Comparison of Rhabdomyosarcoma treatment protocols
C O G vs SpSSG

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- The guideline was developed as a joint project by the European pediatric Soft tissue sarcoma Study Group (EpSSG) & the Cooperative Weichteilsarkom Studiengruppe (CWS) summarized as the European RMS working group supported by European Reference Network on Pediatric Cancer (ERN PaedCan).

The Children's Oncology Group (COG) a member of the National Cancer Institute (NCI) National Clinical Trials Network experts in childhood cancer at more than 220 leading children's hospitals, universities, & cancer centers across the United States, Canada, Australia, New Zealand, & Saudi Arabia in the fight against childhood cancer.

The North American approach to treatment has been defined by Intergroup Rhabdomyosarcoma Study Group (IRS) I-IV.

- Both the Children's Oncology Group (COG) & the European paediatric Soft tissue sarcoma Study Group (EpSSG) utilize chemotherapy regimens, but they differ in their approach to **risk stratification** and **treatment protocols.**

✓ COG relies on a risk stratification system based on **clinical** and **pathological features**, while

✓ EpSSG uses a **similar system with some key differences**.

- Both groups have shown **success in improving survival rates** for children with rhabdomyosarcoma, but the **optimal approach for certain subgroups may vary.**
- The choice of treatment strategy is individualized based on risk stratification & other factors.

- A pediatric or adolescent patient with progressive or persistent unclear symptoms possibly suggesting a soft tissue sarcoma should undergo prompt radiological assessment.

- The pre-treatment work-up should be **completed within 2–3 weeks** after diagnosis & prior to the start of treatment.

- If a delay occurs, **restaging** should be considered.

- **Basic laboratory workup** & **organ function evaluation tests** are recommended as baseline assessments.

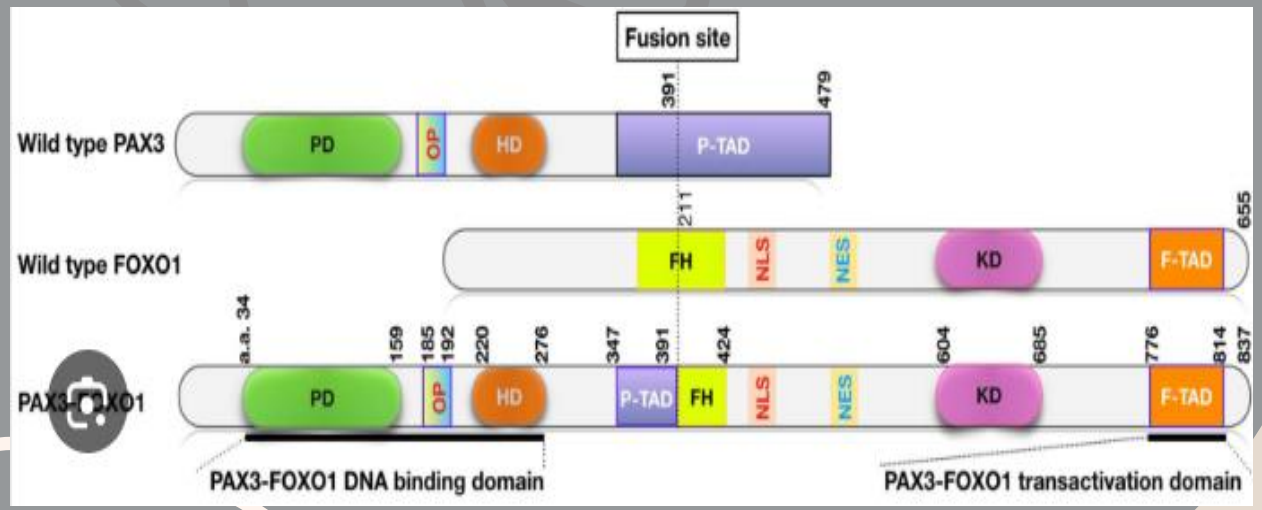
STAGING

- **Ultrasound** ; first radiological investigation, for a first evaluation of lymph nodes.
- **MRI ;**
  - local extent of the tumor,
  - surrounding anatomical structures
  - Loco regional lymph nodes
  - Metastases within the field of view
- **CT;**
  - Primary tumor in RMS is limited to assessing bone destruction with head & neck primaries,
  - Chest-CT is standard of care for evaluation of pulmonary metastases.

- **Metastatic pulmonary :**
  - one or more nodules of 10 mm or more
  - two or more nodules of 5–10 mm
  - 5 or more nodules smaller than 5 mm

❖Patients with **indeterminate lesions**, defined as the presence of no more than four pulmonary nodules of less than 5 mm or one nodule measuring between 5 and less than 10 mm, should be treated as **localized disease** reserving **biopsy only for highly suspicious cases**

- **18F-FDG-PET/CT or -MRI ;**
  - for evaluation of **lymph node involvement, skeletal** or other **non-pulmonary metastatic** lesions & is considered standard of care
  - **Superior to bone scintigraphy**

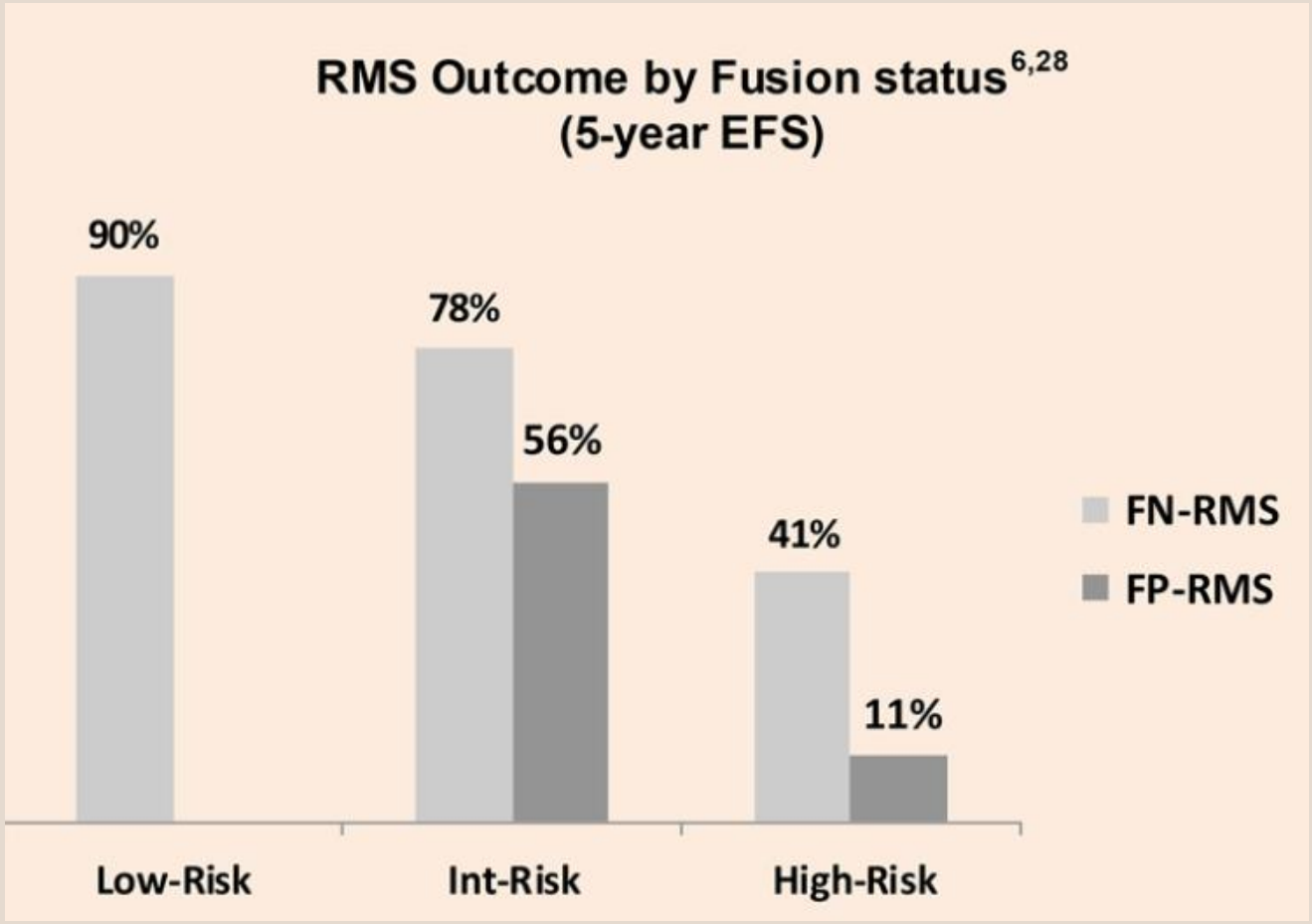


- Approximately 75% of tumors with histologic features of ARMS demonstrate recurrent t(2;13) or t(1;13) translocations, resulting in fusion of the DNA binding domain of PAX3 (2q36.1) or PAX7 (1p36) with the carboxyl terminus of FOXO1 (13q14).

ARMS lacking FOXO1 translocation has a gene expression signature and **clinical behavior** more similar to ERMS

More than 95% of tumors that are morphologically ERMS have no FOXO1 fusion

Presence or absence of the FOXO1 fusion gene drives the clinical behavior of RMS.


RMS Outcome by Fusion status[6,28]
(5-year EFS)
90%
78%
56%
41%
11%
FN-RMS
FP-RMS
Low-Risk
Int-Risk
High-Risk

APPROACH TO TREATMENT

COG:

Outcomes are clearly dependent on **stage** & **risk grouping**

- **Stage** is defined by site & TNM status
- **Clinical group** is determined by the initial surgical procedure.
- **Fusion status** are distilled into low-, intermediate-, high-risk prognostic

- ***Clinical group is important for radiation***

- **EpSSG ;**
- 4 risk groupings: low, standard, high, very high risk.

- Postsurgical stage (I, II, or III)
- Age (< 10 years or ≥ 10 years)
- Tumor size (diameter≤ 5 cm or > 5 cm)
- Histopathological subtype (embryonal or alveolar)
- Site of the primary tumor (favorable or unfavorable)
- Nodal stage (N0 or N1)

- Fusion-positive patients with nodal involvement will be merged with metastatic patients to create a new very high risk

COG Risk Stratification

Stage

Group

I Gross resection, negative mar

II Gross resection, microscopic p
without regional nodal spread

III Biopsy only or gross residual d

IV Distant metastases present (in
pleural/peritoneal effusion, tumor in
involvement)

Stage

1 Favorable site

2 Unfavorable site, < 5 cm (OR
prostate), no evidence of noda

3 Unfavorable site, > 5 cm (OR
involvement)

4 Metastatic disease

Site

Favorable

- Orbit
- Head and neck (not parameningeal)
- Genitourinary (not bladder/prostate)
- Biliary tract/liver

Unfavorable

- Parameningeal
- Extremity
- Bladder/prostate
- Not otherwise specified

Risk Stratification

Low (FN only)	Group I, Stage 1, 2 Group II, Stage 1, 2 Group III, Stage 1 orbit
Intermediate (any)	Group I/II/III FP-RMS any stage Group I/II, Stage 3 FN-RMS Group III any stage FN-RMS (except for orbit) Group IV, Stage 4 FN-RMS age <10 yo
High (any)	Group IV, Stage 4 FN-RMS age > 10 yo Group IV, Stage 4 FP-RMS

FN: Fusion negative
FP: Fusion positive

EpSSG RMS 2005 risk stratification

Risk stratification.

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

ROLE OF SURGERY

- **COG;**
- Initial surgery is dependent on presentation.
- Minority of children with tumors that appear operable with organ preservation, surgery is the initial therapeutic approach

- Most patients, surgery is primarily diagnostic & important for staging of lymph nodes, particularly in patients with tumors of paratesticular & extremity origin, & potentially for any fusion-positive tumor

- Delayed primary excision (DPE) performed after initial chemotherapy does not obviate the need for RT, though in select cases it may allow for a lower dose of RT.

ROLE OF SURGERY

- **The European/EpSSG ;**
- Surgery is essential to establish the diagnosis of RMS at presentation.
- Incisional or core biopsy
- Clinically or Radiologically suspicious lymph nodes
- Surgical resection is a key pillar of local therapy for RMS

- Residual mass can be completely excised (R0/R1 resection) without causing a significant organ or functional impairment.
  - R0 resection , mean avoidance of RT,
  - lower dose of RT to be used.

ROLE OF CHEMOTHERAPY

❑ The European approach to chemotherapy;

a. Multimodality approach involving **chemotherapy** , **surgery** and/or **RT**

b. **Different chemotherapy regimens** & specific guidelines for the application of RT, has been shown efficacious in several clinical trials.

c. **Local control** should be achieved through surgery and/or RT, with a conservative approach recommended, to avoid functional impairment.

d. **Neoadjuvant CHT** to reduce tumor volume is highly recommended in IRS group II/III & IV

Systemic treatment

❖ **Low Risk RMS;**

(LR; Subgroup A*): FN-IRS Group 1-N0 -favorable –Size<5 cm –age <10 yr.*

- VA (**V**CR 1.5 mg/m2, **A**ctinomycin-D 1.5 mg/m2; 3 weekly, with additional weekly VCR –Q 3 weekly cycle for 22weeks

- 8 courses of VA in total.

	V	V	V	V			V	V	V	V			V	V	V	V			V	V	V	V
	A			A			A			A			A			A			A			A
Weeks	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*
Cycle no.	1			2			3			4			5			6			7			8

❖Standard Risk RMS (Subgroups B, C):

- The standard regimen in Europe is IVA (Ifosfamide 6 g/m2, Vincristine 1.5 mg/m2, Actinomycin- D 1.5 mg/m2; 3 weekly; **24 weeks**).

- In Standard Risk patients the use of a **limited cumulative dose of alkylating agents** is possible, therefore a combination of IVA & VA cycles is employed

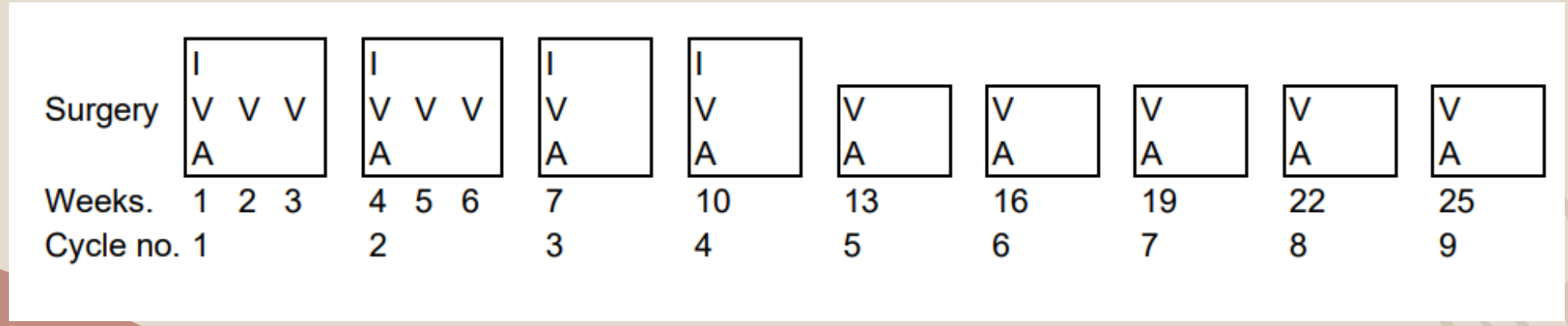
- Number of cycles containing ifosfamide depends on the **risk subgroup** & **local therapy** applied.

❖**Standard Risk RMS (Subgroups B, C):**

- According to subgroups, the following regimen will be administered:

❑Subgroup B , ***FN-IRS Group 1-N0 –site any –Size & age one or both unfavorable***

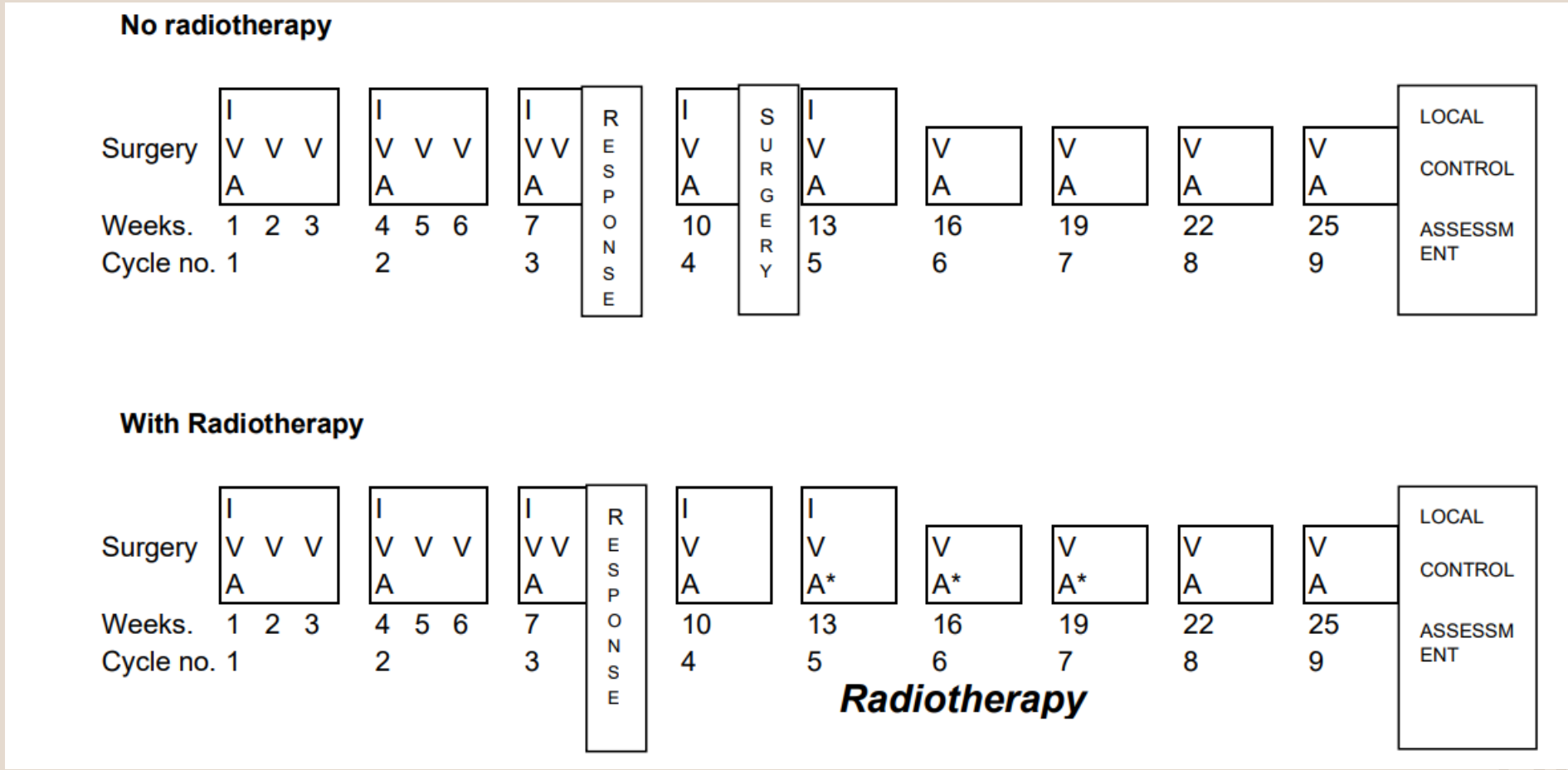
- **4 courses of IVA** followed by **5 courses of VA**



- Subgroup C, ***FN-IRS Group 2,3-N0 – site favorable –Size & age any***
  -
  - 5 courses of IVA & 4 courses of VA when combined with or without RT

- ***All bladder- prostate subgroup C patients, should receive IVA courses, irrespective of receiving RT.***

❖Standard Risk RMS (Subgroups C):



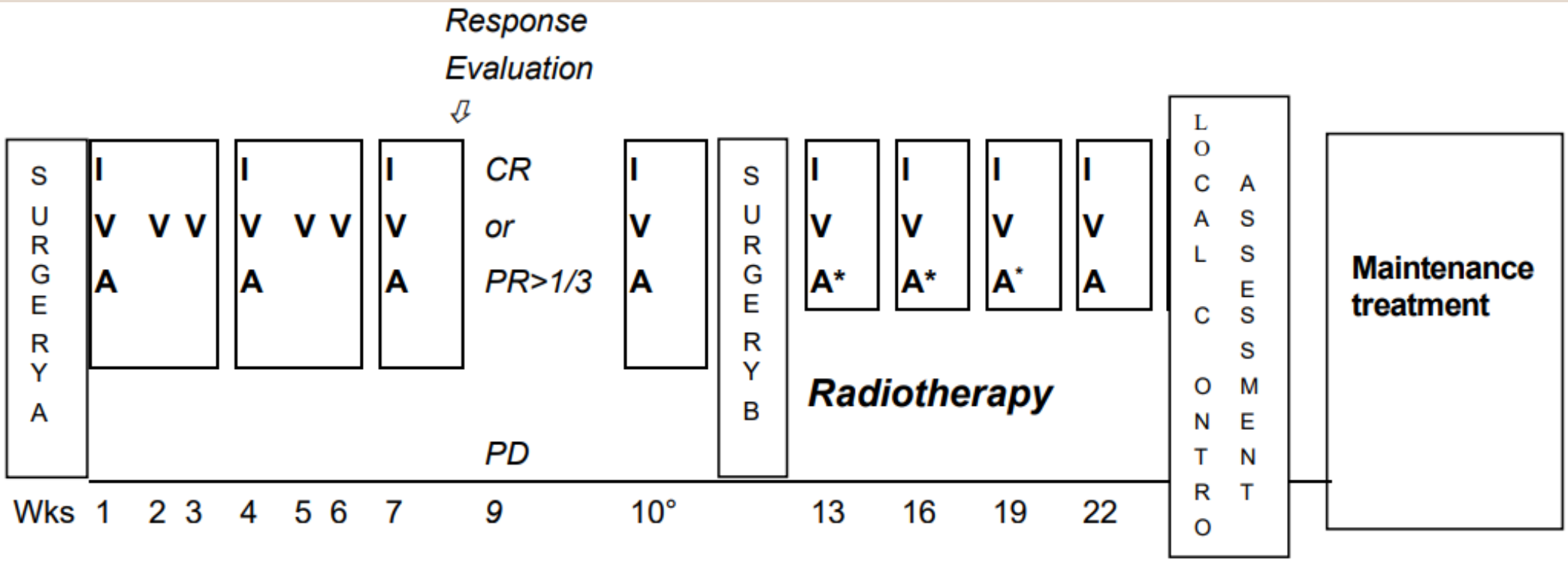
❖ **High Risk RMS ((HR); (**Subgroups D/E/F):

- Doxorubicin has shown no benefit & the current standard in Europe is IVA chemotherapy
  - Subgroup D , ***FN-IRS Group 2,3-N0 –site Unfavourable –Size & age any***
  - Subgroup E , ***FN-IRS Group 2,3-N1–site any –Size & age any***
  - Subgroup F, ***FP-IRS Group 1,2,3 -N0 –site any –Size & age anyunfavorable***

❑ In the subgroups D/E/F , **9 courses of IVA** (*Ifosfamide 6 g/m², Vincristine 1.5 mg/m², Actinomycin-D 1.5 mg/m²; 3 weekly;* ***25 weeks)***

❑ plus **24 weeks** maintenance treatment *(6 cycles of vinorelbine 25 mg/m² on days 1, 8, 15, and daily oral cyclophosphamide 25 mg/m², on days 1–28)* will be administered.

Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
High Risk	*D*	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any

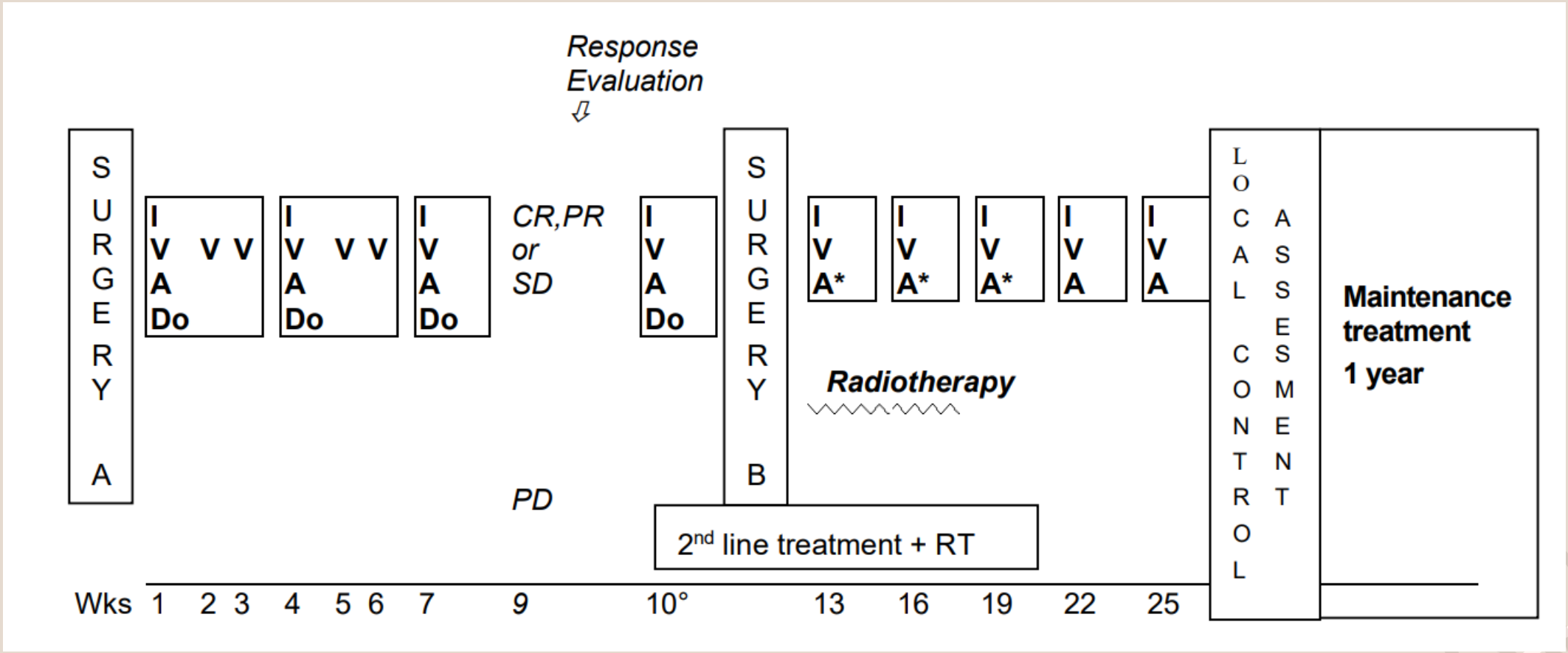


❖**Very High-Risk RMS**,

- *including fusion positive, node positive &metastatic disease (VHR)*
- Subgroups G, H: Intensive chemotherapy including;
  - IVADo (Ifosfamide, Vincristine, Actinomycin, Doxorubicin)
  - CEVAIE (Carboplatin, Epirubicin, Vincristine, Ifosfamide, Actinomycin, Etoposide)

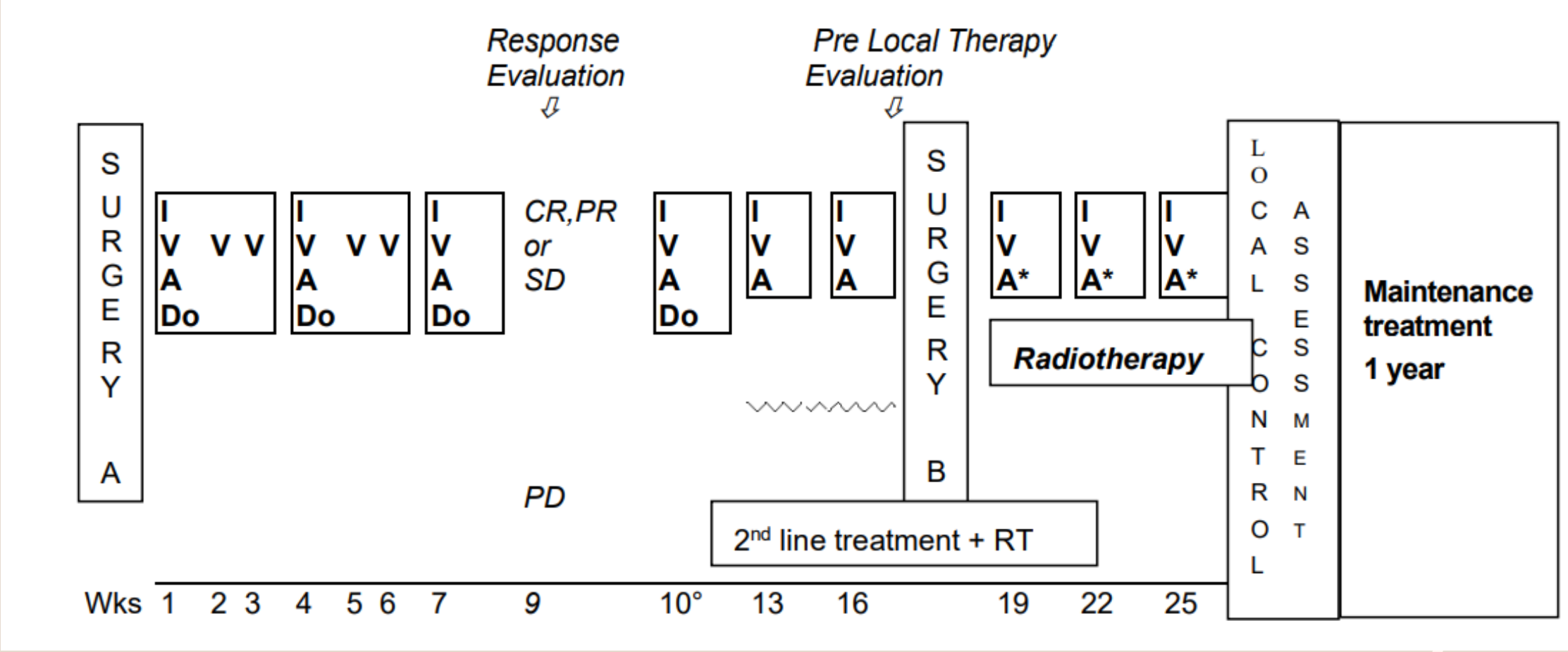
- ***All two combinations seem equally effective ,***
- Carboplatin & Etoposide appear to be dispensable to lower long term toxicity.
- The benefit of anthracyclines in this patient group needs to be proven in future trials.
- The RMS consensus group supports IVADo ***(Ifosfamide 3 g/m2 d1,2, Vincristine 1.5 mg/m2, Actinomycin-D 1.5 mg/m2, Doxorubicin 30 mg/m2 d1,2)*** as unified European standard in VHR RMS,
- In the subgroups G/H **4 courses of IVADo** followed by **5 courses of IVA** plus **48 weeks MT** will be administered.

Subgroup G Alveolar, fusion positive RMS, IRS Group II or III, any site nodes positive , any tumor size or age



Subgroup H

Alveolar/non-alveolar fusion positive/negative RMS, IRS Group IV, any site nodes any , any tumor size or age



❖Maintenance treatment:

- Cyclophosphamide & vinblastine/vinorelbine (CYC/VNB)
- Oral administration of VP16, idarubicin & trofosfamide (O-TIE) in the CWS studies showed **no benefit in the High-Risk group**

✓ ***For metastatic disease, MT seemed superior to high dose chemotherapy followed by autologous stem cell transplantation***

- O-TIE & CYC/VBL seemed **equally effective** in metastatic disease in separate studies

- ***The RMS consensus group supports a year of CYC/VNB as unified European standard MT in metastatic disease.***

- Optimal duration of maintenance with CYC/VNB (**6 vs 12 for HR**, **12 vs 24 cycles** for VHR disease) is currently under evaluation in the Frontline & Relapsed RMS (ClinicalTrials.gov Identifier: NCT04625907).

ROLE OF CHEMOTHERAPY

- **COG;**
- Given the **high rate of micro metastatic disease** that leads to relapse in patients treated only with local therapy, **all RMS patients are treated with adjuvant chemotherapy**
- Multiagent chemotherapy combinations
- Treated with several cycles **(approximately 9–12weeks) of chemotherapy prior to RT**, followed by **additional chemotherapy depending on the prognostic group**

- Systemic therapy based on a backbone of vincristine, dactinomycin, & cyclophosphamide (VAC).

Current and Planned Children's Oncology Group Rhabdomyosarcoma Studies

Risk Group	Stage	Clinical Group	Age	Fusion Status	COG Study	Therapy
Very Low Risk	1	I	Any	*FOXO1* –	ARST2032 * (anticipated activation spring 2022)	VA x 24w
Low Risk	1	II, III (orbit only)				VAC/VA X 24w
	2	I, II				
Intermediate	1	III (non-orbit)	Any	*FOXO1* –	ARST1431	VAC/VI vs VAC/VI + Temsirolimus x 42w + Maintenance (CPM^{PO}Vino) x 24w (all patients)
	1, 2, 3	I, II, III		*FOXO1* +		
	2, 3	III		*FOXO1* –		
	3	I, II		*FOXO1* –		
	4	IV	<10 years	*FOXO1* –		
High	4	IV	>10 years	*FOXO1* –	ARST2031 (anticipated activation summer 2021)	VAC vs VinoAC x 42w + Maintenance (CPM^{PO}Vino) x 24w (all patients)
			Any	*FOXO1* +		

VAC: Vincristine, Dactinomycin, Cyclophosphamide regimen using Cyclophosphamide dose of 1.2g/m2

VinoAC: Vinorelbine, Dactinomycin, Cyclophosphamide regimen using Cyclophosphamide dose of 1.2g/m2

❖ **LOW RISK PATIENTS:**

- Excellent prognosis ,4-year 90% following treatment with;

(Stage 1/2, CG I/II or CG III (orbit only))

  - 48 weeks of vincristine & dactinomycin (VA, as in D9602)

  or

  - 12 weeks of (VAC) followed by 12 weeks of VA (as in ARST0331)

- Decrease the duration of therapy compared to D9602 while adding minimal alkylator therapy.
- Cumulative CPM dose was decreased to 4.8g/m2
- 3-year FFS was 89% & OS was 98 %
- 48 weeks of VA may be administered with similar results, although with a significantly **longer treatment course** & **increased medical costs**

✓ ***Biliary tract/liver site will be considered unfavorable in future studies.***

- Most patients with Stage 1, CG I tumors in D9602 & ARST0331 had **Para testicular disease.**

- **Excellent outcomes without alkylator therapy on D9602** (5-year EFS 96%, OS 100%)29, comparable to the outcomes seen on ARST0331 (3-year FFS 93% , OS 99%).

- European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 trial showed excellent outcomes in their low-risk patients (non-alveolar histology, CG I, age < 10 years, tumor size ≤ 5 cm) with **24 weeks of VA** (5-year EFS of 95.5% - OS of 100%)

- Patients with **CG III orbital disease** have **very good outcomes** but have **high local failure rate** (while retaining a very high OS) with sequential reductions in alkylator & radiation doses.

- using a ***high cumulative dose (26.4 g/m2) of cyclophosphamide*** & ***higher doses of radiation (50.4–59.4 Gy)***

- **ARST2032** will increase radiation dose to 50.4 Gy (from 45Gy in ARST0331) for patients with Stage 1, CG III orbital RMS who do **not achieve radiological CR at week 12**

- Adverse prognostic effect of MYOD1 or TP53 pathogenic mutations, patients whose tumors have these mutations will no longer be considered LR & will be treated in a separate arm in ARST2032

- This molecularly defined LR cohort will then be subdivided into two newly defined risk groups:

1) patients with VLR-RMS (FN, Stage 1, CG I, MYOD1 &TP53 wild type [WT])

  - 24 weeks of VA

2) patients with LR-RMS (FN, Stage 1 CG II, or Stage 2 CG I/II or CG III (orbit only), MYOD1 and TP53 WT)

  - 12 weeks of VAC followed by 12 weeks of VA.
  - **MYOD1 or TP53 pathogenic mutations** -42weeks of VAC therapy using a cumulative CPM dose of approximately 16.8g/m2.

❖ **Intermediate Risk**(IR-RMS) ;

- Most heterogeneous risk group with 5-year EFS rates 50–75%
- Comprise **more than half of newly** diagnosed patients with RMS

❑ Newly diagnosed IR—RMS To VAC versus VAC plus vincristine & irinotecan (VI), using a standard CPM dose of 1.2 g/m2 per dose in each arm.

❑ Both regimens had comparable outcomes (4-year EFS65% vs. 68%),
but VAC/VI was associated with **fewer hospitalizations** &**less hematologic toxicity**

❑ 50% reduction in cumulative CPM dose (8.4 g/m2 vs. 16.8 g/m2) may **decrease the risk of infertility** & **secondary malignancy** in survivors

✓ ***Seven courses of irinotecan (5 days) may be logistically problematic or poorly tolerated due to gastrointestinal toxicity***

❑ ARST1431 is the first IR-RMS study to test a molecularly targeted agent in upfront treatment for RMS.

- Patients are randomized to receive (VAC/VI) or VAC/VI plus temsirolimus, an mTOR inhibitor.
- mTOR pathway is frequently activated in RMS

- Clinical data from a prior randomized COG study for patients with relapsed RMS (ARST0921) demonstrated superior 6-month EFS & response rates for the temsirolimus-containing regimen versus the bevacizumab-containing regimen

- **15 mg/m^2/dose (Dose Level 1) of temsirolimus on days 1, 8 , 15** of each of three weekly VAC and VI cycles for the **first 12 weeks** of induction chemotherapy.

- Weekly temsirolimus at 15 mg/m2/dose during VAC/VI chemotherapy was **feasible** and well **tolerated.** The efficacy of this regimen is currently being tested in a **phase III randomized trial** against VAC/VI chemotherapy alone in the ARST1431 trial.

❑ ***on ARST1431 ;***

- 42 weeks of VAC/VI therapy, with 24 weeks of maintenance therapy with daily low dose oral CPM plus weekly IV vinorelbine on 3 out of every 4 weeks.

- Patients were randomized to receive an additional 24 weeks of maintenance therapy on the same schedule as ARST1431 versus no maintenance therapy.

- Patients who received maintenance had improved **5-year OS of 86.5% vs. 73.7%, (p=0.0097)**, although improvement in **5-year disease free survival did not reach statistical significance (77.6% v. 69.8%, p=0.061]).**

❖ ***High Risk;***

- Patients with HR-RMS comprise **approximately 15%** of all patients with RMS but represent the most challenging to treat, with dismal outcomes.
- The outcome for patients with distant metastatic disease varies greatly depending on risk factors identified by **Oberlin et al.,** including ;
    - Age<1 or >10 years,
    - ≥3 metastatic sites
    - Bone/Bone marrow involvement
    - Unfavorable primary tumor site,

Group IV, Stage 4 ,FP-RMS
or
Group IV, Stage 4 ,FN-RMS , Greater than 10 years of age

- Results from the two most recent HR-RMS COG trials, ARST0431 & ARST08P1, have defined HR-RMS to include patients ;

- (VDC)vincristine, doxorubicin, CPM alternating with ifosfamide & etoposide (IE) into a VAC/VI backbone.

- Patients >10 years old with metastatic FN-RMS did have a better outcome compared to historic controls, & thus may benefit from this more intensive chemotherapy

- Metastatic FP-RMS patients *did not demonstrate improved survival* with this intensified chemotherapy regimen compared to previous trials that included VAC or VAC/VI

- These studies, in an attempt to maximize dose intensity, incorporated all known active agents (VDC , IE & VAC) into an interval compressed, intensified backbone and also evaluated promising novel agents (***irinotecan, temozolomide or cixutumumab).***

- ***Vinorelbine***, a **second generation vinca alkaloid** has been tested as a single agent & in combination with CPM in patients with heavily pre-treated RMS.
- Overall response rate (ORR) observed with single agent vinorelbine (30mg/m2) was 36% C.R - 50% P.R

- Lower dose of vinorelbine (25 mg/m2) was evaluated in combination with CPM - PO
- heavily pre-treated patients with relapsed/refractory RMS. ORR of 36%

- ***Suggesting that vinorelbine is a highly active agent in RMS***

- ARMS have a **41% improved response** rate compared to those with ERMS when treated with vinorelbine alone or in combination with lower dose or oral cyclophosphamide

- Because neither the **CPM dose intensity** on D9802, nor the **intensified backbones** utilized on ARST0431 and ARST08P1 improved outcomes for patients with HR-RMS,

- ARST2031 will employ a VAC backbone with an intermediate cyclophosphamide dose (1.2 g/m2/cycle) and utilize vinorelbine in the experimental arm.

- Role of maintenance as published in the EpSGG RMS 2005 study is unknown in patients with COG-defined HR-RMS.

- ARST2031 will compare induction using VAC versus Vinorelbine-AC (VINO-AC) in a randomized fashion for patients with HR-RMS, while adding maintenance with Vinorelbine-CPM - PO to both arms to improve outcomes of patients with HR-RMS.

RMS Consensus Treatment Algorithm

A.

First Line therapy

Low-Risk RMS	(Preferred)	VAC x 4	LC	VA x 4
	(Alternate)	VA x 4	LC	VA x 12
Intermediate Risk RMS	(Preferred)	VAC/VI (VAC x 3; VI x 2)	LC	VAC/VI (VAC x 4; VI x 5)
	(Alternate)	VAC x 4	LC	VAC x 8
High-Risk FN-RMS >10 yo	(Preferred)	VAC/VI/VDC/IE (51 weeks)	LC	VAC/VI/VDC/IE
High-Risk FP-RMS	(All Reasonable)	VAC/VI (VAC x 7; VI x 7)	LC	VAC/VI
		VAC (VAC x 14)	LC	VAC

VAC
Vincristine 1.5 mg/m^2 max 2 mg
Dactinomycin 0.045 mg/kg max 2.5 mg*
Cyclophosphamide 1200 mg/m^2 *
VA
Vincristine 1.5 mg/m^2 max 2 mg*
Dactinomycin 0.045 mg/kg* max 2.5 mg
VI
Vincristine 1.5 mg/m^2 max 2 mg*
Irinotecan 50 mg/m2 x 5
VDC
Vincristine 1.5 mg/m^2
Doxorubicin 75 mg/m^2 ± dexrazoxane
IE
Ifosfamide 9 g/m^2
Etoposide 500 mg/m^2

Weekly vincristine given in alt weeks
LC: Local control (surgery or radiation)

* dose reduce for age < 3 years
(see Supplemental Table 1 for detailed chemotherapy protocols)

ROLE OF XRT.

- **COG;**
- RT plays an integral part in the cure of most patients with RMS
- **High-quality RT** is predictive of treatment outcome
- RT is delivered in **1.8 Gy fractions**

❑ **Dose** & **Volume of radiation** delivered is dependent on ;

a. Initial stage & clinical group.
b. Modified based on anatomical constraints, the adjacent tissue.
c. Boost volume can be defined based on the post chemotherapy volume,
d. Planning target volume (PTV) ,based on institutional and treatment-specific variables

❑ Optimal timing ;

- **Cycles (12 weeks) of chemotherapy**, even for patients with parameningeal involvement.

✓ ***RT is omitted are those with clinical group 1, fusion-negative (embryonal) tumor.***

ROLE OF XRT.

Radiation doses used in COG

Up-Front Resection Radiation Recommendations

Surgical Group	Margin	Node	XRT (Gy)
I (FN-RMS)	Neg	N0	0
IIA (FP-RMS)	Neg	N0	36
IIA (N0)	Pos	N0	36
IIB (N1)	Neg	N1	36
IIC (N1)	Pos	N1	41.4
III (any)	N/A	Nx	50.4
III (orbit)	N/A	Nx	45 – 5(

Delayed Resection Radiation Recommendations

Resection Margin	Node	XRT (Gy)
Neg.	N0	36
Microscopic	N0	41.4
	N1	41.4
No Resection or Gross residual*	Any	50.4

* Orbital RMS = 45 Gy and complete response to induction chemotherapy, otherwise 50.4 Gy

ROLE OF XRT.

- **EpSSG RMS 2005 study;**

❑RT to site of the primary tumor is indicated for majority patients, particularly those in
  - High risk
  - Very high-risk groups

❑Do not require RT ;

- **Low-risk localized fusion-negative RMS with initial R0 resection** (IRS Group I)
- **Localized fusion-neg RMS of vagina** achieving C.R with induction chemotherapy
- **Standard-risk RMS** arising at a **favorable site** where secondary surgery achieves an **R0** resection (Para testicular, Uterus)

Timing of XRT. In European/EpSSG approach

- Local therapy (delayed surgical excision of the primary tumor and/or RT) at week 13

- ***Local therapy may be delayed beyond week 13, if it is felt that a further response to chemotherapy may facilitate a complex surgical resection or brachytherapy.***

- Optimal timing of a **local therapy differs for a metastatic disease**, response to treatment is assessed after **six cycles of chemotherapy**, a local therapy to the **primary & metastatic sites** is delivered at **week22.**

- **Extensive metastatic disease** may require **RT delivered as two separate courses** to limit bone marrow & other acute toxicities.

- ❖ Late effects of RT in survivors of a childhood **head & neck RMS**, 63% reported one or more severe or disabling consequences

- ❑ Europe with a localized RMS treat with **proton therapy**, or other highly conformal RT techniques such as **intensity-modulated RT**

- ❑ Brachytherapy is an increasingly used modality;
  - ✓ **Fusion negative RMS** arising in the **genitourinary region** (vagina, uterus, bladder/prostate, and perineum).
  - ✓ **Selected head & neck RMS**
  - ✓ The majority of brachytherapy is undertaken following a **complete or partial tumor resection**

- Nodal involvement at diagnosis, again factoring in changes in anatomy, plus a **margin of 3 cm** superiorly & inferiorly (direction of a lymphatic drainage)

- For metastases the(**Gross tumor volume)**GTVm, is extent of metastasis at diagnosis, expanded by 0.5–1.0 cm for appropriate CTVm

- key exceptions are **lung** or extensive **brain metastases,whole-organ irradiation**

- **Diffuse peritoneal disease** where (Clinical Target Volumes)CTVmis the entire peritoneal cavity.

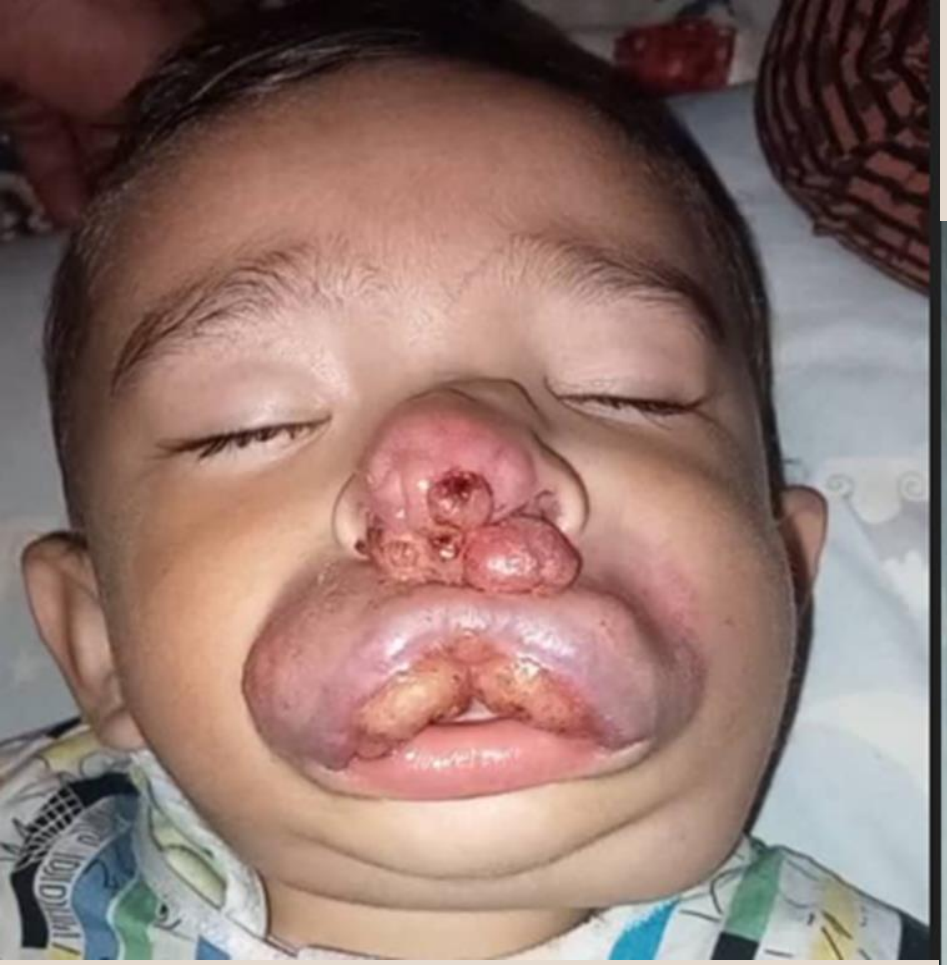
- **RT dose**
- Ranging from 36 Gy to 55.8 Gy.

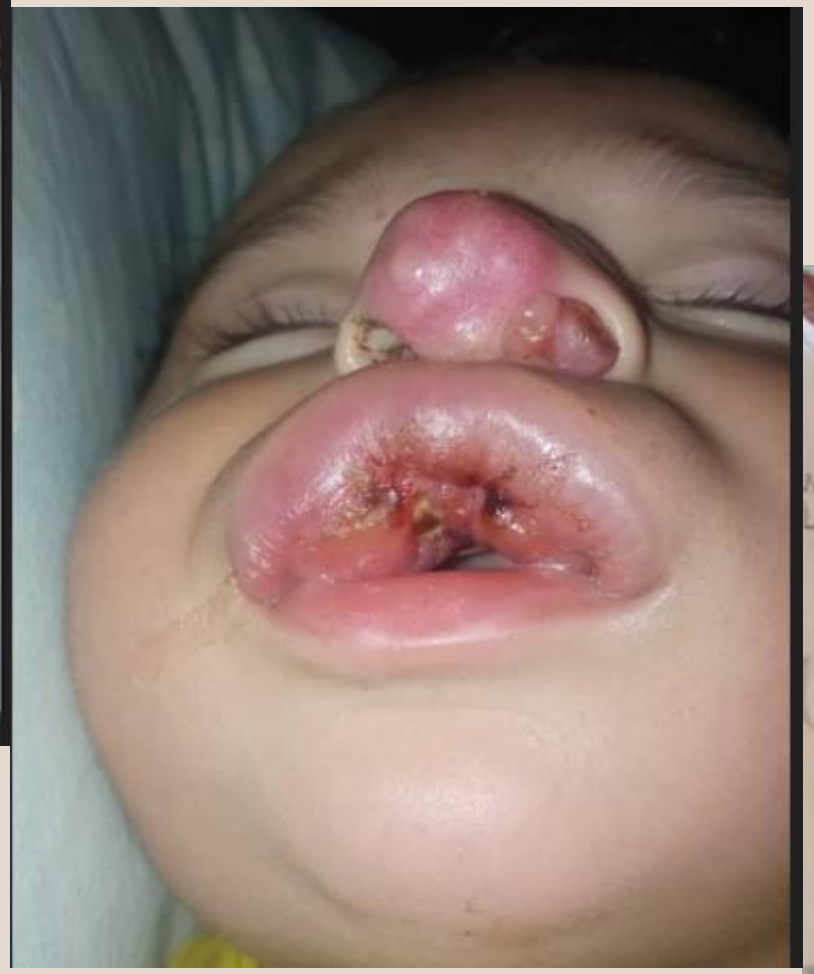
❑In the current EpSSG guidelines, Dosing schedules;

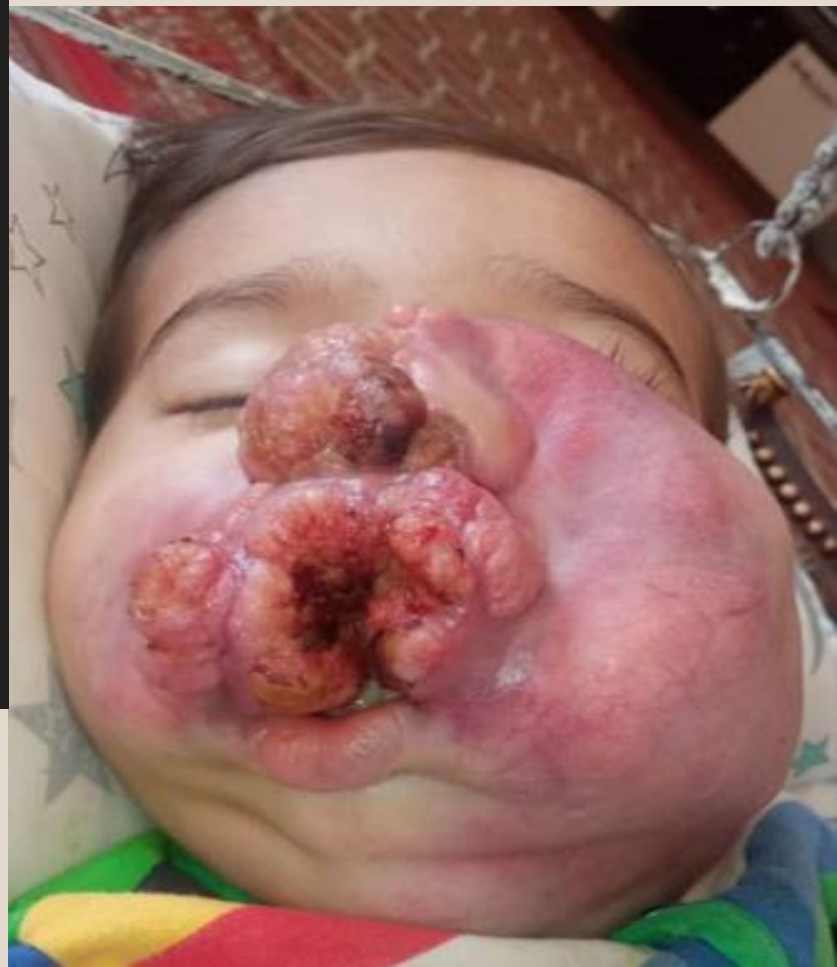
- 41.4 Gy recommended for a microscopic disease
- 50.4 Gy for a macroscopic disease
- Both at 1.8 Gy per fraction

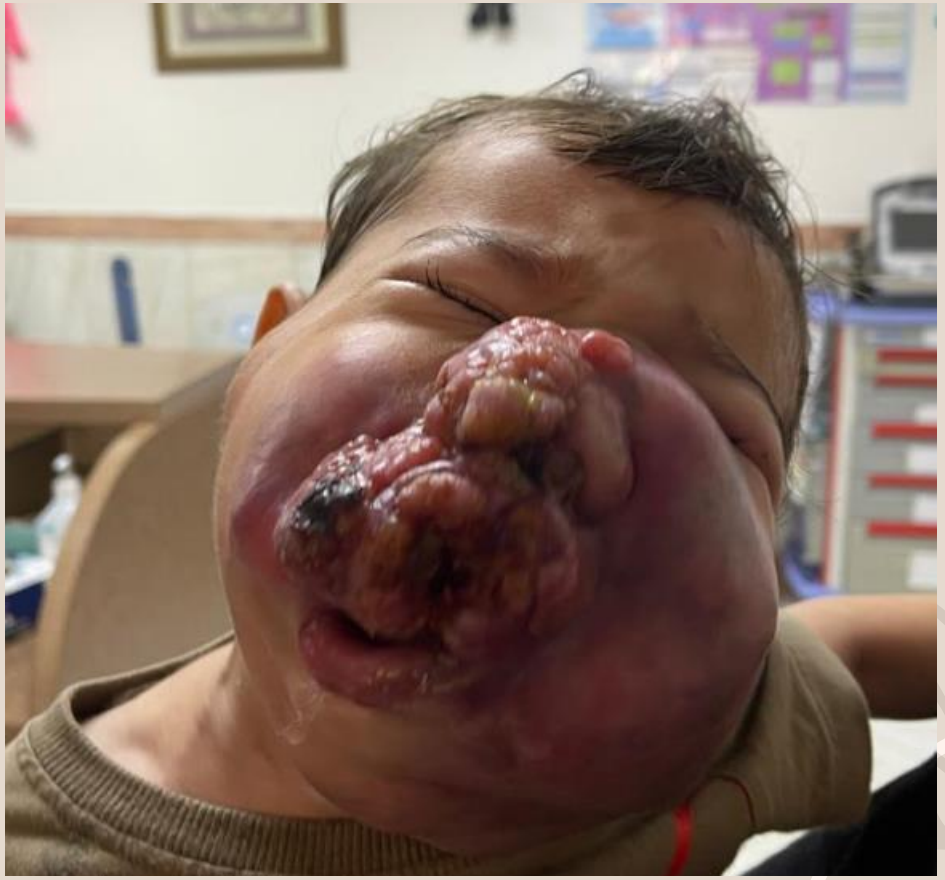
❑Exceptions to this include;

- Wide-field RT to the whole lungs (15 Gy)
- Whole abdominopelvic (24 Gy)
- Both delivered using a lower 1.5 Gy per fraction









RMS Protocol -Regimen 47

Name:	Wt:	Ht:	BSA:

Cyclophosphamide (CPA): 2200 mg/m²	Ifosfamide (IF): 1800 mg/m²	Etoposide (VP16): 100 mg/m²	Actinomycin (Act): 15 µg/kg Max. Dose =0.5 mg	Vincristin (VCR): 1.5 mg/m² Max. Dose =2 mg
Mesna:400 mg/m²				

Week		Date	Protocol			
0		/ /	VCR	mg IV Push		
			VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
1		/ /	VCR	mg IV Push		
2		/ /	VCR	mg IV Push		
3		/ /	VCR	mg IV Push		
			VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
4		/ /	VCR	mg IV Push		
5		/ /	VCR	mg IV Push		
6		/ /	VCR	mg IV Push		
			VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
7		/ /	VCR	mg IV Push		
8		/ /	VCR	mg IV Push		
Evaluation + xRT start						
9	xRT	/ /	VCR	mg IV Push		
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
10		/ /	VCR	mg IV Push		
11		/ /	VCR	mg IV Push		
12		/ /	VCR	mg IV Push		
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
15	xRT End					
16		/ /	VCR	mg IV Push		
			VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
			IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
			Mesna	mg (- - -)		× 5 days
Evaluation						

RMS Protocol -Regimen 47

Name:	Wt:	Ht:	BSA:

Week	Date	Protocol			
20	/ /	VCR	mg IV Push		
		VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
		IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		Mesna	mg (- - -)		× 5 days
21	/ /	VCR	mg IV Push		
22	/ /	VCR	mg IV Push		
23	/ /	VCR	mg IV Push		
		VP16	mg/	ml N/S 0.9% / 2-4 hr	× 5 days
		IF	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		Mesna	mg (- - -)		× 5 days
24	/ /	VCR	mg IV Push		
25	/ /	VCR	mg IV Push		
Evaluation					
29	/ /	VCR	mg IV Push		
		Act	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		CPA	mg/	ml 1/1 2/1 / 4 hr	
		Mesna	mg (- - -)		
30	/ /	VCR	mg IV Push		
31	/ /	VCR	mg IV Push		
32	/ /	VCR	mg IV Push		
		Act	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		CPA	mg/	ml 1/1 2/1 / 4 hr	
		Mesna	mg (- - -)		
33	/ /	VCR	mg IV Push		
34	/ /	VCR	mg IV Push		
38	/ /	VCR	mg IV Push		
		Act	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		CPA	mg/	ml 1/1 2/1 / 4 hr	
		Mesna	mg (- - -)		
39	/ /	VCR	mg IV Push		
40	/ /	VCR	mg IV Push		
41	/ /	VCR	mg IV Push		
		Act	mg/	ml 1/1 2/1 / 4 hr	× 5 days
		CPA	mg/	ml 1/1 2/1 / 4 hr	
		Mesna	mg (- - -)		
42	/ /	VCR	mg IV Push		
43	/ /	VCR	mg IV Push		
46	Evaluation				

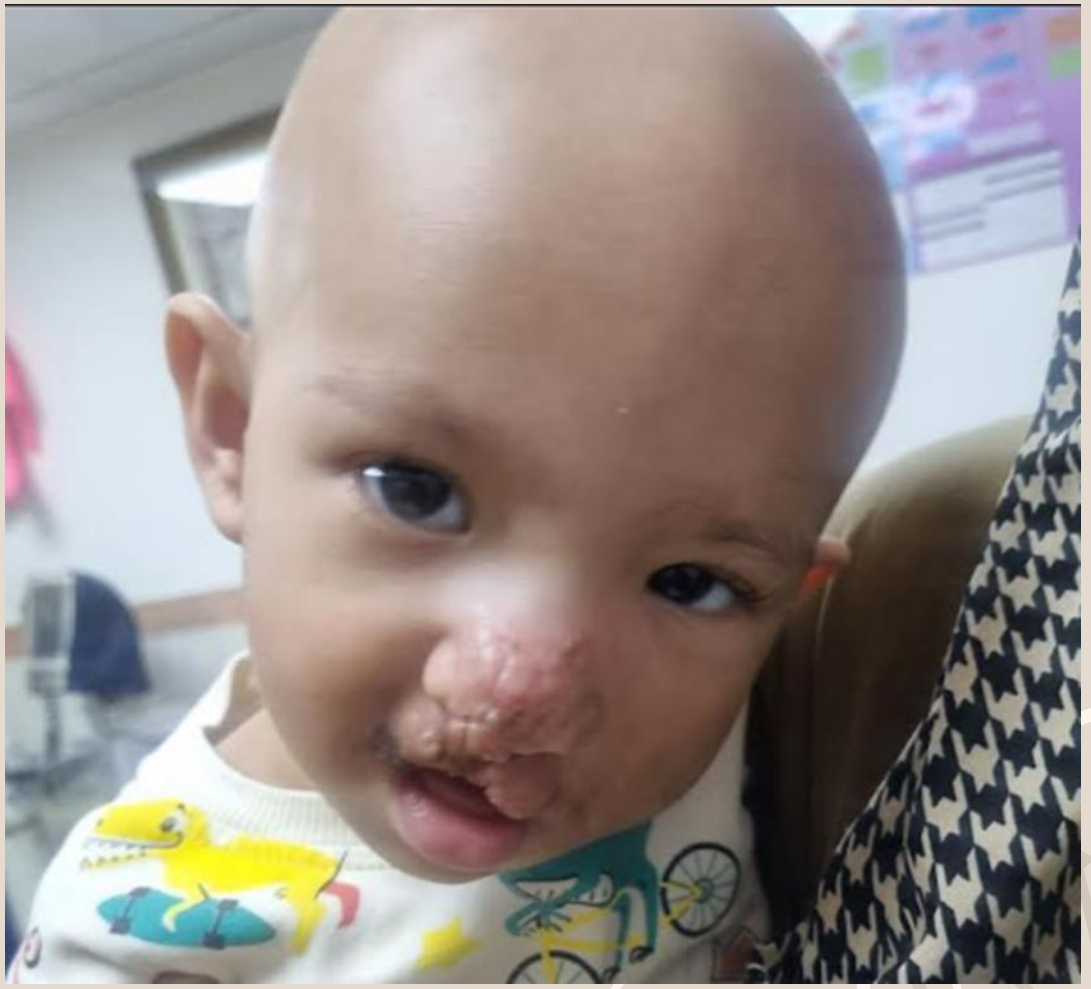
LANZKOWSKY 3th edition

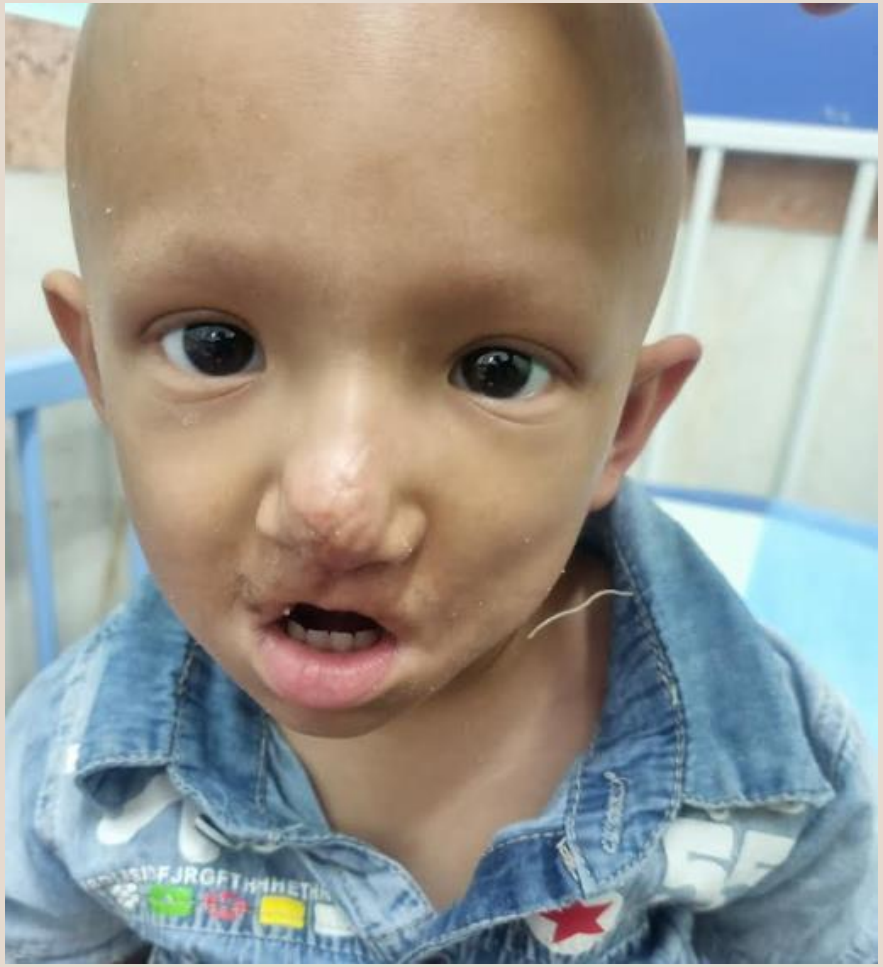
8 Course IEV

Radiotherapy week 9-13

Omit VP16 During XRT.

4 Course VAC





Thank you for your attention

MARYAM TASHVIGHI

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- For patients receiving Ifosfamide , it’s recommended to consider fertility preservation options prior to initiating systemic treatment

- **Assessment of tumour response & treatment decisions**
  - Standardised time points:
    - Localised disease after 3 cycles (week 8)
    - Metastatic disease after 3 cycles (week 8) & 6 cycles (week 17)

- **Volumetric and RECIST response ;**
  - Volumetric progressive disease is defined as any increase in volume ≥73 %, or appearance of new lesions.
  - RECIST, progressive disease is defined as an increase of the (sum) of target lesion(s) in one dimension of at least 20 %, or of non-target lesions, or the appearance of new lesions