Neuroblastoma

Rasin Worawongsakul
Scope

• Introduction
• Natural history
• Screening
• Clinical presentation
• Work-up
• Staging, Prognostic factor & risk group

• Treatment
  ▪ Low risk
  ▪ Intermediate risk
  ▪ High risk
• Radiation dose and volume treatment
• Complications
Introduction

• Neuroblastoma – most common extra-cranial solid tumor in childhood
  ▪ 8-10% of all childhood cancers

• Neuroblastoma cells arise from cells of the neural crest (form adrenal medulla and sympathetic ganglia)

• Some of patients have spontaneous regression of disease
More than 650 new cases diagnosed per year in North America
1 case per 7000 live births
Median age at diagnosis: 2yr
  - Most common cancer diagnosed before age of 12 months
    ▪ 90% diagnosed before 5yr (very rare if >10yr)
White > Black (but African-American more likely to have high-risk disease and poor survival)
Natural history

• Neuroblastoma, ganglioneuroma & ganglioneuroblastoma may arise from any site in the sympathetic nervous system

• More than 70% - metastatic disease at diagnosis

• Highest spontaneous regression rate of human neoplasm
  - Usually by maturation to ganglioneuroma
  - Found >40 times of expected rate from autopsy young infants
Sites of origin

- H&N 5%
- Thorax 15%
- 30-40% Adrenal glands
- Abd+Pel 25%

Common metastatic sites

Neuroblastoma Stage 4
possible metastasis locations

- Lymph Nodes
- Skin
- Liver
- Bones
- Bone Marrow

- No data support neuroblastoma screening

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Screening method</th>
<th>Age at screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quebec/North America (Takeuchi et al. 1995)</td>
<td>340000</td>
<td>Urine VMA, HVA</td>
<td>3wk &amp; 6mo</td>
</tr>
<tr>
<td>Quebec/North America (Woods et al. 2002)</td>
<td>476654</td>
<td>Urine VMA, HVA</td>
<td>3wk &amp; 6mo</td>
</tr>
<tr>
<td>German (Schilling et al. 2002)</td>
<td>1475773</td>
<td>Urine VMA, HVA (Confirm 2 tests)</td>
<td>12mo</td>
</tr>
</tbody>
</table>

Screening

• Screening at age 3wk, 6mo or 1yr did not reduce incidence of advanced disease with unfavorable biology or overall mortality

• Mass screening program – diagnosis of biologically favorable & clinically insignificant tumors

Clinical presentation

- Extremely variable due to anatomic variability and extension

- “Sick child” distinguish from Wilms tumor (usually asymptomatic)
Clinical presentation

- Abdomen: mass, obstruction, distention
- H&N: Horner’s syndrome, periorbital ecchymosis (Raccoon eyes)
- Thorax: airway compromise, dysphagia
- Bone: bone or joint pain
- Paraneoplastic syndromes: catecholamine production
- Opsoclonus myoclonus syndrome
- Constitutional symptoms: weight loss, anorexia, malaise, fever

www.ijdvl.com/articles/2012/78/6/images/ijdvl_2012_78_6_740_102370_f1.jpg
www.globalskinatlas.com/upload/lg1525_2.jpg
Diagnostic work-up

- Tumor imaging
  - Ultrasonography abdomen
  - CT with contrast
  - MRI with contrast (especially paraspinal tumor that might threaten spinal cord compression)
  - Metaiodobenzylguanidine (MIBG)
  - Bone scan
MIBG

- Similar to norepinephrine
- Thyroid gland must be protected
  - Simultaneous administration of non-radioactive iodine (eg. Potassium iodide)
- Can be used with higher doses for treatment (for high risk or recurrence disease)
- Post-induction response for st.4 – prognostic marker EFS, survival

Uptake 90% of cases, specificity 95%
Curie Scoring: Methodology

- 10 segments (1 soft tissue)
- Each segment scored 0-3.
- Summate scores. Max = 30
- Skeletal score (per segment)
  1 = 1 distinct lesion
  2 = 2 distinct lesions
  3 = ≥ 50% of a segment.
- Soft tissue scoring
  1 = 1 MIBG avid ST lesion
  2 = > 1 MIBG avid ST lesion
  3 = occupies ≥ 50% region
    (chest or abd-pelvis)
### Curie (COG) and SIOPEN Scoring Methodology

#### Curie scoring
- 10 segments (1 soft tissue)
- Each segment scored 0-3.
- Summate scores. Max = 30
- Skeletal score (per segment)
  1 = 1 distinct lesion
  2 = 2 distinct lesions
  3 = ≥ 50% of a segment.
- Soft tissue scoring
  1 = 1 MIBG avid ST lesion
  2 = >= 1 MIBG avid ST lesion
  3 = occupies ≥ 50% region (chest or abd-pelvis)

#### SIOPEN scoring
- 12 segments (no soft tissue)
- Each segment scored 0-6.
- Summate scores. Max = 72
- Skeletal score (per segment)
  1 = 1 distinct lesion
  2 = 2 distinct lesions
  3 = 3 distinct lesions
  4 = >= 3 lesions or < 50% diffuse
  5 = 50-95% diffuse uptake
  6 = 100% diffuse uptake

Soft tissue scores analyzed separately

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Society of Pediatric Oncology European Neuroblastoma Network
Comparative MIBG Scoring

Curie score: 1
SIOPEN: 1

Curie score: 2
SIOPEN: 2

Curie score: 2
SIOPEN: 3

Curie score: 3
SIOPEN: 6
COG-A3073 (Post-induction Curie score)

Curie score ≤ 2: 3-yr EFS 44.9%
Curie score > 2: 3-yr EFS 15.4%

p < 0.001

Best cut-off

- Curie score: ≤2 vs >2
- SIOPEN score: ≤4 vs >4

CR after 4\textsuperscript{th} cycle of induction has better prognosis than having residual uptake

But no difference in survival – CR after 6\textsuperscript{th} cycle of induction

Diagnostic work-up

• Lab
  ▪ CBC – Anemia (widespread bone marrow involvement)
  ▪ LFT, BUN, Creatinine, LDH
  ▪ Urine catecholamine metabolites – VMA, HVA
    ➢ Found in 90-95% of pt
  ▪ Serum ferritin, NSE

• Biopsy tumor
• Bone marrow aspiration and biopsy
Pathological classification

- Neuroblastoma – the undifferentiated end of the spectrum of neural crest tumor
- Small round blue cell
  - Dense nests of hyperchromatic cells
  - Homer Wright rosettes with central fibrillary core
  - Positive stains for neurofilaments, neuron-specific enolase (NSE), synaptophysin & chromogranin A

https://imagebank.hematology.org/image/60129/neuroblastoma-bone-marrow
Spectrum of differentiation

https://www.fda.gov/ohrms/dockets/ac/01/slides/3756s1_07_REYNOLDS/img006.gif
**INPC classification (Shimada)**

**NB ≥50%**

**NB <50%**

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### International Neuroblastoma Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically.</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline,* with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs.</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (less than 10% tumor) in infants less than 1 year of age.</td>
</tr>
</tbody>
</table>
Prognostic - clinical

- Age: <18mo have better survival
- Site of origin: better survival for non-adrenal primary tumors
- Stage: powerful independent prognostic indicator
- Regional LN involvement: children older than 1yr (but controversial)
Prognostic - clinical

- Tumor histology (favorable/unfavorable)
- High serum chemistry: more advanced disease, poor prognosis
  - High serum ferritin (>142 ng/mL)
  - High NSE (>100 ng/mL)
  - High LDH (>1500 ng/mL)
Prognostic - Biological

• **N-MYC amplification**: rapid tumor progression & poor prognosis (independent factor)
• DNA: DNA Index (DI) >1 - better prognosis
  ▪ diploidy & tetraploidy decreased survival
  ▪ hyperploidy - better prognosis
• Segmental chromosome aberrations: bad prognosis
  ▪ 1p, 1q, 3p, 11q, 14q, 17p
• 17q gain bad prognosis
• Post induction response – stage 4 (MIBG after induction)
Prognostic - Biological

- ALK (Alkaline Lymphoma Phosphatase) mutations
  - Occurred in 8%
  - Correlated significantly with poorer survival in high- & intermediate-risk NB

- TERT (Telomerase Reverse Transcriptase gene) rearrangements
  - Telomerase expressions
  - Most occur in high risk disease
  - Poor outcome – EFS, OS

Risk assessment INSS

- High risk
  - St.3
    - MYCN amp
    - >1.5yr and UH
  - St.4
    - MYCN amp
    - >1.5 yr
    - 1-1.5yr with either UH or DI=1
  - St. 4s with MYCN amp
### International Neuroblastoma Risk Group Staging System (INRGSS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized disease without image-defined risk factors</td>
</tr>
<tr>
<td>L2</td>
<td>Localized disease with image-defined risk factors</td>
</tr>
<tr>
<td>M</td>
<td>Metastatic disease</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease &quot;special&quot; where MS is equivalent to stage 4S</td>
</tr>
</tbody>
</table>

**MS** - <18mo with metastases confined to skin, liver and/or BM
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral tumour within two body compartments</td>
<td>Neck-chest, chest-abdomen, abdomen-pelvis</td>
</tr>
<tr>
<td>Neck and cervico-thoracic junction</td>
<td>Tumour encasing carotid and/or vertebral artery and/or jugular vein</td>
</tr>
<tr>
<td></td>
<td>Tumour extending to base of skull</td>
</tr>
<tr>
<td></td>
<td>Tumour compressing the trachea</td>
</tr>
<tr>
<td></td>
<td>Tumour encasing the brachial plexus roots</td>
</tr>
<tr>
<td>Thorax</td>
<td>Tumour encasing the aorta and/or major branches</td>
</tr>
<tr>
<td></td>
<td>Tumour compressing the trachea and/or principle bronchi</td>
</tr>
<tr>
<td>Abdomen/pelvis</td>
<td>Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament</td>
</tr>
<tr>
<td></td>
<td>Tumour encasing the branches of the superior mesenteric artery at the mesenteric root</td>
</tr>
<tr>
<td></td>
<td>Tumour encasing the origin of the celiac axis and/or of the superior mesenteric artery</td>
</tr>
<tr>
<td></td>
<td>Tumour invading one or both of the renal pedicles</td>
</tr>
<tr>
<td></td>
<td>Tumour encasing the aorta and/or vena cava</td>
</tr>
<tr>
<td></td>
<td>Tumour encasing the iliac vessels</td>
</tr>
<tr>
<td></td>
<td>Pelvic tumour crossing the sciatic notch</td>
</tr>
<tr>
<td>Intraspinal tumour extension (not an IDRF if no symptoms or evidence of imaging of significant cord compression)</td>
<td></td>
</tr>
<tr>
<td>Infiltration of adjacent organs/structures</td>
<td>Pericardium, diaphragm, kidney, liver, mesentery</td>
</tr>
</tbody>
</table>
INRGSS risk assessment


- High risk
  - MYCN amp (except L1/L2 with GN or GNB intermixed)
  - M stage with age ≥18mo
  - MS stage
    - MYCN amp
    - 11q aberration

TREATMENT
Treatment modalities

- Surgery
- Chemotherapy (CMT)
- Radiation therapy (RT)
- Radionuclide: MIBG treatment
- Immunotherapy
Principles of surgery

- Surgery can be used for treatment and diagnosis
- Primary treatment for low-risk disease
- Resectability depends on
  - Location & mobility
  - Relationship with major nerves & vessels
  - Distant metastasis
  - Patient’s age
Principles of surgery

- St. I neuroblastoma have DFS >90% with surgical excision alone (O’ Neill et al. 1985, Nitschke et al. 1988, De Bernardi et al. 1995)
- Localized disease without MYCN amplification – gross surgical excision is the main curative treatment (De Bernardi et al. 2008)
- Unresectable localized disease has poorer prognosis except
  - Infants (Rubie et al. 2011)
  - Children with favorable biology (Cohn et al. 2009)
Principles of CMT

• Usually includes a combination of drugs
  ▪ Cyclophosphamide or Ifosfamide
  ▪ Cisplatin or Carboplatin
  ▪ Vincristine
  ▪ Doxorubicin
  ▪ Etoposide
  ▪ Topotecan
  ▪ Busulfan and Melphalan (HSCT)
• **Indications**
  - **Low-risk:** low or moderate intensity CMT is reserved only for
    - Tumor cannot be resected
    - Pt with threatening symptoms of spinal cord compression, respiratory or bowel compromise
  - **Intermediate-risk:** moderate intensive multi-agents CMT is used before attempted resection
  - **High-risk:** intensive CMT is used as combined multimodality treatment
Principles of RT

• RT indication reserved for
  ▪ High-risk disease: TBI as HSCT protocol or Local RT
  ▪ Low risk but unresectable disease with:
    ➢ Life threatening complications or tumor-related organ dysfunction unresponsive to emergency CMT
  ▪ Intermediate-risk:
    ➢ Only for emergency therapy as low risk
## Table 5. Treatment Options for Neuroblastoma

<table>
<thead>
<tr>
<th>COG Risk-Group Assignment</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk Neuroblastoma</td>
<td>Surgery followed by observation.</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy with or without surgery (for symptomatic disease or unresectable progressive disease after surgery).</td>
</tr>
<tr>
<td></td>
<td>Observation without biopsy (for perinatal neuroblastoma with small adrenal tumors).</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy (only for emergency therapy).</td>
</tr>
<tr>
<td>Intermediate-Risk Neuroblastoma</td>
<td>Chemotherapy with or without surgery.</td>
</tr>
<tr>
<td></td>
<td>Surgery and observation (in infants).</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy (only for emergency therapy).</td>
</tr>
<tr>
<td>High-Risk Neuroblastoma</td>
<td>A regimen of chemotherapy, surgery, myeloablative therapy and SCT, radiation therapy, and dinutuximab, with interleukin-2/GM-CSF and isotretinoin.</td>
</tr>
<tr>
<td>Stage 4S Neuroblastoma</td>
<td>Observation with supportive care (for asymptomatic patients with favorable tumor biology).</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (for symptomatic patients, very young infants, or those with unfavorable biology).</td>
</tr>
</tbody>
</table>
Low-risk

- COG-P9641
  - Non-randomized phase III
  - Primary endpoint: 3yr-OS
  - Safe primary tumor resection (>50% accept)
  - Immediate CMT reserved for life-threatening or organ-dysfunction could not relieve by surgery
  - St. 1 disease – 50%
  - St. 2a & 2b – 42%

LR-NB: 5-yr EFS 89%, OS 97%

Asymptomatic st.2a & 2b: 5-yr EFS 87%, OS 96%

Prognostic factor for OS
- Age < 18mo vs ≥18mo
- FH vs UH
- Hyperploid vs diploid

Low-risk

- COG-ANBL00p2
  - Age younger 6mo
  - St. I adrenal mass
    - Solid tumor <3.1cm
    - Cystic <5cm
  - 87 pt
    - 83pt – choose observe
    - 4pt – choose surgery


3-yr EFS (Neuroblastoma event)
97.7%, OS 100%

81% of observation group shows Spontaneous regression while avoiding surgery
Low-risk (Stage 4S)

- CCG 3881
  - 80 pt eligible for Evans st.
    - IV-S → only 1 not meet criteria of INSS st. 4s
  - No MYCN tested
  - Major primary: adrenal
  - Most common: metastatic site: liver (81%)
  - Surgery: 49 infants
    - Complete resection: 31 pt
  - 31 stage by MRI


Unfavorable histology predicts poorer EFS, OS

Table 9. ANBL1232 Treatment Assignment for Low-Risk Neuroblastoma

<table>
<thead>
<tr>
<th>INRG Stage</th>
<th>Biology (Histology and Genomics(^a))</th>
<th>Age</th>
<th>Other</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td></td>
<td>&lt;12 months</td>
<td>&lt;5 cm in diameter; confirmatory study if nonadrenal</td>
<td>Observe on study without biopsy</td>
</tr>
<tr>
<td>L2</td>
<td>Favorable histology and genomics(^b)</td>
<td>&lt;18 months</td>
<td>Asymptomatic(^c)</td>
<td>Observe on study</td>
</tr>
<tr>
<td>MS</td>
<td>Any histology and genomics</td>
<td>&lt;3 months</td>
<td>Existing or evolving hepatomegaly or symptomatic</td>
<td>Immediate treatment, response-based chemotherapy, as per protocol</td>
</tr>
<tr>
<td></td>
<td>Favorable histology and genomics(^b)</td>
<td>&lt;3 months</td>
<td>Asymptomatic(^c) without existing or evolving hepatomegaly</td>
<td>Observe per clinical scoring system</td>
</tr>
<tr>
<td></td>
<td>Favorable histology and genomics(^b)</td>
<td>3–18 months</td>
<td>Asymptomatic(^c)</td>
<td>Observe per clinical scoring system</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>Response-based chemotherapy, as per protocol</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Age</td>
<td>Stage</td>
<td>Rx</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>--------------------</td>
<td>--------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>COG-A3961 (2010)</td>
<td>497</td>
<td>&lt;1yr-78.7%</td>
<td>3-53.4% 4-37.1% 4s-6.5%</td>
<td>CMT then Sx FH-4 cycles UH-8 cycles</td>
</tr>
<tr>
<td>NB95-S &amp; NB97 (2008)</td>
<td>340</td>
<td>&lt;1yr</td>
<td>3-27.4% (include all st.1-3)</td>
<td>Observe-27.3% CMT-16.8% Sx (complete or nearly)-55.9%</td>
</tr>
<tr>
<td>SIOPEN/INESS99.1 (2011)</td>
<td>120</td>
<td>&lt;1yr</td>
<td>3-70% 2-30%</td>
<td>Sx (If IDRFs or symptomatic CMT upfront)</td>
</tr>
<tr>
<td>SIOPEN99.2 (2013)</td>
<td>160</td>
<td>&gt;1yr (&gt;18mo-62%)</td>
<td>3-76.7% 2-21.3%</td>
<td>4CMT-Sx-2CMT</td>
</tr>
<tr>
<td>SIOPEN99.2/99.3 (2009)</td>
<td>125+45</td>
<td>&lt;1yr</td>
<td>St. 4&amp;4s</td>
<td>CMT 2-4 cycles ± Sx (54.1%)</td>
</tr>
</tbody>
</table>
High-risk disease

EFS According to Risk Group

- Low-Risk (n=916)
- Intermediate-Risk (n=431)
- High-Risk (n=849)

COG statistical office
High risk disease

- Multimodality of treatment
- Induction 5-6 cycles of induction CMT
- Second look surgery
- Consolidative
- Maintenance: immunological or targeted agents
High risk disease

- Multimodality of treatment
- Induction 5-6 cycles of induction CMT
  - Combination of agents (platinum, etoposide, cyclophosphamide, vincristine + doxorubicin, topotecan)
- Second look surgery
- Consolidative
- Maintainance: immunological or targeted agents
High risk disease

- Multimodality of treatment
- Induction 5-6 cycles of induction CMT
- Second look surgery
- Consolidative
  - HD-CMT with HSCT - CCG 3891
    - Tandem (Thiotepa/CPM+CEM) is better than single CEM – ANBL 0532
    - Bu/Mel is better than CEM – SIOPEN HR-NBL-1
    - Bu/Mel is safe even COG induction protocol – ANBL 12P1
  - Local therapy: RT at local or metastatic site if required
- Maintainance: immunological or targeted agents
High risk disease

- Multimodality of treatment
- Induction 5-6 cycles of induction CMT
- Second look surgery
- Consolidative
- Maintenance: immunological or targeted agents
  - 13-cis-retinoic acid (RA) – CCG 3891
  - Anti-GD2 antibodies: Ch 14/18 antibody (enhanced by GM-CSF, IL2) - ANBL 0032
  - (On going) ALK inhibitor: Crizotinib – ANBL 1531
Rational for RT

• Relapse at primary site: significant challenge
  ➢ Primary tumor usually large, invasive - unsafe for total resection
  ➢ Rarely eradicate primary tumor by CMT
  ➢ Local recurrence occur in 5-74% with high-risk disease (from historical data)
  ➢ No randomized trial for role of radiation
    ➢ No standard radiation dose
Figure 2. Kaplan–Meier Estimates of Survival among the 226 Study Patients Who Had Been Randomly Assigned, According to Treatment Group.

Data are shown for event-free survival (Panel A) and overall survival (Panel B) for all 226 patients and for event-free survival (Panel C) and overall survival (Panel D) for the 179 patients 1 year of age or older at enrollment. The estimated survival (±SE) at 2 years is indicated in each plot.

• Tandem myeloablative arm vs single myeloablative arm
  - 3yr-EFS: 61.4% vs 48.4% (p=0.0081)
  - 3yr-OS: 74% vs 69.1% (p=0.185)
  - No statistically significance in toxicities
• Tandem is superior to single transplant
Rapid COJEC Protocol

Course A: vincristine, carboplatin, and etoposide
Course B: vincristine and cisplatin
Course C: vincristine, etoposide, and cyclophosphamide

Potential timepoints for surgical resection

Stem-cell harvest timeframe
Topotecan, vincristine, and doxorubicin

Two courses if inadequate response

HDT randomisation

Busulfan and melphalan with SCR

Carboplatin, etoposide, and melphalan with SCR

Radiotherapy

Maintenance therapy with or without immunotherapy

Enrolment

Induction therapy

Consolidation therapy

Maintenance therapy

All pts 5-yr EFS 45% vs 33%

BU/MEL CEM

5-yr OS 54% vs 41%

Toxicities: Severe life-threatening: 4% vs 10%

- CEM – more gr3-4 Infection, Stomatitis, General condition
- BU/MEL – more gr1-3 SOS (22% vs 9%)

• Is it safe to use Bu/Mel as conditioning regimen with COG induction protocol?
  ▪ 101 pt with very similar induction response to ANBL 0532
  ▪ 6% severe SOS
Is it safe to combine therapeutic MIBG with Bu/Mel consolidation?
- 99 pt accrued (35 received MIBG + Bu/Mel)
- Risk of SOS at higher dose (18mCi/kg)
<table>
<thead>
<tr>
<th>Author</th>
<th>Radiation dose</th>
<th>Local relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al.(1984)</td>
<td>25-40Gy</td>
<td>74</td>
</tr>
<tr>
<td>Ikeda et al.(1992)</td>
<td>7.5-22Gy + TBI 10Gy</td>
<td>17</td>
</tr>
<tr>
<td>Matthay et al.(1993)</td>
<td>No residual: 10Gy TBI</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Residual: 20Gy</td>
<td></td>
</tr>
<tr>
<td>Kremens et al.(1994)</td>
<td>21Gy (1.5Gy bid)</td>
<td>15</td>
</tr>
<tr>
<td>Sibley et al.(1995)</td>
<td>8-24Gy + TBI 12 GY</td>
<td>16%</td>
</tr>
<tr>
<td>Villablanca et al.(1999)*</td>
<td>21Gy (1.5Gy bid)</td>
<td>5%</td>
</tr>
<tr>
<td>Kushner et al.(2001)</td>
<td>21Gy (1.5Gy bid)</td>
<td>10%</td>
</tr>
<tr>
<td>Hass-Kogan et al.(2002)*</td>
<td>10Gy IORT</td>
<td>9%</td>
</tr>
<tr>
<td>Casey et al.(2016)</td>
<td>21Gy (1.5Gy bid)</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Abstract
RT dose

• No standard dose due to non-randomized study

• CCG 3891 – Radiation administered non-uniformly

• COG A3973 – Radiation administered uniformly

• COG ANBL0532 – Radiation question asked
CCG 3891

- Additional 10Gy TBI + Myeloablative CMT: local control benefit

EBRT:
- 10Gy to mediastinal or intra-abdominal tumors
- 20Gy to extra-abdominal tumors

- 20Gy might be more benefit than 10Gy
• No standard dose due to non-randomized study

• CCG 3891 – Radiation administered non-uniformly
  ▪ Suggested dose-response for radiation to primary site

• COG A3973 – Radiation administered uniformly

• COG ANBL0532 – Radiation question asked
• Radiation administered uniformly
  - 21.6Gy (1.8Gy/F daily) after HSCT

• Primary sites receives radiation regardless of extent of surgery
  - Volume of primary site RT: Pre-surgical tumor volume

• Radiation give to all areas of residual disease

Kreissman SG et al. Lancet Oncol 2013; 14:999-1008
Effects of extent LN RT were not statistically significant

Recommend to cover only involved LN

<table>
<thead>
<tr>
<th>Lymph Node Coverage</th>
<th>N (%)</th>
<th>5-year EFS ± std error (%)</th>
<th>EFS p-value</th>
<th>5-year CILR ± std error (%)</th>
<th>CILR p-value</th>
<th>5-year OS ± std error (%)</th>
<th>OS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40%</td>
<td>75 (23%)</td>
<td>50.8 ± 6.0</td>
<td>0.4923</td>
<td>6.9 ± 3.0</td>
<td>0.5487</td>
<td>61.7 ± 6.2</td>
<td>0.3510</td>
</tr>
<tr>
<td>≥ 40%</td>
<td>255 (77%)</td>
<td>46.2 ± 3.4</td>
<td></td>
<td>9.0 ± 1.8</td>
<td></td>
<td>59.0 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>&lt; 60%</td>
<td>148 (45%)</td>
<td>50.1 ± 4.5</td>
<td>0.5104</td>
<td>6.9 ± 2.1</td>
<td>0.3253</td>
<td>59.6 ± 4.4</td>
<td>0.6153</td>
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<tr>
<td>≥ 60%</td>
<td>182 (55%)</td>
<td>45.0 ± 4.0</td>
<td></td>
<td>9.9 ± 2.2</td>
<td></td>
<td>59.7 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>&lt; 80%</td>
<td>239 (74%)</td>
<td>46.8 ± 3.5</td>
<td>0.8281</td>
<td>8.0 ± 1.8</td>
<td>0.5897</td>
<td>59.0 ± 3.5</td>
<td>0.9973</td>
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<tr>
<td>≥ 80%</td>
<td>91 (26%)</td>
<td>48.2 ± 5.6</td>
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<td>9.9 ± 3.2</td>
<td></td>
<td>61.3 ± 5.5</td>
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</tr>
</tbody>
</table>

RT dose

• No standard dose due to non-randomized study

• CCG 3891 – Radiation administered non-uniformly
  ▪ Suggested dose-response for radiation to primary site

• COG A3973 – Radiation administered uniformly
  ▪ Prophylactic RT uninvolved LN is not recommend

• COG ANBL0532 – Radiation question asked
**ANBL 0532**

**Hypothesis:**

- Increasing dose of local RT for pt with <GTR will reduce local failure

**Dose post-BMT**

- 21.6Gy to pre-operative tumor volume
- 14.4Gy boost to gross residual disease

No result of RT dose response
Dose escalation might be needed for gross disease HR-NB

- Pt with residual viable tumor on MRI and MIBG receive EBRT 36Gy has 3yr-EFS & OS better than pt who did not receive EBRT
- With isolated localized residual disease who receive EBRT: 3yr-EFS & OS 100% both

• Retrospective study of 110 stage 4 NB pt on NB97 trial

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>3-year EFS (%)</th>
<th>3-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in CR after induction chemotherapy and did not receive EBRT (n=74)</td>
<td>61 ± 10</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>Patients with residual disease who <strong>DID</strong> receive EBRT (n=13)</td>
<td>85 ± 10</td>
<td>92 ± 7</td>
</tr>
<tr>
<td>Patients with residual disease who <strong>DID NOT</strong> receive EBRT (n=13)</td>
<td>25 ± 10</td>
<td>51 ± 11</td>
</tr>
<tr>
<td></td>
<td><strong>P&lt;0.001</strong></td>
<td><strong>P=0.003</strong></td>
</tr>
</tbody>
</table>

Dose response

- Retrospective study of 110 stage 4 NB pt on NB97 trial
  - Isolated localized residual disease

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>3-year EFS (%)</th>
<th>3-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with isolated localized residual disease who <strong>DID</strong> receive EBRT (n=8)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Patients with isolated localized residual disease who <strong>DID NOT</strong> receive EBRT (n=6)</td>
<td>20 ± 18 P&lt;0.001</td>
<td>20 ± 18 P&lt;0.001</td>
</tr>
</tbody>
</table>

• Dose escalation might be needed for gross disease HR-NB
  ▪ 331 pt with gross disease at time RT
  ▪ 5yr-LF 36% for <30Gy, 20% for 30Gy & 0% for 36Gy
  ▪ Dose 36Gy may needed for control of gross residual disease at time RT

• Reduced-dose for HR-NB after gross total resection
  ▪ 24 pt enrolled on prospective dose reduction trial after GTR
  ▪ 18Gy (1.5Gy bid)
  ▪ No local failure observed at 2 yr

Casey DL et al. Int J Radiat Oncol Biol Phys 99(2), 2017 (suppl; abstr 56)
Casey DL et al. Int J Radiat Oncol Biol Phys 99(2), 2017 (suppl; abstr 57)
Schematic treatment

Protocol for very low/ low risk neuroblastoma
(ThaiPOG-NB-13LR)

Very Low/ Low risk Neuroblastoma

Stage MS

No complication

- Close observe

Respiratory compromise
- Severe liver dysfunction

- Chemotherapy (low-risk protocol) OR
- 150 cGy 2-3 times to the anterior 2/3 of the liver through lateral oblique ports

Non-stage MS

Surgical removal of 1st tumor

- >50% resection
  - Close observe

- <50% resection
  - Chemotherapy (low-risk protocol)
**Protocol for standard risk neuroblastoma**  
*(ThaiPOG-NB-13SR)*

Chemotherapy doses are adjusted for children < 365 days of age or who are ≤ 12 kg in weight and are given as mg/kg.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>Etoposide</td>
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<td>•</td>
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<tr>
<td>Cyclophosphamide</td>
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<td>•</td>
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<td>•</td>
<td>•</td>
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<tr>
<td>Doxorubicin</td>
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<td>•</td>
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<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>

**After cycle 4:** assess treatment response, and perform surgery if feasible

<table>
<thead>
<tr>
<th>Cycle</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>85</td>
<td>86</td>
<td>87</td>
<td>106</td>
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<tr>
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<td>127</td>
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<tr>
<td>Carboplatin</td>
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<td>•</td>
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<td>•</td>
</tr>
<tr>
<td>Etoposide</td>
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<tr>
<td>Cyclophosphamide</td>
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</tr>
<tr>
<td>Doxorubicin</td>
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<td>•</td>
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<td>•</td>
</tr>
</tbody>
</table>

**After cycle 8:** assess treatment response, and perform surgery if residual primary tumor detected
Protocol for high risk neuroblastoma
(ThaiPOG-NB-13HR)

HIGH RISK NEUROBLASTOMA (ThaiPOG-NB-13HR)

**Ineligible for HSCT**

- **INDUCTION II**
  - ICE x 4 cycles
  - LD-MIBG treatment (optional)

**MAINTENANCE THERAPY**
Topotecan 0.75 mg/m² +
Cyclophosphamide 250 mg/m² (Day 1-5)

3 cycles at 3-4 week intervals

- LOCAL XRT *

13 Cis-retinoic acid

6 cycles of 2 wks on & 2 wks off

**Eligible for HSCT**

- HD-MIBG treatment (optional)
- HSCT
- LOCAL XRT *
- 13 Cis-retinoic acid

6 cycles of 2 wks on & 2 wks off

* Stem cell harvest for auto-HSCT (frozen) – If the frozen collection is not feasible, the stem cell harvest may be done after completing induction II (Δ) only with no HD-MIBG planned

↑ Surgery
* If no viable residual tumor, may consider giving fractionated irradiation (local XRT: dose 2100-2500 cGy) to the primary tumor site. If having viable residual tumor (proven from histology, MIBG or tumor with persistent elevated tumor marker), may consider giving fractionated irradiation (2500 cGy) to the residual tumor
RT volume

- Should treat gross residual tumor remaining after CMT with at least 2cm margin (PTV) to ensure adequate dosimetric coverage.
- Organ motion and set-up uncertainties should be aware.
- Sedated child may require a lesser margin.
- Involved LN should be treated.
- Late spinal deformity should be considered as Wilms tumor (same as other OARs).

Perez and Brady's Principles and Practice of Radiation Oncology. 6th edition; 2013.
• Benefit still controversy – only small retrospective studies with different results

• Currently treat whatever active after induction as COG A3973
- Determine EFS benefit on additional MIBG treatment during induction prior ASCT

- Determine EFS benefit on addition crizotinib in ALK gene mutated patients
ANBL 1531 RT changes

- Update to normal tissue constraints
- Vertebral body coverage
- mGTV identification
- CTV1 margin decrease from 1.5 to 1cm
- Site and technology specific contouring guidelines
If tumor proximity to vertebral body should cover entire vertebral with 18Gy (included posterior elements)
<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Kidney</td>
<td>&lt;75% Mean dose ≤ 18 Gy</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>&lt;100%</td>
<td>14.4</td>
</tr>
<tr>
<td>Contralateral Kidney</td>
<td>&lt;25%</td>
<td>18</td>
</tr>
<tr>
<td>Ipsilateral Lung</td>
<td>&lt;30%</td>
<td>20</td>
</tr>
<tr>
<td>Contralateral Lung</td>
<td>&lt;10%</td>
<td>20</td>
</tr>
<tr>
<td>B/L Lung</td>
<td>&lt;30%</td>
<td>20</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;15% Mean &lt; 15 Gy</td>
<td>30</td>
</tr>
<tr>
<td>Vertebral Bodies</td>
<td>If vertebral body requires treatment, the entire vertebral body and posterior elements mean dose should be &gt;18 Gy. <strong>Remove vertebral body from CTV</strong></td>
<td>Mean dose &gt;18 Gy</td>
</tr>
<tr>
<td>CTVs</td>
<td>&gt;99% receives 95% of prescribed dose</td>
<td></td>
</tr>
<tr>
<td>PTVs</td>
<td>&gt;90% receives 95% of prescribed dose</td>
<td></td>
</tr>
</tbody>
</table>
Complication

• Scoliosis: up to 25% according to retrospective study with 58pt
  ▪ Dose > 17.5Gy are significant
• Audiological sequelae due to platinum
• Ovarian dysfunction
• Hypothyroid: MIBG or neck EBRT
• SOS: very important with regard to Bu/Mel regimen
  ▪ Should keep radiation dose to liver as low as possible (esp. right side tumor)
• Second malignancy

Take home

- Neuroblastoma - most common extra-cranial solid tumor in childhood & highest spontaneous regression rate of human neoplasm
- No benefit for screening
- Even metastatic disease, some still have favorable prognosis (especially stage 4s)
- Risk stratification: shift from INSS (surgical pathology) - > INRGSS (image defined risk with molecular biology)
Take home

• Role of radiotherapy
  ▪ Mainly in high-risk disease: either TBI or focal RT for residual disease after induction therapy
  ▪ Selected case in low or intermediate risk: symptomatic unresectable disease which not response to chemotherapy
Take home

- Radiation dose
  - No standard dose due to non-randomized study
  - Higher dose may have role for residual disease (Data ANBL 0532)
  - Symptomatic relieve - 3-4.5Gy/2-3F
Take home

• Radiation volume
  - COG A3973
    - Primary sites (regardless of extent of surgery): Pre-surgical tumor volume
    - All areas of residual disease
    - Involved nodal RT – no benefit for prophylaxis nodal RT
  - ANBL 1531 (on going)
    - Reduce CTV 1.5cm to 1 cm
    - Update normal tissue constraints
Take home

• Long-term treatment complication should be considered
  ▪ High cure rate for low and intermediate risk
  ▪ 90% of patients diagnose before 5 years old
The End
Tumor microenvironment