Radiation Therapy in Rhabdomyosarcoma

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## Anatomy

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head &amp; Neck</td>
<td>39%</td>
</tr>
<tr>
<td>Parameningeal</td>
<td>25%</td>
</tr>
<tr>
<td>Non Parameningeal</td>
<td>07%</td>
</tr>
<tr>
<td>Orbit</td>
<td>09%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>31%</td>
</tr>
<tr>
<td>Extremity</td>
<td>13%</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>07%</td>
</tr>
<tr>
<td>Trunk</td>
<td>05%</td>
</tr>
<tr>
<td>Other Sites</td>
<td>03%</td>
</tr>
</tbody>
</table>
Epidemiology

Annual incidence (West):
- 4.4 per 1 million whites
- 1.3 per 1 million blacks

Male: Female ratio - 1.5: 1.0
Risk Factors

○ Environmental exposures:
  Paternal cigarette use, X-ray exposure, Maternal drug use

○ Associated with disorders in development:
  CNS, GU, GI, CVS anomalies

○ Congenital disorders:
  Congenital pulmonary cysts
  Gorlin basal cell nevus syndrome
  Neurofibromatosis

○ The most frequently occurring childhood cancer in families:
  Li-Fraumeni syndrome
  Neurofibromatosis type 1
  Beckwith-Wiedemann syndrome
Natural History

- Association of site of primary, age at diagnosis and tumor histology.
  - Urinary bladder/ vagina -- Primarily infants -- Embryonal / Botryoid
  - Trunk/ Extremity -- Adolescents – Alveolar/ Undifferentiated
  - Head & Neck -- throughout childhood -- Embryonal

- Locally invasive/ pseudo-capsule

- Local spread: Fascial/ muscle planes

- Lymphatic extension (15%)
  - Paratesticular, extremity, and truncal tumors: 25%
  - Head & Neck: 15%
  - Orbit: <5%
  - Influenced by Site/ Size/ Invasiveness/ Histology

- Hematogenous dissemination (15-20%)
  - Sites of Met: Lung, Bone Marrow, Bone, Pleural effusion, Ascites
  - Higher incidence from Truncal & Head/ Neck sites
  - Alveolar (25%), Embryonal (13%)
Clinical Features

- **Primary:**
  - Asymptomatic mass
  - Site:
    - Orbit - Proptosis, Ophthalmoplegia.
    - Parameningeal - Nasal, aural, sinus obstruction
    - Cranial nerve palsy, headache
    - Genitourinary - Hematuria, urinary obstruction, constipation

- **Lymphatic:**
  - Regional & distant nodal disease

- **Hematogenous:**
  - Lung/ Pleural effusion – Dyspnoea, cough, chest pain
  - Bone Marrow – Bone pain, weakness, low counts
  - Bone – Pain, fracture
  - Ascites – Abd. distension, discomfort
# Diagnostic Workup

<table>
<thead>
<tr>
<th>All sites</th>
<th>History</th>
<th>Physical Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Investigations</td>
<td>Haemogram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• LFT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RFT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urine Analysis</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow Aspirate &amp; Biopsy</td>
<td>All Patients</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>CECT Scan - Primary &amp; Pulmonary Met</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI Scan - Primary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PET CT Scan - Primary &amp; Met</td>
<td></td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>MRI Scan - Primary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSF Exam - Parameningeal</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>MRI Scan - Primary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystoscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pelvic EUA - If required</td>
<td></td>
</tr>
<tr>
<td>Extremity/ Trunk</td>
<td>MRI Scan/ CECT</td>
<td></td>
</tr>
</tbody>
</table>
Role of PET-CT

Comparison of PET–CT and Conventional Imaging in Staging Pediatric Rhabdomyosarcoma

Sara M. Federico, MD, Sheri L. Spunt, MD, Matthew J. Krasin, MD, Catherine A. Billup, PhD, Jianrong Wu, PhD, Barry Shulkin, MD, Gerald Mandell, MD, and M. Beth McCarville, MD

Background. Over the past decade, PET–CT has been used to assess rhabdomyosarcoma (RMS) in children. However, the role of PET–CT in staging RMS is unknown. Procedure. Thirty subjects with RMS, median age 7.3 years, underwent PET–CT before therapy. PET–CTs and conventional imaging (CI) were independently reviewed by two radiologists and two nuclear medicine physicians to determine the presence of metastases. Accuracy, sensitivity, and specificity of PET–CT for detecting metastases were compared to CI using biopsy and clinical follow-up as reference standards. Maximum standardized uptake values (SUV max) of primary tumors, lymph nodes, and pulmonary nodules were measured. Results. Primary tumors had an average SUV max of 7.2 (range, 2.5–19.2). Accuracy rates for 17 subjects with nodal disease were 95% for PET–CT and 49% for CI. PET–CT had 94% sensitivity and 100% specificity for nodal disease. Of seven pulmonary nodules detected by CI, three were not identified by PET–CT, two were indeterminate, and one was malignant with a SUV max (3.4) > twice that of benign nodules. Two subjects had bone disease; both were identified by PET–CT but only one by CI. Four subjects had bone marrow disease, two had positive PET–CTs but none had positive CI. Two subjects had soft tissue metastases detected by PET–CT but not CI. Conclusions. PET–CT performed better than CI in identifying nodal, bone, bone marrow, and soft tissue disease in children with RMS. CI remains essential for detection of pulmonary nodules. We recommend PET–CT for staging of children with RMS. CI with Tc 99m bone scan can be eliminated.

Key words: conventional imaging; diagnosis; PET–CT; rhabdomyosarcoma; staging

Conventional Imaging (CI) = CT Chest + CT/MRI Primary + Bone Scan

PET Ct Scan: Better detection of Nodes/ Bone Marrow/ Bone/ Soft Tissue
PET-CT in Prognostication

Contribution of PET/CT to Prediction of Outcome in Children and Young Adults with Rhabdomyosarcoma

Sven H. Baum¹, Michael Frühwald², Kambiz Rahbar¹, Johannes Wessling³, Otmar Schober¹, and Matthias Weckesser¹

¹Department of Nuclear Medicine, Münster University Hospital, Münster, Germany; ²Department of Pediatric Hematology and Oncology, Münster University Hospital, Münster, Germany; and ³Department of Clinical Radiology, Münster University Hospital, Münster, Germany

J Nucl Med 2011; 52:1535–1540

Significantly shorter overall survival in primary tumors visually rated as highly metabolically active or with a ratio of SUV(max) to SUV of the liver above 4.6

Metabolically active lymph node and distant site involvement was indicative of significantly lower survival rates

Multivariate Cox regression analysis: impact of SUV(max) of primary tumor on outcome failed to attain significance, although PET performed better than some of the prognostic factors (P = 0.081)
Pathologic Classification

INTERNATIONAL CLASSIFICATION OF RHABDOMYOSARCOMA

I. Superior prognosis
   a. Botryoid rhabdomyosarcoma
   b. Spindle cell rhabdomyosarcoma

II. Intermediate prognosis
   a. Embryonal rhabdomyosarcoma

III. Poor prognosis
   a. Alveolar rhabdomyosarcoma
   b. Undifferentiated sarcoma
   c. Anaplastic rhabdomyosarcoma

IV. Subtypes whose prognosis is not presently evaluable
   a. Rhabdomyosarcoma with rhabdoid features

5 Yr. Survival
88 – 95%
80 – 85%
60 – 65%
50 – 55%
Pathology

Small round blue cell tumors with cross striations/ characteristic Rhabdomyoblast
IHC: Actin, Myosin, Desmin, Myo-D 1

EMBRYONAL

ALVEOLAR

ARMS
80% harbor translocations resulting in PAX 3/FOXO or PAX 7/FOXO fusion gene
Fusion negative ARMS (20%) are similar to patients with ERMS

ERMS
LOH at 11p15 locus
Better prognosis than ARMS
Staging & Prognostication

A. Clinical group
   Surgicopathologic staging developed by IRSG in 1972

B. TNM System
   A. Takes into account tumor size & lymph node burden
   B. Site of disease included
   C. Incorporated IRS-IV onwards
# Intergroup Rhabdomyosarcoma Study
Clinical Grouping

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Extent of disease/ Surgical Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Localized)</td>
<td>A Localized tumor, confined to site of origin, completely resected</td>
</tr>
<tr>
<td></td>
<td>B Localized tumor, infiltrating beyond site of origin, completely resected</td>
</tr>
<tr>
<td>II (GTR)</td>
<td>A Localized tumor, gross total resection, but with microscopic residual disease</td>
</tr>
<tr>
<td></td>
<td>B Locally extensive tumor (spread to regional lymph nodes), completely resected</td>
</tr>
<tr>
<td></td>
<td>C Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease</td>
</tr>
<tr>
<td>III (Incomplete resection)</td>
<td>A Localized or locally extensive tumor, gross residual disease after biopsy only</td>
</tr>
<tr>
<td></td>
<td>B Localized or locally extensive tumor, gross residual disease after major resection (≥50 percent debulking)</td>
</tr>
<tr>
<td>IV (Metastatic)</td>
<td>Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor</td>
</tr>
</tbody>
</table>
Prognostic Factors

Site of Disease

![Survival vs Years](image)

- Orbit
- GU - nonbladder/prostate
- Head and neck
- GU - bladder/prostate
- Parameningeal
- Other
- Extremity

J Clin Oncol 2001;19:3091–3102

S Laskar ICRO 2019
# Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>Tumour stage invasiveness</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit Head &amp; Neck (Non PM) GU (Non Bladder/ Prostate) Biliary tract</td>
<td>T(_1) or T(_2)</td>
<td>a or b</td>
<td>Any N</td>
<td>M(_0)</td>
</tr>
<tr>
<td>2</td>
<td>Bladder/prostate Extremity H&amp;N (Para-meningeal)</td>
<td>T(_1) or T(_2)</td>
<td>a</td>
<td>N(_0) or N(_x)</td>
<td>M(_0)</td>
</tr>
<tr>
<td>3</td>
<td>Bladder/prostate Extremity Cranial Para-meningeal</td>
<td>T(_1) or T(_2)</td>
<td>a</td>
<td>N1</td>
<td>M(_0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b</td>
<td>Any N</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>All</td>
<td>T(_1) or T(_2)</td>
<td>a or b</td>
<td>N(_0) or N(_1)</td>
<td>M(_1)</td>
</tr>
</tbody>
</table>

**T1:** Confined to anatomic site  
**T2:** Extension  
  a: \(\leq 5\) cm in diameter  
  b: >5 cm in diameter  

**N0:** Not clinically involved  
**N1:** Clinically involved  
**NX:** Clinical status unknown  
**M0:** No distant metastases  
**M1:** Distant metastases present
Children vs Adults

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Pleomorphic</td>
<td>Emryonal</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Trunk &amp; extremities</td>
<td>HN, urogenital</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>• Worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Unfavorable location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Invasive tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Propensity for loco-regional &amp; distant spread</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Higher rates of metastases</td>
<td></td>
</tr>
</tbody>
</table>

Stout et al, JCO 1967
S Laskar ICRO 2019
Risk Stratification

- Clinical Grouping
- TNM Staging
- Histology
- Age
Risk Stratification

- **High risk (17%)**
- **Low risk (33%)**
- **Intermediate risk (50%)**

TNM Stage 4 RMS (ERMS/ARMS)

TNM Stage 1 ERMS clinical groups I, II, or III
Stage 2 or 3 ERMS clinical groups I or II

Stage 2 or 3 ERMS clinical group III
Children with ARMS that has not spread to distant parts of the body (Stage 1, 2, or 3)
General Management

Optimal Sequence & Intensity

Disease Control, Organ & Function Preservation, Minimize Morbidity
Chemotherapy

- Chemotherapy is necessary in all cases.

- Drugs demonstrating response as single-agent measured as a percentage response rate:
  - Ifosfamide (86%)  
  - Vincristine (59%) 
  - Cyclophosphamide (54%) 
  - Topotecan (46%) 
  - Mitomycin-C (36%) 
  - Dactinomycin (24%) 
  - Etoposide (15% to 21%) 
  - Irinotecan (23%) 
  - Cisplatin (15% to 21%) 
  - Dacarbazine (11%) 

- Commonly used combination chemotherapy:
  - VAC or VAC + doxorubicin (VACA) 
  - VACA + IE - Unfavorable histology/unfavorable site/ extensive tumor burden
Intergroup Rhabdomyosarcoma Study Group

5 year OS

<table>
<thead>
<tr>
<th>IRS</th>
<th>Period</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>(1972 - 1978)</td>
<td>55%</td>
</tr>
<tr>
<td>II</td>
<td>(1978 - 1984)</td>
<td>63%</td>
</tr>
<tr>
<td>III</td>
<td>(1984 - 1991)</td>
<td>71%</td>
</tr>
<tr>
<td>IV</td>
<td>(1991 - 1997)</td>
<td>71%</td>
</tr>
</tbody>
</table>
Chemotherapy

- Initial intensive CTh: Used for pharmacologic debulking, potentially allowing for a more conservative surgical approach or less-aggressive radiation therapy.

  IRS I&II. Cancer 1990;66:2072–2081
  German COS. Cancer 1992;70:2557–2567
  SIOP MMT 89, J Clin Oncol 2005;23:2618–2628

- Response to induction chemotherapy—whether complete, partial, or no response—does not predict ultimate outcome.

- CTh alone without Sx/RT (H&N, pelvis): poor local control.


- Omission of radiotherapy in partial responders result in inferior survival.

  Pediatr Blood Cancer 2008;51:593–597
  J Clin Oncol 2005;23:2586–2587

- Patients with only microscopic disease after initial resection (group II) require RT


- No improvement in outcome of high risk disease with High Dose CTh/ TBI + BMT

Surgery

- Ablative Surgery only: 20% long-term survival rate

- Concept of reasonable surgery: Complete removal of tumor + maximal conservation of anatomic structures. E.g.:
  - Preservation of bladder, bowel, and sexual function in patients with tumors of genitourinary origin
  - Limb function in patients with extremity tumors
  - Vision, voice, deglutition, and appearance in patients with head and neck tumors

- Primary surgical excision:
  - Removal of tumor + 5mm normal tissue (IRS Gp I) – 20%
  - Compromised surgical procedures (R1) (IRS Gp II) – 20%
  - Unresectable without morbidity (IRS Gp III) – 40%
  - Present with metastatic disease (IRS Gp IV) – 20%

- Amputation, orbital exenteration, mutilating surgery for H&N, RND etc. reserved for failure of initial therapy
Surgery

Second-look surgery (delayed primary excisions): Useful for converting partial responses after chemotherapy into complete responses – may improve survival.

IRS-V: If second-look surgery might allow a reduction in the amount of radiotherapy that is necessary to provide local tumor control.

Preliminary results: only select primary sites are appropriate for this approach

Second-look surgery to avoid RT: Inferior local control and survival.

## Major Clinical Trials

<table>
<thead>
<tr>
<th>Intergroup Rhabdomyosarcoma Studies (IRS)</th>
<th>International Society of Pediatric Oncology (SIOP)</th>
<th>Co-operative Weichteilsarkom Studiengruppe Studies (CWS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USA</strong></td>
<td><strong>Europe</strong></td>
<td><strong>German</strong></td>
</tr>
<tr>
<td>IRS I - V COG</td>
<td>RMS - 75</td>
<td>CWS - 81</td>
</tr>
<tr>
<td></td>
<td>MMT - 84</td>
<td>CWS - 86</td>
</tr>
<tr>
<td></td>
<td>MMT - 89</td>
<td>CWS - 91</td>
</tr>
<tr>
<td>Evaluated efficacy of Chemotherapy &amp; Radiotherapy as a function of surgical stage</td>
<td>To develop strategies to minimize local therapy by using risk adapted intensification of Chemotherapy &amp; salvage pts with local failure</td>
<td>More frequent use of local therapy compared to the MMT studies. Tried to develop strategies to reduce doses of radiation therapy but not eliminate its use</td>
</tr>
</tbody>
</table>
Radiotherapy

Indications

- Un-resectable primaries at diagnosis (IRV Gp III)
- Microscopic residual disease (IRS Gp II)
- Completely resected alveolar histology or lymph node involvement

Wolden SL et al. Indications for radiotherapy and chemotherapy after complete resection in rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Studies I to III.

*J Clin Oncol* 1999;17(11):3468-75
Can Radiotherapy be Avoided?

- No direct head to head comparison in IRSG trials (RT vs. No RT)

- Elimination of RT in para-meningeal RMS patients < 3 yrs age in the MMT trials reduced OS from 62% to 44%.
  

- Improved outcomes in Group II disease in IRS-III& IV
  
  Smith LM. Which patients with rhabdomyosarcoma (RMS) and microscopic residual tumor (Group II) fail therapy? A report from the Intergroup Rhabdomyosarcoma Study Group (IRSG) [abstract 2273B]. Proc Am Soc Clin Oncol 2000;19:577a
De- Escalating Therapy

Local Control and Outcome in Children With Localized Vaginal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group

David O. Walterhouse, MD, Jane L. Meza, PhD, John C. Breneman, MD, Sarah S. Donaldson, MD, Andrea Hayes-Jordan, MD, Alberto S. Pappo, MD, Carola Arndt, MD, R. Beverly Raney, MD, William H. Meyer, MD, and Douglas S. Hawkins, MD

Pediatr Blood Cancer 2011;57:76–83

RMS Vagina
41 Pts
D9602 & ARST0331

Outcomes after Delaying/ Avoiding RT based on CTh Response & Delayed Surgery
5 Yr FFS (ARST0331): 42%
5 Yr FFS (D9602): 70%

Inferior outcome in ARST0331 attributed to: Avoidance of RT & Low Cumulative Cyclophosphamide Dose (4.8g/m2)
RT Timing

- Early RT within 9 weeks preferable
- Delayed RT feasible without compromising OS in a subset (bladder & prostate)
- Meningeal involvement- RT preferably within 2 weeks (LR increase from 18% to 33%)
- WBRT not necessary
# RT Timing

<table>
<thead>
<tr>
<th>S.No</th>
<th>RT On Day 0</th>
<th>RT On Day 21 (Wk 3)</th>
<th>RT On Day 62 (Wk 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intra-cranial extension</td>
<td>Para-meningeal sites&lt;br&gt;Nasopharynx&lt;br&gt;PNS (maxilla/ethmoid/sphenoid)&lt;br&gt;Middle ear&lt;br&gt;Mastoid&lt;br&gt;Pterygopalatine fossa&lt;br&gt;Infra Temporal Fossa</td>
<td>All others</td>
</tr>
<tr>
<td>2</td>
<td>Skull base erosion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cranial nerve palsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# RT Volumes

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>All visible disease prior to starting CTh</td>
</tr>
<tr>
<td>CTV</td>
<td>Pre CTh extent + 2 cm margin (except sites like Orbit/ Pelvis/ Thorax etc)</td>
</tr>
<tr>
<td></td>
<td>Surgical sites/ Biopsy tracts</td>
</tr>
<tr>
<td></td>
<td>Clinically suspicious or involved lymph nodes should be included</td>
</tr>
<tr>
<td></td>
<td>Prophylactic lymph node irradiation not necessary</td>
</tr>
<tr>
<td>PTV</td>
<td>Pt/ Site/ Institute specific - Usually 5mm beyond CTV</td>
</tr>
</tbody>
</table>

- Parameningeal sites (middle ear, paranasal sinuses, nasopharynx, nasal cavity, infratemporal fossa, and parapharyngeal area): Portals should cover the adjacent meninges

  
  IRS III, J Clin Oncol 1995;13:610-630,
  IRS II-IV, Int J Radiat Oncol Biol Phys 2004;59:1027-1038

- Whole Brain RT not indicated
Traditionally used RT dose:

- **Microscopic disease** – 41.4Gy/23#/5Wks @ 1.8Gy/fraction
- **Gross Disease** – 50.4Gy/28#/6Wks @ 1.8Gy/fraction

Dose reduction:

- IRS-V, D9602 - Suggest 45Gy for gross tumor at orbital sites, especially if cyclophosphamide is included in the systemic therapy regimen


Local Control With Reduced-Dose Radiotherapy for Low-Risk Rhabdomyosarcoma: A Report From the Children’s Oncology Group D9602 Study

John Breneman, M.D., * Jane Meza, Ph.D., † Sarah S. Donaldson, M.D., ‡ R. Beverly Raney, M.D., §∥ Suzanne Wolden, M.D., ‾ Jeff Michalski, M.D., ** Fran Laurie, B.S., †† David A. Rodeberg, M.D., †‡ William Meyer, M.D., §§ David Walterhouse, M.D., †¶ and Douglas S. Hawkins, M.D. ¶¶
COG D9602

<table>
<thead>
<tr>
<th>Group</th>
<th>RT dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No RT</td>
</tr>
<tr>
<td>IIA</td>
<td>36</td>
</tr>
<tr>
<td>IIB/C</td>
<td>41.4</td>
</tr>
<tr>
<td>III orbit</td>
<td>45</td>
</tr>
<tr>
<td>III nonorbit*</td>
<td>50.4</td>
</tr>
</tbody>
</table>

* These patients were eligible for second-look operation after Week 12 chemotherapy. If tumor was completely resected, radiotherapy was reduced to 36 Gy for lymph-node negative tumors, and 41.4 Gy was given for lymph-node positive tumors. Girls with vaginal tumors received RT only if there was gross or microscopic tumor after chemotherapy with or without second-look operation.
Table 4  Five-year cumulative local control for Group IIA: favorable site tumors

<table>
<thead>
<tr>
<th>Protocol</th>
<th>RT dose (Gy)</th>
<th>Chemotherapy</th>
<th>Local failure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9602 (n = 62)</td>
<td>36</td>
<td>VA</td>
<td>15*</td>
</tr>
<tr>
<td>IRS III (n = 52)</td>
<td>41.4</td>
<td>VA</td>
<td>11</td>
</tr>
<tr>
<td>IRS IV (n = 43)</td>
<td>41.4</td>
<td>VAC/VAI/VAE</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 5   Five-year cumulative local control for Group IIA: unfavorable site tumors

<table>
<thead>
<tr>
<th>Protocol</th>
<th>RT dose (Gy)</th>
<th>Chemotherapy</th>
<th>Local failure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9602 (n = 16)</td>
<td>36</td>
<td>VAC</td>
<td>0</td>
</tr>
<tr>
<td>IRS III (n = 38)</td>
<td>41.4</td>
<td>VA</td>
<td>14</td>
</tr>
<tr>
<td>IRS IV (n = 28)</td>
<td>41.4</td>
<td>VAC/VAI/VAE</td>
<td>7</td>
</tr>
</tbody>
</table>
**Table 6** Five-year cumulative local control for Group III orbital tumors

<table>
<thead>
<tr>
<th>Protocol</th>
<th>RT Dose (Gy)</th>
<th>Chemotherapy</th>
<th>Local failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9602 (n = 77)</td>
<td>45</td>
<td>VA</td>
<td>14%</td>
</tr>
<tr>
<td>IRS III (n = 71)</td>
<td>41.4–50.4</td>
<td>VA</td>
<td>16%</td>
</tr>
<tr>
<td>IRS IV (n = 50)</td>
<td>50.4–59.5</td>
<td>VAC/VAI/VAE</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Conclusions:** In comparison with Intergroup Rhabdomyosarcoma Study Group III and IV results, reduced-dose radiotherapy does not compromise local control for patients with microscopic tumor after surgical resection or with orbital primary tumors when cyclophosphamide is added to the treatment program. Girls with unresected nonbladder genitourinary tumors require radiotherapy for postsurgical residual tumor for optimal local control to be achieved.
Hyperfractionation
(Dose Escalation)

RESULTS FROM THE IRS-IV RANDOMIZED TRIAL OF HYPERFRACTIONATED RADIOTHERAPY IN CHILDREN WITH RHABDOMYOSARCOMA—A REPORT FROM THE IRSG

SARAH S. DONALDSON, M.D.,* JANE MEZA, PH.D.,† JOHN C. BRENEMAN, M.D.,‡ WILLIAM M. CRIST, M.D.,§ FRAN LAURIE, M.S.,‖ STEPHEN J. QUALMAN, M.D.,¶ AND MOODY WHARAM, M.D.,# FOR THE CHILDREN’S ONCOLOGY GROUP SOFT TISSUE SARCOMA COMMITTEE (FORMERLY INTERGROUP RHABDOMYOSARCOMA GROUP) REPRESENTING THE CHILDREN’S ONCOLOGY GROUP AND THE QUALITY ASSURANCE REVIEW CENTER

Arm A: 59.4 Gy/ 1.1-Gy fractions twice daily at 6-hour intervals for gross disease
Arm B: 50.4 Gy/ 1.8 Gy once daily.

Result: No difference in LRC, FFS, OS

RT Techniques

- 3D CRT
- IMRT
- Proton beam therapy
- Brachytherapy
IMRT for H&N RMS

CLINICAL INVESTIGATION

INTENSITY-MODULATED RADIOTHERAPY FOR HEAD-AND-NECK RHABDOMYOSARCOMA

SUZANNE L. WOLDEN, M.D.,* LEONARD H. WEXLER, M.D.,† DENNIS H. KRAUS, M.D.,‡ MICHAEL P. LAQUAGLIA, M.D.,§ ERIC LIS, M.D.,§ AND PAUL A. MEYERS, M.D.†

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

<table>
<thead>
<tr>
<th>GTV</th>
<th>The gross tumour volume was defined as the extent of disease at diagnosis (pre-chemotherapy volume). Modified to reflect change in anatomy after tumour shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>1 cm margin beyond GTV</td>
</tr>
<tr>
<td>PTV</td>
<td>0.5cm</td>
</tr>
</tbody>
</table>
H&N IMRT

Results (3 Years):

OS - 65%
LC (Primary) - 95%
LC (Node) - 88%
Dist Met Free Survival - 80%

Orbit: No failures
DFS inferior in Alveolar

Acute/ Late toxicities: Similar to previous IRS studies without IGRT
IMRT with reduced margins: Excellent outcomes
IMRT for H&N RMS

LOCAL CONTROL AFTER INTENSITY-MODULATED RADIOTHERAPY FOR HEAD-AND-NECK RHABDOMYOSARCOMA

AMARINTHIA E. CURTIS, M.D.,* M. FATIH OKCU, M.D., M.P.H.,† MURALI CHINTAGUMPALA, M.D.,† BIN S. TEH, M.D.,*‡ AND ARNOLD C. PAULINO, M.D.*‡

*Section of Radiation Oncology, Department of Radiology, Baylor College of Medicine, Houston, TX; †Section of Hematology/Oncology, Department of Pediatrics, Texas Children’s Cancer Center, Baylor College of Medicine, Houston, TX; and ‡Department of Radiation Oncology, The Methodist Hospital, Houston, TX

4 Year LC (92.9%) , OS (76%)

Overall Survival:

Parameningeal: 42.9%

Other Sites: 100%
3D-CRT vs IMRT

**EFFECT OF RADIOTHERAPY TECHNIQUES (IMRT VS. 3D-CRT) ON OUTCOME IN PATIENTS WITH INTERMEDIATE-RISK Rhabdomyosarcoma Enrolled in COG D9803—A REPORT FROM THE CHILDREN’S ONCOLOGY GROUP**

Chi Lin, M.D., Ph.D.,* Sarah S. Donaldson, M.D.,† Jane L. Meza, Ph.D.,‡ James R. Anderson, Ph.D.,‡ Elizabeth R. Lyden, M.S.,‡ Christopher K. Brown, M.P.H.,‡ Karen Morano, C.M.D.,§ Fran Laurie, B.S.,§ Carola A. Arndt, M.D.,¶ Charles A. Enke, M.D.,* and John C. Breneman, M.D.¶

<table>
<thead>
<tr>
<th></th>
<th>3D-CRT</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median FU</td>
<td>5.7 Yrs</td>
<td>4.2 Yrs</td>
</tr>
<tr>
<td>5 Yr Local Rec Free Survival</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>5 Yr Failure Free Survival</td>
<td>72%</td>
<td>76%</td>
</tr>
<tr>
<td>Target Coverage</td>
<td>Inferior</td>
<td>Superior</td>
</tr>
</tbody>
</table>

Parameningeal sites: More likely treated with IMRT
Doses >50Gy more frequently with IMRT
Proton Beam Therapy

- Sharp fall off
- Superior dose distribution
- Greater sparing of normal structures
- Advantageous especially in H&N (para-meningeal) locations
FRACTIONATED, THREE-DIMENSIONAL, PLANNING-ASSISTED PROTON-RADIATION THERAPY FOR ORBITAL RHABDOMYOSARCOMA: A NOVEL TECHNIQUE

EUGEN B. HUG, M.D., *†‡§ JUDY ADAMS, C.M.D., *† MARKUS FITZER, M.D., *† ALEXANDER DE VRIES, M.D., *† AND JOHN E. MUNZENRIDER, M.D. *†

*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, and †Harvard Cyclotron Laboratory, Cambridge, MA; and Departments of ‡Radiation Medicine and §§Pediatrics, Loma Linda University Medical Center, Loma Linda, CA

- Excellent sparing of lens & orbit
- Conformal target dose coverage
PROTON RADIOTHERAPY FOR ORBITAL Rhabdomyosarcoma: Clinical Outcome and a Dosimetric Comparison with Photons

Torunn Yock, M.D., M.C.H., Robert Schneider, C.M.D., Alison Friedmann, M.D., Judith Adams, C.M.D., Barbara Fullerton, Ph.D., and Nancy Tarbell, M.D.

Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Table 4. Average dose and percent savings to CNS structures

<table>
<thead>
<tr>
<th>Structure</th>
<th>X-ray dose average (%)*</th>
<th>Proton dose average (%)*</th>
<th>Difference (%)</th>
<th>Percent savings†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>6.3</td>
<td>0.7</td>
<td>5.6</td>
<td>88.7</td>
</tr>
<tr>
<td>Pituitary</td>
<td>21.7</td>
<td>1.3</td>
<td>20.4</td>
<td>94.1</td>
</tr>
<tr>
<td>Brain</td>
<td>10.4</td>
<td>1.2</td>
<td>9.1</td>
<td>88.1</td>
</tr>
<tr>
<td>Temporal lobe (contralateral)</td>
<td>6.3</td>
<td>0.7</td>
<td>5.6</td>
<td>88.6</td>
</tr>
<tr>
<td>Temporal lobe (ipsilateral)</td>
<td>18.1</td>
<td>3.3</td>
<td>14.8</td>
<td>81.8</td>
</tr>
<tr>
<td>Chiasm</td>
<td>19.8</td>
<td>1.9</td>
<td>17.9</td>
<td>90.4</td>
</tr>
</tbody>
</table>

* Values are average doses in percentage for X-rays and protons.
† Percent savings calculated using the formula: \(\frac{X-ray\ dose - Proton\ dose}{X-ray\ dose} \times 100\)
# PROTON RADIOThERAPY FOR PARAMENINGEAL RHABDOMYOSARCOMA: CLINICAL OUTCOMES AND LATE EFFECTS


Departments of *Radiation Oncology, †Pediatric Oncology, and § Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and ‡Department of Radiation Oncology, University of Wisconsin Cancer Center Johnson Creek, Madison, WI

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## Table 2. Incidence of recorded toxicities in patients with parameningeal rhabdomyosarcoma: Comparison of proton data with previously published studies

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Protons: MGH ($n = 10$)</th>
<th>IRS II-III* ($n = 213$)</th>
<th>IMRT: MSKCC† ($n = 21$)</th>
<th>University of Iowa† ($n = 17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median f/u: 5 y</td>
<td>Median f/u: 7 y</td>
<td>Median f/u: 2 y</td>
<td>Median f/u: 20 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>$%$</td>
<td>$n$</td>
<td>$%$</td>
</tr>
<tr>
<td>Decreased growth velocity</td>
<td>3/10</td>
<td>30</td>
<td>92/190</td>
<td>48</td>
</tr>
<tr>
<td>Growth hormone replacement</td>
<td>2/10</td>
<td>20</td>
<td>36/190</td>
<td>19</td>
</tr>
<tr>
<td>Other endocrinopathies</td>
<td>1/10</td>
<td>10</td>
<td>17/213</td>
<td>8</td>
</tr>
<tr>
<td>Facial hypoplasia</td>
<td>7/10</td>
<td>70</td>
<td>74/76</td>
<td>97</td>
</tr>
<tr>
<td>Visual complications</td>
<td>0</td>
<td></td>
<td>45/213</td>
<td>21</td>
</tr>
<tr>
<td>Auditory complications</td>
<td>0</td>
<td></td>
<td>36/213</td>
<td>17</td>
</tr>
<tr>
<td>Dentition</td>
<td>3/10</td>
<td>30</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Chronic nasal and sinus congestion</td>
<td>2/10</td>
<td>20</td>
<td>35/71</td>
<td>49</td>
</tr>
<tr>
<td>Secondary malignancies</td>
<td>0</td>
<td></td>
<td>4/213</td>
<td>2</td>
</tr>
</tbody>
</table>

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* Laskar ICRO 2019

SUMMARY

• Radiation therapy forms an important component in combined modality treatment of RMS
• Improves local disease control in high risk patients
• Conformal techniques can reduce toxicities without compromising outcomes
• Brachytherapy is a useful tool for radiotherapy in young children
• Quality assurance & compliance to guidelines is essential for optimal disease control
• Avoidance or delaying RT should be done with caution