31 Late Effects in Children and Adolescents with Soft Tissue Sarcoma

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31.1 Introduction

Soft tissue sarcomas represent a very heterogeneous group of rare but generally aggressive tumours which disproportionately affect children and young adults. They represent less than 10% of all childhood cancers but are one of the most frequently diagnosed cancers in paediatric patients. These cancers have a high rate of morbidity and mortality. The prognosis for children with localised rhabdomyosarcoma has improved dramatically since the introduction of coordinated multimodal treatment. Cure rates have improved from 25% in the early seventies, when combination chemotherapy was first implemented, to approximately 70% in more recent years. A major role in developing new strategies has been carried out by cooperative clinical trial groups in Europe and North America. They have optimised the therapy for children with RMS matching the complexity of treatment against known prognostic factors such as site, stage and pathological subtype. In fact the role of radiotherapy, surgery and chemotherapy in different risk groups has been explored in a series of multicentre clinical trials on both sides of the Atlantic. The CWS study group, including not only Germany but centres in Austria, Sweden, Poland, Finland and Switzerland, traditionally cooperated with the AIEOP Soft Tissue Sarcoma Committee (AIEOP STSC, former ICG: Italian Cooperative Group for paediatric soft tissue sarcoma) and the SIOP Malignant Mesenchymal Tumours (MMT) Committee. Having achieved an agreement in risk group definition in RMS tumours, a joint study started in 1996, randomising chemotherapy regimen in the high-risk group (VAIA vs. CEVAIE in the CWS/ICG group and IVA vs. CEVAIE in the MMT SIOP group). The EpSSG protocol for treatment of rhabdomyosarcoma in children and adolescents (EpSSG RMS 2005) has been derived from the evolving cooperation of those European groups. This cooperation will improve the quality of treatment of patients from all over Europe and will enable the study groups to improve their ability to respond to the still unanswered questions regarding therapy and prognosis of children with rhabdomyosarcoma and other soft tissue tumours. Because of the biological diversity, the long-term follow-up should be adjusted to the specific therapeutical approaches.

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J. D. Beck et al. (eds.), *Late Treatment Effects and Cancer Survivor Care in the Young*,
https://doi.org/10.1007/978-3-030-49140-6_31

31.2 Epidemiology

The incidence of soft tissue sarcomas in children in Germany is 1.0/100.000 [1]. The same incidence is seen worldwide. Soft tissue sarcoma represents the fifth most common tumour group in children and adolescents after leukaemias, CNS tumours, lymphomas and sympathetic nervous system tumours. Soft tissue sarcoma represents an extremely heterogeneous group of tumours, and the subtype with the highest incidence per year (0.5/100.000 in patients <15 years) is rhabdomyosarcoma. Boys are nearly equally affected by RMS tumours as girls (1.1:1 boys vs. girls). The peak incidence is seen early in childhood with a median age at diagnosis of about 5 years. The soft tissue sarcoma trials of the CWS, ICG and SIOP have been the only studies for the treatment of localised soft tissue sarcomas in childhood and adolescents within their participating countries. The CWS study has registered about 64 German RMS patients <21 years per year in the last 15 years, which means that about 95% of all RMS patients registered in the German Childhood Cancer Registry (Deutsches Kinderkrebsregister, DKKR) are documented in and treated according to the CWS recommendations.

31.3 General Remarks

Rhabdomyosarcoma (RMS) is thought to arise from primitive mesenchymal cells committed to develop into striated muscles. It can be found virtually anywhere in the body, including those sites where striated muscles are not normally found. The aetiology is not yet known. Genetic factors may play an important role as demonstrated by an association between RMS and familial cancer syndrome (Li-Fraumeni), congenital anomalies (involving the genitourinary and central nervous system) and other genetic conditions, including neurofibromatosis type 1 [2].

Depending on histological appearance, two main forms of RMS have been distinguished: the *embryonal* (which accounts for approximately 80% of all RMS) and the *alveolar* subtypes (15–20% of RMS). It has been shown that RMS subtypes have an impact on survival. In 1995 pathologists from the different cooperative groups agreed on a new classification, which identified prognostically significant and reproducible subtypes [3]. 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.
3. *Poor prognosis*: including alveolar RMS and its variant solid alveolar RMS.

This classification system does not include the pleomorphic category, as this is very rarely observed in children.

Molecular biology studies have identified two characteristic chromosomal alterations in RMS: reciprocal chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14) in alveolar RMS [4], whilst genetic loss on chromosome 11p15.5 has been shown in embryonal RMS [5]. Different staging systems have been developed to classify RMS. The most widely used are the pre-treatment TNM staging and the postoperative IRS Grouping system. However, with the evolution of treatment and trial results, a new and more complex categorization has been used to better tailor the treatment to the risk of relapse.

Based on the results of cooperative studies, different patient- and tumour-related factors with relevance for prognosis have been defined. The most important are histology, tumour site and size as well as post-surgical stage [6–9]. More recently the patient's age at diagnosis has been recognised as a predictor of survival, showing that older children (≥10 years) have a worse outcome [6, 10]. Patients are treated according to risk stratification (Tables 31.1 and 31.2).

31.3.1 Risk Stratification for Rhabdomyosarcoma

- **Pathology**:
  - *Favourable* = All embryonal, spindle cells, botryoid RMS
  - *Unfavourable* = All alveolar RMS (including the solid alveolar variant)

Table 31.1 Risk stratification for rhabdomyosarcoma

Risk group	Sub-groups	Pathology	Post-surgical stage (IRS group)	Site	Node stage	Size and age
Low	A	Favourable	I	Any	N0	Favourable
Standard	B	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High	E	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable	I, II, III	Any	N0	Any
Very high	H	Unfavourable	II, III	Any	N1	Any

Table 31.2 Risk stratification for rhabdomyosarcoma-like soft tissue sarcoma (SySa, STET, UDS)

Risk group	Pathology	Post-surgical stage (IRS group)	Initial tumour size	Node stage
Localised RMS-like	SySa, STET (EES/pPNET), UDS	I, II, III	Any	Any
Metastatic disease		IV	Any	Any

- **Post-surgical stage**:
  - *Group I* = Primary complete resection (R0)
  - *Group II* = Microscopic residuals (R1) or primary complete resection but N1
  - *Group III* = Macroscopic residuals (R2)
- **Site**:
  - *Favourable* = orbit, genito-urinary non-bladder/non-prostate (i.e. paratesticular or vagina/uterus), non-parameningeal head and neck
  - *Unfavourable* = all other sites (parameningeal, extremities, genito-urinary bladder/prostate and "other site")
- **Node stage**:
  - *N0* = no clinical or pathological node involvement
  - *N1* = clinical or pathological nodal involvement
- **Size and age**:
  - *Favourable* = tumour size (maximum dimension) ≤5 cm *and* age <10 years
  - *Unfavourable* = all others (i.e. size >5 cm and/*or* age ≥10 years).

31.3.2 Risk Stratification "RMS-Like" Tumours

31.4 Treatment Strategies

A multimodality approach involving surgery, chemotherapy and radiotherapy is necessary in the treatment of children and adolescents with RMS. The optimal timing and intensity of these three treatment modalities must be planned with regard to the prognostic factors and considering possible late effects of treatment.

Local control is necessary to cure children with RMS, and this may be achieved with surgery and/or radiotherapy. A conservative approach is recommended, and tumour resection or irradiation is usually performed taking into account the activity of chemotherapy in reducing the tumour volume.

Different drug combinations have proved to be effective against RMS. The most widely used regimen are VAC (vincristine, actinomycin-D, cyclophosphamide), VACA (vincristine and cyclophosphamide plus adriamycin alternating with actinomycin-D), IVA (ifosfamide, vincristine, actinomycin-D) and VAIA (ifosfamide and vincristine with adriamycin alternating with actinomycin-D). The multimodality approach according to different strategies and different chemotherapy regimens has been tested in several clinical trials run by the Cooperative Groups already named.

31.4.1 Treatment of Patients with Rhabdomyosarcoma

31.4.1.1 Local Treatment

Local treatment is an essential part of the multimodal therapy of soft tissue tumours. It is achieved by surgery, radiotherapy or both. The choice of local treatment in order to cure the patient with minimal long-term sequelae depends on site, size, invasiveness of the primary tumour, age of the patient and response to neoadjuvant chemotherapy.Biopsy should be the initial surgical procedure (after imaging of primary tumour and regional lymph nodes) in all patients except when primary excision with adequate margins is possible (rare except for paratesticular tumours). Radiotherapy as an integral part of local control will be needed in most cases. This should be considered from the very beginning of therapy, because timing of radiotherapy has to be coordinated with surgery.Concerning radiotherapy, it has been concluded that volume reduction after preoperative chemotherapy and primary tumour size in patients with residual tumour can be used as a basis for risk-adapted radiation. Early (10–13 weeks) hyperfractionated, accelerated radiation given simultaneously to chemotherapy improved local tumour control in patients with a good response after preoperative chemotherapy. The dose of 32 Gy when given accelerated and hyperfractionated simultaneously to chemotherapy is adequate for local tumour control in patients showing a good response to preoperative chemotherapy. Whether the same principle can be applied to other histological entities cannot be answered on the basis of the CWS studies.

31.4.1.2 Chemotherapy

Low Risk

This represents a very select group of patients, accounting for 6–8% of the whole population of localised RMS, with an excellent outcome. Most of these patients are represented by children with paratesticular RMS [11, 12].

Reducing the toxicity without jeopardizing the results is therefore the goal for this group of patients. The VA chemotherapy adopted in the previous protocols RMS-88, CWS/RMS-96 and SIOP MMT-95 showed good results with event-free and overall survival above 80% and 90%, respectively [13]. The results achieved in MMT-89 with 12 of 41 stage I patients relapsing after only 2 courses of VA suggest caution in further reducing the treatment in this subset of patients [14].

In conclusion, VA for 22 weeks (4 VA courses) represents a low-toxic, effective regimen for this group of patients.

Standard Risk

This group includes patients with a satisfactory prognosis for whom the goal is to reduce the treatment without compromising survival. These patients have been treated with IVA (nine courses over 25 weeks) both in MMT-95 and CWS/RMS-96. This represented a treatment reduction for the CWS group that used anthracyclines in the previous protocol. The total length of therapy has also been reduced from 35 (CWS-81 and ICG) to 25 weeks.

Results of the CWS-96 study show mainly local recurrences in the Standard Risk Group (15% local relapse, 3% combined and 1% metastatic relapses, 81% of the patients without failure) with a good EFS of 75% and an OS of 95% [7].

Three subgroups of Standard Risk patients have been identified with a similar outcome. However, their characteristics are quite different, and it has not been possible to design an identical treatment. Three treatment groups have been proposed, maintaining IVA as the regimen of reference.

Standard Risk, Subgroup B

These patients are similar to the ones included in the Low Risk Group, but tumour size and age are unfavourable. Most of these patients are represented by children with paratesticular RMS older than 10 years and/or with a large tumour (>5 cm).

There is increasing evidence from the European and US experience that older children (≥10 years) with low-risk characteristics fare worse than their younger counterparts [13, 14]. In the IRS studies, an increased risk of nodal relapse has been seen in Group I patients with

paratesticular tumour and age ≥10 years. This prompted the IRSG colleagues to return to a surgical staging for older patients [10]. The European experience reported a lower rate of nodal involvement. Here laparotomy with nodal exploration is avoided, but caution has been recommended in reducing the treatment in such patients. Subgroup B has been created to upgrade these patients and treat them with a limited dose of alkylating agents with the aim of reducing the risk of relapse and avoiding important toxicity.

Modern treatment concepts for **bladder/prostate rhabdomyosarcoma (BPRMS)** are designed to improve survival, to reduce therapy intensity and to increase bladder preservation **rates. Radiotherapy was used less frequently, and** the bladder preservation rate was slightly higher. Novel concepts will be required in the future to improve bladder preservation rates [15].

Vaginal/uterine rhabdomyosarcoma is one of the most favourable RMS sites. Ten-year event-free (EFS) and overall survival (OS) were 74% (95% CI, 67–79%) and 92% (95% CI, 88–96%), respectively. Local control using brachytherapy was excellent (93%). Fifty-one (51.5%) of the 99 survivors with known primary therapy and treatment for relapse were cured with chemotherapy with or without conservative surgery. About half of all patients with VU RMS can be cured without systematic RT or radical surgery. When RT is indicated, modalities that limit sequelae should be considered, such as brachytherapy [16].

Standard Risk, Subgroup C

This group is mainly represented by **orbital and head/neck non-parameningeal RMS** (favourable site). The German, Italian and North American experience is in favour of the use of systematic irradiation in these patients. However, the MMT studies have demonstrated that some children can successfully be treated with chemotherapy alone and eventually salvaged after relapse with irradiation [17]. In the more recent IRS-IV study, patients with orbital RMS in IRS Group I or II have been treated with VA and irradiation with an excellent outcome [10, 18]. The same strategy is currently used for all orbital RMS in the ongoing IRS-V study.

Therefore it seems possible in this subgroup:

- To reduce the cumulative dose of alkylating agents compared with previous European protocols using radiotherapy.
- To try to prospectively select patients with favourable features in whom irradiation can be avoided. These patients will be selected according to chemotherapy response (CR after the initial three courses of IVA) and favourable tumour size and age of the patients.

Radiotherapy (RT) as a first-line treatment of patients with head/neck non-parameningeal RMS was independently prognostic for event-free survival even if it did not impact OS. High rates of locoregional relapse were seen in head and neck rhabdomyosarcoma that should be prevented by more frequent use of RT in this primary [18].

Standard Risk, Subgroup D

An analysis of patients included in the High Risk category according to CWS/ICG RMS-96 and MMT-95 stratification showed that children with embryonal RMS, N0, favourable age and favourable tumour have a prognosis comparable to patients treated in the Standard Risk group of CWS/ICG RMS. Consequently, these patients have been included in the subgroup D in this protocol and downstaged to receive the treatment planned for the Standard Risk Group. These patients will continue to receive the IVA regimen as in the MMT-95 study, but this represents a treatment reduction in comparison with the CWS/ICG-96 protocol where the VAIA regimen was used.

High Risk

Patients with large embryonal RMS (>5 cm) localised in unfavourable sites, alveolar N0 RMS, and embryonal N1 tumours are included in this group. The different subgroups included in this category share the same unsatisfactory prognosis and therefore the need for a more effective strat-

egy. The CWS Study Group, the SIOP Malignant Mesenchymal Tumours Committee (MMT) and the AIEOP Soft Tissue Sarcoma Committee agreed in 1996 to randomize chemotherapy in the identically defined High Risk Group: The final analysis performed in 2004 did not show differences in EFS between VAIA vs. CEVAIE (3 years EFS 59% vs. 59%, 3 years OS 78% vs. 74%, CWS group, unpublished data) or IVA vs. CEVAIE (3 years EFS 65% vs. 63%, 3 years OS 81% vs. 79%, MMT study group, unpublished data). This analysis was the basis for the European consensus declaring the IVA regimen as the standard therapy, as this treatment turned out to be the less toxic one.

Alveolar Paratesticular Tumours

Despite unfavourable pathology this very small group of patients showed a good outcome in previous European studies. In the CWS/AIEOP-STSC experience, they represented 8% of all paratesticular RMS, and the 5-year survival rate was 93% after IVA ± doxorubicin chemotherapy [19, 20]. However, four relapses occurred. An evaluation of the SIOP data showed similar results. According to these data, patients with paratesticular alveolar RMS will be kept in the High Risk Group and treated with IVA × 9 (avoiding anthracyclines) [21–24].

Parameningeal Tumours

Parameningeal (PM) site is a well-known adverse prognostic factor in children with localized rhabdomyosarcoma (RMS). In a recent report, pooled data from 1105 patients treated in 10 studies conducted by European and North American cooperative groups were analysed. Ten-year EFS and OS were 62.6% and 66.1% for the whole group. Patients without initial RT showed worse survival (10-year OS 40.8% versus 68.5% for RT treated patients). A multivariate analysis focusing on 862 patients who received RT as part of their initial treatment revealed four unfavourable prognostic factors: age <3 or >10 years, signs of MI, unfavourable site and tumour size. Utilizing these prognostic factors, patients could be classified into different risk groups with 10-year OS ranging between 51.1% and 80.9%. While, in general PM localization is regarded as an adverse prognostic factor, the current analysis differentiates those with good prognosis (36% of patients with 0–1 risk factor, 10-year OS 80.9%) from high-risk PM patients (28% with 3–4 factors, 10-year OS 51.1%). Furthermore, this analysis reinforces the necessity for RT in PM RMS [25].

Very High Risk

An analysis of the High Risk Group of the CWS/RMS-96 has been made in an attempt to better define patients in the High Risk Group according to their risk of relapse. The group of patients with alveolar RMS and nodal involvement showed the poorest outcome, compared to that of IRS group IV patients. In CWS/RMS-96, the 3-year EFS were 28% and OS 29%. Results in the SIOP studies showed only partially better results with a 5-year EFS of 39%.

Until more effective treatment regimens are found, this patient group should therefore be treated with the VAIA regimen.

A randomized phase-III trial of the CWS for localized high-risk RMS and localized RMS-like soft tissue sarcoma, CWS-2007-HR, is ongoing. The primary objectives are to investigate whether the addition of oral maintenance chemotherapy with O-TIE (etoposide, idarubicin, trofosfamide) for 6 months improves the event-free survival (EFS) in patients with localised high-risk RMS and RMS-like soft tissue.

Analogous to this phase-III trial, the EpSSG recently published their data on maintenance therapy for localized high-risk RMS with cyclophosphamid/vinorelbine: In the intention-to-treat population, 5-year disease-free survival was 77.6% (95% CI 70.6–83.2) with maintenance chemotherapy versus 69.8% (62.2–76.2) without maintenance chemotherapy (hazard ratio [HR] 0.68 [95% CI 0.45–1.02]; $p = 0.061$), and 5-year overall survival was 86.5% (95% CI 80.2–90.9) with maintenance chemotherapy versus 73.7% (65.8–80.1) without (HR 0.52 [95% CI 0.32–0.86]; $p = 0.0097$). Adding maintenance chemotherapy seems to improve survival

for patients with high-risk rhabdomyosarcoma. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials [26].

31.4.2 Treatment of Patients with Synovial Sarcoma

Chemosensitivity of synovial sarcoma (SySa), especially to ifosfamide and anthracyclines, is well known [27], but well-designed, randomised studies addressing the value of adjuvant chemotherapy in children and adolescents are lacking. Existing studies in adult patients mostly summarize a variety of different subtypes of soft tissue sarcoma without coherent and transferable results. Since 1981 the CWS Study Group and the Italian ICG study group (since 1988) have recommended systemic chemotherapy in combination with local therapy for paediatric synovial sarcoma patients. The results of these CWS/ICG studies are the only reports throughout the literature providing information about consistently documented SySa patients who were treated according to a uniform treatment Scheme [28]. The results revealed were superior to those previously published, so the therapy will be continued with two cycles of VAIA III for IRS Group I and II tumours (six courses) and three cycles VAIA III for patients with IRS Group III and all T2b tumours independent on IRS Group (nine courses) in combination with local therapy [29–33].

Patients with **localised SySa** were enrolled on the European Paediatric Soft tissue Sarcoma Study Group (EpSSG) NRSTS2005 and on the Children Oncology Group (COG) ARST0332 trials, treated with surgery alone. Patients must have undergone initial complete resection with histologically free margins, with a grade 2 tumour of any size or a grade 3 tumour ≤5 cm. The 3-year event-free survival was 90% (median follow-up 5.2 years, range 1.9–9.1). All patients with recurrence were effectively salvaged, resulting in 100% overall survival. This joint prospective analysis showed that patients with adequately resected ≤5 cm SySa, regardless of grade, can be safely treated with a surgery-only approach. Avoiding the use of adjuvant chemotherapy and radiotherapy in this low-risk patient population may decrease both short- and long-term morbidity and mortality [34].

The overall prognosis of **primary metastatic synovial sarcoma** is poor. However, individuals with oligometastatic lung metastases had very good chance for long-term survival when treated with adequate multimodal therapy [33].

31.4.3 Treatment of Patients with Other "RMS-Like" Tumours (STET (EES/pPNET), UDS)

Patients with localised soft tissue Ewing tumours (STET, consisting of extraosseus Ewing's tumour (EES) and peripheral primitive neuroectodermal tumours (pPNET)) and the undifferentiated sarcoma (UDS) showed a 5-year EFS of 57%, 53% and 55% and a 5-year OS of 81%, 69% and 72% in the CWS-96 study. The 3-year EFS rate of patients with bony counterpart of the STET treated according to the EICESS 92 study (European Cooperative Ewing's Sarcoma Study) is 66% [35, 36]. Since the primary localisation of the extraskeletal STET is quite different in comparison with classical bony tumours (i.e. parameningeal site, abdomen, genitourinary), the treatment of these patients according to the recommendation of the protocol for soft tissue sarcoma, especially concerning the local therapy, seems to be of major benefit for the patients. VAIA III cycles with increased dose intensity of ADR in combination with local control modalities are recommended following the treatment of EES, pPNET and UDS until new and better therapies are found for this tumour group [37, 38].

31.4.4 Treatment of Patients with "Non-RMS" Tumours

The so-called "non-RMS" tumours display a heterogeneous group of rare soft tissue tumours

in children and adolescents with different histiotypes and biological behaviour [39]. Some of these STS are more common in adults. In the past the different non-rhabdomyosarcoma-like soft tissue tumours (NRSTS) have been treated and studied as one group.

With the aim of improving not only the quality of treatment but also the prognosis in children with NRSTS in Europe and to gain understanding in the biology of the different histiotypes, the CWS group (in cooperation with the AIEOP STSC) introduced a risk-adapted therapy recommendation for patients with NRSTS in the CWS-96 and the CWS-2002-P studies (Table 31.3). To understand more about the different histiotypes, CWS and AIEOP STSC cooperated in performing selective retrospective analysis for any single histiotype in the past [40–44]. Tumour size and surgery (post-surgical stage = IRS grouping) are the most significant prognostic factors. Reference pathology is essential for risk stratification of NRSTS and the evaluation of prognosis. The grading of NRSTS represents one of the most debated and complex subjects concerning the information that the pathologist must give to the clinician. Different grading systems (generally three-grade systems) have been defined by paediatric and adult oncologists for predicting clinical course and prognosis of disease and to be able to define a risk-adapted treatment [45, 46]. Many NRSTS are considered moderate or poorly chemosensitive tumours [47–50]. Surgery (±radiotherapy) is therefore the mainstay of treatment and an important stratification factor. The quality of surgery is critical, and it is recommended that soft tissue sarcoma patients should be referred to specialized centres for local treatment, preferably prior to the biopsy.

The infantile fibrosarcoma is very recently discussed as a so-called NRTK fusion positive tumour, sensitive to NTRK inhibitors [51–54]. Mutilating surgery should be avoided. International consensus recommendations treating these infants are urgently needed.

Table 31.3 Risk stratification for "non-RMS-like" tumours

Risk group	Histology	Node stage	IRS group	Initial tumour size
Low	Any (except MRT and DSRCT)[a]	N0	I	≤5 cm
Standard	Any (except MRT and DSRCT)[a]	N0	I	>5 cm[b]
		N0	II	Any
		N0	III	≤5 cm[c]
High	MRT/DSRCT	N0/N1	I, II, III	Any
	Any	N0	III	>5 cm
	Any	N1	II, III	Any
Stage IV	Any	N0/N1	IV	Any

[a]**MRT** (malignant rhabdoid tumour), **DSRCT** (desmoplastic small and round cell tumour): treatment in the **High Risk Group**

[b]Exception: typical low-grade tumours (grade 1) might be treated in the **Low Risk Group**

[c]Exception: high-grade tumours (grade 2 or 3) might be treated in the **High Risk Group**

31.4.4.1 Risk Stratification "Non-RMS-Like" Tumours

- **Post-surgical stage**:
  - *Group I* = primary complete resection (R0), no microscopic tumour residuals
  - *Group II* = microscopic tumour residuals (R1) or primary complete resection but N1
  - *Group III* = macroscopic tumour residuals (R2)
- **Node stage**:
  - *N0* = no clinical or pathological node involvement
  - *N1* = clinical or pathological nodal involvement
- **Initial tumour size**:
  - *Favourable* = tumour size (maximum dimension) ≤5 cm (Ta)
  - *Unfavourable* = tumour size >5 cm (Tb)

NRSTS Low Risk Group

Low Risk patients do not require further local or systemic treatment, but careful follow-up exami-

nations at short, regular intervals are strongly recommended.

NRSTS Standard Risk Group

All patients in Standard Risk Group should be irradiated. Exception: in patients with typical low-grade tumours (grade 1), >5 cm, IRS Group I irradiation might be avoided. The role of adjuvant chemotherapy in this risk group remains unclear and has to be evaluated in a randomised way. Application of chemotherapy is therefore not routinely recommended in this guidance. Exception: patients with high-grade (grades 2–3) NRSTS and IRS Group III might be treated in the High Risk Group.

NRSTS High Risk Group

In this group, adjuvant or neoadjuvant VAIA III chemotherapy should be administered. Radiotherapy for local tumour control is clearly indicated.

NRSTS Stage IV

Patients with primary metastasized "non-RMS-like" tumours (stage IV) should be allocated to stage-IV therapy independent from other risk factors.

31.4.4.2 Treatment

Local Treatment

Local treatment decisions will follow general recommendations for localised soft tissue sarcoma.

Surgery: Surgery is the mainstay of treatment for local tumour control in NRSTS tumours. The possibility of a wide tumour resection in combination with an early reconstruction has to be considered and planned carefully. Particular care must be taken to ascertain completeness of resection (R0). A primary R1 resection in combination with subsequent radiotherapy may be the only feasible treatment concept in "non-RMS-like" tumours depending on tumour size and localisation. Tumours, which initially presented as non-resectable tumours and did not show response to chemotherapy, usually require radical resection even with functional impairment or mutilating surgery ("salvage surgery"). Careful consideration of risk and benefit of such an extensive surgical measure in interaction with the patient and its parents/guardian is strongly recommended. Experimental options such as isolated limb perfusion [55, 56], hyperthermia or hyperthermic intraperitoneal chemotherapy (HIPEC) [57, 58] can be an option in case of non-response in order to avoid "mutilating" surgery but should only be considered. Radical lymph node dissections are not routinely indicated.

Radiotherapy: Irradiation of NRSTS tumours mainly depends on post-surgical stage (IRS group), patient's age and initial tumour size. Patients in Low Risk Group (tumour size ≤5 cm and completely resected tumour, IRS group I) should not be irradiated. Patients with a maximal tumour diameter >5 cm should be irradiated regardless of their primary resection status (R0 or R1)—exception: in R0 resected low-grade tumours (grade 1), greater than 5 cm radiotherapy might be avoided. In patients with initial IRS group III, radiotherapy is indicated prior to or after delayed surgery.

Chemotherapy

Only patients in the "Non-RMS-like" High Risk Group receive chemotherapy with VAIA III. The treatment consists of alternating courses of ifosfamide, vincristine and adriamycin (I^2VAd), ifosfamide, vincristine and actinomycin-D (I^2VA) and I^2VAd again for six courses, followed by three courses of I^2VA alone (treatment scheme *VAIA III*). The interval between the courses is 3 weeks, and duration of chemotherapy is 25 weeks. Local treatment (radiotherapy + surgery) will be administered at week 13 (at least after the fourth course).

Treatment of Patients with Metastatic Disease (Stage IV)

The European Intergroup Studies (MMT-89 and MMT-91) comprising SIOP-MMT, CWS and ICG study groups investigated the effectiveness of a very intensive six-drug multiagent regimen, including most of the drugs thought

to be active against STS: ifosfamide, epirubicin, vincristine, carboplatin, dactinomycin and etoposide (CEVAIE). They were used in a concentration close to the maximum-tolerated doses when given in combination. As a result, 73% of the patients received complete remission, 46% of these with chemotherapy alone. Responses to chemotherapy (CR + PR) at week 9 and 18 were 83% and 92%, respectively [59]. The overall CR rate achieved in this trial revealed superior results compared to CR rates reported by other studies of metastatic rhabdomyosarcoma [60, 61]. Myelosuppression was the most frequent adverse effect. 5-year OS and EFS for the whole group were 24% and 20%, respectively. Thus the good response as measured by reduction of tumour mass was not translated into improved survival. The prognostic relevant factors in 201 patients with primary metastatic tumours treated according to the CWS studies from 1981 to 1996 were age (≥10 years, $p < 0.03$) and B/BM metastases ($p < 0.014$). Patients with stage IV disease, ≥10 years with B/BM metastases, had a dismal 5-year survival rate of 6 ± 4%. In contrast, the outcome of metastatic patients <10 years of age without B/BM metastases was much better with a cure rate of 41 ± 7%. Histology, single vs. multiorgan metastases and consolidation with HDC were not related to prognosis.

According to a recent data obtained from 788 patients treated in nine studies performed by the European and American cooperative groups, clinical factors, including age, histology, site of primary and site(s) and number of sites of metastatic disease were correlated with event-free survival (EFS) and overall survival (OS). Three-year EFS was significantly and adversely influenced by age, alveolar histology, location of primary tumour in unfavourable site (defined as extremity and "other" sites), presence of three or more sites of metastatic disease and the presence of bone or bone marrow involvement. EFS was strongly correlated to all factors except histology. This analysis identified subsets of patients with metastatic rhabdomyosarcoma with different outcomes to current therapy and offers a strategy to define patient candidates for experimental approaches to treatment [62].

The standard therapy recommendation for patients with metastatic STS is CEVAIE as an induction therapy and O-TI/E maintenance as consolidation for patients <10 years without B/BM metastases. The role of high-dose chemotherapy followed by autologous stem cell transplantation in patients with very-high-risk sarcoma was not effective, but oral maintenance treatment (OMT) was very promising. The proportional hazard analysis for patients with rhabdomyosarcoma (RMS) or "RMS-like" tumours demonstrated an independent benefit of OMT on outcome [63].

In conclusion, the treatment of patients with rhabdomyosarcoma is continually evolving and should be constantly adapted as new evidence emerges from clinical trials. This evolving process has led to the improved survival seen over the last decades and should continue in the future.

- Histology, staging (IRS grouping), nodal involvement, tumour site, tumour size and patients' age have been identified as major prognostic factors.
- A group of patients with localised RMS, who can be treated with less intensive treatment (VA alone ± radiotherapy), has been selected. The acute and late sequelae of alkylating agents and anthracyclines can be avoided in this group without compromising survival.
- Chemotherapy regimens based on the VAC or IVA combinations appear equally effective and may be considered the "reference regimen" for most children and adolescents with RMS. However a substantial proportion of children and adolescents are not cured with such regimens, and the search for new combinations must continue. The value of the addition of other drugs should be investigated in randomised clinical trials.
- Local treatment is a fundamental part of RMS, but the advantages and disadvantages of aggressive surgery and/or radiotherapy should be balanced against the late effects for young children and adolescents.
- Conservative surgery is recommended, and experience should be gathered to select those children and adolescents for whom surgery may be the only necessary local treatment.

- Although it is possible to cure about 30% of patients without radiotherapy, only a subgroup of them (i.e. embryonal tumour completely resected at diagnosis) can confidently be identified at diagnosis. Further efforts should be made to better define a favourable population for whom irradiation and its late effects can be avoided.

Increasing international collaboration should improve the treatment stratification and explore through well-designed, randomised studies better treatment strategies for children and adolescents with RMS and other soft tissue sarcomas.

31.5 Investigations at the End of Treatment

According to the CWS group investigations required at this point are:

- Thorough physical and neurological examination (weight, height, pubertal status).
- MRI/CT/ultrasound of primary tumour site including regional lymph nodes.
- Cerebral MRI.
- CT of the lung.
- Chest X-ray.
- Abdominal ultrasound.
- Evaluation of metastatic lesions in stage IV patients.
- Blood: full blood cell count, differential blood cell count, liver enzymes, K, Na, Ca, PO_4, Cl, Mg, glucose, AP, H_2CO_3, creatinine, immunglobulines, and viral serum analysis.
- Ifosfamide nephrotoxicity monitoring (see above).
- Urine: Na, Ca, glucose, PO_4, creatinine, pH, total protein; *24 h urine*: calculate GFR, 24 h Ca, PO_4 and glucose loss, max. PO_4 reabsorption/GFR.
- Echo, ECG, EEG, paediatric audiometry and ocular fundus examination.
- Other investigations if indicated (e.g. PET, CSF, hormonal status).
- Bone marrow aspiration and/or bone marrow biopsy plus EDTA-blood sample at week 27 in case of initial bone marrow involvement.

31.6 Disease-Related Follow-Up After Completion of Chemotherapy

Tumour status should thoroughly be monitored depending on tumour localisation and adapted to the patients' risk group. Recommended routine controls for all patients after end of treatment are shown in Table 31.4. These recommendations however only refer to patients who have been treated according to this guidance. In case of alternative therapies or inadequate local treatment, the prognosis and relapse pattern can be different. In the experiences of the CWS Study Group gained during more than 25 years, relapses are more common, and patients have a poorer prognosis if they were treated individualized and not according to a guidance or protocol.

Tumour-directed follow-up should correspond with the estimated risk of relapse. The value of more intense disease-related follow-up is unclear in paediatric soft tissue sarcoma. Most relapses are however detected due to clinical signs and symptoms, and the patients/parents should be educated to contact the paediatric oncologist immediately in case of unclear symptoms. An improved post-relapse survival of patients with imaging-detected recurrences could also not be shown [64, 65]. The risk of relapse and thus the frequency of tumour-directed follow-up in paediatric STS depend on histiotype, primary stage and—in localised rhabdomyosarcoma (see Table 31.5a–c)—tumour size.

Chest X-rays during follow-up are less sensitive to detect tumour recurrences compared with CT scans, but the incorporated radiation dose is also much lower depending on the imaging protocols that are employed. They may therefore be used if the expected relapse risk in the thorax is considered to be low. If chest X-rays are performed, they should include a postero-anterior (PA) view, and right-anterior-oblique (RAO) and left-anterior-oblique (LAO) views should be considered. According to experience, the oblique views allow a better interpretation of the phrenicocostal angles compared to lateral views. The cumulative radiation dose of PA, RAO and

LAO views are similar to a PA and lateral view [66, 67]. The risk of possible later detection of lung metastases using X-rays compared with CT scans must be taken into account and discussed with the parents/patients/guardians.

Guidelines for optimizing CT protocols for children and adolescents according to the ALARA principle (as low as reasonably achievable) can be found under www.imagegently.org.

31.7 Disease-Related Follow-Up for Soft Tissue Sarcoma Apart from Localised RMS

Some STS histiotypes show a propensity to develop metastases in sites, which are uncommon in STS otherwise. Note, e.g. the propensity of alveolar rhabdomyosarcoma to develop metastases in the breast(s) of post-pubertal girls/women or the possibility that intracranial metastases can develop in, e.g. alveolar soft part sarcoma or alveolar rhabdomyosarcoma.

Most STS histiotypes do not recur later than 5 years after first diagnosis. Because of the rarity of these tumours, the possibility of late recurrences can however not be excluded. Please consider that some STS histiotypes characteristically develop late relapses, such as alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, synovial sarcoma or mesenchymal chondrosarcoma.

31.8 Disease-Related Follow-Up for Localised RMS

Localised RMS account for the largest group of patients with localised STS. Disease recurrence must be expected in every third patient with localised RMS, mainly as a locoregional relapse. More than 90% of recurrences occur within 4 years after diagnosis [68–70]. According to the CWS experience, tumour size and histologic subtype can discriminate two groups with consistent risk of relapse and distinctive post-relapse prognosis [68]:

1. *RME ≤5 cm*: this group accounts for approximately 40% of all localised RMS. The overall relapse risk is lower compared to RME >5 cm and RMA, and the proportion of systemic/metastatic recurrences is also relatively low. Recurrences involving bone/bone-marrow

Table 31.4 Routine controls after treatment for all soft tissue sarcoma apart from localised RMS according to the CWS group

Date	Investigations at primary tumour site	Staging	Additional investigations
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound abdomen/pelvis (at least every **6 months**) Bone scan (risk-adapted, once a **year**) *For stage IV*: MRI/CT evaluation of metastases	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray every **6 months** Ultrasound abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

occur rarely. In case of relapse, these patients have a rather good salvage option as well, especially if a possibility for radiation therapy remains.

2. *RME >5 cm and RMA*: the overall relapse risk and proportion of systemic/metastatic relapses are much higher in this group, and the post-relapse prognosis is much poorer in these patients compared to RME ≤5 cm.

31.9 Late Effects Related to Follow-Up

The following regular examinations are recommended for patients to evaluate late effects. Pain in the primary site 5–10 years after therapy warrants investigation for the development of secondary bone tumours. This is applicable to all radiation treated sites. The risk of **development**

Table 31.5 Recommended routine controls after treatment for localised RMS according to the CWS group

Date	Investigations at primary tumour site	Staging	Additional investigations
(a) For localised embryonal rhabdomyosarcoma (RME) ≤5 cm			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound of the abdomen/pelvis (at least every **6 months**)	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray every **6 months** Ultrasound of the abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound or MRI with contrast (frequency at the discretion of the responsible physician)	Frequency at the discretion of the responsible physician or only in case of clinical symptoms	
(b) For localised embryonal rhabdomyosarcoma >5 cm			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound of the abdomen/pelvis (at least every **6 months**)	Liver and kidney-function (glomerular und tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray or CT thorax every **6 months** Ultrasound of the abdomen/pelvis (at least every **6 months**)	
3rd–5th year	See above, but **6–12 months'** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

(continued)

Table 31.5 (continued)

Date	Investigations at primary tumour site	Staging	Additional investigations
(c) For localised alveolar rhabdomyosarcoma			
1st year after treatment	Ultrasound (tumour site, regional lymph nodes, abdomen, pelvis) MRI/CT with contrast (every **4 months**; alternating, if applicable)	Chest-X-ray or CT thorax (intervals risk-adapted, at least every **6 months**) Ultrasound abdomen/pelvis (at least every **6 months**) In postpubertal girls/women: consider imaging of the breasts (ultrasound, MRI in case of unclear findings)	Liver and kidney function (glomerular and tubular) Echocardiogram/24 h ECG Hormone status (growth and puberty) Functional impairment (continence, visual and hearing faculty; musculoskeletal system) Additional investigations (according to clinical symptoms)
2nd year	See above, but **6 months'** intervals	See above Chest-X-ray or CT thorax every **6 months** Ultrasound abdomen/pelvis (at least every **6 months**) In postpubertal girls/women: consider imaging of the breasts	
3rd–5th year	See above, but **6–12 months** intervals	See above, **yearly**	
>5th year	Ultrasound (see above) MRI/CT with contrast (frequency at the discretion of the responsible physician)	See above (frequency at the discretion of the responsible physician)	

of a second malignant neoplasm (e.g. leukaemia, lymphoma or solid tumours) should be considered.

Post therapy, all patients should be tracked for possible tumour relapse and to monitor treatment side effects (Tables 31.4 and 31.5a–c, respectively Tables 31.6 and 31.7). By improving the multimodal therapies for malignant diseases in children and adolescents carried out in multicentre trials, the overall 5-year survival rate increased up to 75%. In the evaluation of an antineoplastic therapy, not only survival should be taken into account but also the state of health after cessation of therapy. A significant group of survivors has to deal with severe impairments decreasing their quality of life [71].

Up to now, most published data on late effects resulted from retrospective investigations (limitation, selected patient groups) or investigations performed in a single centre (limitation, small sample sizes). Large prospective investigations in a well-established nationwide network of therapy trials and a follow-up system for the detection of major late sequelae are rare. In 1988, the Society of Paediatric Oncology and Haematology (GPOH) established a late effects working (Beck 1988) group consisting of oncologists as well as experts in organ toxicities, initially performing retrospective studies of major late sequelae. In 1998, the prospective and multicentre Late Effects Surveillance System (LESS) was started to investigate the late effects of patients suffering from Ewing's sarcoma, osteosarcoma or soft tissue sarcoma in Germany, Austria and Switzerland [72–77]. The main aims are the analyses of incidence, risk factors and prognosis of late effects. However these published data were restricted mainly to a follow-up of less than 5 years after finishing the oncological therapy.

Patients registered in CWS SoTiSaR will be included in these projects. A comparable group for the evaluation of radiation-associated late effects [78] was founded under the auspices of the GPOH as well as a research group investigating the quality of life [79, 80].

LESS, RiSK and QoL closely cooperate with the CWS Study Group Centre by means of regular transfers of basic patient data. LESS has also developed recommendations for the surveillance of late effects [81]. The data forms should be filled out about 4 weeks after cessation of therapy and in yearly intervals afterwards. In case of a late effect, an enhanced data form should be filled out.

During the last years, two large projects, PanCareSurFup [82] and PanCareLIFE [83], funded by the European Commission, have been performed on late effects and the development of guidelines. The later ones were structured in a harmonization group in cooperation with colleagues of the United States, Australia, New Zealand and other countries [84].

The results of these projects will be adapted and implemented in the follow-up systems of the GPOH, to improve them and to make them comparable with other countries.

The references for late effects of patients suffering from a soft tissue sarcoma and his therapy and the follow-up for those suffering from an osteosarcoma are similar, and therefore the above mentioned references on late effects are listed in the osteosarcoma chapter.

The following specific primary tumour sites may require special monitoring and late effects examinations.

Table 31.6 Recommended examinations

General examinations	
Height and weight	At 6 months' and 1 year intervals. Any child showing a growth deceleration of 20–25 percentile units on standard growth charts from the pre-treatment height should be evaluated for thyroid and pituitary function
Blood pressure	Measurements annually
Tanner staging	Annually for girls and boys until maturity. If there is delayed appearance of secondary sexual maturation, the patient warrants evaluation of gonadal hormone values, i.e. at 12–14 years of life for girls (FSH, LH and oestradiol) and boys (FSH, LH and testosterone)
Testicular size	Annual measurements in boys using volume measured by Prader orchidometer if possible. The vast majority of patients on this study will receive alkylating agents and may accrue damage to the germinal epithelium of the testis
Menstruation	Onset of menstruation in girls and regularity of periods. Because of local radiotherapy or alkylating agents therapy, ovarian failure may occur in some patients
School performance, behavioural pattern	History should include school performance and behavioural disturbances so that early intervention is possible

Table 31.7 Recommended examinations—by specific primary site

Examinations in specific primary site	
Head/neck	
Growth measurements	Annually, plotted on standard growth curves
Eyes	Annual ophthalmologic examination if eye was in radiotherapy field
Teeth	Annual dental examination if maxillary/mandibular sites were in radiotherapy field
Ears	Annual auditory examination if the ears were in the irradiated field
Bones	Bone X-rays of the primary site every 1–2 years until maturity if radiotherapy was given to the primary site. Include opposing normal side for comparison of degree of bone hypoplasia
Thyroid	Thyroid function (TSH, T3, T4) every 2 years in case of irradiation on the neck
Trunk	
Lung	Special notation on exercise intolerance or shortness of breath, if radiotherapy was given to primary tumours of the chest or to pulmonary metastases.

(continued)

Table 31.7 (continued)

Examinations in specific primary site	
Heart	Cardiac toxicity examinations, if part of heart was in radiotherapy field as well as additionally application of doxorubicin
Bone	X-rays of the bone in the primary site with the opposite normal side for evaluation of bone hypoplasia every 2 years
Abdomen/ pelvis	Monitoring of problems following abdominal/pelvic irradiation, e.g. bowel obstruction, chronic diarrhoea, inadequate absorption, rectal stenosis and sphincter problems
Kidney	Annual measurements of kidney function in patients receiving para-aortic node irradiation or other abdominal irradiation including the kidney/urogenital area
Femur/hip joints	Monitoring of limp or pain as symptoms for slipped capital femoral epiphyses, which may occur several years after therapy
Genito-urinary	
Bladder	Regularly tested kidney function in children without a bladder and with various types of urinary diversion Imaging studies every 1–2 years for hydronephrosis, evidence of pyelonephritis and renal function Kinking of ileal loops, stenosis or reflux of the ureters detected by contrast studies Bladder volume and function tests (cysto-urethrograms or other imaging studies), if radiotherapy was given to the bladder
Genital organs	Girls with uterine or vaginal tumours should be followed for sexual maturation and ovarian failure (see above). Vaginal examination under anaesthesia until 5 years' follow-up and after depending on the treatment received Boys treated for bladder, prostate or paratesticular primaries should be followed (see above). History in teenage boys should include questions of normal ejaculatory function, particularly in patients with bladder/prostate or paratesticular primaries. Semen analysis as described above
Extremities	
Growth measurements	Annual bilateral limb length measurements, if radiotherapy was given
Bones	X-rays of primary sites for bone growth abnormalities if indicated in comparison with normal site
Function	History should address limp, evidence of pain and other dysfunction of the involved extremity

For details and a late effects focussed follow-up schedule, see LESS, Late Effects Surveillance System, Nachsorgeplan Weichteilsarkome, on www.kinderkrebsinfo.de or the CWS homepage www.cws.olgahospital-stuttgart.de.

31.10 Recomendation for a Long-Term Follow-Up Schedule

Long-term follow-up is performed according to the recommendations of the International Guideline Harmonisation Group (www.ighg.org), of the Children's Oncology Group (COG) (http://www.survivorshipguidelines.org/) and the LESS group (www.nachsorge-ist-vorsorge.de) in Germany.

31.11 Psychosocial Follow-Up

The reader is also referred to the guidelines prepared by the PSAPOH (Psychosoziale Arbeitsgruppe in der Pädiatrischen Onkologie und Hämatologie) for the psychosocial care of childhood and adolescent cancer patients, even if the main focus is on acute care (www.awmf.org/leitlinien/detail/ll/025-002.html).

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