Rhabdomyosarcoma Basics & Overview

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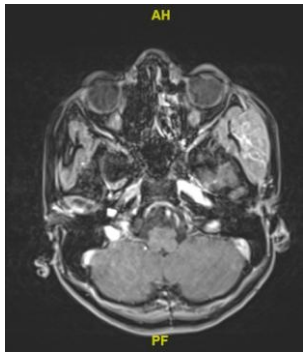
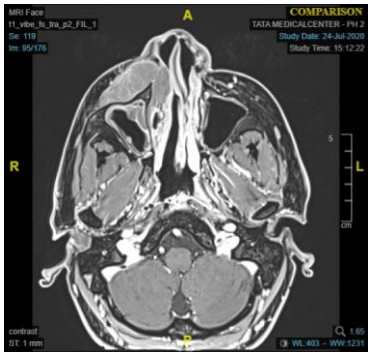
Rhabdomyosarcomas - Discussion Plan

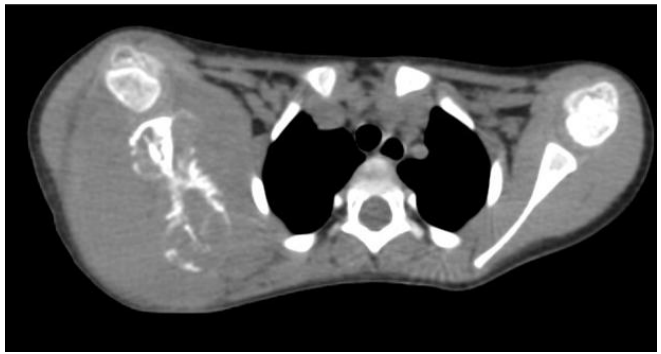
- Definition & Epidemiology
- Pathology - Identify known histopathologies, differentials
- Molecular Genetics
- Anatomic sites
- Clinical presentation & workup
- Risk stratification & staging
- Treatment - Differentiate treatment options for each risk group
- Follow up and late effects
- Importance of improving multidisciplinary care coordination

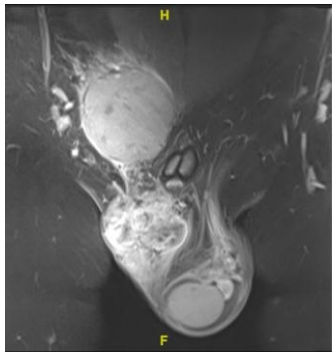
Rhabdomyosarcomas - Definition

- Family of sarcomas with morphological and/or immunophenotypic evidence of skeletal muscle differentiation
- A malignant tumour - thought to arise from primitive mesenchymal cells committed to skeletal muscle lineage





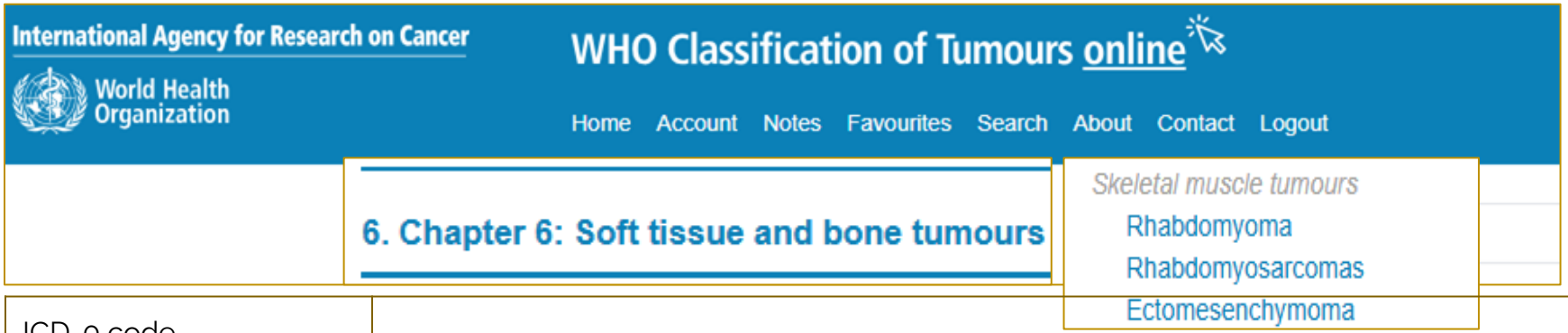




Rhabdomyosarcomas - Epidemiology

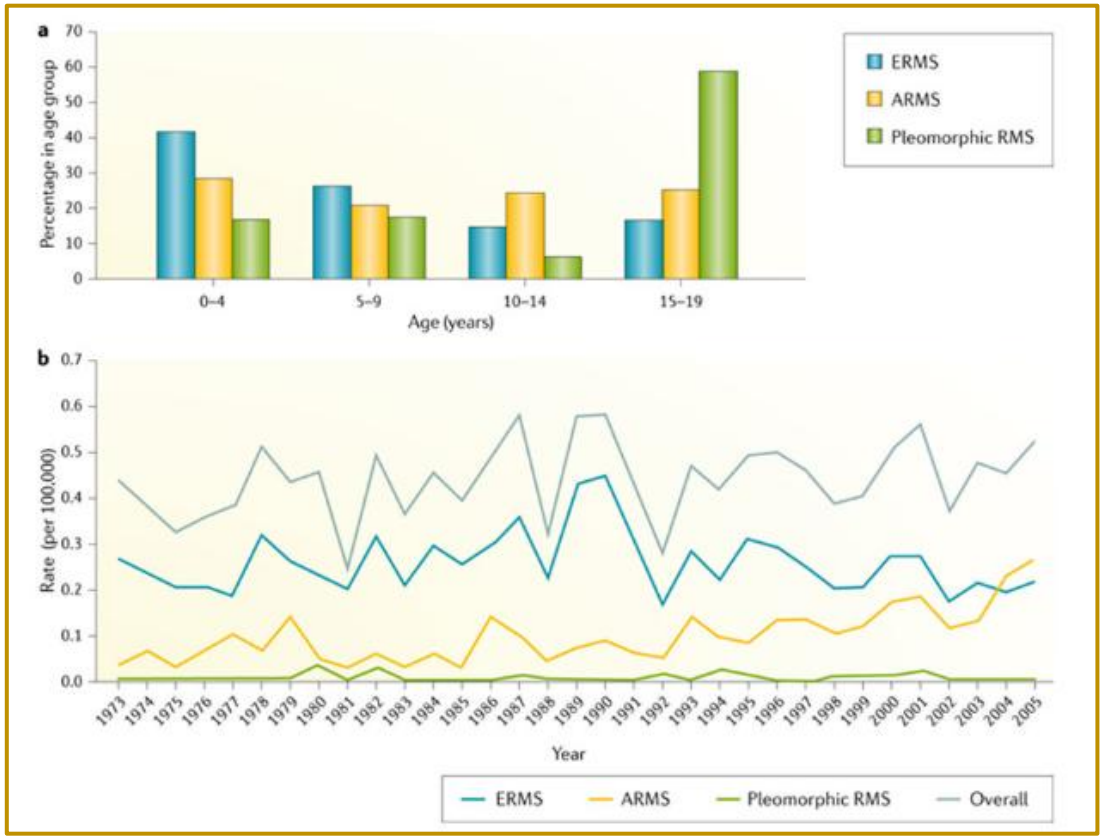
- Approximately 4 - 5 % of all childhood malignancies
- Annual incidence of 5.3 per million children under the age of 15
- RMS - Most common paediatric soft tissue sarcoma
- 40% of all pediatric soft tissue sarcomas
- Slight male preponderance
- Peak incidence - a median age at diagnosis of around 5 years
- Lower in parts of Asia - just over 2 per million individuals reported in Japanese, Indian, and Chinese populations

Rhabdomyosarcomas - Pathology

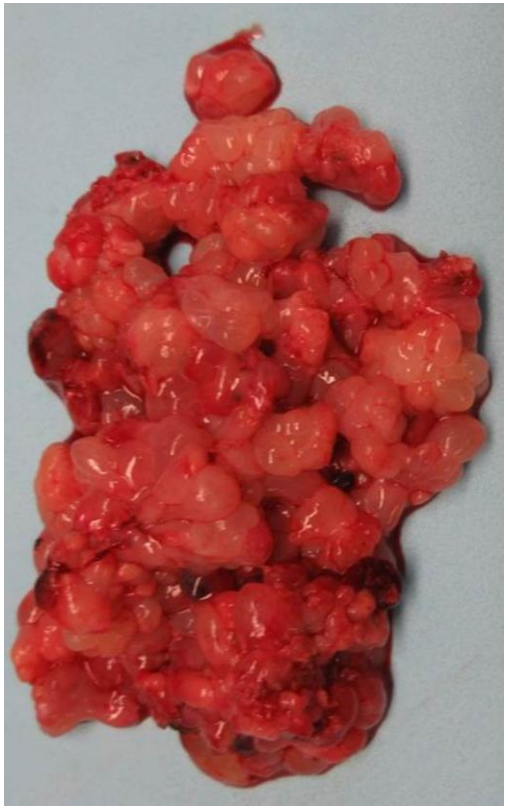


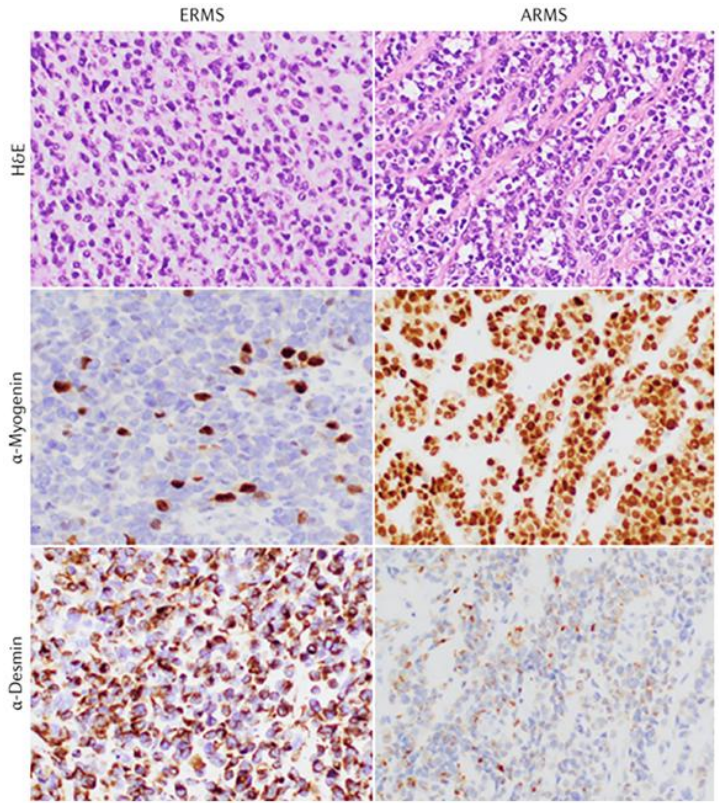
ICD-0 code	
8910/3	Embryonal rhabdomyosarcoma (75% cases) (also botryoid & spindle variants)
8910/3	Anaplastic embryonal rhabdomyosarcoma
8920/3	Alveolar rhabdomyosarcoma
8901/3	Pleomorphic rhabdomyosarcoma (25%)
8912/3	Spindle cell / sclerosing rhabdomyosarcoma

Rhabdomyosarcomas - Influence of Age

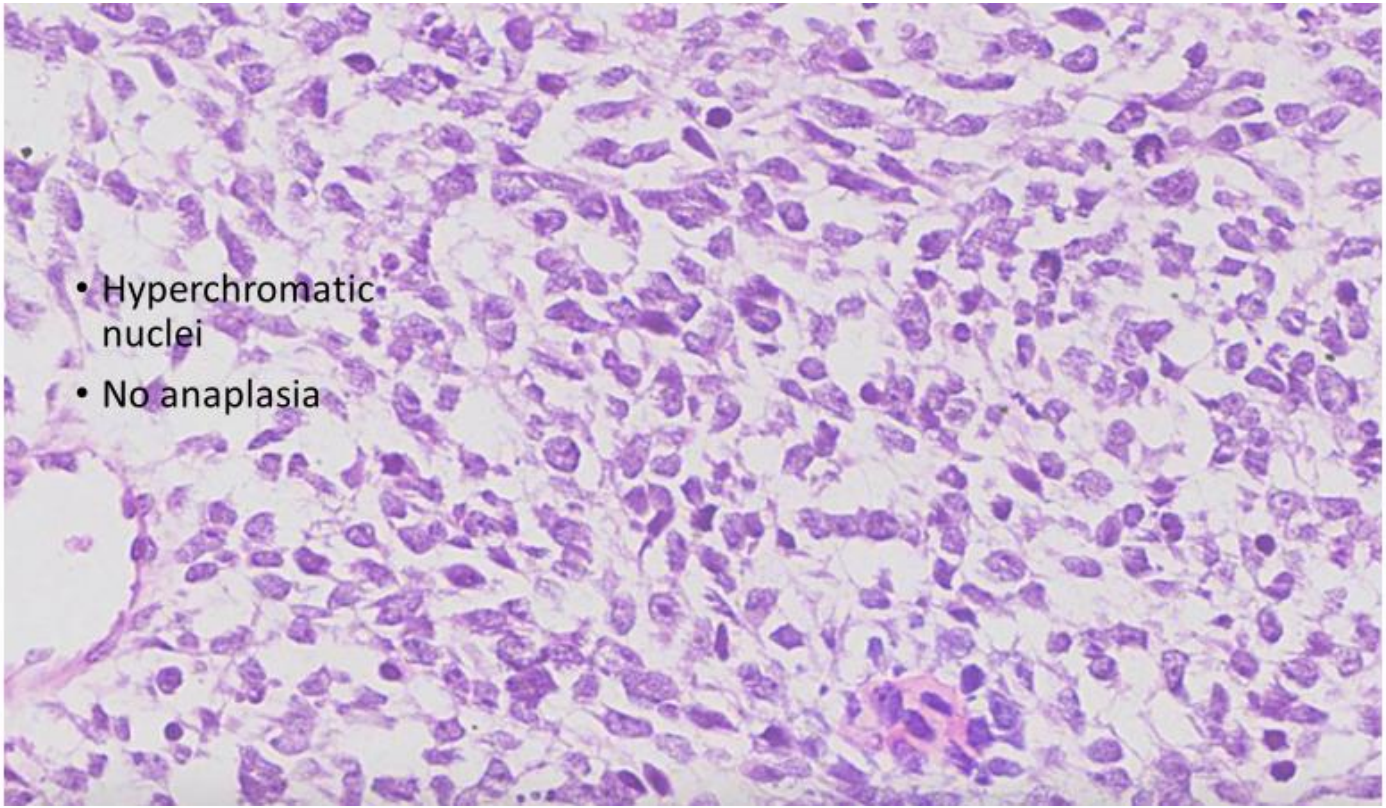


Rhabdomyosarcomas - Pathology





Rhabdomyosarcomas - Pathology differentials?



Rhabdomyosarcomas - Pathology differentials?

- Small round blue cell tumor (MR LEMONS - mnemonic)
  - Melanoma, rhabdomyosarcoma, lymphoma, Ewing's sarcoma, medulloblastoma, olfactory (esthesioneuroblastomas), neuroblastoma, small cell carcinoma
- RMS is divided into 3 histologic subtypes (arranged from the most favorable to the least favorable prognosis)
  - Embryonal (75% of RMS cases)
  - Includes botryoid and spindle variants
  - Alveolar (25% of RMS cases)
  - Pleomorphic / Undifferentiated

Rhabdomyosarcoma - Molecular Genetics

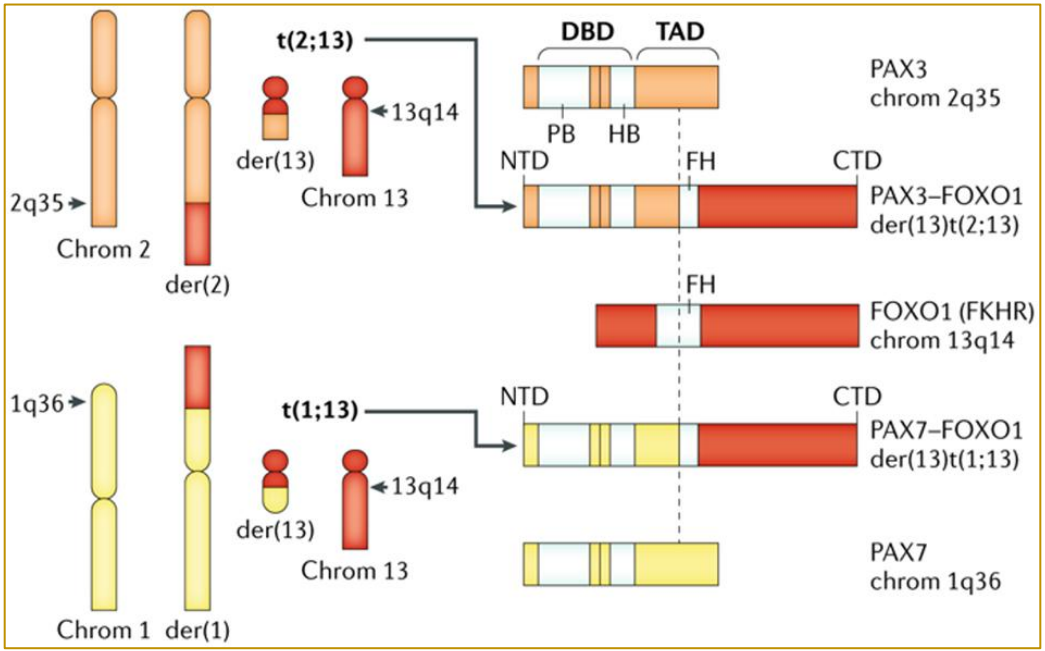
Embryonal

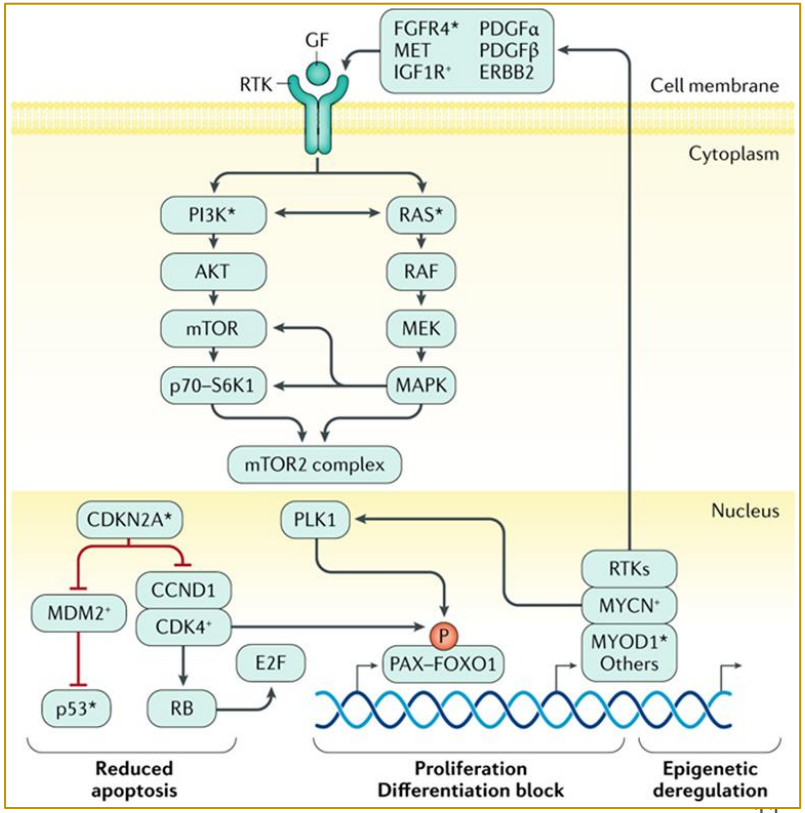
Loss of heterozygosity of 11p15.5

Alveolar

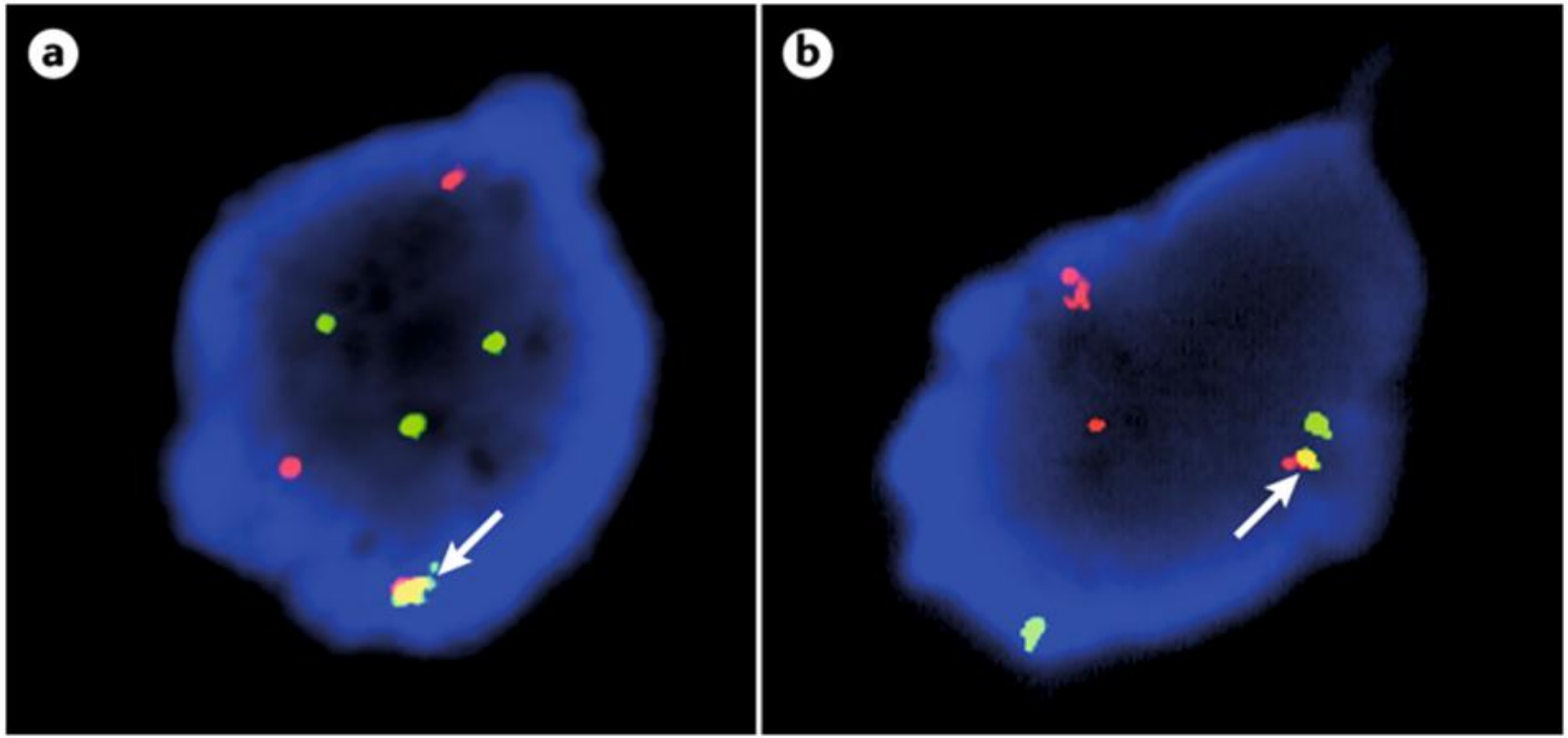
- Translocations of: t(2:13)
- Chromosome 2: PAX3
- Chromosome 13: FOX01 t (1:13)
- Chromosome 1: PAX7
- These translocations result in PAX-FOXO1 Fusion Genes = Forkhead fusion patients have a worse prognosis

Rhabdomyosarcoma - Molecular Genetics

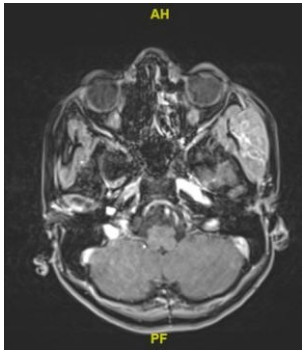


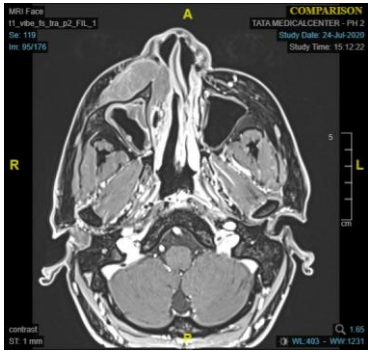


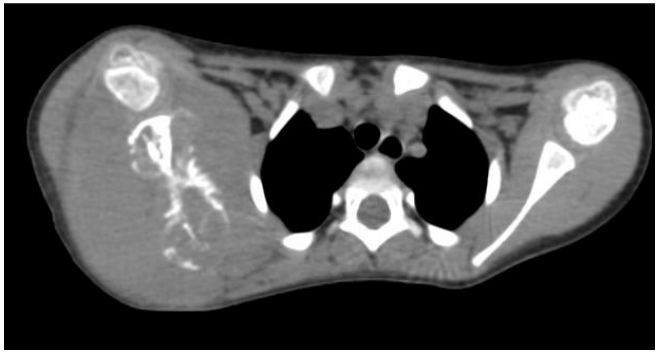
Rhabdomyosarcoma - Molecular Genetics
PAX–FOXO1 translocation can be detected by FISH

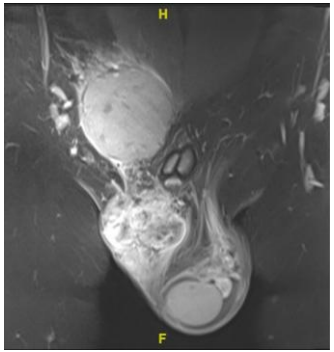


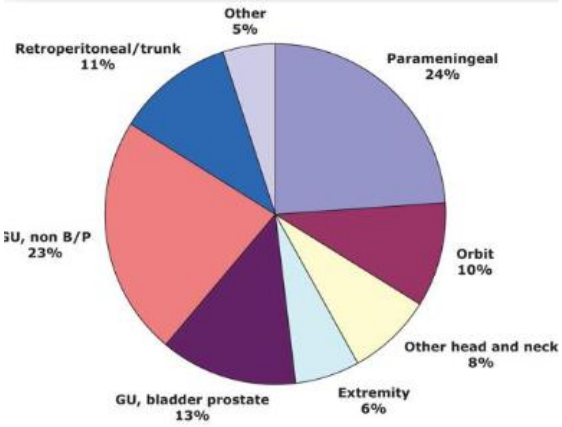
Rhabdomyosarcoma - Anatomic Sites









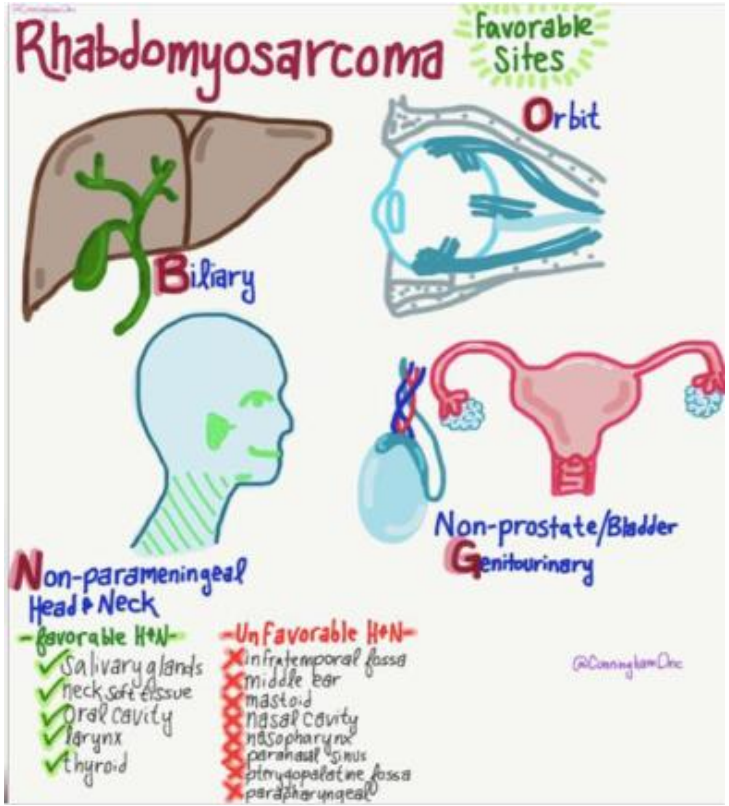


- Can occur anywhere
- Head and neck - commonest
- Genitourinary tract - second most common

Rhabdomyosarcoma - Anatomic Sites

@CunninghamOnc

Danielle A. Cunningham, MD



Favourable sites = BONG

Rhabdomyosarcoma - Clinical Presentation | Work up

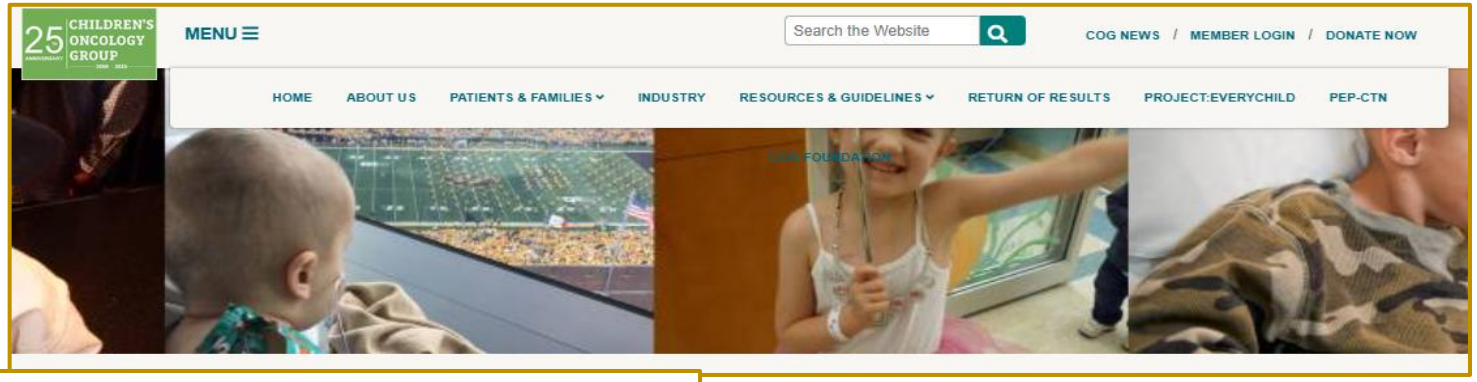
- Site dependent
- Asymptomatic mass - frequently described by parents
- Background of hereditary disorders
- Atypical presentations

- Blood works
- CT/MRI of the primary site
- PET CT (or CT CAP and bone scan)
- Biopsy the primary site
- Bone marrow biopsy

Site Dependent

- Lumbar puncture if parameningeal tumor (if CSF positive, obtain MR spine)
- Sentinel lymph node biopsy for extremity cases
- Ipsilateral retroperitoneal lymph node dissection for paratesticular sites greater than 10 y

Rhabdomyosarcoma - IRS studies? COG? EpSSG?JRSG?



Rhabdomyosarcoma - Risk Stratification

Pre-operative staging and post-operative grouping

Combining these = risk group (low, intermediate, high, very high*) = determine treatment

*SIOPe

Rhabdomyosarcoma - Staging

TABLE 56.5: IRSG Staging System

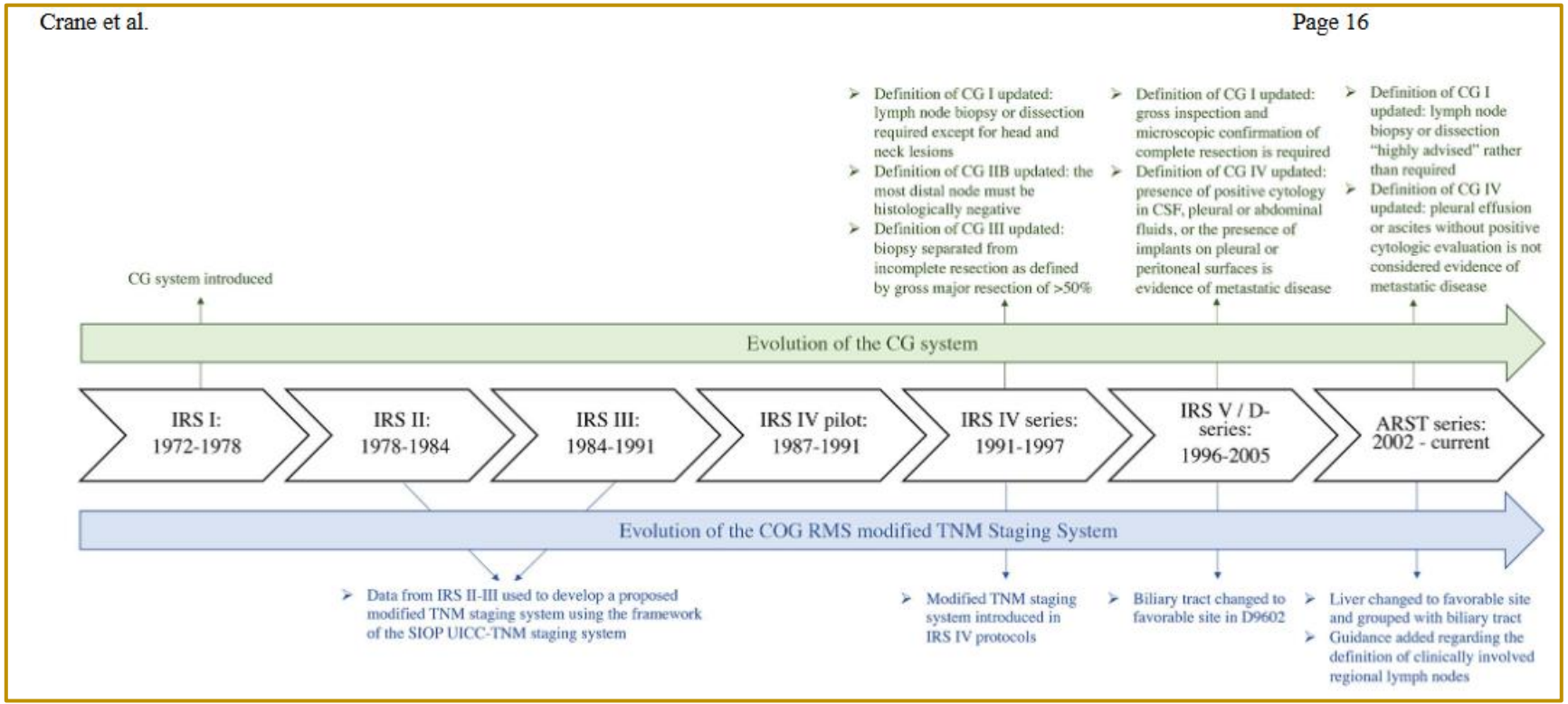
Stage	Sites	Size	N	M	3-yr Failure-Free Survival[19]
I: Favorable site	Orbit Head and Neck (non-PM) GU (non-bladder/prostate) Biliary tract	Any size	Any N	M0	86%
II: Unfavorable site, N0 and ≤5 cm	Bladder/Prostate Extremity Parameningeal Other (including: RP, perineal, perianal, intrathoracic, GI) Liver (nonbiliary)	≤5 cm	N0 or Nx	M0	80%
III: Unfavorable site, >5 cm or node-positive	Same as Stage II	≤5 cm	N1	M0	68%
		>5 cm	Any N	M0	
IV: Metastatic	All	Any size	Any N	M1	25%

T1, Confined to anatomic site of origin; T2, Extension and/or fixation to surrounding tissue; a, ≤5 cm in diameter; b, >5 cm in diameter; N0, Not clinically involved; N1, Clinically involved; Nx, Clinical status unknown; M0, No distant metastases; M1, Distant metastases.

Rhabdomyosarcoma - Grouping

TABLE 56.6: IRSG Grouping Classification	
Group I	Localized disease, completely resected A: Confined to muscle or organ of origin B: Infiltration outside the muscle or organ of origin
Group II	*Gross total resection with:* A: Microscopic residual disease B: Regional LN spread, completely resected C: Regional LN resected with microscopic residual
Group III	*Incomplete resection with gross residual disease* A: After biopsy only B: After major resection (>50%)
Group IV	Distant metastasis at onset

Rhabdomyosarcoma - Clinical group evolution



Rhabdomyosarcoma - Grouping, COG Updates 2022

Published in final edited form as:
Pediatr Blood Cancer. 2022 June ; 69(6): e29644. doi:10.1002/pbc.29644.

Clinical group and modified TNM stage for rhabdomyosarcoma: a review from the Children's Oncology Group

Current and Updated Clinical Group Classification System

Clinical Group	Current Classification	Our Updated Classification
Clinical Group I	Localized disease, completely resected a. Confined to muscle or organ of origin b. Contiguous involvement – infiltration outside the muscle or organ of origin, as through fascial planes. Note: Gross inspection and microscopic confirmation of complete resection is required. Note: Regional nodes not involved – lymph node biopsy or sampling is highly advised, except for head and neck lesions. Any nodes that may be inadvertently taken with the specimen must be negative.	Localized disease, completely resected Note: Gross inspection and microscopic confirmation of complete resection is required. Note: Regional nodes not involved.
Clinical Group II	Total gross resection with evidence of regional spread a. Grossly resected tumor with microscopic residual disease. Surgeon believes that he has removed all of the tumor, but the pathologist finds tumor at the margin of resection and additional resection to achieve clean margin is not reasonable. No evidence of gross residual tumor. No evidence of regional node involvement. b. Regional disease with involved nodes, completely resected with no microscopic residual. In contrast to Clinical Group IIa, regional nodes are involved, but completely resected and the most distal node is histologically negative. c. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node in the dissection.	Localized disease, grossly resected with microscopic residual disease or regional disease, grossly resected with or without microscopic residual disease a. Localized disease, grossly resected tumor with microscopic residual disease, regional nodes not involved b. Regional disease with involved nodes, completely resected with no microscopic residual (including most distal node is histologically negative) c. Regional disease with involved nodes, grossly resected with evidence of microscopic residual and/or histologic involvement of the most distal regional node in the dissection
Clinical Group III	Incomplete resection with gross residual disease a. After biopsy only b. After gross major resection of the primary (>50%)	Localized or regional disease, biopsy only or incomplete resection with gross residual disease
Clinical Group IV	Distant Metastatic disease present at onset (Lung, liver, bones, bone marrow, brain, and distant muscle and nodes) The following are also considered evidence of metastatic disease and place the patient in Group IV: 1. The presence of positive cytology in CSF, 2. Positive cytology in pleural or abdominal fluids, 3. The presence of implants on pleural or peritoneal surfaces NOTE: The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favorable grouping. NOTE: The presence of a pleural effusion or ascites without positive cytologic evaluation is not considered evidence of metastatic disease and the patient will not be considered to have Group IV disease.	Distant metastatic disease present at onset Although not limited to these, the following are considered evidence of metastatic disease: 1. The presence of positive cytology in CSF, 2. Positive cytology in pleural or abdominal fluids, 3. The presence of implants on pleural or peritoneal surfaces Note: Regional lymph node involvement and adjacent organ infiltration are not considered metastatic disease Note: The presence of a pleural effusion or ascites without positive cytologic evaluation is not considered evidence of metastatic disease

CG I
Localised, R0, N0

CG II
Localised, R1, N0
Localised/regional, R0, N+
Localised/regional, R1, N+

CG III
Localised/regional, R2, N+

CG IV
Distant metastatic disease present at onset

Rhabdomyosarcoma - COG Risk stratification

- Stage 4, Group 4 is High Risk
  - Unless you are fusion negative and less than 10 years old
- Alveolar is Intermediate Risk
- For Embryonal, to fall into low risk....you must fusion negative AND:
  - All BONG
  - Not BONG, Not Gross Residual

Table 60.7: Risk Stratification Based on Pre-Op Staging + Post-Op Grouping

Risk Group	Involved Groups
Low (~35%)	Favorable histology (embryonal) *and* PAX/FOX01 fusion negative *and* – Favorable site (stage I): groups I–III – Unfavorable site (stages II–III): groups I–II
Intermediate (~50%)	– Favorable histology (embryonal), PAX/FOX01 fusion negative, unfavorable site (stages II–III): groups III – Favorable histology (embryonal), PAX/FOX01 fusion positive, any site (stages I–III): groups I to III – Unfavorable histology (alveolar), PAX/FOX01 fusion positive or negative, any site (stages I–III): groups I–III – Stage IV, group IV, PAX/FOX01 fusion negative, <10 years old
High (~15%)	– Stage IV, group IV, PAX/FOX01 fusion negative, ≥10 years old – Stage IV, group IV, PAX/FOX01 fusion positive, any age

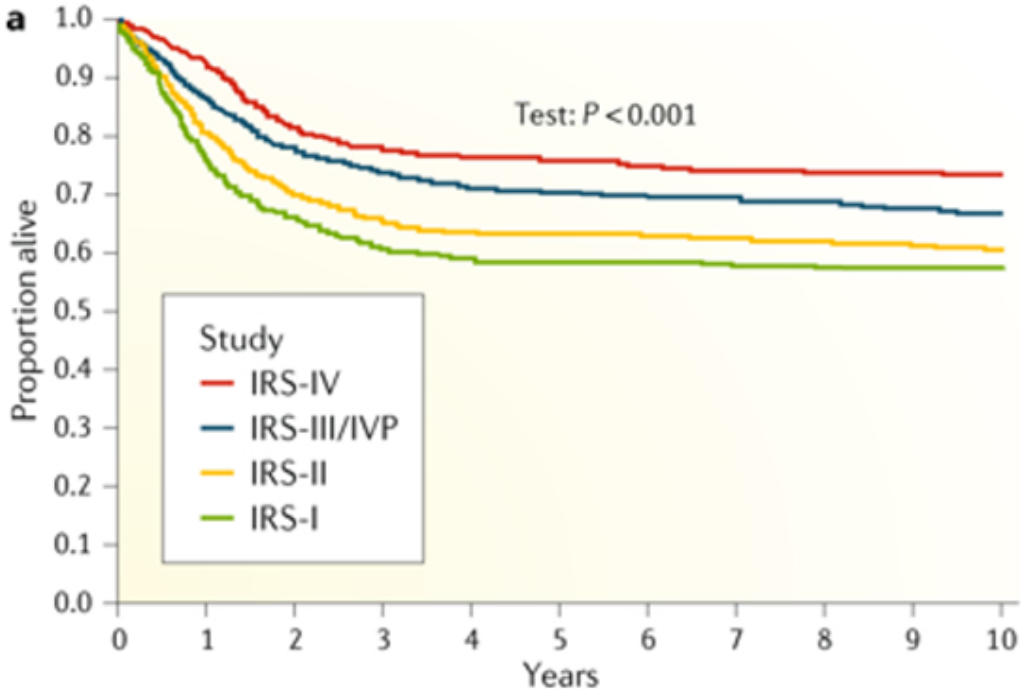
Rhabdomyosarcoma - SIOP Risk stratification

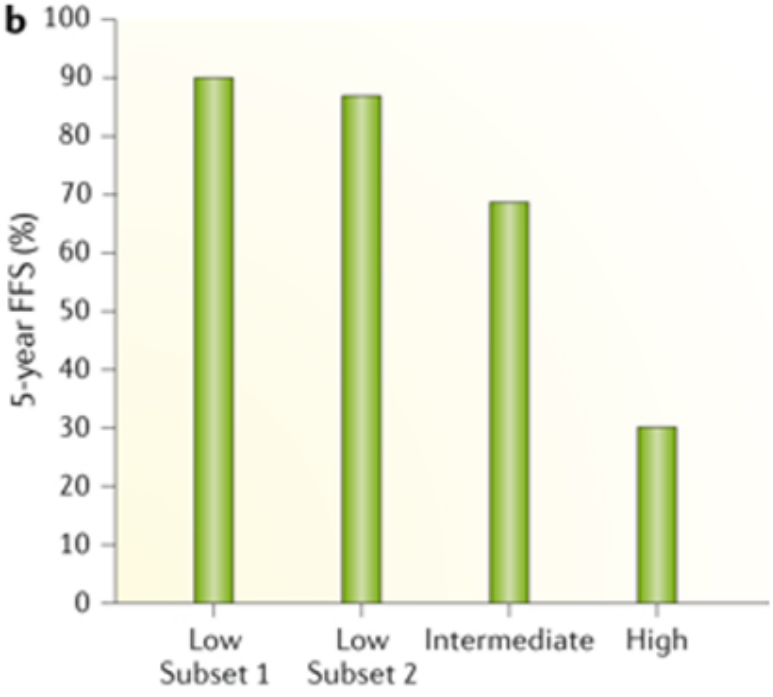
- Stage 4, Group 4 is High Risk
  - Unless you are fusion negative and less than 10 years old
- Alveolar is Intermediate Risk
- For Embryonal, to fall into low risk....you must fusion negative AND:
  - All BONG
  - Not BONG, Not Gross Residual

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	A	Negative	I	Any	N0	Both Favourable
Standard Risk	B	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	D	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Ongoing international efforts through the **International Soft Tissue Sarcoma Consortium (INSTRuCT)** to share clinical data and harmonize approaches to classification of RMS

Rhabdomyosarcoma - Principles of Treatment





Rhabdomyosarcoma - Principles of Treatment

- This will vary based on risk group and protocol used
- Surgery | Chemotherapy | Radiotherapy
- Optimal timing and intensity important - function of risk group

	Non morbid Surgery/Biopsy	
Upfront chemotherapy VCR-ACT-Cyc (COG) Ifos-VCR-ACT (Europe)	W 0 - W 11	Ifosfamide replaces Cyc in Europe No outcome differences
	Re evaluation	
Local Treatment (Radiation)	W 13 - W 17	
Consolidative chemotherapy	W 18 - W 42	

Rhabdomyosarcoma - Non morbid Surgery/Biopsy

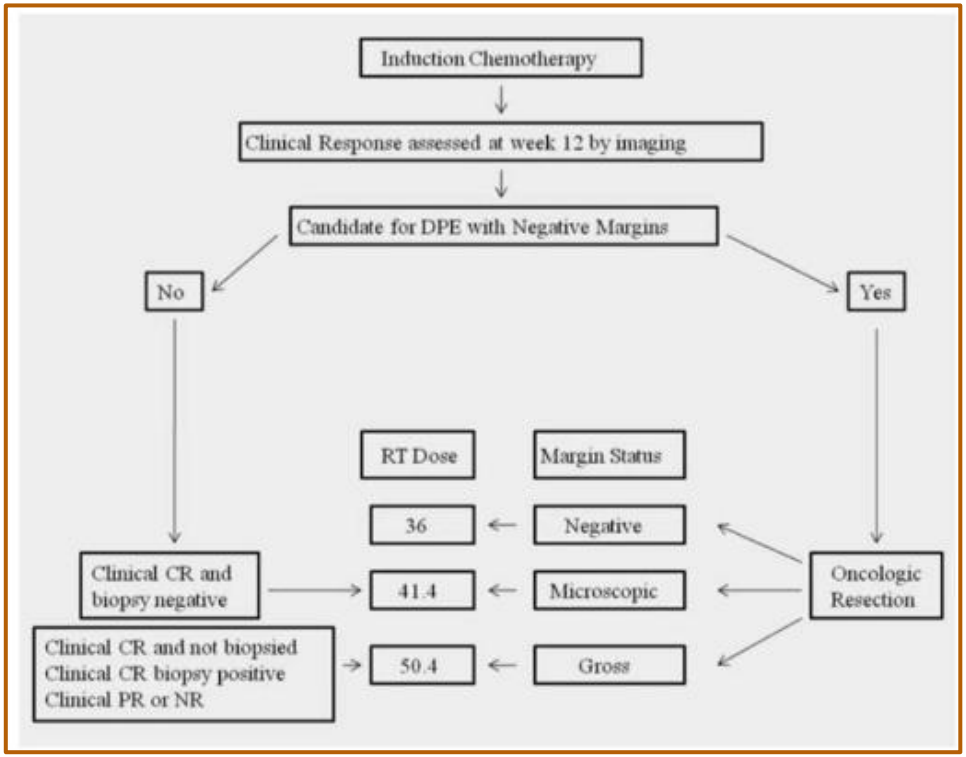
- Non-Morbid Surgery
    - If this is not possible, a simple incisional biopsy will do
    - This tumor is radiosensitive so do not handicap the patient
- If possible: complete excision with 5 mm margins
- Extremity RMS must have at least sentinel lymph node biopsy
- Paratesticular RMS in boys > 10 years should have a retroperitoneal lymph node dissection

Rhabdomyosarcoma - Delayed Primary Excision (DPE) COG 9803

Chemotherapy will cause tumor shrinkage

1. Make it resectable
2. Post resection, allow a lower dose of RT
3. Non mutilating procedures
4. Selected patients benefit, not all

Rhabdomyosarcoma - Delayed Primary Excision (DPE) COG 9803



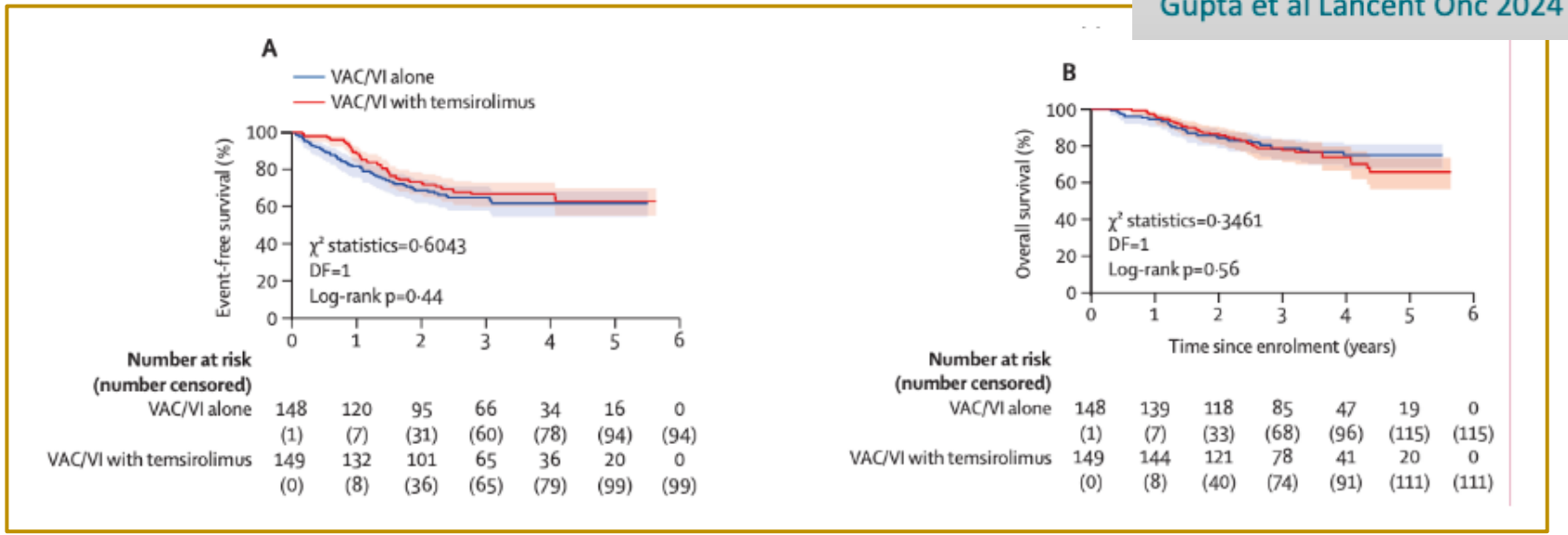
Rhabdomyosarcoma - Chemotherapy

Follow the protocol selected in your institution: COG or SIOP

1. Vincristine
2. Actinomycin
3. Cyclophosphamide/Ifosfamide
4. Doxorubicin
5. Irinotecan; Temozolomide
6. Maintenance - Vinorelbine/Cyclophosphamide
7. Temsirolimus

Rhabdomyosarcoma - Targeted therapy ARST1431 results: No difference in EFS/OS with temsirolimus

Gupta et al Lancent Onc 2024



Rhabdomyosarcoma - Radiation Therapy

Key exceptions which do not require radiotherapy are:

- Localised fusion negative rhabdomyosarcoma with initial R0 resection (IRS Group I)
- Localised fusion negative rhabdomyosarcoma of the vagina achieving complete remission with induction chemotherapy **with standard doses of cyclophosphamide**
- A highly selected group of patients with IRS Group III Standard Risk fusion negative RMS, arising at a favourable site, where secondary surgery achieves an R0 resection

Cannot omit RT for vaginal RMS in setting of lower cyclophosphamide

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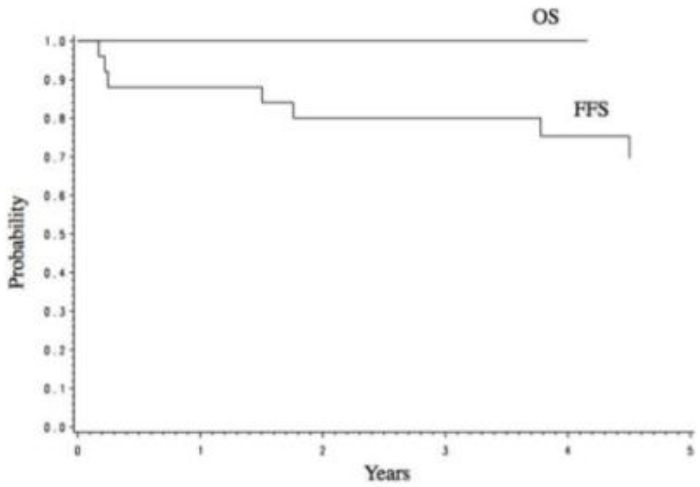
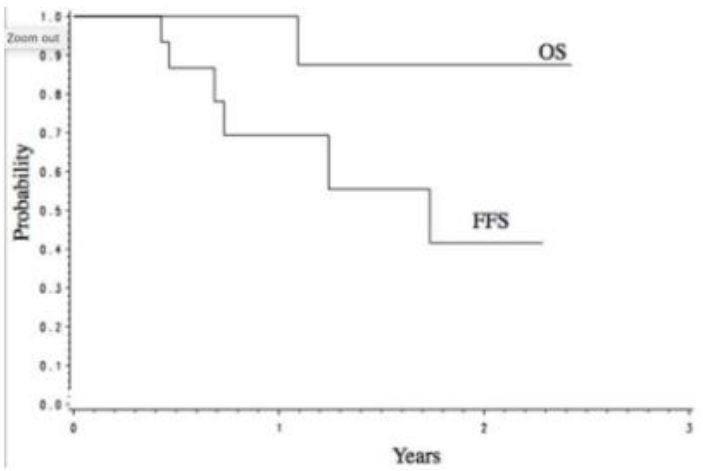


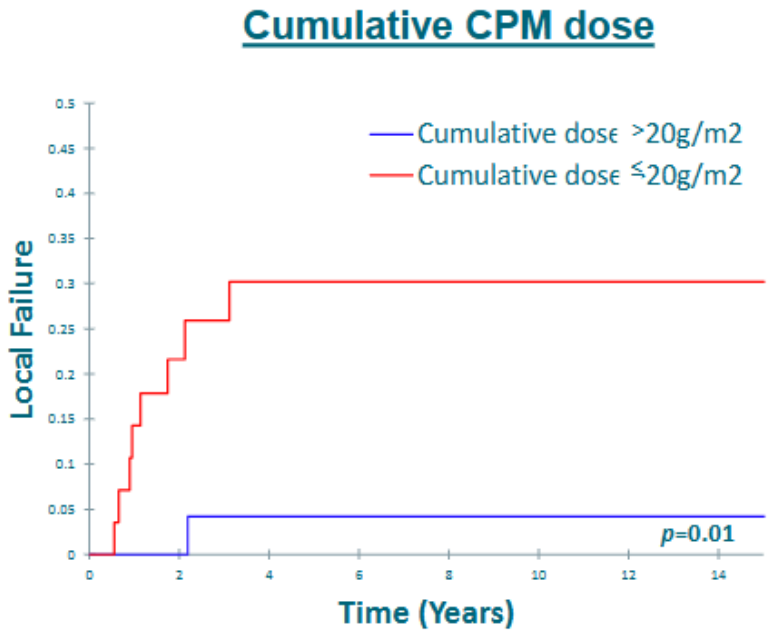
5-year LR 26%

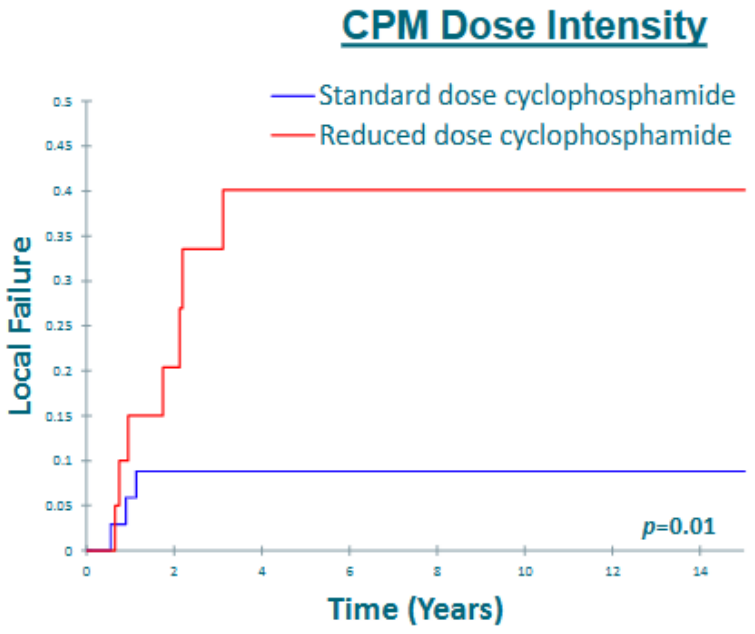
ARST0331



5-year LR 43%

Cyclophosphamide dose may influence local failure after RT





Rhabdomyosarcoma - Radiation Therapy Doses

In pediatric and hematolymphoid malignancies - radiation dose is a function of the mother protocol

COG (IRS, ARSTS)

Clinical Group	Dose
I, Embryonal or FOX01 fusion negative	0 Gy
I, FOX01 fusion positive	36 Gy
II	36 Gy
III, < 5 cm	50.4 Gy
III, > 5 cm	59.4 Gy

SIOP (EpSSG)

5.2.6. Radiotherapy dose prescription

5.2.6.1 Primary tumour

Resectable (R0/ R1) postoperative radiotherapy = 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre.

Unresectable complete response (to induction chemotherapy) = 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre.

Unresectable incomplete response (to induction chemotherapy) = 50.4Gy in 28 fractions over 5.5 weeks (or equivalent) total. Phase 1: 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVp_post.

Alternatively for patients with unresectable large tumours with poor response to induction chemotherapy 55.8Gy in 31 fractions can be given (as per previous EpSSG RMS 2005 & CWS protocols): Phase 1: 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre, Phase 2: 14.4Gy in 8 fractions (or equivalent) to PTVp post.

5.2.6.2 Involved lymph nodes

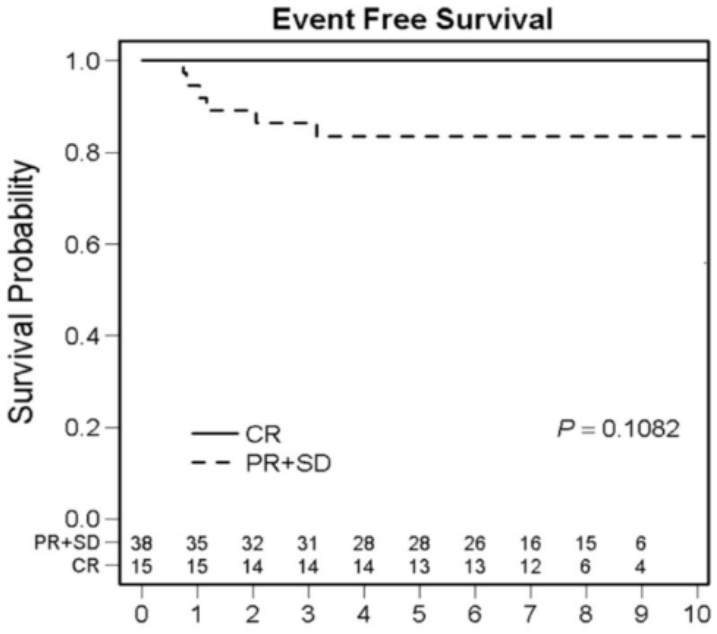
41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVn.

For bulky residual involved lymph nodes only, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVn_post.

5.2.6.3 Metastatic sites

The radiotherapy dose for metastatic sites is at the discretion of the treating physician. For patients with limited or oligometastatic disease then radical dose fractionation or stereotactic ablative radiotherapy can be considered. For other patients, fractionation such as 30Gy in 10 fractions (or equivalent dose/fractionation) are commonly used. The benefit of lung radiation is still matter of debate. There is no clear evidence concerning the benefit of whole lung irradiation [81, 82]. For patients receiving whole lung radiotherapy a dose of 15 Gy in 10 fractions should be used.

Orbital Rhabdomyosarcoma
45 Gy not sufficient for orbital tumors that do not achieve CR



IRS-IV local control: 96%

ARST0331 local control: 83%

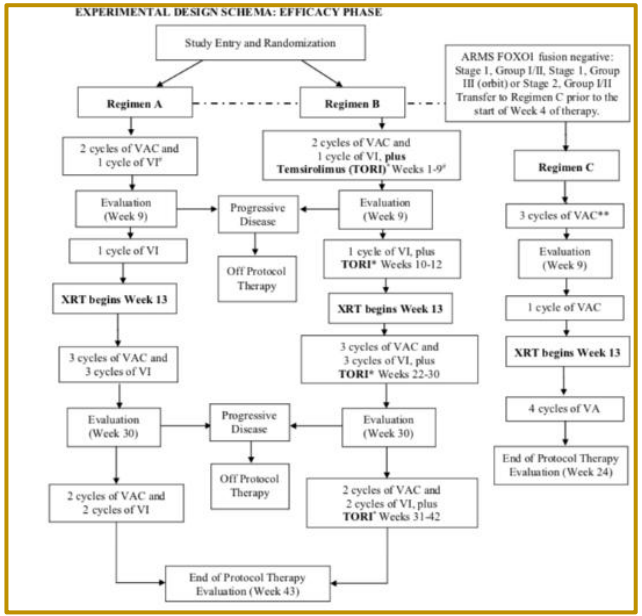
Rhabdomyosarcoma - Radiation Target Volume

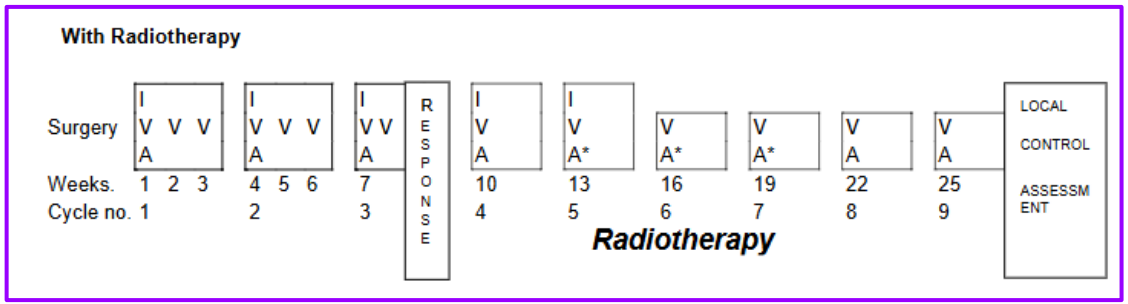
- Comfortable and appropriate immobilisation
- GTV 1 or GTVp_Pre
  - The volume is defined as disease prior to any surgical debulking or chemotherapy
- GTV 2 or GTVp_Post (boost volume)
  - The volume is defined as disease after chemotherapy (this is the cone-down)
- CTV 1 - GTV 1 + 1 cm
- CTV 2 - GTV 2 + 1 cm
- PTV 1 and PTV 2 - Function of immobilisation and site (0.3 cm - 1.0 cm)

Be mindful of soft tissue extensions & post chemotherapy stranding

Rhabdomyosarcoma - Radiation Timing

In pediatric and hematolymphoid malignancies - radiation timing is a function of the mother protocol (W13 IR | W20 for high risk) - COG | SIOP

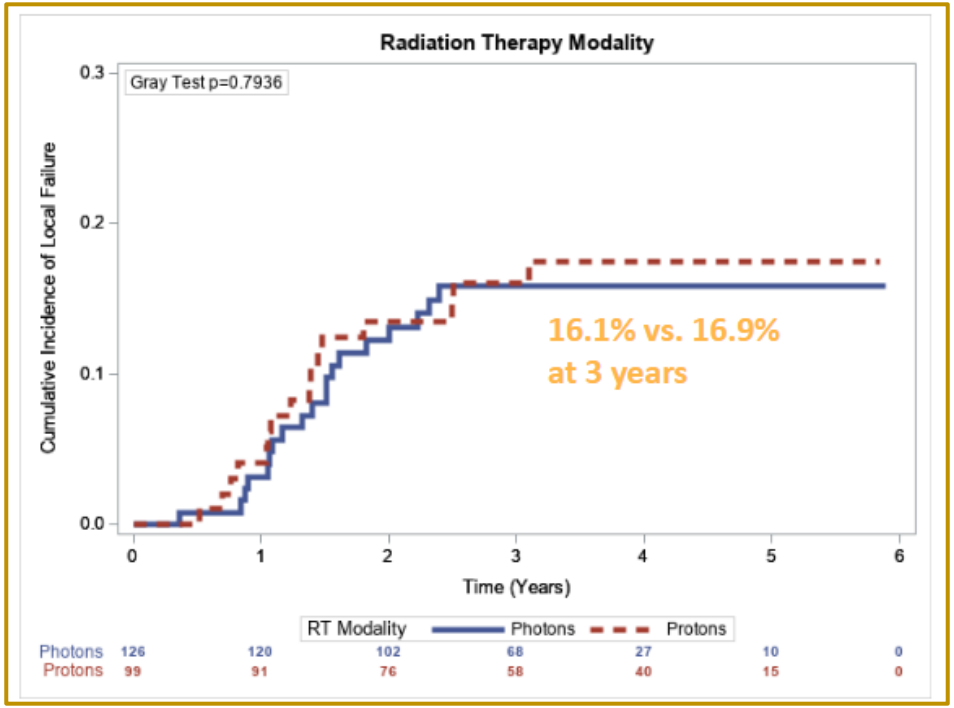




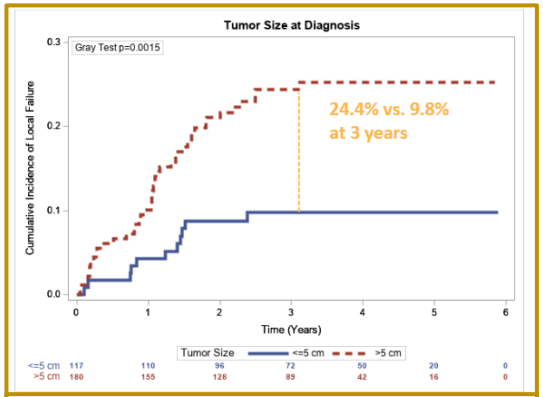
Rhabdomyosarcoma - Radiation Modality

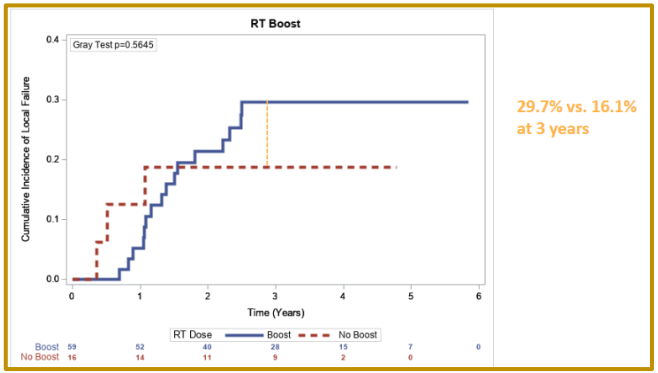
No difference in local failure with proton vs photons

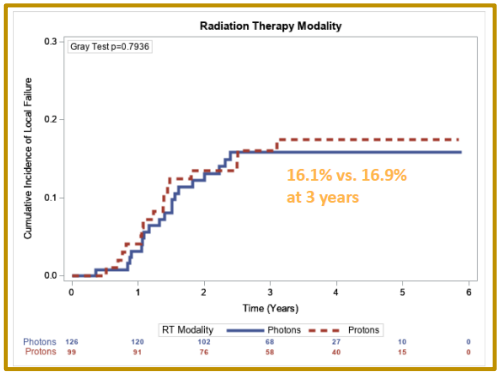
Jackson et al ASCO 2024

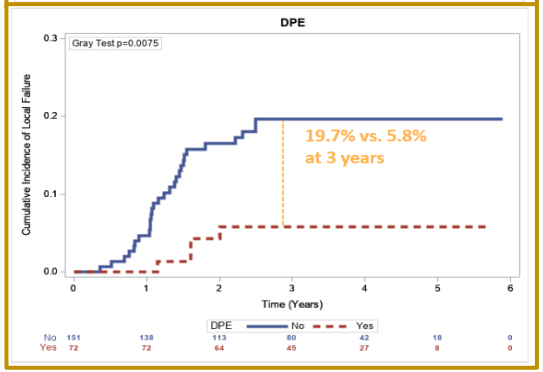


Rhabdomyosarcoma - Local failure take home ARST1431



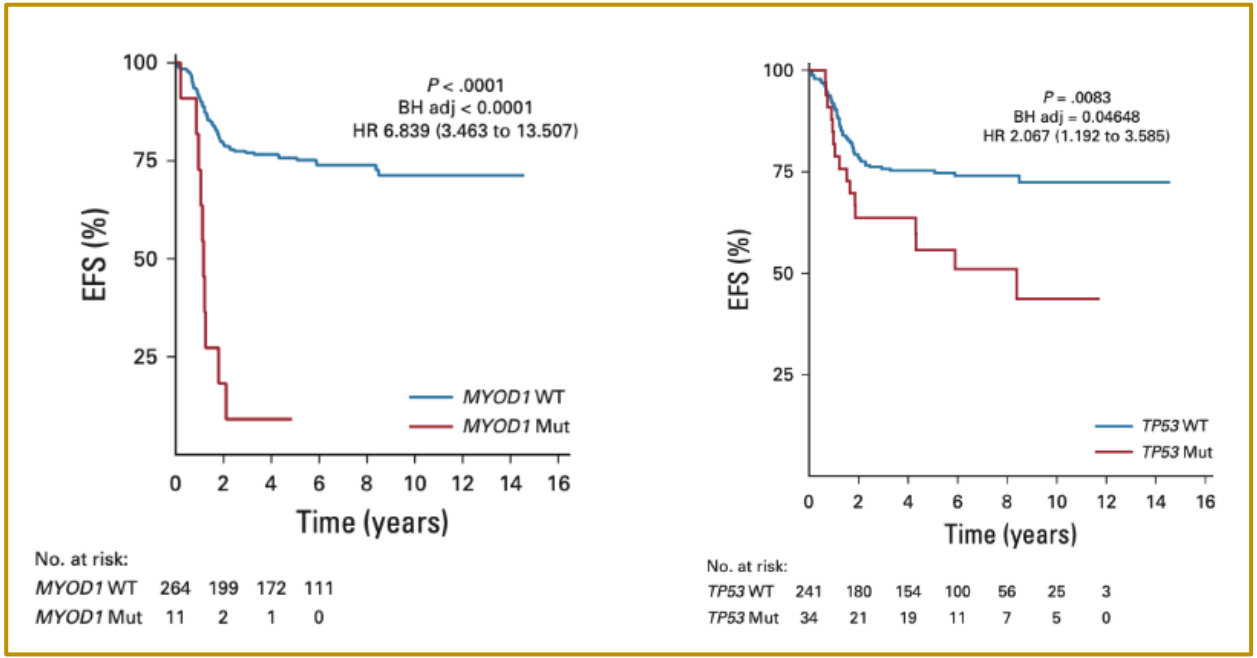




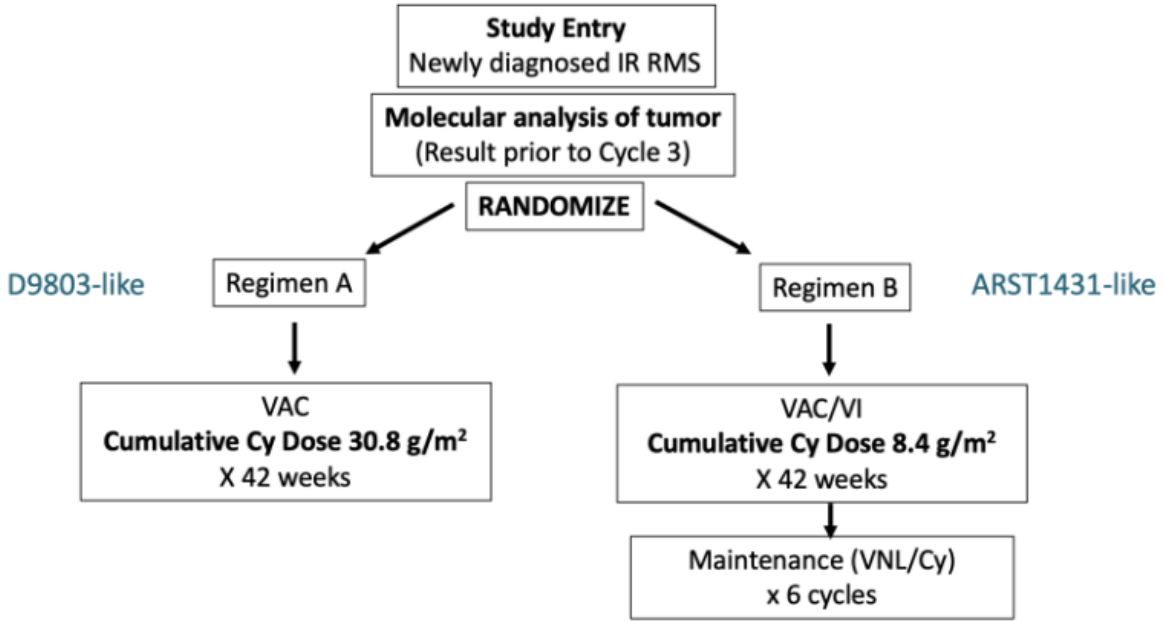


- Modality - no difference
- >5cm at diagnosis again a risk factor
- Radiotherapy dose-escalation to 59.4 Gy did not improve outcomes for patients with large tumours
- For select patients - DPE improved local control

Rhabdomyosarcoma: Molecular adapted?
TP53 and MYOD1 mutations are associated with worse outcomes



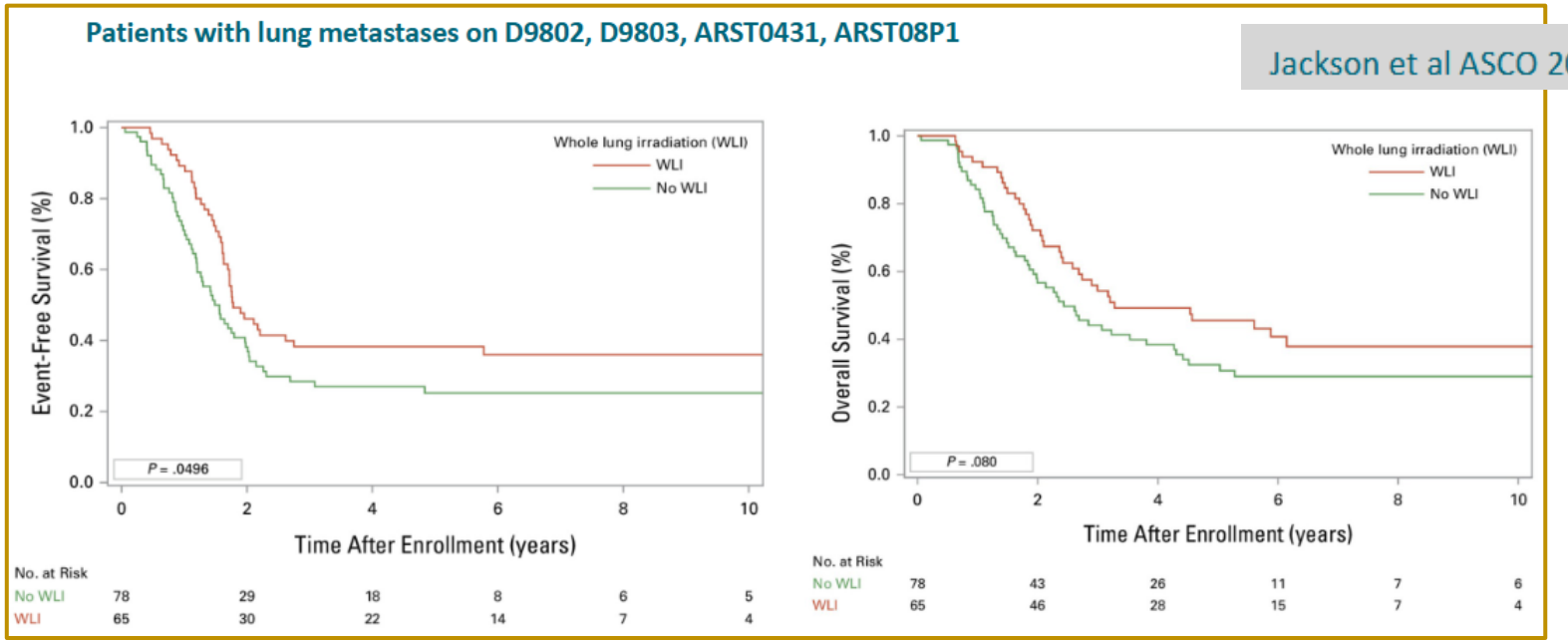
Rhabdomyosarcoma: Molecular adapted?
IR - ARST2531



- Radiation recommendations – stop at 50.4 Gy, no boost to 59.4 Gy for tumors >5cm
- After DPE for fusion negative tumors (node negative), considering omission of radiation (TBD)

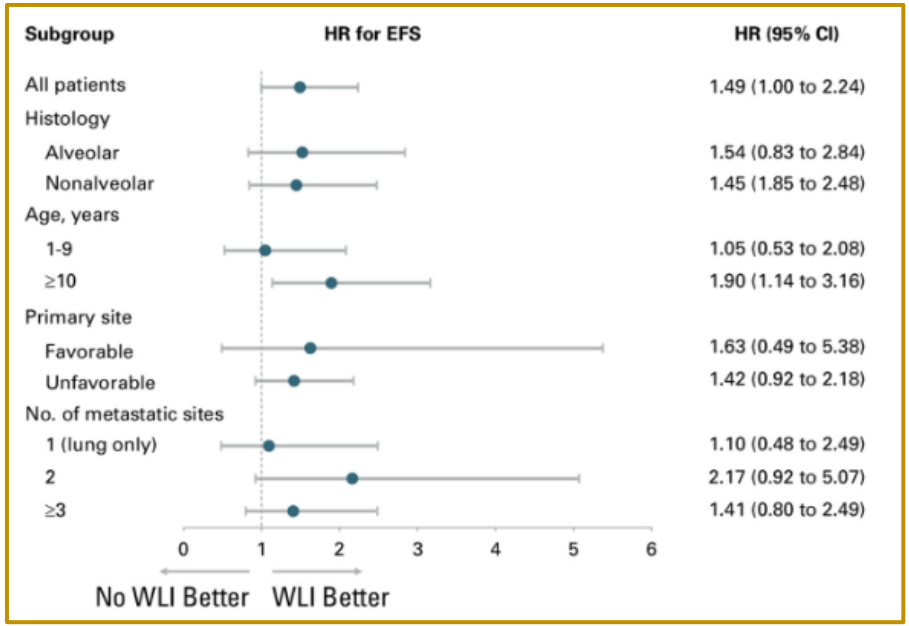
Rhabdomyosarcoma - Management of metastatic sites (Lung as use case)

WLI improves EFS, OS on recent trials



Rhabdomyosarcoma - Management of metastatic sites (Lung as use case)

WLI improves EFS, OS on recent trials - 15 Gy 10 fr 2 weeks



Luo et al JCO 2024

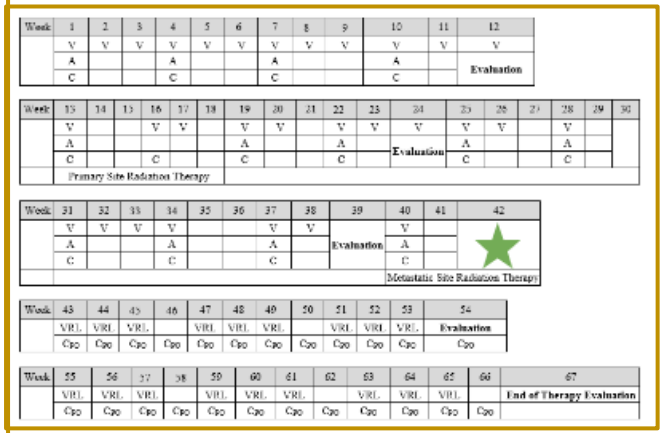
Rhabdomyosarcoma - Management of metastatic sites

Metastatic-directed radiation improves outcomes: summary of studies

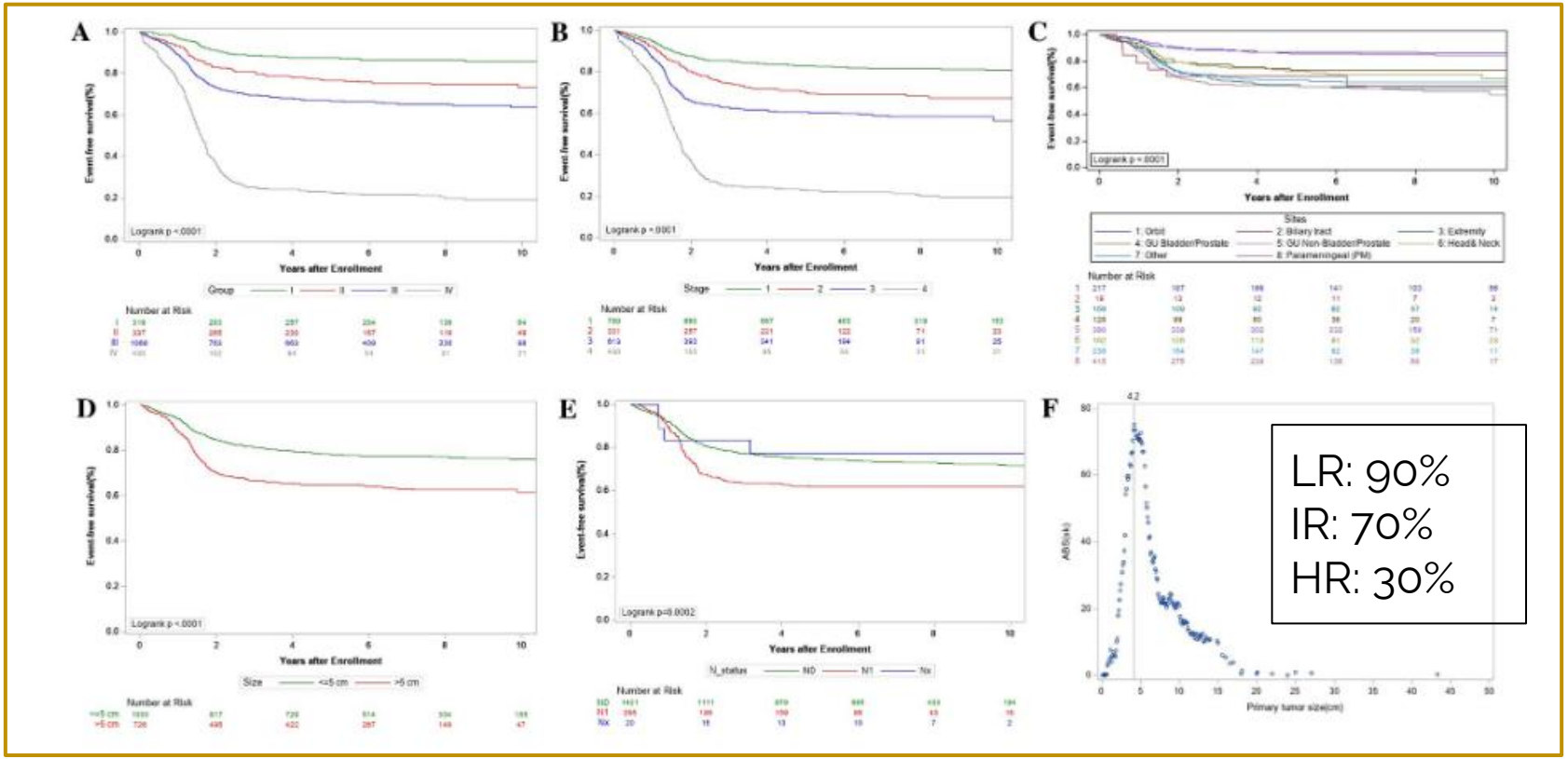
Study	Eligibility	Total No. of Patients	Radical vs. Partial vs. None RT	EFS Outcome	OS Outcome
BERNIE[1]	Age < 18, mRMS	97	28% vs. 47% vs. 25%	3Y: 61% vs. 41% vs. 9% (p=0.016)	3Y: 84% vs. 54% vs. 23% (p=0.00018)
Milan[2]	Age < 21, mRMS	80	21% vs. 49% vs. 4%	5Y: 71% vs. 5% vs. 0% (p<0.001)	5Y: 76% vs. 12% vs. 0% (p<0.001)
Texas Children[3]	Age 1-16, mRMS	35	46% vs. 54% vs. NA	5Y: 31% vs. 0% (p=0.002)	5Y: 37% vs. 0% (p<0.001)
Johns Hopkins[4]	Age < 39, mRMS or mES	34 (85 including ES)	40% vs. 60% vs. NA	3Y: 72% vs. 26% (p=0.002)	3Y: 74% vs. 43% (p=0.016)

Rhabdomyosarcoma - COG ARST2031 (Ongoing high-risk trial) with RT for met sites

- Timing of RT: Week 40, before maintenance
- WLI : for anyone with lung metastases
- Should treat any metastases close to primary during primary site RT
- Definitive RT recommended to all other sites not in CR after consolidation chemotherapy
- SBRT specifically recommended to all metastatic sites ≤5 cm
- SBRT: 30-35 Gy in 5 fractions
- Conventional: 30-45 Gy in 10-15 fractions



Rhabdomyosarcoma - Event Free Survival



Rhabdomyosarcoma - Follow Up

Best strategy for RMS patients' follow up has not been established yet

Long term follow up essential - Site adapted investigations

	1st year	2nd year	3rd year	4th and 5th year
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Every 6 month
Primary tumour site Ultrasound ± CT scan or MRI	Every 3 months	Every 4 months	-*	-*
Lung Chest x ray alternating with CT scan	Every 3 months	Every 4 months	Every 4 months	Every 6 months

Rhabdomyosarcoma - Summary & Future

RMS - most common STS in children & represents a high-grade neoplasm of skeletal myoblast-like cells

Decades of clinical & basic research - optimise care

Two major subtypes - different driver mutations

Risk adapted therapy (TP53 and MYOD1 mutations are associated with worse outcomes)

Local treatments - Always a function of the mother protocol

Late effects of therapy are real

Glimpses from LTFU clinic, TMC, K