Neuroblastoma

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For COG, 2016
Stage 4S Neuroblastoma
Age 3 months
Neuroblastoma

- Derived from sympathetic nervous system
- Most common extra-cranial solid tumor of childhood
- Most common malignancy in newborn period
- Outcome depends on tumor biology
EFS According to Risk Group

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

COG Statistical Office
High-risk Neuroblastoma

Induction

Consolidation

MRD Therapy

Diagnosis

Surgery

XRT

Log Tumor Cells

Acquired Drug Resistance
Is local recurrence a dominant form of disease relapse?

Does radiation to the primary site contribute to local control?

How should local RT be incorporated into multimodality treatment of neuroblastoma?

Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?
Relapse at the primary site presents a significant challenge:

- Primary tumors are large, invasive and rarely eradicated by chemotherapy.
- Local recurrences occur in 5-74% of patients with high-risk disease.

No randomized trials have addressed the role of radiation in stage IV neuroblastoma.
## High-Risk Neuroblastoma: Local Recurrence

<table>
<thead>
<tr>
<th>Author</th>
<th>Radiation dose</th>
<th>Local relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen <em>et al.</em>, 1984</td>
<td>25-40 Gy</td>
<td>74%</td>
</tr>
<tr>
<td>Kremems <em>et al.</em>, 1994</td>
<td>21 Gy (1.5 bid)</td>
<td>15%</td>
</tr>
<tr>
<td>Ikeda <em>et al.</em>, 1992</td>
<td>7.5-22 Gy (+10 Gy TBI)</td>
<td>17%</td>
</tr>
<tr>
<td>Villablanca <em>et al.</em>, 1999*</td>
<td>21 Gy (1.5 bid)</td>
<td>5%</td>
</tr>
<tr>
<td>Sibley <em>et al.</em>, 1995</td>
<td>8-24 Gy (+12 Gy TBI)</td>
<td>16%</td>
</tr>
<tr>
<td>Haas-Kogan. <em>et al</em> 2002*</td>
<td>10 Gy IORT</td>
<td>9%</td>
</tr>
<tr>
<td>Kushner <em>et al.</em>, 2001</td>
<td>21 Gy (1.5 bid)</td>
<td>10%</td>
</tr>
<tr>
<td>Matthay <em>et al.</em>, 1993</td>
<td>Residual dz: 20 Gy</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>No residual: 10 Gy TBI</td>
<td>31%</td>
</tr>
</tbody>
</table>

* abstract
Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?
CCG 3891 Schema

Surgery
Radiation

Initial chemotherapy

Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5

RANDOMIZE

Myeloablative therapy
TBI + ABMT

Cycle 1
Cycle 2
Cycle 3

RANDOMIZE

Continuation chemotherapy

RANDOMIZE

13-cis-retinoic acid

No 13-cis-retinoic acid
Local radiation was NOT administered in a randomized fashion.

External beam radiation therapy (EBRT) administered to gross residual disease prior to ABMT or continuation chemo (CC).

Dose: 20 Gy (2 Gy qD) to extra-abd tumors.
10 Gy to mediastinal or intra-abd tumors.

Matthay et al. NEJM 1999; 341:1165-1173
Primary Site Relapse by Treatment Received (CCG 3891)

CC (N=253)

ABMT (N=129)

P<0.01
Patients with \textit{MYCN} amplification: Primary Site Relapse (CCG 3891)

\textbf{CC (N=69)}

\textbf{ABMT (N=29)}

$P < 0.01$
Does radiation to the primary site contribute to local control?

- Examined a group with more uniform patient characteristics by evaluating separately the group that received EBRT for gross residual disease.

- Ask whether the addition of 10 Gy of TBI as a component of ABMT improved local control.
Patients Receiving EBRT: Primary Site Relapse (CCG 3891)

PROBABILITY

YEARS

CC (N=79)

ABMT (N=29)

P=0.02
Word of caution: all ABMT patients received myeloablative chemotherapy as well as additional radiation in the form of TBI.

Nevertheless: the results suggest that 20 Gy in the form of 10 Gy TBI + 10 Gy EBRT (as part of ABMT) may improve local control compared to 10 Gy alone (without ABMT).
Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?
Patients Receiving 13-cis-retinoic acid: 5-year Event Free Survival

No EBRT (N=48)

EBRT (N=105)

P=0.05
The benefit of local control emerges as metastases are better controlled by treatment directed at systemic and minimal residual disease.

- myeloablative therapy.
- 13-\textit{cis}-retinoic acid.
Rationale for Radiation Guidelines

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?
Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?

**Surrogate question:**

- How did we arrive at our current “standard” dose of radiation?

**Answer:**

- Empirically!!
- Based on studies performed during a time period in which all but stage I patients received radiation.
Results:

- Doses of 9-15 Gy for patients <1 yr and 12-19 Gy for patients 1-2 yrs prevented all local recurrences.
- Data did not support benefit of doses higher than 20 Gy.

Stage: II, III, IV

Patient #: 21, 0

“Pediatric Neuroblastoma: Postoperative Radiation Therapy Using Less Than 2000 Rad”

Jacobson HM, Marcus RB, Thar TL, Million RR, Graham-Pole JR, Talbert JL.
Evidence for a dose-response?

- Analysis of CCG 3891, in which local radiation was NOT administered in a randomized fashion. Rather, external beam radiation therapy (EBRT) administered to gross residual disease prior to ABMT or continuation chemo (CC).
  
  **Dose:** 20 Gy (2 Gy qD) to extra-abdominal tumors.
  
  10 Gy to mediastinal or intra-abdominal tumors.

- Examine the subgroup of patients who received 20 Gy for extra-abdominal primary tumors.

- Of 36 patients with extra-abdominal primaries, 6 patients received 20 Gy EBRT while 30 patients received no EBRT.
20 Gy to Extra-Abdominal Primary: Primary Site Relapse

P = 0.088

No 20 Gy EBRT (N=30)
20 Gy EBRT (N=6)
More pronounced benefits in local control and EFS are seen in the small group in which EBRT consisted of 20 Gy rather than 10 Gy.

Perhaps a dose-response exists for radiation administered to the primary tumor.
Do patients with less than a complete resection need higher radiation doses?

- 99 high-risk neuroblastoma pts in 1st remission.
- RT to primary site delivered after dose-intensive chemotherapy and tumor resection.
- Dose: 1.5 Gy bid to 21 Gy total.
- Probability of primary-site failure was 10.1% at 36 months after RT.
- No primary-site failures among the 23 patients whose tumors were excised at diagnosis.
- Three primary-site relapses occurred among seven patients who received local RT with evidence of residual disease at the primary site.

Kushner et al., JCO (2001) 19:2821-2828
Intensified external beam radiation therapy improves the outcome of stage 4 neuroblastoma in children >1 year with residual local disease.

Retrospective study of 110 stage 4 neuroblastoma patients on NB97 trial: induction chemotherapy, surgery, ABMT.

Intensified local EBRT (36 Gy) for residual viable tumor on MRI and MIBG.

- 74 patients had CR to induction chemotherapy: no EBRT.
- 23 had residual disease but did not receive EBRT.
- 13 with residual disease underwent EBRT (36 Gy).
### Evidence for a dose-response?

<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 DID receive EBRT (n=13)</td>
<td>85 ± 10</td>
<td>92 ± 7</td>
</tr>
<tr>
<td>Patients with residual disease who DID NOT receive EBRT (n=13)</td>
<td>25 ± 10, P&lt;0.001</td>
<td>51 ± 11, P=0.003</td>
</tr>
</tbody>
</table>

Authors Conclude: EBRT (36 Gy) “seems to compensate for the disadvantage of incomplete response to induction therapy.”

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University Children’s Hospital in Cologne  
### 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</td>
<td>20 ± 18</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

On multivariate analysis, EBRT was an independent prognostic factor for EFS (HR=0.27, 95% CI 0.09-0.76) and OS (HR=0.17, 95% CI 0.04-0.81).
Hypothesis:
- Increasing the dose of local radiation for patients with \(<\text{GTR}\) will reduce local tumor failure rates.
- Dose for post-\text{ABMT} radiation to the primary tumor bed based on residual disease:
  - 21.6 Gy for \text{GTR}
    - pre-operative tumor volume
  - 36.0 Gy for \(<\text{GTR}\)
    - 21.6 Gy to pre-operative tumor volume
    - 14.4 Gy boost to gross residual disease

Historical comparison with primary tumor relapse rates on \text{A3973}

Question:
- Can we detect an improvement in local control after an additional 14 Gy administered to children with \(<\text{GTR}\)?
Radiation Therapy for Neuroblastoma: Important Questions

- Is local recurrence a dominant form of disease relapse?
- Does radiation to the primary site contribute to local control?
- How should local RT be incorporated into multimodality treatment of neuroblastoma?
- Is there a dose-response to primary site irradiation and does a subtotal resection require a higher radiation dose?
Progress in COG high-risk neuroblastoma studies

- CCG 3891: Radiation administered non-uniformly
- COG A3973: Radiation administered uniformly
- COG 0532: A radiation question asked
Progress in COG high-risk neuroblastoma studies

CCG 3891: Suggested a dose-response for radiation to the primary site

COG A3973: Radiation administered uniformly

COG 0532: A radiation question asked
Progress in COG high-risk neuroblastoma studies

- **CCG 3891**: Radiation administered non-uniformly

  ➔

- **COG A3973**: Radiation administered uniformly

  ➔

- **COG 0532**: A radiation question asked
A Randomized Study of Purged versus Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma
Radiation given following myeloablative stem cell transplant to all areas of residual disease.

Primary site receives radiation regardless of extent of resection.

Volume of primary site RT: pre-surgical tumor volume, regardless of extent and timing of the surgical resection or response to chemotherapy.

Dose: 21.6 Gy in 1.8 Gy daily fractions.
High-risk neuroblastoma, A3973:

- Immunomagnetic tumor-selective PBSC purging in stem-cell transplantation for autologous stem-cell transplantation did not improve outcome, perhaps because of incomplete purging or residual tumor in patients. Non-purged PBSC are acceptable for support of myeloablative therapy of high-risk neuroblastoma.
- Radiation results pending.
Progress in COG high-risk neuroblastoma studies

- **CCG 3891**: Suggested a dose-response for radiation to the primary site
- **COG A3973**: Radiation administered uniformly
- **COG 0532**: A radiation question asked
COG A3973 Protocol for High-Risk Neuroblastoma Patients

A Randomized Study of Purged versus Unpurged Peripheral Blood Stem Cell Transplant Following Dose Intensive Induction Therapy for High Risk Neuroblastoma

- 486 eligible patients
- 156 had no radiation, were ineligible, or not data submitted
- Reviewed 339 radiation plans and associated diagnostic scans and clinical data
What is the best approach to radiation of un-involved lymph nodes stations?

- What do we base our lymph node coverage on?
- What does the literature support?

Not much…

- A3973 helped us answer the question
Effects of extent of lymph node irradiation were neither clinically nor statistically significant.

<table>
<thead>
<tr>
<th>Lymph node coverage</th>
<th>N (%)</th>
<th>EFS ± std error (%)</th>
<th>EFS p-value</th>
<th>CILR ± std error (%)</th>
<th>CILR p-value</th>
<th>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 46.2 ± 3.4</td>
<td>0.49</td>
<td>6.9 ± 3.0 9.0 ± 1.8</td>
<td>0.55</td>
<td>61.7 ± 6.2 59.0 ± 3.4</td>
<td>0.35</td>
</tr>
<tr>
<td>≥ 40%</td>
<td>255 (77%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60%</td>
<td>148 (45)</td>
<td>50.1 ± 4.5 45.0 ± 4.0</td>
<td>0.51</td>
<td>6.9 ± 2.1 9.9 ± 2.2</td>
<td>0.32</td>
<td>59.6 ± 4.4 59.7 ± 4.0</td>
<td>0.61</td>
</tr>
<tr>
<td>≥ 60%</td>
<td>182 (55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 80%</td>
<td>239 (74)</td>
<td>46.8 ± 3.5 48.2 ± 5.6</td>
<td>0.83</td>
<td>8.0 ± 1.8 9.9 ± 3.2</td>
<td>0.59</td>
<td>59.0 ± 3.5 61.3 ± 5.5</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 80%</td>
<td>91 (26)</td>
<td></td>
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</tr>
</tbody>
</table>
Progress in COG high-risk neuroblastoma studies

- CCG 3891: Radiation administered non-uniformly
  - COG A3973: Do not extend primary site RT fields to include uninvolved lymph node stations, treated prophylactically
    - ANBL 0532: A radiation question asked
Progress in COG high-risk neuroblastoma studies

CCG 3891
Radiation administered non-uniformly

COG A3973
Do not extend primary site RT fields to include uninvolved lymph node stations, treated prophylactically

ANBL 0532
A radiation question asked
High-Risk Neuroblastoma Study

ANBL0532

Phase III Randomized Trial of Single versus Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma
High risk task force consensus schema

CEM=Carboplatin/Etoposide/Melphalan
To Ultra-high risk study if:
• PD during induction therapy, or
• “Bad” PR defined by Relative Curie score after 4 cycles

Randomization time point
Disease assessment
COG ANBL 0532

Primary Aim: Is 3-year EFS of high-risk patients improved using a tandem consolidation of Thiotepa/Cyclophosphamide followed by Carboplatin/Etoposide/Melphalan (CEM) superior when compared to single CEM consolidation

- 652 patients
- 3-year EFS and OS were 50.9% and 68.0%.
- The 3-year EFS following tandem myeloablative therapy (63.2%) was statistically significantly superior to single myeloablative therapy (48.6%; \(p=0.0064\))
- The 3-year OS following tandem myeloablative therapy versus single myeloablative therapy was 73.5% and 68.8% \(p=0.2207\)
Hypothesis:
There is a dose-response to primary site irradiation and a subtotal resection requires a higher radiation dose.
High-Risk Patients Often Relapse in Previously Involved Metastatic Sites

DIAGNOSIS  
CR PRE-SCT (+6 mo)  
RELAPSE (+2 yrs)
Relapses at New Sites is Unusual

18% of sites at relapse previously uninvolved

Polishchuk et al., IJROBP 2014
• 21 metastatic sites in 14 patients irradiated for persistence following induction therapy

• 4/21 (19%) irradiated residual sites relapsed as compared to 126/504 resolved un-irradiated sites (25%)

Radiation Therapy Effective at Preventing Relapse At Residual Metastatic Sites

Polishchuk et al., IJROBP 2014
ANBL 09P1: Closed to Accrual 1/6/16

Question: Is it safe to combine Bu-Mel consolidation with therapeutic MIBG?
ANBL 12P1: Closed to accrual on 4/17/15

Is it safe to use Bu-Mel as a conditioning regimen in the framework of a COG induction platform (as opposed to a SIOPEN induction platform)?

**Experimental Design Schema**

![Experimental Design Schema Diagram]

- **Induction therapy**
  - 1
  - 2
  - 3
  - 4
  - 5
  - PBSC harvest
  - Surgical resection
  - Induction Cycles 1 & 2: topotecan, cyclophosphamide
  - Induction Cycles 3 & 5: cisplatin, etoposide
  - Induction Cycle 4: cyclophosphamide, doxorubicin, vincristine.
  - PBSC harvest: Peripheral blood stem cell harvest.
  - ASCT: autologous stem cell transplant (busulfan, melphalan)
  - XRT (Radiotherapy) to primary and metastatic sites, beginning ≥ 28 days post-ASCT.
High-risk NB study in development: ANBL 1531

**Post-Consolidation Therapy:**
Ch14.18 + cytokines and isotretinoin as per ANBL0032 regimen
• Should we decrease our margins for CTV and PTV?
• Superior/inferior pre-chemotherapy volumes?
• Only expand into areas where the tumor was before chemotherapy
• Should we decrease upfront surgery treatment volumes?
• Change deviation criteria and normal tissue constraints
• Should we increase the metastatic dose to 36 Gy if persistently MIBG positive?
• Hypofractionation option/biological advantage? Can we treat more metastatic lesion with a hypofraction scheme? 3 Gy per fraction?
• Normal tissue constraint changes
**ANBL 1531 Normal Constraint and Deviation Criteria Suggested Modifications**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Kidney</td>
<td>&lt;75%</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mean dose ≤ 18 Gy</td>
<td></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%</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean &lt; 15 Gy</td>
<td></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>
Acknowledgements

A3973 Study Committee:
Chair (Sue Kreissman)
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