RADIOTherapy IN MedulloBLAStoma

Rationale & Results

Dr. Tejpal Gupta
Assistant Professor, Radiation Oncology
Tata Memorial Centre

ACTREC
Introduction

- Commonest malignant brain tumor in children
- 20-25% of all childhood brain tumors
- Belongs to family of small blue RCT
- Median age at presentation: 5-8 years
- High propensity of CSF dissemination (20-30%)
- Current standard of care: Maximal safe resection followed by adjuvant radiation therapy +/- chemotherapy
Role of Radiotherapy

“In the course of our growing acquaintance with these baffling tumours, we suspected from their peculiar cytology that they might be susceptible to radiation and the first of the cases so treated both by the X-rays and radium was in December, 1919. Here at least was a new therapeutic recourse and we began with renewed encouragement to attack them with renewed vigour”

Harvey Cushing, 1930
Rationale

- Generally a radiosensitive disease
- Historical controls: No long term survivors without RT
- High recurrence rates with focal (posterior fossa only) RT
- High recurrence rates for reduced dose CSI without CT

Cranio-spinal Irradiation (CSI)
- Cornerstone of adjuvant treatment
- Most challenging planning in RT

Landberg 1953
Issues in RT for Medulloblastoma

- Positioning and Immobilization
- Planning and Verification
- Pertinent Questions for RT
- Newer perspectives in RT
- Clinical Trials
Positioning & Immobilization for CSI

Prone vs Supine

*Prone preferred due to direct verification*

Disadvantages

- Relatively poor reproducibility
- Larger scope for patient movement
- Discomfort to the patient
- Difficult anesthesia if needed
Customized immobilization

- Customized immobilization with use of commercially available prone head rests integrated with vacuum bags achieves maximum set up accuracy
- Alternatively CT-based planning and/or virtual simulation and verification needed for supine position
Field matching in CSI

- A geometrical method of orthogonal field separation (Werner et al.)

\[ S = \frac{1}{2} \cdot L \cdot \frac{d}{SSD} \]

\( d \rightarrow \) depth at which the orthogonal fields are allowed to join
Matching Craniospinal Fields

- **Technique A**
  - Bilateral cranial fields adjacent to a spinal field
  - The inferior border of cranial field meet at a point midway on the posterior neck surface
- **Technique B**

  - Rotation the couch and collimator

    \[ \theta_{\text{coll}} = \arctan\left( \frac{1}{2} \cdot L_1 \cdot \frac{1}{SSD} \right) \]
    \[ \theta_{\text{couch}} = \arctan\left( \frac{1}{2} \cdot L_1 \cdot \frac{1}{SAD} \right) \]
• Technique C
  - Rotation of the collimator only with using hemiblock of the cranial fields

\[ \theta_{\text{coll}} = \arctan \left( \frac{1}{2} \cdot L_1 \cdot \frac{1}{SSD} \right) \]

- Calculation of the collimator angles \( \theta_{\text{coll}} \) only
Field shaping & Dose distribution

Customized shielding (MLC) & Verification
Posterior Fossa Boost: Conventional Simulation
## Current Risk Stratification for Medulloblastoma

<table>
<thead>
<tr>
<th></th>
<th><strong>Average</strong></th>
<th><strong>High</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Age</strong></td>
<td>≥ 3 Yrs</td>
<td>&lt; 3 Yrs</td>
</tr>
<tr>
<td><strong>Residual Tumor</strong></td>
<td>≤ 1.5 cm²</td>
<td>&gt; 1.5 cm²</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>M₀</td>
<td>M₁ – M₄</td>
</tr>
<tr>
<td>Pathology</td>
<td>Desmoplastic</td>
<td>Anaplastic</td>
</tr>
<tr>
<td>Brain Stem invasion</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Trk – C protein mRNA</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>C-myc &amp; ERBB2</td>
<td>Low</td>
<td>Amplified</td>
</tr>
<tr>
<td>Tumor DNA Content</td>
<td>Diploid</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>Apoptotic Index</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
Doses and volumes as per risk stratification

**CSI for average-risk disease**

(age > 3 yrs, M0 status, and residual < 1.5 cm²)

- Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#
- Reduced dose CSI: 23.4 Gy/13#/2.5 weeks @ 1.8 Gy/# (+ adj CT)
- Very reduced dose CSI: 18 Gy/10#/2 weeks @ 1.8 Gy/# (+ adj CT)

**Boost for average-risk disease**

- If Standard dose CSI: PF or TB boost: 19.8 Gy/11#/2 weeks
- If reduced dose CSI: Tumour bed boost: 32.4 Gy/18#/3.5 weeks
- If very reduced dose CSI: Tumour bed boost: 39.6 Gy/22#/4.5 weeks

Total tumour bed dose: 54-56 Gy/30-33#/6.6.5 weeks (conventional #)
High-risk medulloblastoma

CSI for high-risk disease
(age <3 yrs, M+ status, and residual >1.5 cm2)

- Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#
- Higher dose spinal RT: 39.6 Gy/22#/4.5 weeks @1.8 Gy/#

Boost for high-risk disease
- Whole posterior fossa boost: 19.8 Gy/11#/2 weeks
- Boost for gross focal spinal deposit: 7.2-9 Gy/4-5#/1 week
Can the dose of CSI be reduced

*Average-risk disease*:
Definitely **NOT** without CT
Probably **YES** with CT

*High-risk disease*
Definitely **NOT**
Long-term survival with full dose CSI

<table>
<thead>
<tr>
<th>Series (date) details</th>
<th>Reference</th>
<th>Study (5 yr)</th>
<th>n (10 yr)</th>
<th>RT follow-up</th>
<th>Chemotherapy</th>
<th>Entire group</th>
<th>Median</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al. (1990)</td>
<td>6</td>
<td>1975–1981</td>
<td>88</td>
<td>*</td>
<td>Adjuvant (n = 88)</td>
<td>65%</td>
<td></td>
<td>5 yr</td>
</tr>
<tr>
<td>Hershatter et al. (1986)</td>
<td>7</td>
<td>1940–1983</td>
<td>127</td>
<td></td>
<td>Adjuvant (4/127)</td>
<td>33%</td>
<td>21%</td>
<td>26 yr</td>
</tr>
<tr>
<td>Jenkin et al. (1990)</td>
<td>8</td>
<td>1977–1987</td>
<td>72 (y)</td>
<td></td>
<td>Adjuvant (3%)</td>
<td>71%</td>
<td>63%</td>
<td>7 yr</td>
</tr>
<tr>
<td>Stiller and Lennox (1983)</td>
<td>14</td>
<td>1971–1977</td>
<td>304</td>
<td>*</td>
<td>Adjuvant (94/304)</td>
<td>35%</td>
<td>30%</td>
<td>9 yr</td>
</tr>
<tr>
<td>Tait et al. (1990)</td>
<td>15</td>
<td>1975–1979</td>
<td>141</td>
<td>*</td>
<td>Adjuvant (n = 141)</td>
<td>53%</td>
<td>45%</td>
<td>12 yr</td>
</tr>
<tr>
<td>Tarbell et al. (1991)</td>
<td>16</td>
<td>1970–1989</td>
<td>89</td>
<td>**</td>
<td>Pre-RT (n = 39)</td>
<td>65%</td>
<td>48%</td>
<td>9 yr</td>
</tr>
<tr>
<td>Merchant et al. (1995)</td>
<td>17</td>
<td>1979–1994</td>
<td>100</td>
<td></td>
<td>Adjuvant (49%)</td>
<td>50%</td>
<td>25%</td>
<td>8 yr</td>
</tr>
</tbody>
</table>
Low-Stage Medulloblastoma: Final Analysis of Trial Comparing Standard-Dose With Reduced-Dose Neuraxis Irradiation

Standard dose (36 Gy CSI; 54 GyPF)
5 yr-  67±7.4%
8 yr-  67±8.8%

Reduced dose (23.4 Gy CSI; 54 Gy PF)
5 yr-  52±7.7%
8 yr-  52±11%

Trial closed prematurely at N=126
Reduced dose CSI negatively impacts EFS  

Thomas JCO 2000
Treatment of Children With Medulloblastomas With Reduced-Dose Craniospinal Radiation Therapy and Adjuvant Chemotherapy: A Children's Cancer Group Study

N=65 patients

Conc wkly VCR followed by 8 cycles of CCNU, CDDP and VCR
PFS- 86±4% at 3 years, 79±7% at 5 years.
Results better than earlier study using reduced dose CSI alone
Positive impact of adjuvant chemotherapy on EFS

Packer JCO 1999
How much can the CSI dose be reduced

23.4 Gy: Probably YES
18 Gy: Immediately NOT
0 Gy: MUST BE KIDDING

Ongoing CCG trial randomizing to 23.4 Gy CSI vs 18 Gy CSI in average-risk MB followed by same CT
Updated results of a pilot study of low dose craniospinal irradiation plus chemotherapy for children under five with cerebellar primitive neuroectodermal tumors (Medulloblastoma)

- < 5 Yrs age, median f/u = 6.3 yrs
- < 1.5 cm2 RD, No SAS spread.
- Total / Near total resection – 8 pts
  Sub total resection - 2
- 18 Gy CSI + PF Boost upto 55.8 Gy
- Concurrent VCR → Maintenance
  VCR + Cisplatin + CCNU
- Trial stopped when 3rd patient presented with relapse
- 7/10 patients = long term DFS
- Minimal neurocognitive damage

Fig. 1. Actuarial survival of 10 children treated with 18 Gy CSRT.

Goldwein IJROBP 1996
Is it necessary to treat the entire posterior fossa

Average-risk disease
Probably NOT

High-risk disease
Probably YES
PATTERNS OF FAILURE FOLLOWING TREATMENT FOR MEDULLOBLASTOMA: IS IT NECESSARY TO TREAT THE ENTIRE POSTERIOR FOSSA?

- N = 114 Patients, 27 Recurrence (Median Age 8.6 Yrs, Median time to recurrence 19.5 Mths.)
- Failure was defined as MRI or CT evidence of recurrence or positive cerebrospinal fluid cytology.
  - Local Relapse = within the original tumor bed
  - Regional = Outside of the tumor bed but still within the PF.

<table>
<thead>
<tr>
<th>Site of first failure</th>
<th>Only site of failure</th>
<th>Any component of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor bed</td>
<td>2 (7%)</td>
<td>14 (52%)</td>
</tr>
<tr>
<td>PF outside TB</td>
<td>1 (3%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Spine</td>
<td>5 (19%)</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>2 (7%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Extraneural</td>
<td>2 (7%)</td>
<td>3 (11%)</td>
</tr>
</tbody>
</table>

Table 3. Patterns of failure

<table>
<thead>
<tr>
<th>Site of Failure</th>
<th>Only site of failure</th>
<th>Any component of failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB + PF outside TB</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>TB + spine</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>PF outside TB + spine</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>PF outside TB + supratentorial</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Spine + supratentorium</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>TB + PF outside TB + spine</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4. Sites of failure

Fukunaga IJROBP 1998
Patterns of Failure Using a Conformal Radiation Therapy Tumor Bed Boost for Medulloblastoma

- N = 32 (Standard risk - 27, High risk - 5)
- CT + RT – 28 Pts, RT Alone - 4 Pts
- Recc = 6
  - 4 = extensive leptomeningeal inv with out significant post fossa component
  - 1 = supratentorial only
  - 1 = post fossa
- DFS at 5 yrs – 84% and OAS at 5 yrs – 85%
- Freedom from distant failure
  - Std dose – 100% at 10 yrs and Low dose – 63% ($P = 0.06$, trend.)
- Freedom from posterior fossa failure was 100% and 86% at 5 and 10 years

Conformal treatment to the tumor bed allows for significant sparing of critical structures. The posterior fossa failure rate in this series is similar to that reported when the entire posterior fossa is treated. This approach should be investigated further in a phase III trial

Wolden JCO 2003
Long-term sequelae of RT in Medulloblastoma

- Neurocognitive & neurophysiological dysfunction
- Endocrine abnormalities & hormonal imbalance
- Growth retardation - spinal component
- Ototoxicity - particularly with platinum based adj CT
- Cerebrovascular accidents
- Gonadal toxicity & reduced fertility
- Second malignant neoplasms
Does reduction in dose and volume impact upon long-term outcomes

- Neuro-cognitive dysfunction: **YES** (Reduced)
- Neuro-physiologic dysfunction: **YES** (Reduced)
- Endocrine dysfunction: **YES** (Lesser)
- Oto-toxicity: **EQUIVOCAL** (Reduced cochlear dose offset by addition of platinum)
- Hematologic: **YES** (Significantly increased with CT)
- GI toxicity: **YES** (Significantly increased with CT)
- Second malignant neoplasms: **EQUIVOCAL** (conflicting data)
Benefit of reducing CSI dose and boost volumes

Mulhern R: Lancet Oncol 2004;5:399-408
Long Term Intellectual Outcome with Different volume & dose of radiation

31 Children with various post fossa tumours irradiated at the mean age of 6 years assessed after a mean period of 5 years Post RT

Grill IJROBP 1999
Neurocognitive Consequences of Risk-Adapted Therapy for Childhood Medulloblastoma

- 111 patients, 3 – 20 yrs of age
- 37 High risk (CSI std dose 36 – 40 Gy + conf boost + 4# CT)
- 74 Avg. Risk (Low dose CSI 23.4 Gy + conformal boost + 4# CT)
- Greatest declines in HR patients who were < 7 yrs of age.
- No significant diff between low dose Vs high dose CSI

<table>
<thead>
<tr>
<th></th>
<th>AR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>- 0.99 (NS)</td>
<td>- 3.0</td>
</tr>
<tr>
<td>Reading</td>
<td>- 2.9</td>
<td>- 3.08</td>
</tr>
<tr>
<td>Spelling</td>
<td>- 2.7</td>
<td>- 3.4</td>
</tr>
<tr>
<td>Math</td>
<td>- 1.57</td>
<td>- 2.4</td>
</tr>
</tbody>
</table>

Mulhern JCO 2001
Is there a role for modified fractionation

Maybe **YES**

Strong radio-biologic rationale

**Average-risk disease**

Hyper-fractionated Radiation Therapy (HFRT):
CSI: 36 Gy/36#/4 wks, 1 Gy BID, 6 hrs apart, 5 days/wk
Boost: 32 Gy/32#/2.5 wks, 1 Gy BID, 6 hrs apart, 5 days/wk

**High-risk disease**

Hyper-fractionated Accelerated Radiation Therapy (HART):
CSI: 36 Gy/36#/3 wks, 1 Gy BID, 6 hrs apart, 6 days/wk
Boost: 24 Gy/20#/2 wks, 1.2 Gy BID, 6 hrs apart, 6 days/wk

Ongoing HFRT/HART trials: SIOP PNET IV, HIT 2000 and CNS 2001
CONFORMAL RADIOTHERAPY, REDUCED BOOST VOLUME, HYPERFRACTIONATED RADIOTHERAPY, AND ONLINE QUALITY CONTROL IN STANDARD-RISK MEDULLOBLASTOMA WITHOUT CHEMOTHERAPY: RESULTS OF THE FRENCH M-SFOP 98 PROTOCOL.

Table 2. Acute toxicities observed during radiotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>1</td>
<td>1</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>11</td>
<td>3</td>
<td>14 (29)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>2</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>3</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Fig. 1. Overall survival distribution (Kaplan-Meier method. 48 patients).

Carrie C: IJROBP 2005
Decline in IQ with HFRT

Fig. 3. Intelligence quotient (IQ) changes during early post-radiation therapy (MSFOP98) period—Wechsler scales (22 patients).

Fig. 4. Full-scale intelligence quotient (IQ) (individual patient data)—No significant full-scale IQ variation.
Is there an impact of RT deviations on outcome

A RESOUNDING YES

GOOD RADIOTHERAPY

• CRUCIAL
• CRITICAL
• CENTRAL

FOR SUCCESSFUL OUTCOME
67% risk of tumour relapse at 3 years with 2 major deviations
78% risk of tumour relapse at 3 years with 3 major deviations
Insignificantly increased risk of relapse with minor deviations

Carrie C: IJROBP 1999
Radiotherapy Parameters Affecting Outcome

UKCCSG PNET-3 study

217 children: chemo + RT vs RT alone. 176 analyzable

131 RT Planning films reviewed
PF recurrence in 34% with deviations vs 16% if no deviation in PF fields (P=0.04)

Taylor: IJROBP 2004
RADIOThERAPy IN PEDIATRIC MEDULLOBLASTOMA: QUALITY ASSESSMENT OF PEDIATRIC ONCOLOGY GROUP TRIAL 9031

Fig. 1. Event-free survival of 183 eligible patients by treatment deviation.

Table 1. Summary on treatment deviations of 160 patients fully evaluable for all treatment parameters

<table>
<thead>
<tr>
<th>Type</th>
<th>Deviation</th>
<th>Number of patients (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatments</td>
<td>0</td>
<td>69 (43%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>50 (31%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>31 (19%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9 (6%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Brain</td>
<td>No</td>
<td>119 (74%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>41 (26%)</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>No</td>
<td>96 (60%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>64 (40%)</td>
</tr>
<tr>
<td>Spine*</td>
<td>No</td>
<td>149 (92%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>No</td>
<td>133 (83%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>27 (17%)</td>
</tr>
</tbody>
</table>
How best to integrate CT with RT

- Delay in starting RT results in inferior outcome: Halperin
- Prolongation of RT duration negatively impacts upon survival: Del Charco & SIOP PNET 3
- Pre RT CT inferior to post RT CT: CCG 921 and HIT 91
- Pre RT CT does not improve survival compared to RT alone: SIOP II & SIOP PNET 3
- Pre RT CT followed by reduced dose CSI inferior: SIOP II
Does adjuvant CT improve survival

Average-risk disease
Definitely NOT
CCG 942 & SIOP I

High-risk disease
Definitely YES
Evans, Tait et al
HIT 91, CCG 942 & SIOP I
POG 9031 & SIOP PNET 3
Results of a Randomized Study of Preradiation Chemotherapy Versus Radiotherapy Alone for Nonmetastatic Medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children’s Cancer Study Group PNET-3 Study

- 1st large multicentre RCT to show better EFS with CT (74.2% vs 59.8%; p=0.0366)
- M0-M1 PreRT CT Vs RT alone
- VCR + Eto + Carbo/Cyclo → CSI
- 217 pts (179 analyzable), 5 year f/u
- Overall survival – not different
- Significant impact of RT duration on EFS

Taylor JCO 2003
Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Fig 1. Event-free survival (EFS) and survival from study entry.

Packer: JCO 2006
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 or 4 Regimen A/B</th>
<th>Grade 4 Regimen A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>97/98</td>
<td>82/90</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12/11</td>
<td>1.7/2.2</td>
</tr>
<tr>
<td>Renal</td>
<td>9.0/6.0</td>
<td>1.1/0.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3.4/2.2</td>
<td>1.6/1.6</td>
</tr>
<tr>
<td>Nervous system</td>
<td>51/46</td>
<td>5.4/3.8</td>
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<tr>
<td>Hearing</td>
<td>28/23</td>
<td>5.8/6.7</td>
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<tr>
<td>Electrolytes</td>
<td>6.2/12</td>
<td>1.7/3.9</td>
</tr>
<tr>
<td>Infection</td>
<td>18/30</td>
<td>1.6/6.9</td>
</tr>
<tr>
<td>Performance</td>
<td>21/14</td>
<td>4.9/4.8</td>
</tr>
</tbody>
</table>
Randomized Controlled Trial

Least Toxic Standard Dose RT alone schedule

Vs

Reduced dose CSI + CT

(average-risk disease)

OVERKILL or OVERDUE
Maximizing Cure
Minimizing Sequelae

Radiotherapy for brain tumours
Newer perspectives in RT for Medulloblastoma

Stereotactic Conformal Radiation Therapy for Tumour Bed Boost
Protons vs photons for Medulloblastoma
IMRT for CSI