RT in Patients with CNS Germ Cell Tumors

Paul J Chuba
St John Providence Health Systems
Detroit and Warren MI
The ancient Egyptian symbol Wadjet (the Eye of Horus) means god/goddess and bears a striking resemblance to the anatomy of the pineal gland and brainstem. It has been postulated that “near-death experiences” are caused by a massive release of dimethyltriptamine (DMT) from the pineal gland. The French philosopher René Descartes studied the pineal gland extensively and referred to it as “the principal seat of the soul.” (Source)
Germ Cell Tumors

- Variety of Histologies
- Common Origin: Primordial Germ Cell
- Gonadal and Non-Gonadal Presentation
  - Testis, Ovary
  - Mediastinum
  - Retroperitoneum
  - Pineal/Suprasellar
Definitions

- **Dysgerminoma**: A malignant neoplasm of the ovary (counterpart of seminoma of the testis) composed of undifferentiated gonadal germinal cells
- **Seminoma**: A malignant neoplasm of the testis of young males
- **Germinoma**: A neoplasm of the germinal tissue of the gonads, mediastinum, or pineal region
Malignant CNS Germ Cell Tumors

- Germ cell tumors (GCTs) make up about 3% of childhood malignancies.
- Germ cell neoplasia:
  - Requires formation of a transformed pluri-potential cell from a totipotential precursor germ cell which would otherwise be destined to gametogenesis.
  - Differentiation into embryonal-like (somaically differentiated) tumors, as well as extra-embryonally differentiated (choroid and yolk sac) tumors.
  - Occurs without fertilization and requires “erasing” of imprinting.
  - Overexpression of cyclin D2 cell cycle G1/S checkpoint regulator.
Overview

- What we have learned
  - Background GCT and NGGCT
- Some Results of Trials
  - Europe and Japan
  - POG and Single Institutions
  - ACNS0122 for NGGCT
  - ACNS0232 for GCT
- Where we are going
  - Newly opened COG trial
    - ACNS1123 response adapted RT for NGGCT and pure GCT
CNS GCT Location

GCT

- 37% suprasellar
- 41% pineal
- 22% bifocal

Secreting GCT

- 62% suprasellar
- 33% pineal
- 5% bifocal
PRIMARY CNS GCT
Histopathology (SIOP)

- Germinoma: 58%
- sGCT: 37%
- Pure teratoma: 5%
CNS Germ Cell Tumors

Incidence (per million)

Age at Diagnosis

Incidence
Germinoma

Touch Prep: High N/C Ratio

PAP

Beta-HCG
Pineal Choriocarcinoma from 12 yo Female

Tendency to Hemorrhage

HCG Reactivity
PRIMARY CNS GCT
NGGCTs

Choriocarcinoma (βHCG)

Yolk sac tumour (αFP)

embryonal carcinoma
(αFP + βHCG)
Immature Pineal Teratoma
12 yo Male

Cartilage,
Mucin Producing
Columnar Epithelium.,
Spindle Cell Stroma
Mature Teratoma
Resembles Benign
Adult Cartilage,
Respiratory Epithelium,
Loose Fibrous Stroma
High Tech Radiation?
The Eye of Horus: Symbol of Power and Good Health
Horus Was Ancient Sky God Depicted as A Falcon
(Mirror Image or Left Eye Sometime Represented the Moon)
Table 1: Incidence of CNS NGGCT
Projected in the U.S. Population per year
Based on SEER 1997

<table>
<thead>
<tr>
<th>Age</th>
<th>STD US Pop'n</th>
<th>Brain (C71.x)</th>
<th>Other CNS (C72.x)</th>
<th>Pituitary (C75.1)</th>
<th>Pineal (C75.3)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4</td>
<td>18.90</td>
<td>15.5</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
<td>16.6</td>
</tr>
<tr>
<td>5 to 9</td>
<td>19.70</td>
<td>1.2</td>
<td>1.2</td>
<td>0</td>
<td>2.5</td>
<td>4.9</td>
</tr>
<tr>
<td>10 to 14</td>
<td>19.90</td>
<td>6.5</td>
<td>0</td>
<td>5.2</td>
<td>10.4</td>
<td>22.1</td>
</tr>
<tr>
<td>15 to 19</td>
<td>19.90</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>10.7</td>
<td>13.4</td>
</tr>
<tr>
<td>20 to 24</td>
<td>18.50</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>27.1</td>
<td>2.3</td>
<td>5.2</td>
<td>24.8</td>
<td>59.4</td>
<td></td>
</tr>
<tr>
<td>Author Year (ref)</td>
<td>Chemotherapy</td>
<td>Germinomas</td>
<td>NG-GCTs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------</td>
<td>------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rustin 1986 (34)</td>
<td>PBVcrMTX/ECyActD; IT Mtx</td>
<td></td>
<td>1/2 CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsutani 1987 (35)</td>
<td>VPB for 2 years</td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen 1987 (3)</td>
<td>Cy (1.8-2.4 g/m²); VPB/Cy (4.9 g/m²)</td>
<td>7 CR, 1 PR</td>
<td>2 PR, 1 PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyamachi 1988 (36)</td>
<td>VcrPB</td>
<td>3 CR/ 2 PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demeocq 1988 (37)</td>
<td>VPB / CyAct D</td>
<td>6/7: &gt;75% PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mizuno 1989 (38)</td>
<td>EP</td>
<td>2/2 CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayashida 1989 (39)</td>
<td>EP</td>
<td>1 CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinkerton 1990 (40)</td>
<td>EBCb</td>
<td>1 CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jereb 1990 (41)</td>
<td>Cy (80 mg/kg)</td>
<td>3/3 CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baumgarten 1992 (42)</td>
<td>VPBE</td>
<td>6/10 CR’s (GCT’s and NG-GCT’s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plowman 1993 (24)</td>
<td>VcrE/Cb</td>
<td>4/5 CR / 1 PR</td>
<td>1 CR/1 PR/1 SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elyan 1993 (19)</td>
<td>P/Cb</td>
<td>5/7 Cr</td>
<td>2/4 alive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skinner 1993 (20)</td>
<td>EP/VcrMtxB/ECb/VCrmx/ xB/IT Mtx</td>
<td>2 CR / 1 PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrman 1993 (21)</td>
<td>EPB/VPhos</td>
<td>3/3 responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshida 1993 (43)</td>
<td>EP</td>
<td>7 CR / 9 PR of 30 patients (GCT’s and NG-GCT’s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calaminus 1993 (44)</td>
<td>VBP pre-XRT / Ifos/E post; or HDP/VB pre Ifos / E post</td>
<td>5/12 PFS*;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finlay 1993 (25)</td>
<td>BECb (1g/m²) + Cy (3.9 g/m²)</td>
<td>21/23 CR</td>
<td>16 CR/13 PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen 1994 (24)</td>
<td>Cb (150 mg/m²/wk x 4)</td>
<td>7 CR / 3 PR / 1 NE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Phase II Consortium
Robertson et al 2005 (U of M, Beth Israel, CHOP, Vancouver)

- CNS NGGCT or Secretor (n=27)
  - CDDP, IFOS, VP-16
  - RT 36 Gy CSI Except Localized Disease With CR After Surgery or CHT (WV RT + Boost)
  - For Less than CR, 2nd Look Sx plus Carbo/CTX x 2 with PBSC Support
- Better PFS in Cases Achieving Initial CR
- 9/27 Relapsed
- 3/6 Relapsed Outside RT Field
  - “Emphasizes Need for CSI”
Amulets
POG 9530
Wharam/Kretschmar et al

- A Phase II Study of Chemotherapy/XRT for Primary Malignant Germ Cell Tumors of the Central Nervous System (i.e. both GCT and NGGCT)

- **Rationale**
  - Safer Biopsy Available to Identify Histologic Subtype
  - Platinum Based Chemotherapy Found to Be Effective

- **Objectives**
  - Reduce Radiotherapy Dose by Using Chemo for Good Risk Patients (i.e. GCT)
  - Improve Prognosis for Poor Risk Patients (i.e. Non-germinoma histology, elevated AFP, HCG >50)

- **Four Courses CDDP/VP-16 alternating with Cytoxan/VCR followed by Radiation**
  - CDDP 40 mg/m²/d IV and VP-16 100 mg/m²/d IV x 5 days alternating with Cyt 2g/m² for 2 days and VCR 1.5 mg/m² IV days 1,8,15.
## POG 9530 Schema

<table>
<thead>
<tr>
<th></th>
<th>Neuraxis</th>
<th>Spine Gross Disease</th>
<th>Brain Gross Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>low risk, CR not disseminated</td>
<td>0</td>
<td>0</td>
<td>3060 cGy</td>
</tr>
<tr>
<td>low risk, &lt;CR not disseminated</td>
<td>0</td>
<td>0</td>
<td>5040 cGy</td>
</tr>
<tr>
<td>low risk, CR disseminated*</td>
<td>2340 cGy</td>
<td>3060 cGy</td>
<td>3060 cGy</td>
</tr>
<tr>
<td>low risk &lt; CR disseminated*</td>
<td>3600 cGy</td>
<td>4500 cGy</td>
<td>5040 cGy</td>
</tr>
<tr>
<td>high risk, CR</td>
<td>3060 cGy</td>
<td>4500 cGy</td>
<td>5040 cGy</td>
</tr>
<tr>
<td>high risk, &lt;CR</td>
<td>3600 cGy</td>
<td>4500 cGy</td>
<td>5400cGy</td>
</tr>
</tbody>
</table>

*Any patient with more than one site of disease is considered to have dissemination.*
POG 9530 Results

- 11 of 14 NGGCT Patients Were Progression Free at Median 58 Mos (Range 42-71 Mos).
  - One Inevaluable Patient Received Only One Course of Chemo and Died During RT
  - One Patient With SD Died at 21 Mos of a Seizure at Home
  - One Patient With Mixed Yolk-sac Tumor Developed PD Before RT and Died of Disease 9 Months Later
- EFS Was 79% +/-11 % for High-risk or NGGCT (N=14).
- Accrual
- Response Rate (5 of 9) and PFS Comparable to Previous Reports
<table>
<thead>
<tr>
<th>no</th>
<th>sex</th>
<th>age</th>
<th>path</th>
<th>site</th>
<th>hcg</th>
<th>hcg csf</th>
<th>afp</th>
<th>afp csf</th>
<th>sx</th>
<th>Matsut. Class</th>
<th>rr</th>
<th>status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>12.5</td>
<td>terato-choriocarcinoma</td>
<td>pineal</td>
<td>2424</td>
<td>220</td>
<td>10.5</td>
<td>4.5</td>
<td>gtr</td>
<td>Poor</td>
<td>not eval.</td>
<td>PFS 67 mos</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>13.9</td>
<td>germinoma</td>
<td>pituitary</td>
<td>5496</td>
<td>nd</td>
<td>nl</td>
<td>nd</td>
<td>pr</td>
<td>interim</td>
<td>PR 96%</td>
<td>PFS 71 mos</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>16.3</td>
<td>none</td>
<td>pineal</td>
<td>nl</td>
<td>nl</td>
<td>286</td>
<td>314</td>
<td>shunt only</td>
<td>?int/poor</td>
<td>PR</td>
<td>PFS 61 mos</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>16.9</td>
<td>yolk-sac teratoma</td>
<td>pineal</td>
<td>13</td>
<td>nl</td>
<td>5190</td>
<td>26</td>
<td>75%</td>
<td>poor</td>
<td>early death</td>
<td>DOD 2 mos</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>18.1</td>
<td>mixed yolk-sac teratoma</td>
<td>pineal</td>
<td>13</td>
<td>nd</td>
<td>274</td>
<td>nd</td>
<td>pr</td>
<td>poor</td>
<td>PD</td>
<td>DOD 15 mos</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>11.2</td>
<td>germinoma met</td>
<td>pineal/frontal</td>
<td>9990</td>
<td>9800</td>
<td>1141</td>
<td>153</td>
<td>biopsy</td>
<td>interim</td>
<td>PR</td>
<td>PFS 64 mos</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>10.4</td>
<td>adenoca-teratoma</td>
<td>pineal</td>
<td>nl</td>
<td>nl</td>
<td>nl</td>
<td>nl</td>
<td>gtr</td>
<td>interim</td>
<td>not eval.</td>
<td>PFS 61 mos</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>11.6</td>
<td>germinoma met</td>
<td>pineal/csf</td>
<td>74</td>
<td>59</td>
<td>nl</td>
<td>nl</td>
<td>biopsy</td>
<td>interim?</td>
<td>CR</td>
<td>PFS 58 mos</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>7.1</td>
<td>none</td>
<td>pineal</td>
<td>165</td>
<td>1550</td>
<td>14</td>
<td>8</td>
<td>none</td>
<td>interim?</td>
<td>SD</td>
<td>PFS 43 mos</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>10.7</td>
<td>germ-chorio</td>
<td>pineal</td>
<td>nl</td>
<td>471</td>
<td>nl</td>
<td>nl</td>
<td>gtr</td>
<td>poor</td>
<td>not eval.</td>
<td>PFS 52 mos</td>
</tr>
<tr>
<td>11</td>
<td>f</td>
<td>6.5</td>
<td>germ-chorio</td>
<td>suprasellar</td>
<td>nl</td>
<td>2392</td>
<td>nl</td>
<td>nl</td>
<td>pr</td>
<td>poor</td>
<td>SD</td>
<td>died of sz 21 mos</td>
</tr>
<tr>
<td>12</td>
<td>m</td>
<td>16.2</td>
<td>none</td>
<td>pineal</td>
<td>200</td>
<td>74</td>
<td>80</td>
<td>12</td>
<td>none</td>
<td>poor?</td>
<td>SD</td>
<td>PFS 51 mos</td>
</tr>
<tr>
<td>13</td>
<td>f</td>
<td>14</td>
<td>mixed</td>
<td>suprasellar</td>
<td>719</td>
<td>3247</td>
<td>pr</td>
<td>intern</td>
<td>CR</td>
<td>PFS 50 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>m</td>
<td>10.4</td>
<td>mixed yolk sac teratoma</td>
<td>pineal</td>
<td>4</td>
<td>156</td>
<td>nl</td>
<td>gtr</td>
<td>poor</td>
<td>not eval.</td>
<td>PFS 50 mos</td>
<td></td>
</tr>
</tbody>
</table>
18 Secretors 10 AFP, 2 HCG, 6 Both
- 6 Cycles of Chemotherapy
  - Vinblastine-bleomycin - Carboplatin or Etoposide - Carboplatin/ifosfamide – Etoposide

Fifteen Patients Were Treated According to the Protocol By:
- Chemotherapy Alone (N=13)
- Or Chemotherapy and Radiation of Residue (2).

Twelve of the 13 Non Irradiated Patients Relapsed
- 8 in Local And/or Regional Area, 3 in Cerebrospinal Area and 1 Undetermined

12/18 Patients Alive With a Median Follow up of 68 Months.
- All but One Had Focal Radiation As Part of Treatment.

Six Patients in 2nd CR
- Chemotherapy And/or Surgery, Then Consolidation With Radiation And/or High Dose Chemotherapy or Craniospinal Radiation

‘Focal Radiotherapy Should Be Part of the Treatment’
SFOP with Focal RT
Barenzelli et al

- 27 Secreting GCT
  - 15 AFP, 7 HCG, 5 Both
  - Rx Carbo/VP Alt. IFOS (6-8 Courses)
  - Focal RT 55 Gy, CSI for Mets (n=3)
  - 14/27 Had Sx for Residual

- Median F/U 53 Mos
  - 20/27 Alive, 8/27 Relapsed
SIOP CNS GCT Study 96
SIOP 2005 Report

- 13 CNS NGGCT CDDP, VP-16, Ifos x 4
  - Local Disease IF RT 54 Gy
  - Met Disease 30 Gy CSI + 24 Gy Boost
- Median F/U 39 Mos
  - PFS 67% for Localized
  - 72% for Metastatic
- Residual After Induction and AFP >1000 Poor Prognosticators
- Spinal Failure Rate?
26 Of 123 NGGCT Were Metastatic
- Metastatic divided into CSF positive and Macroscopic.
- Non-metastatic includes Bifocal

Relapses “Mostly Ventricular”

Survival
- 77% at 72 months for localized
- 66% at 72 months for metastatic

Residual disease at end of therapy?
- EFS 82% vs 45%
“Pure” Malignant Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma

- 5 year OS of Less than 10 percent
- Greater than 70% OS for Mixed Tumors

Concluded:

- Treat Germinoma With Combination Chemotherapy and Reduced Dose Radiation Therapy
- Intermediate risk NGGCT Cis or Carbo Combination with Radiation
- Poor Risk: Need More Aggressive Chemotherapy
Matsutani
12th Peds Neuro-Onc Symposium

- 38 HCG Secreting Germinoma (Treated As Pure Germinoma)
  - CARE followed by local RT 24 Gy
  - 5/38 Recurrences
  - 5 yr OS 100%
- 40 NGGCT
  - Intermediate Prognosis Group (n=40)
    - Malignant Teratoma and Mixed Tumor Mainly composed of germinoma or Teratoma
      - CARE (Carbo/VP-16) Followed by Local RT 50 Gy
      - 5 Yr OS 97%
  - Poor Prognosis Group (n=27):
    - Choriocarcinoma, Yolk Sac, Embryonal, Mixed
      - ICE followed by CSI then ICE x 5
      - 5 Yr OS 56%
<table>
<thead>
<tr>
<th>Histology</th>
<th>n=</th>
<th>1-yr</th>
<th>3-yr</th>
<th>5-yr</th>
<th>10 yr</th>
<th>15 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinoma</td>
<td>50</td>
<td>100</td>
<td>95.4</td>
<td>95.4</td>
<td>92.7</td>
<td>87.9</td>
</tr>
<tr>
<td>Germinoma with STGC</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>83.3</td>
<td>83.3</td>
<td>NC</td>
</tr>
<tr>
<td>Mature Teratoma</td>
<td>16</td>
<td>100</td>
<td>92.9</td>
<td>92.9</td>
<td>92.9</td>
<td>NC</td>
</tr>
<tr>
<td>Malignant Teratoma</td>
<td>11</td>
<td>100</td>
<td>70.7</td>
<td>70.7</td>
<td>70.7</td>
<td>NC</td>
</tr>
<tr>
<td>Pure Malignant Germ Cell Tumor</td>
<td>11</td>
<td>45.5</td>
<td>27.3</td>
<td>27.3</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Mixed Tumor</td>
<td>39</td>
<td>87.2</td>
<td>61</td>
<td>57.1</td>
<td>40.1</td>
<td>NC</td>
</tr>
<tr>
<td>Germinoma nd Teratoma (MGT)</td>
<td>17</td>
<td>94.1</td>
<td>94.1</td>
<td>84.7</td>
<td>70.6</td>
<td>NC</td>
</tr>
<tr>
<td>Germinoma or Teratoma (MXB)</td>
<td>10</td>
<td>80</td>
<td>70</td>
<td>52.5</td>
<td>35</td>
<td>NC</td>
</tr>
<tr>
<td>Mainly Pure Elements (MXM)</td>
<td>12</td>
<td>83.3</td>
<td>9.3</td>
<td>9.3</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

NC= not calculable
The Questions?

- Is Chemotherapy Effective and Are Responses Durable? YES
  - cf Testicular Tumors
- Is RT Needed? YES
  - SFOP: 6 Cycles of Chemotherapy (with Surgery and Focal Radiation for Viable Residual. 12 of 13 non-irradiated patients relapsed
  - Kellie et al: Intensive chemo w/o RT effective in about 1/3 of patients
- If RT then how much? Dose and Field Size
  - CSI
    - Popularity
    - Neurocognitive Function and Bone Growth Delay
    - Second Malignancy? Endocrine?
- What Are the Spinal failure Rates?
  - Predilection to Involve CNS
3.2.2 Histologic Diagnosis

3.2.2.1 Eligible Histological Diagnosis (See Section 15.0)
   a) Endodermal sinus tumor (yolk sac tumor)
   b) Embryonal carcinoma
   c) Choriocarcinoma
   d) Immature teratoma and teratoma with malignant transformation
   e) Mixed germ cell tumor

Any histologically confirmed germinoma tumor with elevation of serum and/or CSF beta HCG >50 IU/dl or any elevation of serum and/or CSF alpha fetoprotein >10 IU/L (ng/mL) or institutional norm.

Histologically unconfirmed pineal and/or suprasellar tumors with serum and/or CSF tumor markers of beta HCG >50IU/dl or any elevation of alpha fetoprotein >10 IU/L (ng/mL) or institutional norm.

Patients with normal AFP and B-HCG < 50IU/dl without histologic diagnosis of a NGGCT are ineligible and patients with pure germinoma without elevation of tumor marker are ineligible.
ACNS0122 Eligibility

- Age 3 to <25 yrs
- Histological Diagnosis
  - Yolk Sac
  - Embryonal Carcinoma
  - Choriocarcinoma
  - Immature Teratoma & Teratoma With Malignant Transformation
  - Mixed Germ Cell tumor
- Histologically confirmed Germinoma with serum &/or CSF $\beta$-HCG > 50lu/l
- Pineal &/or suprasellar tumors with serum &/or CSF $\beta$-HCG > 50lu/l; or AFP > 10
ACNS0122 NGGCT

- All patients received 6 cycles of chemotherapy (alternating Carboplatin/Etoposide & Ifosfamide/Etoposide)
- Patients with radiographic response and marker normalization treated with CSI 36 Gy f/b IFRT to primary tumor to total dose of 54 Gy
- Second look surgery was encouraged for residual disease
- Thiotepa/Etoposide f/b PBSC rescue was encouraged for patients with viable disease
ACNS0122 NGGCT

- 104 patients enrolled
- 15 recurrences, 6 deaths
- Median f/u 2.8 years
2 year EFS 84% ± 4%
OS 94% ± 3%

Median TTP 0.4 years
Median TTD 0.77 years

Courtesy of Stewart Goldman, MD
Relapses mainly local

- 9 local recurrences
- 4 distant
  - 2 spinal
  - 1 spine and distant brain
  - 1 abdominal carcinomatosis
- 2 markers only
Second look surgery for poor response (15)
  - Teratoma (6)
  - Malignant teratoma (3)
  - Fibrosis (4)
  - NGGCT (2)
Second look surgery for progressive disease (6)
  - Growing Teratoma Syndrome (4)
  - Embryonal (2)

Too few patients went on to HD chemotherapy f/b PBSC to assess efficacy
Pure Germinoma/ACNS 0232

- ACNS0232 randomized trial comparing:
  - 1) RT alone (WVRT 24 Gy f/b IFRT to total 45 Gy) – STANDARD ARM
  - 2) Chemotherapy followed by response-based RT (2-4 cycles* f/b IFRT to 30 Gy).

*carboplatin/etoposide x2 f/b response assessment;
If CR no further therapy & if < CR cisplatin/cyclophosphamide x 2
Ventricular Relapse

Reports of high rates of ventricular relapse led several cooperative groups to abandon IFRT as a treatment option.

ACNS0232 closed to poor accrual.
Conclusions

1. Increased risk of relapse with chemotherapy followed by IFRT
2. Radiation volume cannot be reduced from WVRT to IFRT

Can we reduce radiation dose for patients who are responding to chemotherapy?
PLANNED STRATEGY IN SIOP CNS GCT 2003
- SECRETING GCTs -

**AFP > 25 ng/ml or ßHCG > 50 IU/l in serum or CSF**

**standard risk**
- AFP ≤ 1000 ng/ml
- and age > 5 years
- and complete workup

3 x PEI → CR

1 x PEI → metastatic
- TU 54 Gy
- CSI 30 Gy
- +TU 24 Gy

**high risk**
- AFP > 1000 ng/ml
- or age ≤ 5 years
- or incomplete workup

3 x PEI → CR

HD PEI → non-metast.
- TU 54 Gy
- metastatic
- CSI 30 Gy
- +TU 24 Gy

only if age > 5 yrs else STOP

3 x PEI → PR

1 x PEI → Res

CR → PR

Res

CR

Res
ACNS1123
Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized
Central Nervous System
Germ Cell Tumors

NGGCT

Germinoma
ACNS1123

- Combines NGGCT and pure GCT (2 strata)
- Primary objectives:

  1. To determine, as measured by 3 year PFS if volume/dose of RT can be reduced for NGGCT and if chemotherapy f/b low dose WVRT plus IF RT is effective for pure GCT
  2. To prospectively evaluate the cognitive, social, and behavioral functioning of children and young adults who are treated with reduced RT dose/volume
Eligibility

- Only for patients with localized disease
  - Bifocal tumors eligible
  - Patients with disease found on endoscopic examination of ventricles eligible
Eligibility

- **Stratum 1 (NGGCT)**
  - Patients with identified levels:
    - Serum and/or CSF β-HCG >100 mIU/mL, or,
    - Any elevation of serum and CSF AFP > 10 ng/mL, or,
    - institutional norm
  - Biopsy not required

- Patients with any of the following elements on biopsy/resection, irrespective of serum and/or CSF β-HCG and AFP levels:
  - endodermal sinus tumor (yolk sac), embryonal carcinoma, choriocarcinoma, malignant/immature teratoma, mixed GCT with malignant GCT elements.
Eligibility

- **Stratum 2 (Germinoma)**
  - Patients with institutional normal AFP and β-HCG 5 - ≤ 50 mIU/mL in serum and/or CSF (biopsy not required)
  - Patients with bifocal involvement or pineal lesion with DI and β-HCG ≤ 100 mIU/mL and institutional normal AFP in serum/CSF (biopsy not required)
  - Patients with histologically confirmed germinoma or germinoma mixed with mature teratoma and β-HCG ≤ 100 mIU/mL and institutional normal AFP in serum/CSF
ACNS1123- pure GCT

- Chemotherapy
  - 4 cycles of Carboplatin/Etoposide
- Radiation
  - WVRT to 18 Gy
  - IFRT to bring primary disease to total 30 Gy
RT Guidelines

- 3D planning required
- 3D photons, IMRT, protons allowed
- 2 CTV’s
  - Whole Ventricles
  - Involved Field
- Involved field CTV must be contoured upfront and added to whole ventricle volume to ensure full coverage
WVRT

- While few patients were treated with WVRT on prior studies, all patients enrolled on ACN1123 will receive WVRT
- Difficult volume to contour with variability among clinicians
- Review of volumes from ACNS0232 demonstrated need for clear guidelines
- ACNS1123 will allow for smaller margins and more conformal techniques
Whole ventricle atlas

- To improve consistency
- Provide a visual guide
- Decrease protocol violations

- Will be available on QARC website
Stem Cell Research Points The Way To The Cell of Origin For Intracranial Germ Cell Tumors


- Neural Stem Cell leads to GCT?

- Parental Chromosome Duplications
  Implies Possible Pre-Meiotic Event

- Proposed Cell of Origin, the Germ Cell Progenitor, Would Not Normally Be Found In The Brain

- No Other Class Of Primary Cancer Arises From A Cell From A Distant Organ

- Evidence For Model Of Transformation Of Endogenous Brain Cells
Conclusions:
North American Approach to CNS GCTs

- Incremental Progress?
- Different Strategies Compared
  - Europe
  - Japan
- ACNS 0122, ACNS 1123
- Goal: Define Risk – Tailor Treatment
- Future:
  - Radiation Questions?
  - Achieve Consensus?