Rhabdomyosarcoma
Evolution of management based on Cooperative groups

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Epidemiology

- Most common soft tissue sarcoma in childhood. 350 cases/year in USA
- 4-5% of childhood malignancies
- 5.3/million children <15 years of age
- Peak incidence in early childhood. Median age 5 years.
- Males>females

Aetiology

- Largely unknown

- Genetic predisposition
  - -Li Fraumeni syndrome
  - -Association with congenital anamolies
  - -Other Syndromes:
    - Neurofibromatosis type1
    - Costello Syndrome

Histology

- Arise from primitive mesenchymal cells which are committed to develop into striated muscles

- Two major subtypes
  - Alveolar(15-20%)
  - Embryonal (80-85%)
  - (Pleomorphic<1% in children)

- 1995:Modification
  - Superior:
    - Botyroid/spindle cell/leiomyomatous
  - Intermediate:Embryonal
  - Poor: Alveolar/solid alveolar

Relative incidence of the different tumor sites

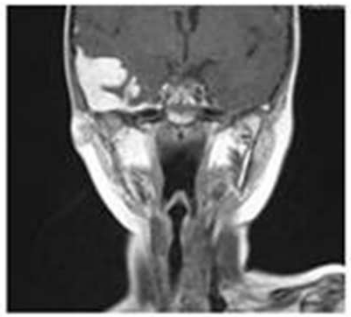
Head-neck region – 40%
- parameningeal region 20%
- orbit 10%
- other 10%

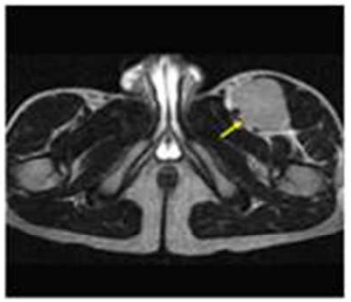
Trunk - 10%

Other - 10%

Genito-urinary region - 20%
- bladder-prostate 12%
- paratesticular 6%
- vagina 2%

Extremity - 20%





Overall survival by site

	5 year OS
Paratesticular - vagina	90-95%
Orbit	85-90%
Bladder Prostate	75-80%
Para Meningeal	70%
Other	60-65%
Extremity	55%

Molecular biology

- Two characteristic chromosomal translocations seen in alveolar subtype

  -t(2;13)(q35:q14) *PAX3-FKHR*

  -t(1:13)(p36;q14) *PAX7-FKHR*

- Embryonal:

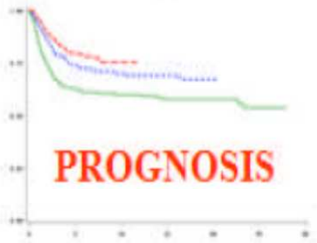
  Loss of heterozygosity 11p15.5

Prognostic factors and risk stratification

Prognostic factors for rhabdomyosarcoma

related to the PATIENT
- age

related to the TUMOR
- histology
- tumor size
- tumor site
- stage



related to the TREATMENT
- modalities used
- response to therapy

Favourable prognostic factors	Unfavourable prognostic factors
embryonal histology	alveolar histology
initial complete resection (IRS group I)	incomplete resection / unresectability (IRS group II-III)
tumor confined to the organ or tissue of origin (T1)	local invasiveness (T2)
small tumor size (<5 cm)	large size (>5 cm)
no regional lymph node involvement (N0)	nodal involvement (N1)
localized disease (M0)	distant metastases at diagnosis (M1 – IRS group IV)
age between 1 and 10 years	age over 10 years - age less than 1 years
favourable sites:	unfavourable sites:
non-parameningeal head-neck (orbital)	parameningeal region
non-bladder/prostate genito-urinary (paratesticular, vagina)	bladder and prostate, abdomen
	trunk
	extremities

European SSG Staging Systems

RISK GROUP	HIST	IRS	N	SITE	SIZE & AGE	%	EFS-OS
A	fav	I	N0	any	fav	6%	90-95%
B	fav	I	N0	any	unfav	6%	78% - 90%
C	fav	II-III	N0	fav	any	18%	72% - 88%
D	fav	II-III	N0	unfav	fav	9%	80% - 85%
E	fav	II-III	N0	unfav	unfav	27%	55% - 60%
F	fav	II-III	N1	any	any	8%	50% - 60%
G	unfav	I-II-III	N0	any	any	20%	50% - 60%
H	unfav	I-II-III	N0	any	any	6%	40% - 50%

IRS staging

IRS staging system		
	group I	completely-excised tumors with negative microscopic margins
	group II	grossly-resected tumors with microscopic residual disease and/or regional lymph nodal spread
	group III	gross residual disease after incomplete resection or biopsy
	group IV	metastases at onset

IRS V stratification

Stratification and treatment in the IRS-V study

[modified by Raney RB, et al. J. Pediatr. Hematol. Oncol. 23(4),215-220 (2001)]

Risk	Stage	Group	Site	Size	Age	Histology	M	N
Low - A	1	I	favorable	any	any	embryonal	0	N0
	1	II	favorable	any	any	embryonal	0	N0
	1	III	orbit only	any	any	embryonal	0	N0
	2	I	unfavorable	≤5cm	any	embryonal	0	N0 – NX
Low - B	1	II	favorable	any	any	embryonal	0	N1
	1	III	orbit only	any	any	embryonal	0	N1
	1	III	fav. (excl. orbit)	any	any	embryonal	0	any
	2	II	unfavorable	≤5cm	any	embryonal	0	N0 – NX
	3	I-II	unfavorable	≤5cm	any	embryonal	0	N1
	3	I-II	unfavorable	>5cm	any	embryonal	0	any
Intermediate	2	III	unfavorable	≤5cm	any	embryonal	0	N0 – NX
	3	III	unfavorable	≤5cm	any	embryonal	0	N1
	3	III	unfavorable	>5cm	any	embryonal	0	any
	1-2-3	I-II-III	any	any	any	alveolar	0	any
	4	IV	any	any	<10yrs	embryonal	M1	any
High	4	IV	any	any	≥10yrs	embryonal	M1	any
	4	IV	any	any	any	alveolar	M1	any

Evolution of treatment

- All RMS are presumed to be micrometastatic
- Multimodality therapy/Multidisciplinary
- Optimal use of these modalities must be planned
  - -prognostic factors
  - -late effects of treatment
- All patients require chemotherapy
- Local control is necessary
  - -conservative approach taking into account response to chemotherapy

Chemotherapy

- Most successful regimens

VAC	Vincristine, actinomycin,cyclophosphamide
VACA	Vincristine, actinomycin, cyclophosphamide, doxorubicin
IVA	Ifosfamide,Vincristine, actinomycin
VAIA	Vincristine, actinomycin, cyclophosphamide, doxorubicin

Cooperative groups

		5yr EFS	5yr OS
Italian Cooperative Group - Associazione Italiana Ematologia Oncologia Pediatrica (ICG-AIEOP)			
	RMS79	55%	62%
	RMS88	63%	72%
	RMS96	67%	81%
International Society of Pediatric Oncology Malignant Mesenchymal Tumour Committee (SIOP-MMT)			
	MMT84	52%	72%
	MMT98	57%	71%
German Soft Tissue Sarcoma Cooperative Group (Co-operative Weichteilsarkomen Studie – CWS)			
	CSW81	70%	71%
	CWS86	79%	84%
	CWS95	67%	81%
Intergroup Rhabdomyosarcoma Study (IRS)			
	IRS I (1972-1978)	-	55%
	IRS II (1978-1984)	55%	63%
	IRS III (1984-1990)	65%	71%
	IRS IV (1991-1997)	78%	84%

SIOP MMT studies

- Philosophy:
  - -More intensive primary chemotherapy
  - -To reduce intensity of local therapy

SIOP 75:

- 1975-1984
- VAC pre-surgery Vs VAC post surgery
- No difference in overall survival(52%)
- Less aggressive local therapy in patients who received pre-surgery chemotherapy.

MMT 84 study

- Aim to avoid aggressive local therapy

  -use only conservative surgery and chemotherapy
- Intensive chemotherapy: IVA
- 48% went into CR with chemotherapy alone
- RT given to only to patients in

  -partial remission,

  -parameningeal

  -age >12 years
- High CR rate (91%) OS:68% EFS:53%
- Only 34% needed intensive local therapy

MMT 89 study

- Overall objective: Continue to reduce systematic use of local therapy

- Std/High risk:
  - Modify therapy for poor responders
  - Explore role of increased Ifosfamide
  - 6 drugs for high risk/parameningeal RMS
  - RT: Children>Parameningeal disease
    - No CR with surgery/chemo

MMT 89 Study

- Very good prognosis:
  - -completely resected at favourable sites.
  - -Avoid Alkylating agents
- Good prognosis tumours: decrease therapy

MMT 89 study results

- Overall survival was 71%, EFS 57%
  -No better than MMT84

- However
  -Local therapy ‘limited’ in 49% of survivors
  -6 drugs better in Stage 3 disease
  (60% OS Vs 42% in MMT84)
  -Pt1/Low risk disease- 2 drugs
  Vcr/Act D were sufficient
  EFS: 67% Vs 85%

MMT studies-Local control issues

- Higher local relapse rate *'expected'* when local therapy is restricted.

  However can they be salvaged subsequently?

- Worked well for orbital/bladder-prostate tumours and not for the rest

- Mature data showed that modification was necessary

  -Age >3 year with alveolar

  -non-parameningeal head and neck

  -limb primary(>10 years)

SIOP MMT studies summary

- IVA is the best standard and high risk regimen.
- Withholding systematic-local therapy RT has been beneficial to certain subsets of patients
- Some clearly need aggressive local therapy

GPOH-CWS (German)

- CWS 4 studies
  - CWS-81 (1981-1986)
  - CWS-86 (1986-1990)
  - CWS-91 (1991-1996)
  - CWS-96 (1996-2002)

Chemotherapy CWS Study

- CWS 81:4 drugs VACA

- CWS 86: VAIA-response rate better
  No improvement in survival outcomes

- CWS 91: VACA back for good prognosis
  EVAIA for poor prognostic group

  -No benefit of adding VP16
  -Intensification did not reduce RT
  (CWS 81-77%, 86-79%, 91-85%)

Local therapy CWS studies

- CWS-81 RT given to micro/macroscopic residual disease

- CWS-86:

  RT given prior to surgery and concurrently with chemotherapy.

  Degree of size reduction determined the dose

  Accelerated hyperfractionated RT

Local therapy CWS studies

- CWS-91

  -RT stratified according T stage, response to chemo and results of second look surgery.

  -Accelerated hyperfractionated RT

- Outcome much better in 86 and 91 (69% vs 67% Vs 41%)

Conclusions of CWS studies

- Tumour size and volume reduction with pre-op chemotherapy are prognostic value.
- Early hyperfractionated RT given simultaneously to pre-op chemo has better outcome. 32Gy is adequate
- Whether this applies to all histological types??

AIEOP/Italian studies

- RMS 79 and 88
- RMS 79: VAC/CAV 11 courses Grp 1
  12 courses Grp 2 + RT
  18 courses for alveolar/Limb

- RMS 88: VA for low risk IRS1
  Increased Vincristine for II and III,
  Ifosfamide rather than CPM (II & III)
  RT was hyper fractionated

Outcome-AIEOP studies

- Outcome RMS 79: 64%(OS) and 53%(EFS)
- RMS 88: 82% (I), 72%(II) , 59%(III)
- Improved outcomes

Embryonal
parameningeal
Large primary,
node negative

Conclusion:

Low risk no need for anthracyclines/Alkylating agents

Intensification improved outcomes in high risk.

Present European strategy

EpSSG RMS 2005

RISK GROUP	HIST	IRS	N	SITE	SIZE & AGE	%	EFS-OS
A	fav	I	N0	any	fav	6%	90-95%
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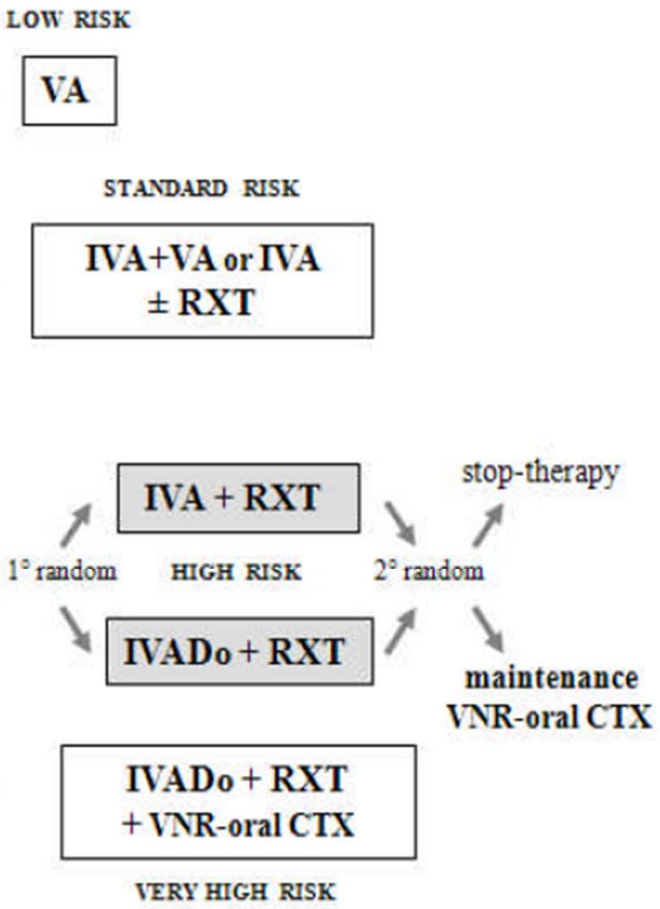

Intergroup Rhabdomyosarcoma study group (USA)

IRS 1	1972-1978
IRS 2	1978-1984
IRS 3	1984-1991
IRS 4	1991-1997
IRS 5	1997-

IRS studies surgical-pathological staging

Table 1. *IRSG surgical–pathologic grouping system*

Group	Definition
I	Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement
II	Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both
III	Localized tumor, with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

IRSG staging system

Table 2. *IRSG staging system*

Stage	Sites of primary tumor	Tumor size (cm)	Regional lymph nodes	Distant metastases
1	Orbit, non-PM head/neck; GU non-bladder/prostate; biliary tract	Any size	N0, N1	M0
2	All other sites	≤5	N0	M0
3	All other sites	≤5	N1	M0
		>5	N0 or N1	
4	Any site	Any size	N0 or N1	M1

PM, Parameningeal; GU, genito-urinary; N0, regional nodes not clinically involved by tumor; N1, regional nodes clinically involved by tumor; M0, no distant metastases; M1, distant metastases at diagnosis.

Major conclusions from IRS studies

IRS I-IRS IV studies

- Surgical
- Radiotherapy
- Chemotherapy
- pathobiology

Surgery

- Localised completely resected-good prognosis
- Wide re-excision only if cosmetically/functionally-good outcome
- Orbit/Vagina/Bladder-favourable sites

  Extensive surgery not required

  Chemotherapy/RT
- Paratesticlar RMS-Age is an important factor for lymph nodal spread

Radiotherapy

- No RT for Group I Embryonal RMS
- Graded doses for other groups
- Group IV; RT to both primary and metastatic areas
- Local failure rates improved with RT in head/neck, genitourinary sites
- Hyperfractionated RT: No benefit in group III
- Whole Brain RT/intrathecal chemotherapy not required in parmeningeal tumours

Chemotherapy

- No benefit of adding doxorubicin in Group III/IV
- No benefit of adding Etoposide/Cisplatin
- VAC as good as VAI or VIE
- Higher dose cyclophosphamide 2.2 gm/sq.m has better outcome in ERMS
- Topotecan has good activity in advanced RMS

Present IRS V strategy

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	4	IV	any	any	<10yrs	embryonal	M1	any
High	4	IV	any	any	≥10yrs	embryonal	M1	any
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VA ±RXT

VAC ±RXT

VAC ±TOPO +RXT

CPT-11 +VAC +RXT

Other treatment strategies

- Role of Topotecan/irinotecan
- Role of Melphalan/Platinum agents
- High dose chemotherapy
- Role of maintenance therapy
- Targeted therapies

Conclusions

- Treatment of RMS in children undergoing continuous evolution and being constantly adapted
- More accurate prognostic assessment needed
- Need better selection of good prognostic group to avoid late effects
- VAC and IVA are equally effective regimens

Conclusions

- Local therapy; fundamental aspect

  Balance risk of relapse with long term sequelae
- Surgery: more conservative now
- 30% can be cured without RT-but identification of this group is not easy
- International collaborative studies