Radiotherapy in Management of Neuroblastoma

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Apollo Cancer Hospital, Hyderabad
**Neuroblastoma: Factsheet**

477,000 new cancer cases per year  
(GLOBOCAN, IARC 2012)

7600 – 22800 childhood cancer, <15 yrs age  
(Arora et al, IJC 2009)

304-912 neuroblastoma cases per year  
(Jignasa B et al, NJCM India 2011)

750-800 new cases per year in US
Radiotherapy in Neuroblastoma

- Whom to treat?
- When to treat?
- What to treat?
- How to treat?
“It is a capital mistake to theorize before you have all the evidence. It biases the judgment”…

Sherlock Holmes
Neuroblastoma

- Unique biology
- Commonest malignancy in infants & 3rd most common in children
- Molecular biological assays influence treatment and prognosis
Natural History

- Arise from any site in Sympathetic NS
  - Adrenal medulla, paraspinal ganglia, thorax, H&N.

- >70% metastatic disease at presentation
  - nodes, bone, liver, marrow, skin.

- Spontaneous remission known
Blue Round Cell Tumor

Ganglioneuroma

Ganglioneuroblastoma

Neuroblastoma

Shimada Grading System
- Favorable OR Unfavorable

Stromal Development, MKI, neuroblastic differentiation

Shimada H et al, J Natl Cancer Inst 1984

BE ReD RAM With MeN!!

Burkitt’s lymphoma and other lymphoblastic lymphoma
Ewing Sarcoma
Retinoblastoma
Desmoplastic small round blue cell tumor
Rhabdomyosarcoma
Acute lymphoblastic Leukemia
Medulloblastoma, and other PNET
Wilms tumor
Mesothelioma, small cell
Neuroblastoma
## International Neuroblastoma Staging System (INSS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 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>Stage 2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>Stage 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>Stage 3</td>
<td>Unresectable unilateral tumor infiltrating across the midline,(^a) 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>Stage 4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S).</td>
</tr>
<tr>
<td>Stage 4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow(^b) (limited to infants, 1 year of age).</td>
</tr>
</tbody>
</table>

\(^a\)The midline is defined as the vertebral column. Tumors originating on one side and “crossing the midline” must infiltrate to or beyond the opposite side of the vertebral column.

\(^b\)Marrow involvement in stage 4S should be minimal, that is, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if done) should be negative in the marrow.

*Brodeur GM, JCO 1993*
<table>
<thead>
<tr>
<th>International neuroblastoma staging system</th>
<th>Age (Days)</th>
<th>MYCN</th>
<th>Histology</th>
<th>Ploidy</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Low</td>
</tr>
<tr>
<td>2A/2B</td>
<td>Any</td>
<td>Nonamplified</td>
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<td>Any</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>&lt;547</td>
<td>Nonamplified</td>
<td>Any</td>
<td>Any</td>
<td>Intermediate</td>
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<tr>
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</table>
Surgery –
- Pivotal role both diagnostic & therapeutic
- Second look surgery
- Extent of Resection – ‘Controversial’

Chemotherapy –
- Dominant modality in IR and HR disease
- Low Risk patients with symptomatic involvement of vital organs

Radiotherapy –
- Radiosensitive BUT not a radiocurable tumor
- Limited role –
  - High Risk patients, Unresectable, Progressive disease, Palliation, TBI
Treatment Recommendations and Role of Radiation

Low Risk Group
### Low Risk Group

<table>
<thead>
<tr>
<th>INSS Stage</th>
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</table>
Treatment: Low Risk NB

Surgical removal in Stage 1 and 2

No role of radiotherapy in INSS 1 or 2
(even with macroscopic residual disease)

Role of chemotherapy or RT –
✓ Cord compression, respiratory compromise
✓ In Unresectable tumors after chemotherapy
Treatment: Low Risk NB

Surgical removal in Stage 1 and 2

**Perez et al, JCO 1991:**
93% EFS for Stage 1 with Surgery alone

6/10 recurrences – distant, OS - 99%

**Atkinson JB et al, CCG Study, JCO 2000:**
233 stage 2 pts, no MYCN amplification, Sx alone

4yr EFS – 81%, 4yr OS – 98%
Low Risk NB

No role of chemotherapy or radiotherapy in INSS 1 or 2 (even with macroscopic residual disease)

Strother D et al, COG P9641, JCO 2012 –

Prospective study, 915 INSS Stage 2A/2B pts

Sx alone, Chemotherapy for <50% resection or progression

Stage 2A/2B – 5yr EFS: 89%, OS: 97%
Stage 1 – 5yr OS:99%
Stage 4S – 5yr OS:91%

Role of chemotherapy or RT –
Cord compression, respiratory compromise

In Unresectable tumors as pre-op chemotherapy
Chemotherapy or Radiation Did not Improve DFS

Matthay’s series, non randomized, EDIIA disease

<table>
<thead>
<tr>
<th># of pts</th>
<th>Treatment</th>
<th>6 yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>Surgery alone</td>
<td>89%</td>
</tr>
<tr>
<td>66</td>
<td>Surgery+ Chem or RT</td>
<td>94%, p=NS</td>
</tr>
<tr>
<td>40 (R1/R2)</td>
<td>Surgery alone</td>
<td>92%</td>
</tr>
<tr>
<td>59 (R1/R2)</td>
<td>Surgery+RT</td>
<td>90%, p=NS</td>
</tr>
</tbody>
</table>

No improvement in DFS with RT in patients with gross or microscopic residual disease!

Matthay KK et al, JCO, 1989
Radiotherapy in Neuroblastoma
Low Risk

- **Whom to treat?**
  Cord compression, Respiratory compromise

- **When to treat?**
  Immediate or Sx/chemotherapy failure

- **What to treat?**

- **How to treat?**

No role in low risk, completed resected, localized disease
Treatment Recommendations and Role of Radiation

Intermediate Risk Group
## Intermediate Risk NB

<table>
<thead>
<tr>
<th>INSS Stage</th>
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<th>Histology</th>
<th>Ploidy</th>
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<td>&lt;547</td>
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<td>Favorable</td>
<td>-</td>
<td></td>
</tr>
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<td>≥365 &lt;547</td>
<td>Non amplified</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&lt;547</td>
<td>Non amplified</td>
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<tr>
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<td>Any</td>
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</table>
Treatment: IR NB

Options –

- Surgery + Adjuvant Chemotherapy
- Pre-op CT (if unresectable) followed by Surgery
- Surgery + Observation in infants
- Radiotherapy – Limited role/Controversial
Successful Treatment of Stage III Neuroblastoma
Based on Prospective Biologic Staging:
A Children’s Cancer Group Study

By Katherine K. Mathews, C. Thomas Black, Barbara F. Shimada, James B. Atkinson, and John N. Lukens

Purpose: To identify an unfavorable subset of patients and improve survival of high-risk patients.

Patients and Methods: Of 228 patients, 143/228 met IR criteria, and 65/143 underwent CT f/b Sx. RT for R2 resection. Results –

1. Normal MYCN, Fav Shimada/ Low Sr Ferritin: 4yr EFS = 100%
2. Infants with at least one unfav factor: 4yr EFS = 90%, OS = 93%
3. >1yr and atleast one unfav factor: 4yr EFS = 75%
4. RT not prognostic for EFS

Multivariate analysis – Age, MYCN有利
Radiotherapy Improves the Outlook for Patients Older Than 1 Year With Pediatric Oncology Group Stage C Neuroblastoma


• Phase 3 Trial
• >1yr <21, POG Stage C, +ve regional nodes
• Randomised to CT alone or CT+RT

RT –
24Gy (age 12-24mths), 30Gy (age>24mths)@1.5Gy/#

Results –
Significant increase in EFS & OS with RT

Prospective randomized trial
age > 1 yr
minimal gross residual post-op or involved nodes
Randomization: (1) RT (20-30 Gy) OR (2) no RT
No difference in RFS rate
Outcomes after Reduced Chemotherapy for Intermediate-Risk Neuroblastoma


ORIGINAL ARTICLE

BACKGROUND
The survival rates in patients with intermediate-risk neuroblastoma (IR, normal MYCN) are variable, and the role of dose-intensive chemotherapy is uncertain. It is unclear whether patients with defined favorable features should receive reduced chemotherapy.

METHODS
We conducted a prospective, randomized, phase III study of intermediate-risk neuroblastoma (IR, normal MYCN) in patients aged 1 to 12 years with advanced stage disease with a 2-year metastatic free survival of at least 90% after surgery. Patients were randomized to receive 4 cycles of pre-operative chemotherapy with cisplatin and topotecan, followed by 3 cycles of post-operative chemotherapy, or 8 cycles of pre-operative chemotherapy. The primary endpoint was 3-year overall survival (OS).

RESULTS
Between 1993 and 2005, a total of 479 eligible patients were enrolled in this trial (270 patients with stage 3 disease, 178 with stage 4 disease, and 31 with stage 4S disease). A total of 231 patients had tumors with favorable biologic features, and 141 had tumors with unfavorable biologic features. The overall survival estimate for the entire group was 96±1%, with an overall survival rate of 98±1% among patients who had tumors with favorable biologic features and 93±2% among patients who had tumors with unfavorable biologic features.

CONCLUSIONS
A very high rate of survival among patients with intermediate-risk neuroblastoma was achieved with a biologically based treatment assignment involving a substantially reduced duration of chemotherapy and reduced doses of chemotherapeutic agents as compared with the regimens used in earlier trials. These data provide support for further reduction in chemotherapy with more refined risk stratification. (Funded by the Children’s Oncology Group; NCT00224984.)

Prospective study, 479 pts
IR, normal MYCN
Pre-op CT –
4 cycles – pts with fav features
8 cycles – unfav profile or incomplete response
Results –
3yr OS – 96%
Fav biology – 98%, Unfav features – 93%
# Role of Radiation in Neuroblastoma

## Intermediate Risk, EDII, LN- pts

<table>
<thead>
<tr>
<th>Institution</th>
<th>Radiation</th>
<th>Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCSG</td>
<td>No</td>
<td>76</td>
<td>89%</td>
</tr>
<tr>
<td>SJCRH</td>
<td>No</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>POG</td>
<td>No</td>
<td>61 (14III)</td>
<td>87%</td>
</tr>
<tr>
<td>CCSG</td>
<td>Yes</td>
<td>66</td>
<td>94%</td>
</tr>
<tr>
<td>Duke</td>
<td>Yes</td>
<td>7</td>
<td>86%</td>
</tr>
<tr>
<td>SJCRT</td>
<td>Yes</td>
<td>9</td>
<td>100%</td>
</tr>
<tr>
<td>HSC,UK</td>
<td>Yes</td>
<td>24</td>
<td>79%</td>
</tr>
</tbody>
</table>

Radiation is therefore not warranted for this group.
Results of Surgery and Chemotherapy

Intermediate Risk


Complete resection

Incomplete resection

Event free survival with INSS stage 2B or 3, treated by POG 8742 and 9244

Positive surgical margin does not warrant postoperative radiation therapy in intermediate risk neuroblastoma

## Role of Radiation in Neuroblastoma

**Intermediate Risk, EDIII/POG C or LN+pts**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Radiation</th>
<th>Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJCRT</td>
<td>No</td>
<td>27</td>
<td>41%</td>
</tr>
<tr>
<td>CHOP</td>
<td>No</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td>POG</td>
<td>No</td>
<td>29</td>
<td>41%</td>
</tr>
<tr>
<td>ICGN</td>
<td>No</td>
<td>129 (B&amp;C)</td>
<td>52%</td>
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<tr>
<td>Duke</td>
<td>Yes</td>
<td>13</td>
<td>69%</td>
</tr>
<tr>
<td>JCRT</td>
<td>Yes</td>
<td>16</td>
<td>81%</td>
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<tr>
<td>CHOP</td>
<td>Yes</td>
<td>7</td>
<td>86%</td>
</tr>
<tr>
<td>ICGN</td>
<td>Yes</td>
<td>14</td>
<td>64%</td>
</tr>
<tr>
<td>POG</td>
<td>Yes</td>
<td>33</td>
<td>73%</td>
</tr>
</tbody>
</table>

Radiation may improve tumor control & survival rates in this group.
Radiotherapy in Neuroblastoma
Intermediate Risk

Whom to treat?

- Unresectable Primary s/p Chemotherapy
- Progressive disease post Surgery/Chemotherapy
- Stage 3, node +ve pts (Level III evidence)

When to treat?

- Post surgery for node +ve pts
- Post chemotherapy for unresectable disease

What to treat?

How to treat?

No unequivocal recommendations in Stage 3 disease
Treatment Recommendations and Role of Radiation

High Risk Group
<table>
<thead>
<tr>
<th>INSS Stage</th>
<th>Age (days)</th>
<th>MYCN</th>
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<tbody>
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</tr>
</tbody>
</table>
Treatment: High Risk NB

- Poor survival rates (15-30% @ 5yrs)
- Intensive protocols
- Three phases –
  - Induction Therapy – max reduction in bulk at primary & metastatic sites
  - Consolidation Therapy – eliminate resistant tumor clones
  - Maintenance Therapy – eradicate any residual tumor cells

Local control (Stage 4 Neuroblastoma)
- Predilection of recurrences in previous sites of disease
- Surgical resection of primary a/w improved local control & survival
- Role of RT @ Primary site & bulky metastatic sites to improve tumor control rates

Matthay KK, JCO 1993; Sibley GS, IJROBP 1995
LOCAL CONTROL WITH MULTIMODALITY THERAPY FOR STAGE 4 NEUROBLASTOMA

Suzanne L. Wolden, M.D.,* Smitha V. Gollamudi, M.D.,* Brian H. Kushner, M.D.,† Michael LaQuaglia, M.D.,‡ Kim Kramer, M.D.,† Nancy Rosen, M.D.,§ Sara Abramson, M.D.,§ and Nai-Kong V. Cheung, M.D., Ph.D.†

Departments of *Radiation Oncology, †Pediatrics, ‡Surgery, and §Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY

Purpose: To evaluate the efficacy of 21 Gy hyperfractionated radiotherapy for local control in conjunction with surgery and intensive systemic therapy for patients with Stage 4 neuroblastoma.

Methods and Materials: After achieving a partial or complete remission, 47 children, ages 1–10 years, with Stage 4 neuroblastoma were treated on four consecutive institutional protocols (N4–N7) with dose-intensive multiagent chemotherapy, maximal surgical debulking, and hyperfractionated radiotherapy (1.5 Gy twice a day to 21 Gy). Radiotherapy fields encompassed the initial tumor volume and regional lymph nodes plus a 3-cm margin. This was followed by consolidation with either autologous bone marrow transplantation (N4 and N5) or immunotherapy (N6 and N7).

Results: Forty-five of 47 patients had a complete response to surgery and chemotherapy prior to radiotherapy. Five-year actuarial rates of local control, progression-free survival, and overall survival were 84%, 40%, and 45%, respectively. Among 26 patients who relapsed, 1 failed only at the primary site, 22 developed distant metastases exclusively, and 3 had both local and distant failures. There were no acute complications of radiotherapy.

Conclusion: Hyperfractionated radiotherapy to 21 Gy, in conjunction with dose-intensive systemic therapy and aggressive surgical resection, is well tolerated and is associated with durable local control for most patients with Stage 4 neuroblastoma. © 2000 Elsevier Science Inc.
IMPACT OF RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA: A CHILDREN’S CANCER GROUP STUDY

DAPHNE A. HAAS-KOGAN, M.D.,,* PATRICK S. SWIFT, M.D.,† MICHAEL SELCH, M.D.,‡ GERALD M. HAASE, M.D.,§ ROBERT C. SEEGER, M.D.,¶ ROBERT B. GERBING, M.A.,# DANIEL O. STRAM, PH.D.,** AND KATHERINE K. MATTHAY, M.D.††

Departments of *Radiation Oncology and ‡Pediatrics, University of California San Francisco, San Francisco, CA; †Department of Radiation Oncology, Children’s Hospital of Oakland, Berkeley, CA; §Department of Radiation Oncology, University of California School of Medicine, Los Angeles, CA; ¶Department of Pediatric Surgery, Children’s Hospital, Denver, CO; Departments of *Pediatrics and **Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA; ††Department of Pediatrics, Children’s Hospital, Los Angeles, CA; #Children’s Oncology Group, Arcadia, CA

Purpose: To assess the effect of local radiation administered to primary disease sites in children with high-risk neuroblastoma.

Methods and Materials: A total of 539 eligible patients were entered on protocol CCG-3891, consisting of chemotherapy, primary surgery, and 10 Gy of external beam radiation therapy (EBRT) to gross residual disease, followed by randomized assignment to continuation chemotherapy (CC) or autologous bone marrow transplantation (ABMT). ABMT patients received total body irradiation (TBI).

Results: Estimated event-free survival and overall survival at 5 years were 25% ± 2% and 35% ± 2%, respectively. Estimated 5-year locoregional recurrence rates were 51% ± 5% and 33% ± 7% for CC and ABMT patients (p = 0.004). For patients who received 10 Gy of EBRT to the primary, the addition of 10 Gy of TBI and ABMT decreased local recurrence compared with CC (22% ± 12% and 52% ± 8%, p = 0.022). EBRT did not increase acute toxicity, except for increased total parenteral nutrition administration.

Conclusions: In combination with EBRT to the primary tumor site, the addition of 10 Gy of TBI as a component of high-dose chemotherapy with ABMT improved local control compared with CC without TBI. Results suggest a dose–response relationship for local EBRT. Short-term toxicity of local EBRT is limited. © 2003 Elsevier Inc.
EXEMPLARY LOCAL CONTROL FROM RADIATION THERAPY FOR HIGH-RISK NEUROBLASTOMA

HEATHER G. GATCOMBE, M.D.,* R. B. MARCUS, JR., M.D.,§ HOWARD M. KATZENSTEIN, M.D.,† MOURAD TIGHOUART, PH.D.,‡ AND NATIA ESIASHVILI, M.D.*

*Department of Radiation Oncology, †Children’s Healthcare of Atlanta, ‡Biostatistics and Informatics at Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; and §Department of Radiation Oncology, University of Florida, Gainesville, FL.

Purpose: Local recurrence has been demonstrated in previous studies to be one of the obstacles to cure in neuroblastoma. Radiation therapy indications, optimal dose, and technique are still evolving. Here we report our experience of high-risk neuroblastoma patients who received local radiation therapy as part of their cancer management.

Methods and Materials: We conducted a retrospective study of 34 high-risk neuroblastoma patients who received radiation therapy to local sites of disease from March 2001 until February 2007 at our institution as part of their multimodality therapy.

Results: At a median follow-up of 33.6 months, 6 patients died of disease, 7 patients were alive with disease, and 21 patients were in clinical remission. Eleven patients relapsed, all distantly. Two patients failed locally in addition to distant sites. Both of these patients had persistent gross disease after induction chemotherapy and surgery. Our 3-year local control, event-free survival, overall survival were 94%, 66%, and 86%, respectively.

Conclusion: Patients with high-risk neuroblastoma in our series achieved excellent local control. Doses of 21–24 Gy to the primary tumor site appear to be adequate for local control for patients in the setting of minimal residual disease after induction chemotherapy and surgery. Patients with significant residual disease may benefit from radiation dose escalation, and this should be evaluated in a prospective clinical trial. © 2009 Elsevier Inc.
Clinical Investigation

Radiation Therapy to the Primary and Postinduction Chemotherapy MIBG-Avid Sites in High-Risk Neuroblastoma

Ali Mazloom, MD, Chrystal U. Louis, MD, Jed Nuchtern, MD, Eugene Kim, MD, Heidi Russell, MD, PhD, Wendy Allen-Rhoades, MD, Robert Krance, MD, and Arnold C. Paulino, MD

Houston Methodist Hospital, Texas Children’s Hospital, and Baylor College of Medicine, Houston, Texas

Received May 14, 2014, and in revised form Jun 17, 2014. Accepted for publication Jul 14, 2014.

Summary

Radiation therapy to the primary site and postinduction metaiodobenzylguanidine (MIBG)-positive metastatic sites were associated with favorable local control in children with high-risk neuroblastoma. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

Purpose: Although it is generally accepted that consolidation therapy for neuroblastoma includes irradiation of the primary site and any remaining metaiodobenzylguanidine (MIBG)-avid metastatic sites, limited information has been published regarding the efficacy of this approach.

Methods and Materials: Thirty patients with high-risk neuroblastoma were treated at 1 radiation therapy (RT) department after receiving 5 cycles of induction chemotherapy and resection. All patients had at least a partial response after induction therapy, based upon international neuroblastoma response criteria. The primary sites were treated with 24 to 30 Gy whereas the MIBG-avid metastatic sites were treated with 24 Gy. RT was followed by high-dose chemotherapy with autologous stem cell rescue and 6 months of cis-retinoic acid.

Results: The 5-year progression-free survival (PFS) and overall survival (OS) rates were 48% and 59%, respectively. The 5-year locoregional control at the primary site was 84%. There were no differences in locoregional control according to degree of primary surgical resection. The 5-year local control rate for metastatic sites was 74%. The 5-year PFS rates for patients with 0, 1, 2, and >3 postinduction MIBG sites were 66%, 57%, 20%, and 0% (P < .0001), respectively, whereas 5-year OS rates were 80%, 57%, 50%, and 0%, respectively (P < .0001).

Conclusions: RT to the primary site and postinduction MIBG-positive metastatic sites was associated with 84% and 74% local control, respectively. The number of MIBG-avid sites present after induction chemotherapy and surgery was predictive of progression-free and overall survival.

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Radiotherapy in Neuroblastoma
High Risk

حماية: من يكون المبتور؟

الموقع الرئيسي (لا يهم مدى تمكين الجراحة)

مواقع الأمراض المعدومة مع نشاط MIBG

ارتباط: متى نعالج؟

بعد الجراحة قبل فترة التجميع

ماذا نعالج؟

كيف نعالج؟
Radiotherapy in Neuroblastoma
RT Planning

- Patient Positioning & Immobilisation
- Target volumes & Critical structure delineation
- Dose
- Techniques
Radiotherapy in Neuroblastoma
Positioning & Immobilization

- Supine position, usually sedated
- Arms overhead
- Thermoplastic mould or Vac-Lock
- Contrast CT/MRI scans (3mm axial images)
Radiotherapy in Neuroblastoma

Target Delineation

◆ Pre surgery or Pre chemo (if unresectable) imaging studies determine volume of irradiation

◆ Nodal sites –
  • If radiologically/pathologically involved
  • Routine un-involved or next echelon nodal irradiation not done
  • Symmetrical irradiation of bone
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Target Delineation

**GTV** – if any residual disease or volume of tumor prior to Sx, but after CT

**CTV** – GTV+1.5-2cm margin
    (include all areas of microscopic disease as per I/o and Path findings)

**PTV** – Institution protocol (5-10mm)

**OARs** – Kidneys, Spleen, Liver, Stomach, Iliac crests, Bowel, Gonads
Radiotherapy in Neuroblastoma

Dose

- Debatable (10-45Gy)
- Conventional or Hyperfractionated RT
- May be age dependent \((\text{Jacobson GM, Am J Clin Oncol 1984, Rosen EM, JCO 1984})\)
- Presence of residual disease
Dose response analysis of pediatric neuroblastoma to megavoltage radiation.

Jacobson GM, Sause WT, O'Brien RT.

Abstract

Children with neuroblastoma treated in Salt Lake City from 1966 through 1982 were analyzed in an attempt to develop guidelines for radiation therapy. Special attention was addressed to time-dose relationships in those undergoing surgery and post-resection (Stages II and III). Altogether, 76 patients were analyzed. Complete response rates were: Stage I–100%; Stage II–84%; Stage III–69.2%; Stage IV–14.3%; Stage V–0%. Disease control was correspondingly better in younger children and in infants. Local control with radiation therapy in this population were: unresectable or gross remaining disease; stage of the primary tumor; regional lymph nodes or positive surgical margins. Local control was achieved in a majority of patients undergoing surgery and radiation for limited disease. In children younger than 1 year of age, no local failures were observed at doses above 1200 rad. In children between 1-2 years of age, no local failures were observed with doses as low as 1440 rad. In children older than 3 years, local failures were observed up to 4500 rad.
LOCAL CONTROL WITH MULTIMODALITY THERAPY FOR STAGE 4 NEUROBLASTOMA

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Purpose: To evaluate the efficacy of 21 Gy hyperfractionated radiotherapy for local control in conjunction with surgery and intensive systemic therapy for patients with Stage 4 neuroblastoma.

Methods and Materials: After achieving a partial or complete remission, 47 children, ages 1–10 years, with Stage 4 neuroblastoma were treated on four consecutive institutional protocols (N4–N7) with dose-intensive multi-agent chemotherapy, maximal surgical debulking, and hyperfractionated radiotherapy (1.5 Gy twice a day to 21 Gy). Radiotherapy fields encompassed the initial tumor volume and regional lymph nodes plus a 3-cm margin. This was followed by consolidation with either autologous bone marrow transplantation (N4 and N5) or immunotherapy (N6 and N7).

Results: Forty-five of 47 patients had a complete response to surgery and chemotherapy prior to radiotherapy. Five-year actuarial rates of local control, progression-free survival, and overall survival were 84%, 40%, and 45%, respectively. Among 26 patients who relapsed, 1 failed only at the primary site, 22 developed distant metastases exclusively, and 3 had both local and distant failures. There were no acute complications of radiotherapy.

Conclusion: Hyperfractionated radiotherapy to 21 Gy, in conjunction with dose-intensive systemic therapy and aggressive surgical resection, is well tolerated and is associated with durable local control for most patients with Stage 4 neuroblastoma.
RT Dose

10Gy EBRT + 10Gy TBI
RT Dose
36Gy to the residual disease

Abstract
BACKGROUND AND PURPOSE: In neuroblastoma, the value of radiation therapy in high-intensive first-line treatment protocols is still not exactly known but radiation-associated long-term effects need to be considered. The impact of external-beam radiation therapy (EBRT) on event-free (EFS) and overall survival (OS) of the 2397 trial was analyzed.

PATIENTS AND METHODS: Ten stage 4 neuroblastoma patients were treated with high-dose chemotherapy with stem cell transplantation without relapse. Intensified local EBRT (36 Gy) of the residual tumor volume was reserved for patients with residual viable tumor documented by MRI and corresponding metaiodobenzylguanidine (MIBG) uptake.

RESULTS: 13 patients who received EBRT for local residual disease had similar outcome (3-year EFS 85 ± 10%, 3-year OS 92 ± 7%) as 74 patients without any MIBG residual (3-year EFS 61 ± 6%, 3-year OS 75 ± 6%). Outcome was worse in 23 children without EBRT to residual primary (3-year EFS 25 ± 10%, 3-year OS 51 ± 11%). Separate analysis of 14 patients with isolated localized residual disease found far better outcome of eight patients with EBRT (3-year EFS 100%, 3-year OS 100%) compared to six patients without EBRT (3-year EFS 20 ± 18%, 3-year OS 20 ± 18%). Multivariate analysis identified EBRT as influential on EFS (hazard ratio 0.27) and OS (hazard ratio 0.17) in addition to MYCN amplification and presence of primary tumor site MIBG residual.

CONCLUSION: EBRT appeared effective in high-intensive treatment of stage 4 neuroblastoma. It seems to compensate the disadvantage of incomplete response to induction chemotherapy. These retrospective results need confirmation by a prospective randomized trial.
RT Dose

Primary site – 24 to 30Gy
MIBG avid Mets – 24Gy
Radiotherapy in Neuroblastoma

Dose Recommendations

Completely resected tumor –

✓ 21Gy, either 1.8Gy daily or 1.5Gy BD

Residual disease – boost up to 30-36Gy

✓ Microscopic disease, min 15 Gy wide field, followed by 5-10 Gy boost
✓ Gross disease 15-20 Gy initial volume, followed by 5-10 Gy boost
✓ For gross disease, age dependent:
  <1 Yr - 12 Gy, 1-4 Yr - 25 Gy, >4Yr - >25 Gy

Jackson GM Am J Clin Oncol 1984
Radiotherapy in Neuroblastoma
Ongoing trial

ANBL0532, COG High Risk Phase III Trial

Incompletely resected pts -

RT – 21.6Gy to pre-op primary tumor volume
14.4Gy to the gross residual volume
Radiotherapy in Neuroblastoma

Dose Recommendations

**Liver** –
- Dose to whole liver not to exceed 19Gy. 21Gy is acceptable for one lobe
- <50% to receive 9Gy and <25% more than 18Gy

**Spinal Cord** –
- A dose of 21Gy is acceptable for any length of spinal cord

**Kidney** –
- If single kidney, then dose should not exceed 12Gy
- A dose of 21Gy is acceptable for up to half a kidney, if the patient has both kidneys
- Contralateral Kidney - <50% to receive >8Gy & <20% to receive >12Gy

HR-NBL-1/SIOPEN Study Protocol
Radiotherapy in Neuroblastoma

Dose Recommendations

**Bone** –
- Maintain the symmetry by irradiation of whole vertebra
- If possible, shield the epiphysis of bone

**Gonads** –
<5Gy if possible
Radiotherapy in Neuroblastoma

Technique

- Parallel opposed, 3DCRT, IMRT, VMAT
- Individualization for each patient
- IMRT for abdominal/pelvic disease, Re- irradiation
  Better renal sparing
  Watch for mean doses to stomach, spleen etc
- Laterally placed tumor – either of the technique
2/F
L1-L3 Paraspinal mass
Dumbbell NB, ‘IR’
Limited Excision + CT
Two 3DCRT plans

1st Plan - more spillage in bowel, better conformity
Conv vs Rapid Arc Plans

Rarc -
Better conformity,
Less spillage in high dose region

30% isodose region
Conv – liver, bowel
RArc - s/c tissues
Rarc Plan –
Better conformity & homogeneity
Lower doses to OARs
Case 2

11/F
Paraparesis
D10/L1 paraspinal mass
Sx+Chemotherapy
Residual/Recurrent disease
Case 2

Dose -
Phase 1 PTV – 21.6/12frs
Phase 2 PTV – 32.4Gy/18frs

Mean dose:
Lt Kidney – 15Gy
Rt Kidney – 10Gy
Case 3

1/F

D1-8 Pre/Para vertebral mass

Limited Excision+Chemo
Rapid Arc Plan
24Gy/15frs, 1.6Gy/fr
Less spillage in low dose region
Low dose to OARs – Lungs, Breast buds, Heart
1yr/F
Lt Suprarenal mass
Stage 4S, liver mets
Post Chemo – CR
Recurrent Tm – s/p Sx
Rapid Arc Plan, 25.2Gy/14frs
Good conformity
Mean Dose –
Lt Kidney – 9.9Gy
Rt Kidney – 5.6Gy
Liver - 7.3Gys
Radiotherapy in Neuroblastoma

**Metastatic sites**

- Generous margins for the bony lesions
- Orbital mets – treat entire orbit
- Liver mets – adequate margins (no whole liver irradiation)

**Dose/# -**
- symptoms, volume, life expectancy
  - 16-20Gy in 4/5 fractions
  - Or 20-30Gy in 2 to 3Gy/fraction, if large fields
Radiotherapy in Neuroblastoma

Hepatomegaly in Stage 4S –

- Entire liver need not be irradiated
- Spare kidneys, ovaries
- Usually lateral opposed
- 2-6Gy in 2-4 fractions

Borders –
Anterior – 2cm ant to liver
Posterior – anterior vertebral body
Superior – 2cm sup to liver
Inferior – superior iliac crest to avoid ovarian exposure
Radiotherapy in Neuroblastoma

Intraoperative Radiotherapy –

Rationale:
Increased risk of late toxicities with EBRT as large volume of normal tissue exposed

Reduced renal function which may compromise tolerance to chemotherapy with SCT

Higher dose deliverable with minimal exposure to normal tissues
LONG-TERM OUTCOME AND TOXICITIES OF INTRAOPERATIVE RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA

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Purpose: To review a historical cohort of consecutively accrued patients with high-risk neuroblastoma treated with intraoperative radiotherapy (IORT) to determine the therapeutic effect and late complications of this treatment.

Methods and Materials: Between 1986 and 2002, 31 patients with newly diagnosed high-risk neuroblastoma were treated with IORT as part of multimodality therapy. Their medical records were reviewed to determine the outcome and complications. Kaplan-Meier probability estimates of local control, progression-free survival, and overall survival at 36 months after diagnosis were recorded.

Results: Intraoperative radiotherapy to the primary site and associated lymph nodes achieved excellent local control at a median follow-up of 44 months. The 3-year estimate of the local recurrence rate was 15%, less than that of most previously published series. Only 1 of 22 patients who had undergone gross total resection developed recurrence at the primary tumor site. The 3-year estimate of local control, progression-free survival, and overall survival was 85%, 47%, and 60%, respectively. Side effects attributable to either the disease process or multimodality treatment were observed in 7 patients who developed either hypertension or vascular stenosis. These late complications resulted in the death of 2 patients.

Conclusions: Intraoperative radiotherapy at the time of primary resection offers effective local control in patients with high-risk neuroblastoma. Compared with historical controls, IORT achieved comparable control and survival rates while avoiding many side effects associated with external beam radiotherapy in young children. Although complications were observed, additional analysis is needed to determine the relative contributions of the disease process and specific components of the multimodality treatment to these adverse events.
Radiotherapy in Neuroblastoma

Complications

**Acute Side-effects:**
Nausea/Vomiting
Diarrhea, Abdominal pain
Hematological toxicity

**Long term Sequelae:**
Musculoskeletal –
  Kyphoscoliosis, bone shortening

Hearing loss

Hypothyroidism, ovarian dysfunction

Vascular – Middle Aortic syndrome
Radiation in Neuroblastoma

Conclusions

- Radiation is only indicated in very rare occasion in **Low risk** patients

- Radiation is controversial in **Intermediate** risk patients

- In **High** risk group, local radiation may be used as a boost to primary or bulky metastatic site, TBI as a part of BMT, palliative measure in life threatening situations

Structure Delineation:

- Pre surgery CT/MIBG scans
- Nodal irradiation for involved nodes ONLY
- Symmetrical irradiation of vertebrae

Dose - 21Gy for R0 resection, 30-36Gy for R1/R2 resection
Thank You