
- Primary tumor (compression, tumor lysis, hemorrhage)
- Metastasis (BM, bone, LN, liver, intracranial/orbit)
- *Catecholamine release (headache, flushing, sweating)*
- *Hypertension (renovascular)*
- *Paraneoplastic (VIP, OMAS)*

# Clinical presentation


# Labs

- Basic : CBC, RFT, LFT, electrolyte, coagulation
- Catecholamine metabolites: **HVA and VMA**
  - elevated in urine > 90-95 %
  - **diagnosis and monitoring of response
- Indicators of tumor burden: LDH, ferritin, NSE
  - Indicate prognosis and used in monitoring

# 4. Imaging

*Staging, IDRF

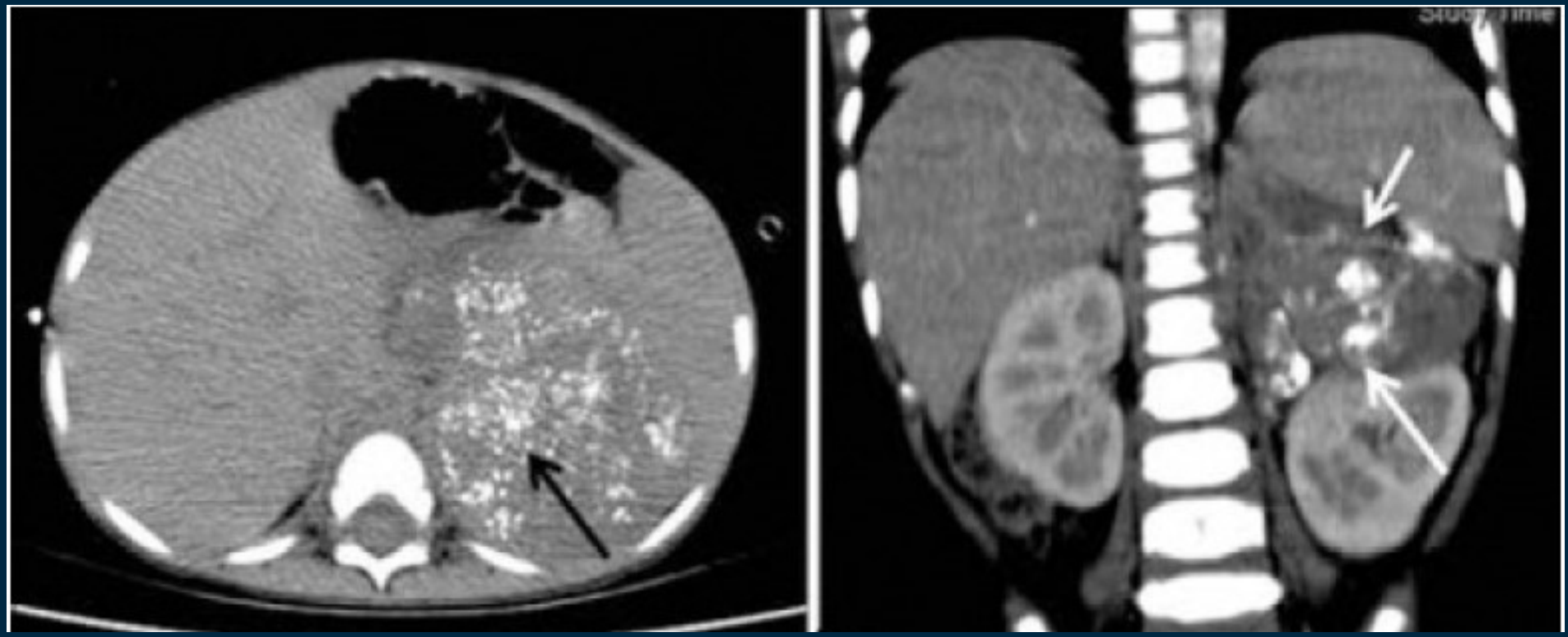
# Imaging: Mandatory

- Locoreigonal disease extent
  - Cross sectional imaging (CT or MRI)
- Metastatic disease evaluation
  - Chest X-ray
  - MIBG scan
- Response Evaluation to neo-adjuvant
  - CT or MRI (localized disease)
  - MIBG (high risk/metastatic)

# Imaging: Other

- Problem solving (depending on findings)
  - Chest CT
  - Bone scan
  - PET/CT
- Surveillance (post treatment)
  - No clear guideline
  - Ultrasound vs CT/MRI

# Imaging



# Imaging: NB vs WT

- Stippled calcification or LN with calcification
- displace the kidney inferiorly
- crossing the midline
- Encasing/displace vessels
- Paravertebral mass, spinal extension

# Staging

- INSS (1988, 1993): Surgicopathologic
- INRG (2009): Imaging

# Staging: INSS

| International neuroblastoma staging system | |
|---|---|
| 1 | Localized, complete gross excision, LN negative |
| 2 A | Localized, incomplete gross excision, LN negative |
| 2B | Localized, ipsilateral LN positive |
| 3 | Unresectable, infiltrating across midline or Localized with contralateral LN involvement |
| 4 | Metastasis: Distant LN, bone, BM, liver, skin … |
| 4S | - Age < 1 year<br>- Primary tumor stage 1 or 2<br>- Mets limited to skin, liver, BM |

# Staging: INRGSS

| International neuroblastoma risk group staging system | |
|---|---|
| L1 | Localized (one body compartment)<br>Not involving vital structures (defined by IDRF) |
| L2 | Locoreigonal (ipsilateral body compartment)<br>Presence of one or more IDRF |
| M | Metastasis (40%-50%) |
| MS | -Children < 18 mo<br>- Mets confined to skin, liver, BM (<10%) |

## Image-Defined Risk Factors for Primary Resection of Localized Neuroblastoma

Neck

1. Tumor encasing major vessel(s) (e.g., carotid artery, vertebral artery, internal jugular vein)
2. Tumor extending to base of skull
3. Tumor compressing the trachea
4. Tumor encasing the brachial plexus

Thorax

1. Tumor encasing major vessel(s) (e.g., subclavian vessels, aorta, superior vena cava)
2. Tumor compressing the trachea or principal bronchi
3. Lower mediastinal tumor, infiltrating the costovertebral junction between T9 and T12 (may involve the artery of Adamkiewicz supplying the lower spinal cord)

Abdomen

1. Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
2. Tumor encasing the origin of the celiac axis and/or the superior mesenteric artery
3. Tumor invading one or both renal pedicles
4. Tumor encasing the aorta and/or vena cava
5. Tumor encasing the iliac vessels
6. Pelvic tumor crossing the sciatic notch

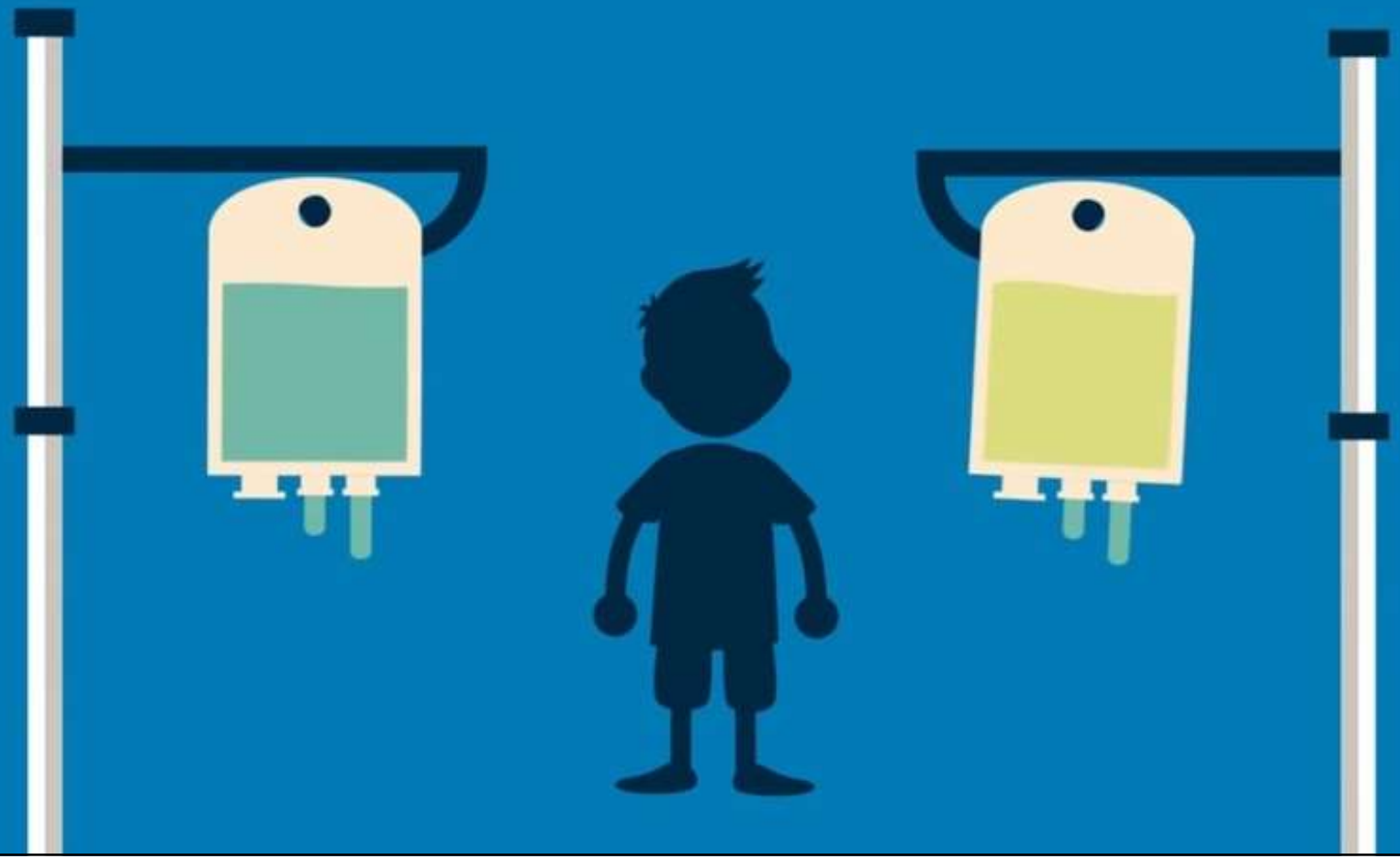
Dumbbell tumors with symptoms of spinal cord compression: Any location

Infiltration of adjacent organs/structures: Diaphragm, kidney, liver, duodenopancreatic block, and mesentery

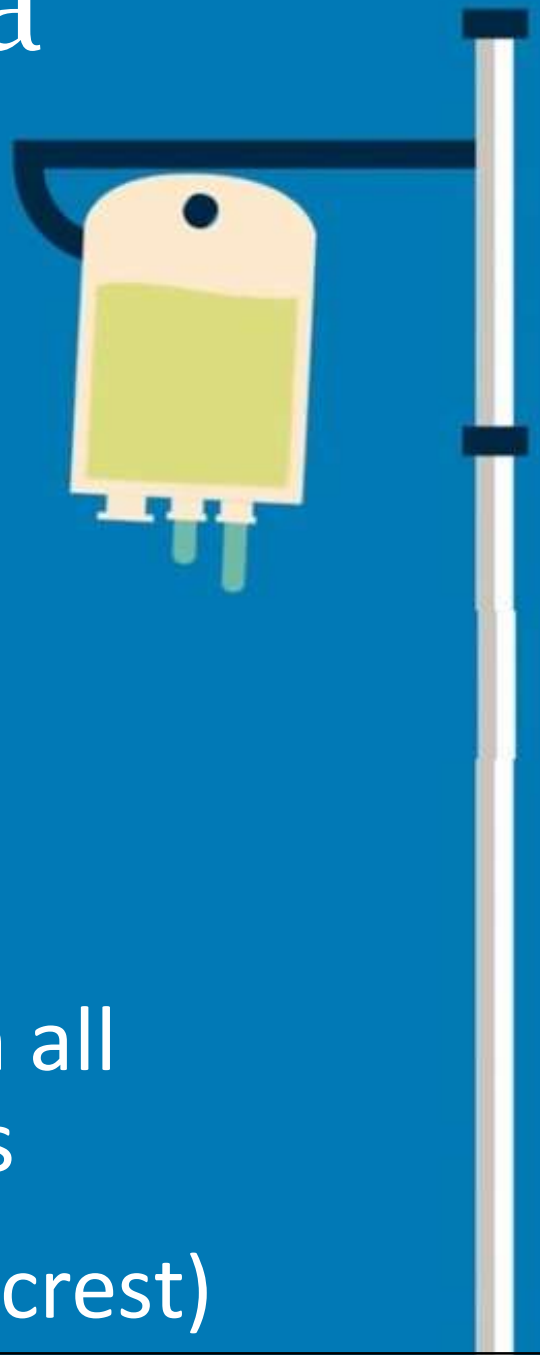
# 5. Treatment Protocols

*diagnosis, risk stratification

*sub-Saharan Africa



# Diagnosis: Criteria



- Surgical biopsy alone
  - Primary or metastatic tumor tissue
  - Excisional if resectable
- BM aspirate/biopsy + cathecolamines
  - Should be determined in all newly diagnosed patients
  - 4 samples (bilateral iliac crest)

# ? Percutaneous biopsy *

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

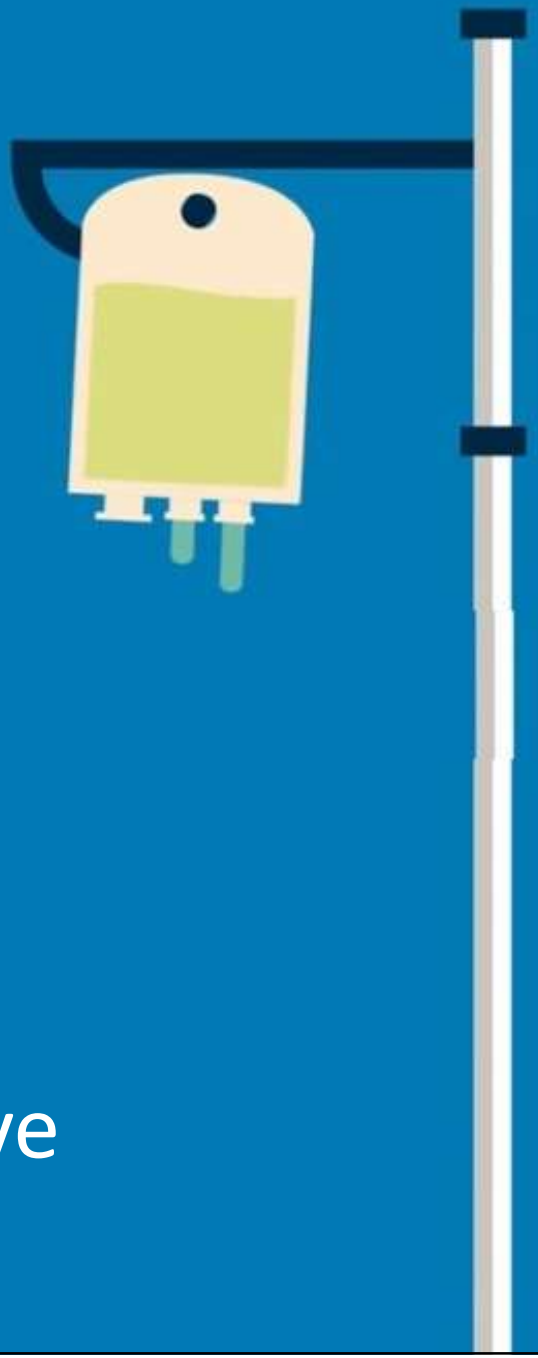
Oncology

## Diagnostic utility of core needle biopsy versus open wedge biopsy for pediatric intraabdominal solid tumors: Results of a prospective clinical study

Scott Deeney [a,b,*], Camille Stewart [a,b], Amanda L. Treece [c], Jennifer O. Black [c], Mark A. Lovell [c], Timothy Garrington [a,d], Frederick Karrer [a,b], Jennifer Bruny [a,b]

# Prognosis

- Dramatic contradistinction in prognosis
- Best outcome in young patients, differentiating tumor ( >90% survival)
- Poor prognosis in High risk patients even with aggressive therapy (40% survival)



# Risk assessment: COG

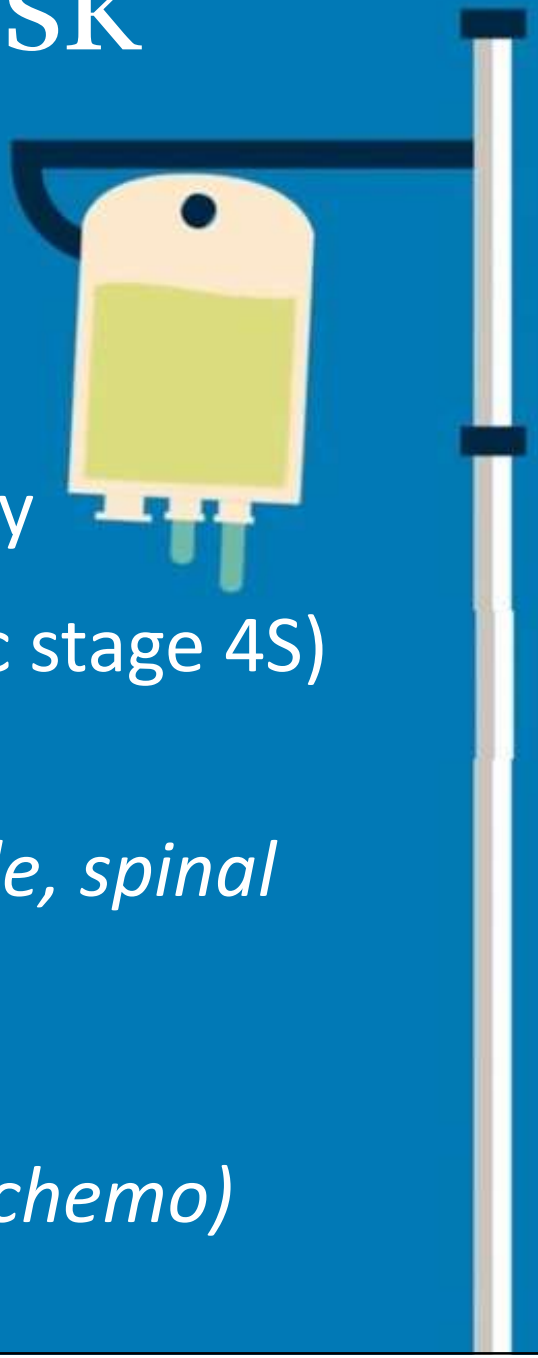
| Stage | Age | MYCN | Pathology | DNA ploidy | Risk Group |
|---|---|---|---|---|---|
| 1 | | | | | Low |
| 2 | <1 yr | | | | |
| | >1yr | NA | | | |
| | >1yr | Amp | favorable | | |
| | >1yr | Amp | unfavorable | | High |
| 3 | <1yr | NA | | | Intermediate |
| | <1yr | Amp | | | High |
| | >1yr | NA | Favorable | | Intermediate |
| | >1yr | NA | unfavorable | | High |
| | >1yr | Amp | | | |
| 4 | <1yr | NA | | | Intermediate |
| | <1yr | Amp | | | High |
| | >1yr | | | | |
| 4S | < 1yr | NA | Favorable | >1 | Low |
| | | NA | | 1 | Intermediate |
| | | NA | unfavorable | | |
| | | Amp | | | High |

# Risk assessment: INRG

TABLE 66-5 **International Neuroblastoma Risk Group (INRG) Pretreatment Classification**

| 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 | | NA | | | B Very low |
| | | GN maturing or GNB intermixed | | Amp | | | K High |
| L2 | <18 | Any, except | | NA | No | | D Low |
| | | GN maturing or GNB intermixed | | | 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 | | | Q High |
| | >18 | | | | | | P High |
| MS | <18 | | | NA | No | | C Very low |
| | | | | | Yes | | Q High |
| | | | | | | | R High |

# Treatment: Low risk

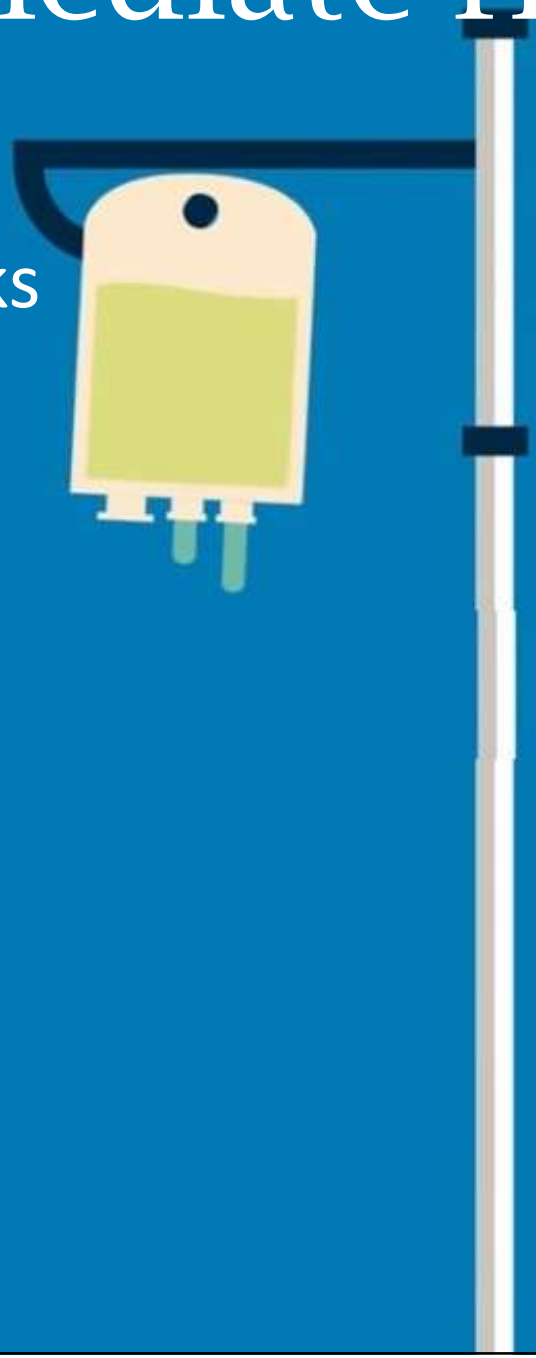


- Surgery alone is mainstay
- Observation without surgery

(infants, localized or asymptomatic stage 4S)

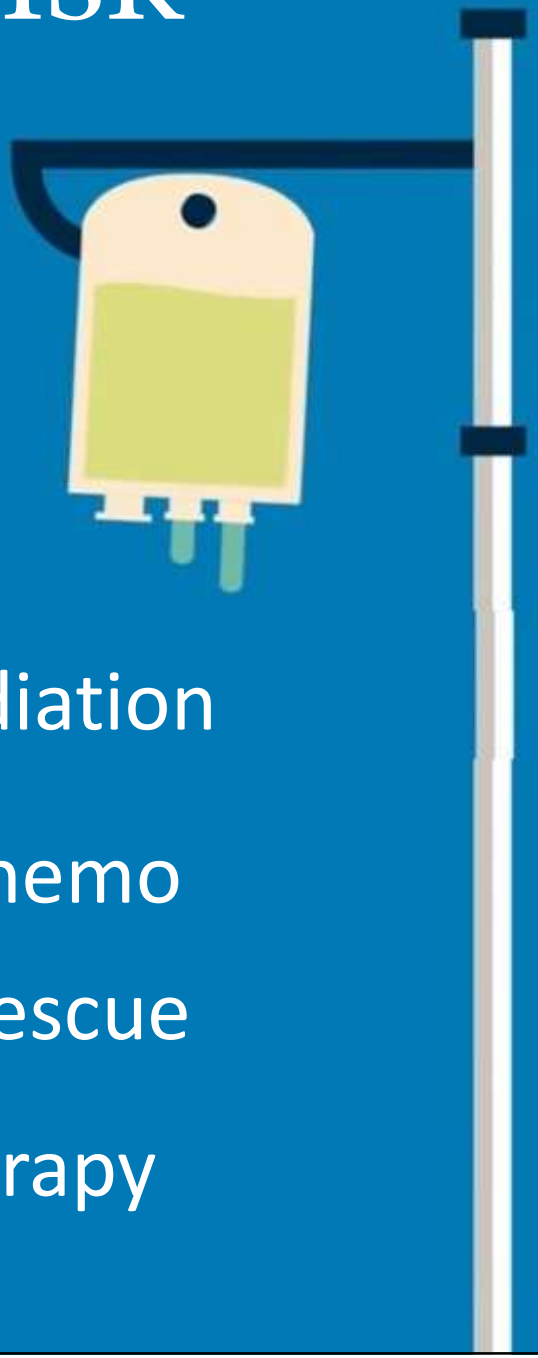
- *additional chemo (unresectable, spinal cord compression)*
- *radiotherapy (unresponsive to chemo)*

# Treatment: Intermediate risk



- Chemo typically for 12-24 wks **(surgical biopsy is necessary)
- Surgery when resection is possible
- *radiotherapy (unresponsive to chemo)*

# Treatment: High risk



- Aggressive multimodal approach
  - Induction - intensive chemo
  - Local control – surgery + radiation
  - Consolidation - High dose chemo
    + stem-cell rescue
  - Maintenance – immunotherapy

# International neuroblastoma response evaluation criteria

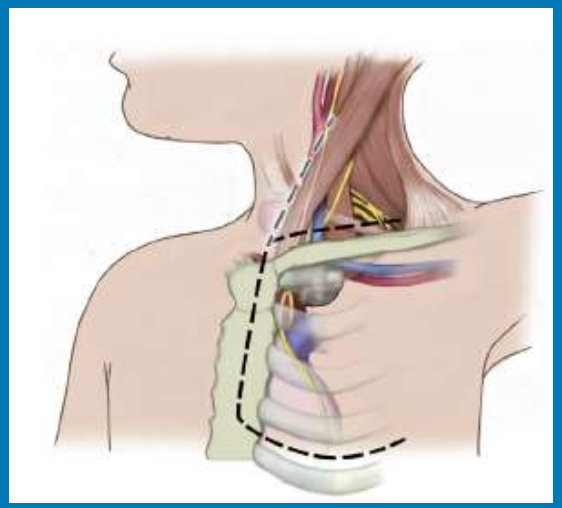
| Response | Primary tumor | Metastatic disease |
|---|---|---|
| Complete response | No tumour | No tumour, normal catecholamines |
| Very good partial response | Decreased by 90%-99% | No tumour, normal catecholamines, Improved bone scan |
| Partial response | Decreased by >50% | All sites decreased by >50%, no >1 positive bone marrow sites |
| Mixed response | No new lesions; >50% decrease of any measurable lesion (primary or metastatic) with 50% decrease in any other; 25% increase in any existing lesion | |
| No response | No new lesions, <50% decrease but <25% increase in any existing lesion | |
| Progressive disease | Any new lesion, increase of any measurable lesion by >25% | |

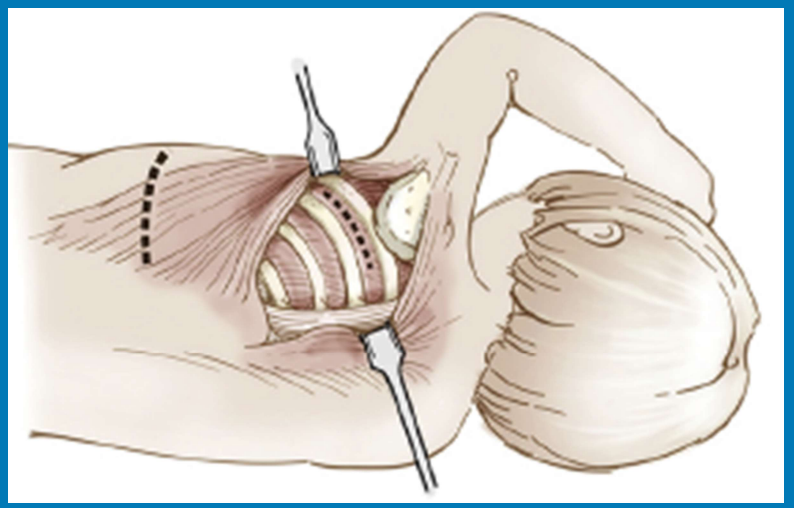
# Role of surgery: Decision

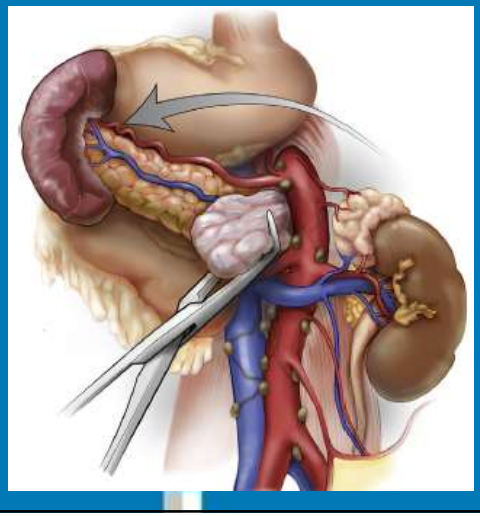
- Primary tumor Resection
  - Localized, low risk - determined by location, mobility, relationship to vessels
  - Localized, high risk – attempt only if doesn't delay chemo
- Delayed resection (after neoadjuvant)
  - Metastatic – extent is controversial
  - Localized - if <50% can be safely removed

# Role of surgery: Principles

- Expose tumor and determine relation to…
  - Abdomen – aorta, IVC and major branches
    - Right side – porta hepatis
  - Pelvic – iliac vessel, sacral plexus
  - Thoracic – intervertebral foramina







# Role of surgery: Principles

- approach as a vascular operation
- Dissect along pseudocapsule but may remove the tumor piecemeal
- Dissect proximal and distal to tumor; with deliberate dissection of mesenteric and renal vessels
- Evaluate lymph nodes and accurately describe extent of primary tumor resection

# Role of surgery: complications

- 80% Blood loss requiring transfusion
- 10% Injury to major vessels
- 5% Injury to other viscera
- < 5% Wound complication, bowel obstruction
- Other = hypertension, diarrhea, chyle leak, pleural effusion, prolonged TPN

# Role of Surgery: Intraspinal extension ('dumb bell' tumors)

- Urgent treatment is required if neurologic symptoms occur
- All 3 modalities have been used
  - Chemo :
  - Surgery: orthopedic sequele
  - Radiotherapy:
- laminotomy instead of laminectomy to access the tumor, may allow reconsideration

# The Tragedy of Africa

- unlikely to meet standards of pathology, radiology and labs required by European and American protocols, even in the distant future
- Pragmatic Approach: potentially favourable outcomes should be treated as aggressively as possible and resources should not be expended on patients for whom the outlook is grim
- Surgeons align with principle of neo-adjuvant chemo due to difficult experiences

# References


- Ashcraft's pediatric surgery 6th edition, **2014**
- The surgery of childhood tumors 3rd edition, **2016**
- Uptodate articles on Neuroblastoma, **2016-2017**