RHABDOMYOSARCOMA

Tumorigenesis

- Embryonal Rhabdomyosarcoma
  - Malignant transformation of myogenic progenitor cells of postnatal muscle
  - Activated in a myogenic regulatory factor related way for growth or remodelling after tissue injury

- Alveolar Rhabdomyosarcoma
  - Mesenchymal stem cell transformation
  - PAX3 /7-FOXO & PAX3-FKHR translocation
  - Marrow origin of stem cells – so called leukemic variant
  - PAX 3 vs. PAX 7 translocation
  - Translocation negative ARMS

Anatomy

Head & Neck	39%
Parameningeal	25%
Non Parameningeal	07%
Orbit	09%
Genitourinary	31%
Extremity	13%
Retroperitoneum	07%
Trunk	05%
Other Sites	03%

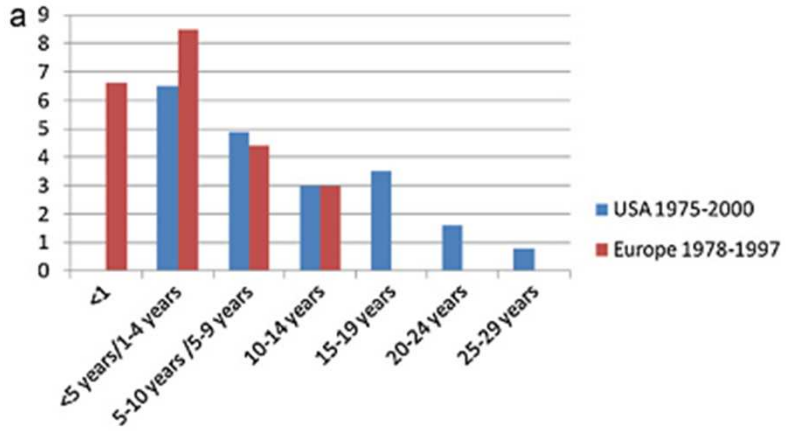
Epidemiology

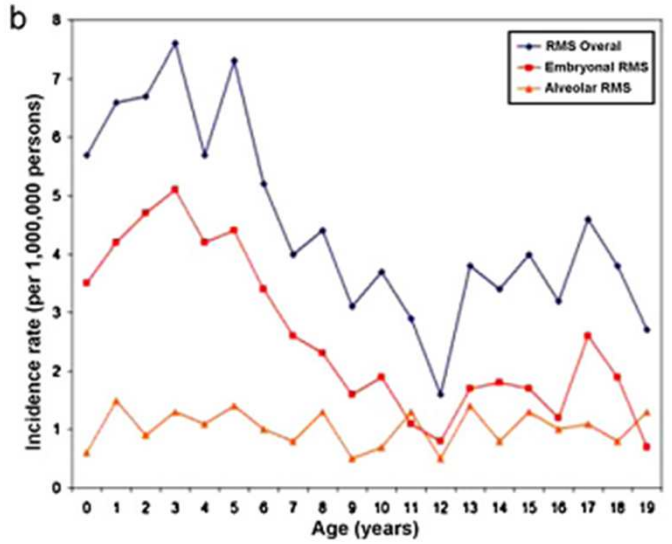
Annual incidence (West):

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
  - Costello 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%)
  - Sites of Met: Lung, Bone Marrow, Bone, Pleural effusion, Ascites
  - Higher incidence from Truncal & Head/ Neck sites

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

All Patients	*Optional*
All sites	
History	
Physical examination by several observers (including a pediatric oncologist, surgical oncologist and radiation oncologist)	Examination under anesthesia for infants and youngsters
Laboratory studies	Plain films of bones abnormal on scans
Complete blood count	Abdomen-pelvis CT, MRI, or ultrasound
Liver function tests	
Renal function tests	
Urinalysis	
Imaging studies	
PET-CT (this study can likely replace chest/abdomen/pelvis CT and bone scan studies)	
MRI or CT of primary tumor	
Bone marrow biopsy and aspirate	
Head and neck	
MRI or CT of primary tumor (with contrast)	Plain films of area
Lumbar puncture with cytologic examination of fluid (in parameningeal primary tumors)	Dental evaluation and x-rays
	Paranasal sinus and skull films
	MRI of spine if cerebrospinal fluid is positive or patient is symptomatic
Genitourinary	
CT of MRI of abdomen-pelvis (with contrast)	Ultrasound of pelvis
Pelvic examination under anesthesia	Cystoscopy
Extremity and truncal lesions	
MRI or CT of primary lesion (with contrast)	Plain films of primary site
	Ultrasound
	Barium gastrointestinal contrast studies

BM Bx & Aspirate

ERMS – perce

ARMS – percen

CSF (Parameningeal) – percen

Role of PET –CT

Pediatr Blood Cancer

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

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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. Pediatr Blood Cancer

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

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

PET-CT in Prognostication

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

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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. On multivariate Cox regression analysis, the impact of intensity or SUV(max) of the primary tumor on outcome failed to attain significance, although PET performed better than some of the prognostic factors established in larger patient groups (P = 0.081).

Staging

INTERGROUP RHABDOMYOSARCOMA STUDY
CLINICAL GROUPING CLASSIFICATION

Group I	Localized disease, completely resected
A	Confined to organ or musde of origin
B	Infiltration outside organ or musde of origin; regional nodes not involved
Group II	Compromised or regional resection
A	Grossly resected tumor with microscopic residual disease
B	Regional disease, completely resected, in which nodes may be involved or extension of tumor into adjacent organ may exist
C	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease
Group III	Incomplete resection or biopsy with gross residual disease
Group IV	Distant metastases at diagnosis

The Intergroup Rhabdomyosarcoma Study: Objectives & Clinical Staging Classification.
J Pediatr Surg 1980;15:371-372

Staging

INTERGROUP RHABDOMYOSARCOMA STUDY
PRETREATMENT STAGING SYSTEM

Stage	Site[a]	Invasiveness	Size	Nodal Status	Metastases
I	Favorable	T1 or T2	a or b	N0 or N1	M0
II	Unfavorable	T1 or T2	a	N0	M0
III	Unfavorable	T1 or T2	b	N0	M0
			a or b	N1	M0
IV	Any site		T1 or T2	N0 or N1	M1

T1, tumor confined to site or organ of origin; T2, regional extension beyond the site or organ of origin; a, ≤5 cm; b, >5 cm; N0, no evidence of regional node involvement; N1, evidence of regional node involvement (enlargement of nodes on radiographic imaging is considered evidence of involvement, although histologic confirmation is recommended when possible); M0, no distant metastasis; M1, evidence of distant metastasis.

[a]Favorable sites: orbit, head and neck (nonparameningeal), genitourinary (non–bladder-prostate); unfavorable sites: genitourinary (bladder-prostate), extremity, parameningeal, other.

Pathologic Classification

Classification of RMS initially used by the IRS investigators

Four histologic subtypes:

- Embryonal
- Botryoid subtype of embryonal
- Alveolar
- Pleomorphic.

Other variants:

- Solid alveolar - subtype of alveolar RMS
- Spindle cell - subtype of embryonal RMS
- Diffuse anaplastic variant

Pathologic Classification

INTERNATIONAL CLASSIFICATION OF RHABDOMYOSARCOMA

	5 Yr. Survival
I. Superior prognosis	88 – 95%
a. Botryoid rhabdomyosarcoma	
b. Spindle cell rhabdomyosarcoma	
II. Intermediate prognosis	80 – 85%
a. Embryonal rhabdomyosarcoma	
III. Poor prognosis	
a. Alveolar rhabdomyosarcoma	60 – 65%
b. Undifferentiated sarcoma	50 – 55%
c. Anaplastic rhabdomyosarcoma	
IV. Subtypes whose prognosis is not presently evaluable	
a. Rhabdomyosarcoma with rhabdoid features	

Prognostic Factors

Anticancer Res. 2012 Oct;32(10):4485-97.

THE IMPACT OF AGE on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study.
Van Gaal JC1, Van Der Graaf WT, Rikhof B, Van Hoesel QG, Teerenstra S, Suurmeijer AJ, Flucke UE, Loeffen JL, Sleijfer S, De Bont ES.

PATIENTS AND METHODS: Data were collected from three Dutch University Medical Centers between 1977-2009. The effect of age and clinical prognostic factors on relapse-free and disease-specific survival (DSS) were analyzed.

RESULTS: Age as a continuous variable predicted poor survival in multivariate analysis. Five-year DSS was highest for non-metastatic embryonal RMS, followed by non-metastatic alveolar RMS and was poor in metastatic disease. Higher age correlated with unfavorable histological subtype (alveolar RMS) and with metastatic disease at presentation in embryonal RMS. In non-metastatic embryonal RMS and in all alveolar RMS, higher age was an adverse prognostic factor of outcome.

CONCLUSION: This study indicates that age is a negative predictor of survival in patients with embryonal and alveolar RMS.

Cancer. Vol.115, Issue 18, 15 Sept 2009, 4218–4226

Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005

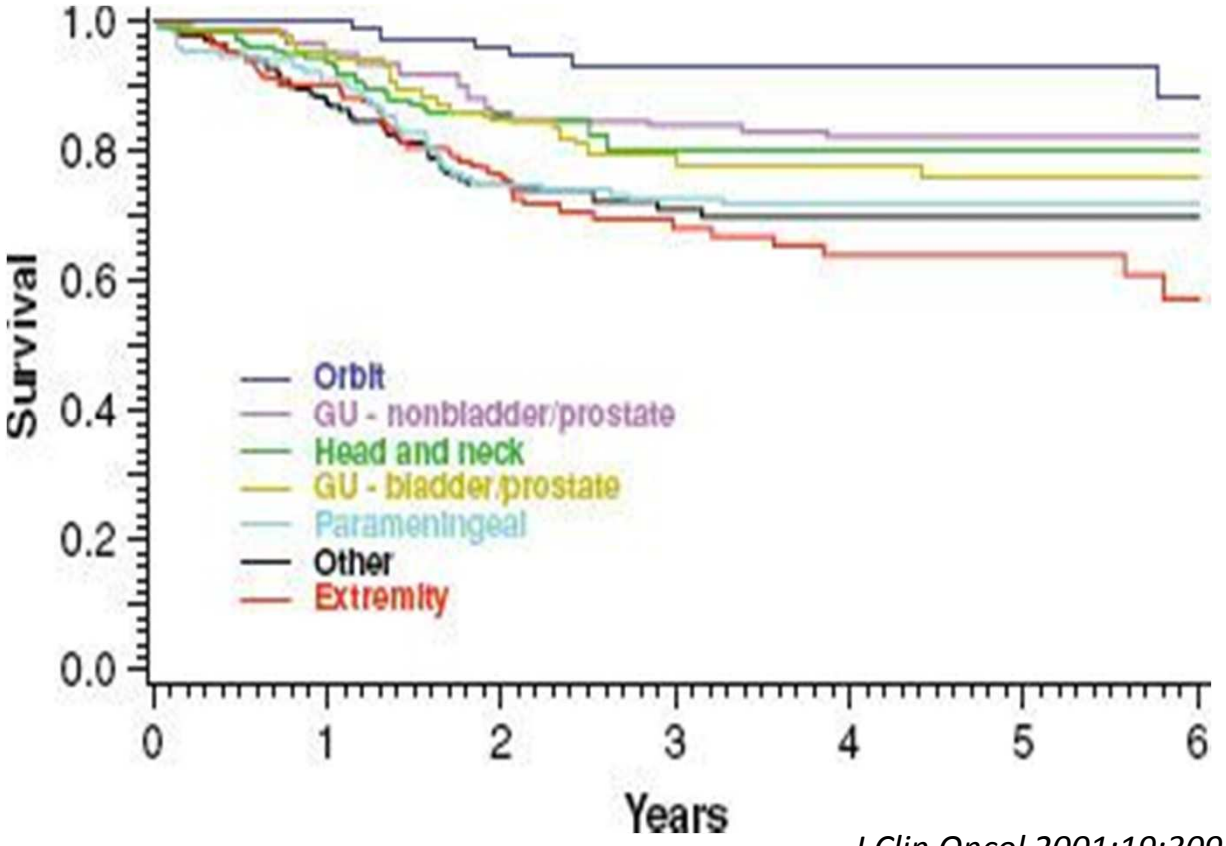
RESULTS:Between 1975 and 2005, the incidence of ERMS was stable, whereas a significant increase in the incidence of ARMS was observed (APC, 4.20%; 95%CI, 2.60%-5.82%). This trend may have been attributable in part to shifts in diagnosis, because a significant negative trend in RMS, not otherwise specified was observed concurrently. Five-year survival rates for RMS and ERMS increased during the period from 1976 to 1980 (52.7% and 60.9%, respectively) to the period from 1996 to 2000 (61.8% and 73.4%, respectively), whereas there was little improvement for ARMS (40.1% and 47.8%, respectively).

CONCLUSIONS: *Observed differences in incidence and survival for 2 major RMS subtypes across sex and age subgroups further supported the hypothesis that there are unique underlying etiologies for these tumors*. Exploration of these differences presents an opportunity to increase current knowledge of RMS.

Older Age & Female Sex: Inferior Outcomes

Prognostic Factors

Site of Disease



J Clin Oncol 2001;19:3091–3102

Prognostic Factors

- Orbit (Favourable):
  - Easy detection
  - Paucity of lymphatics
  - Most have embryonal histology
  - Hematogenous metastasis at diagnosis uncommon
  - 10% are alveolar histology – prognosis for these children is more guarded

- RT dose: Standard - 50 Gy
  - IRS-V study suggest 45 Gy sufficient if combined with cyclophosphamide-containing chemotherapy combination. *J Clin Oncol* 2011;29:1312–1318 *IJROBP* 2012;83(2):720–726

- CT+R: Cure rates >90% can be achieved *J Clin Oncol* 1995;13:610–630

- CT without RT: Increased local relapse & inferior EFS. *J Clin Oncol* 1994;12:516–5213

- Salvage RT : curative but poor function preservation

Prognostic Factors

Metastatic Disease

Hematogenous / distant lymph node metastasis at diagnosis - poor outcome

Subset of patients who are:

<10 years of age

Only one or two sites of metastatic disease may have survival >50%.

J Clin Oncol 2003;21:78–84

Intensive multiagent chemotherapy plays a major role in the treatment

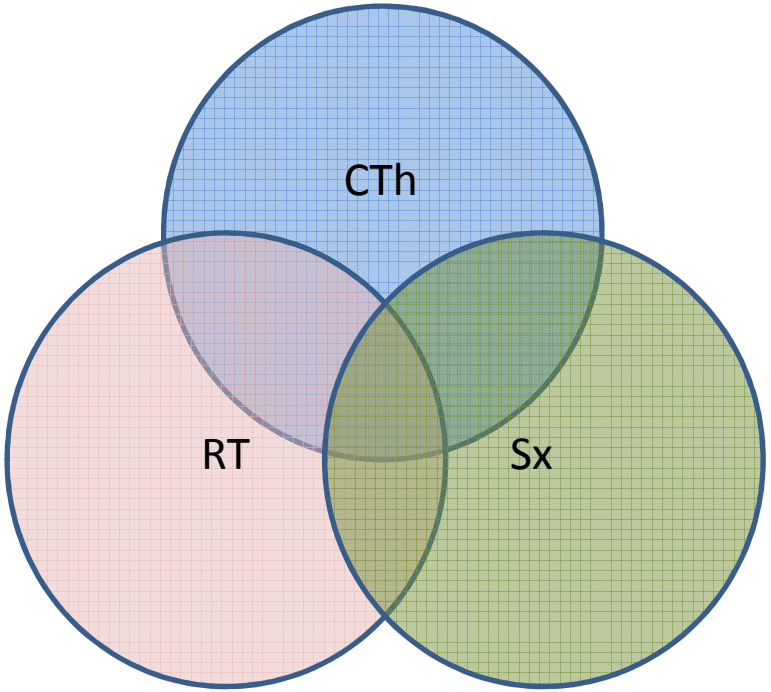
BMT not proven superior to conventional CTh .

Eur J Cancer 2010;46:1588–1595.68

Local control of the primary tumor – As per standard

Metastatic sites – treated with radiotherapy when feasible.

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

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.

  Med Pediatr Oncol 1991;19:89–95
  SIOP MMT 84 Clin Oncol 1994;12:516–521,

- 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

  J Clin Oncol 2004;22:143–149

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

  SIOP MMT-98. Eur J Cancer 2010;46:1588–1595.

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.43

IRS-V study to investigate 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.

AIEOP Study.Pediatr Blood Cancer 2008;51:593–597

Second-look operations: used to evaluate therapeutic response after chemotherapy or radiation therapy. In the IRS-III study, 28% patients categorized as having clinical partial response and 43% of those scored as having no response to induction chemotherapy were reclassified as having pathologic complete response after second-look operation. These children enjoyed a survival rate similar to that of children who were able to undergo complete surgical excision at the time of initial diagnosis. Therefore, a clinical or radiographic evaluation indicating residual tumor after initial therapy may be misleading.

Organ Preservation

CLINICAL INVESTIGATION **Sarcoma**

LOCAL THERAPY FOR RHABDOMYOSARCOMA OF THE HANDS AND FEET: IS AMPUTATION NECESSARY? A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

TRANG H. LA, M.D.,* SUZANNE L. WOLDEN, M.D.,† ZHENG SU, PH.D.,* CORINNE LINARDIC, M.D., PH.D.,‡ R. LOR RANDALL, M.D.,§ DOUGLAS S. HAWKINS, M.D.,‖ AND SARAH S. DONALDSON, M.D.*

Results: Actuarial 10-year local control was 100%; 10-year event-free survival and overall survival rates were 62% and 63%, respectively. Poor prognostic factors for recurrence included gross residual (Group III) disease and nodal involvement ($p = 0.01$ and 0.05, respectively). More patients in the RT group had alveolar histology, Group III disease, and nodal involvement, as compared with the surgery group. There was no difference in 10-year event-free survival (57% vs. 66%) or overall survival (63% vs. 63%) between patients who underwent surgery or local RT. Among relapsing patients, there were no long-term survivors. No secondary malignancies have been observed.

Conclusions: Despite having high-risk features, patients treated with local RT achieved excellent local control. Complete surgical resection without amputation is difficult to achieve in the hand or foot. Therefore, we recommend either definitive RT or surgical resection that maintains form and function as primary local therapy rather than amputation in patients with hand or foot RMS.

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 206–212, 2011

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%.

  Defachelles AS. Treatment of nonmetastatic cranial parameningeal RMS in children younger than 3 years old: results from SIOP MMT 89 and 95. J Clin Oncol 2009;27(8):1310–5.

- Improved outcomes in Group II disease in IRS-III& IV

  Smith LM. Which patients with rhabdomyosarcoma (RMS) and micro-scopic 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

Pediatr Blood Cancer 2011;57:76–83

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,[1]* Jane L. Meza, PhD,[2] John C. Breneman, MD,[3] Sarah S. Donaldson, MD,[4] Andrea Hayes-Jordan, MD,[5] Alberto S. Pappo, MD,[6] Carola Arndt, MD,[7] R. Beverly Raney, MD,[5] William H. Meyer, MD,[8] and Douglas S. Hawkins, MD[9]

Background. The local control approach for girls with non-resected vaginal rhabdomyosarcoma (RMS) enrolled onto Intergroup RMS Study Group (IRSG)/Children's Oncology Group (COG) studies has differed from that used at other primary sites by delaying or eliminating radiotherapy (RT) based on response achieved with chemotherapy and delayed primary resection. ***Procedures.*** We reviewed locoregional treatment and outcome for patients with localized RMS of the vagina on the two most recent COG low-risk RMS studies. ***Results.*** Forty-one patients with localized vaginal RMS were enrolled: 25 onto D9602 and 16 onto Subset 2 of ARST0331. Only four of the 39 with non-resected tumors received RT. The 5-year cumulative incidence of local recurrence was 26% on D9602, and the 2-year cumulative incidence of local recurrence was 43% on ARST0331. Increased local failure rates appeared to correlate with chemotherapy regimens that incorporated lower cumulative doses of cyclophosphamide. Estimated 5-year and 2-year failure free survival rates were 70% (95% CI: 46%, 84%) on D9602 and 42% (95% CI: 11%, 70%) on ARST0331, respectively. ***Conclusions.*** To prevent local recurrence, we recommend a local control approach for patients with non-resected RMS of the vagina that is similar to that used for other primary sites and includes RT. We recognize that potential long-term effects of RT are sometimes unacceptable, especially for children less than 24 months of age. However, when making the decision to eliminate RT, the risk of local recurrence must be considered especially when using a chemotherapy regimen with a total cumulative cyclophosphamide dose of ≤ 4.8 g/m^2. Pediatr Blood Cancer 2011;57:76–83.

Key words: female; genitourinary; radiotherapy; rhabdomyosarcoma; vagina

RT Timing

INFLUENCE OF RADIATION THERAPY PARAMETERS ON OUTCOME IN CHILDREN TREATED WITH RADIATION THERAPY FOR LOCALIZED PARAMENINGEAL RHABDOMYOSARCOMA IN INTERGROUP RHABDOMYOSARCOMA STUDY GROUP TRIALS II THROUGH IV

JEFF M. MICHALSKI, M.D.,*† JANE MEZA, PH.D.,†‡ JOHN C. BRENEMAN, M.D.,†§
SUZANNE L. WOLDEN, M.D.,†‖ FRAN LAURIE,†¶ MARYANN JODOIN,†¶ BEVERLY RANEY, M.D.,†#
MOODY D. WHARAM, M.D.,†** AND SARAH S. DONALDSON, M.D.†††

- 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

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 4, pp. 1027–1038, 2004

RT Timing

S.No	RT On Day 0	RT On Day21 (Wk 3)	RT On Day 62 (Wk 9)
1	Intra-cranial extension	Para-meningeal sites Nasopharynx PNS (maxilla/ethmoid/sphenoid) Middle ear Mastoid Pterygopalatine fossa Infra Temporal Fossa	All others
2	Skull base erosion		
3	Cranial nerve palsy		

RT Volumes

GTV –	All visible disease prior to starting CTh
CTV –	Pre CTh extent + 2 cm margin (except sites like Orbit/ Pelvis/ Thorax etc.
	Surgical sites/ Biopsy tracts
	Clinically suspicious or involved lymph nodes should be included
	Prophylactic lymph node irradiation not necessary
PTV -	Pt/ Site/ Institute specific – Usually 5mm beyond CTV

- 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

RT Dose

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

Raney R. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 2011;29:1312–1318.

Breneman J. Local control with reduced dose radiotherapy for low-risk rhabdomyosarcoma: a report from the Children's Oncology Group D9602 study. Int J Radiat Oncol Biol Phys 2012;83(2):720–726.

RT Dose Reduction

Clinical Investigation: Pediatric Cancer

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.‖‖

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COG D9602

Table 2 Radiotherapy (RT) doses

Group	RT dose (Gy)
I	No RT
IIA	36
IIB/C	41.4
III orbit	45
III nonorbit*	50.4

* 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.

COG D9602

Table 4 Five-year cumulative local control for Group IIA: favorable site tumors

Protocol	RT dose (Gy)	Chemotherapy	Local failure rate (%)
D9602 ($n = 62$)	36	VA	15*
IRS III ($n = 52$)	41.4	VA	11
IRS IV ($n = 43$)	41.4	VAC/VAI/VAE	2

COG D9602

Table 5 Five-year cumulative local control for Group IIA: unfavorable site tumors

Protocol	RT dose (Gy)	Chemotherapy	Local failure rate (%)
D9602 ($n = 16$)	36	VAC	0
IRS III ($n = 38$)	41.4	VA	14
IRS IV ($n = 28$)	41.4	VAC/VAI/VAE	7

COG D9602

Table 6 Five-year cumulative local control for Group III orbital tumors

Protocol	RT Dose (Gy)	Chemotherapy	Local failure rate
D9602 ($n = 77$)	45	VA	14%
IRS III ($n = 71$)	41.4–50.4	VA	16%
IRS IV ($n = 50$)	50.4–59.5	VAC/VAI/VAE	4%

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

Conclusions: HFRT, as given in this study, did not improve local/regional control, FFS, or OS compared with CFRT. The risk of local/regional failure was comparable to that of distant failure in children with Group III RMS. The standard of care for Group III RMS continues to be CFRT with chemotherapy.

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 3, pp. 718–728, 2001

Compliance to RT Guidelines

Non-compliance to RT treatment schedules:

- Omission/ Dose reduction/ Volume reduction results in a higher rate of local recurrences in postsurgical group II disease

  Million L, Anderson J, Breneman J, et al. Influence of noncompliance with radiation therapy protocol guidelines and operative bed recurrences for children with rhabdomyosarcoma and microscopic residual disease: a report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2011;80(2):333–8

- Association with age suggests that lower doses, often given to infants and youngsters, are associated with higher relapse rates.

  Malempati S, Rodeberg DA, Donaldson SS, et al. Rhabdomyosarcoma in infants younger than 1 year: a report from the Children's Oncology Group. Cancer 2011;117(15):3493–3501

Other RT Techniques

- 3D CRT
- IMRT
- Proton beam therapy
- Brachytherapy

IMRT for H&N RMS

CLINICAL INVESTIGATION **Head and Neck**

INTENSITY-MODULATED RADIOTHERAPY FOR HEAD-AND-NECK RHABDOMYOSARCOMA

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GTV	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
CTV	1 cm margin beyond GTV
PTV	0.5cm

Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 5, pp. 1432–1438, 2005

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

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Results: **The 4-year overall survival and local control rates were 76% and 92.9%, respectively. One patient developed a local failure in the high-dose region of the radiation field; there were no marginal failures. Distant metastasis was seen in 4 patients. Overall survival was 42.9% for parameningeal sites and 100% for other sites ($p < 0.01$). Late toxicities were seen in 7 patients. Two secondary malignancies occurred in 1 child with embryonal RMS of the face and a p53 mutation.**

Conclusions: **Local control was excellent in patients receiving IMRT for head-and-neck RMS. Patterns of local failure reveal no marginal failures in this group of patients.**

I. J. Radiation Oncology ● Biology ● Physics Volume 73, Number 1, 2009

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

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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.‖

	3D-CRT	IMRT
Median FU	5.7 Yrs	4.2 Yrs
5 Yr Local Rec Free Survival	18%	15%
5 Yr Failure Free Survival	72%	76%
Target Coverage	Inferior	Superior

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

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1764–1770, 2012

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

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ALEXANDER DE VRIES, M.D.,*† AND JOHN E. MUNZENRIDER, M.D.*†

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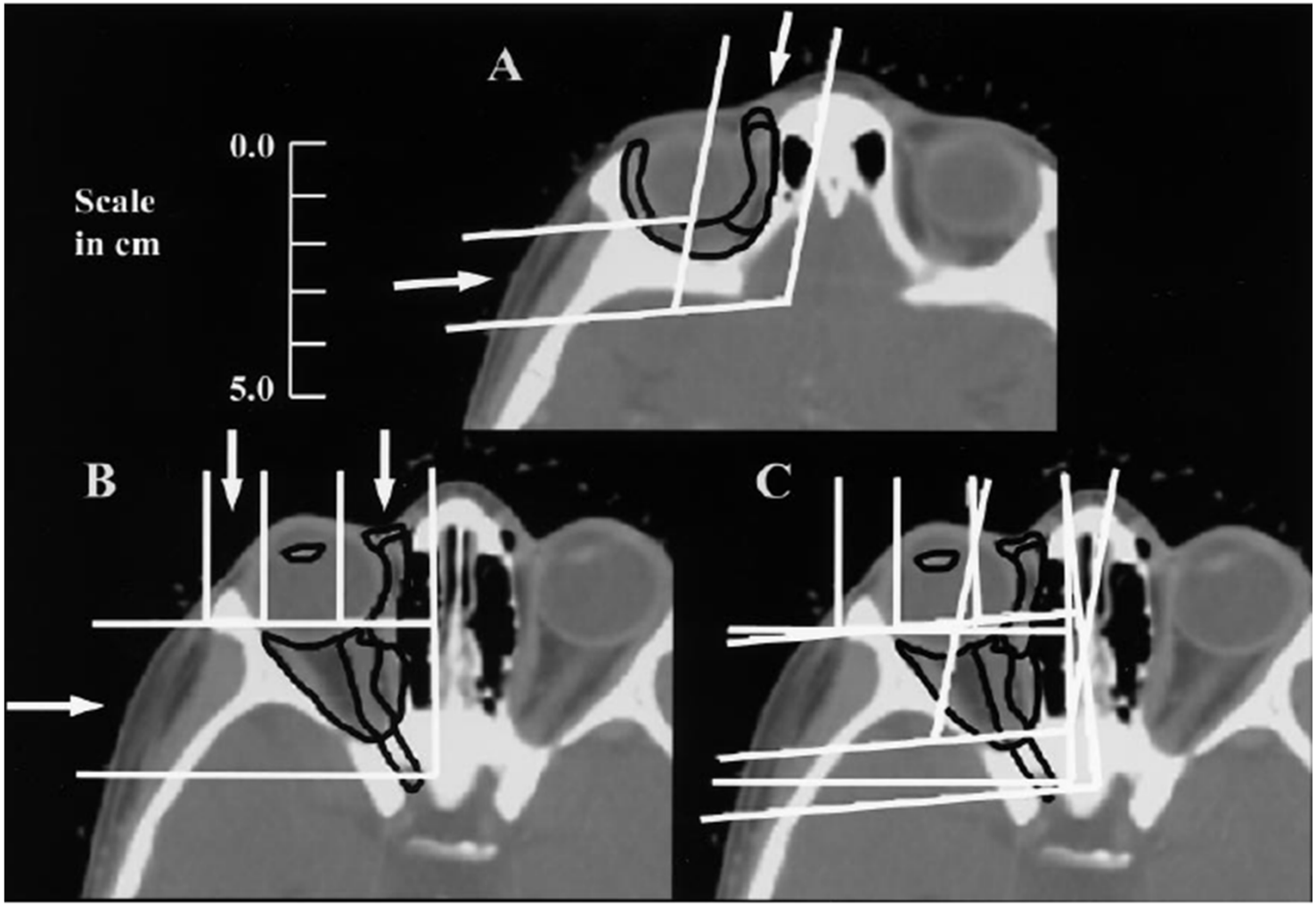
Conclusion: PRT can offer excellent sparing of lens and selected intraorbital and ocular normal structures, while maintaining conformal target-dose coverage. The steep dose gradient beyond the orbit minimizes irradiation of normal brain parenchyma, with almost complete sparing of the pituitary gland. Reduction of integral irradiation exposure of the periorbital region will, hopefully, reduce the risk of second malignancy later in life. Reduced radiation dose to specific organs in close proximity to, but not part of the target region promises improved functional outcome and better cosmesis for childhood cancer survivors. © 2000 Elsevier Science Inc.

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 979–984, 2000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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.

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Table 4. Average dose and percent savings to CNS structures

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

Results: Seven children were treated for orbital rhabdomyosarcoma with proton irradiation and standard chemotherapy. The median follow-up is 6.3 years (range, 3.5–9.7 years). Local and distant controls compare favorably to those in other published accounts. There was an advantage in limiting the dose to the brain, pituitary, hypothalamus, temporal lobes, and ipsilateral and contralateral orbital structures. Tumor size and location affect the degree of sparing of normal structures.

Conclusions: Fractionated proton radiotherapy is superior to 3D conformal photon radiation in the treatment of orbital RMS. Proton therapy maintains excellent tumor coverage while reducing the radiation dose to adjacent normal structures. Proton radiation therapy minimizes long-term side effects.

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 4, pp. 1161–1168, 2005

PROTON RADIOTHERAPY FOR PARAMENINGEAL RHABDOMYOSARCOMA: CLINICAL OUTCOMES AND LATE EFFECTS

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

	Protons: MGH (n = 10) Median f/u: 5 y		IRS II-III* (n = 213) Median f/u: 7 y		IMRT: MSKCC† (n = 21) Median f/u: 2 y		University of Iowa‡ (n = 17) Median f/u: 20 y	
Toxicity	n	%	n	%	n	%	n	%
Decreased growth velocity	3/10	30	92/190	48	NR		9/15	60
Growth hormone replacement	2/10	20	36/190	19	1/21	5	6/15	40
Other endocrinopathies	1/10	10	17/213	8	NR		1/15	7
Facial hypoplasia	7/10	70	74/76	97	1/21	5	11/15	73
Visual complications	0		45/213	21	2/21	10	9/11	82
Auditory complications	0		36/213	17	NR		6/8	75
Dentition	3/10	30	NR		NR		7/7	100
Chronic nasal and sinus congestion	2/10	20	35/71	49	4/21	19	NR	
Secondary malignancies	0		4/213	2	2/21	10	1/17	6

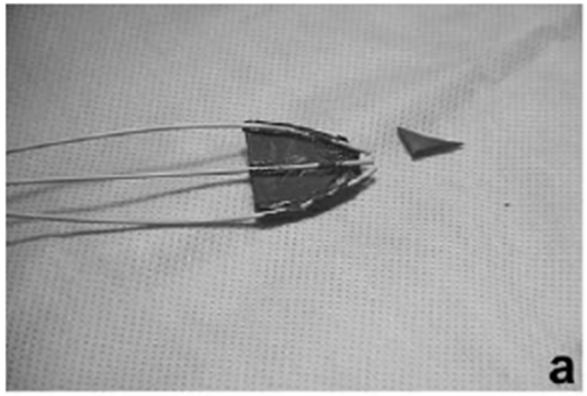
Conclusions: Proton radiotherapy for patients with PM-RMS yields tumor control and survival comparable to that in historical controls with similar poor prognostic factors. Furthermore, rates of late effects from proton radiotherapy compare favorably to published reports of photon-treated cohorts.

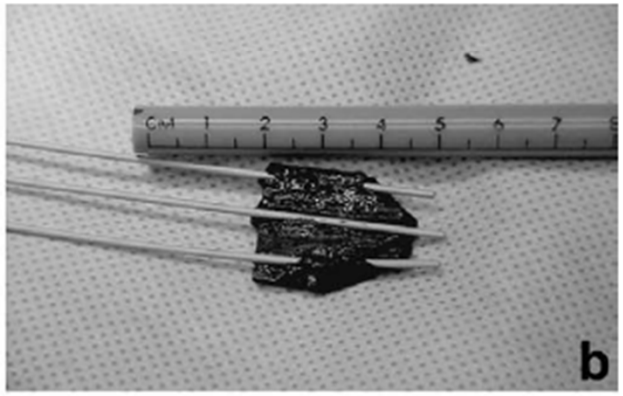
Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 635–642, 2012

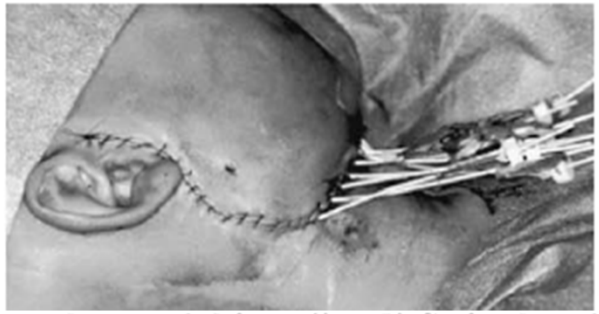
Brachytherapy

- Highly conformal dose distributions
- Excellent sparing of normal structures
- Possibility of dose escalation
- Allows for organ preservation in genitourinary primaries
- Valuable tool for re-irradiation

THE AMORE PROTOCOL FOR ADVANCED-STAGE AND RECURRENT NONORBITAL RHABDOMYOSARCOMA IN THE HEAD-AND-NECK REGION OF CHILDREN: A RADIATION ONCOLOGY VIEW







Results: Dose to the clinical target volume varied from 40 to 50 Gy for the primary treatment (31 patients) and salvage treatment groups (11 patients). There were 18 females and 24 males treated from 1993 until 2007. Twenty-nine tumors were located in the parameningeal region, and 13 were located in the nonparameningeal region. Patient age at the time of AMORE was 1.2–16.9 years (average, 6.5 years). Follow-up was 0.2–14.5 years (average, >5.5 years). Eleven patients died, 3 with local recurrence only, 6 with local and distant disease, 1 died of distant metastases only, and 1 patient died of a second primary tumor. Overall 5-year survival rates were 70% for the primary treatment group and 82% for the salvage group. Treatment was well tolerated, and acute and late toxicity were mild.

Conclusions: The AMORE protocol yields good local control and overall survival rates, and side effects are acceptable.

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1555–1562, 2009

VULVAL AND VAGINAL RHABDOMYOSARCOMA IN CHILDREN: UPDATE AND REAPPRAISAL OF INSTITUT GUSTAVE ROUSSY BRACHYTHERAPY EXPERIENCE

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ALAIN GERBAULET, M.D.,* DANIEL CHASSAGNE, M.D.,* AND CHRISTINE HAIE-MEDER, M.D.*

Table 3. Patterns of failure by treatment year

Failure pattern *(n)*	Treatment year: Before 1990 (Group 1; n = 20)	Treatment year: After 1990 (group 2; n = 19)	Total (n = 39)
Local	1 (2.6)	1 (2.6)	2 (5.2)
Pelvic	1 (2.6)	—	1 (2.6)
Distant	3 (7.7)	4 (10.2)	7 (17.9)

Table 4. Survival results according to treatment year

Variable	Treatment year: Before 1990 (Group 1; *n* = 20)	Treatment year: After 1990 (Group 2; *n* = 19)	Total (*n* = 39)
Local disease-free survival (%)			
5-y	95.0	95.0	94.9
10-y	95.0	95.0	94.9
Distant disease-free survival (%)			
5-y	90.0	94.7	92.3
10-y	85.0	78.9	89.7
Overall survival (%)			
5-y	85.0	89.5	87.0
10-y	80.0	84.2	82.1

Conclusion: Reducing the BT volume coverage, better indications for surgery, and more efficient chemotherapy, all combined within a multidisciplinary approach, tended to improve results in terms of both survival and long-term sequelae.

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 3, pp. 878–883, 2008

BRACHYTHERAPY AS PART OF THE MULTIDISCIPLINARY TREATMENT OF CHILDHOOD RHABDOMYOSARCOMAS OF THE ORBIT

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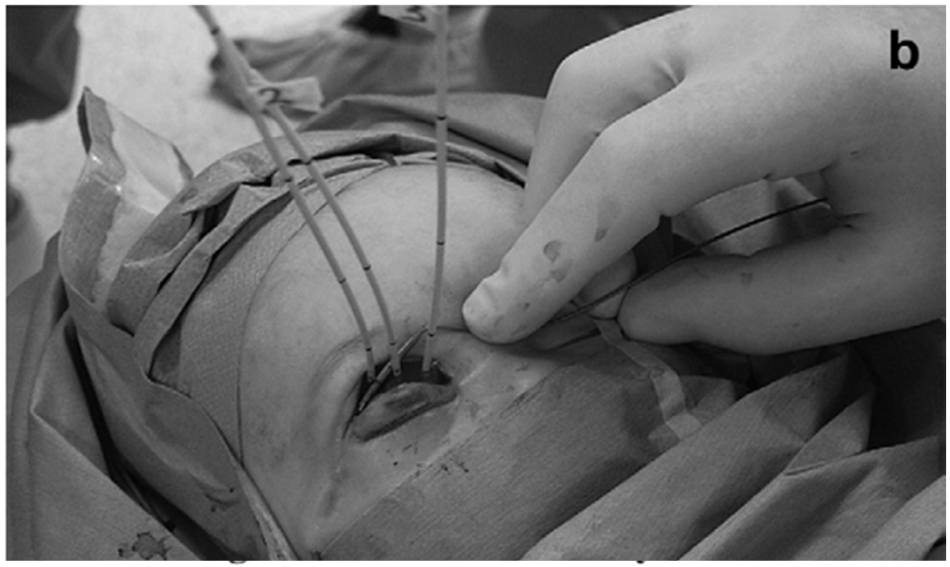

Results: Three patients of Group I and 1 patient of Group II developed local recurrence and underwent exenteration. The progression-free survival in Group I is 71.9% (95% CI 0.44–1.0), in Group II 85.7% (95% CI 0.60–1.0), the overall 5-year survival rate of the entire group is 92% (95% CI 0.76–1.0). During treatment, no serious side effects were observed. The late complications encountered in this series were cataract in 2 patients, 1 of whom also developed mild retinopathy. Two patients with ptosis needed surgical correction. No facial asymmetries or bone growth anomalies were observed.

Conclusions: This entire procedure of brachytherapy with a mold offers a tailor-made treatment for orbital rhabdomyosarcomas with only few signs of late toxicity.

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 5, pp. 1463–1469, 2010

Pediatr Blood Cancer

Interstitial Brachytherapy for Childhood Soft Tissue Sarcoma

Siddhartha Laskar, MD,[1]* Gaurav Bahl, MD,[1] Mary Ann Muckaden, MD,[1] Ajay Puri, MS,[2] Manish G. Agarwal, MS,[2] Nikhilesh Patil, MD,[1] Shyam K. Shrivastava, MD,[1] and Ketayun A. Dinshaw, FRCR[1]

Background. To evaluate the efficacy of interstitial brachytherapy (BRT) in children undergoing combined modality treatment for soft tissue sarcomas (STS). ***Procedure.*** From September 1984 to December 2003, 50 children (median age 13 years, range 1 to 18) with STS who received BRT as part of loco-regional treatment were included. There were 30 males and 20 females, the majority (68%) had primary lesions, synovial sarcoma (32%) was the most common histological type, and 26% had high-grade lesions. Treatment included wide local excision and BRT with or without external beam radiotherapy (EBRT). Thirty children (60%) received BRT alone. ***Results.*** After a median follow-up of 51 months, the local control (LC), disease-free survival, and overall survival were 82%, 68%, and 71%, respectively. LC was superior in patients with tumor size ≤ 5 cm versus >5 cm (96% vs. 67%, $P=0.04$), symptom duration <2 months versus >2 months (100% vs. 73%, $P=0.05$), and Grade I versus Grade II versus Grade III tumors (100% vs. 93% vs. 57%, $P=0.03$). Children receiving a combination of BRT and EBRT had comparable LC to those receiving BRT alone (78% vs. 84%, $P=0.89$). There was no significant difference in LC for patients receiving LDR versus HDR BRT (77% vs. 92%, $P=0.32$, for BRT alone; and 67% vs. 100%, $P=0.17$, for BRT+EBRT). ***Conclusion.*** Interstitial BRT with or without EBRT appears to result in satisfactory outcome in children with STS. Radical BRT alone, when used judiciously in select groups of children, results in excellent local control and functional outcome with reduced treatment-related morbidity. Pediatr Blood Cancer

Key words: interstitial brachytherapy; pediatric; radiotherapy; soft tissue sarcoma

Local Control: 82%

Disease Free Survival: 68%

Overall Survival: 71%

Laskar et al, Pediatric Blood & Cancer 2007

Major Clinical Trials

Intergroup Rhabdomyosarcoma Studies (IRS)	International Society of Pediatric Oncology (SIOP)	Co-operative Weichteilsarkom Studiengruppe Studies (CWS)
USA	Europe	German
IRS I – V COG	RMS – 75 MMT – 84 MMT – 89	CWS – 81 CWS – 86 CWS – 91
Evaluated efficacy of Chemotherapy & Radiotherapy as a function of surgical stage	To develop strategies to minimize local therapy by using risk adapted intensification of Chemotherapy & salvage pts with local failure	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

Future Directions

Chromosomal Aberrations	PAX3 & PAX7 FKHR gene translocation --- Oncoprotein --- Cell Growth Dysregulation & Transformation. Suggestive of target genes involved in RMS pathogenesis --- Development of Vaccines against fusion proteins
Proto-Oncogene Research	N-myc amplification seen in Alveolar RMS --- Poor Survival ---- Related to PAX3-FKHR fusion gene --- Potential target for biologic manipulation Histone 3 Lysine 9 (H3K9) Methyltransferase KMT1A overexpression --- Block differentiation of ARMS --- Potential target for biologic manipulation
Hedgehog Pathway	Activated in some ERMS & fusion negative ARMS --- Poor outcome compared to similar phenotypes without activation --- Inhibitors of Hedgehog pathway potential option
Therapy/ Intensity Optimisation	Reduce CTh duration for favorable risk group RT at week 4 for intermediate risk RMS along with conc. Irinotecan
Radiation Therapy Technology	Proton Beam Therapy
Imaging Studies	PET-CT: Prognostic value of early response