



CLINICAL PRACTICE GUIDELINES FOR PATIENTS WITH RHABDOMYOSARCOMA

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1. BACKGROUND AND RATIONALE

1.1 Background and epidemiology

Rhabdomyosarcoma (RMS) is a malignant tumour and is thought to arise from primitive mesenchymal cells committed to skeletal muscle lineage. RMS can be found virtually anywhere in the body, including those sites where striated muscles are normally not found. Soft tissue sarcomas comprise a heterogeneous group of tumours with Rhabdomyosarcoma being the most common soft tissue sarcoma in children and young adults. RMS accounts for approximately 4 - 5 % of all childhood malignancies with an annual incidence of 5.3 per million children under the age of 15. The peak incidence is seen early in childhood with a median age at diagnosis of around 5 years. RMS occurs more frequently in males than females.

The aetiology remains unknown, however genetic factors may play an important role as demonstrated by an association between RMS and several germ-line genetic disorders such as Li Fraumeni syndrome, congenital anomalies (involving the genitourinary and central nervous system) and other genetic conditions, including neurofibromatosis type 1 and DICER1 tumour predisposition syndrome [1].

Since the first classification of RMS in 1958 by Horn and Enterline, multiple modifications to their classification have been made. There are four main subtypes of RMS, distinguished by histopathology: embryonal subtype (which accounts for approximately 80% of all RMS), alveolar subtype (15 - 20% of RMS) and the rarer pleomorphic and sclerosing/spindle cell RMS.

It has been shown that histological subtype has an impact on survival, and so in 1995 pathologists from the different Cooperative Groups agreed a new classification which identified prognostically significant and reproducible subtypes [2]. Three main classes have been identified:

- 1) Superior prognosis: including botryoid RMS and spindle cell or leiomyomatous RMS;
- 2) Intermediate prognosis: represented by embryonal RMS (eRMS);
- 3) Poor prognosis: including alveolar RMS (aRMS) and its variant solid alveolar.

This classification system does not include the pleomorphic category, as this is very rarely seen in children, and requires a different approach.

Molecular biology studies have revealed a series of genetic aberrations and non-random chromosomal translocations leading to a further sub classification of RMS: Fusion-positive and fusion-negative RMS. In aRMS two characteristic chromosomal alterations are seen: The more frequent reciprocal chromosomal translocations t(2;13)(q 35; q14) or the less frequent t(1;13)(p36;q14) [3]. Genetic loss on chromosome 11p15.5, point mutations in TP53, NRAS, KRAS, HRAS, PIK3CA, CTNNB1, NF1, and FGFR4, as well as MDM2 amplifications and aneuploidy has been shown in eRMS [4]. Different studies have demonstrated that the presence of the t(2;13) or t(1;13) translocation has a prognostic value with alveolar RMS fusion positive having a worse prognosis in comparison with those fusion negative [1]. However it is still not clear if the t(1;13) might be more favourable than the t(2;13).

Various staging systems have been developed over the years to try to classify RMS into categories from which treatment can be planned and prognosis predicted. The most widely used are the pre-treatment TNM staging and the postoperative IRS Grouping system (see appendix 2/3). However, with the evolution of new treatments and published trial data, new, more complex, risk groupings are now available to better tailor the treatment to the risk of relapse.

Modern risk grouping attempts to take all the factors shown to be prognostically important into account. Stage, site and histology are considered to be the most important risk factors. They are also interdependent with, for instance, orbital tumours being almost exclusively of the embryonal subtype and limb tumours overrepresented amongst those with alveolar histology. More recent analyses show that fusion status (presence or absence of a PAX3/7-FOXO1 fusion) has a stronger impact on prognosis than histology. Therefore, in current treatment stratification fusion status replaces histology. Where fusion status is unknown, histology can be used [5].

The size of the tumour has a prognostic impact similar to that of other soft tissue sarcomas. More recently the patient's age at diagnosis has been recognised as a predictor of survival, with the older children (≥ 10 years old) having the worse outcome [6].

1.2 Treatment strategies

A multimodality approach involving surgical treatment, chemotherapy and radiotherapy is necessary in the treatment of children with RMS. According to the patient's individual risk group assignment, the optimal timing and intensity of these three treatment modalities must be evaluated with taking into consideration prognostic factors but also the late effects of treatment.

Local control is a main pillar of treatment in localized RMS, but is also necessary in more advanced stages. Local control may be achieved with surgery and/or radiotherapy. Here a conservative approach is recommended, avoiding mutilating interventions and so neoadjuvant chemotherapy to reduce tumour volume is highly recommended. In addition, chemotherapy is essential to treat micro metastatic disease.

Different drug combinations proved to be effective against RMS and vincristine and actinomycin based chemotherapy is used combined with an alkylating agent in most risk group categories. The most widely used regimens are VAC (vincristine, actinomycin D, cyclophosphamide), VACA (VAC plus Adriamycin alternating with actinomycin D), IVA (as VAC, but with ifosfamide replacing cyclophosphamide) and VAIA (IVA with adriamycin alternating with actinomycin D). Based on the two most recent European and COG trials the intensity of chemotherapy is tailored on the risk of relapse. Patients included in the low risk group are treated with the VA combination, excluding therefore the use of alkylating agents. In standard risk patients the use of a limited cumulative dose of alkylating agents is possible, therefore a combination of IVA and VA cycles is employed. For patients with high risk disease, doxorubicin has been abandoned and the current standard in Europe is IVA chemotherapy [7] and VAC or VAC-Irinotecan in North America [8].

Intensive chemotherapy including the VAIA, IVADo and CEVAIE regimens have been administered to very high risk and metastatic patients. No combination proved to be more effective and therefore there is no standard chemotherapy for metastatic patients.

Maintenance treatment was introduced in the EpSSG RMS2005 study in the high risk group and proved to increase patients' survival. The administration of 6 months of vinorelbine and low dose continuous cyclophosphamide is now standard of care in Europe for high risk patients and has been adopted in very high risk and metastatic patients (12 months duration) in the attempt to improve their prognosis [9]. Other types of maintenance (i.e. the oral administration of Etoposide, Idarubicin and Trofosfamide in the CWS studies [10]) or the length of maintenance (6 vs 12 vs 24 in the Frontline and Relapsed-RhabdoMyoSarcoma (FAR-RMS study) are under evaluation.

The multimodality approach based on different strategies and different chemotherapy regimens that have been evaluated and proven efficacious in several clinical trials run by different cooperative groups constitute the evidence for this guideline.

1.3. Rationale

This treatment guideline aims to provide comprehensive, up-to-date and evidence-based recommendations for risk-adapted rhabdomyosarcoma (RMS) treatment in children, adolescents, and young adults in Europe. It is our goal to harmonize and improve the care of patients with RMS across Europe by providing standards for diagnostics, treatment and follow-up.

The information presented in this guidelines is based on a consensus of the different clinical trial groups across Europe.

2.0 PATIENT MONITORING AND ASSESSMENT

2.1 Patient Group

This guideline document should be applied in patients with a pathologically proven diagnosis of Rhabdomyosarcoma with the following characteristics:

- localized or metastatic disease
- at first diagnosis
- all histological subtypes (excluding pleomorphic RMS)

This guideline can also be used in adult patients (> 18 years) with rhabdomyosarcoma with the exception of those with a pleomorphic RMS. These guidelines could also be applied in patients usually excluded from trials such as those

- with long interval between diagnostic surgery/biopsy and start of treatment
- pre-treated (adaptation may be needed taking into account the treatment already delivered).
- with RMS as a second tumour (adaptation may be needed taking into account the treatment given to treat the first tumour)

Patients with pre-existing illness can be treated according to these guidelines but the treating physician may need to adapt the strategy (i.e. avoid nephrotoxic drugs in patients with renal damage or anthracyclines in those with cardiac disease). Furthermore, patients with cancer predisposition syndromes may benefit from this guideline, but again, modifications may be required as directed made by the treating physician.

2.2. Diagnostic Criteria

To assure an appropriate staging and risk group allocation, several standard of care pre-treatment investigations are recommended and described here. However, these recommendations may need to be adapted to locally available infrastructure (e.g. availability of PET scan).

Moreover it is advised that the pre-treatment work-up should be completed no longer than one month before the start of treatment. If a delay occurs, one may reconsider a restaging.

Imaging of the primary and metastatic sites will need to be performed at predefined time points during the course of treatment to evaluate treatment response and determine mode of local treatment, and at completion of therapy. In addition, one should consider repeat imaging if a surgical biopsy at diagnosis has led to significant reduction of tumour volume and in case progression is suspected, see section 2.2.2 for imaging suggestions.

See appendix 1 for a table of baseline assessment.

For loco regional evaluation MRI is the method of choice, CT should not be used for soft tissue tumours if MRI is available. The role of CT in imaging of the primary tumour is mainly limited to those cases where evaluation of subtle bone destruction is needed or in rare cases e.g. when the tumour is located in the thorax.

A thorough history must be taken including the family history to identify a cancer-predisposition syndrome that might be associated with the rhabdomyosarcoma

Next, a complete physical examination including vital signs, measurement of height and weight should be performed. Specific attention should be focused on the primary tumour site and potential involvement of regional lymph nodes.

2.2.1 Laboratory workup and organ function

We recommend the following laboratory parameters/organ function tests as a baseline assessment:

- Full blood count (FBC) and differential white blood count, blood type.
- Basic renal and liver function
- Basic Serum electrolytes including phosphate and bicarbonate
- Coagulation profile
- FT4, TSH and IGF-1, IGF-BP3 for patients with head and neck site
- Serum virology according to standard of care
- ECG, cardiac function tests according to standard of care

- Audiometry for patients with head and neck site
- Sperm cryopreservation is strongly recommended in male patients of appropriate age.

2.2.2 Imaging modalities

- MRI of the primary site: The field of view of the MRI should include loco-regional lymph nodes and possible loco-regional extension of disease. Besides routine T1 and T2 weighted sequences and post Gadolinium sequences, diffusion-weighted Magnetic Resonance Imaging (MRI) imaging should be undertaken. For DWI-MRI of the primary tumour preferably the following 4 B-values may be used: 0, 100, 500 and 1000 s/mm². DWI should be performed in the axial plane. For a comprehensive summary on technical settings (orientation, slice thickness, voxel size, echo time, repetition time, b values) please refer to van Ewijk et al. "European guideline for imaging in paediatric and adolescent rhabdomyosarcoma" provided in Online Supplementary Material 1 [11].
Imaging of the primary site should include tumour volume measurement and examination of regional lymph nodes especially if not evaluable clinically or if clinically suspicious.
- Chest CT scan: The presence of lung metastases must be evaluated in all patients at diagnosis by CT scan and postero-anterior and lateral chest radiographs (for comparison with follow-up chest radiographs). Slice thickness of the CT scan should be 1 mm or 1.5 mm at maximum. The examination should preferably be performed in supine position and full inspiration. Reading should be performed at minimum in axial and coronal plane; the use of maximum intensity projections is advised to improve sensitivity. Also see section of lung lesion evaluation below for further details.
- FDG-PET-CT/MRI, alternatively whole body MRI: It is advised to be done at diagnosis for evaluation of nodal and distant metastases. FDG-PET-CT should be performed in line with current European Association of Nuclear Medicine (EANM) guidelines [12].
- Bone scintigraphy: Not indicated and should no longer be performed.
- Ultrasonography: Is indicated in case of equivocal findings regarding lymphadenopathy or liver metastases. Ultrasonography cannot be used to monitor treatment response.

2.2.3 Evaluation of radiological findings

Primary tumour site

At diagnosis and follow-up tumours must be assessed using one-dimensional measurements according to RECIST 1.1 [13]. Here the longest diameter (one-dimensional) in any orthogonal plane should be recorded. Only lesions > 10 mm are selected as target lesions.

Lymph nodes

Defining lymph node involvement is critical to staging, although accurately evaluating pathological lymph nodes (LN) on imaging can be challenging. MRI and FDG PET-CT/MRI are the primary modalities to assess lymph node involvement. On MRI, pathologic lymph nodes must meet the criterion of a short axis of ≥ 15 mm. On FDG PET-CT/MRI visual assessment using Deauville like score, where liver uptake as reference tissue is used, is recommended to detect lymph nodes suspicious for malignancy. Any FDG positive lymph node with a short axis < 15 mm should be considered suspicious. It is strongly recommended to perform a biopsy in the case of doubtful or suspected nodal involvement; based on imaging characteristics (abnormal node morphology), short axis > 10 mm or equivocal FDG uptake [14].

Regional lymph nodes are defined as those appropriate to the site of the primary tumour: see appendix 4 "Definition of Sites", table 5.

Pulmonary lesions

Assessing pulmonary spread of tumour is critical to staging. According to the E ρ S ρ SSG criteria, the following three categories of findings are defined:

- No metastatic disease, defined as no pulmonary lesions present.
- Indeterminate pulmonary lesions, defined as the presence of either:
 - One well-defined nodule measuring 5 to <10 mm in diameter or;
 - Maximum of four well-defined nodules smaller than 5 mm in diameter.
- Pulmonary metastases, defined as the presence of either:
 - One or more pulmonary nodules of 10 mm or more in diameter;

-
- Two or more well-defined nodules of 5 to 10 mm in diameter;
 - Five or more well-defined nodules smaller than 5 mm in diameter.

For an extensive imaging guideline, we refer to

Van Ewijk R et al, on behalf of the CWS Imaging Group, the ESPR Oncology Task Force and the EpSSG Imaging Group. European guideline for imaging in paediatric and adolescent rhabdomyosarcoma: a joint statement by the European paediatric Soft tissue sarcoma Study Group, the Cooperative Weichteilsarkom Studiengruppe and the Oncology Task Force of the European Society of Paediatric Radiology [11].

2.3. Tumour biopsy

The primary biopsy should either be performed in the oncology treatment center where the definitive resection will be done, or planned in direct communication with that team.

Biopsy of a suspected rhabdomyosarcoma is the default primary procedure with two exceptions: 1. if a paratesticular tumour can be resected with a microscopic radical (R0) inguinal orchiectomy (section 5.1.5.4) upfront and 2. in case of very small tumors that can be easily resected with microscopic negative margins without compromising form or function. If rhabdomyosarcoma is suspected a FDG-PET-CT is preferably done before surgery, to avoid false positive reactive findings.

Tumour biopsy can be performed as an image-guided core needle, incisional, or endoscopic biopsy, and enough material should be obtained for histology, immunohistochemistry, cytogenetics, fluorescence in situ hybridization (FISH), biological studies and tumour banking. An image-guided core needle biopsy (CNB) using a 16 or 14 Gauge coaxial needle to obtain at least 4 to 8 cores, is preferred over an incisional biopsy (IB) as the diagnostic rate of both techniques is similar and CNB is associated with fewer complications compared to IB [15]. The biopsy must be performed so that the scar and biopsy track can be easily included in the subsequent definitive surgical procedure or radiotherapy field.

After pathological diagnosis is clear, a primary resection of the tumour is only indicated if the tumour can be excised with R0 margins in a non-mutilating procedure.

2.3.1 Lymph node biopsy

In case of radiological and/or clinical suspected lymph node involvement, a histological confirmation is highly recommended, independent on the histological subtype. The sentinel node procedure offers a structured method to sample the lymph nodes [16].

- **Paratesticular RMS:**

Accurate staging of regional nodal metastases in paratesticular RMS is important as lymph node involvement is relatively frequent (26% in IRS I & II trials) and patients with positive nodes require intensified chemotherapy and RT. All patients should have FDG-PET-MRI/CT imaging of the retroperitoneal nodes, and those ≥ 10 years of age should also undergo surgical staging of the lymph nodes.

Template retroperitoneal lymph node dissection (RPLND) has frequently been avoided due to concern about potential complications. Sampling between 7-12 lymph nodes taken from multiple areas in the ipsilateral retroperitoneum up to the renal vessels may be similarly efficacious to identify nodal involvement while minimizing the complications of template RPLND [17, 18].

- **Extremity RMS:**

Upper and lower limb tumours must have surgical evaluation of axillary or inguinal nodes respectively, even if nodes are clinically/radiologically normal. This applies for all histological entities. A sentinel node procedure is recommended if available; alternative is random sampling.

2.3.2 Bone marrow biopsy

For the evaluation of bone marrow involvement, at least one bone marrow aspirate and representative trephine should be performed. Patients with evidence of node or distant metastases and all those with fusion positive tumours, or alveolar histology (in case no fusion status available) should have bilateral aspirates and trephines.

2.3.3 CSF Examination

For parameningeal tumours a cerebral spinal fluid examination for cytospin and cell count is recommended.

2.4. Histopathology

The information provided below is not meant to be a comprehensive review of the histopathology of RMS. For full description and morphologic-based classification refer to Soft Tissue Tumours, Enzinger & Weiss, Diagnostic Soft Tissue Pathology, Markku Miettinen and WHO Classification of Tumours of Soft Tissue and Bone [19, 20] [21].

2.4.1 Classification [22-25]

Rhabdomyosarcoma can be broadly classified into different subtypes, namely the embryonal, the alveolar, the sclerosing/spindle cell, the rarer pleomorphic subtype, mixed subtypes, not otherwise specified RMS and last RMS with anaplasia. In some subtype further sub classifications can be distinguished:

2.4.1.1. Embryonal RMS

ERMS can be divided into the three sub classification: ERMS classic including botryoid, ERMS dense cellular and ERMS with spindle cell component.

2.4.1.1.1 ERMS classic including botryoid

Classic Embryonal RMS (ERMS) form poorly circumscribed, fleshy, pale masses that may show areas of haemorrhage, necrosis and even cyst formation.

These tumours have a variable pattern ranging from poorly differentiated tumours to well differentiated neoplasms. There are a number of features common to all these tumours:

- i. myxoid stroma;
- ii. a mixture of small cells with hyperchromatic spindle shaped cells and other cells showing variable degrees of rhabdomyoblastic differentiation;
- iii. variable degree of cellularity with dense areas usually around vessels alternating with loose, hypo cellular myxoid areas.

Note – foci of immature cartilage can be seen in some Embryonal RMS

Two differential diagnoses that can cause problems are fetal rhabdomyoma and pseudosarcomatous myofibroblastic tumour and require special attention.

Botryoid ERMS is characterised macroscopically by its polypoid (grape-like) growth. Most are found in mucosa-lined hollow regions such as the nasal cavity, vagina and urinary bladder. Histologically they are characterised by a cambium layer beneath an intact epithelium, in at least one microscopic field – irrespective of the gross description, and therefore supersedes the gross demonstration of a 'grape-like' tumour. The degree of differentiation of rhabdomyoblasts may vary from slight to well differentiated

2.4.1.1.2 ERMS with predominant spindle cell component

This form is seen particularly in paratesticular tumours. At this site where primary resections are undertaken, small foci of more-typical ERMS are usually present as well. This subtype, however is difficult to diagnose in biopsies from other sites.

2.4.1.1.3 ERMS dense cellular [26]

Dense cellular embryonal RMS is a fusion-negative RMS characterised by a uniform, dense population of tumour cells often confused morphologically with alveolar RMS, particularly solid variant ARMS. They can be distinguished by more variability in the size and shape of cells, angulated nuclei and prominent nucleoli. Immunohistochemistry may also help in distinguishing between the two: dense cellular

embryonal RMS displays relatively reduced nuclear staining for myogenin (generally <80%) compared to ARMS (usually >80%), but overlap does occur, and therefore the molecular biology is important.

2.4.1.2. Spindle Cell/Sclerosing RMS

Spindle cell /Sclerosing RMS accounts for approximately 3-10% of RMS. It has been described in infants, children, and adults.

In children this tumour is commonly seen in the paratesticular region, followed by the head and neck region, but can occur in other sites. Grossly the tumour is firm and well circumscribed but not encapsulated. The cut surface shows a nodular pattern often with a whorled appearance.

Histologically the tumour is composed almost exclusively of spindle cells with cigar shaped or ovoid or fusiform, centrally located nuclei with small inconspicuous nucleoli.

Spindle cell RMS is characterized by cellular fascicles of spindle cells with an intersecting or herringbone growth pattern, resembling leiomyosarcoma or fibrosarcoma, but some tumours are rich in collagen, and are less cellular. In addition, primitive undifferentiated areas with round cells and hyperchromatic nuclei may be present focally.

Sclerosing RMS show prominent hyalinization and /or sclerosis, with tumour cells arranged in cords, nests, microalveoli, or trabeculae in a pseudovascular growth pattern. The three subtypes show typical genetic characteristics:

Spindle cell rhabdomyosarcoma typical of young children (< 2 years)

Variant which shows *VGLL2/NCOA2/CITED2* rearrangements [27, 28].

MYOD1-mutant spindle cell / sclerosing rhabdomyosarcoma

Variant which shows MYOD1 mutations [29-31].

Intraosseous spindle cell rhabdomyosarcoma

Variant which shows the typical spindle cell morphology, and areas of epithelioid cells in sheets and fascicles, it has been associated with either an *EWSR1/FUS-TCF2* gene fusion or a *MEIS1-NCOA2* gene fusion [32].

2.4.1.3. Alveolar RMS

ARMS with the two sub classifications: classic (with varying translocations) and solid variant ARMS.

2.4.1.3.1 Classic alveolar RMS

Alveolar RMS is a rapidly growing, soft-tissue tumour with a fleshy, grey tan appearance. ARMS displays a nesting alveolar or solid pattern of cells. The cells have monotonous, round to oval nuclei and inconspicuous nucleoli, but some can have prominent nucleoli.

In the classic type, tumour cells are arranged in nests separated by fibrovascular septa, with central loss of cohesion, with peripheral cells adhering to the fibrous septa. Multi-nucleated tumour cells with eosinophilic cytoplasm and nuclei arranged in a 'wreath-like' fashion are seen in the alveolar structures and can be helpful in the diagnosis of alveolar RMS especially in small biopsies. The characteristic "alveolar" pattern is well recognised.

Some alveolar RMS present with bone marrow infiltration and the only material available for diagnosis is a trephine biopsy. The same criteria for making the diagnosis apply.

2.4.1.3.2 Solid variant ARMS

A poorly differentiated, cellular tumour composed of sheets of cells with no fibrous septa. They share the same cytomorphological features of ARMS and may have thin, fibrous septa, but lack well defined alveolar spaces.

70 to 80% of ARMS have translocations resulting in the fusion of PAX3 or PAX7 gene to FOXO1. In fusion positive cases PAX3-FOXO1 accounts for 70-90% and PAX7-FOXO1 for 10-30% [33-40].

Less common fusion gene variants (approximately 1%) include the fusion of PAX3 to FOXO4, NCOA1, and the fusion of FOXO1 to FGFR1.

2.4.1.3.3 Mixed ERMS/ARMS

Some tumours display mixed embryonal and alveolar morphologies; however, these cases typically lack the *FOXO1* gene rearrangements, but some cases of so called mixed ERMS/ARMS with evidence of PAX3/7-FOXO1 translocations have been reported.

2.4.1.4 Rhabdomyosarcoma NOS (not otherwise specified)

Please note, RMS NOS. is not a subtype; it indicates that a diagnosis of RMS can be made but no further subtyping is possible. This usually arises when the biopsy is very small, sometimes with crushing artefact; it is only possible for the histopathologist to make a diagnosis of RMS. When clinically feasible, a re-biopsy is indicated to ensure subtyping and molecular characterization.

2.4.1.5. Rhabdomyosarcoma with anaplasia

Anaplasia is diagnosed if RMS (both embryonal and alveolar) contains cells with large, lobulated hyperchromatic nuclei (at least 3 times the size of neighbouring nuclei) and atypical (multipolar) mitoses. The presence of anaplasia needs to be documented. Furthermore, it is important to document whether these cells are focal or diffuse. There is a reported association of anaplastic RMS with germline mutations in Tp53 [41-43].

2.4.2. Grading

Please note, grading of RMS is not recommended

2.4.3. Immunohistochemistry

Immunostaining with monoclonal antibodies against the intranuclear myogenic transcription factors myogenin (MYF4) and MyoD1 is recommended for all RMS subtypes. These are excellent markers show high sensitivity and specificity. Desmin, myogenin (MYF4) and MYOD1 are antibodies used routinely in the diagnosis of rhabdomyosarcoma.

The nuclear expression of myogenin is diffuse (>80%) in most cases of ARMS, with less staining seen in ERMS. However, some cases of ERMS notably dense cellular ERMS can show staining which is >50%.

Both ERMS and ARMS can show focal staining for cytokeratin, S100, NFP, and neuroendocrine markers [44-47].

Spindle cell / Sclerosing rhabdomyosarcoma is characterized by diffuse expression of desmin in all cases, with only focal expression of myogenin (MYF4) in most cases. MYOD1 staining can be focal or diffuse in the spindle cell tumours, but it is usually present in a diffuse pattern in the sclerosing cases.

2.4.4. Molecular

70-80% of ARMS cases have translocations resulting in fusion of the PAX3 or PAX7 gene with FOXO1. Further translocations have been described, however occur much rarer.

Several studies have shown that fusion positive ARMS has a worse prognosis and that ARMS lacking characteristic fusion genes are clinically and molecularly similar to ERMS.

Testing for these fusion genes in RMS is regarded as standard practice.

The emerging subset of MYOD1 mutant Spindle cell / Sclerosing RMS is associated with high mortality and overall poor outcome [32]. This highlights the need of further molecular testing.

2.4.5. Handling of specimen

2.4.5.1. Biopsy

The CNB should be counted and measured to obtain an overall length measurement. If adequate biopsy material is available, it should be separated and embedded in more than one cassette, to allow maximal use of material.

Likewise, incisional biopsies should also be divided into more than one cassette.

All primary and post-chemotherapy resection specimens need margins to be evaluated by the pathologist.

1. Surface of specimen should be inked before incision.
2. Specimen should be weighed and measured in mm (in 3 dimensions).
3. Orientation of specimen is important – this may need to be done with the surgeon. The distance of tumour from the nearest resection margin is important. In resected specimens, tumour depth e.g. dermal, subcutaneous, subfascial, intramuscular, needs to be specified macroscopically and microscopically.
4. Ideally the specimen should be photographed, including the cut surface, and a block guide prepared.
5. At least a block per centimetre of greatest tumour diameter needs to be sampled. However, it is strongly recommended that, where feasible, the entire specimen should be processed to ensure adequacy of excision and for accurate histological sub-typing of RMS.
6. The cut surface(s) should be examined and the pathologist should sample as above as well as taking blocks from areas which look macroscopically different in consistency or texture from other areas, in particular, take note of nodularity and sample.
7. Document macroscopic % of necrosis – sample areas of necrosis.
8. The pathologist should assess what tissue has been kept for molecular diagnostics/research. This can be done in one of two ways, either A – do a frozen section from the cut surface to assess i) tumour is present and ii) tumour is not necrotic, or B – a paraffin section, identified as representative section of tissue sent for molecular diagnostics/research can be taken and assessed as per frozen section.
9. Lymph nodes - please note – site of lymph nodes sampled should be documented as this is important in staging. All lymph nodes received by the pathologist should be examined. The entire lymph node or lymph nodes should be processed to ensure accurate assessment. Multiple levels need to be examined to exclude micro metastases, and when presence of tumour is equivocal immunohistochemistry should be undertaken.
10. Molecular characterisation (see schematic diagram).

2.4.5.2. Handling of Bone Marrow Trephine Biopsy

1. Sample should be fixed in buffered formalin and decalcified according to the laboratory protocol.
2. Multiple levels (H&E stain) should be examined to exclude metastatic RMS. Reticulin stain is helpful in highlighting small foci of tumour.
3. It is also important that when cutting levels intermediate sections are kept for immunostaining to avoid cutting out of micrometastases.
4. Routinely stain for desmin, MYF4 and MyoD1.

2.5. Risk Groups

In Europe, patients have been stratified in 8 Subgroups (A through H) that are grouped in 4 Risk Groups: low, standard, high and very high (see table at end of section). Treatment should be assigned according to the patient's individual risk group assignment, which should be done before treatment has commenced. The following factors are used to assign risk group:

- **Biology and pathology:**

We recommend patients to be stratified according to the fusion status, but if this would not be available then histology (favourable* vs unfavourable*) should be used

Favourable = PAX3 or 7/FOXO1 negative

Unfavourable = PAX3 or 7/FOXO1 positive

*Favourable = all embryonal, spindle cells (not MYOD1 mutated), botryoid RMS

*Unfavourable = all alveolar tumours (including the solid-alveolar variant)

- **Post-surgical stage:**

According to the IRS grouping.

Group I = primary complete resection (equivalent to SIOP pT1);

Group II = microscopic residual (equivalent to SIOP pT3a) or primary complete resection but node involvement (N1);

Group III = macroscopic residual (equivalent to SIOP pT3b).

For more details on IRS grouping system see also appendix 3 “IRS Clinical Grouping Classification”

- **Site:**

Favourable = orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus), GU Bladder prostate and head & neck non PM, biliary tract

Unfavourable = parameningeal, extremities, and “other site”

- **Node stage**

According to the TNM classification

N0 = no clinical or pathological node involvement

N1 = clinical or pathological nodal involvement

- **Size & Age:**

Favourable = Tumour size (maximum dimension) ≤ 5 cm AND age < 10 years

Unfavourable = all others (i.e. Size >5 cm OR age ≥ 10 years)

Note: patients with malignant effusion (i.e. tumour cell in peritoneal or pleural fluid) or cells in the spinal fluid should be treated according to the protocol for metastatic RMS

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

Table 1 Risk Stratification for RMS

3.0 TREATMENT DETAILS-CHEMOTHERAPY

3.1. Low Risk Group (A)

This group of patients must be selected with great accuracy as they receive limited chemotherapy. It is important to discuss the resection margins with both the surgeon and the pathologist before allocating a low risk treatment arm.

Primary re-excision is justified here if it can be done without important functional or cosmetic sequelae, and if there is a realistic prospect of achieving complete microscopic resection (R0). If the primary re-excision confirms clear margins, whether or not there is residual tumour in the resected specimen, the patient will be classified in the Low Risk Group and treated accordingly. If there is any doubt whatsoever about the completeness of resection, the patient should be allocated and treated in the Standard Risk Group.

Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	A	Negative	I	Any	N0	Favourable

3.1.1. Subgroup A Treatment

All patients with the following characteristics:

Localized non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,

and

nodes negative

and

tumour size < 5 cm

and

age < 10 years

The treatment consists of 8 courses of Vincristine (V) and Actinomycin D (A) separated by a 3-week rest period. Weekly vincristine will be administered between cycle 1 and 2, 3 and 4, 5 and 6, 7 and 8. The total duration of chemotherapy is 22 weeks.

	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

V = Vincristine 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection.

A = Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection.

Growth factors may be used at the physicians' discretion. We recommend to use them after each cycle if life threatening neutropenic CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

VA cycles should not be started unless all these condition are present: 2 x10⁹/l WBC or 1 x10⁹/l neutrophils + 80 x10⁹/l platelets + absence of any relevant organ dysfunction.

Weekly vincristine should be administered irrespective of pancytopenia providing the child is clinically well.

3.1.2. Local treatment

After the initial complete resection, no further local treatment procedure should be required. If there is any doubt whatsoever about the completeness of resection, the patient should be allocated and treated in the Standard Risk Group.

3.2. Standard Risk Group (B and C)

Patients included in the subgroups B, C are part of the Standard Risk Group. The treatment varies between the different standard risk subgroups.

Note: Patients with paratesticular RMS have to undergo lymph node biopsy. Only if negative, they will be treated according to standard risk group.

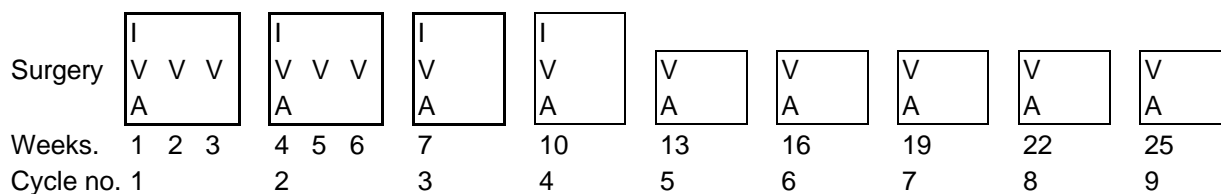
Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Standard Risk	B	Negative	I	Any	N0	Unfavourable

3.2.1. Subgroup B Treatment

All patients with the following characteristics:

Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,
 and
nodes negative
 and
tumour size > 5 cm or age > 10 years

The treatment comprises of 4 cycles of Ifosfamide, Vincristine and Actinomycin D (IVA) followed by 5 courses of Vincristine and Actinomycin D (VA). The total duration of chemotherapy is 25 weeks.



- I Ifosfamide 3 g/m² is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m²) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m²).
- V Vincristine 1.5 mg/m² (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- A Actinomycin D 1.5 mg/ m² (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

Growth factors may be used at the physicians' discretion. We recommend to use them after each cycle if life threatening neutropenia CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: $2 \times 10^9/l$ WBC or $1 \times 10^9/l$ neutrophils) + $80 \times 10^9/l$ platelets + absence of any relevant organ dysfunction

3.2.2. Local Treatment

These patients are in complete remission after initial surgery therefore they will not receive further local treatment (no RT or second look surgery). If there is any doubt whatsoever about the completeness of resection, and the tumour is at a favourable site, the patient should be allocated and treated in the Standard Risk Subgroup C; if the tumour is at an unfavourable site, patient should be treated according to subgroup D.

3.2.3. Subgroup C treatment (ARM SR-C)

Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Standard Risk	C	Negative	II, III	Favourable	N0	Any

All patients with the following characteristics:

**Non alveolar RMS, IRS Group II or III,
localised in orbit, head and neck non PM or GU including bladder-prostate,
and
nodes negative
and
any size or age**

Chemotherapy regimen depends on whether radiotherapy is given:

The treatment comprises of 5 courses of Ifosfamide, Vincristine and Actinomycin (IVA) and 4 courses of Vincristine and Actinomycin (VA) \pm Ifosfamide when combined with radiotherapy.

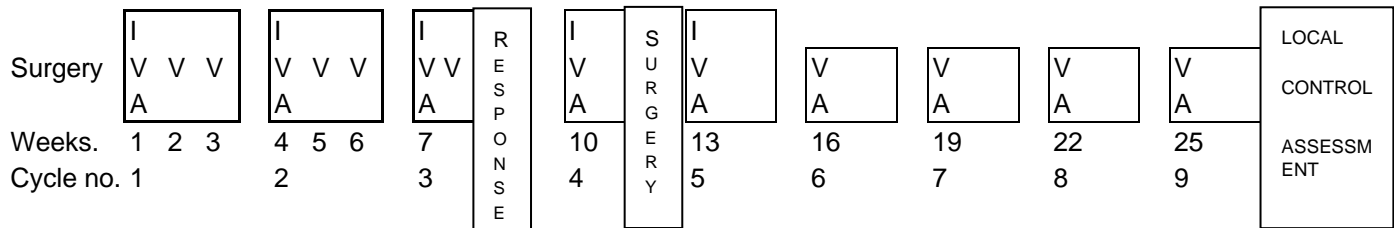
Where no radiotherapy is planned, patients should receive 9 IVA courses

Local treatment will be administered at week 13.

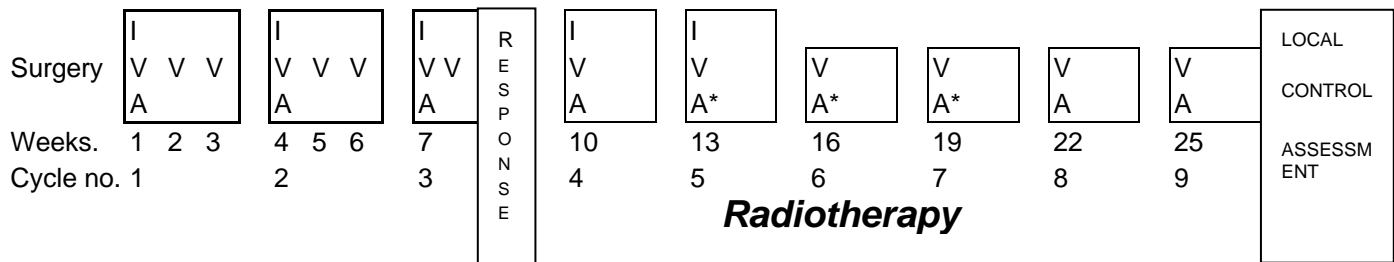
Note:

1. **Bladder-Prostate primary tumours** are now regarded favourable site based on favourable outcome in RMS 2005 but **ALL should receive 9xIVA chemotherapy irrespective of receiving radiotherapy.**

No radiotherapy



With Radiotherapy



- I Ifosfamide 3 g/m² is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m²) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m²).
- V Vincristine 1.5 mg/m² (max. single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- A Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

* Actinomycin can be given at the very beginning of RT, but should not be given during RT and two weeks after, with the exception of peripheral extremity tumours in which Actinomycin may be given also during RT. Ifosfamide in cycle 5 can be delayed to a later cycle to coincide with RT.

Growth factors may be used at the physicians' discretion. We recommend to use them after each cycle if life threatening neutropenia CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10⁹/l WBC or 1 x10⁹/l neutrophils) + 80 x10⁹/l platelets + absence of any relevant organ dysfunction.

3.2.4 Local treatment

Local treatment will be administered at week 13.

For details please refer to surgical therapy and radiotherapy in section 5.0 "Local Treatment"

3.2.5 Assessment of tumour response and treatment decisions

See chapter 4. "Assessment of tumour response and treatment decisions"

3.3. High risk patients (groups D, E and F)

The High risk group includes patients with different characteristics, however the treatment is the same for the different subgroups.

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

3.3.1. Intensive Treatment

All patients with the following characteristics:

Subgroup D

non alveolar, fusion negative RMS, IRS Group II or III, localised in parameningeal, extremities, or “other sites”

and

nodes negative

and

any tumour size or age

Subgroup E

non alveolar, fusion negative RMS, IRS Group II or III, any site

and

nodes positive

and

any tumour size or age

Subgroup F

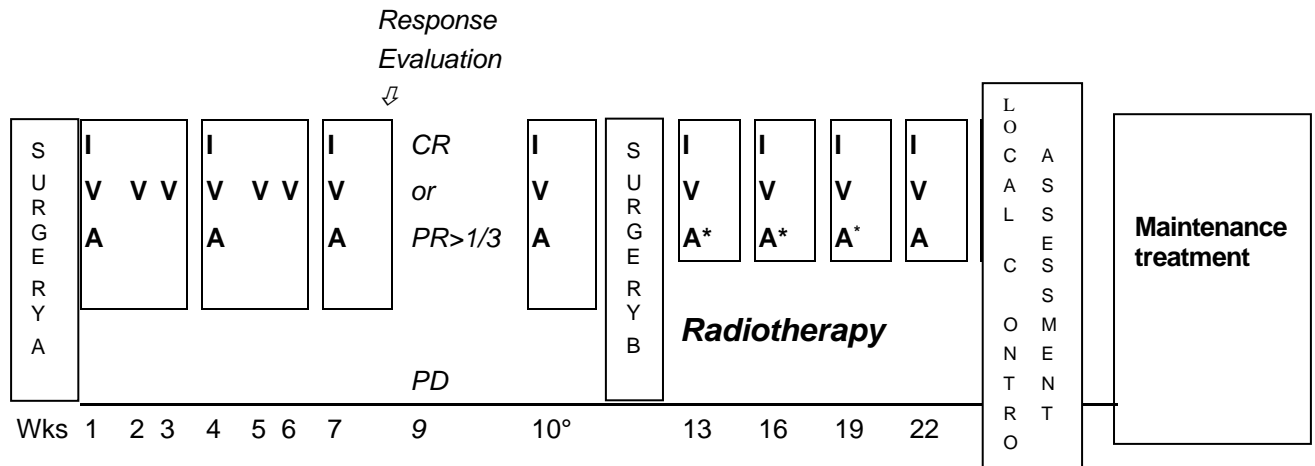
Alveolar, fusion positive RMS, IRS Group I or II or III, and any site

and

nodes negative

and

any tumour size or age



- I Ifosfamide 3 g/m² is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m²) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m²).
- V Vincristine 1.5 mg/m² (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- A Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

* Actinomycin can be given at the very beginning of RT, but should not be given during RT and two weeks after, with the exception of peripheral extremity tumours in which Actinomycin may be given also during RT.

Growth factors may be used at the physician' discretion. We recommend to use them after each cycle if life threatening neutropenia CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10⁹/l WBC (or 1 x10⁹/l neutrophils) + 80 x10⁹/l platelets + absence of any relevant organ dysfunction.

3.3.2. Maintenance schema: Vinorelbine / cyclophosphamide

Maintenance should be started if the patient is in clinical CR after completing 9 cycles of IVA. Maintenance treatment will be given for 6 months. Minimal radiological anomalies may be evident and reasonably suspected not to be disease (i.e. fibrosis) as frequently occurs in parameningeal RMS. If the patient is not in clinical CR, then do not start maintenance. It may be appropriate to give additional chemotherapy in order to achieve CR. At this point, maintenance may be started.

VNL	↓	↓	↓		↓	↓	↓
CPM							
days	1	8	15	21	28/1	8	15
Cycle	1				2		21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days	1	8	15	21	28/1	8	15
Cycle	3				4		21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days	1	8	15	21	28/1	8	15
Cycle	5				6		21

VNL: Vinorelbine 25 mg/m² i.v. over 5-10 minutes day 1,8,15 of each cycle.

CPM: Cyclophosphamide 25 mg/m² per os every day (no rest between cycles)

N.B. Cyclophosphamide is only available in capsules of 50 mg, which cannot be cut in smaller capsules so the doses should be divided over more days. Capsules should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.

Oral liquid formulation of cyclophosphamide (oral liquid) – shall be used, where licensed formulation available. Please refer to oral cyclophosphamide dosing chart in appendix 5 “Oral cyclophosphamide dosing chart”.

3.3.3. Local treatment:

Local treatment will be delivered at week 13. For details please refer to surgical therapy and radiotherapy in section 5.0 “Local Treatment”.

3.3.4. Assessment of tumour response and treatment decisions

See chapter 4. “Assessment of tumour response and treatment decisions”

3.4. Very High Risk Fusion positive AND node positive patients (Subgroup G):

Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Very High Risk	G	Positive	II, III	Any	N1	Any

3.4.1. Intensive treatment

All patients with the following characteristics:

Subgroup G

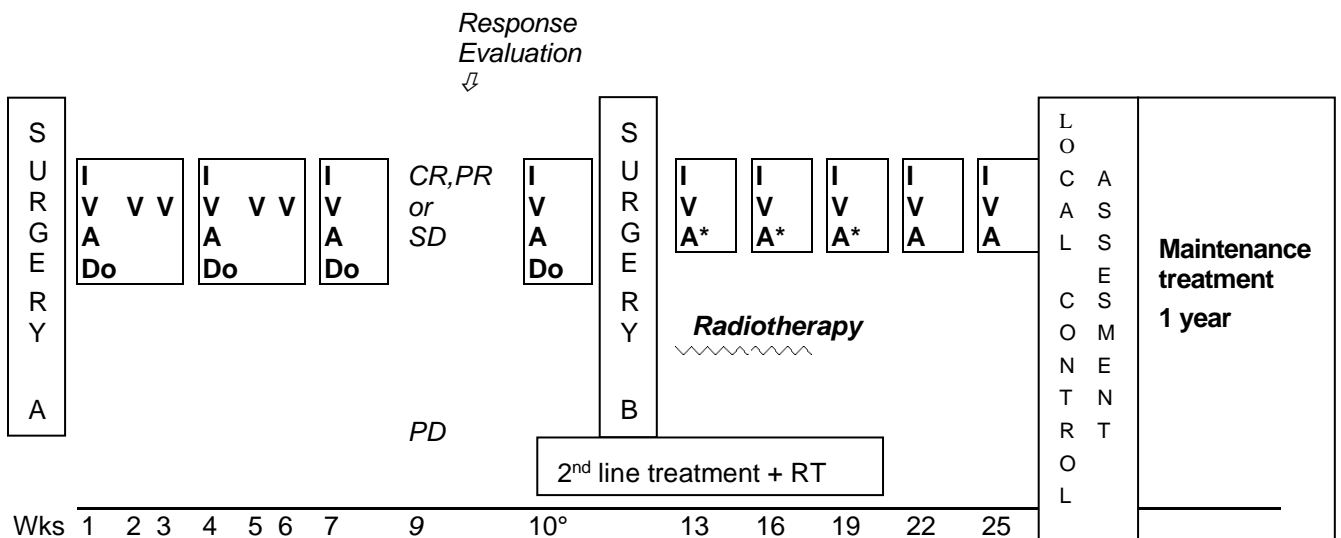
Alveolar, fusion positive RMS, IRS Group II or III, and any site

and

nodes positive

and

any tumour size or age



- I Ifosfamide 3 g/m² is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m²) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m²).
- V Vincristine 1.5 mg/m² (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- A Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.
- Do Doxorubicin 30 mg/m² given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m²).

* Actinomycin can be given at the very beginning of RT, but should not be given during RT and two weeks after, with the exception of peripheral extremity tumours in which Actinomycin may be given also during RT.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: $2 \times 10^9/l$ WBC (or $1 \times 10^9/l$ neutrophils) + $80 \times 10^9/l$ platelets + absence of any relevant organ dysfunction.

For children ≤ 1 month VA only should be administered in the 1st cycle. For children ≤ 1 year (or ≤ 10 kg body weight) first cycle doses will be calculated by body weight and increased in the following cycles if tolerated.

Growth factors may be used at the physicians' discretion. We recommend to use them after each cycle if life threatening neutropenia CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

3.4.2. Maintenance Treatment

Maintenance should be started if the patient is in clinical CR after completing 9 cycles of IVA. Following the 9th block of chemotherapy, if there is radiological evidence of residual abnormality, biopsy or resection of the lesion should be performed. Patients should not commence maintenance treatment if viable tumour is found and the clinician should consider further intensive chemotherapy where appropriate. Maintenance treatment will be given for 12 months.

VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 1	8	15	21	28/1 2	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 3	8	15	21	28/1 4	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 5	8	15	21	28/1 6	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 7	8	15	21	28/1 8	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 9	8	15	21	28/1 10	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 11	8	15	21	28/1 12	8	15 21

VNL: Vinorelbine 25 mg/m² i.v. over 5-10 minutes day 1,8,15 of each cycle or Vinorelbine 60 mg/m² orally; for oral vinorelbine dosing please refer to oral vinorelbine dosing chart in appendix 6 “Oral vinorelbine dosing chart”.

CPM: Cyclophosphamide 25 mg/m² per os every day (no rest between cycles)

This treatment is given on an outpatient basis.

Note that for the VHR groups vinorelbine may be given orally or intravenous; please note the higher dosing for oral vinorelbine (60 mg/m²) compared to iv vinorelbine (25 mg/m²)
Cyclophosphamide is only available in capsules of 50 mg, which cannot be cut in smaller capsules so the doses should be divided over more days. Capsules should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity. Oral liquid formulation of cyclophosphamide (oral liquid) – shall be used, where licensed formulation available. Please refer to oral cyclophosphamide dosing chart in appendix appendix 5 “Oral cyclophosphamide dosing chart”.

3.4.3 Local treatment:

Local treatment will be delivered at week 13.

For details please refer to surgical therapy and radiotherapy in section 5.0 “Local Treatment”

3.4.4 Assessment of tumour response and treatment decisions

See chapter 4 “Assessment of tumour response and treatment decisions”

3.5. Very high risk: Metastatic patients (Subgroup H):

Risk Group	Subgroups	Fusion Status	Post-surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Very High Risk	H	Any	IV	Any	Any	Any

3.5.1. Intensive Treatment

All patients with the following characteristics:

Subgroup H

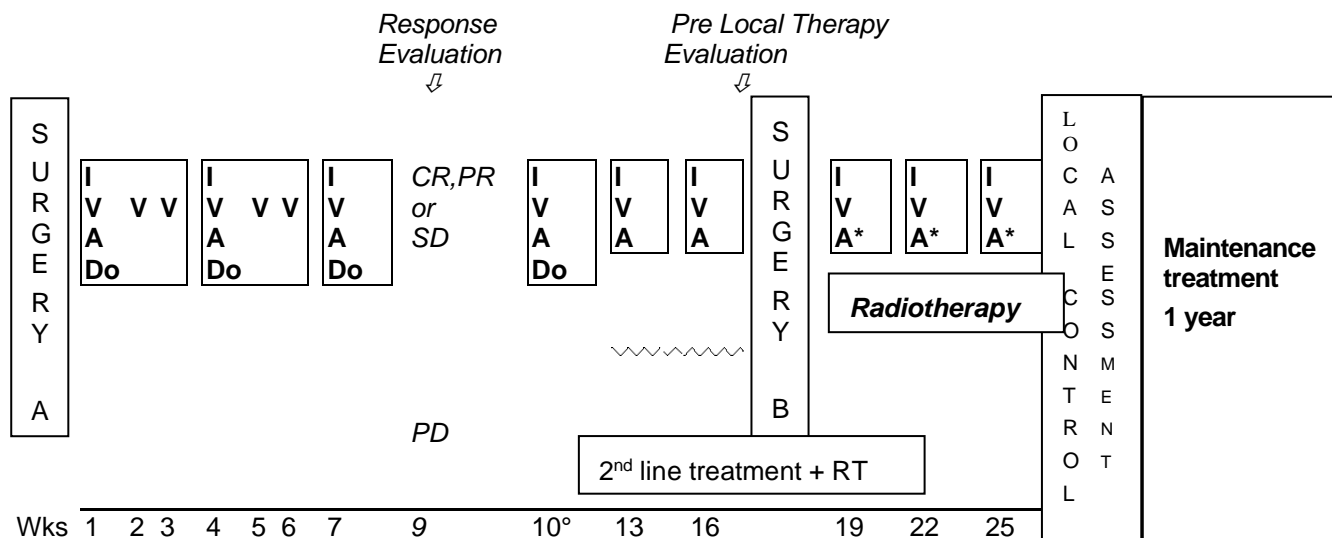
Alveolar/non-alveolar fusion positive/negative RMS, IRS Group IV, and any site

and

nodes any

and

any tumour size or age



- I Ifosfamide 3 g/m² is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m²) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m²).
- V Vincristine 1.5 mg/m² (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.
- A Actinomycin D 1.5 mg/m² (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.
- Do Doxorubicin 30 mg/m² given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m²).

* Actinomycin can be given at the very beginning of RT, but should not be given during RT and two weeks after, with the exception of peripheral extremity tumours in which Actinomycin may be given also during RT.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: $2 \times 10^9/l$ WBC (or $1 \times 10^9/l$ neutrophils) + $80 \times 10^9/l$ platelets + absence of any relevant organ dysfunction.

For children ≤ 1 month VA only should be administered in the 1st cycle. For children ≤ 1 year (or ≤ 10 kg body weight) first cycle doses will be calculated by body weight and increased in the following cycles if tolerated.

Growth factors may be used at the physicians' discretion. We recommend to use them after each cycle if life threatening neutropenia CTC grade III-IV infection, or treatment delay > 1 week due to toxicity has occurred after the previous cycle.

3.5.2. Metastatic patients: Maintenance Treatment

Maintenance should be started if the patient is in clinical CR after completing 9 cycles of IVA. Following the 9th block of chemotherapy, if there is radiological evidence of residual abnormality, biopsy or resection of the lesion should be performed. Patients should not commence maintenance treatment if viable tumour is found and the clinician should consider further intensive chemotherapy where appropriate. Maintenance treatment will be given for 12 months.

VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 1	8	15	21	28/1 2	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 3	8	15	21	28/1 4	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 5	8	15	21	28/1 6	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 7	8	15	21	28/1 8	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 9	8	15	21	28/1 10	8	15 21
VNL	↓	↓	↓		↓	↓	↓
CPM							
days Cycle	1 11	8	15	21	28/1 12	8	15 21

VNL: Vinorelbine 25 mg/m² i.v. over 5-10 minutes day 1,8,15 of each cycle or Vinorelbine 60 mg/m² orally; for oral vinorelbine dosing please refer to oral vinorelbine dosing chart in appendix 6 “Oral vinorelbine dosing chart”.

CPM: Cyclophosphamide 25 mg/m² per os every day (no rest between cycles)

This treatment is given on an outpatient basis.

Note that for the VHR groups vinorelbine may be given orally or intravenous; please note the higher dosing for oral vinorelbine (60 mg/m²) compared to iv vinorelbine (25 mg/m²)
Cyclophosphamide is only available in capsules of 50 mg, which cannot be cut in smaller capsules so the doses should be divided over more days. Capsules should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity. Oral liquid formulation of cyclophosphamide (oral liquid) – shall be used, where licensed formulation available. Please refer to oral cyclophosphamide dosing chart in appendix 5 “Oral cyclophosphamide dosing chart”.

3.5.3. Local treatment

Local treatment will be administered before week 19.

For details, please refer to surgical therapy and radiotherapy in section 5 “Local treatment”

3.5.4. Assessment of tumour response and treatment decisions

See chapter 4 “Assessment of tumour response and treatment decisions”

4. ASSESSMENT OF TUMOUR RESPONSE AND TREATMENT DECISIONS

Treatment evaluation should ideally be performed with the same methods as during primary staging.

4.1 Definition of response

It is recommended to collect local clinical/radiological response at each imaging time point. Where available as part of standard reporting, volumetric and RECIST response will also be collected. Progressive disease is defined as a cumulative increase of target lesions in one dimension of at least 20% or more. In case of multiple target lesion, progressive disease is defined as minimum of 20% or more increase for the sum of longest diameters of the target lesions.[13]

Primary Tumour	Metastatic lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	PR	No	PR
PR	CR	No	PR
PR	PR	No	PR
SD	SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If, during the course of initial treatment, no signs of progression are present, a 1st assessment should be done for RMS low risk patients (subgroup A) at the end of treatment and for standard risk (subgroup B, C), high risk (subgroup D, E, F) and very high risk (subgroup G) as follows. For metastatic patients (Subgroup H) please see section 4.3:

4.2. Assessment for standard risk, high risk and very high risk non-metastatic (subgroups B, C, D, E, F, G)

4.2.1 First assessment

After the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

Patients with PD will be eligible for 2nd line treatment.

4.2.2 Second assessment

After 3 cycles of chemotherapy (week 13) a full clinical and radiological assessment of all tumour sites will be performed to plan local treatment. Any patient with progressive disease must proceed to 2nd line treatment.

➡ At this time local control modality must be decided.

4.2.3 Third assessment

A third assessment must be performed after 9 courses of chemotherapy (end of standard treatment). At this point surgery should be reconsidered (Local control assessment) in case of residual tumour. These suggestions are meant for subgroup H patients. For other subgroups, please see chapter 4.

4.3 Assessment for very high risk metastatic subgroup H

4.3.1 First assessment

After the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

Patients with PD will be eligible for 2nd line treatment.

4.3.2 Second assessment

After 6 cycles of chemotherapy (week 18) a full clinical and radiological assessment of all tumour sites will be performed to plan local treatment. Any patient with progressive disease must proceed to 2nd line treatment.

➡ At this time local control modality must be decided.

4.3.3 Third assessment

A third assessment must be performed after 9 courses of chemotherapy (end of standard treatment). At this point surgery may be reconsidered (Local control assessment) in case of residual tumour.

5.0 LOCAL TREATMENT

5.1 Surgical Guidelines

Optimal local control, in combination with systemic therapy, is an important part of treatment in the majority of patients with rhabdomyosarcoma and is achieved with surgery and/or radiotherapy (external beam RT (photon or proton) and/or brachytherapy [48, 49]).

Surgical planning should be done after adequate diagnostic imaging and take into consideration expected surgical margins, reconstructive options, radiotherapy planning and age of the patient.

5.1.1. Primary Surgery and Staging

Biopsy of the primary tumor after cross-sectional imaging should be the initial diagnostic procedure, with the exception of paratesticular tumours that typically achieve complete upfront resection (R0). Biopsy is performed taking into consideration the subsequent definitive tumor surgery (section 5.1.5). Following biopsy and confirmation of the histological diagnosis, excision of the primary tumor should only be performed for small tumors when an R0 resection can be achieved without mutilation. Please refer to sections 2.3 and 2.3.1 "Tumour biopsy and Lymph node biopsy" for staging procedures.

5.1.2. Pretreatment re-excision

Pretreatment re-excision (PRE) is a wide, non-mutilating re-excision that should be considered to achieve a complete resection (R0 margin) in patients with microscopic residual disease after a primary procedure, which could have been a biopsy or incomplete tumour excision [50].

PRE needs to be done before other adjuvant therapies begin and as soon as possible after the primary resection, preferably within 2 weeks but never beyond 4 weeks after the first procedure. If R0. If R0 margins are obtained at the PRE operation, the patient should then be classified as IRS group I with its associated improved survival and potential for a decreased intensity of therapy.⁷

Primary surgery involves correct assignment of nodal involvement. Clinically or radiologically doubtful regional lymph nodes should be sampled. Patients with extremity tumours and patients older than 10 years with paratesticular tumours, should have surgical nodal staging regardless of clinical or radiological outcome [51]. For details please refer to chapter 2.3.1 "Lymph node biopsy".

Techniques that can be employed to minimize morbidity and improve accuracy of nodal assessment include sentinel node sampling (SLNB) and laparoscopic node sampling [16].

Please see Table 5 (Regional lymph node definition) in appendix 4 "Definition of Sites" for regional lymph nodes assignment [11, 52].

5.1.3. Delayed Excision of the primary tumour

Delayed excision (DE) will be performed after induction chemotherapy - 3 cycles (week 13) for patients with localised disease, 6 cycles (week 22) for those with metastatic disease if the tumour can be macroscopically removed without danger or mutilation. Debulking operations are not recommended and there is no evidence that this improves oncological outcome compared with biopsy alone [53].

Timing and planning of local therapy should be discussed in the multidisciplinary panels.

In patients needing radiotherapy regardless of surgical margins, radiotherapy can be performed pre- or post-operatively. If preoperative radiotherapy is to be undertaken the timing of surgery after is important, allowing recovery of acute radiotherapy effects, including skin, but before the development of fibrosis and longer-term vascular effects. The recommended window for surgery is between 6- 8 weeks from the last dose of radiotherapy [54].

If an R1 resection (microscopically involved margins) is expected or preferred to minimize functional impairment (e.g. in bladder prostate RMS or head and neck RMS), close cooperation with the radiotherapist is needed to discuss the possible radiotherapy modality (external beam, proton, brachytherapy) and timing [55, 56].

Radical lymph node dissection is not indicated and involved lymph nodes should be irradiated. There are rare occasions when, if radiotherapy is contraindicated (e.g. age \leq 3 years), a lymph node dissection may be considered as definitive local treatment.

5.1.4. Fertility preservation

Fertility preserving procedures, such as gonadal transposition, should be considered early before RT, according to national guidelines [57]. In pubertal patients, sperm or egg storage should be offered if it can be performed without undue treatment delay, otherwise gonadal cryopreservation may be considered. In prepubertal patients, gonadal cryopreservation may be discussed with the parents [58, 59].

5.1.5. Site specific surgical treatment

5.1.5.1. Head and Neck RMS

Orbit

Excellent long-term local control and overall survival can be achieved with chemotherapy and radiotherapy alone, and surgical resection is usually mutilating [60, 61]. However a combination procedure utilizing surgery and brachytherapy, can sometimes be considered with appropriate referral to a specialized centre [55]. Diagnostic biopsy is performed in such a way as to avoid meningeal contamination.

Parameningeal RMS

As a rule, primary complete resection should not be attempted for parameningeal RMS. Radiotherapy is always necessary. Radiotherapy alone should be used for parameningeal sub-sites including the middle ear, sphenoid and ethmoid sinuses, nasal cavity and nasopharynx.

Where surgery is to be considered, close collaboration with the surgical and radiotherapy teams is mandatory to plan local therapy, especially for base of the skull and meningeal treatment [62, 63]. The rate of post-operative complications is higher after pre-operative radiotherapy. Delayed wound healing with salivary leakage can lead to life-threatening hemorrhage from the major blood vessels. CSF leaks or brain exposure can lead to fatal meningeal infections. Therefore, when both surgery and radiotherapy are considered necessary for optimal local control for these highly selected cases of parameningeal RMS, pre-operative radiotherapy should be avoided. A combination procedure utilizing surgery and brachytherapy, can be considered with appropriate referral to a specialized centre [55].

Non-parameningeal RMS

In non-parameningeal Head and Neck RMS surgery plays a more central role in local treatment.

Incisional biopsy is still the main approach; this must not be an excisional biopsy [64]. Some sub-sites are amenable to core needle biopsy: scalp, parotid, cheek, thyroid and neck. Biopsies during endoscopic examination are needed for lesions of the hypopharynx, larynx, base of the tongue and oropharynx. A carefully planned core biopsy should avoid tumour contamination.

In selected cases primary surgery may be considered for very small tumours of the scalp, parotid, cheek and neck, but is often not feasible. Therefore, neoadjuvant chemotherapy should be given, including tumours of the naso-labial site, oral cavity, pharyngeal space, larynx and thyroid gland.

Delayed surgery is sometimes possible at these sites without resulting in major side effects or the need for post-operative radiotherapy where an R0 resection can be achieved without mutilation.

5.1.5.2. Bladder / Prostate RMS

The aim of local treatment for bladder/prostate RMS is oncological control in conjunction with preservation of bladder and sexual function [65]. Local treatment needs early planning and is determined by an experienced multidisciplinary team. Endoscopy or percutaneous biopsies, may achieve sufficient material for biology and pathology and should be favored over more invasive surgical techniques. To achieve optimal outcomes this team needs to offer the spectrum of local treatment modalities including surgery and reconstruction, as well as radiotherapy including brachytherapy and proton beam radiotherapy [56, 65-68]. These treatment options are selected following assessment of tumour spread, and response to systemic therapy, obtained by imaging, pre-operative endoscopy and ultimately the intra-operative findings of the surgeon and radiation oncologist.

Bladder-sparing surgery with brachytherapy should be considered when tumours are within access of brachytherapy, do not extend beyond the level of the bladder trigone, the tumour does not necessitate

resection of the urethral sphincter or more than half of the trigone, and more than half of the bladder wall remains for reconstructive procedures.

5.1.5.3. Vaginal RMS

Tumours at this site are generally very chemo-sensitive. Patients with favourable histology and biopsy proven complete response to chemotherapy, do not require any local therapy [69]. For those with residual disease after chemotherapy, local control is necessary. Patients with unfavourable histology must receive RT. Intra-cavitary brachytherapy has generally replaced surgery for local control, combined with temporary ovarian transposition away from the radiation field [70].

Resection should only be considered if a R0 resection can be achieved with preservation of function and fertility.

5.1.5.4. Paratesticular RMS (PT-RMS)

PT-RMS should be removed by radical orchiectomy through an inguinal approach [71]. The cord should be clamped at the internal ring before mobilisation of the tumour. Care is taken not to breach the tunica vaginalis when the tumour, testis and entire cord up to the internal ring are removed as a single specimen. When scrotal skin is fixed or invaded by tumour, it should be resected en-bloc with the specimen, otherwise there is no indication for hemi-scrotectomy. The inguinal incision could be extended to the scrotum if the tumour is too big for a single inguinal incision, to prevent tumour rupture [14].

PRE without formal hemi-scrotectomy is required after incomplete resection to remove tumour contaminated scrotal and/or cord tissue [14, 72]. Hemi-scrotectomy is indicated if the tumour invades into the scrotal skin or if there is macroscopic disease at the scrotal skin, then the scrotal skin should be removed en bloc during tumour excision. Failure to remove this clinically apparent invading disease would result in the patient being classified as Clinical Group III with a resulting worse outcome [14].

In rare cases, the tumour may not be primarily resectable if there is proximal extension of the tumour through the inguinal canal, or extension into the urethra and base of the penis. In these patients, an inguinal approach for tumour biopsy (incisional or needle) is appropriate, followed by induction chemotherapy. These patients would be IRS Group III and historically comprise <3% of patients. For accurate staging of nodal metastases in PT-RMS please refer to section 2.3.1 "Lymph node biopsy".

5.1.5.5. Extremity RMS

In extremity RMS, a diagnostic biopsy is always the preferred primary surgical procedure. (see section 2.3) After diagnosis is complete a PRE can only be considered in small tumours where a R0 resection without mutilation can be performed.

Lymph node sampling at diagnosis is crucial and should be performed regardless of clinical and radiological findings. The sentinel node procedure offers a structured method to sample the lymph nodes [16]. If not available, distant extremity tumours need assessment of distal regional lymph nodes (popliteal or epitrochlear).

In the majority of patients a delayed excision is the preferable procedure. When optimal treatment requires nerve reconstruction and/or blood vessel replacement, early participation by relevant surgical subspecialties plays an important role. After induction chemotherapy, the indicated local therapy should be discussed in the MDT considering the possible resection margins, indication for RT and reconstructive procedures. Local treatment strategy might differ in proximal or distal extremity tumours.

An incision is made along the major axis of the anatomical compartment containing the tumour and must include en-bloc resection of previous biopsy and drain sites. An R1 (microscopically involved margins) resection with RT usually achieves oncological control whilst maintaining optimal functional outcome.

5.1.5.6. Bile ducts & Liver RMS (BD-RMS)

Patients with BD-RMS usually present with jaundice, pruritus and dilatation of the biliary tract. Ultrasound, MRI with MRCP (Magnetic resonance cholangiopancreatography) demonstrates the extent of the primary lesion and lymph node involvement, as well as ruling out other causes of biliary obstruction. These tumours usually have a favourable subtype (fusion-negative/botryoid histopathology) that respond well to chemotherapy. Biopsy, endoscopic retrograde cholangiopancreatography (ERCP) and stenting, when there is bile duct obstruction is a prerequisite

before chemotherapy is commenced. Endoscopic biopsy for lower hepatic duct RMS, or transhepatic percutaneous biopsy with external biliary drainage for intrahepatic or hilar ones are preferred rather than primary excisional surgery [73]. Definitive local control may be planned after induction chemotherapy [74]. Complete tumour resection can be considered which may require partial hepatectomy, however RT has similar outcomes to DPE, but the long-term effects of RT to the hepatic pedicle are unknown in young patients [75]. Patients with central unresectable liver RMS should be considered for liver transplantation [73]. Because of the rarity of this tumour, these cases should be discussed at diagnosis with an experienced hepatobiliary paediatric surgical and liver transplant team.

5.1.6. Surgery for distant metastases

There is little evidence-based data regarding the optimal local treatment for metastatic sites of RMS. Current standard of care recommends, systematic irradiation of all metastatic sites that can feasibly be treated without disruption of bone marrow function, however it is not clear whether this strategy improves outcome.

Expert opinion recommends an attempt at curative resection of persistent metastatic lesions which are resectable and show regression after chemotherapy and radiotherapy

Pneumonectomy or extensive liver resections are not appropriate, but organ-sparing resection of liver and lung metastases may be considered.

Diagnostic biopsy to ascertain the status of regressive or stable lesions may direct further treatment.

5.2. Radiotherapy guidelines

The recommended radiotherapy practice for rhabdomyosarcoma is detailed below.

5.2.1. Planning and Delivery Requirements

Radiotherapy should be delivered using IMRT/VMAT, proton therapy, electrons, brachytherapy, or other 3D conformal techniques. Stereotactic ablative radiotherapy (SBRT or SRT) can be considered for treatment of metastatic sites for selected patients. The dose is prescribed according to ICRU recommendations [76-79]. Treatment to distant metastatic sites will normally be given at the same time as primary and nodal radiotherapy.

5.2.2. Fractionation

Conventional fractionation using 1.8 Gy daily, 5 day/ week is the standard of care. In patients receiving radiotherapy with large field size (e.g. whole abdominal-pelvic or whole lung radiotherapy), and/or those who are <3 years of age, a lower dose per fraction can be used (e.g. 1.5- 1.6 Gy per fraction). Simultaneous integrated boost schedules are being assessed in the FaR RMS study and can be considered (see below). Dose per fraction ≥ 2.1 Gy should only routinely be used for SBRT/ SRT or palliative radiotherapy.

5.2.3. Dose to Organs at Risk

Radiation dose to normal tissues/organs at risk (OAR) should respect the accepted normal tissue tolerances, without compromising CTV/PTV coverage whenever possible. In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided where possible because of the risk of asymmetric growth, particularly the vertebrae [80].

5.2.4. Timing of radiotherapy

The decision to proceed to local therapy (surgery and/or radiotherapy) should be made after 3 cycles of induction chemotherapy (or after 6 cycles for patients with metastatic disease). Delivery of pre-operative RT is an individual choice and a feasible option with surgery then 4- 6 weeks after completion of radiotherapy, but should be discussed within a multidisciplinary board and is topic of research in the current FaR-RMS Trial (EudraCT: 2018-000515-24 and Clinicaltrials.gov: NCT04625907)

Definitive primary radiotherapy for localised disease should be delivered after 4th cycle of chemotherapy (week 13), or after 7th cycle of chemotherapy for metastatic disease (week 22).

Postoperative radiotherapy should commence 4-6 weeks after surgery usually with the 2nd cycle of postoperative chemotherapy, surgery having taken place at after 4th cycle of chemotherapy for localised disease (week 13), or after 7th cycle of chemotherapy for metastatic disease (week 22).

5.2.5. Indications for radiotherapy

Radiotherapy to the site of the primary tumour is indicated for the HR and VHR Groups; and the majority of Standard Risk Subgroup C patients.

Key exceptions which do not require radiotherapy are:

- Localised fusion negative rhabdomyosarcoma with initial R0 resection (IRS Group I) i.e., subgroups A and B
- Localised fusion negative rhabdomyosarcoma of the vagina achieving complete remission with induction chemotherapy
- A highly selected group of patients with IRS Group III Standard Risk Subgroup C fusion negative RMS, arising at a favourable site, where secondary surgery achieves an R0 resection.

5.2.5.1 Nodal disease

Radiotherapy should be delivered to all regional nodal sites involved at the time of presentation, irrespective of any additional surgical resection.

5.2.5.2 Metastatic disease

Whenever feasible, local treatment with radical intent to all metastatic sites is recommended, and radiotherapy can be considered for unresectable/incompletely resected metastases. Feasibility of metastatic irradiation should be determined by the local radiation oncologist. Stereotactic techniques and ablative radiotherapy doses can be considered.

In children <2 years of age the decision to proceed with radiotherapy is at the discretion of the treating clinicians, taking into consideration tumour histology, tumour site, response to chemotherapy, and the potential late sequelae of local therapy.

Synchronous application of radiotherapy and chemotherapy:

- Actinomycin can be given at the very beginning of RT, but should not be given during RT and two weeks after, with the exception of peripheral extremity tumours in which Actinomycin may be given also during RT.
- Doxorubicin should be avoided.

5.2.6. Radiotherapy dose prescription

5.2.6.1 Primary tumour

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

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

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

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

5.2.6.2 Involved lymph nodes

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

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

5.2.6.3 Metastatic sites

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

5.2.7. Delineation of Target Volumes

Target volumes will be defined according to ICRU 83 [78], and ICRU 78 [79] for any additional proton considerations. Delineation of all target volumes is based on a planning computed tomography (CT) as well as surgical notes and pathology; co-registered images CT-magnetic resonance imaging (MRI) are recommended for delineation purposes.

5.2.7.1 Primary tumour

Gross tumour volume (GTVp)

GTVp_Pre is defined as the extent of disease at diagnosis. Contouring of the GTV must respect anatomic boundaries of tumour extension taking into account changes in anatomy and organ displacement resulting from chemotherapy related tumour shrinkage, or surgical resection.

GTVp_Post (boost volume): Required for definitive primary radiotherapy, and whenever there is gross residual tumour after surgery. The GTVp_Post boost volume will be defined based on the extent of the residual primary tumour on imaging obtained post induction chemotherapy.

Clinical target volume (CTVp)

Clinical Target Volumes (CTV) for the Primary tumour (CTVp) will be generated using the following margins:

- GTVp_Pre to CTVp_Pre: 1 cm.
- For extremity primary tumour sites, superior and inferior CTV margins of 2 cm are required, with 1cm expansion circumferentially.
- Skin, scar, drain or biopsy sites should not routinely be included in the CTVp, except in cases of involvement with gross tumour.
- GTVp_Post to CTVp_Post: 0.5 cm.
- For tumours arising adjacent to body cavities (e.g. thorax, abdomen, pelvis) that extend or 'push' into the cavity but do not infiltrate adjacent organs or tissues, then the GTVp should only be expanded, by 1cm (GTVp_Pre) or 0.5cm (GTVp_Post), in the direction of potential infiltration, and there should be no extension of the CTVp into the adjacent, uninvolved body cavity.
- To avoid severe lymphedema in extremity sarcoma, strip of normal tissue (NT^Corridor) is contoured at the discretion of the treating radiation oncologist but should have a minimum diameter of 1.5 cm and be spared from high dose irradiation e.g. V20 <50% [83].
- In case of abdominal/pelvic irradiation ovarian transposition can be considered in order to exclude the ovary from the CTVs/PTVs.

Internal target volume (ITVp)

For primary tumour sites where respiratory-related motion needs to be considered (e.g. thorax, upper abdomen) the use of 4DCT and an Internal Target Volume (ITV) approach is allowed, based on local practice. This will be denoted as ITVp.

Planning target volume (PTVp)

Expansion from the CTVs or ITVp to PTVs is to be undertaken as per local standard of care, based on the specific radiotherapy technique, image guidance strategy and set up errors, and is usually in the range of 3 to 10 mm.

5.2.7.1 Involved lymph nodes

Gross tumour volume (GTVn)

The nodal GTV (GTVn) is delineated based on the gross extent of nodal involvement at diagnosis taking into account changes in anatomy and organ displacement resulting from chemotherapy related tumour shrinkage, or surgical resection. For exceptional cases with pathologically enlarged bulky macroscopic residual nodal disease post induction chemotherapy an additional boost should be delivered with this residual disease delineated as GTVn_Post.

Clinical target volume (CTVn)

GTVn to CTVn: 2-3cm superiorly and inferiorly (or in direction of nodal drainage), and circumferentially to include adjacent lymph nodes in the anatomically constrained lymph node site. Wherever possible, displaced normal tissue should be excluded from the CTVn. In cases of uncertainty, or where particular concern, about exact extent of nodal involvement at diagnosis then an involved field concept should be used.

For bulky residual involved lymph nodes, GTVn_Post to CTVn_Post: 0.5 cm.

Internal target volume (ITVn)

As stated for primary tumour.

Planning target volume (PTVn)

As stated for primary tumour.

6. SUMMARY OF KNOWN ADVERSE EVENTS ASSOCIATED WITH TREATMENT RECOMMENDATION

6.1. Dose Modifications and delays

Scheduled administration of chemotherapy is an essential aspect of treatment. However, toxicity monitoring, dose modifications and treatment delays must be considered where clinically appropriate.

All anticancer agents should be modified according to age and weight. For patients <12 months and/or <10 kg, please see table 2 below.

Here you can find the starting doses. It is important to underline that **they may be increased if patient's tolerance is good and/or when the child is older or the weight has increased.**

Age ≤ 1 month

These patients should be initially treated with VA only and doses calculated *by weight* without further reduction.

Ifosfamide should be added when the child is > 1 month old.

Age > 1 month and ≤ 3 months

These patients should be initially treated with VA or IVA, according to the risk group. Vincristine and Actinomycin D doses will be calculated by weight without further reduction.

Ifosfamide dose should be calculated by weight and then reduced to 50%.

Age > 3 months and ≤ 6 months

Drug doses should be calculated by weight without further reduction.

Age > 6 months and ≤ 12 months (or ≤ 10 kg body weight)

Drug dose should be calculated by weight without further reduction. The chemotherapy courses should not be started unless all these conditions are present:

- $2 \times 10^9/l$ WBC, or $1 \times 10^9/l$ neutrophils
- $80 \times 10^9/l$ platelets are reached.
- absence of any relevant organ dysfunction (especially heart, kidney or liver)

Age	Drugs and dose calculation	Regimen
0 – ≤ 1 months	Drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose No IFO or Doxo administration. Add IFO when the child is > 1 months	VA only (to be modified when the child > 1 months)
1- 3 months	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO: dose calculated by body weight and then reduced to 50%. The resulting dose is - IFO 50 mg/kg/dose	VA or IVA

	No Doxo administration.	
> 3 - ≤ 6 months	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO and Doxo: dose calculated by body weight and then reduced to 50%. The resulting dose is: - IFO 50 mg/kg/dose - Doxo: 0.5 mg/kg/dose	VA or IVA (IVADo only for very high risk group)
> 6 – ≤ 12 months > 6 months and/or ≤ 10 kg	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO: 100mg/kg/dose by weight and then reduced to 50%. The resulting dose is: - IFO 50 mg/kg/dose Doxo: the dose is 0.75 mg/kg/dose	VA, IVA or IVADo (depending on risk group)
> 12 months and > 10 kg	Full m ² dose	VA, IVA or IVADo (depending on risk group)

Table 2 Age and Drug dose calculation

6.2. Drug Information and mode of administration

Actinomycin D (ACT)

Mechanism of action: inhibition of DNA synthesis

Side effects: gastrointestinal irritation (nausea, vomiting, diarrhoea, ulcerative stomatitis, gastroenteritis), hepatotoxicity (veno-occlusive disease, particularly in young children), bone marrow suppression, alopecia, exanthema. It is a radiosensitizer and may enhance radiotherapy damage when given concomitantly.

Extravasation may cause severe local and regional ulceration.

Dose and mode of administration in this protocol:

ACT-D: 1,5 mg/m² iv. as bolus injection. Single doses should not exceed 2 mg.

The drug can be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

Cyclophosphamide (CPM)

Mechanism of action: alkylating agent (CPM has to be activated by hepatic hydroxylation)

Side effects: bone marrow suppression (nadir 8-14 days), haemorrhagic cystitis (Mesna uroprotection), gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), alopecia, dermatitis, infertility, immunosuppression. Rarely cardiotoxicity and SIADH have been reported.

Dose and mode of administration in this protocol:

CPM: 25 mg/m² orally every day (no rest between cycles)

Oral cyclophosphamide is only available in capsules of 50 mg which cannot be cut in smaller capsules so the doses should be divided over more days.

For example, in the case of a patient with a body surface of 1.3 m², the daily dose should be 32.5 mg, corresponding to about 100 mg every 3 days: therefore one entire tablet (50 mg) for two consecutive days followed by one day off should be given.

Oral liquid formulation of cyclophosphamide (oral liquid) – shall be used, where licensed formulation available. Please refer to oral cyclophosphamide dosing chart in appendix 5 “Oral cyclophosphamide dosing chart”.

It is advised to administer CPM capsules early in the day to decrease the amount of drug remaining in the bladder overnight. During the treatment, an adequate fluid intake (at least 1 L/ m²) is recommended in order to minimize damage of transitional epithelium.

Doxorubicin (Adriamycin) (DOXO)

Mechanism of action: inhibition of DNA synthesis

Side effects: bone marrow suppression, acute and late cardiotoxicity, gastrointestinal irritation (nausea, vomiting, ulceration), allergic reactions with skin rash and fever, alopecia.

Extravasation causes local ulceration.

Dose and mode of administration in this protocol:

Doxo: 30 mg/ m² day 1 and 2 (60 g/ m² total) in 4 hour infusion.

Longer infusion does not seem cardioprotective and may increase the risk of mucositis, especially if Doxo is administered along with actinomycin.

The drug can be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

Ifosfamide (IFO)

Mechanism of action: alkylating agent (IFO has to be activated hepatic hydroxylation)

Side effects: haemorrhagic cystitis (Mesna uroprotection), nephrotoxicity (tubulopathy with glucosuria, aminoaciduria, loss of phosphate and Ca, full range of tubulopathies from subclinical changes to a full Fanconi syndrome), bone marrow suppression, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), alopecia, neurotoxicity with transient somnolence and mental disturbance, infertility, immunosuppression

Dose and mode of administration in this protocol:

IFO: 3 g/m² day 1 and 2 (6 gram total) as iv. infusion over 3 hours in each block.

Hyperhydration 3 L/ m²/day and Mesna 3 g/ m², day 1 and 2, are required until 12 hrs after completion of IFO .

Vincristine (VCR)

Mechanism of action: mitotic inhibitor; block microtubule polymerization

Side effects: peripheral neuropathy (including constipation and/or paralytic ileus, ptosis, vocal cord paralysis, jaw pain, areflexy, paresthesia, muscular weakness, ataxia), central neurotoxicity (including hallucinations, convulsions, SIADH), arthralgia, myalgia, minimal bone marrow suppression, alopecia.

Extravasation causes local ulceration.

Dose and mode of administration in this protocol:

VCR: 1,5 mg/ m² iv. as bolus injection day 1 of each cycle (weekly during the first 7 weeks).

Single doses should not exceed a maximum of 2 mg.

The drug should be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

Vinorelbine (VNL)

Mechanism of action: mitotic inhibitor; block microtubule polymerization

Side effects: myelosuppression, alopecia, mucositis, neurotoxicity. Vesicant.

Dose and mode of administration in this protocol:

VNL: 25 mg/ m² i.v. day 1,8,15 of each cycle or vinorelbine 60 mg/ m² orally for the very high risk group; for oral vinorelbine dosing please refer to oral vinorelbine dosing chart in appendix 6 “Oral vinorelbine dosing chart”.

The drug is given on an outpatient basis, diluted in isotonic solution to a concentration between 1.5 and 3 mg/dl and infused over 5 to 10 minutes into either a large central vein or a free-flowing infusion of 0.9% sodium chloride or 5% dextrose into a fixed peripheral venous infusion device. In patients who receive vinorelbine in a peripheral vein, the vein should be then flushed with a rapid infusion of at least 75 to 125 ml of normal saline solution to reduce the risk of chemical phlebitis.

6.3. Toxicities

6.3.1. Haematological toxicity

Anaemia should be treated by transfusion if necessary (Hb 7-8 g/l) according to national or centre guidelines but is not an indication to modify the treatment schedule.

Thrombocytopenia should be treated by transfusion if platelets count $<10 \times 10^9/l$ or in hemorrhagic patients with thrombocytopenia.

Neutropenia: Primary prophylaxis with G-CSF is not required for the chemotherapeutical regimen outlined in these guidelines.

In case of life-threatening neutropenic infection, or treatment delay > 1 week due to neutropenia, the use of growth factors with subsequent courses is recommended.

In other cases if infectious complications (neutropenic fever) or prolonged neutropenia develops administration of growth factors can be considered according to Centre guidelines.

G-CSF should be continued until WBC $> 1 \times 10^9/l$ for 3 consecutive days.

6.3.2. Cardiotoxicity

Careful monitoring for possible acute or late cardiotoxicity is recommended.

Significant deterioration in cardiac function is indicated by a shortening fraction (SF) $<28\%$. In this event, temporarily withdraw Doxorubicin.

A fall in shortening fraction by an absolute value of >10 percentile units but with an actual SF value $>28\%$ (i.e. from SF 42% to SF 31%) may also represent a significant deterioration in function. In this event omit Doxorubicin in the next course.

If the decrease is not persistently proven, i.e. if repeated investigations (after a week) cannot reproduce the dysfunction, Doxorubicin can be recommenced (and the omitted dose of Doxorubicin should be supplied instead of ACT with the first possible cycle).

If persistent deterioration of myocardial function occurs, e.g. persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening below 28%, consider further avoidance of Doxorubicin and the patient should be referred to a cardiologist.

6.3.3. Bladder toxicity

Haemorrhagic cystitis with ifosfamide is rare if hydration and mesna are utilised appropriately.

Microhaematuria usually can be tolerated. In case of macrohaematuria it is important to continue (or re-implement) hydration. In case of cystic bleeding under or within 24 hours of completion of IFO-infusion mesna protection should be continued or started again. Only recurrent macroscopic haematuria is an indication for discontinuing IFO, in which case CPM at a dose of 1500 mg/m² per course may be substituted.

6.3.4. Renal Toxicity

Serious renal toxicity may occur with exposure to IFO and is more likely to occur with an increasing cumulative dose. Prospective monitoring is therefore necessary. If nephrotoxicity (tubular or glomerular toxicity $> \text{grade } 2$) occurs discontinue IFO and substitute CPM at a dose of 1500 mg/m² per course for the remaining courses of treatment.

Be careful because increased excretions of tubular enzymes, amino acid or proteins may be evident shortly after IFO infusion. This tubular dysfunction is usually transient, and does not require dose modification.

6.3.5. Liver Toxicity and SOS/VOS

Liver dysfunction related to chemotherapy or abdomen irradiation may occur. Patients with signs of liver dysfunction should be monitored carefully.

A particular type of hepatic toxicity is represented by the Sinusoidal obstruction syndrome SOS (former veno-occlusive disease (VOD)). SOS appears related to the administration of different drugs and actinomycin-D (ACT-D) in particular. No specific predisposing factor has been found to identify the patient at risk. A prior persistent or slow recovery of thrombocytopenia may be an indicator of SOS. In case of SOS actinomycin D should not be given until the main abnormalities have returned to normal and half the dose should be given for the first following course. If tolerated ACT-D dose may be increased progressively in the following cycles.

If the symptoms reappear during ACT-D treatment, this drug should be withdrawn permanently.

6.3.6. Neurological Toxicity

Serious neurological toxicity from IFO is rare but more likely to occur in patients with impaired renal excretion of the drug, either from an obstructed urinary tract at initial diagnosis or from renal impairment later in treatment. Evidence of IFO encephalopathy may be mild initially but should be considered in any patient who demonstrates altered level of consciousness during or shortly after the drug infusion.

If seizures occur, methylen-blue may be given: 30 mg/m² (max 50 mgs) as a 2% aqueous solution, given by slow i.v. injection. The reversal of encephalopathic features should occur over the next 30-60 minutes.

If grade 3 or 4 central neurotoxicity occurs (somnolence > 30% of the time, disorientation / hallucination / echolalia / perseveration / coma) consider omitting further IFO and substitute with cyclophosphamide @ 1500 mg/m² per cycle.

Peripheral neurotoxicity from vincristine is a common but usually mild side effect. If grade 3-4 peripheral neurotoxicity occurs (intolerable paresthesia, marked motor loss, paralysis or paralytic ileus) one or two injections of vincristine should be omitted and restarted at a 50% dose.

7. SUPPORTIVE TREATMENT

The treatment of patients with RMS requires a multidisciplinary approach with a high degree of medical competence existing only in institutions familiar with the administration of intensive chemotherapy and adequate infrastructure to provide the necessary supportive care.

7.1. Central line

The use of central lines is recommended (it may be omitted in patients treated with vincristine and actinomycin D only - low risk regimen).

7.1.1. Paravasation/extravasation

Intravenous injection or infusion should not be administered near big joints because of the danger of serious irreversible functional impairment in case of para- or extravasation. The procedures in case of para- or extravasation:

- Immediately stop infusion/injection. Leave the application needle where placed
- Only work with gloves on
- Cytostatics must be disconnect from the infusion line
- Try to aspirate as much as possible from the drug with a sterile disposable syringe from the needle
- In case of paravasation of vinca-alcaloids (vincristine, vinblastine or vinorelbine) apply antidote hyaluronidase (apply 1-6 ml of 1.500 I.E./ml hyaluronidase solved in 10 ml NaCl 0.9% through the same needle and subcutaneous in the adjacent tissue. Apply mild warmth.
- Remove needle in case of extravasation with other drugs. Keep the paravasation site cool for 24 hours. In case of anthracyclines, high dose cisplatin, carboplatin, ifosfamide and cyclophosphamide topically apply dimethylsulfoxide (DMSO) 99%, e.g. 4 drops per 10 cm² skin surface, treat the double size of paravasated skin. Dry in the air. Repeat treatment every 8 hours for 7 days.
- The extremity or in case of central line the corpus should be elevated for 24-48 h. Leave site of paravasation open, no bandage, no steroid treatment.
- In severe cases, consult plastic surgeons for support and intraoperative lavage and treatment, and further if signs of necrosis occur.
- Thorough diagnostics (e.g. ultrasound) and observation of the affected site
- Documentation in patient's record and information of the study centre, if possible by photography.

7.2. Nausea and Vomiting

These symptoms are expected with all drug combinations described in this document except single dose vincristine. Antiemetic therapy should be given with each major block of therapy, according to the institutional policy

7.3. Infections

Neutropenic Fever

Episodes of neutropenic infection are likely to occur following chemotherapy. All participating Institutions must be familiar with management of febrile neutropenia, with prompt investigation (e.g. blood culture) and rapid management using empiric antibiotic treatment according to centre guidelines.

Varicella or herpes

Patients who develop varicella or herpes should receive acyclovir and chemotherapy should not be restarted until one week after the resolution of the rash.

Fungal

Patients who develop systemic fungal infection should receive extensive radiological workup and in case of lung involvement undergo bronchoalveolar Lavage. Treatment with antifungal treatment according to institutional guidelines should be started.

7.4. Pneumocystis jirovecii Infection Prophylaxis

Pneumocystis carinii prophylaxis may be started according to the recommendations of the national groups.

7.5. Constipation

Constipation is a common side effect and laxatives should be prescribed when weekly vincristine is given and thereafter if needed to prevent constipation.

8. PATIENT FOLLOW UP

Imaging follow up:

For a comprehensive imaging follow up, please see van Ewijk et al's publication "European guideline for imaging in paediatric and adolescent rhabdomyosarcoma..." [11].

Following completion of treatment, the frequency of follow-up imaging assessments should be every 3-4 months for the first 2 years. A total of 6 assessments of the local tumour are advised in total. For the first two years, the frequency of chest radiography is similar to local tumour evaluation. After two years chest radiography is performed according to local practice.

Disease related follow-up checks should include:

- Appropriate imaging of primary tumour; for superficial tumours ultrasound may be used. In all other cases MRI is the preferred imaging modality.
- Chest radiograph (if an abnormality is found a CT of the chest should be obtained)

The best strategy for RMS patients' follow up has not been established yet [84].

Briefly, for those patients, that received Ifosfamide creatinine and tubular function should be monitored on a yearly base.

For those patients, that received doxorubicin echocardiographs should be done after completion of chemotherapy and at least every 5 years subsequently.

Patients with head and neck RMS that received RT, growth and pubertal development should be closely followed, as well as assessment of the pituitary axis on an annually. Further checks of dental status and neuropsychological development regularly, and audiometry where indicated [85].

Follow up may change according to tumour characteristics and in particular tumour site and regional and distant involvement and chemotherapy received and be warranted according to national guidelines.

The schema reported below is a suggestion that can be adapted to national/institutional guidelines and after discussions with parents/patients.

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

Table 3 Follow up investigations

* Only if clinically indicated

9. APPENDIX

Appendix 1 Assessments

	Screening (28 days)	INDUCTION THERAPY Cycles 1-9			MAINTENANCE THERAPY HR: 6 cycles VHR: 12 cycles		
		Prior 3 days	During	After	Prior 3 days	During	After
		Demographics	•				
Medical history	•						
Clinical Exam (to include neurological examination and vital signs) ^a	•	•			•		
Cryopreservation as per local practice	•						
Assessment for active Infection ^b	•						
Pregnancy Test ^c	•	•					
Haematology (as standard of care)	•	•	As clinically indicated		•	As clinically indicated – including vinorelbine titration	
Blood Biochemistry (as standard of care, to include liver function and serum creatinine tests)	•	•	As clinically indicated		•	As clinically indicated	
(e)GFR and Tubular Function	•	Cycle 1 then as per institutional guidelines	As clinically indicated		•	As clinically indicated	
Echocardiography ^d	•		After 3 cycles then as clinically indicated				
Staging as per local practice	•						
Imaging tumour site(s) ^e	•			After cycles 3, 6, (After 6 for group H)		After cycles 6 (HR), 12 (VHR)	
CT Chest ^f	•		If positive, after 3 cycles repeat after cycle 6	If positive, at end of treatment		As clinically indicated	
FDG-PET CT/MRI	•	As per local practice					
Histological Diagnosis	•	National Central Pathology Review					
Fusion Status	•						
Fresh frozen tumour (strongly recommended)	•						
BM Aspirate/trephine biopsy (as standard of care)	•			If positive, after cycles 3, 6, 9 or until negative ^g			
CSF Cytology	• ^h						

- a. For example: temperature, blood pressure, heart rate, respiratory rate
- b. Assessment to include testing for Hepatitis B, C and HIV in patients with deranged liver function and/or HIV if clinically indicated
- c. A highly sensitive test: for female patients of child bearing potential only. Screening pregnancy test to be carried out within 14 days of starting treatment. Ongoing pregnancy tests are required during treatment, recommended prior to each cycle.
- d. VHR only: echocardiogram required for all patients at baseline. Repeat assessment during treatment only required for patients who receive doxorubicin
- e. MRI is recommended. Use same mode of investigation (MRI or CT) of tumour sites throughout study.
- f. Repeat chest CT only if there is pulmonary involvement at entry.
- g. Only if positive at diagnosis
- h. Primary tumours with a parameningeal location only – if positive, repeat as standard of care

Appendix 2 TNM Classification

Pre treatment TNM

Tumour:

- T0: No evidence of tumour
- T1: Tumour confined to organ or tissue of origin
- T1a: Tumour ≤ 5 cm in greatest dimension
- T1b: Tumour > 5 cm in greatest dimension
- T2: Tumour not confined to organ or tissue of origin
- T2a: Tumour ≤ 5 cm in greatest dimension
- T2b: Tumour > 5 cm in greatest dimension
- TX: No information on size and tumour invasiveness

Lymph nodes:

- N0: No evidence of lymph node involvement
- N1: Evidence of regional lymph node involvement
- NX: No information on lymph node involvement

Metastasis:

- M0: No evidence of metastases or non-regional lymph nodes
- M1: Evidence of distant metastasis or involvement of non-regional lymph nodes
- MX: No information on metastasis

Appendix 3 IRS CLINICAL GROUPING CLASSIFICATION**Group I:** Localized disease, completely resected

(Regional nodes not involved – lymph node biopsy or dissection is required except for head and neck lesions)

- a) Confined to muscle or organ of origin
- b) Contiguous involvement – infiltration outside the muscle or organ of origin, as through facial planes.

Notation: This includes both gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative. If the latter should be involved microscopically, then the patient is placed in Group IIb or IIc (See Below).

Group II: Total gross resection with evidence of regional spread

- a) Grossly resected tumour with microscopic residual disease.
(Surgeon believes that he has removed all of the tumour, but the pathologist finds tumour at the margin of resection and additional resection to achieve clean margin is not feasible.) No evidence of gross residual tumour. No evidence of regional node involvement. Once radiotherapy and/or chemotherapy have been started, re-exploration and removal of the area microscopic residual does not change the patient's group.
- b) Regional disease with involved nodes, completely resected with no microscopic residual.

Notation: Complete resection with microscopic confirmation of no residual disease makes this different from Groups IIa and IIc.

Additionally, in contrast to Group IIa, regional nodes (which are completely resected, however) are involved, but the most distal node is histologically negative.

c) Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.

Notation: The presence of microscopic residual disease makes this group different from Group IIb, and nodal involvement makes this group different from Group IIa.

Group III: Incomplete resection with gross residual disease

- a) After biopsy only
- b) After gross or major resection of the primary (>50%)

Group IV: Distant metastatic disease present at onset

Notation: The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favourable grouping (as noted above under Group II).

The presence of positive cytology in CSF, pleural or abdominal fluids as well as implants on pleural or peritoneal surfaces are regarded as indications for placing the patient in Group IV.

Appendix 4 Definition of Sites

To define the site of origin may be difficult in some cases of RMS. A correct site assignment is of importance in the choice of treatment. The following definitions are given to facilitate the clinician in the appropriate site classification.

We acknowledge the permission given by the IRSG to modify and use their original document on site definitions.

Orbit

1. Eyelid

This site is sometimes erroneously designated as “eye”. Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.

2. Orbit

This refers to the bony cavity, which contains the globe, nerve and vessels and the extra-ocular muscles. Tumour in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumour which is clearly adjacent to the skull base and its meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of bone at the base of the skull.

Parameningeal

1. Middle ear

This refers to a primary that begins medial to the tympanic membrane. This tumour is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the “middle ear” designation should be picked as it implies the more aggressive therapy required of parameningeal sites.

2. Nasal Cavity and Para nasal Sinuses

The three Para nasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity, and a primary in one will frequently extend to another. It can be difficult to determine the exact site of origin, but the choice is academic as the treatment is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumour arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and Para nasal sinus is unclear, the site selected should be Para nasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx.

3. Nasopharynx

This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.

4. Infratemporal Fossa/Pterygopalatinand Parapharyngeal Area

This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumours in this region may extend through the parotid gland and present as a mass of the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term “infratemporal”. The distinction between this and the “parapharyngeal” area is academic.

5. Orbital tumours with bone erosion

Tumours arising in the orbit but with intracranial extension or important bone erosion are included in the parameningeal group.

In addition the following are classified as parameningeal tumours:

- Tumours involving vessels or nerves with direct intracranial connection (Arteria carotis interna, vertebralis, N. opticus, trigeminus, facialis etc).
- All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal extension should be designated as paraspinal, see "Other site" definition)
- All tumours with cranial nerve paresis (excluding parotid tumours with facial nerve palsy)
- CSF tumour cell positive patients

Head and Neck

1. Scalp

This site includes primaries arising apparently in, or just below, the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose and the forehead, but not the eyelids or cheek.

2. Parotid

The parotid gland lies just in front of, and under, the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid primary should not, on radiographic studies, reveal a mass in the infratemporal fossa.

3. Oral Cavity

This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek, but the distinction is academic. This would also include those lesions arising in or near the lips.

4. Larynx

This refers to primaries arising in the subglottic, glottic, or supraglottic tissues. Tumours of the aryepiglottic folds can be impossible to distinguish from the hypopharynx, but the distinction is academic.

5. Oropharynx

This includes tumours arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumours arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumour as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.

6. Cheek

This refers to the soft tissues of the face that surround the oral cavity. Tumours arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.

7. Hypopharynx

This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic.

8. Thyroid and Parathyroid

Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the neck or, rarely, the trachea.

9. Neck

This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately this site overlaps with the designation "paraspinal" included under the site group "trunk". Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space, especially if posteriorly placed.

Genito-Urinary Bladder and Prostate

1. Bladder

Our criteria for identifying the bladder as a primary site has included the appearance of tumour within the bladder cavity, which can be biopsied under cystoscopy or occasionally at laparotomy. We do not recognize as primary bladder tumours those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic tumours, unless otherwise specified.

2. Prostate

It is important to differentiate true prostatic tumours from pelvic tumours.

3. Bladder/Prostate

In approximately 20% of males with bladder or prostatic tumours, the precise site cannot be determined even at autopsy. The histologic features are similar. Although it is desirable to have an indication of the "most probable" site from the institution, and one should try to get this, it may not be possible.

Genito-Urinary non Bladder and Prostate

1. Paratesticular

The tumours arises from mesenchymal elements of the spermatic cord, epididymis, and testicular envelopes, producing a painless scrotal mass.

2. Testis

This designation is wrong because the tumours arise from paratesticular structures and may invade the testis.

3. Uterus

A tumour in this primary site may be difficult to differentiate from a primary vaginal site, because a tumour originating in the uterus (corpus or cervix) may fill the vagina. After a therapeutic response, the distinction is usually clear. In general there is a wide separation of age range between these two groups, with the vaginal cases occurring in infancy or early childhood and uterine primaries in adolescents or young adults.

4. Vagina

A patient with a primary vaginal lesion must have evidence of a visible tumour on the vaginal surfaces which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

5. Vulva

Primary lesions in this site arise in the labia minora or majora.

Extremities

1. Hand

Refers to the area from the top of the fingers to the wrist

2. Forearm

Refers to the area from the wrist to the elbow joint

3. Arm

Refers to the area from the elbow joint to the shoulder joint. Tumours arising in the axilla are considered as extremity lesions.

4. Shoulder

The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

5. Foot

Refers to the area from the toes to the ankle

6. Leg

Refers to the area from the ankle to the knee

7. Thigh

Refers to the area from the knee to the hip joint

8. Buttocks

These are extremity lesions.

Other sites

This term conventionally groups tumours originating from the sites not mentioned above. Prognosis is similar and usually not satisfying.

The following specific sites have been defined:

1. Thorax

Includes tumours arising in the following sites:

a) Thoracic wall:

includes tumours arising from the thoracic muscles and the parietal pleura

b) Mediastinum:

occasionally a primary rhabdomyosarcoma may arise from trachea, heart or nearby areas.

c) Lung:

includes tumours arising from the lung parenchyma, bronchus and visceral pleura

d) Breast**e) Diaphragm****2. Abdomen****a) Abdominal Wall (including Lumbar or lumbo-sacral wall)**

This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and posterior iliac crests to the paraspinal region.

b) Liver

True liver rhabdomyosarcoma are less frequent than bile duct tumours.

c) Bile duct

Bile Duct is a specific site and can be recognised as such at surgery. This might also be called “choledochus” or “biliary tract”. There is probably no way one can distinguish an intrahepatic bile duct site from a primary liver site except by examining the excised specimen.

d) Pancreas**e) Bowel****f) Abdomen**

The term abdominal refers to tumours arising in the intraperitoneal cavity, when a specific organ of origin such as liver, bile duct, pancreas or intestine cannot be determined.

g) Retroperitoneum

The term retroperitoneal is reserved for those posteriorly situated abdominal tumours in which there does not seem to be a more specific site. Tumours in a retroperitoneal site are in the posterior aspect of the abdominal and/or pelvis. The term “psoas” as a site is not very specific, as the muscle extends through the posterior lower abdomen, pelvis and into the leg.

3. Paraspinal

When tumours are described as adjacent to the vertebral column, arising from the paraspinal muscles. This designation is preferable to “abdominal wall” or “trunk” or “neck”. They often show an intraspinal component and this should be specified.

4. Pelvis

It is difficult to define the site of origin when there is a large tumour in the abdomen. The pelvis designation is reserved for lesions involving the lower part of the abdomen when no more specific site is appropriate.

5. Perianal

These sites are ordinarily “perirectal” or “perianal”. They are distinguished with difficulty from perineal and vulval sites; but the latter distinction is important.

6. Perineum

This should include the site which appear between the anus and the scrotum in males and the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and perianal sites.

Lymph nodes

Assignment of lymph nodes to region

Region	Definition
Extremities	
Upper extremity	Axillary, brachial, epitrochlear, infraclavicular nodes
Lower extremity	Inguinal, femoral, popliteal nodes
GU	
Bladder – prostate	pelvic (hypogastric, obturator, iliac, peri-vesical, pelvic, sacral, and presacral lymph nodes) (note: para-aortic nodes are distant nodes)
Cervix	pelvic (hypogastric, obturator, iliac, peri-vesical, pelvic, sacral, and presacral lymph nodes) (note: para-aortic nodes are distant nodes)
Uterus	pelvic, retroperitoneal nodes at renal vessels or below
Paratesticular / gonadal	Ipsilateral pelvic, retroperitoneal nodes at renal vessels or below (inguinal if the scrotum is involved)
Vagina	retroperitoneal, pelvic nodes at or below common iliac vessels, inguinal nodes
Vulva	Inguinal nodes
Head and neck	
Head / neck	ipsilateral parotid, occipital and cervical nodes (all levels). Tumours close to the midline may show bilateral metastasis and retropharyngeal nodes may be involved in parameningeal tumours.
Orbit/Eyelid/ Cheek/External ear/Temporal region	parotid, ipsilateral jugular, pre-auricular, cervical nodes
Trunk	
Intrathoracic	Internal mammary, mediastinal nodes
Retroperitoneum/pelvis	Pelvic, retroperitoneal nodes
Intra-abdominal	Sub diaphragmatic, intra-abdominal and iliac lymph nodes according to site
Abdominal wall	Inguinal, femoral nodes
Chest wall	Axillary, internal mammary, infraclavicular nodes
Other	
Biliary / liver	porta hepatis nodes
Perianal, perineal	inguinal, pelvic nodes; may be bilateral

Table 5. Regional lymph node definition [11, 52]

Appendix 5 – Oral cyclophosphamide dosing chart

BSA	Daily dose (mg.)	Total weekly dose (mg.)	Dose schedule (1 50mg tablet each day)	Number of 50mg tablets/week	Dose difference from calculated
0.50	12.5	87.5	Mon & Thur	2	14%
0.55	13.75	96.25	Mon & Thur	2	4%
0.60	15	105	Mon & Thur	2	-5%
0.65	16.25	113.75	Mon & Thur	2	-12%
0.70	17.5	122.5	Mon & Thur	2	-18%
0.75	18.75	131.25	Mon, Wed & Fri	3	14%
0.80	20	140	Mon, Wed & Fri	3	7%
0.85	21.25	148.75	Mon, Wed & Fri	3	1%
0.90	22.5	157.5	Mon, Wed & Fri	3	-5%
0.95	23.75	166.25	Mon, Wed & Fri	3	-10%
1.00	25	175	Mon, Wed, Fri, & Sun	4	14%
1.05	26.25	183.75	Mon, Wed, Fri, & Sun	4	9%
1.10	27.5	192.5	Mon, Wed, Fri, & Sun	4	4%
1.15	28.75	201.25	Mon, Wed, Fri, & Sun	4	-1%
1.20	30	210	Mon, Wed, Fri, & Sun	4	-5%
1.25	31.25	218.75	Mon, Wed, Fri, & Sun	4	-9%
1.30	32.5	227.5	Mon, Wed, Fri, & Sun	5	10%
1.35	33.75	236.25	Mon, Wed, Fri, Sat & Sun	5	6%
1.40	35	245	Mon, Wed, Fri, Sat & Sun	5	2%
1.45	36.25	253.75	Mon, Wed, Fri, Sat & Sun	5	-1%
1.50	37.5	262.5	Mon, Wed, Fri, Sat & Sun	5	-5%
1.55	38.75	271.25	Mon, Wed, Fri, Sat & Sun	5	-8%
1.60	40	280	Mon, Wed, Thur, Fri, Sat & Sun	6	7%

1.65	41.25	288.75	Mon, Wed, Thur, Fri, Sat & Sun	6	4%
1.70	42.5	297.5	Mon, Wed, Thur, Fri, Sat & Sun	6	1%
1.75	43.75	306.25	Mon, Wed, Thur, Fri, Sat & Sun	6	-2%
1.80	45	315	Mon, Wed, Thur, Fri, Sat & Sun	6	-5%
1.85	46.25	323.75	Mon, Wed, Thur, Fri, Sat & Sun	6	-7%
1.90	47.5	332.5	Daily	7	5%
1.95	48.75	341.25	Daily	7	3%
2.00	50	350	Daily	7	0%

Table 5. Oral cyclophosphamide dosing chart

Appendix 6 – Oral vinorelbine dosing chart

BSA	Calculated dose (60mg/m ²)	Number of capsules			Dose administered (mg.)	Difference
		20mg.	30mg.	80mg.		
0.5	30		1		30	0%
0.55	33		1		30	-9%
0.6	36	2			40	11%
0.65	39	2			40	3%
0.7	42	2			40	-5%
0.75	45	1	1		50	11%
0.8	48	1	1		50	4%
0.85	51	1	1		50	-2%
0.9	54	1	1		50	-7%
0.95	57		2		60	5%
1	60		2		60	0%
1.05	63		2		60	-5%
1.1	66	2	1		70	6%
1.15	69	2	1		70	1%
1.2	72	2	1		70	-3%
1.25	75			1	80	7%
1.3	78			1	80	3%
1.35	81			1	80	-1%
1.4	84			1	80	-5%
1.45	87		3		90	3%
1.5	90		3		90	0%
1.55	93		3		90	-3%
1.6	96	1		1	100	4%
1.65	99	1		1	100	1%
1.7	102	1		1	100	-2%
1.75	105	1		1	100	-5%
1.8	108		1	1	110	2%
1.85	111		1	1	110	-1%
1.9	114		1	1	110	-4%
1.95	117	2		1	120	3%
2	120	2		1	120	0%

Table 6. Oral vinorelbine dosing chart

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