Rhabdomyosarcoma Review 2017: Children's Oncology Group

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CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Outline

- Epidemiology
- Patterns of Involvement
- Pathology
- Staging
- Clinical Evaluation and Work-up
- Treatment
- Results of Treatment
- Significant Clinical Trials
- Complications of Treatment

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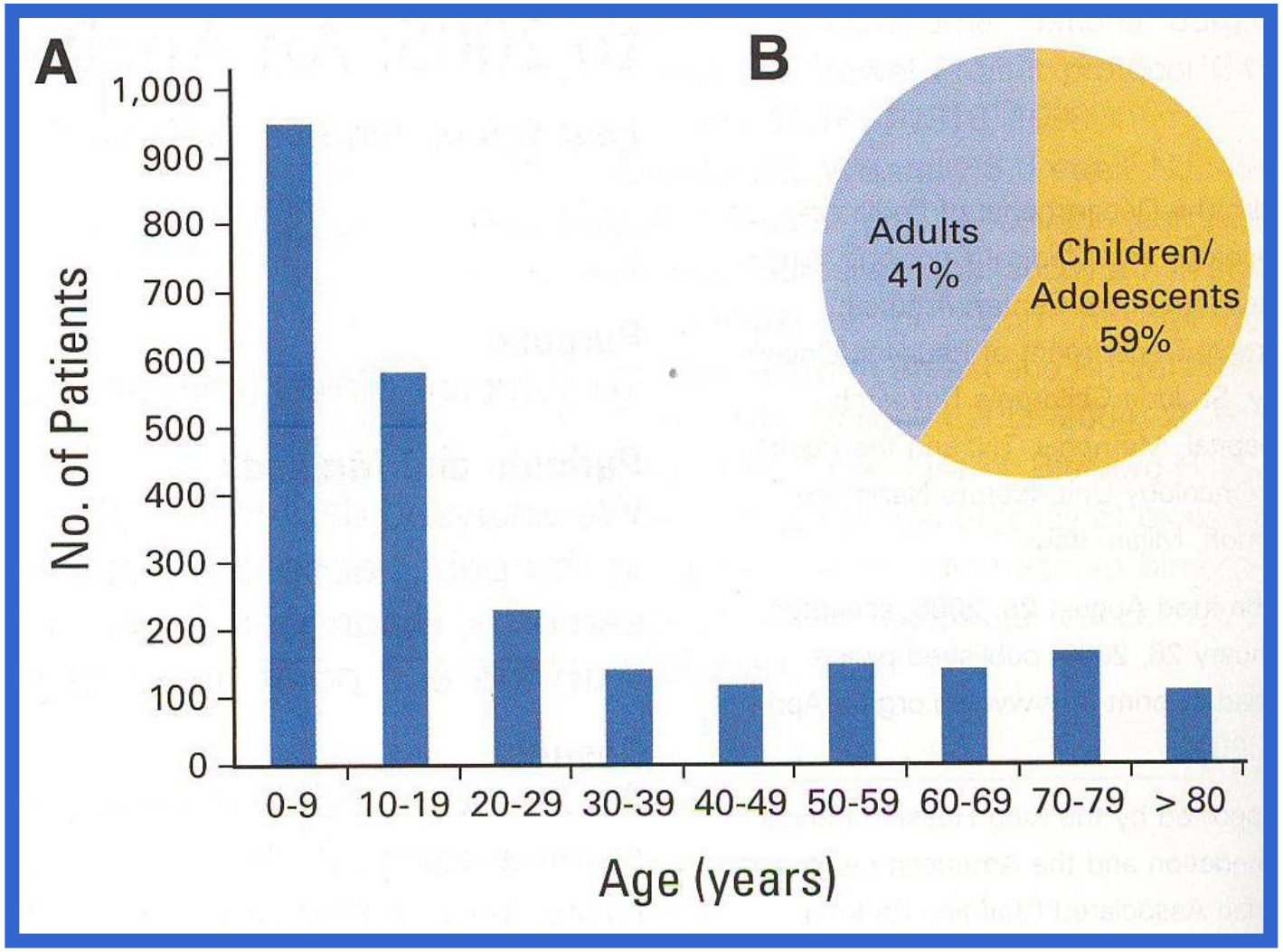
Epidemiology

- Accounts for 3% of childhood cancers and 2% of adolescent cancers
- Embryonal RMS (approximately 50% of cases): incidence is highest in children aged younger than 5 years
- Alveolar RMS (approximately 40% of cases): incidence does not vary by age in children and adolescents

Adult & Pediatric Rhabdomyosarcoma SEER 1973 - 2005



Sultan, I, JCO 27: 2009

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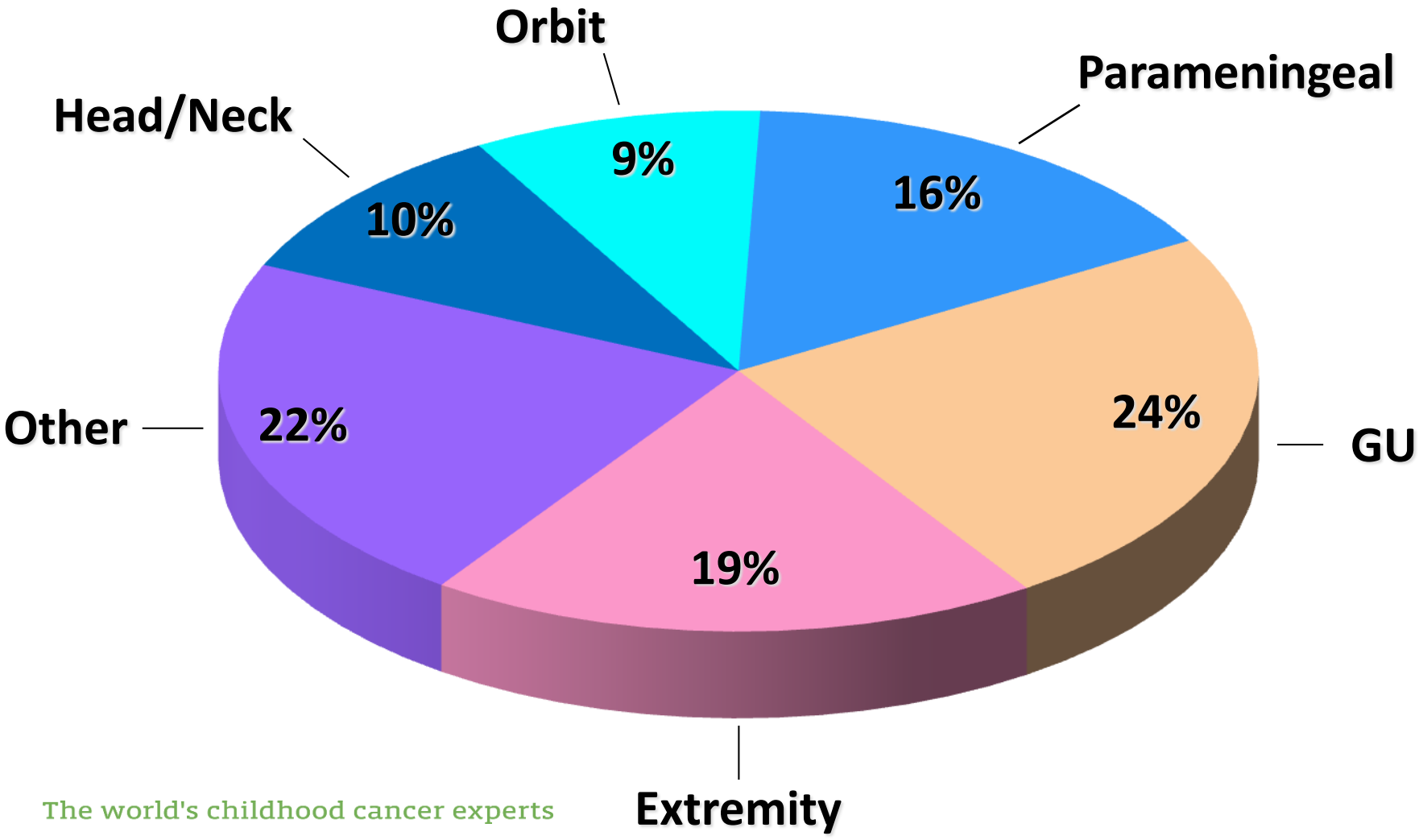
Distribution of Sites



Sites of Metastatic Involvement (IRS-IV)

Lung	39%
Bone Marrow	32%
Lymph Nodes	30%
Bone	27%
Omentum/Ascites	16%
Soft Tissue	16%

REGIONAL NODAL BASINS FOR RHABDOMYOSARCOMA

Extremity
Lower Extremity –inguinal, femoral, popliteal nodes (rarely involved)
Upper extremity – axillary, brachial, epitrochlear, infraclavicular nodes (infraclavicular)

Genitourinary
Bladder/Prostate – pelvic, retroperitoneal nodes at renal artery level or below
Cervix and Uterus– pelvic, retroperitoneal nodes at renal artery level or below
Paratesticular – pelvic, retroperitoneal nodes at renal artery level or below
Vagina – retroperitoneal, pelvic nodes at or below common iliacs inguinal nodes
Vulva – inguinal nodes

Head and Neck
Head/Neck – ipsilateral cervical, jugular, preauricular, occipital, supraclavicular nodes for laterally placed tumors (excluding scalp); may have bilateral adenopathy with centrally placed tumors
Orbit/Eyelid – ipsilateral jugular, preauricular, cervical nodes

Intrathoracic
Internal mammary, mediastinal nodes

Retroperitoneum/Pelvis –
Pelvic, retroperitoneal nodes

Trunk
Abdominal Wall – inguinal, femoral nodes
Chest Wall – axillary, internal mammary, infraclavicular nodes

OTHER
Biliary/Liver – liver hilar nodes
Perianal/Perineal – inguinal, pelvic nodes; may be bilateral

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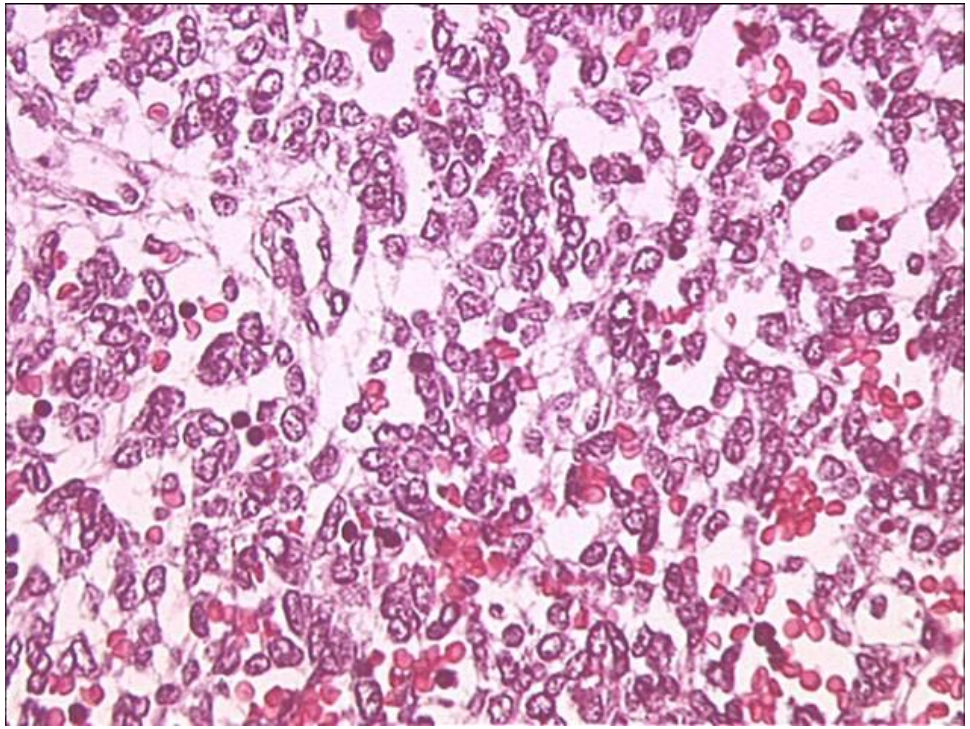
Pathology

- **Accurate pathology requires:**
  1) **H and E**
  2) **Immunohistochemistry**
  3) **Molecular genetics**

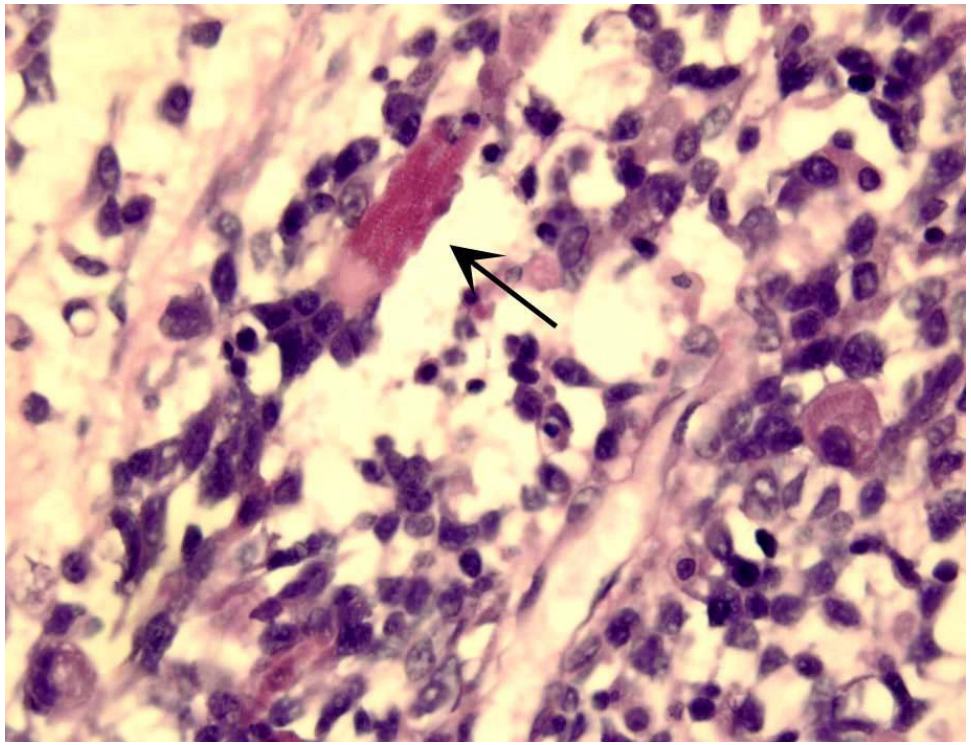
Embryonal Rhabdomyosarcoma (Botryoid)



www.pedsoncologyeducation.com

Botryoid ERMS is a less common variant of embryonal RMS with improved prognosis. Most commonly arises from mucosal surfaces of the vagina, bladder, uterus, bile duct, nasopharynx and middle ear. These tumors are generally localized and non-invasive and have a grape like configuration macroscopically.

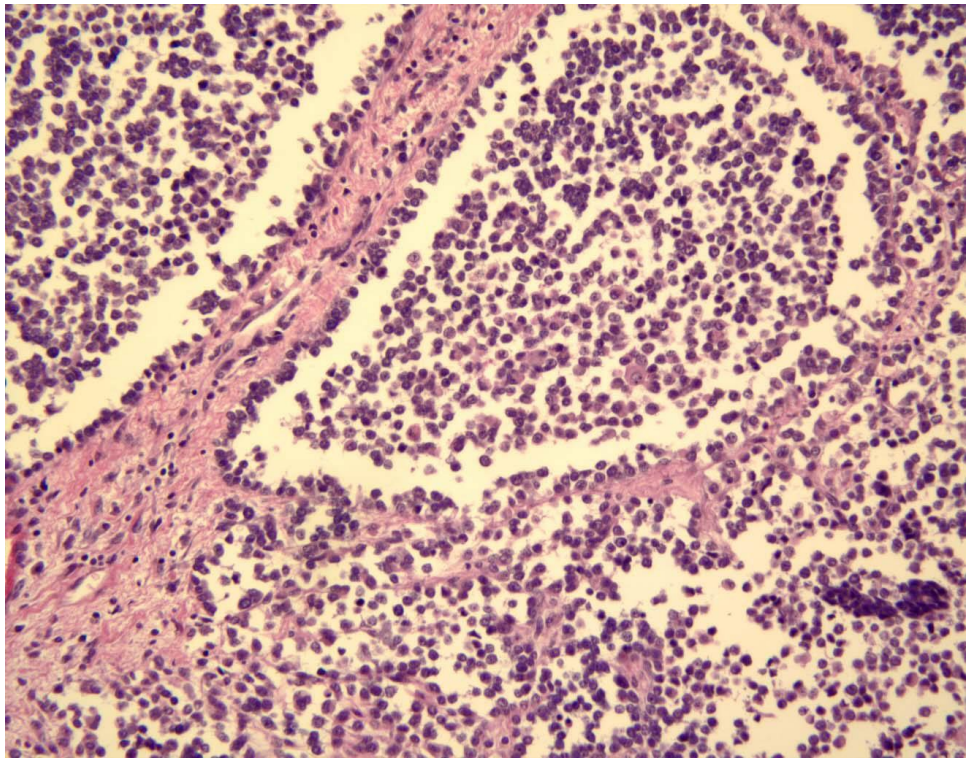
Embryonal Rhabdomyosarcoma



Medscape.com

Embryonal rhabdomyosarcoma is evidenced by a variable cell population consisting of small, round tumor cells with hyperchromatic nuclei and of large, polygonal-shaped tumor cells with abundant eosinophilic cytoplasm, which often contains diagnostic cross striations.

Alveolar Rhabdomyosarcoma



Medscape.com

Alveolar rhabdomyosarcoma is evidenced by uniform cell population consisting of cells with a high nuclear-to-cytoplasmic ratio. The cells are arranged in variably sized nests separated by fibrous tissue septa. In places, the cells appear loosely dispersed, mimicking a pulmonary alveolar pattern.

Molecular Genetics of RMS

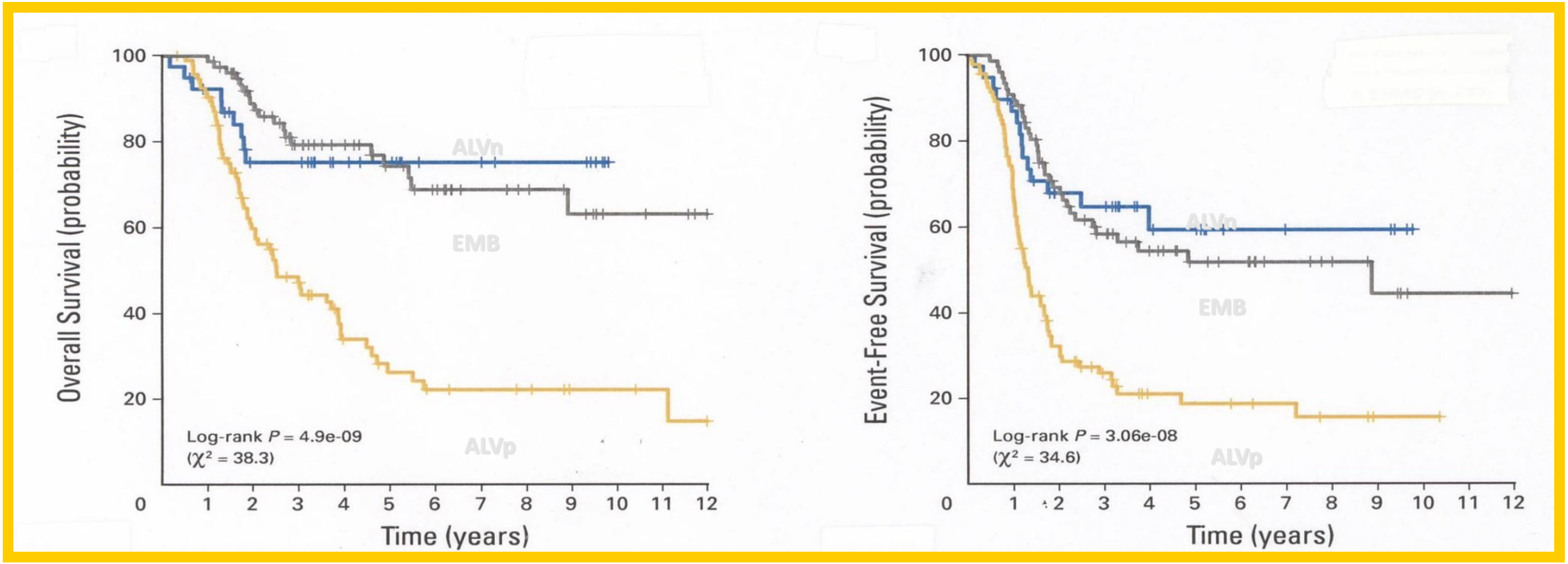
Embryonal RMS

- Loss of heterozygosity at 11p15 locus
  - Location of the IGF-II gene

Alveolar RMS

- t(2;13)(q35;q14)
  - Translocation between long arms of chr 2 and 13 fusing FOX01 transcription factor to PAX3
- t(1;13)(p36;q14)
  - Fuses FOX01 to PAX7

Risk Stratification Gene Expression Status

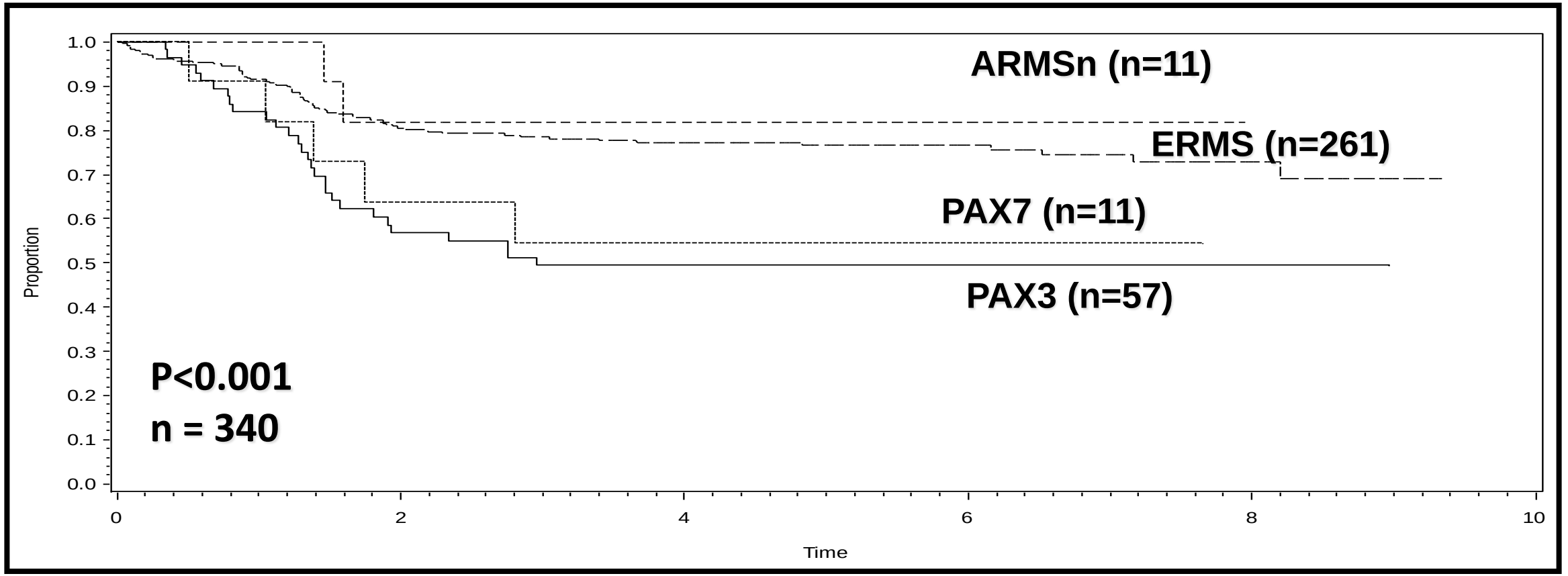


- **Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma.**
- **Fusion gene status is useful in risk stratification.**

Williamson, JCO, 2010

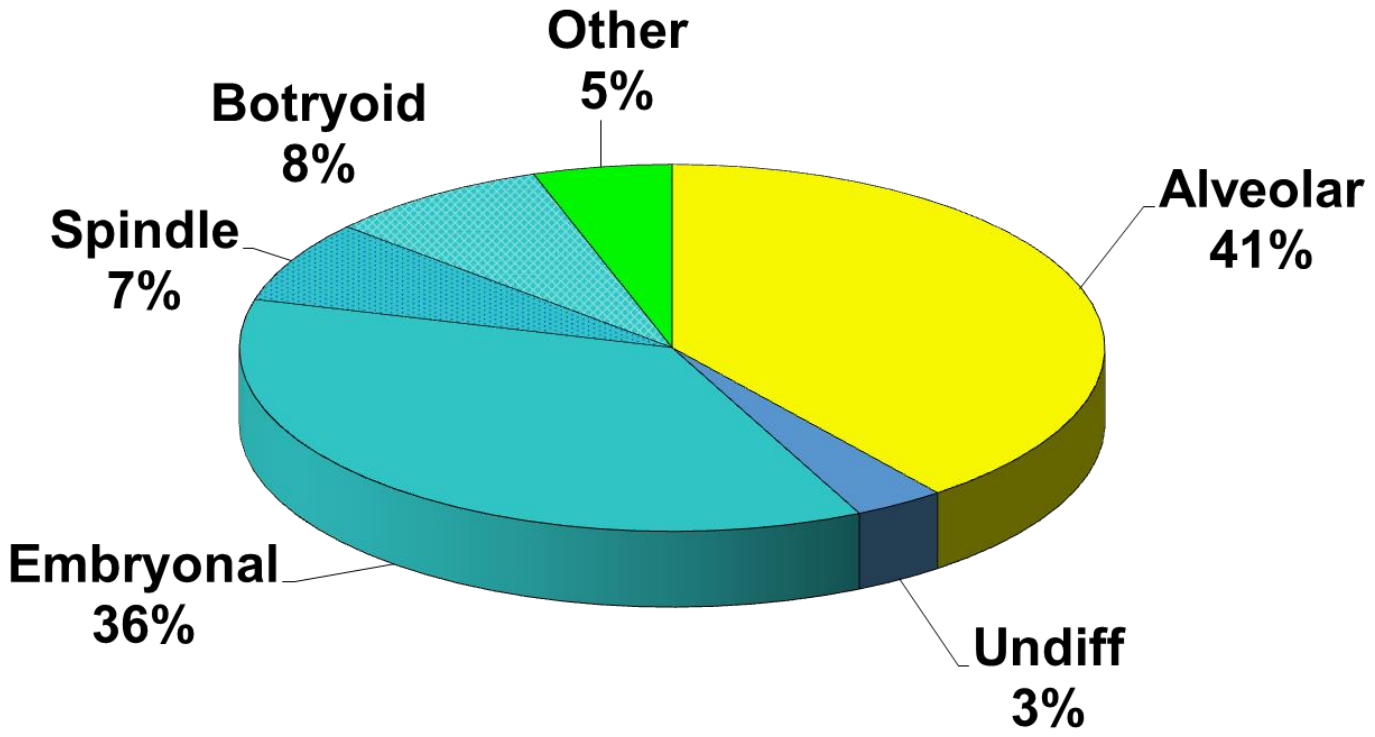
PAX / FOXO1 predicts outcome

D9803- Intermediate Risk RMS



Skapek S, Pediatr Blood Cancer, 2013

IRS V - Pathology



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TNM Staging

- T1 – Confined to site of origin
- T2 – Invasive into surrounding tissues
  - a - ≤5 cm in size
  - b - >5 cm in size

- N0 – No involved regional nodes
- N1 – Regional nodes are involved

Staging

Stage	Site*	Invasiveness	Size	Nodal status	Mets
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

Favorable sites: orbit, head and neck (non-parameningeal), genitourinary (non–bladder-prostate);
Unfavorable sites: genitourinary (bladder-prostate), extremity, parameningeal, other.

Group I		**Localized disease, completely resected**
	A	Confined to organ or muscle of origin
	B	Infiltration outside organ or muscle 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**

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Clinical Evaluation and Work-up

- Laboratory Studies:
  - CBC
  - Liver function tests
  - Renal function tests
  - Urinalysis (UA)
  - Blood electrolyte and chemistry

Clinical Evaluation and Work-up

- Imaging Studies:
  - Plain radiography: Radiography of the primary site and of the chest is helpful in determining the presence of calcifications and bone involvement of the primary tumor and to search for metastatic lung lesions.
  - CT Chest
  - CT or US of the liver
  - CT or MRI of primary site, pending location
  - Bone scan or PETCT for metastatic assessment
  - Echocardiography: Assess cardiac function before chemotherapy

Clinical Evaluation and Work-up

- Procedures:
  - Biopsy: Open biopsy preferred, resection typically reserved for post-chemotherapy administration
  - Cytogenetics, fluorescent in situ hybridization (FISH)
  - Reverse transcriptase–polymerase chain reaction (RT-PCR) testing when cytogenetic testing is unavailable
  - Bone marrow aspiration and biopsy

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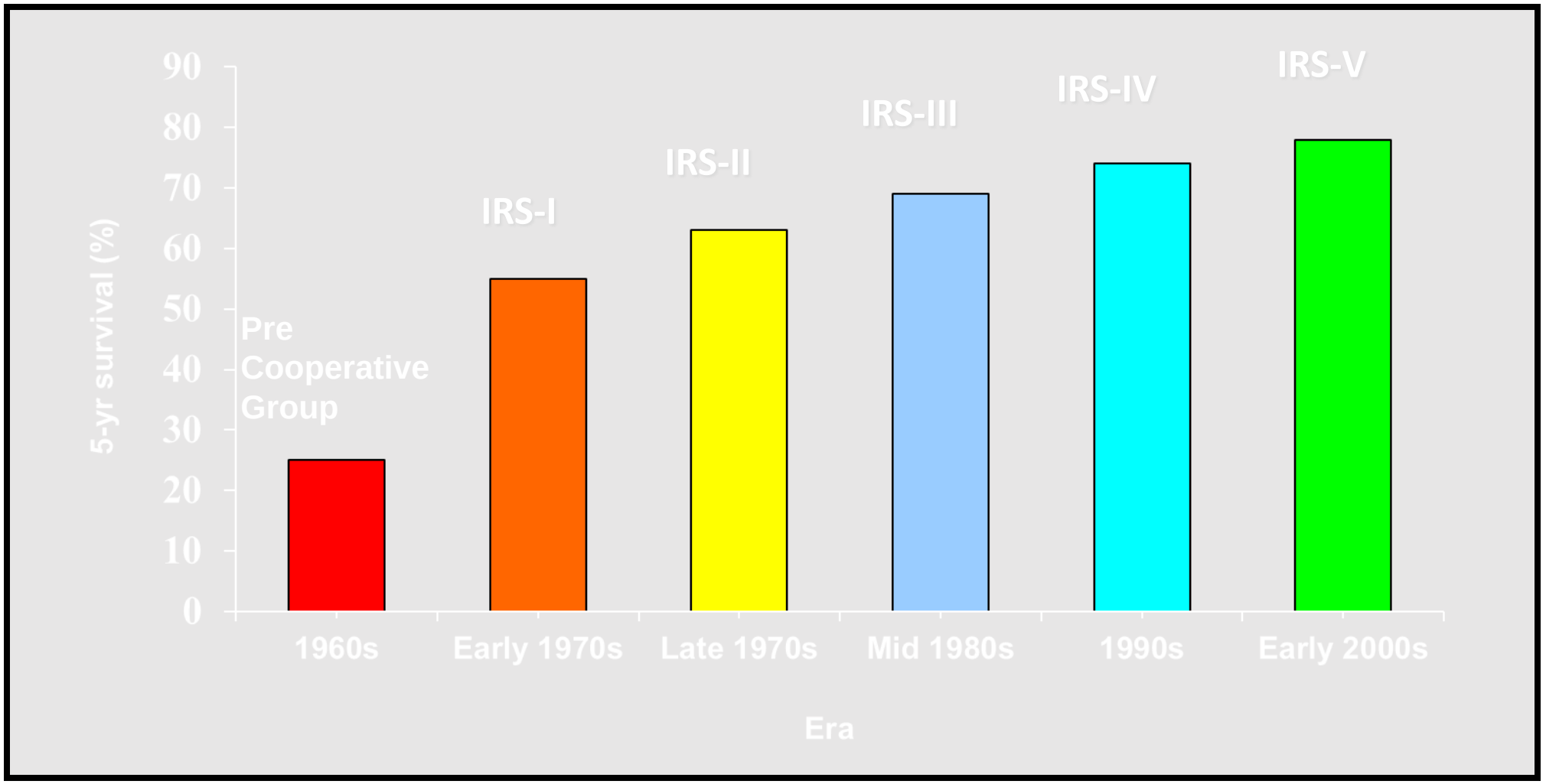
Survival in Rhabdomyosarcoma Four Decades of Progress



The Intergroup Rhabdomyosarcoma Study-I: A Final Report
MAURER H, BELTANGADY M, GEHAN E, et al. *Cancer* 61: 209-220, 1988

TABLE 2. Number of Patients Required, Entered, and Eligible by Treatment

Clinical group	Treatment	No. of patients		
		Required	Entered	Eligible and analyzed
I	A (VAC)	87*	50	43
	B (VAC + XRT)	87	47	43§
	G (Amputees, VAC)	—	10	10
II	C (VA + XRT)	87*	101	87‖
	D (VAC + XRT)	87	99	90¶
III and IV	E (VAC + XRT)	100†	247	208#
	F (VAC + ADR + XRT)	100	240	205**
	Non-random‡		5	
	Total		799	686††
	Total		799	686

VAC: vincristine, dactinomycin, cyclophosphamide; XRT: radiation therapy; VA: vincristine, dactinomycin; ADR: Adriamycin (doxorubicin).

The Intergroup Rhabdomyosarcoma Study-I: A Final Report
MAURER H, BELTANGADY M, GEHAN E, et al. *Cancer* 61: 209-220, 1988

Conclusions:

1) Clinical Group I:
    1) 5y DFS 80% and 5y OS 83%
    2) **Addition of postoperative RT to VAC chemotherapy provided no advantage**

2) Clinical Group II:
    1) 5y DFS 65% and 5y OS 70%
    2) Adding cyclophosphamide (oral) to vincristine/dactinomycin did not result in any significant improvement

3) Clinical Groups III/IV
    1) CR in group III was 69% and group IV 50% with no difference between arms
    2) 5y OS 52% in group III and 20% in group IV, no difference between arms

The Intergroup Rhabdomyosarcoma Study II

Maurer H, Gehan E, Beltangady M, et al. CANCER 71(5) 1904-22, *1993*

Table 1. Number of Patients Required, Entered, and Eligible by Treatment

Clinical group	Treatment	No. of patients		
		Required	*Entered*	*Eligible*
I (excluding extremity alveolar)	21 VAC (2 yr)	25	48	37
	22 VA (1 yr)	50	67	64
II (excluding extremity alveolar)	23 VA + XRT (1 yr)	38	49	45
	24 pulse VAC + XRT (1 yr)	75	90	85
III (excluding certain pelvic sites) and IV	25 pulse VAC + XRT	93	340	294
	26 pulse VADRC → VAC + XRT	93	320	285

XRT: radiation therapy; V: vincristine; A: dactinomycin; C: cyclophosphamide; ADR: Adriamycin (doxorubicin).

Radiation therapy was not given to patients with Clinical Group I disease, but was begun with chemotherapy as initial treatment for Clinical Group II patients randomized to regimen 23. Patients in Clinical Group II, who were randomized to regimen 24, and patients in Clinical Groups III and IV received 6 weeks of chemotherapy before beginning radiation therapy. The radiation therapy recommendations included delivering 40 to 45 Gy in 4 to 5 weeks to the primary tumor, but not to clinically uninvolved regional nodes in Clinical Group II patients. For Clinical Group III patients the radiation dose was dependent upon the patient's age and tumor diameter before initiation of chemotherapy. Children younger than 6 years of age with tumor less than 5 cm in diameter received 40 to 45 Gy, whereas those with tumor equal to or greater than 5 cm in diameter received 45 to 50 Gy. Children 6 years of age and older were given 45 to 50 Gy if the tumor was less than 5 cm, and 50 to 55 Gy in 5 to 6 weeks if it was 5 cm or greater in size. Patients in Clinical Group IV were treated the same as those in Clinical Group III, but, in addition, received radiation to sites of metastatic disease. Lung metastases were treated with bilateral pulmonary radiation, not exceeding 18 Gy in nine equal fractions. Bone and soft tissue metastases were treated with 50 to 55 Gy in 5 to 6 weeks. Metastases were treated simultaneously with radiation of the primary site. Radiation was delivered at a rate of 9 to 10 Gy in five fractions per week with megavoltage equipment.

The Intergroup Rhabdomyosarcoma Study II

Maurer H, Gehan E, Beltangady M, et al. CANCER 71(5) 1904-22*, 1993*

Conclusions:

1) Cyclophosphamide did not contribute to the success of treatment in Clinical Groups I and II patients (extremity alveolar patients excluded)

2) Repetitive-pulse chemotherapy for 2 years increased survival rates in children with Group III but not IV disease

3) Adriamycin offered no advantage over dactinomycin and was associated with more fatal toxicities

4) Approach to treating patients with parameningeal sarcoma used in IRS-II, including compliance with radiation dose and volume and earlier timing, was successful in preventing CNS recurrence and increased survival rates

5) Treatment of "special" pelvic tumors with primary repetitive-pulse VAC primary chemotherapy did not result in durable bladder salvage, although survival rate was not compromised

6) There was some indication that repetitive-pulse VAC chemotherapy improved the prognosis of patients with Clinical Groups I and I1 extremity alveolar rhabdomyosarcoma

The Intergroup Rhabdomyosarcoma Study II

Maurer H, Gehan E, Beltangady M, et al. CANCER 71(5) 1904-22*, 1993*

Table 4. Types of Failures (Relapse, Death, or Other) for Patients Who Achieve CR

Clinical group	Treatment	No. of CR	No. of failures	Local	Regional	Distant	Local + distant	CNS ext.	Toxic deaths	Other*
I	21	37	7	2 (5%)	2 (5%)	2 (5%)	1 (3%)	—	—	—
	22	64	18	9 (14%)	5 (8%)	3 (5%)	—	—	1 (2%)	—
II	23	45	13	3 (7%)	5 (11%)	3 (7%)	—	—	1 (2%)	1 (2%)
	24	85	24	9 (11%)	4 (5%)	6 (7%)	3 (4%)	—	1 (1%)	1 (1%)
III	25	156	40	18 (12%)	9 (6%)	7 (4%)	2 (1%)	1 (1%)	1 (1%)	2 (1%)
	26	154	48	16 (8%)	4 (5%)	14 (9%)	3 (2%)	1 (1%)	6 (6%)	4 (3%)
IV	25	43	27	6 (14%)	2 (5%)	15 (35%)	3 (7%)	1 (2%)	—	—
	26	47	28	5 (11%)	4 (9%)	13 (28%)	6 (13%)	—	—	—

CNS: central nervous system; ext.: extension; CR: complete response.

* Patients listed as "other" failed to respond to therapy for the following reasons: treatment 23, 1 suicide; treatment 24, 1 case entered as a Clinical Group II, classified by Surgery Committee as a Clinical Group IV, and patient did not achieve CR; Group III treatment 25, 2 deaths from second malignancies; Group III treatment 26, 1 second malignancy and 3 patients who died of reasons unrelated to treatment.

Local Control of ~90% in groups II-IV (regimens 23-29 contain RT)

The Third Intergroup Rhabdomyosarcoma Study

Crist W, Gehan E, Abdelsalam R, et al. J Clin Oncol 13:610-630, 1995

Table 1. Number of Patients Required, Entered, and Eligible by Treatment in IRS-III and in Relevant Comparison Groups from IRS-II

	IRS-II				IRS-III					
Clinical Group	Treatment and Duration	Regimen	Entered*	Eligible*	Treatment and Duration	Regimen	Randomized	Required	Entered†	Eligible
I (favorable histology)	VAC, 2 years	21	47	36	Cyclic-sequential VA, 1 year	31	No	69	174	163
	VA, 1 year	22	63	60						
II (favorable histology)	VA + RT, 1 year	23	24	21	VA + RT, 1 year	32§	Yes	20	26	23
	Pulsed VAC + RT, 1 year	24	53	50	VA + ADR + RT, 1 year	33	Yes	51	61	51
III (excluding special pelvic and selected other sites) and IV	Pulsed VAC + RT, 2 years	25	288	246	Pulsed VAC + RT, 2 years‡	34 *v* 35 *v* 36§	Yes	75	97	87
	Pulsed VADRC-VAC, 2 years	26	273	241	Pulsed VADRC-VAC + CDDP + RT, 2 years‡		Yes	151	199	178
					Pulsed VADRC-VAC + CDDP + VP-16 + RT, 2 years		Yes	151	199	174
III (special pelvic sites)	Pulsed VAC ± RT ± surgery, 2 years	27	116	108	Pulsed VADRC-VAC + CDDP ± AMD + VP-16 ± RT ± surgery, 2 years‡	37 A and B§	No	77	118	114
I and II (unfavorable histology)	Pulsed VAC ± RT, 1 year	21-25	90	89	Pulsed VADRC-VAC + CDDP + RT, 1 year	38§	No	109	105	99
Orbit and head (favorable histology)					VA + RT, 1 year	32	No	49	157	146
Group II	VA + RT or VAC + RT	23, 24	17	15				—	52	48
Group III	VAC or VADRC + RT	25, 26	90	84				—	105	98
Paratesticular (group II, favorable histology)	VA + RT or VAC + RT	23-24	16	16	VA + RT, 1 year	32	No	—	27	27

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The Third Intergroup Rhabdomyosarcoma Study

Crist W, Gehan E, Abdelsalam R, et al. J Clin Oncol 13:610-630, 1995

Conclusions:

1) 5y survival estimate increased by 8% compared with IRS-II (71% 2% *v* 63% ± 2%) and by 16% (71% ± 2% *v* 55% ± 2%) compared with the result for IRS-I.
   - improved therapy for patients with group III tumors, except for selected head and orbit sites and those with group I or II alveolar tumors

2) Patients with favorable-histology tumors in an orbital or a nonparameningeal head site, in clinical group I, II, or III, responded as well to cyclic sequential, thus, it should be possible to delete this alkylating agent from future protocols

3) Therapy for children with RMS should be risk-directed and based primarily on tumor site and the extent of disease
   - limited-stage tumors (group I or II) generally respond well to surgery, VA chemotherapy, and RT (group II only)
   - All other patients seem to require more intensive multimodality therapy
   - We believe that chemotherapy of increased dose intensity, with concomitant use of hematopoietic growth factors, should be further exploited to improve cure rates for patients with moderate or high-risk RMS

Intergroup Rhabdomyosarcoma Study-IV: Results for Patients With Nonmetastatic Disease

Crist W, Anderson J, Meza J, et al. J Clin Oncol 9: 3091-3102, 2001

Table 2. IRSG Presurgical Staging Classification

Stage	Sites	Tumor (T)	Size	Node (N)	Metastases (M)
I	Orbit, head and neck (excluding parameningeal) GU: nonbladder/nonprostate	T_1 or T_2	a or b	N_0, N_1, or N_x	M_0
II	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a	N_0 or N_x	M_0
III	Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a	N_1	M_0
			b	N_0, N_1, or N_x	
IV	All	T_1 or T_2	a or b	N_0 or N_1	M_1

NOTE. Tumor: T_1, confined to anatomic site of origin, (a) ≤ 5 cm in diameter in size, (b) > 5 cm in diameter in size; T_2, extension and/or fixative to surrounding tissue, (a) ≤ 5 cm in diameter in size, (b) > 5 cm in diameter in size; regional nodes: N_0, regional nodes not clinically involved; N_1, regional nodes clinically involved by neoplasm; N_x, clinical status of regional nodes unknown; metastasis: M_0, no distant metastasis; M_1, metastasis present.

Abbreviation: GU, genitourinary.

Table 1. IRSG Postsurgical Grouping Classification

Group 1	Localized disease, completely excised, no microscopic residual
A	Confined to site of origin, completely resected
B	Infiltrating beyond site of origin, completely resected
Group 2	Total gross resection
A	Gross resection with evidence of microscopic local residual
B	Regional disease with involved lymph nodes, completely resected with no microscopic residual
C	Microscopic local and/or nodal residual
Group 3	Incomplete resection or biopsy with gross residual
Group 4	Distant metastases

Table 3. Patients Entered and Eligible by Treatment in IRS-IV

Clinical Subgroup	Treatment	Length of Treatment	No. of Patients	
			Entered	Eligible
Paratesticular (group 1) or orbit/eyelid (groups 1/2)	VA	36 weeks	144	134
Stages I–III with significant renal abnormalities	VAC	1 year	61	56
Stage I (except paratesticular group 1 and orbit/eyelid groups 1/2) and stages II and III without renal abnormalities)	VAC		263	235
	VAI		254	222
	VIE		267	236
	Total		784	693
Group 3	Conventional RT		280	251
	Hyperfractionated RT		279	239
	Total		559	490

Intergroup Rhabdomyosarcoma Study-IV: Results for Patients With Nonmetastatic Disease
Crist W, Anderson J, Meza J, et al. J Clin Oncol 9: 3091-3102, 2001

Conclusions:

1) 3y FFS estimates remain unchanged, despite use of intensive, multimodal therapy, from that of IRS-III (~76%)

2) Patients with local or regional tumors with embryonal histology fared significantly better on VAC, VAI, or VIE plus surgery and RT than did similar patients treated on IRS-III (3-year FFS rates, 83% *v* 74%).
   - -Improvement seemed to be restricted to patients with stage I/II, group 1/2 disease, many of whom received VA chemotherapy on IRS-III
   - -Majority of the improvement is probably attributable to the addition of alkylating agent to the therapy received by patients treated on IRS-IV, although changes in RT, surgery, and/or supportive care may have played a role

3) Therapy for pediatric RMS should be risk-directed and based primarily on tumor site, tumor history, and extent of disease

4) Group III patients randomized to standard fractionation versus hyperfractionated RT, statistically equivalent

Intergroup Rhabdomyosarcoma Study-IV: Results for Patients With Nonmetastatic Disease
Crist W, Anderson J, Meza J, et al. J Clin Oncol 9: 3091-3102, 2001

Conclusions:

5) Younger patients (<10 years old) with embryonal, group 1 tumors arising in the paratestis fared well with surgery and VA chemotherapy, whereas similar adolescents require more accurate staging with retroperitoneal LN dissection, followed by RT and VAC chemotherapy for those with group 2 tumors

6) Group 2/3 orbit or eyelid tumors generally fare well with surgery + VA chemotherapy (group 1) or surgery + RT + VA chemotherapy (group 2).

7) Most other patients appear to require more intensive multimodality therapy, and the relatively poor outcome for some patient subsets indicates that new therapeutic approaches, including effective new agents, are required (Topotecan is the most promising new agent for rhabdomyosarcoma)

8) Infants and adolescents have worse outcome than do children with rhabdomyosarcoma, perhaps due in part to their higher frequency of undifferentiated or alveolar histiotypes and thus may especially benefit from this new approach

Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol
Raney B, Walterhouse D, Meza J, et al. J Clin Oncol 29: 1312-1318, 2011

Purpose:

•ERMS patients with localized, grossly resected, or gross residual (orbital only) disease have good 5y FFS (83%) and OS (95%)

•Objectives were to decrease toxicity in similar patients by reducing RT and eliminating cyclophosphamide for the lowest-risk patients

Patients and Methods

•Subgroup A (lowest risk, ERMS, stage 1 group I/IIA, stage 1 group III orbit, stage 2 group I):
-vincristine plus dactinomycin (VA)

•Subgroup B (ERMS, stage 1 group IIB/C, stage I group III nonorbit, stage 2 group II, stage 3 group I/II):
-VA plus cyclophosphamide

•Patients in group II/III received RT:
-Compared with IRS-IV: Stage 1 group IIA reduced from 41.4 to 36 Gy and group III orbit from 50 or 59 to 45 Gy

Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol
Raney B, Walterhouse D, Meza J, et al. J Clin Oncol 29: 1312-1318, 2011

Conclusions:

1) 5y FFS rates were 89% for subgroup A and 85% for subgroup B

2) 5y FFS rates were 81% for stage 1 group IIA and 86% forgroup III orbit tumors

3) These rates were similar to those observed in comparable IRS-III patients, including patients receiving reduced RT doses, but were lower than in comparable IRS-IV patients receiving VA plus cyclophosphamide

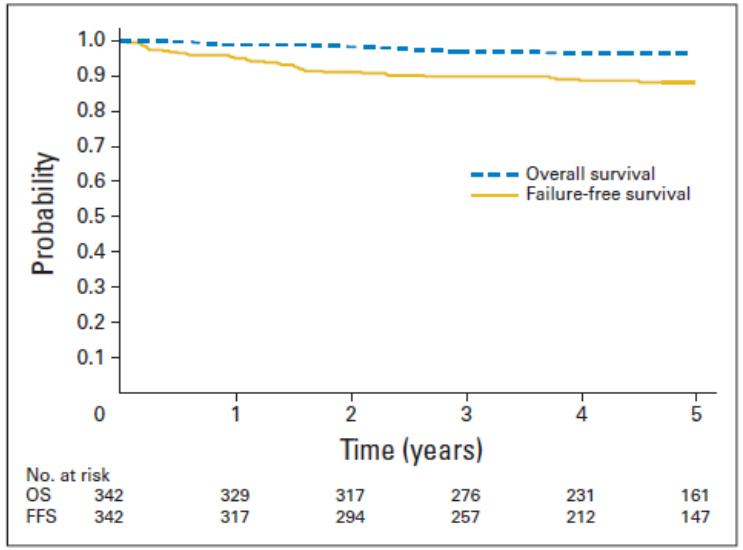

Fig 1. Failure-free survival (FFS) and overall survival (OS), D9602.

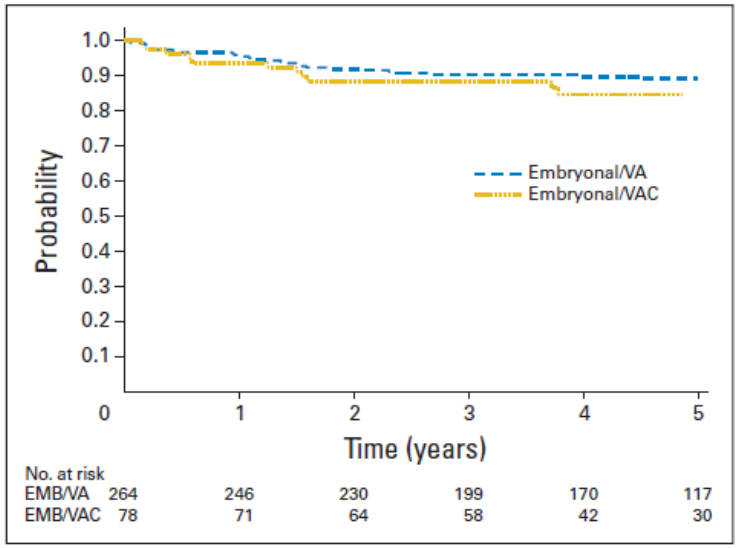

Fig 2. Failure-free survival, D9602, by subgroups. EMB, embryonal; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, and cyclophosphamide.

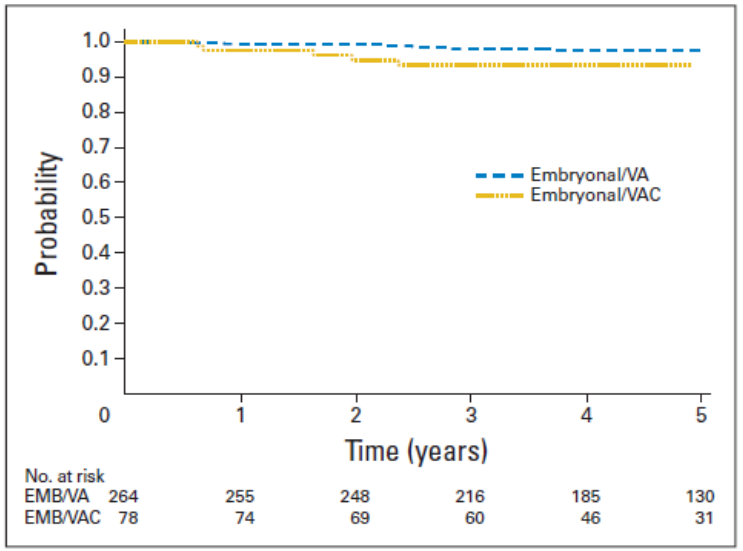

Fig 3. Overall survival, D9602, by subgroups. EMB, embryonal; VA, vincristine and dactinomycin; VAC, vincristine, dactinomycin, and cyclophosphamide.

Shorter-Duration Therapy Using Vincristine, Dactinomycin, and Lower-Dose Cyclophosphamide With or Without Radiotherapy for Patients With Newly Diagnosed Low-Risk Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group (ARST0331)

Walterhouse D, Pappo J, Meza J, et al. J Clin Oncol 32: 3547-3552, 2014

Purpose

- IRSG III and IV showed improved FFS with VAC over VA for patients with stage 1/2 group I/II ERMS or stage 1 group III orbit ERMS
- Objective of Children's Oncology Group ARST0331 was to reduce the length of therapy without compromising FFS for this subset of low-risk patients using VA in combination with lower-dose cyclophosphamide (total cumulative dose, 4.8 g/m_2) plus radiotherapy

Shorter-Duration Therapy Using Vincristine, Dactinomycin, and Lower-Dose Cyclophosphamide With or Without Radiotherapy for Patients With Newly Diagnosed Low-Risk Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children's Oncology Group (ARST0331)

Walterhouse D, Pappo J, Meza J, et al. J Clin Oncol 32: 3547-3552, 2014

Conclusions

1) Shorter-duration therapy that included lower-dose cyclophosphamide and RT did not compromise FFS for patients with subset-one low-risk ERMS

2) 3y FFS 89% and OS 98%

3) Patients with paratesticular tumors had the most favorable outcome

4) 3y cumulative incidence rates for any local, regional, or distant failures were 7.6%, 1.5%, and 3.4%, respectively.

Local therapy is critical in localised pelvic rhabdomyosarcoma: Experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee

Re'guerre Y, Martelli H, Rey A, et al. European Journal of Cancer 48: 2020–2027, 2012

Purpose:

- Localized pelvic rhabdomyosarcomas (pRMS) are rare tumours with a poorer prognosis than the majority of RMS
- This study analyzed patient outcome according to the type of local therapy delivered and the effect of disease-related factors on prognosis

Local therapy is critical in localised pelvic rhabdomyosarcoma: Experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee

Re'guerre Y, Martelli H, Rey A, et al. European Journal of Cancer 48: 2020–2027, 2012

Table 5 – univariate analysis for EFS and OS and multivariate analysis for OS.

Variables	No.	5 year EFS %	*p*	5 year OS %	*p*	Relative risk for OS	Confidence interval of RR	*p*
Total	97	51		66				
Gender								
Boys	49	43	NS	57	NS			
Girls	48	60		75	(0,1)			
Age (year)								
<10	80	59	<0.001	74	<0.001	1		
10+	17	18		29		3.6	(1.7–7.8)	0.001
Pathology								
Non alveolar	68	53	NS	68	NS			
Alveolar	29	48		62				
T status								
T1	23	57	NS	70	NS			
T2	71	51		66				
Unknown	3							
Tumour size								
<5 cm	20	69	NS	85	NS			
>5 cm	76	46		60	(0,1)			
Unknown	1							
LN involvement								
No	60	58	0.02	77	<0.001	1		
Yes	27	33		44		3	(1.5–6.4)	<0.003
Unknown	10							
IRS group								
I/II	20	75	0.04	84	0.03	1		
III	77	45		61		4.6	(1.1–19.4)	0.04
Site								
Intra pelvic	59	56	NS	69	0.03			
Perineal/anal	22	32		40				
Genital	9	67		89				
Other	7	54		86				

Abbreviations: LN, lymph node; NS, non significant.

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Local therapy is critical in localised pelvic rhabdomyosarcoma: Experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee

Re'guerre Y, Martelli H, Rey A, et al. European Journal of Cancer 48: 2020–2027, 2012

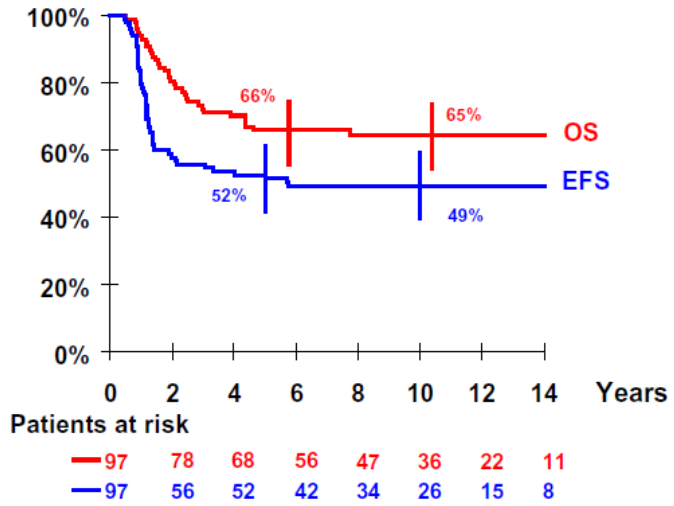
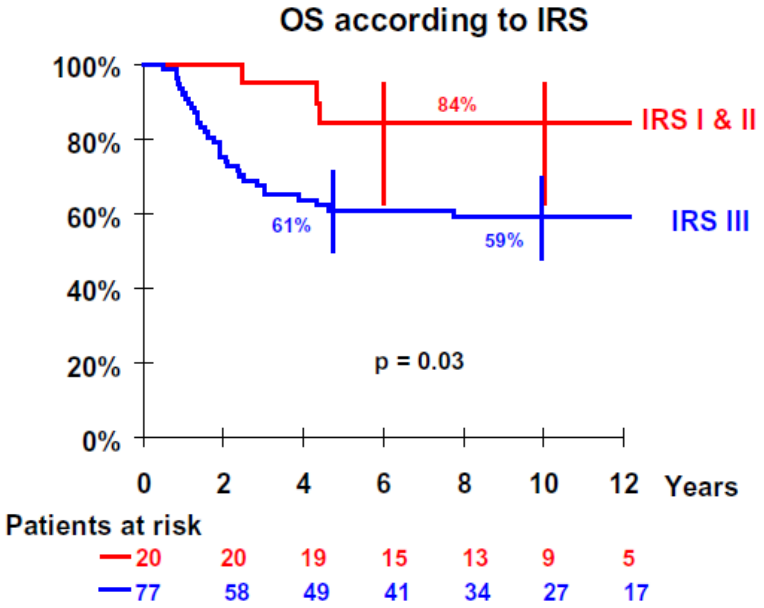
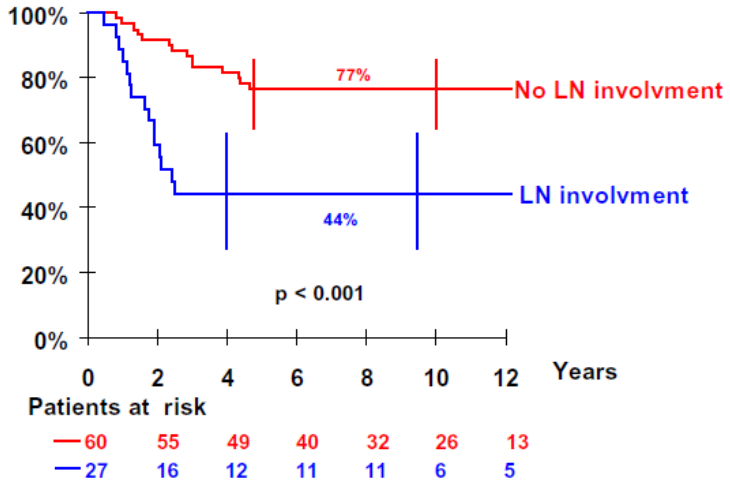
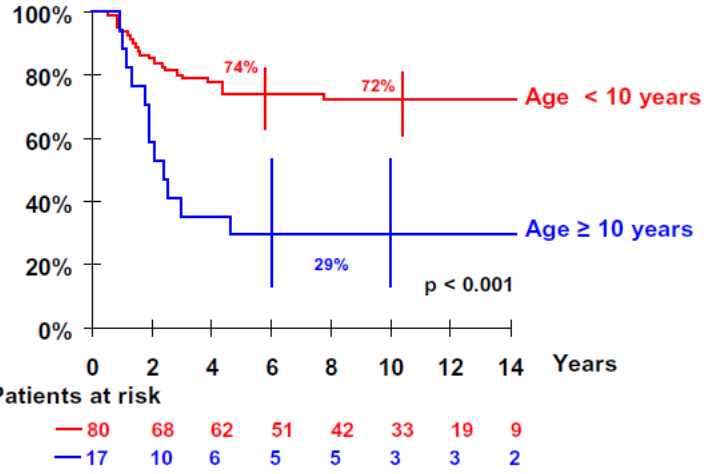


Fig. 1 – Overall survival of the entire population.







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Local therapy is critical in localised pelvic rhabdomyosarcoma: Experience of the International Society of Pediatric Oncology Malignant Mesenchymal Tumor (SIOP-MMT) committee

Re'guerre Y, Martelli H, Rey A, et al. European Journal of Cancer 48: 2020–2027, 2012

Conclusions:

1) 87 patients achieved local control (90%), 37 relapsed (43%), mainly locally (84%)

2) 5y OS was 66% and EFS was 52%

3) In multivariate analysis, IRS staging, age greater than 10 years and lymph node involvement had a negative impact on OS

4) Perineal/perianal locations had a trend towards a worse prognosis

5) Radiotherapy or brachytherapy is necessary for all IRS-III patients including those with radiological complete remission after neoadjuvant chemotherapy with or without surgery

6) Radiotherapy may be withheld in IRS-I patients and children under 3 years with IRS-II pRMS

Local Control for Intermediate-Risk Rhabdomyosarcoma: Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's Oncology Group
Wolden S, Lyden E, Arndt C, et al. Int J Radiat Oncol Biol Phys 93(5): 1071–1076 , 2015

Objective:

- Determine local control according to clinical variables for patients with intermediate-risk rhabdomyosarcoma (RMS) treated on Children's Oncology Group protocol D9803.

Patients and Methods:

- 702 patients enrolled, 423 patients analyzed
  - 280 group III embryonal, 102 group III alveolar and 41 group I-II alveolar
- Patients received 42 weeks of VAC (vincristine, dactinomycin, cyclophosphamide) or VAC alternating with VTC (T = topotecan)
- Group III: 50.4 Gy radiation therapy with or without delayed primary excision began at week 12
- Group I/II alveolar RMS received 36–41.4 Gy

Local Control for Intermediate-Risk Rhabdomyosarcoma: Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's Oncology Group
Wolden S, Lyden E, Arndt C, et al. Int J Radiat Oncol Biol Phys 93(5): 1071–1076, 2015

Conclusions:

- Group I/II alveolar RMS:
  - 5y EFS 69% and LF of 10%
- Group III RMS:
  - 5y EFS 70% and LF of 19%
- Local failure rates did not differ by histology, nodal status, or primary site
- Trend for increased LF for retroperitoneal tumors (P = .12)
- Tumors ≥5 cm were more likely to fail locally than tumors <5 cm (25% vs 10%, P = .0004)
  - Almost all (98%) RP tumors were ≥5 cm, with no difference in LF by site when the analysis was restricted to tumors ≥5 cm (P = .86)

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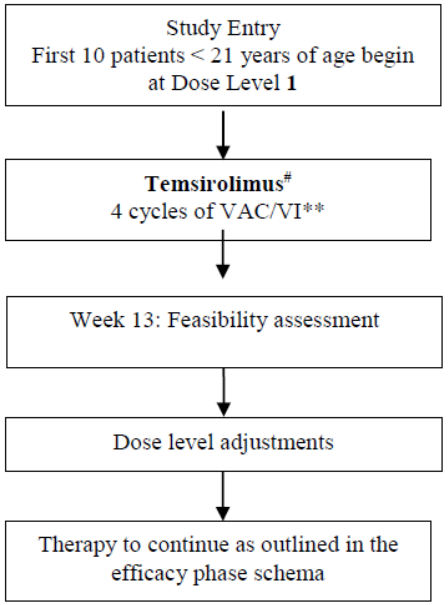
ARST1431

A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

EXPERIMENTAL DESIGN SCHEMA: FEASIBILITY PHASE

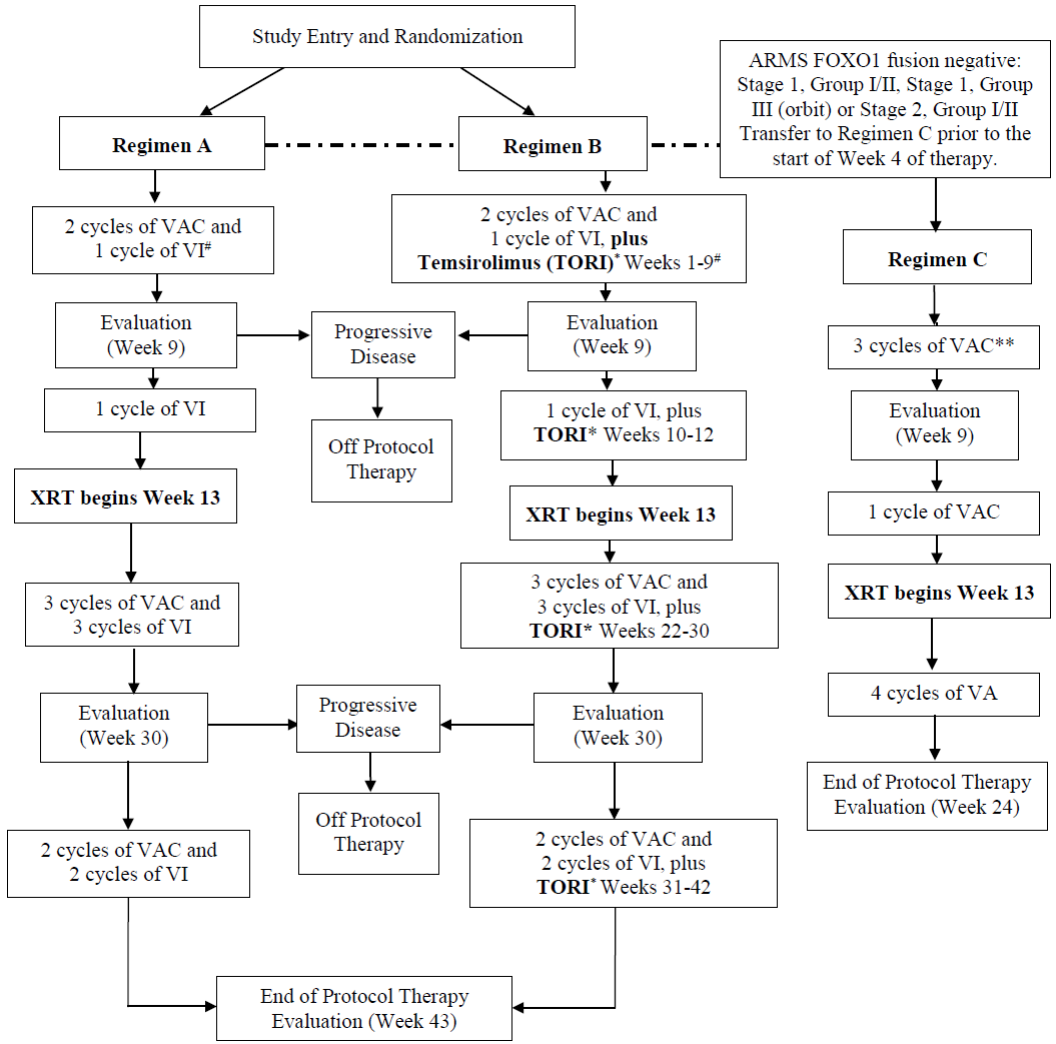
During the feasibility (dose-finding) phase, patients will be non-randomly assigned to treatment with VAC/VI plus temsirolimus.



#Temsirolimus

Dose Level	Temsirolimus Dose
1	15 mg/m^2 IV, Days 1, 8 and 15 of each cycle
0	10 mg/m^2 IV, Days 1, 8 and 15 of each cycle
-1	10 mg/m^2 IV, Days 1 and 8 of each cycle

EXPERIMENTAL DESIGN SCHEMA: EFFICACY PHASE

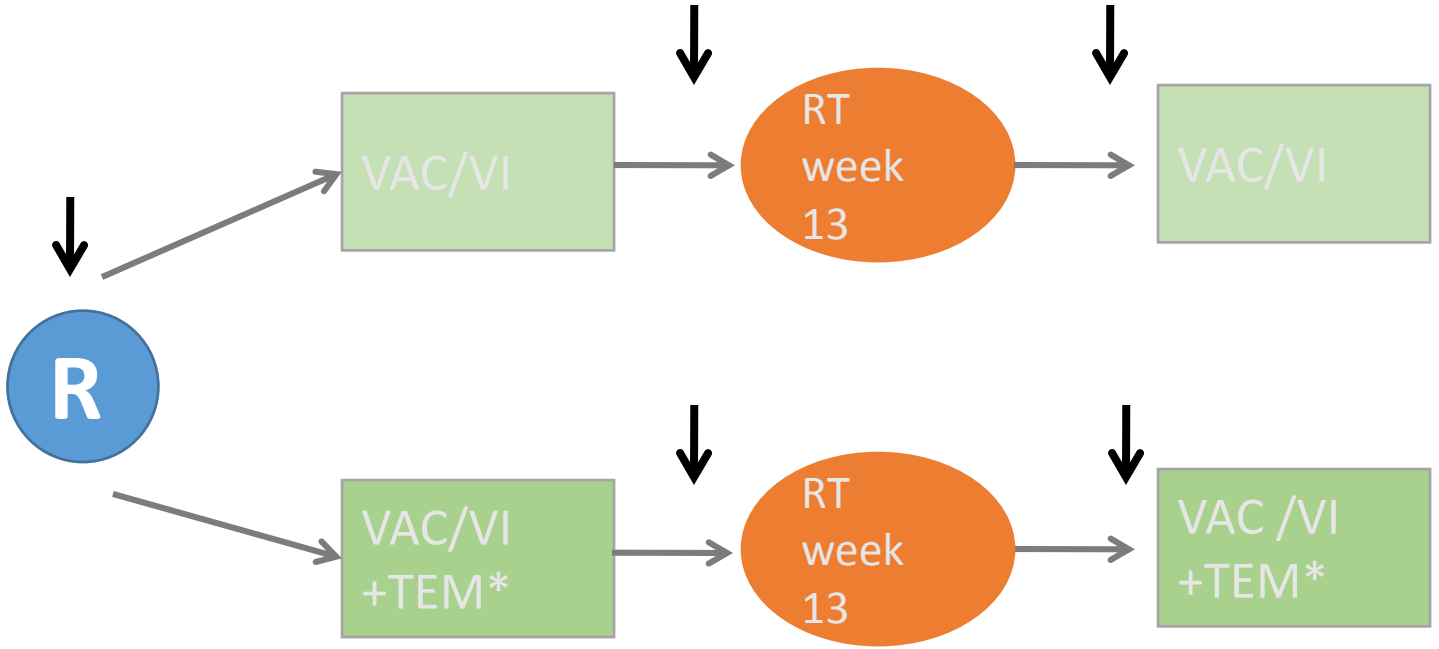


A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

Rationale for Investigation of an mTOR inhibitor in Children with Newly Diagnosed RMS: Temsirolimus (Torisel®)

Results of COG ARST0921, a randomized phase 2 selection design study in relapsed RMS that compared bevacizumab (BEV) to TORI, both administered in combination with cyclophosphamide and vinorelbine, showed that the TORI arm had a superior 6-month EFS (65%, 95% CI: 44%, 79%) compared to the bevacizumab arm (50%, 95% CI: 32%, 66%, p=0.0031).[18] There was also a higher proportion of partial responses on the TORI arm (33%) versus the BEV arm (18%). Furthermore, the complete response (CR) + partial response (PR) rate for the TORI arm was 47% compared with 28 % for the BEV arm. Based upon this clinical evidence of activity in heavily pre-treated patients with RMS, TORI is a high priority agent to evaluate in a large phase 3 study.

ARST1431 Study Design



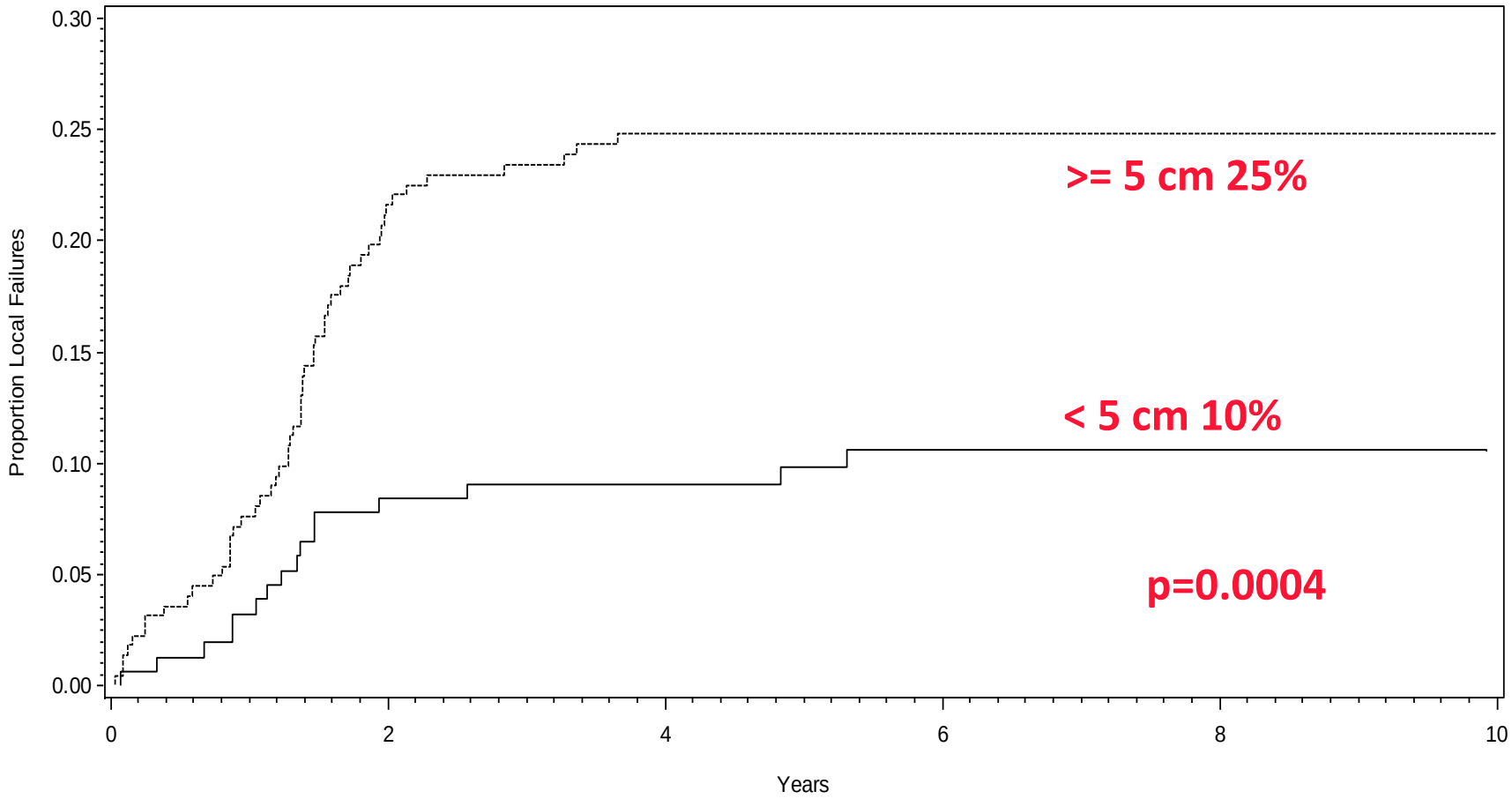
***Temsirolimus:**
mTOR inhibitor

↓ FDG-PET optional – week 1, 9, 30

Guidelines for ARST 1431

- All primary site RT at week 13
  - Protocol recommends rad onc consultation at diagnosis to assess imaging, credentialing, etc
  - No early RT for high risk parameningeal tumors
  - Emergent RT only in rare case of failure to respond to chemotherapy
- Protons, IMRT, 3D and brachytherapy allowed
  - Expect 50:50 proton and IMRT

D9803: Local failure Group III by size at diagnosis



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Guidelines for ARST 1431

- Dose escalation to 59.4 Gy mandatory for tumors >5cm at study entry (not at time of RT)
- Cone-down at 36 Gy to residual gross disease
  - If no reduction in size, no cone-down
- In rare case of CR, total dose will be 36 Gy
  - Must be no residual abnormality on CT/MRI AND
  - Negative PET OR negative biopsy to confirm
- If DPE, 36 Gy if margins neg, 41.4 if positive

Role of PET scans on 1431

- PET scans encouraged but not mandated
- Reduction in RT dose to 36 in cases of CR
  - Requires complete resolution of tumor on CT/MRI
  - Additional requirement that biopsy be negative OR PET be negative is redundant and primarily an inducement to do PET scans
- PET response and outcomes will be studied but in practice, PET response is not impacting treatment on ARST1431

Dose to primary tumor: ARST 1431

Clinical Group	no CR at Week 9**	CR at Week 9**	post DPE with negative margin	post DPE with microscopic margin	post DPE, gross residual disease
I, FOXO1 +	36	36	N/A	N/A	N/A
II	36	36	N/A	N/A	N/A
III, ≤5cm*	50.4	36	36	41.4	50.4
III, >5cm*	59.4	36	36	41.4	59.4

*Based on size at diagnosis

**CR defined as 1) Radiological CR by both PET and CT/MRI or 2) biopsy that shows no residual tumor.

Patients ≤ 24 months old

- Adherence to guidelines is encouraged
  - Outcome was poorer for these patients on 0531
- Deviation allowed only for children ≤ 24 months who are FOXO1 negative
  - Will be noted as “variation” but not formal “deviation”
  - Rationale and treatment must be submitted to IROC

Optional SBRT for bone mets <5cm: ARST 1431

Bone mets in SD/PR

	Dose/fraction (Gy)	Dose (Gy)
PTV2 =GTV2	7.0	35
PTV1= CTV2 + 2mm	6.0	24
After 15Gy whole lung		
PTV2 = GTV2	6.0	30
PTV1 = CTV2+2mm	5.0	25

Bone mets in CR

PTV2 =GTV2	6.0	30
PTV1= CTV2 + 2mm	5.0	25
After 15Gy whole lung		
PTV2 = GTV2	5.0	30
PTV1 = CTV2+2mm	4.0	20

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	Total Dose - Gy		post DPE - Dose Gy		
Clinical Group	if no CR at Week 9**	if CR at Week 9**	if GTR post DPE with negative margin	if GTR post DPE with microscopic margin	if post DPE, gross residual disease
I, FOXO1 +	36	36	N/A	N/A	N/A
II	36	36	N/A	N/A	N/A
III, ≤5cm*	50.4	36	36	41.4	50.4
III, >5cm*	59.4	36	36	41.4	59.4

*Based on size at diagnosis

CR defined as Radiological CR by CT/MRI (see Section 10.2.4.3) and 1) CR by FDG-PET; **or 2) biopsy that shows no residual viable tumor.

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A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

RT for Metastatic Sites

Definitive radiation therapy	Unresected tumor > 5cm
Definitive SBRT	Unresected/post-operative gross disease in bone mets that were < 5 cm at diagnosis
Post-operative radiation therapy	(1) Post-operative gross or microscopic residual tumor (2) Intra-operative spill
Special presentations	(1) Pulmonary metastases (2) Pathologically involved lymph nodes

All patients with any lung metastasis(es) or malignant pleural effusion at the time of diagnosis should receive bilateral whole lung radiotherapy. The dose will be 15 Gy in 10 fractions of 1.5 Gy.

17.7.5 Standard (non-SBRT) radiation dose guidelines for individual metastatic lesions requiring irradiation (all non-bone sites, all non-lung sites and bone sites >5cm).

	Dose (Gy)
Sites of initial metastases in CR	40 in 20 fractions
Lesions which are SD or PR	50 in 25 fractions

17.7.6 SBRT Dose Guidelines for lesions that are SD or PR at completion of chemotherapy

	Dose/fraction (Gy)	**Dose (Gy)**
PTV2 =GTV2	7.0	35
PTV1= CTV2 + 2mm	6.0	30
After 15Gy whole lung		
PTV2 = GTV2	6.0	30
PTV1 = CTV2+2mm	5.0	25

17.7.7 SBRT Dose Guidelines for lesions that are CR at completion of chemotherapy

PTV2 =GTV2	6.0	30
PTV1= CTV2 + 2mm	5.0	25
After 15Gy whole lung		
PTV2 = GTV2	5.0	30
PTV1 = CTV2+2mm	4.0	20

A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

GTV1

GTV1 is defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET scan) prior to any surgical debulking or chemotherapy. For patients who undergo initial surgery, operative notes and pathology reports may be helpful. For patients with initial tumors that extend into body cavities (*i.e.*, thorax, abdomen) the GTV may require modification. If the tumor has been resected or responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV excludes the volume which extends into the cavity. Examples include tumors which compress but not invade the lung, intestine or bladder that radiographically return to normal anatomic position

CTV1 – RT to Nodal Disease

If there are no sites that warrant irradiation for potential occult tumor, then the CTV1 is defined as GTV1 + 1cm (but not extending outside of the patient). It also includes regional lymph node chains for clinically or pathologically involved nodes. For tumors with no evidence of nodal involvement (N_0), the draining regional lymph nodes are not irradiated. For some sites, the definition of CTV is modified to account for specific anatomic barriers to tumor spread. **When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.** The definition of "clinically involved" nodes will be clarified as those including the following features: 1) > 1 cm on CT or MRI; OR 2) FDG avid on PET-CT, OR 3) pathologically confirmed to have microscopic disease. **RT to the nodal basin will be required for clinically involved nodes, unless they are biopsied and deemed pathologically negative.**

PTV1

For external beam photon techniques, the PTV1 is defined as the CTV1 plus an institutional specified margin to account for day-to-day setup variation related to the ability to immobilize the patient and physiologic motion of the CTV1. The minimum margin is 0.3cm but does not have to be uniform in all dimensions. For proton planning, beam specific PTV expansions will be required.

GTV2

GTV2 is defined as residual visible or palpable tumor as assessed by CT, MRI, PET scan or physical exam following induction chemotherapy.

CTV2

CTV2 is defined as the GTV2 + 1cm (but not extending outside the patient) and areas at risk for microscopic disease and modified to account for specific anatomic barriers to tumor spread.

PTV2

PTV2 is defined as the CTV2 with an institution and modality specific margin (minimum 0.3cm) to account for day to day setup variation and physiologic motion of the CTV2. For proton planning, beam specific PTV expansions will be required.

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A Randomized Phase 3 Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) Versus VAC/VI Plus Temsirolimus (TORI, Torisel, NSC# 683864, IND# 122782) in Patients with Intermediate Risk (IR) Rhabdomyosarcoma (RMS)

17.10.1 Organs at risk dose recommendations

Organ	Volume (%)	Dose (Gy)
Single organs		
Bladder	100%	45
Heart	100%	30
Liver	100%	23.4
	50%	30
Rectum	100/%	45
Optic chiasm	100%	54
Small Bowel	50%	45
Spinal Cord	Any volume	45
Paired organs		
Kidney (bilateral)	50%	24
Kidney (bilateral)	100%	14.4
Lung (bilateral)	20%	20
Lung (bilateral)	100%	15
Optic nerve	100%	54
Lens	100%	14.4
Lacrimal Gland/Cornea	100%	41.4

Paired organs - % refers to **one** of the paired organs unless specified as bilateral (kidney, lung) in which **both** of the paired organs are included in the %.

RT Volume Guidelines

Group III

- **IRS I** **Involved muscle compartment**
- **IRS II** **Initial tumor volume + 5 cm**
- **IRS III** **Initial tumor volume + 5 cm**
- **IRS IV** **Initial tumor volume + 2 cm**
- **IRS V** **3D – CRT to GTV + 1.5 cm CTV + 0.5 cm PTV**
- **Current** **IMRT to GTV + 1.0 cm CTV + 0.3 cm PTV**

Outline

- Epidemiology
- Patterns of Involvement
- Pathology
- Staging
- Clinical Evaluation and Work-up
- Treatment
- Results of Treatment
- Significant Clinical Trials
- Complications of Treatment

Preliminary Results of a Phase II Trial of Proton Radiotherapy for Pediatric Rhabdomyosarcoma
Ladra M, Szymonifka J, Mahajan A, et al. J Clin Oncol 32:3762-3770, 2014

Prospective phase II study:

- 57 pediatric patients with localized RMS or metastatic embryonal RMS enrolled between February 2005 and August 2012

- All patients were treated with chemotherapy (vincristine, actinomycin, and cyclophosphamide or vincristine, actinomycin, and ifosfamide–based) and proton

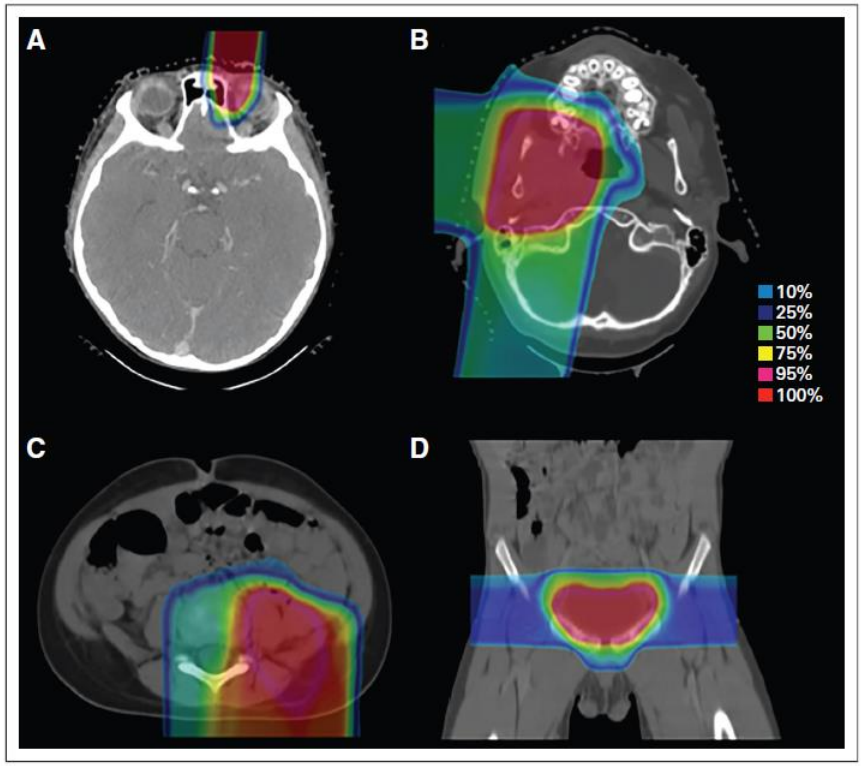

Fig 1. Proton treatment plans for patients with primaries at (A) orbital, (B) paramenin-geal, (C) trunk, and (D) prostate sites.

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Preliminary Results of a Phase II Trial of Proton Radiotherapy for Pediatric Rhabdomyosarcoma
Ladra M, Szymonifka J, Mahajan A, et al. J Clin Oncol 32:3762-3770, 2014

Conclusions:

- 5y EFS 69%, OS 78% and LC 81%
- 5y LC by risk-group: Low-risk 93% and high-risk 77%
- 5y LC, EFS, and OS rates were similar to those observed in comparable trials with photon RT
- Acute and late toxicity rates were favorable:
  - 13 patients with grade 3 acute toxicity
  - 3 patients with grade 3 late toxicity
  - No acute or late toxicities higher than grade 3

Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy
Leiser D, Calaminus G, Malyapa R, et al. Radiotherapy and Oncology 120:163–168, 2016

Objective:

- To assess clinical outcomes in children with RMS treated with pencil beam scanning proton therapy

Methods and materials:

- 83 RMS (89% embryonal) patients treated between January 2000 and December 2014 included
- All received systemic chemotherapy according to prospective protocols
- Low-risk 27%, intermediate-risk 63%, andhigh-risk13% of cases, respectively
- Median total dose delivered was 54 Gy(RBE) (range, 41.4–64.8

Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy

Leiser D, Calaminus G, Malyapa R, et al. Radiotherapy and Oncology 120:163–168, 2016

Table 2
Univariate Cox regression on local control in 83 RMS patients treated with PBS proton therapy.

Explanatory variables		HR (Hazard ratio)	HR lower + upper 95% CI	Overall Score (log rank) test
Age at first diagnosis	>=4.5	1.018	[0.3818–2.714]	$p = 0.9716$
Age at first diagnosis	>=10	0.3145	[0.04151–2.383]	$p = 0.2369$
Gender	Female	0.903	[0.3362–2.425]	$p = 0.8395$
Tumour site	Other vs PM	0.2342	[0.0667–0.8226]	$p = 0.0136$
IRS Group	>=IIIb	3.095	[1.119–8.563]	$p = 0.02195$
COG Stage	>=3	7.014	[1.593–30.87]	$p = 0.002683$
COG Risk group:	High vs low/int.	3.782	[1.302–10.98]	$p = 0.00865$
Histology of disease:	Alveolar vs embryonal	0.6109	[0.08061–4.629]	$p = 0.6299$
Size at diagnosis	>5 cm	3.126	[1.008–9.692]	$p = 0.03733$
Positive LN at diagnosis	Yes	2.367	[0.7613–7.357]	$p = 0.1248$
Total dose	>=54	2.147	[0.7454–6.185]	$p = 0.1471$
In PM RMS:	Intracranial extension	4.857	[0.6314–37.37]	$p = 0.09272$

Abbreviations: IRS: COG: Children's Oncology Group; RMS: rhabdomyosarcoma; PM: parameningial; LN: lymph node.

Table 3
Late toxicities observed in 83 RMS patients treated with PBS proton therapy.

Type of toxicity	PM RMS ($n = 46$) Any grade/(grade 3) *	Orbital RMS: ($n = 17$) Any grade/(grade 3) *	UG RMS ($n = 10$) Any grade/(grade 3) *	Others RMS ($n = 10$) Any grade/(grade 3) *
Localised alopecia	8/(N/A) **	1/(N/A) **	0/(N/A) **	1/(N/A) **
Growth Hormone deficiency	11/(N/A) **	3/(N/A) **	0/(N/A) **	0/(N/A) **
Other endocrinopathies	6/(0)	2/(0)	0/(0)	1/(0)
Facial hypoplasia	9/(0)	5/(0)	0/(0)	0/(0)
Visual complications	9/(3)	13/(10)	0/(0)	0/(0)
Hearing impairment	7/(2)	0/(0)	1/(0)	0/(0)
Dental growth impairment	3/(0)	0/(0)	0/(0)	0/(0)
Chronic nasal and sinus congestion	2/(0)	0/(0)	0/(0)	0/(0)
Urinary complication	0/(0)	0/(0)	3/(0)	0/(0)
Defecation problems	0/(0)	0/(0)	2/(0)	0/(0)
Secondary cancer (radiation induced)	0/(0)	0/(0)	0/(0)	1/(1)

Abbreviations: RMS: rhabdomyosarcoma; PM: parameningial RMS; UG: urogenital
* CTCAE ver.4.0.
** N/A: not applicable according CTCAE ver.4.0.

CHILDREN'S ONCOLOGY GROUP

Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy

Leiser D, Calaminus G, Malyapa R, et al. Radiotherapy and Oncology 120:163–168, 2016

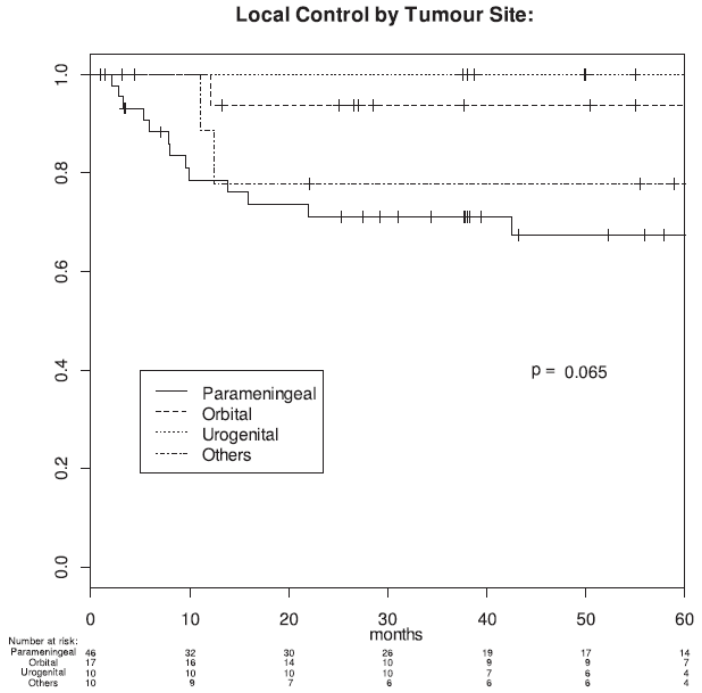

Fig. 1. Local tumour control as a function of tumour site in 83 patients with RMS treated with PBS proton therapy. The number of patients at risk is shown for each strata at the indicated time points. The *p* value for curves was calculated using a log rank test.

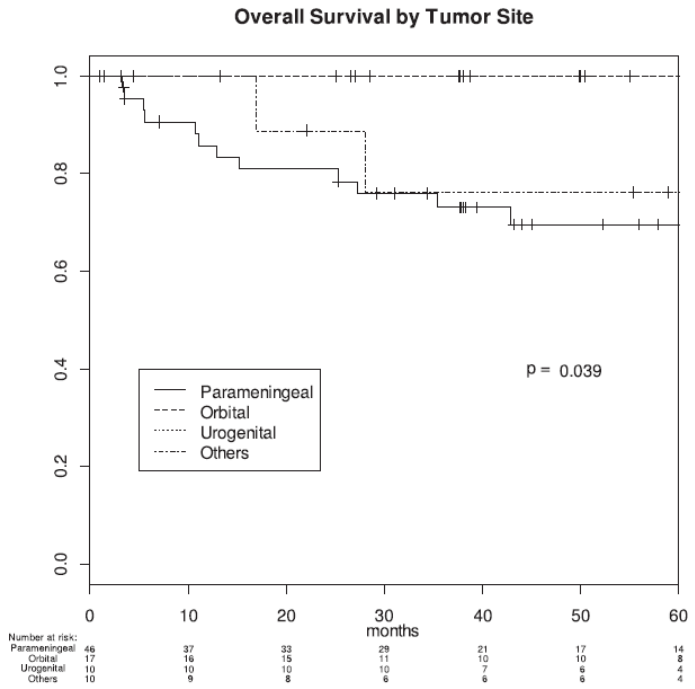

Fig. 2. Overall survival as a function of tumour site in 83 patients with RMS treated with PBS proton therapy. The curves were compared using a log rank test. The number of patients at risk is shown for each strata at the indicated time points.

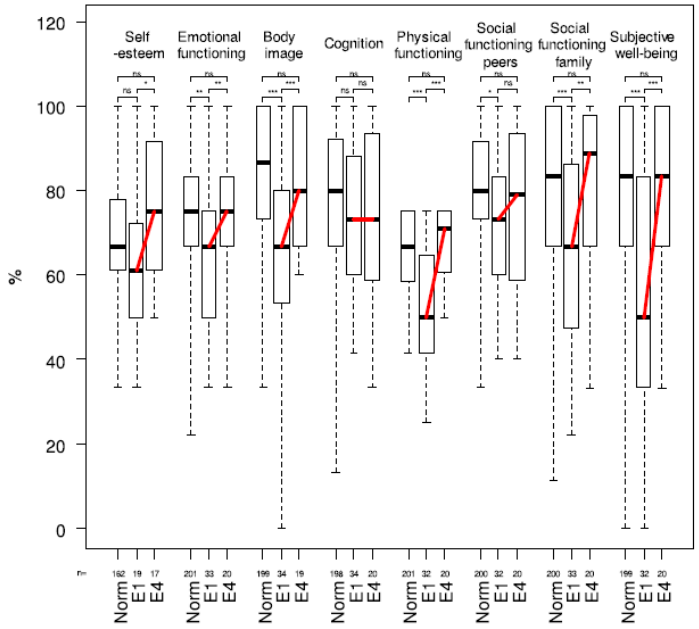

Fig. 3. Quality of Life (QoL) in rhabdomyosarcoma (RMS) patients treated with pencil beam scanning (PBS) proton therapy (PT) compared to a proxy norm population. E1 = Time point at start of PBS PT, E4 = Time point 2 years after end of PBS PT. The box plots with horizontal lines show 25%, 50% (median), and 75% quartiles. The error bars indicate minimum/maximum. n = Number of patients evaluated. *P* = *P*-value calculated by Mann–Whitney *U*-Test for independent samples and Wilcoxon signed-rank test for dependent samples (ns = not significant, * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$). Red lines show the differences in QoL median scores between E1 and E4. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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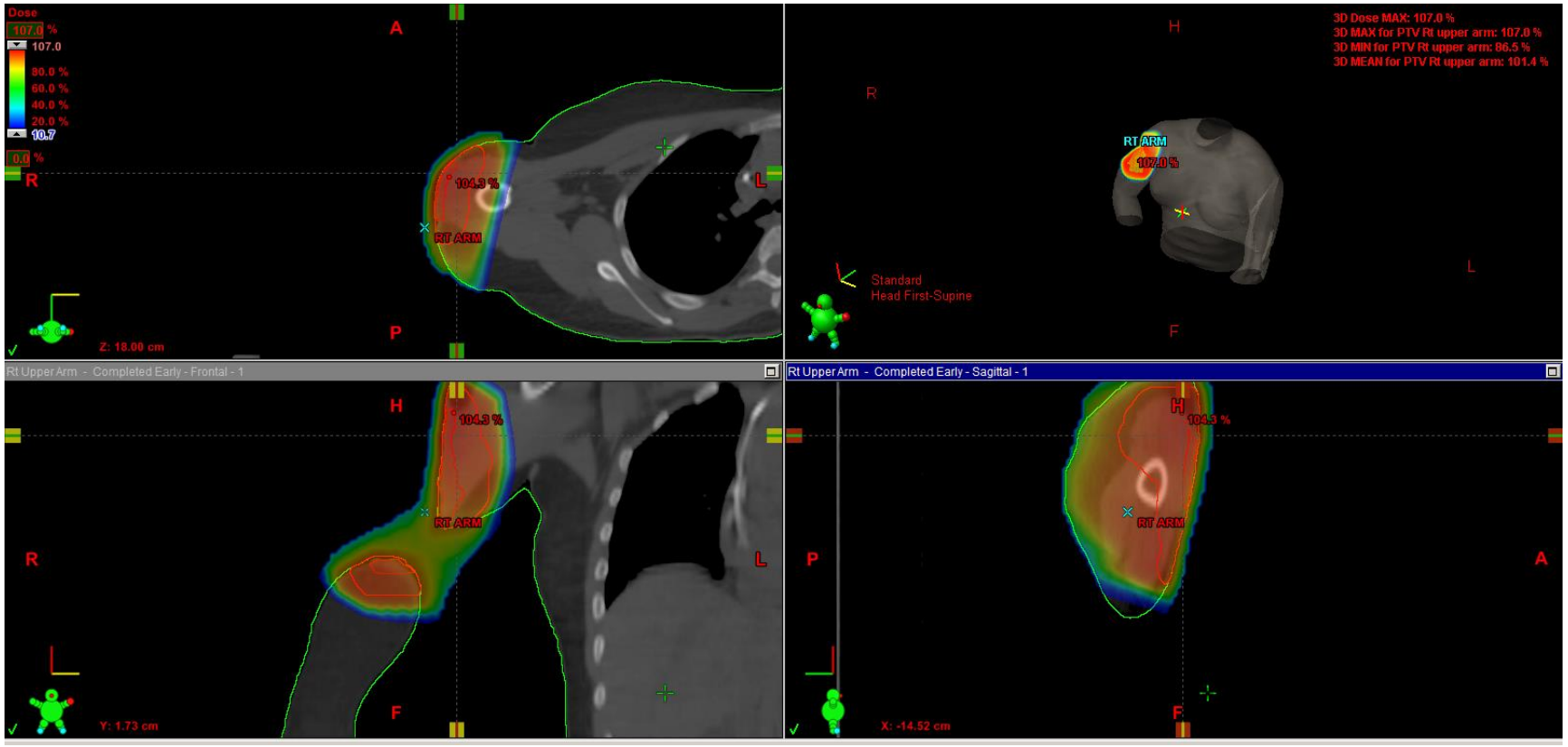
Conclusions:

- 5y LC 78.5% and OS 80.6%
- 5y incidence of grade 3 non-ocular late toxicity was 3.6%
- No grade 4–5 late toxicities observed
- One radiation-induced malignancy (1.2%)
- QoL scores increased significantly after PT compared to baseline

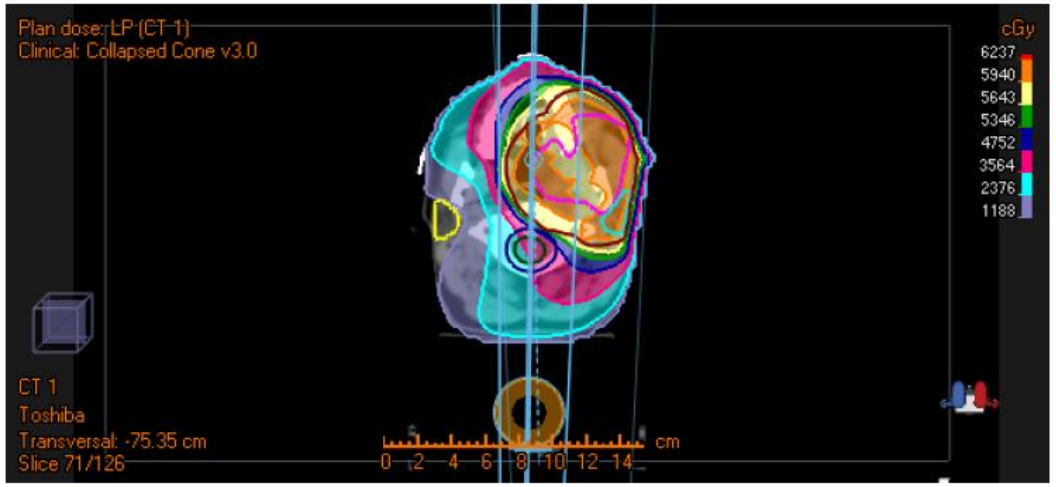
Clinical Case 1:

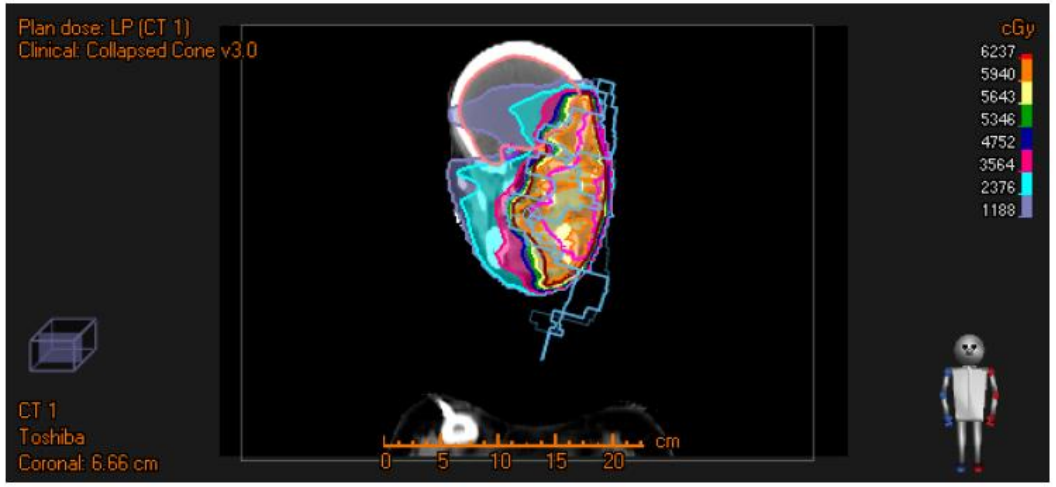
28 year old female with stage 3, group III spindle cell rhabdomyosarcoma of the right upper extremity s/p chemotherapy per ARST0531, Regimen A and s/p wide local excision with full thickness skin graft. Patient was noted to have 65% viable tumor and tumor was present within 2mm of the deep resection margin.



Clinical Case :

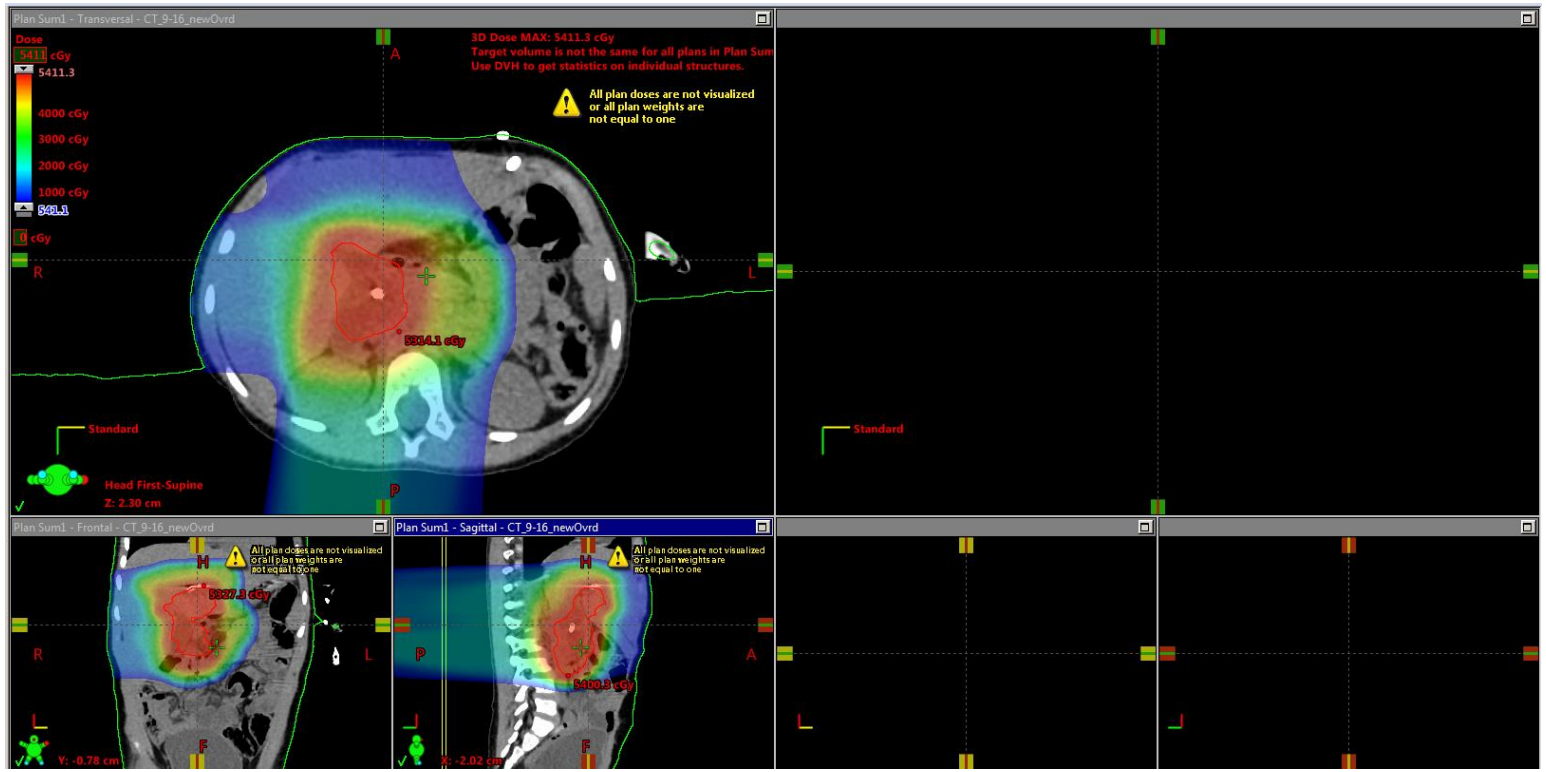
21 year old female with a parameningeal spindle cell rhabdomyosarcoma of left face, stage 3, group 3 s/p VAC chemotherapy as per ARST 0531 Group B, with progression of disease despite chemotherapy. Her chemotherapy was transitioned to VDC as per ARST0431.





Clinical Case 3:

4 year old female with a biliary tree ERMS, stage 1, group III. Slow initial response to chemotherapy.



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Conclusions

- Significant improvements in outcomes over past several decades
- Local control remains significant risk
  - Improved understanding of risk factors now guiding treatment
- Treatment related toxicity modified by dose deescalation when feasible and improved radiotherapy delivery