Curie Scoring of MIBG Scans: A Prognostic Indicator

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Neuroblastoma

- Most common extra-cranial solid tumor in children
- Originates as a primary tumor of the sympathetic nervous system
- Often metastasizes to bone or bone marrow
- 15% of patients who present with metastatic disease at diagnosis are refractory to induction chemotherapy
- 40% of those with metastatic disease will relapse after having a complete response or partial response

Poor Prognostic Features In Neuroblastoma

- Age > 18 months
- Advanced stage disease
- MYCN amplification
- Poorly differentiated or undifferentiated tumor histology
- Diploid DNA content

15% of childhood cancer mortality
Despite the use of preoperative induction chemotherapy, surgery, post-operative high dose chemotherapy (with or without total body irradiation), and autologous bone marrow transplant, the prognosis for those with high risk neuroblastoma has improved only slightly over the past decade.
Neuroblastoma

- Tailoring treatment to risk group stratification
  - Improves outcome
  - Decreases toxicity
- How do we identify responders from those who will be resistant to induction therapy?
- Identify a prognostic indicator
- Gauge response through a scoring methodology that is:
  - Easy to use, short training times
  - Reliable and reproducible
  - Facilitates comparison between results obtained by different investigators and centers
  - Readily adapted to multi-center use
MIBG scoring

• How is it performed?
  - Curie score (COG) and SIOPEN scores

• What have we learned from its use?
  - Can MIBG scoring predict outcome?
  - How well do methodologies compare?

• How will MIBG scoring be used in the future?
  - Risk stratification by MIBG scoring.
Early scoring systems

• **Nakajo et al:** J Nucl Med 1983; 24:672-682
  • Semiquantitative scoring system for the normal distribution of MIBG using an intensity scale (0-4)

• **Baulieu et al:** J Biophys Med Nucl 1984; 8:47-53
  • Adapted semiquantitative intensity scale scoring (0-3) of MIBG scans to assess disease in neuroblastoma

• **Philip et al:** Pediatr Hematol Oncol 1987;4:25-31
  • Considered a classification that included MIBG scans and response to disease; not quantitative
MIBG scoring

  - Curie Institute, Paris, France
  - MIBG scoring of multiple (9) anatomical regions (0-3)
  - Reported use of modified Curie score
  - Noted importance of % reduction in scores between two time points. (Relative Scores)
- Messina et al. 2006: high inter-observer concordance
- SIOPEN scoring method developed in 2000’s
  - Ladenstein, Boubaker, Valteau
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
• Review Committee: Central review of > 1000 MIBG scans (309 pts)
• MIBG scans scored at diagnosis, post-induction, post-BMT, post-cis RA.
• All 309 patients rec’d cis RA. 46 patients rec’d ch14.18 on ANBL0032.

Stem cell harvest post cycle 2 of induction;
surgical resection post cycle 5 of induction

Curie Scores at Diagnosis and EFS

Median Curie score at Diagnosis = 12, range 0-30.

Patients with MIBG negative disease at diagnosis were censored from further analysis.
Post-Induction Curie scores:
Highly predictive of survival

Poor EFS if Curie score > 2 post-induction.

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

p < 0.001
Impact of Post-Induction Curie scores in patients with *MYCN* amplified disease

For *MYCN* amplified tumors: Poor EFS if Curie score > 0

Curie score 0: 3-yr EFS: $49.6 \pm 7.7\%$

Curie score > 0: 3-yr EFS: $11.8 \pm 7.8\%$

$p < 0.01$
Post-transplant Curie Scores and EFS

- 

CS = 0 (n = 133)

CS > 0 (n = 45)

p = 0.009
Can MIBG scores predict early events?

The initial Curie score, obtained at the time of diagnosis, was unable to predict patients who were going to have an “early event,” i.e. PD or death within 12 months of diagnosis.

<table>
<thead>
<tr>
<th>Status</th>
<th>No. pts</th>
<th>Median CS at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis + Early Event</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td>No early event</td>
<td>207</td>
<td>13</td>
</tr>
</tbody>
</table>
Tumor burden versus Tumor response

- Which is more important at the end of induction?
  A) Achieving a specified reduction in Curie score,
  OR
  B) Achieving a low Curie score (Curie Score ≤ 2).
Tumor burden versus Tumor response

- Which is more important at the end of induction?
  A) Achieving a specified reduction in Curie score,
  OR
  B) Achieving a low Curie score (Curie Score ≤ 2).
Tumor burden versus Tumor response

Patients with Post-induction Curie Scores > 2 did poorly, regardless of the % reduction from diagnosis

<table>
<thead>
<tr>
<th>“Relative Reduction”</th>
<th>3-yr EFS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% Reduction</td>
<td>18.8 ± 12.0%</td>
<td>0.508</td>
</tr>
<tr>
<td>&lt; 50% Reduction</td>
<td>13.9 ± 5.8%</td>
<td></td>
</tr>
<tr>
<td>≥ 75% Reduction</td>
<td>22.9 ± 9.6%</td>
<td>0.571</td>
</tr>
<tr>
<td>&lt; 75% Reduction</td>
<td>14.0 ± 5.3%</td>
<td></td>
</tr>
</tbody>
</table>

Tumor burden at end of induction matters more than response
Does % Reduction even matter? Impact of “Relative Scores”

Matthay K, JCO 2003

Relative Scores may be useful at interval time points “during” induction therapy. This will be validated when we analyze scans from ANBL0532, in which MIBG scans were obtained at interval time points.
Post-Induction Scores and EFS
Curie score vs SIOPEN score

Poor EFS if Curie Score > 2 or SIOPEN score > 3

However, the Curie score includes extraosseous disease. SIOPEN scores do not. So…
Excluding extraosseous disease, a Curie score > 3 or a SIOPEN score > 3 post-induction are both highly significant.
Curie and SIOPEN scores

- Striking similarity in post-induction results
- Cross-validation of each method planned
- INRC Metastatic Imaging Committee:
- Goals:
  - To develop consensus scoring criteria.
  - To develop MIBG based response criteria.
    - CR: MIBG score = 0
    - PR: ≥ 50% reduction in MIBG score
    - SD: < 50% reduction in score
    - PD: Increase in score
Summary

• MIBG scoring *CAN* define patients with poor outcomes:
  
  a. Curie Score > 2 or SIOPEN > 3 at end of induction
  
  b. Excluding extraosseous disease:
      • MIBG score > 3 post-induction is highly significant

• MIBG scoring is here to stay.
• We just need to work out the details.