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REVIEW ARTICLE

Diagnosis and Management of Rhabdomyosarcoma in Children and Adolescents: ICMR Consensus Document

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Abstract Rhabdomyosarcoma (RMS) is a highly malignant tumor which is thought to originate from the pluripotent mesenchyme. It is the most common soft-tissue sarcoma of childhood. This review article summarizes the recent and older published literature and gives an overview of management of RMS in children. RMS can arise in a wide variety of primary sites, some of which are associated with specific patterns of local invasion, regional lymph nodal spread, therapeutic response and long term outcome, hence requiring physicians to be familiar with site-specific staging and treatment details. Most common primary sites include the head and neck region, genitourinary tract, and extremities. Prognosis for children and adolescents with RMS has recently improved substantially, especially for patients with local or locally extensive disease because of the development of multi-modal therapy incorporating surgery, dose-intensive combination chemotherapy, and radiation therapy. Despite aggressive approaches the outcome for patients who present with metastatic disease remains unsatisfactory. Clinical trials are ongoing to reduce toxicity and improve outcomes of such patients; newer agents in combination are being investigated.

Keywords Rhabdomyosarcoma · Embryonal · Alveolar · Pediatric · Treatment

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Introduction

Rhabdomyosarcoma (RMS) is a malignant tumor of mesenchymal origin thought to arise from cells committed to a skeletal muscle lineage. It is the commonest soft tissue sarcoma in childhood and accounts for 3.5% of childhood cancers seen in the 0–14 y age group [1]. More than 50% of the tumor occurs in the first decade of life [2]. Data from the hospital based cancer registries across 7 cities in India revealed an incidence of 1–4.5% of all childhood malignancies to be RMS [3]. Most of the reports are institutional retrospective case series. The current manuscript is written with the objective of developing a consensus guideline for practitioners at a national level.

Material and Methods

This document on consensus guideline for management of rhabdomyosarcoma was arrived after an initial round of meeting with national experts in the field of pediatric oncology. Thereafter, an exhaustive review of literature of national and international data was undertaken and the manuscript was drafted. This was then presented in a second round meeting with the experts till a final consensus was obtained after multiple rounds of discussion. The final consensus document was once again sent to all authors for proofing and then submitted.

Histological Classification

There are three distinct histological subtypes; embryonal, alveolar and the pleomorphic (anaplastic) type. Embryonal histology accounts for 70–80% of cases. It includes classical embryonal, botryoid, and the spindle cell subtypes. Predominantly, these tumors arise in the head and neck region or the genitourinary tract. Botryoid variant typically occurs in the vagina, urinary bladder, biliary tract and nasopharynx. The spindle cell variant is common in the paratesticular region. Both botryoid and spindle cell variants have a favourable outcome [4, 5]. Alveolar RMS accounts for 15–20% of cases. It typically occurs in the second decade and is more common in extremities, trunk, perineal and perianal region. It has an unfavourable outcome especially if metastatic at diagnosis [4]. The third variant, called the pleomorphic or anaplastic variant typically occurs in adults and has a poor outcome [6].

Site of Tumor

Any part of the body part can be affected [6]; however, the most common primary sites include the head and neck region (36%), genitourinary tract (23%), extremities (19%) and others (22%). Head and neck RMS can arise in the orbit, parameningeal sites (middle ear, nasal cavity, paranasal sinuses, nasopharynx, and infratemporal fossa), or other non-parameningeal locations (scalp, parotid gland, oral cavity, pharynx, thyroid and parathyroid glands, and neck). Fewer than 25% cases of RMS are metastatic at presentation. The lung is the commonest site of metastases (40–50%). Other sites either isolated or in conjunction with multi-metastatic disease include bone marrow (20–30%), bone (10%) and lymph node (up to 20% depending on the site of primary tumor) [6].

Prognostic Factors

Various cooperative groups across the world have evaluated a number of clinical and biological variables with proven or possible prognostic significance.

Age

Children younger than 1 y and older than 10 y fare poorly compared to those aged 1–9 y. The poor prognosis in infants has been attributed to the reluctance in using aggressive local therapy due to predicted late morbidity [7]. Again their bone marrow is less tolerant to chemotherapy than older children. Adolescents have more frequent unfavorable tumor characteristics, including alveolar histology, unfavorable sites (mainly extremities), regional lymph node involvement, and metastatic disease, accounting for their poor prognosis [8, 9].

Site of Primary Tumor

The sites of occurrence of the primary tumor have been classified as favorable and unfavorable sites based on outcome. Favorable sites include non-parameningeal head and neck, orbit, genitourinary (non-bladder, non-prostate, non-kidney) and biliary tract. Unfavorable sites include all sites of primary tumor other than the above listed under favorable sites. These commonly include extremity, parameningeal, bladder and prostate [10].

Histopathological Subtype

Alveolar histology portends poor outcome compared to embryonal subtype. Pooled data from Intergroup Rhabdomyosarcoma Study Group (IRS) I, II and III show that 5-y survival is related to the histology with 95% for sarcoma botryoides, 75% for pleomorphic sarcoma, 66% for embryonal, 54% for alveolar and 40% for undifferentiated RMS. IRSG III study showed that the outcome of localised alveolar RMS is comparable to embryonal RMS, when treated with more intense therapy. Metastatic alveolar RMS has a worse outcome [10, 11].

Metastases and Lymph Node Involvement

Children with metastatic RMS have a poorer prognosis; 3 y Event free survival (EFS) of 25%. Outcome is dependent on the histology of the primary, site of metastases and number of sites of metastases. Embryonal RMS fares better compared to alveolar type. Patients with metastatic genitourinary (nonbladder, nonprostate) primary tumors have a more favorable outcome than do patients with metastatic disease from primary tumors at other sites. Lung-only metastases have a better prognosis as compared with metastases at other sites. Children with regional nodal disease fare worse compared to patients without regional nodal involvement [12].

Extent of Resection

Extent of resection after primary surgical procedure (Surgical-pathologic group/ Clinical group *i.e.*, CG) is correlated with outcome [10]. As per IRSG-III study, patients with gross residual disease after initial surgery had a worse outcome [CG-III, 5 y OS (Overall survival) –70%] compared to patients with microscopic disease (CG-II, 5 y OS–80%) or no residual (CG-I, 5 y OS–90%) [13]. Patients with CG-IV or TNM stage 4 fare worse than others.

Diameter of the Tumor

Patients with smaller tumors (≤ 5 cm) have better survival. Both tumor volume and maximum tumor diameter are associated with outcome [14].

Response to Therapy

In a retrospective review of 107 patients, SUV (Standardized uptake value) in PET (Positron emission tomography) scan done at baseline predicted PFS (Progression free survival) and OS, but not local control; a negative PET after induction chemotherapy correlated with statistically significantly better PFS. A positive scan after local therapy predicted worse PFS, OS, and local control [15, 16].

Molecular Sub-Classification

Molecular sub-classification in RMS may be useful for diagnostic confirmation, assigning therapy and predicting outcome. Nearly three-quarters of alveolar RMS are characterized by translocations between *FOXO1* gene on chromosome 13 and either the *PAX3* gene on chromosome 2, t(2:13) (q35;q14) or the *PAX7* gene on chromosome 1, t(1;13)(p36;q14). Fusion-positive patients have a lower EFS (*PAX3* 54% and *PAX7* 65%) than those with embryonal RMS (77%). Patients with fusion-negative alveolar RMS have outcomes similar to those with embryonal RMS [17]. Recent studies demonstrate that fusion status is a better predictor of outcome than histology and will replace histology in subsequent COG (Children's Oncology Group) studies [18]. Embryonal RMS are characterized by loss of heterozygosity of chromosome 11p15 and gains of chromosome 8. These, however, have not been reported to be of any prognostic value.

Work Up of a Patient with RMS

Tests performed should be directed to confirm the diagnosis, complete staging work-up to determine the extent of disease and baseline work-up for chemotherapy. Summary of investigations for patients with suspected RMS is as follows:

1. Baseline Investigations:

- Complete blood count
- Renal and liver function tests
- Serum electrolytes, uric acid
- Coagulation profile

2. Diagnostic Investigations

- CT scan of primary site with contrast or MRI (especially in parameningeal, paraspinal, pelvic masses including bladder and prostate RMS)
- Histopathology of tru-cut biopsy or excised specimen [Fine needle aspiration cytology (FNAC) of the tumor is discouraged]
- FISH for t(1;13) or t(2;13) (desirable)

3. Staging Investigations

- CT thorax
- Bone scan
- Bilateral bone marrow aspirates and biopsy
- Cerebrospinal fluid (CSF) for malignant cell in parameningeal RMS
- PET-CT scan if available (with bone marrow examination)

Biopsy and Pathology Guidelines

Both open incisional biopsy and image guided core needle (Tru-Cut) biopsies are appropriate. Endoscopic biopsies are appropriate for bladder, prostate or vaginal tumors. Adequate tissue should be collected for diagnosis, histological subtyping, immunohistochemistry (Desmin, Vimentin, MyoD1, Myogenin, S100, EMA, LCA, fli1 and Mic2), cytogenetics and where possible, tissue for biobanking. To be classified as alveolar, the tumor must have greater than 50% alveolar subtype. The pathology report must routinely include the RMS histologic subtype, percentage of necrosis (in resected specimens post chemotherapy), margins, comment on vascular/lymphatic invasion and involvement of regional lymph nodes. There is now emerging evidence that regional lymph nodes should be subjected to biopsy or FNAC especially in limb primary even when there is no clinico-radiological evidence of lymph nodal spread.

Radiology Guidelines

In locoregional evaluation, MRI is preferable in head and neck tumors, paraspinal tumors, limb and genitourinary primaries. CT scan is recommended for tumors in the chest and abdomen. Craniospinal MRI is recommended if intraspinal extension or meningeal involvement is suspected. Paratesticular tumors must have evaluation of regional (para-aortic) lymph nodes by CT/

Table 1 Soft Tissue Sarcoma Committee of the Children's Oncology Group: pretreatment staging system

Stage	Sites of primary tumor	T stage	Tumor size	Regional lymph nodes	Distant metastasis
1	Favorable sites	T1 or T2	Any size	N0 or N1 or NX	M0
2	Unfavorable sites	T1 or T2	a < 5 cm	N0 or NX	M0
3	Unfavorable sites	T1 or T2	a < 5 cm b > 5 cm	N1 N0 or N1 or NX	M0
4	Any site	T1 or T2	Any size	N0 or N1 or NX	M1

N0 Absence of nodal spread; *N1* Presence of regional nodal spread beyond the primary disease; *NX* Unknown nodal status; *M0* Absence of metastatic spread; *M1* Presence of metastatic spread beyond the primary site and regional lymph nodes; *T1* Tumor confined to anatomic site of origin (non-invasive); *T2a* Tumor extension and/or fixation to surrounding tissues (invasive); Tumor less than or equal to 5 cm in maximum diameter; *T2b* Tumor extension and/or fixation to surrounding tissues (invasive); Tumor greater than 5 cm in maximum diameter

Favorable site Orbit; non-parameningeal head and neck; genitourinary tract other than kidney, bladder and prostate; biliary tract; *Unfavorable site* Any other site of primary other than favorable

MRI and ultrasound. Lower limb and upper limb primary RMS should have evaluation of regional lymph nodes by CT/MRI even in clinically normal lymph nodes. Both MRI and CT scan should be carried out with the use of IV contrast when evaluating the primary tumor. Imaging of the primary site should be performed (again) after surgical excision biopsy if significant volume has been resected. CT chest (non-contrast) is recommended for evaluation of lung metastases.

Status of PET-CT Scan for Staging Evaluation of RMS

There is emerging evidence that PET-CT scan may be more accurate than conventional imaging in staging of children with RMS. PET-CT has potential to increase the accuracy of initial staging and is more sensitive in detecting nodal disease and distant metastases. There is however little evidence on the role of PET-CT in assessment of therapeutic response or post-treatment assessment. The ultimate impact of this investigation on treatment outcomes is still unclear and needs to be evaluated systematically in a large prospective cohort of patients [14, 15].

Staging and Risk Stratification

Risk stratification of RMS is relatively complex and involves a three-step process:

1. Stage assignment: TNM (Tumor, node, metastasis classification of malignant tumors) staging/pretreatment staging system (Table 1).
2. Surgical-pathologic group (IRS clinical group): Determined by status post surgical resection/biopsy (Table 2).
3. Assigning a risk group: Based on stage, group and histology (Table 3).

This risk grouping appears complex to apply in day-to-day practice; another simple derivation of the above three-stage process is given below

Table 2 Surgical-pathologic group system developed by Soft Tissue Sarcoma Committee of the Children's Oncology Group

Group	Incidence	Definition
I	Approximately 13%	Localized tumor, completely removed with microscopically clear margins and no regional lymph node involvement. Lymph node biopsy or sampling is encouraged if lymph nodes are clinically or radiographically suspicious.
II	Approximately 20%	Localized tumor, completely removed with: (a) microscopic disease at the margin, (b) regional disease with involved nodes, grossly removed regional lymph nodes without microresidual disease, or (c) regional disease with involved nodes, grossly removed but with microscopic residual and/or histologic involvement of the most distal node from the primary tumor.
III	Approximately 20%	Localized tumor, incompletely removed with gross, residual disease after: (a) biopsy only, or (b) gross major resection of the primary tumor (>50%).
IV	Approximately 18%	Distant metastases are present at diagnosis. This category includes: (a) radiographically identified evidence of tumor spread, and (b) positive tumor cells in cerebrospinal fluid, pleural, or peritoneal fluids, or implants in these regions.

Table 3 Soft Tissue Sarcoma Committee of the Children's Oncology Group: rhabdomyosarcoma risk group classification

Risk group	Histology	Stage	Group
Low-risk	Embryonal	1	I, II, III
	Embryonal	2,3	I, II
Intermediate-risk	Embryonal	2,3	III
	Alveolar	1,2,3	I, II, III
High-risk	Embryonal or alveolar	4	IV

High-risk RMS:All Metastatic (M1) diseases irrespective of histology

Intermediate-risk RMS: Locoregional RMS–alveolar subtype

Unresectable RMS (embryonal) at unfavorable site

Low-risk RMS: All other tumors (embryonal only)

European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) Risk Classification

The EpSSG has developed a risk stratification (Table 4) for non-metastatic RMS based on analyses of studies conducted by the SIOP-MMT (International Society of Paediatric Oncology Malignant Mesenchymal Tumors studies), CWS (German Cooperative Weichteilsarkom Studies) and AIEOP (Associazione Italiana di Ematologiae Oncologia Pediatrica group) study groups. The new stratification has been developed taking into account histology (alveolar *vs.* non-alveolar), post surgical stage (according to IRS grouping), tumor site and size, node involvement and patient age.

Treatment of RMS

Treatment for RMS involves a multimodality approach**.** Treatment should be undertaken at dedicated pediatric oncology centres where multidisciplinary teams exist with experience in managing such tumors. Systemic chemotherapy is to be administered to all RMS patients in conjunction with local therapy. Local therapy has to be individualized based on expertise available. It may be surgery, radiotherapy or both to maximize local tumor control. Primary surgical resection may be performed before chemotherapy if it results in no substantial functional compromise or organ dysfunction or disfigurement. This should only be undertaken if the tumor is deemed resectable (like paratesticular tumors) with negative margins. The majority of patients fall into group III (gross residual disease or biopsy only) and would need radiotherapy (RT) as treatment modality for local control. In some patients with initially unresectable tumor, a second look surgery (delayed primary excision) may be undertaken for removal of the residual tumor. This is especially recommended when there is likelihood of reduction in radiation dose which would significantly reduce late effects. RT is recommended for clinically or radiologically suspicious lymph nodes unless the nodes are biopsied and shown to be free of tumor.

Management of Low-Risk RMS

The IRS V and the COG soft tissue sarcoma committee estimate 35% of all RMS to fall under the category of low-risk category (Tables 5 and 6). These have excellent survival rates

Table 4 EpSSG risk stratification for non-metastatic rhabdomyosarcoma

Risk group	Subgroups	Pathology	Post surgical stage (IRS Group)	Site	Node stage	Size & age
Low-risk	*A*	Favourable	I	Any	N0	Favourable
Standard-risk	*B*	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High-risk	*E*	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very High-risk	*H*	Unfavourable	I, II, III	Any	N1	Any

Pathology: Favourable = All embryonal, spindle cells, botryoid RMS, Unfavourable = All alveolar RMS (including the solid-alveolar variant); **Post surgical stage**: Group I = Primary complete resection (R0), Group II = Microscopic residual (R1) or primary complete resection but N1, Group III = Macroscopic residual (R2); **Site**: Favourable = Orbit, genitourinary non-bladder prostate (*i.e.,* paratesticular and vagina/uterus) and non-parameningeal head and neck, Unfavourable = all other sites (parameningeal, extremities, genitourinary bladder-prostate and "other sites"; **Node stage**: N0 = No clinical or pathological node involvement, N1 = Clinical or pathological nodal involvement; **Size & Age**: Favourable = Tumor size (maximum dimension) ≤ 5 cm and age < 10 y, Unfavourable = All others (*i.e.,* size >5 cm or age ≥ 10 y)

Table 5 Dosing of chemotherapy for low-risk disease

Drug	Weeks to be administered	Dose
Vincristine	0,1,2,3,4,5,6,7,8,12,13,14,15 16,17,18,19,20,24,25,26,27 28,29,30,31,32,36,37,38,39 4041,42,43,44	<1 y: 0.025/kg 1–3 y: 0.05 mg/kg >3 y: 1.5 mg/m^2 (max dose 2 mg)
Actinomycin D*	0,3,6,9,12,15,18,21,24, 27,30,33,36,39,42,45	< 1 y: 0.025/kg > 1 y: 0.045 mg/kg (max dose 2.5 mg)
Cyclophosphamide (for subset B only) (with MESNA)	0,3,6,9,12,15,18,24, 27,30,36,39,42	< 1 y: 36 mg/kg 1–3 y: 73 mg/kg > 3 y: 2.2 g/m^2

*Actinomycin D to be omitted during radiation therapy

with long-term survival reaching over 90% [19]. The low-risk RMS are further subgrouped into subgroup A and B.

Subgroup A

- Histology: Embryonal / Botryoid
- Stage 1, Groups I, II (N0)
- Stage 1, Group III (N0) orbit only
- Stage 2, Group I (N0)

Subgroup B

- Histology: Embryonal /Botryoid
- Stage 1, Group II (N1) – microscopic residual disease
- Stage 1, Group III (N1) orbit only – gross residual disease
- Stage 1, Group III (N0) – gross residual disease
- Stage 2, Group II (N0) – microscopic residual disease, < 5 cm primary
- Stage 3, Group I or II (N0) – < 5 cm with + lymph nodes or >5 cm primary regardless of lymph node status, − margins or microscopic residual disease

The results of the COG D9602 study were inferior to those in IRS IV especially for subset A patients; a further trial (COG-ARST0331) demonstrated similar EFS with four cycles of VAC (Vincristine, Actinomycin D and Cyclophosphamide) and shorter duration of Vincristine/ Actinomycin D [20]. A further reduction of therapy for the very low-risk group is presently undergoing trial by the EpSSG.

Management of Intermediate-Risk RMS

Chemotherapy for intermediate-risk RMS has mainly involved VAC regimen: Vincristine, Actinomycin D and Cyclophosphamide (See dosing in Table 7). A randomized study comparing VAC regimen with VIE (Vincristine, Ifosfamide and Etoposide) and VAI (Vincristine, Actinomycin D and Ifosfamide) showed outcomes to be similar. However since VAC is easier to administer and is a single day chemotherapy dosing–this regimen has become frontline chemotherapy for all intermediate-risk RMS [21]. A further COG randomized study evaluated the addition of topotecan /cyclophosphamide cycles to standard VAC regimen. This study did not find any additional benefit of adding topotecan to VAC regimen [22]. A combination of Vincristine/ Doxorubicin/Cyclophosphamide (VDC) alternating with Ifosfamide/Etoposide (IE) was also used to treat patients with intermediate-risk RMS. The relative efficacy of this approach *vs*. the standard approach requires further investigation [23]. Thus VAC remains the frontline regimen for treating children with intermediate-risk RMS.

The EpSSG has traditionally used ifosfamide instead of cyclophosphamide for patients who are similar to intermediate-risk RMS. Other drugs which are under evaluation is the role of doxorubicin (in addition to VAC) and maintenance chemotherapy with vinorelbine and cyclophosphamide. The expected outcome from previous studies is over 70% in this group of patients (5 y EFS 73% and OS 78%).

Management of High-Risk RMS

High-risk RMS includes patients who have one or more distant metastases at diagnosis. These patients continue to have a

Table 6 Chemotherapy for low-risk disease (as per COG D9602 trial)

Low-risk RMS	Chemotherapy	Additional therapy	Expected outcome
Subset A	Vincristine Actinomycin D Total duration: 48 wk	RT 36Gy (Group IIa) RT 45Gy (Group III orbit)	5 y EFS 89% 5 y OS 97%
Subset B	Vincristine Actinomycin D Cyclophosphamide Total duration: 48 wk	RT 36Gy (Group IIa) RT 45Gy (Group III orbit)	5 y EFS 85% 5 y OS 93%

RT Radiotherapy; *EFS* Event free survival; *OS* Overall survival

Table 7 VAC regimen

Drug	Weeks to be administered	Dose
Vincristine	0,1,2,3,4,5,6,7,8,9,10,11,12, 15,18,19,20,21,22,23,24, 27,30,33,34,35,36,39	< 1 y: 0.025/kg 1–3 y: 0.05 mg/kg >3 y: 1.5 mg/m^2 (max dose 2 mg)
Actinomycin D*	0,3,6,9,12,15,18,21,24,27, 30,33, 36,39	< 1 y: 0.025/kg > 1 y: 0.045 mg/kg (max dose 2.5 mg)
Cyclophosphamide (with MESNA)	0,3,6,9,12,15,18,21,24,27, 30,33,36,39	< 1 y: 36 mg/kg 1–3 y: 73 mg/kg > 3 y: 2.2 g/m^2

*Actinomycin D to be withheld during radiation therapy

poor outcome (5 y survival rate of 50% or lower) with current therapy [24].

The standard systemic therapy for this group of patients remains the three drug regimen VAC (Table 7). Despite many trials which have tried to improve outcome by addition of other chemotherapeutic agents or substituting newer agents for the conventional VAC, there has been no significant improvement in outcome demonstrated. The drug combinations which have undergone clinical trials and have not shown to improve outcome are vincristine/melphalan, topotecan/cyclophosphamide, ifosfamide/doxorubicin, vincristine/irinotecan and also a European trial which looked at 6 drug-chemotherapy including sequential high dose monotherapy. Hence VAC still remains the standard chemotherapeutic regimen in high-risk RMS [25]. High-dose chemotherapy with autologous stem cell rescue has been evaluated in a small number of patients, but this intense therapy has not been shown to improve outcome both in newly diagnosed and recurrent RMS [26].

The prognosis of metastatic RMS is dependent on several adverse factors. Age < 1 y and more than 10 y, unfavourable primary site, bone and/or bone marrow involvement, and three or more sites of metastases have all adverse outcomes. The EFS is 50% for patients with none of the adverse factors, 42% for one adverse factor, 18% for two adverse factor, 12% for three adverse factors and 5% for four adverse factors [25].

Treatment of Recurrent RMS

Outcome from salvage therapy of a recurrent RMS is dependent on various factors: time of recurrence (<18 mo), metastatic (as opposed to local) recurrence, previous radiotherapy, previous tumor size >5 cm. The prognosis is favorable for children who initially presented with stage I/group I disease, embryonal histology and have a locoregional recurrence only. The role of high dose chemotherapy with autologous stem cell rescue has not been established in a recurrent setting. The chemotherapy regimens that have been used for salvage are listed below:

- Carboplatin/etoposide
- Ifosfamide/carboplatin/etoposide
- Vincristine/irinotecan
- Cyclophosphamide/topotecan
- Vinorelbine/cyclophosphamide.

Radiotherapy Guidelines

Tables 8 and 9 summarize details of indication, dose and timing of radiotherapy.

Table 8 Radiation therapy (RT): indications and dose

S. no.	Abdominal tumor stage/ Histology	RT field	RT dose
1.	Group I		
	Embryonal	No RT	
	Alveolar	Pre-chemotherapy primary site	36Gy
2.	Group II		
	N0 (Microscopic residual disease after surgery)	Pre-chemotherapy primary site	36Gy
	N1 (Resected regional lymph node involvement)	Pre chemotherapy primary site + Nodes	41.4Gy
3.	Group III		
	Orbital and Non-orbital tumors	Pre-chemotherapy primary site	50.4Gy
	Invasive tumors	Phase I: Pre-chemotherapy primary site	36Gy
	Non-invasive pushing tumors	Phase II: Volume reduction (if excellent response to chemotherapy)	14.4Gy
	Patients undergoing delayed surgical resection with negative margins	Pre-chemotherapy primary site	36Gy
4.	Group IV	Treat primary site as for other groups + all metastatic sites if technically feasible and safe	

Table 9 RT timing

S. no.	Disease extent	Timing of RT
1.	Intracranial extension Cranial nerve palsy Base skull involvement	Day 0 of chemotherapy
2.	Para-meningeal involvement	Week 3 of chemotherapy
3.	All other sites	Week 9 of chemotherapy

Radiotherapy for Special Situations

Very young children (Aged ≤36 mo) They pose a therapeutic challenge because of their increased risk for treatment-related morbidity. However, for infants who are unable to undergo surgical resection, radical doses of RT remain appropriate.

Orbital RMS It should be treated with chemotherapy and radical RT. It is not necessary to include entire orbit in the target volume.

Non-Orbital Head & Neck RMS

Parameningeal: These do not require whole-brain irradiation unless tumor cells are present in the CSF at diagnosis. Patients should receive RT to the site of primary tumor with a 1.5 cm margin to include the meninges adjacent to the primary tumor and the region of intracranial extension, if present, with a 1.5 cm margin.

Non-Parameningeal: Surgical resection should be done only if a wide local excision is feasible without causing significant morbidity. Most patients should be treated with chemotherapy and definitive RT.

Intra-abdominal/Intra-thoracic Post-operative RT improves EFS. Patients with peritoneal disease and ascites benefit with whole abdominal RT.

Biliary tree/ anus and perineum Chemotherapy and definitive RT should be offered if surgical resection is not feasible or associated with significant morbidity.

Paratesticular For patients requiring adjuvant RT, testicular transposition into the adjacent thigh should be considered.

Bladder/ Prostate Except for patients with lesions exclusively involving the bladder dome who can undergo adequate surgical resection, rest of the patients should be treated with chemotherapy and RT.

Table 10 Suggested surveillance schedule to detect tumor relapse and late effects specific to site of primary (and prior therapy)

Site	Likely local therapy	Late effects monitoring
Orbit	Radiotherapy	Annual eye check
Maxillary/mandibular	Surgery/Radiotherapy	Annual dental examination
Other head and neck sites	Radiotherapy to ears	Auditory evaluation annually
	Radiotherapy to neck	Thyroid function 2 yearly
Thorax (primary or metastases)	• Pulmonary Radiotherapy • Radiotherapy to chest primary	• Exercise intolerance • Pulmonary function test • 2D ECHO (if heart in radiation field) • Breast cancer screening
Abdominal tumors	• Surgery • Radiotherapy	• Kidney function in case of kidneys in radiation field • Monitor for bowel problems, rectal stenosis, sphincter problems *etc*. • RT port involving hip joints–monitor for slipped capital femoral epiphysis
Extremity sites	• Radiotherapy • Surgery	• Limb length discrepancy • Mobility problems
Genitourinary	• Surgery • Radiotherapy	• Kidney function • Bladder function • Ovarian failure/testicular failure • Erectile dysfunction

*To detect tumor relapse, clinical examination should be done every 3 monthly in 1st year, 6 monthly in 2nd-3rd year and then every year till 5 y post completion of therapy. Imaging of primary site (USG/CT Scan/ MRI) and X-ray chest should be done 3 monthly in 1st year, 6 monthly in 2nd-3rd year and then every year till 5 y

Vulva/ Vagina/ Uterus Radical surgery should be avoided at these sites. Patients treated with chemotherapy and radical RT (External RT and brachytherapy) achieve good outcomes with function preservation. The COG-ARST0331 study reported an unacceptably high rate of local recurrences in girls with group III vaginal tumors who did not receive RT.

Post Treatment Surveillance

All patients post-treatment should be followed-up for 5 y for possible tumor relapse and until adulthood for treatment side-effects. A suggested surveillance schedule is summarized below (Table 10).

Future Challenges

Biologic studies involving anti-angiogenic agents like TNP-470, antibody to vascular endothelial growth factors and peptides derived from *PAX3*/*FKHR* fusion protein are underway. All these novel strategies will need long-term evaluation so that they can subsequently be added to the current armamentarium.

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