Rhabdomyosarcoma
Evolution of management based on Cooperative groups

Girish Chinnaswamy
Paediatric oncology
CMC Vellore
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 anomalies
  - Other Syndromes:
    - Neurofibromatosis type 1
    - 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:
    - Botryoid/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:

- Paratesticular - vagina: 90-95%
- Orbit: 85-90%
- Bladder-Prostate: 75-80%
- Para Meningeal: 60-65%
- Other: 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 TUMOR
  - histology
  - tumor size
  - tumor site
  - stage

related to the PATIENT
  - age

related to the TREATMENT
  - modalities used
  - response to therapy

Favourable prognostic factors
- embryonal histology
- initial complete resection (IRS group I)
- tumor confined to the organ or tissue of origin (T1)
- small tumor size (<5 cm)
- no regional lymph node involvement (N0)
- localized disease (M0)
- age between 1 and 10 years
- favourable sites:
  - non-parameningeal head-neck
  - (orbital)
  - non-bladder/prostate genito-urinary
  - (paratesticular, vagina)

Unfavourable prognostic factors
- alveolar histology
- incomplete resection / unresectability (IRS group II-III)
- local invasiveness (T2)
- large size (>5 cm)
- nodal involvement (N1)
- distant metastases at diagnosis (M1 – IRS group IV)
- age over 10 years - age less than 1 years
- unfavourable sites:
  - parameningeal region
  - bladder and prostate, abdomen
  - trunk
  - extremities
## European SSG Staging Systems

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>HIST</th>
<th>IRS</th>
<th>N</th>
<th>SITE</th>
<th>SIZE &amp; AGE</th>
<th>%</th>
<th>EFS-OS</th>
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<tbody>
<tr>
<td>A</td>
<td>fav</td>
<td>I</td>
<td>N0</td>
<td>any</td>
<td>fav</td>
<td>6%</td>
<td>90-95%</td>
</tr>
<tr>
<td>B</td>
<td>fav</td>
<td>I</td>
<td>N0</td>
<td>any</td>
<td>unfav</td>
<td>6%</td>
<td>78% - 90%</td>
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<tr>
<td>C</td>
<td>fav</td>
<td>II-III</td>
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<td>18%</td>
<td>72% - 88%</td>
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<td>80% - 85%</td>
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<td>fav</td>
<td>II-III</td>
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<td>50% - 60%</td>
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<td>20%</td>
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<td>40% - 50%</td>
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## IRS staging

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<th>IRS staging system</th>
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<tbody>
<tr>
<td>group I</td>
<td>completely-excised tumors with negative microscopic margins</td>
</tr>
<tr>
<td>group II</td>
<td>grossly-resected tumors with microscopic residual disease and/or regional lymph nodal spread</td>
</tr>
<tr>
<td>group III</td>
<td>gross residual disease after incomplete resection or biopsy</td>
</tr>
<tr>
<td>group IV</td>
<td>metastases at onset</td>
</tr>
<tr>
<td>Risk</td>
<td>Stage</td>
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<td>-----------</td>
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<td>Low - A</td>
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<tr>
<td>High</td>
<td>4</td>
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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**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Components</th>
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<tr>
<td>VAC</td>
<td>Vincristine, actinomycin, cyclophosphamide</td>
</tr>
<tr>
<td>VACA</td>
<td>Vincristine, actinomycin, cyclophosphamide, doxorubicin</td>
</tr>
<tr>
<td>IVA</td>
<td>Ifosfamide, Vincristine, actinomycin</td>
</tr>
<tr>
<td>VAIA</td>
<td>Vincristine, actinomycin, cyclophosphamide, doxorubicin</td>
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Cooperative groups

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

<table>
<thead>
<tr>
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<th>IRS</th>
<th>N</th>
<th>SITE &amp; AGE</th>
<th>%</th>
<th>EFS-OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>fav</td>
<td>I</td>
<td>N0</td>
<td>any fav</td>
<td>6%</td>
<td>90-95%</td>
</tr>
<tr>
<td>B</td>
<td>fav</td>
<td>I</td>
<td>N0</td>
<td>any unfav</td>
<td>6%</td>
<td>78% - 90%</td>
</tr>
<tr>
<td>C</td>
<td>fav</td>
<td>II-III</td>
<td>N0</td>
<td>fav any</td>
<td>18%</td>
<td>72% - 88%</td>
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<tr>
<td>D</td>
<td>fav</td>
<td>II-III</td>
<td>N0</td>
<td>unfav fav</td>
<td>9%</td>
<td>80% - 85%</td>
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<tr>
<td>E</td>
<td>fav</td>
<td>II-III</td>
<td>N0</td>
<td>unfav unfav unfav</td>
<td>27%</td>
<td>55% - 60%</td>
</tr>
<tr>
<td>F</td>
<td>fav</td>
<td>II-III</td>
<td>N1</td>
<td>any any</td>
<td>8%</td>
<td>50% - 60%</td>
</tr>
<tr>
<td>G</td>
<td>unfav</td>
<td>I-II-III</td>
<td>N0</td>
<td>any any</td>
<td>20%</td>
<td>50% - 60%</td>
</tr>
<tr>
<td>H</td>
<td>unfav</td>
<td>I-II-III</td>
<td>N0</td>
<td>any any</td>
<td>6%</td>
<td>40% - 50%</td>
</tr>
</tbody>
</table>

LOW RISK
- VA

STANDARD RISK
- IVA+VA or IVA ± RXT

HIGH RISK
- IVA + RXT
- IVADO + RXT

VERY HIGH RISK
- stop-therapy
- maintenance VNR-oral CTX

1° random
2° random
# Intergroup Rhabdomyosarcoma study group (USA)

<table>
<thead>
<tr>
<th>IRS 1</th>
<th>1972-1978</th>
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<tr>
<td>IRS 2</td>
<td>1978-1984</td>
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<tr>
<td>IRS 3</td>
<td>1984-1991</td>
</tr>
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<td>IRS 4</td>
<td>1991-1997</td>
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<tr>
<td>IRS 5</td>
<td>1997-</td>
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IRS studies surgical-pathological staging

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement</td>
</tr>
<tr>
<td>II</td>
<td>Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both</td>
</tr>
<tr>
<td>III</td>
<td>Localized tumor, with gross residual disease after grossly incomplete removal, or biopsy only</td>
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<tr>
<td>IV</td>
<td>Distant metastases present at diagnosis</td>
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### Table 2. IRSG staging system

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

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
- Paratesticular 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

### Stratification and treatment in the IRS-V study

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