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Diagnosis and treatment of rhabdomyosarcomas

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ABSTRACT

Rhabdomyosarcoma (RMS) is a soft tissue sarcoma. The primary tumor is most commonly localized in the head and neck, the urogenital system, or the limbs. Classification by the World Health Organization has distinguished four histopathological RMS subtypes: embryonal, alveolar, pleomorphic, and spindle cell/sclerosing. Differential diagnosis of RMS includes melanoma, malignant neoplasm of peripheral nerve sheaths, liposarcoma, and PE-Coma. Among typical cytogenetic changes in RMS are chromosomal translocations t(2;13)(q35;q14) and t(1;13)(p36;q14). They lead to the formation of fusion genes that have a prognostic value. In the course of RMS, changes may also be present in signaling pathways, including RAS-PI3K, Wnt/β-catenin, receptor tyrosine kinase pathways, and myogenesis regulation. In 30% of patients at the time of diagnosis of RMS, distant metastases are present, most commonly to lungs, lymph nodes, bones, and bone marrow. Treatment of patients with RMS requires a multidisciplinary approach, and steadily perfected diagnostic techniques contribute to the individualization of therapeutic strategies. Optimal treatment of localized RMS is based on surgery combined with radiotherapy and chemotherapy. If distant metastases are present, the basic therapeutic method is multidrug chemotherapy, most frequently based on vincristine, dactinomycin, ifosfamide/cyclophosphamide, and etoposide. Despite intensive treatment, the 5-year survival index for RMS is not greater than 50%. There are still no unequivocal guidelines concerning the treatment in patients with local or distant recurrences.

Key words: rhabdomyosarcoma, sarcoma, soft tissue sarcomas, RMS, RAS, translocation

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Introduction

Sarcomas are a heterogeneous group of malignant neoplasms derived from mesenchymal tissue. The usual classification includes sarcomas derived from bone and soft tissue sarcomas [1]. Rhabdomyosarcoma (RMS) is a soft tissue sarcoma, whose cells differentiate in the direction of striated muscles, which is proved by the expression of skeletal muscle markers [2]. The current World Health Organization (WHO) classification divides RMS into four histological types: alveolar rhabdomyosarcoma (ARMS), embryonic rhabdomyosarcoma (EMRS), pleomorphic rhabdomyosarcoma (PRMS) and spindle cell/sclerosing rhabdomyosarcoma (SCRMS) [3]. In the last several decades, a small improvement in the survival of

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patients with RMS has been observed. This is due to the development of diagnostic methods allowing correct diagnosis of the disease and improving access to multidisciplinary treatment, including modern radiotherapy (RT) techniques. Establishing uniform standards of the procedure that included pediatric treatment protocols in the therapy of adult patients has led to the increase of the 5-year survival rate from 36% to 54% in comparison to treatment with other protocols [4]. Nevertheless, the diversity of anatomical localization of primary RMS tumors, limited methods of treating metastatic disease, and the current lack of targeted therapies make for an unfavorable prognosis in this group of patients. In retrospect, the median overall survival (OS) for RMS patients with distant metastases is from 7 to 22 months [5–7]. Direct toxicity (e.g. cardiotoxicity) and other undesirable effects (e. g. neutropenia) of cytotoxic drugs used in RMS treatment, both in the localized stage and in the disseminated one, remain a large limitation in the choice of optimal treatment [8].

Epidemiology

The incidence of soft tissue sarcomas in Poland is determined to be 4–5 cases per 100 000 persons, which is about 1000 new patients per year [9]. Simultaneously they constitute not more than one percent of all malignant neoplasms in adults [9–11]. Rhabdomyosarcoma is very rare in adults and is responsible for about 3% of soft tissue sarcomas [12]. Epidemiological analysis of 2600 patients with RMS indicated that slightly over 40% of all RMS cases are in adults [13]. These sarcomas occur four times more frequently in the white than in the black population The largest cohort of adults with RMS described so far includes 1071 persons [13]. Moreover, there is a small number of publications from reference centers in Europe, the United States, and Asia, which includes groups from several dozen to several hundred patients. The median age of adults with RMS is very differentiated and varies from 26 to 71.5 years [7, 14].

Risk factors

Based on the available literature two main groups of risk factors for RMS can be distinguished, that is genetic and environmental factors. Persons with some heritable genetic syndromes including Li-Fraumeni [15] or Noonan syndrome [16] are at an increased risk of RMS (Tab. 1). Most patients with RMS do not have any first-degree relatives with neoplastic diseases in their medical history; however, neoplasms among first-degree relatives under 30 years of age are more frequent in RMS patients than in the healthy population. Congenital RMS cases have also been described [17, 18]. Among other factors which increase the risk of RMS are congenital defects [19], prenatal exposure to

Table 1. Genetic syndromes predisposing to rhabdomyosarcoma

Genetic syndromes	Responsible genes	References
Beckwith-Wiedemann	*IGF2, CDKN1C, H19, and KCNQ1OT1*	[23]
Costello	*HRAS*	[24]
DICER1	*DICER1*	[25]
Type 1 neurofibromatosis	*NF1*	[19, 26, 27]
Li-Fraumeni	*TP53*	[15]
Noonan	*BRAF, KRAS, NRAS, PTPN11, RAF1 and SOS1*	[16]
CMMRD	*MLH1, MSH2, MSH6, PMS2*	[28]
Rubenstein-Taybi	*CREBBP*	[29]
Hereditary retinoblastoma	*RB1*	[30]
Gorlin	*PTCH1, PTCH2, and SUFU*	[31, 32]
Cardiofaciocutaneous	*BRAF, MAP2K1, MAP2K2, KRAS*	[33]

IGF2 — insulin-like growth factor 2 gene; CDKN1C — cyclin dependent kinase inhibitor 1C gene; H19 — H19 imprinted maternally expressed transcript gene; KCNQ1OT1 — KCNQ1 opposite strand/antisense transcript 1 gene; HRAS — HRAS proto-oncogene; NF1 — neurofibromin 1 gene; DICER1 — dicer 1, ribonuclease III gene; TP53 — tumor protein p53 gene; NRAS — NRAS proto-oncogene; KRAS — KRAS proto-oncogene; BRAF — B-Raf proto-oncogene; PTPN1— protein tyrosine phosphatase non-receptor type 1; RAF1— Raf-1 proto-oncogene; SOS1 — SOS Ras/Rac guanine nucleotide exchange factor 1 gene; MLH1 — mutL homolog 1 gene, MSH2 — mutS homolog 2 gene; MSH6 — mutS homolog 6 gene; PMS2 — PMS1 homolog 2 gene; CREBBP — CREB binding protein gene; RB1 — RB transcriptional corepressor 1 gene; PTCH1 — patched 1 gene; PTCH2 — patched 2 gene; SUFU — suppressor of fused homolog; CMMRD — constitutional mismatch repair deficiency

Table 2. Changes in intracellular signal pathways in rhabdomyosarcoma

Signal pathway	Altered genes	Remarks	References
RAS-PI3K	*NRAS, KRAS, HRAS PTPN11, NF1, BRAF, PIK3CA*	Over 80% of RMS tumors show PI3K pathway activation. In 1/3 of FNRMS tumors, RAS pathway perturbations are present. Mutations of the PI3K/AKT signal pathway define an ERMS subgroup with an unfavorable clinical course	[57, 58, 72–75]
RTK	*FGFR2, FGFR4, IGF1R, ERBB2, EPHA3, EFNA1, PDGFRA*	*FGFR4* mutations occur in about 7% of FNRMS *IGFR1* overexpression is observed in FPRMS *PDGFRA* gene overexpression is characteristic of FPRMS tumors	[46, 76–80]
Oncogenesis suppression pathways	*PTEN, TP53, MDM2, CDKN2A, CDKN1C*	*PTEN* gene mutation occurs in FNRMS tumors *TP53* gene mutation occurs in about 12% of FNRMS tumors	[36, 81–83]
Wnt/β-catenin	*CTNNB1*	*CTNNB1* gene mutation (encoding β-catenin) is common in FNRMS tumors	[83]
Sonic Hedgehog signal pathway	*GLI1*	In ERMS an excess of genetic material from the 12q13 may be present, where the transcription factor GLI1, which is frequently overexpressed, is located	[57]
Pathways of regulating epigenetics and myogenesis	*MYOD1, BCOR, ARID1A*	*MYOD1* mutations are characteristic of a particularly aggressive form of FNRMS	[57, 64, 84]

NRAS — NRAS proto-oncogene; KRAS — KRAS proto-oncogene; HRAS — HRAS proto-oncogene; PTPN11 — protein tyrosine phosphatase non-receptor type 11, NF1 — neurofibromin 1 gene; BRAF — B-Raf proto-oncogene; PIK3CA — phosphatidylinositol-4,5-biphosphonate 3-kinase catalytic subunit alpha oncogene; FGFR2 — fibroblast growth factor receptor 2 gene; FGFR4 — fibroblast growth factor receptor 4 gene; IGF1R — insulin-like growth factor 1 gene, ERBB2 — Erb-B2 receptor tyrosine kinase 2 gene, EPHA3 — EPH receptor 3 gene; EFNA1 — ephrin A1 gene, GLI1 — GLI family Zinc Finger 1 gene; PDGFRA — platelet derived growth factor receptor alpha gene, PTEN — phosphatase and tensin homolog gene, TP53 — tumor protein p53 gen; MDM2 — MDM2 proto-oncogene; CDKN1C — cyclin-dependent kinase inhibitor 1C gene; CDK2NA — cyclin dependent kinase inhibitor 2A gene; CTNNB1 — catenin beta 1 gene; MYOD1 — myogenic differentiation 1 gene, BCOR — BCL6 corepressor gene; ARID1A — AT-rich interaction domain 1A gene, RTK — receptor tyrosine kinases

ionizing radiation [20], cocaine and cannabinoid use by the mothers and fathers [21], or pre-term birth [22].

Pathogenesis

Even though RMS cells differentiate in the direction of myoblasts, it is not clear if they develop from the same cell lines from which striated muscle differentiates. Considering the anatomical variety of this neoplasm and the range of its oncogenic lesions, it can be assumed that they attain the myoblast phenotype by induction of the expression of genes characteristic of skeletal muscle [34]. Moreover, it has been shown that RMS can form as a result of oncogene expression both in skeletal myoblast cell lines [35, 36] and in non-myogenic cell lines [37]. Rhabdomyosarcomas may be derived from tissues such as skin, fat, or nerves [38]. The pathogenesis of RMS is based both on genetic material mutations (see subchapter 5) and the resulting perturbations of signal transduction pathways regulating cell function (Tab. 2). A high tumor mutational burden defined as the sum of somatic mutations of the genetic material of the tumor correlates with a poorer prognosis for RMS patients [39].

Cytogenetic aberrations

Alveolar RMS

The most characteristic chromosomal translocations present in ARMS are t(2;13)(q35;q14) and t(1;13)(p36;q14), leading to the formation of fusion genes *PAX3-FOXO1* and *PAX7-FOXO1* [40]. The former of these translocations are more common (55% *vs.* 23%). Their presence is associated with a poorer clinical prognosis [41]. The protein products of these genes are transcription factors. Their expression is stronger in comparison to the products of corresponding genes which did not undergo fusion (wild-type) [42, 43]. Additionally, the products of fusion genes are stabilized at the post-translational stage by the phosphorylation of the chimeric protein, which decreases their intracellular degradation [44]. Transcription factor PAX3-FOXO1 increases the expression of the following genes: *ALK* receptor tyrosine kinase gene, encoding the anaplastic lymphoma kinase, *FGFR4*, fibroblast growth factor receptor 4 gene, protooncogene *MYCN*, *MYOD1* myogenic differentiation 1 gene, and *MYOG* (myogenin gene) [34]. In about 80% of ARMS, strong cytoplasmic ALK expression has been observed, most commonly associated with the amplification of this gene. In single cases, the presence of mutations has also been observed (substitution or the loss of a whole exon) [45]. Moreover, PAX3-FOXO1 interacts with proteins participating in modulating chromatin activity

Table 3. Molecular analyses to identify the PAX/FOXO1 fusion

Alveolar rhabdo-myosarcoma	*PAX3-FOXO1*	t(2;13)(Q35;Q14)
	PAX7-FOXO1	t(1;13)(p36;q14)
	PAX3-FOXO4	t(X;2)(q13;q36)
	PAX3-NCOA1	t(2;2)(p23;q36)
	PAX3-NCOA2	t(2;8)(q36;q13)
	FOXO1-FGFR1	t(8;13;9)(p11;q14;q32)

including BRD4, (bromodomain-containing protein 4) and CHD4 (chromodomain helix DNA-binding protein 4) [46, 47]. A role in the development and invasiveness of RMS is also played by excessive activation of the *MET* protooncogene, which takes place probably as a result of the activity of the fusion protein [48]. Amplification of 13q31 with the MIR17HG region (encoding miR-17-92, which also undergoes amplification in other neoplasms), occurring mainly in ARMS with the PAX7-FOXO1 fusion, is probably associated with a poorer clinical course of the disease [49]. The 12q13-14, amplification with the CDK4 locus characteristic almost exclusively for ARMS with the PAX3-FOXO1 fusion, has a similar prognostic value [50]. In about 20% of ARMS, the fusion of FOXO1(FKHR) or PAX3 is not present. These tumors, both in the molecular and clinical aspect, resemble ERMS (embryonal RMS) more closely, which indicates the key role of genetic diagnosis and creates a natural division of ARMS into fusion-positive (FPRMS) and fusion-negative (FNRMS) types [38]. For this reason, molecular investigations aimed at identifying PAX/FOXO1 fusions are recommended in all cases of alveolar and embryonal RMS [51] (Tab. 3).

Embryonal ERMS

In as many as 25–50% of ERMS tumors, chromosomal number aberrations are present [52]. They generally concern additional copies of chromosome pairs 2, 7, 8 (even in 70% of cases), 11, 12, 13, and 20 [53]. The loss of chromosome pairs 9 and 10 and 15 is described in 30% of ERMS cases. If gene amplification occurs, it is detected in chromosome regions 12q13-q15, whereas in region11p15.5. homo- or heterozygous deletions are common. Moreover, in this region, the phenomenon of uniparental disomy and gene imprinting may occur [54–56]. Mutations in oncogenes and suppressor genes are more characteristic for ERMS than for ARMS. In both subtypes, changes in cellular signaling associated with receptors for growth factors RAS/PI3K are common through somatic mutations (more common in ERMS) or changes in the expression of key genes for this pathway (through specific fusions in ARMS) (tab. 2, 4) [57].

Pleomorphic RMS

RMS pathogenesis at the molecular level is poorly characterized. A complex karyotype is most commonly present in PRMS with numerous structural and numerical aberrations but without specific changes, which has been confirmed by molecular analyses [53, 58]. A common gene mutation in PRMS is probably a mutation of the *TP53* gene, especially in tumors appearing at a young age [59].

Spindle cell/sclerosing RMS

Spindle cell/sclerosing rhabdomyosarcoma is the most recent RMS to be distinguished in the histopathological classification. Within this subtype successive ones are distinguished with characteristic molecular changes and clinical appearance [60]. The first group are variants with rearrangement of the *VGLL2*/*NCOA2* genes, which occur in children under the age of 5 years or as congenital neoplasms [61] (Tab. 5).

They are characterized by a good prognosis with a tendency to local recurrence [62]. Other possible gene fusions occurring in RMS with this clinical presentation are *SRF*/*NCOA2, TEAD1*/*NCOA2*, *VGLL2*/*CITED2* [60]. A separate group is spindle cell/sclerosing RMS with a somatic activating mutation of the *MYOD1* gene at position Lys122, occurring both in children and adults [63]. The mutation may be homo- or heterozygous and the mutated gene interacts with the *MYC* oncogene [64]. Tumors of this type are characterized by a poor prognosis, especially in children and adolescents [63]. In adolescents the mutation *MyoD1* p.Leu122Arg — associated with a very poor prognosis — is characteristic. The third group are patients with spindle cell RMS without molecular changes and the fourth patients with a diagnosis of spindle cell RMS developing in bones with *EWSR1*/*FUS-TFCP2* or *MEIS1-NCOA2* translocations. In adults the presence of bone tumors is correlated with very poor prognosis and is characteristic for spindle cell/sclerosing RMS with the fusion of *MEIS1*/*NOAC2* or *EWSR1*/*/FUS-TFCP2* genes, and so far it is known only from the description of several dozen cases [65–70]. The remaining cases of spindle cell RMS, which do not have the alterations described above, occur most commonly around the area of the testes or within the abdominal cavity [71].

Clinical picture

Rhabdomyosarcoma may occur in almost any anatomical localization, most commonly in the extremities (approx. 25%), head and neck region (approx. 20%), and urogenital tract (approx. 20%) [13].

Table 4. Histopathological differential diagnosis of Rhabdomyosarcoma (RMS)

Neoplasm	Morphological characteristics	Immunohistochemical markers						Other information
		Keratin	Desmin	Protein S100	Myogen /MyoD1	HMB-45/Melan A	SMA	
ERMS	Ovoid and star-shaped cells loosely placed in myxoid stroma, less commonly morphology of small, round cells, presence of cells with the character of immature rhabdomyoblasts	+/–	+	–/+	+	–	+/–	Lack of characteristic cytogenetic marker, in most cases loss of heterozygosity at locus 11p15 [136]
ARMS	Small, round, and monomorphic myoblasts separated by empty oval or elongated spaces (similar to lung tissue structure)	+/–	+	–/+	+	–	+/–	70–90% of cases show translocations: t(2;13)(q35;q14) or t(1;13)(p36;q14) [137], FISH with set of *FOXO1* (*FKHR*) and *PAX3* probes used in diagnosis
Ewing sarcoma	Visible areas composed of small monomorphic cells; Homer-Wright rosettes present	+/–	–	–/+	–	–	–	Positive staining for FLI-1 in about 80% of cases [138], Positive staining for CD99
Melanoma	Pleomorphic, epithelial, or fusiform cells with poor cohesion, melanin, presence of distinct nucleoli	–	–	+	–	+	–	BRAF mutations in approx. 50% of patients
MPNST	Various numbers of cells within neoplastic lesions, cells in bundles, coils, or "herringbone pattern"	–	–	+/–	–	–	–	In over 80% of cases neurofibromin 1 (*NF1*) gene mutations present [139], loss of nuclear expression of H3K27me3/INI1
PEComa	Perivascular proliferation of epithelial and fusiform cells with light, acidophilic cytoplasm with granulocytes; nucleoli visible	–	+/–	–	–	+	+	In about 80% of cases deletions and/or loss of heterozygosity (LOH) in the 16p13.3 region [140, 141]
DFSP	Large density of cell arrangement in histological appearance with poorly visible borders of neoplastic lesions, radial arrangement of cells with fusiform morphology	–	–	–	–	–	–	Characteristic translocation t(17;22)(q22;q13) [142], CD34 expression [143]

ARMS — alveolar rhabdomyosarcoma; DFSP — dermatofibrosarcoma protuberans; ERMS — aembryonic rhabdomyosarcoma; MPNST — malignant peripheral sheath tumor; PEC-oma — perivascular epithelioid cell tumors; SMA — smooth muscle actin

Table 5. Variants with rearrangement of the *VGLL2/NCOA2* genes occurring in children under the age of 5 years or as congenital neoplasms

Spindle cell/sclerosing rhabdomyosarcoma congenital/infant	*SRF-NCOA2*	t(6;8)(p21;q13)
	TEAD1-NCOA2	t(8;11)(q13;p15)
	VGLL2-NCOA2	t(6;8)(q22;q13)
	VGLL2-CITED2	t(6;6)(q22;q24)

Localization within the head and neck also encompasses the area of the eye socket [85] and the parameningeal area including the nasal cavity [86], sinuses [87–89], the nasopharyngeal cavity [90], and the subtemporal fossa. It may develop within the parotid glands [91], the thyroid [92], and the oral cavity [93]. RMS within the urogenital tract may occur, among others, in the bladder [94], prostate [95], urethra [96], uterus [97, 98], vulva [99], or scrotum [100]. In adult RMS patients it more commonly develops in an unfavorable anatomical localization, i.e. other than the head and neck (except for parameningeal areas), urogenital tract (except for the bladder and prostate), and the biliary pathways [13, 101, 102]. A few cases of RMS are described in more rare localizations such as the liver [103], breast [104, 105], mediastinum [106], bronchi and lung [107, 108], cardiac muscle [109], pericardium [110], diaphragm [111], retroperitoneal space [112, 113], esophagus [114], stomach [115], or ileum [116].

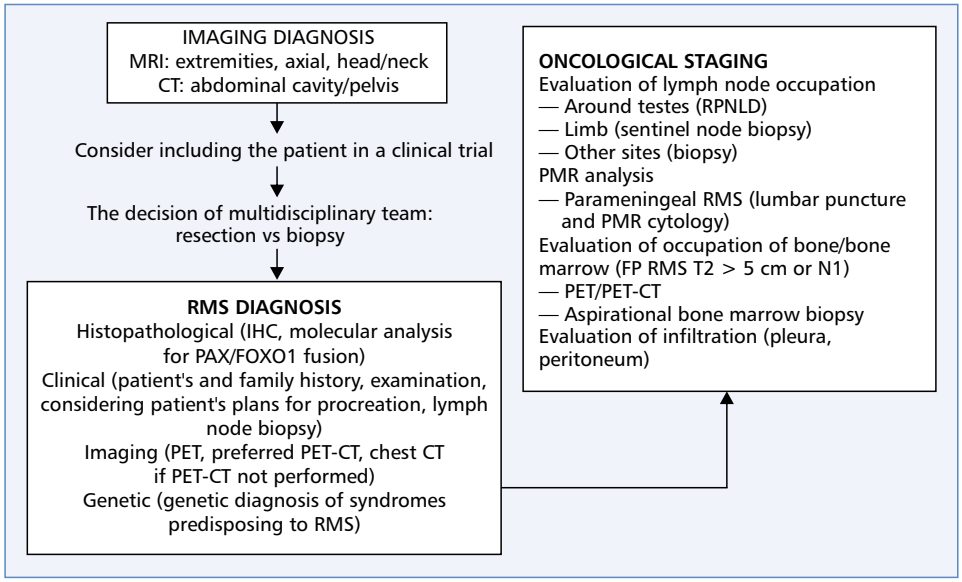

Figure 1. Diagnostic algorithm procedure for rhabdomyosarcoma (RMS). Based on [51]; IHC — immunohistochemistry staining; PET — positron emission tomography; PET-CT (positron emission tomography-computed tomography; MRI — magnetic resonance imaging; PMR — spinocerebral fluid

Primary RMS is, in general, characterized by rapid and aggressive growth with the formation of a pseudobursa. The multiplicity of possible localizations is associated with a differentiated clinical picture. In the initial stages, the course of the disease may be asymptomatic [38]. The symptoms of focal damage of the nervous system appear in the case of RMS of the perimeningeal area. Within the eye socket, it may cause exophthalmos, perturbations of eyeball mobility, or vision perturbations [117–119]. Localized within the head and neck it may give symptoms of chronic or acute sinusitis, purulent or bloody discharge from the nasal cavity or ear canal, their obturation, or swallowing difficulti es [55, 120]. Because of aggressive growth in a limited anatomical space, cranial nerve paralysis may occur [121]. Rhabdomyosarcoma localized within the urogenital pathways, pelvis minor, or the abdominal cavity may give various symptoms such as chronic abdominal pain [122], bleeding from the birth canal [97], dysuria [123], jaundice [124], intussusception [125], or intestinal obstruction [126]. Edema, often painless, appearing in the case of RMS of the extremities or in the vicinity of the genital organs, may be ascribed to mechanical damage, which delays appropriate diagnosis. There are also descriptions of cases of disseminated RMS, where the first symptoms were perturbations of muscle strength of the extremities or limb paralysis [98]. Metastases may disseminate both through the lymphatic system and blood vessels [127, 128]. The most common localizations of metastases encompass the lungs, lymph nodes, and bone marrow. However, RMS may give metastases to almost all organs. In the literature, there are descriptions of metastatic RMS foci in the breast, peritoneum, pleura, central nervous system, and skin [14, 129, 130]. Bone metastases may manifest as bone pain and hypercalcemia and massive occupation of the bone marrow may cause symptoms typical for leukemia (cytopenia, bleeding, and infections) [45, 131–133]. Epidemiological analysis including 1017 adults with RMS indicated that over 28% of distant metastases were present at the moment of diagnosis, whereas regional dissemination (occupation of regional lymph nodes or primary lesions crossing the boundaries of the primary organ) was present in over 25% of the patients [5].

Diagnostic procedure

Preliminary diagnosis

If RMS is suspected, it is indispensable to carefully plan the whole diagnostic procedure (Fig. 1). The procedure is initiated by coarse needle biopsy with a pathological diagnosis in a sarcoma treatment reference center. Before performing the biopsy, it is recommended to evaluate the progress of the disease by visual imaging (computed tomography [CT] or magnetic resonance imaging MRI]) of the primary focus and the regional lymph flow to optimally plan the biopsy and eventual further surgical treatment. A significant element of primary diagnosis is also a clinical and radiological evaluation of not only regional but also distant lymph nodes, whose

occupation constitutes a generalized neoplastic disease. The criteria of occupation of lymph nodes in RMS have so far not been standardized, and, generally, a node larger than 1 cm in diameter is considered suspicious, regardless of its appearance in radiological imaging [56].

Histopathological diagnosis

Histopathological diagnosis of RMS is difficult, which is confirmed by the statistics of the international Intergroup Rhabdomyosarcoma Study Group (IRSG), according to which every fifth RMS diagnosis was incorrect [101]. In a light or electron microscope, cells can be seen that show differentiation in the direction of skeletal muscle cells — "myoblast-like cells". The next step is to perform immunohistochemical staining for the expression of proteins characteristic for muscle, which include muscle-specific actin and myosin, desmin, myoglobin, the MyoD1 protein, and myogenin [134]. The last two proteins are considered the most important markers of rhabdomyoblastic neoplasm differentiation [52]. Morphologically, RMS myoblasts can have different forms: they may be poorly differentiated (spherical, oval), fusiform, or fully differentiated [52]. Highly differentiated rhabdomyoblasts present as spherical or oval cells containing an acidophilic grainy cytoplasm with an eccentric or central spherical, single or double nucleus [52]. It should be, however, kept in mind that demonstrating rhabdomyoblastic differentiation among the cells of a neoplasm does not by itself determine an RMS diagnosis, as other neoplasms such as mesenchymal chondrosarcomas or sarcomatoid cancers are also characterized by the presence of these cells [135]. Rhabdomyosarcoma embryonal and alveolar belongs to the group of small round blue cell tumors, which are characterized by a low grade of differentiation and morphological similarity (small cell with a large, spherical strongly hyperchromatic nucleus, staining navy blue with hematoxylin) [55]. Other neoplasms that must be considered in the differential diagnosis of RMS are malignant peripheral nerve sheath tumor (MPNST), dermatofibrosarcoma protuberans (DFSP), perivascular epithelioid cell tumors (PEC-oma), melanoma, Ewing sarcoma, ectomesenchymoma, sarcoma-like cancer, including skin and salivary gland cancer, melanoma, liposarcoma, malignant teratoma, anaplastic thyroid cancer and neoplasms derived from nervous tissue. Differential diagnosis is presented in Table 4.

During histopathological diagnosis, the RMS subtype must be established.

Alveolar RMS

Alveolar RMS constitutes about 25% of all RMS diagnoses in adults [13, 144]. In the adult population, it is most common in 10–25 years old but may occur at any age. It is often localized in the soft tissues of the extremities, head and neck, retroperitoneal space, the urinary bladder, or the reproductive organ [145]. It is made up of tightly placed, small, circular, and monomorphic cells separated by empty oval or elongated spaces, which resemble lung alveoli in the histopathological picture. Cell aggregates may also be separated by connective tissue. The cells show a high nucleo-cytoplasmic ratio and are characterized by a high mitotic index. Some ARMS do not have the characteristic segmented location of cells, and their cells are uniformly clustered (the so-called solid form of ARMS), which makes the differential diagnosis with ERMS difficult [146]. Molecular methods including FISH with the FOXO1A set of probes are useful in diagnosing tumors with a solid structure, less characteristic for ARMS (Fig. 2).

Embryonal RMS

According to the available data including the largest group of adult patients with RMS, the frequency of occurrence of this subtype is 20–30% of all histopathological RMS diagnoses [144, 147]. A frequent site for this neoplasm is the head and neck, in particular the eye socket, tissues associated with the meninges, middle ear, nasopharyngeal cavity, and the urogenital system, soft tissues of the extremities, the pelvis, and the retroperitoneal space [148]. It is built of acidophilic primitive ovoid cells, less commonly of round cells resembling

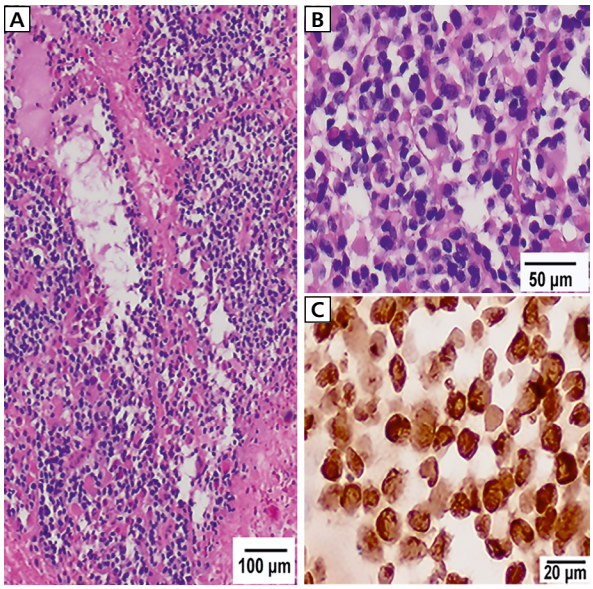

Figure 2. Alveolar rhabdomyosarcoma; **A.** Typical architecture with pseudoalveolar spaces (H&E, 40×); **B.** Neoplastic cells with acidophilic cytoplasm and eccentric cell nucleus — differentiation in the direction of rhabdomyoblasts (H&E, 100×); **C.** In general, strong and diffuse myogenin expression (IHC clone F5D, Dako, 200×)

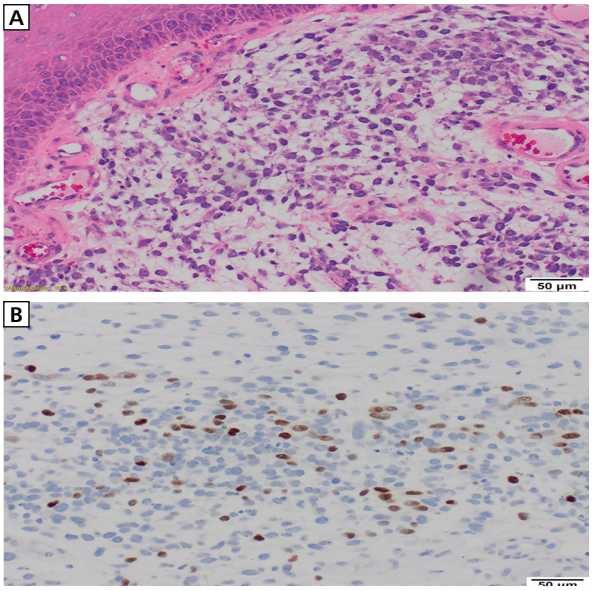

Figure 3. Embryonal Rhabdomyosarcoma of the vaginal wall of a 5-year-old patient (botryoid alveolar subtype); **A.** Primitive, small and ovoid neoplastic cells with poorly expressed differentiation in the direction of rhabdomyoblasts, placed loosely in a myxoid stroma. Supra-epithelial densification of cells visible – the cambial layer H&E, 100×); **B.** Myogenin expression is generally visible only focally (IHC clone F5D, Dako, 200×)

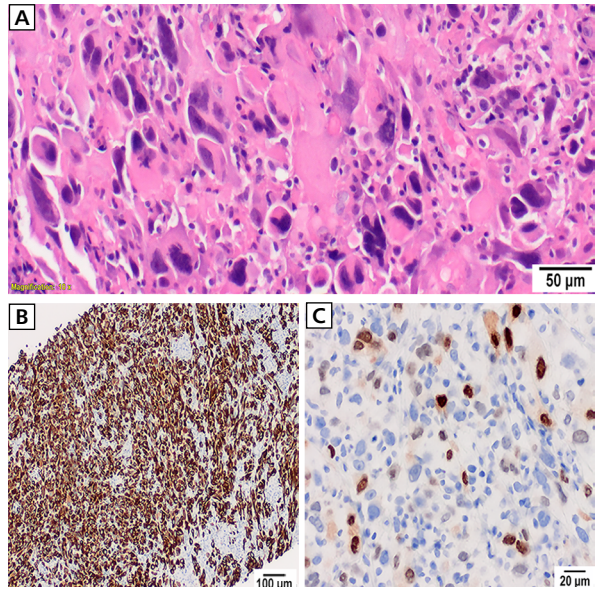

Figure 4. Pleomorphic rhabdomyosarcoma; **A.** Atypical polygonal and fusiform neoplastic cells typical for pleomorphic sarcomas; **B.** Desmin expression is generally multifocal or diffuse, but this marker does not allow for reliable differentiation of RMS from pleomorphic leiomyosarcoma (IHC clone D33, Dako, 40×); **C.** Myogenin is a highly specific marker for RMS, but in pleomorphic RMS, its expression may be poor (IHC F5D, Dako, 200×)

immature rhabdomyoblasts. They are loosely disseminated in myxoid stromal tissue [149]. The cells are not distributed in an alveolar fashion characteristic for ARMS [149]. Cellular composition of ERMS reflects embryonal striated muscle development as very poorly differentiated cells up to fully differentiated cells may appear [52]. Anaplastic cells with a hyperchromatic enlarged nucleus are present in about 3–13% ERMS, and their presence may correlate with a poorer prognosis for the patients [150, 151]. In the botryoid form of ERMS (botryoid RMS), neoplastic cells form a layer called the cambial layer. This ERMS subtype with a good prognosis is characterized by a linear placement of neoplastic cells and occurs, in general, in the vicinity of mucous membranes, e.g. in the bladder [60]. Botryoid ERMS also often occupies the vagina, biliary pathways, the nasopharynx, and the nasal cavity [152]. In the anaplastic form of ERMS, which is a subtype with a poorer prognosis, the cells have an atypical multiform morphology. Immunohistochemical staining for myogenin indicates a heterogeneous and punctate expression of this protein in ERMS cells, but expression can also be uniform [153] (Fig. 3).

Pleomorphic RMS

Pleomorphic RMS (PRMS)occurs almost exclusively in adults, in particular, after the sixth decade of life, and constitutes even up to 43% of RMS in adults [154, 155]. Its localization is most commonly in soft tissues of the lower extremities (especially the thighs), retroperitoneal space, abdominal cavity, chest, spermatid cord, and the vicinity of the testes [156]. The histopathological picture shows a very low degree of differentiation in the direction of rhabdomyoblasts and requires careful differentiation with undifferentiated pleomorphic sarcoma [38]. Cells that show signs of atypia are pleomorphic; they have shapes from small epithelial to large cells with segmented nuclei and distinct nucleoli. They may be placed in groups, be linear, or be irregularly disseminated [38]. Cellular pleomorphism is diffuse in contrast to disseminated anaplastic cells in ERMS. PRMS is also characterized by poor myogenin expression, however, the largest study including 38 cases indicated that each of the tumors showed positive staining for at least one skeletal muscle marker [60] (Fig. 4).

Spindle cell/sclerosing RMS

In 2013, SCRMS was distinguished as a distinct variant of RMS on the basis of its genetic profile, whereas previously it had been identified as an ERMS subtype [3, 157]. According to WHO, it is the rarest RMS subtype [158]. In the pediatric population, SCRMS is associated with a better prognosis, but in the few descriptions of cases with this neoplasm in adult patients, this no longer holds [159, 160]. Spindle cell/sclerosing rhabdomyosarcoma with the pres-

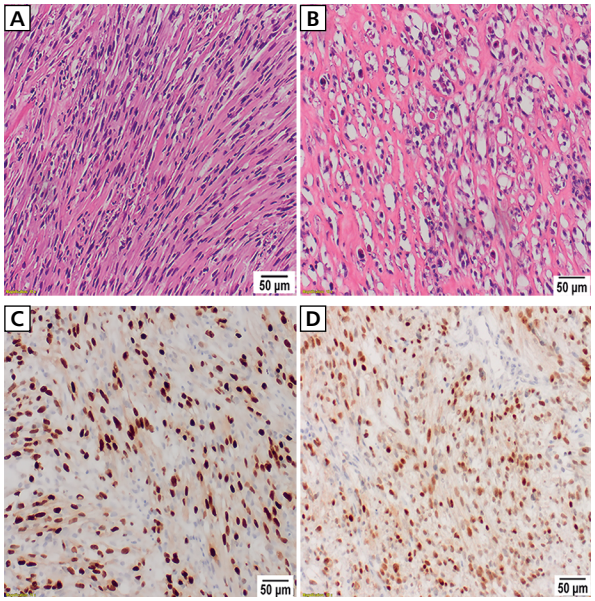

Figure 5. Spindle cell/sclerosing rhabdomyosarcoma; **A.** Fusiform morphology of cells arranged in long bundles (H&E, 100×); **B.** Another part of the same tumor with a more sclerosing and homogeneous stroma and spherical cells — sclerosing variant of RMS (H&E, 100×). Spindle cell/sclerosing rhabdomyosarcoma is the morphological spectrum of the same neoplasm (both photos: H&E, 100×); **C.** Nuclear myogenin expression does not differentiate between particular RMS subtypes (IHC clone F5D, Dako, 100×); **D.** Strong and diffuse MyoD1 expression, often stronger than myogenin expression, is characteristic of SCRMS and is generally a result of the *MYOD1* gene mutation at position L122R (IHC clone 5.8A, Dako, 100×)

ence of the *NCOA2* and *VGLL2* translocation is correlated with a better prognosis in infants [62]. A poorer clinical prognosis is characteristic of tumors in the parameningeal area and associated with *MYOD1* [62, 161]. In adults, the most common SCRMS localization is the head and neck, less commonly, the extremities and the retroperitoneal space [160]. Histopathologically, the tumor tissue is composed of fusiform cells arranged in bundles or placed in a swirl. The cells have an elongated and spoke-like nucleus, small nucleoli, and eosinophilic cytoplasm and present varied nuclear atypia, mitotic activity, and pleomorphism [162]. These tumors often contain a rich collagen stroma with disseminated small neoplastic cells, hence the description sclerosing of this RMS variant [163]. Some cases show properties of sclerosing with gaps simulating vessels [158]. Immunohistochemical studies indicate strong positive staining for desmin and MyoD1, local or disseminated myogenin, and no or local immunoreactivity to cytokeratins [164, 165] (Fig. 5).

Extended diagnostic evaluation

After confirming RMS, the next step is to evaluate disease progression and qualification for treatment. The following analyses are recommended: blood morphology with a smear, extended biochemical blood analysis, urine analysis, chest, abdominal and pelvic CT, bone scintigraphy or PET-CT (detecting metastases to lymph nodes and bones), trepanobiopsy of the bone marrow, brain and spine MRI, and cerebrospinal fluid puncture (primary focus within the meninges and if the occupation of meninges is suspected), and sometimes a diagnostic biopsy of suspected lymph nodes [45]. In the case of extremity and trunk RMS, where the percentage of metastases to regional lymph nodes is particularly high, mapping of the lymph system and evaluation of the sentinel lymph node is possible to consider [166, 167].

Bone scintigraphy or PET-CT and two-sided aspirational bone marrow biopsy allow the evaluation of the possible occupation of the bone system and/or bone marrow. In selected cases (tumor < 5 cm, FN-RMS, no evidence of lymph node occupation), it is possible not to evaluate the diagnosis of RMS metastases to bones [51]. Imaging studies allow determining the risk group, which is the basic criterium determining prognosis and treatment intensity (Tab. 6, 7). The TNM RMS system was elaborated by the Intergroup Rhabdomyosarcoma Study Group (IRSG) in 2001 for the pediatric population and young adults [167]. For adult patients both the above-mentioned TNM IRSG system and the TNM classification, according to the American Joint Committee on Cancer for soft tissue sarcomas, can be used [168].

General principles of treating localized disease

Treatment sequence

Rhabdomyosarcomas should be treated in a multidisciplinary fashion in reference centers for pediatric and adult sarcomas. The treatment regimens are based on resection of the primary tumor and eventual metastases to lymph nodes with perioperative radiotherapy or radical radiotherapy when surgical treatment is not possible. Methods of local treatment should be combined with multidrug chemotherapy based on cyclophosphamide or ifosfamide in combination with anthracycline, or dactinomycin and vincristine, or dacarbazine.

Surgery

Surgery is the basic therapeutic option for RMS patients, regardless of the risk group to which they belong. Local treatment must be considered first after

Table 6. Evaluation of the degree of RMS progression according to the classification of the Intergroup Rhabdomyosarcoma Study Group TNM

Stage	Localization	T	Size	N	M
1	Favorable	**T1/T2**	a/b	Any	M0
2	Unfavorable	T1/T2	a	N0/Nx	M0
3	Unfavorable	T1/T2	a	N1	M0
			b	Any N	M0
4	Any	T1/T2	a/b	Any	M1

T: locally advanced	**N: lymph nodes**	**M: distant metastases**
T1: locally limited, not infiltrating T2: locally advanced, infiltrating Diameter: a ≤ 5 cm b > 5 cm	N0: not occupied N1: occupied regional lymph nodes (> 1 cm in CT/MRI/18F-FDG) Nx: unknown status	M0: distant metastases absent M1: distant metastases present, spinal cord and the presence of metastatic tumor in the pleura or peritoneum]metastases in extra-regional lymph nodes as well the presence of free tumor cells in the pleural, peritoneal, and cerebral fluid
Good localizations	Eye socket, head, and neck (except for the parameningeal area), urogenital system (except for bladder and prostate)	
Poor localizations	Parameningeal area, limbs, retroperitoneal space, bladder, prostate, biliary pathways*, other	

*As modified by Children's Oncology Group [169]

Table 7. Prognostic RMS evaluation according to the Intergroup Rhabdomyosarcoma Study Group classification

Prognosis (EFS, *event-free survival*)	Stage acc. to IRSG TNM	Clinical group	Localization	Size	FOX01 rearrangement (fusion)	M	N
Excellent (> 85%) Low-risk subgroup A	1	I	Favorable	a/b	Negative	M0	N0
	1	II	Favorable	a/b	Negative	M0	N0
	1	III	Eye socket	a/b	Negative	M0	N0
	2	I	Unfavorable	a	Negative	M0	N0/Nx
	1	II	Favorable	a/b	Negative	M0	N1
Very good (70–85%) Low-risk subgroup B	1	III	Eye socket	a/b	Negative	M0	N1
	1	III	Favorable, except for eye socket	a/b	Negative	M0	N0/N1/Nx
	2	II	Unfavorable	a	Negative	M0	N0/Nx
	3	I/II	Unfavorable	a	Negative	M0	N1
	3	I/II	Unfavorable	b	Negative	M0	N0/N1/Nx
Good (50–70%) Moderate risk subgroup	2	III	Unfavorable	a	Negative	M0	No/Nx
	3	III	Unfavorable	a	Negative	M0	N1
	3	III	Unfavorable	b	Negative	M0	N0/N1/Nx
	1/2/3	I/II/III	Any	a/b	Positive	M0	N0/N1/Nx
	4	IV	Any	a/b	Negative	M1	N0/N1/Nx
Poor (< 30%) High-risk subgroup	4	IV	Any	a/b	Negative	M1	N0/N1/Nx
	4	IV	Any	a/b	Positive	M1	N0/N1/Nx

diagnosis with the intent of complete resection of the tumor and obtaining microscopically radical surgical margins. Currently, surgery is frequently preceded by chemotherapy and/or radiotherapy [170]. In some cases, there are indications for radical regional lymphadenectomy. If metastases to regional lymph nodes are

Table 8. Classification of patients to clinical groups taking into consideration the extent of the surgery and the progression of the disease according to the Intergroup Rhabdomyosarcoma Study Group

Clinical group* (CG)	Stage plus result of surgery
I	A — localized disease, no infiltration of surrounding structures and spaces, microscopically radical resection
	B — localized disease, infiltration of surrounding structures and spaces, microscopically radical resection
II	A — localized disease, no infiltration of surrounding structures and spaces, resection microscopically non-radical, macroscopically radical
	B — regional lymph nodes occupied, microscopically radical resection
	C — regional lymph nodes occupied, resection microscopically non-radical, macroscopically radical
III	A — tumor regardless of local stage and regional lymph node occupation, exclusively biopsy
	B — tumor regardless of local stage and regional lymph node occupation, surgery macroscopically non-radical, more than 50% of tumor volume
IV	Any local stage, any surgery result, presence of distant metastases

*As modified by Children's Oncology Group [169]. Clinical group I defines a localized disease, after microscopically radical resection, without involvement of regional lymph nodes (subgroups IA and IB are no longer distinguished). There are also no subgroups in clinical group III

present, radical RT is used. Taking into consideration the complications of radiotherapy, histological examination of the lymph nodes should be performed to exclude non-neoplastic reactive lymphadenopathy [51]. For localizations in the extremities sparing treatments are preferred [144]. If radical surgery cannot be performed because of considerable local disease progression, localization, or other contraindications for surgery, qualifying the patient for radical RT should be considered. In the case of ARMS, performing non-radical surgery, decompression treatments, or aggressive mutilating palliative surgery does not improve the prognosis but only delays the moment of initiating systemic treatment (an exception are ERMS metastases to the retroperitoneal space). The scope of the used surgical treatment is important for further planning of radiotherapy. In clinical practice, the classification into clinical groups (CG) according to IRSG is used (Tab 8).

Radiotherapy

Supplementary radiotherapy is indicated in all patients with RMS stages 1–3 according to IRSG TNM and CG I–III except for ARMS without the FOX01 rearrangement (then a decision should be taken based on risk and benefit analysis). Typically, treatment should be started after the fourth course of chemotherapy. Experience so far suggests that even if cranial nerves are affected or the tumor infiltrates the base of the skull, RT can only be started in week 12 of treatment if it was preceded by a rapid start of neoadjuvant chemotherapy [171]. Radiotherapy should be initiated urgently, regardless of the number of received chemotherapy courses in a situation of vision loss or spinal compression.

Depending on the localization and clinical group (supplementary RT after surgery or radical RT) the used total doses vary in the range of 50–65 Gy. Because of complications after irradiation (particularly visible in children), the aim is to reduce the total dose or to use other methods or RT techniques T [172, 173]. The results of recent IRSG studies indicate that in the pediatric population simultaneously treated with chemotherapy, the RT doses can be decreased to 36–50.4 Gy (28 fractions of 1.8 Gy) without affecting the treatment results. There are no data concerning optimal RT regimens in the adult population. The target volume should be the volume of the primary tumor before chemotherapy and surgery and regional lymph nodes (clinically suspected or in imaging studies). Using modern techniques of RT, proton radiotherapy, or brachytherapy may be associated with the protection of critical organs and contribute to decreasing the percentage of distant treatment complications. RT use in CG II improves local effectiveness from 65% to 83%. The comparison of the results of European (MMT) and American (IRS) studies suggests that in localized forms (low and intermediate-risk group) early use of local treatment using RT may be associated with better local control and OS (84% in IRS-IV studies *vs.* 71% in MMT89 studies, where local treatment, mainly by surgery, was used after obtaining a response to chemotherapy). Also, the percentages of 5-year progression-free survivals were higher in the IRS-IV study, 78% *vs.* 57% in the MMT89 study. A higher number of complications of surgical treatment was, however, observed.

In clinical practice, preferred regimens of irradiation depend on CG:

— CG I: 41.4 Gy in 23 fractions of 1.8 Gy;
— CG II: 45 Gy in 25 fractions of 1.8 Gy;
— CG III in localization other than the eye socket with residual tumor < 5 cm: 50.4 Gy in 25 fractions of 1.8 Gy;
— CG III in localization other than the eye socket with residual tumor > 5 cm: 50.4 Gy in 25 fractions

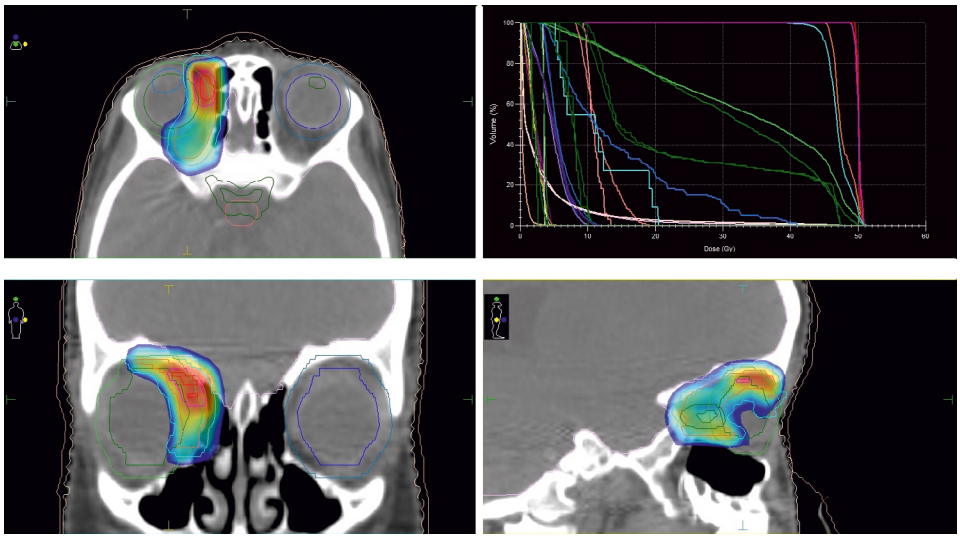

Figure 6. The treatment plan for a 5-year-old boy with a diagnosis of embryonal RMS of the right eye socket (superior medial wall) after chemotherapy. Plan performed by the VMAT SIB technique assumed giving a 45 Gy dose on the area of the primary tumor with the margin (eye socket), with an increase to 50 Gy in the area of the residual tumor in 25 fractionated doses of 1.8 Gy and 2 Gy, respectively

of 1.8 Gy, simultaneous increase of total dose on the residual tumor to 56 Gy in fractions of 2 Gy;

— CG III in eye socket localization: 45 Gy in 25 fractions of 1.8 Gy with simultaneous chemotherapy based on a regimen containing cyclophosphamide;
— Parameningeal localization (the nasal cavity, nasopharynx, paranasal sinuses, middle ear, mastoid process, subtemporal fossa, pterygopalatine fossa): the elective volume is the primary tumor, adjacent meninges, and the intracranial area, preferred fractionation scheme is 54–59.4 Gy in 30-33 fractions of 1.8 Gy.

The described regimens apply to the pediatric patient population. For decisions on adult patients concerning fractionation, regimens should be individually taken for each case (Fig. 6, 7).

Chemotherapy

Adding neo- and adjuvant chemotherapy to the treatment of patients without metastases allowed to obtain 60–90% percent of 5-year survival. In patients over 16 years of age and adults, both in multicenter studies and in retrospective analyses, the results of treatment are worse, and the percentage of 5-year survival is in the range of 30–40%. The intensity (2- or 3-drug treatments) and the duration of treatment (6, 12, or 24 months) depend on the risk group (Tab. 6, 7).

In the trials patients both in the disseminated and the localized stage were treated with various chemotherapy regimens, among the most common were doxorubicin monotherapy, doxorubicin plus ifosfamide, doxorubicin plus ifosfamide plus dacarbazine. Some of the patients received regimens in agreement with pediatric standards of RMS treatment, most commonly: ifosfamide plus vincristine plus actinomycin D, ifosfamide plus vincristine plus doxorubicin plus dacarbazine, and ifosfamide plus vincristine plus actinomycin D plus doxorubicin. In over 30% of treated patients, local recurrence of the neoplastic disease was observed, and another 40% developed distant metastases, but both using radiotherapy ($p = 0.011$) and chemotherapy according to pediatric protocols ($p = 0.003$) were associated with statistically better overall survival (OS) in multifactorial analysis. Moreover, using pediatric chemotherapy regimens in treating localized RMS in adults was described in the research of Kojima et al. [174]. This included the following protocols: 1) vincristine 1.5 mg/m^2 (days 1, 8 and 15) plus cyclophosphamide 2.2 mg/ m^2 (day 1) plus actinomycin D 1.5 mg/m^2 (day 1); 2) vincristine plus dactinomycin plus another component chosen among: ifosfamide, etoposide, or doxorubicin. Not only the pediatric chemotherapy regimens but also the whole therapeutic procedure for the adult patient with localized RMS according to pediatric recommendations for the treatment of this disease affects OS and increases the percentage of patients with 5-year local recurrence-free survival (LRFS) [144].

Basic treatment regimens for ERMS and ARMS are presented in Table 8. VAC and VAI/IVA regimens appear to be equivalent. Adding other active drugs to the basic regimen (VAC), such as doxorubicin, etoposide, cisplatin, carboplatin, ifosfamide, or melphalan,

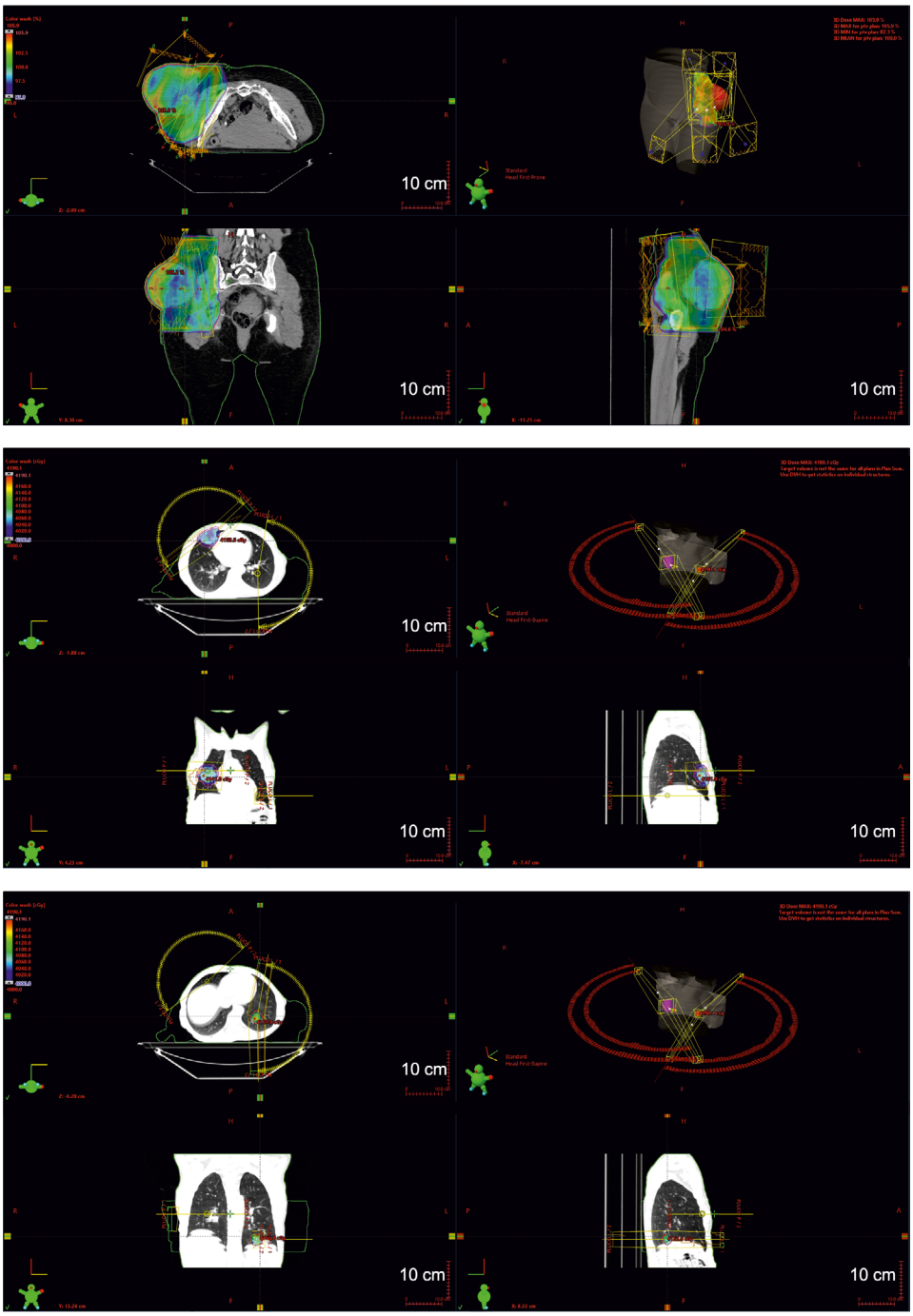

Figure 7. Radiotherapy plans of an adult female patient with pleomorphic rhabdomyosarcoma with a limited number of metastases to the lungs (oligometastatic disease) diagnosed during pregnancy. The patient received chemotherapy based on doxorubicin up to the moment of birth. After the birth of a healthy child, she was qualified for hypofractionated preoperative radiotherapy 5 × 5 Gy (**A**), resection, postoperative chemotherapy, and stereotactic radiotherapy 10 × 4 Gy on the volume of two lung metastases (**B** and **C**)

according to trial results published so far, did not have a statistically significant effect on OS in patients with RMS in clinical groups III and IV (Tab. 8). Evaluation of the combination of standard therapy VAC/VAI with irinotecan or topotecan is the subject of the ongoing trial IRS-V. The results of the European trial with random selection of patients European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS2005 (population < 18 years old) have not been published yet, its aim, among others, was to evaluate in a subgroup of patients

with ARMS with the N1 characteristic the effect of adding doxorubicin to standard IVA chemotherapy and the effectiveness of supportive care with vinorelbine and cyclophosphamide (altogether 50 weeks). Based on available data, it is difficult to unequivocally determine the duration of systemic treatment and indications for supportive treatment in adult patients. In adult patients (with ARMS high-risk group), treatment should last up to 48–52 weeks. In the case of RMS treated in the AI regimen (doxorubicin, ifosfamide plus mesna) or MAID (doxorubicin, ifosfamide plus mesna, dacarbazine), systemic treatment is generally performed until the maximum dose of doxorubicin has been used (if the progression of the disease is not noted previously during the treatment) [14, 175–178]. No clinical trials have evaluated specific chemotherapy regimens of patients with pleomorphic RMS. Most patients receive adjuvant chemotherapy (anthracyclines and alkylating cytostatics) with local tumor treatment by surgery and/or radiotherapy. Because of the differences in the biology and phenotype of this RMS subtype in comparison with ERMS and ARMS, multicomponent pediatric chemotherapy regimens may not be applicable in such cases. On the contrary, in the case of adult patients with RMS other than pleomorphic, the use of regimens described in pediatric guidelines for the treatment of this neoplasm is recommended, and the criteria of age for the inclusion in clinical trials evaluating the effects of treatment with pediatric regimens are often extended from the pediatric population to adults [51, 144] (Tab. 9, Fig. 8).

Observation after treatment

After completion of the treatment, the patient should be observed carefully. The recommended procedure includes the physical examination and imaging studies in the form of CT or MRI of the primary localization and CT of the chest, abdominal cavity, and pelvis using a contrast agent. Medical visits should take place every three months for the first two years, then every six months for the next three years, and subsequently once a year.

General principles of treating disease with distant metastases

In a high percentage of patients, distant metastases are found at the moment of diagnosis, which is linked with a poor prognosis. Treating the patient with distant metastases will include each of the three methods used for localized disease, that is surgery, RT, and chemotherapy. Some authors recommend limiting chemotherapy to VAC or VAC/VI regimens taking into consideration the patient's quality of life and the poor prognosis in this group [51]. Surgery and/or RT of the primary tumor are used for RMS with a limited number of metastases to limit the risk of failure of subsequent therapy. In the case of multiple metastases, the priority is obtaining control of the disease, and if this is successful, local treatment can be considered. In most patients with RMS with numerous metastases, therapeutic procedures are palliative in character. In a retrospective multicenter analysis of RMS patients in stage 4 according to IRSG TNM, among 13 patients included in the trial two underwent resection of the primary tumor, six received palliative RT, and seven palliative chemotherapy [7]. Median OS was 7.1 months. The most common chemotherapy regimens were doxorubicin monotherapy, ifosfamide with doxorubicin, and multicomponent chemotherapy vincristine plus doxorubicin plus cyclophosphamide. Among 14 patients receiving chemotherapy admitted to hospitals with primary disseminated neoplastic disease and progressing to metastatic disease, only in 7 patients a clinical benefit was observed in response to chemotherapy [PR (partial response) or SD (stable disease)]. The only responses after administration of successive lines of chemotherapy in patients with a partial response or stable disease after the first line were observed in patients receiving chemotherapy according to the VAC protocol (vincristine, doxorubicin, cyclophosphamide). Median progression-free survival (PFS) was 2.3 months. Another retrospective study included 4 patients with RMS M1 and palliative chemotherapy was initiated in all patients, and in one of them, treatment was supplemented by palliative radiotherapy [6]. The median overall survival of the treated patients was 21.7 months. In an observational study by Bompas et al. [147] among 46 patients with stage M1 RMS, 19 received surgery, 26 radiotherapy, and 29 received palliative chemotherapy (doxorubicin ± ifosfamide or multidrug therapy based on ifosfamide, vincristine, actinomycin with or without supporting chemotherapy with cyclophosphamide). Complete remission in this group was obtained in only 13 patients (28%). Five-year survival of patients with metastatic disease was 5% (median: 13 months). The results of the clinical trial VIT-0910 indicated that adding temozolomide to the vincristine and irinotecan regimen improves the survival of patients with recurring or resistant RMS [190]. The results of studies in centers treating RMS indicate that the most common chemotherapy regimens used in such patients are multicomponent regimens using combinations such as vincristine, doxorubicin, and cyclophosphamide (VAC), or ifosfamide with doxorubicin or doxorubicin, ifosfamide, dacarbazine, and mesna (MAID) [38]. There are single descriptions of treating RMS patients with a small molecule tyrosine kinase inhibitor pazopanib which suggest that this drug could find application

Table 9. Chemotherapy regimens used in rhabdomyosarcoma treatment

Regimen name	Administered drugs	References
Most common regimens of RMS treatment		
VA	Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Dactinomycin 0.15 mg/kg/d. (max. 0.5 mg/d.), day 1–5.	[179]
VAC	Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Dactinomycin 0.15 mg/kg/d. (max. 0.5 mg/d.), day 1–5 Cyclophosphamide 2.2 g/m^2 plus mesna, day 1.	[179]
VAC	Vincristine 1.4 mg/m^2 (maximum dose 2 mg), day 1, 8, 15 Actinomycin D 1.25 mg/m^2 (maximum dose 2mg), day 1. Cyclophosphamide 1200 mg/m^2, day 1.	[180]
VAC/IE	Vincristine 1.6 mg/m^2, day 1. Actinomycin D 0.45 mg/kg, day 1. Cyclophosphamide 1200 mg/m^2, day 1. Ifosfamide 1800 mg/m^2 plus mesna days 21–25. Etoposide 100 mg/m^2, day 21. Second line of treatment: cisplatin and etoposide	[88]
VAI	Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Dactinomycin 0.15 mg/kg/d. (max. 0.5 mg/d.), day 1–5. Ifosfamide 1.8 g/m^2/d. plus mesna, day 1–5.	[179]
VIE	Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Ifosfamide 1.8 g/m^2/d. plus mesna, day 1–5. Etoposide 100 mg/m^2/d., day 1–5.	[179]
IVA	Ifosfamide 3 g/m^2/d. plus mesna, day 1.–3. Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Dactinomycin 1.5 mg/m^2 (max. 2 mg/d.), day 1.	[179]
IVADo	Ifosfamide 3 g/m^2/d. plus mesna, day 1–2. Vincristine 1.5 mg/m^2 (max. 2 mg), day 1. Dactinomycin 1.5 mg/m^2 (max. 2 mg/d.), day 1. Doxorubicin 30 mg/m^2, 4-hour infusion, day 1–2.	[179]
VDC	Vincristine 1.5 mg/m^2 (max. 2 mg) Dactinomycin 75 mg/m^2 Dexrazoxane	[51]
IE	Ifosfamide 9 g/m^2 Etoposide 500 mg/m^2	[51]
VI	Vincristine 1.5 mg/m^2 (max. 2 mg) Irinotecan 50 mg/m^2	[51]
VA	Vincristine 1.5 mg/m^2 (max. 2 mg) Dactinomycin 0.045 mg/kg (max. 2.5 mg)	[51]
VAC	Vincristine 1.5 mg/m^2 (max. 2 mg) Dactinomycin 0.045 mg/kg (max. 2.5 mg) Cyclophosphamide 1200 mg/m^2	[51]
Less common regimens of RMS treatment		
–	Vincristine 2 mg Doxorubicin 75–90 mg/m^2 72 h infusion plus dexamethasone (cardioprotection) Ifosfamide 10 g/m^2 divided in boluses for 4–5 days	[38]
–	First line of treatment: Doxorubicin 60 mg/m^2 Cyclophosphamide 600 mg/m^2 Second line of treatment: Cisplatin 75 mg/m^2 Taxol 200 mg/m^2 Next line of treatment: Gemcitabine 1000 mg/m^2 Carboplatin AUC 5	[98]

→

Table 9 cont. Chemotherapy regimens used in rhabdomyosarcoma treatment

Regimen name	Administered drugs	References
–	Preoperative chemotherapy: Doxorubicin (50 mg/m^2) Dacarbazine (1000 mg/m^2) Vincristine (1.4 mg/m^2) Cyclophosphamide (700 mg/m^2) Postoperative: Methotrexate (2 g/m^2)	[181]
–	Cyclophosphamide 1200 mg/m^2 day 1. Vinorelbine 25 mg/m^2 day 1 and 8. Temsirolimus 15 mg/m^2 day 1, 8, and 15 (maximum 12 cycles of treatment).	[182]
–	Cyclophosphamide 250 mg/m^2 day 1–5. Topotecan 0.75 mg/m^2 day 5.	[183]
–	Cyclophosphamide 25 mg/m^2 each day of the cycle Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 28 of the cycle	[184]
–	Dactinomycin 25 mg/m^2 day 1–3. Ifosfamide 2500 mg/m^2 day 1–4.	[185]
–	Dactinomycin 75 mg/m^2 day 1 (every 21 days up to 6 cycles)	[185]
Vinorelbine in monotherapy	Vinorelbine 30 mg/m^2 on days 1 and 8 of the cycle every 3 weeks OR Vinorelbine 33.75 mg/m^2 every week for 6 weeks, then 2 weeks without the drug.	[186, 187]
–	Vincristine 1.5 mg/m^2, day 1 and weeks 1, 2, 4 and 5. Irinotecan 50 mg/m^2 for 5 days in week 1 and 4.	[188]
GD	Gemcitabine 900 mg/m^2 day 1 and 8. Docetaxel 100 mg/m^2 day 8. In a 21-day cycle.	[189]

RMS — rhabdomyosarcoma; VA — vincristine, dactinomycin; VAC — vincristine, actinomycin, cyclophosphamide; IE — ifosfamide and etoposide; VAI — vincristine, dactinomycin, ifosfamide; VIE — vincristine, ifosfamide, etoposide; IVA — ifosfamide, vincristine, dactinomycin; IVADo — ifosfamide, vincristine, dactinomycin, doxorubicin; GD — gemcitabine, docetaxel

in patients previously treated with standard chemotherapy regimens [191, 192]. Unfortunately, another small-molecule tyrosine kinase inhibitor (crizotinib), which, among others, inhibits ALK kinase, did not have clinically significant activity in monotherapy of ARMS patients [193].

Procedure in the case of disease progression during or after treatment

In at least one-third of patients with RMS local or general recurrence will occur [51]. In patients in whom the disease has progressed during the first line of treatment, the prognosis is particularly poor. Patients who completed RMS treatment often do not obtain a full radiological response in layered imaging studies, despite normalization of the PET scan picture, which is probably due to the scarring of the primary tumor site or the differentiation of that tissue. For that reason, the biopsy of the tumor bed after removal of the primary tumor is not recommended except for situations where the primary tumor increases in size or pain occurs [194]. Patients whose PET scan indicates an enhanced signal in the site of the primary tumor pose a particular challenge in respect to the choice of further therapy. Indubitably, they belong to the group of patients with an increased risk of local recurrence and development of distant metastases, and the decision on performing a biopsy of the primary site of the tumor or further surgical resection should be taken after stratification of both risks and potential benefits [195]. A definite suspicion of RMS recurrence requires taking tissue material using a biopsy and histopathological confirmation. Surgical resection of the tumor may be considered if access to the site of recurrence allows this. Radiotherapy is quite often used for the treatment of the primary tumor (if it had not been treated previously) and metastases to the bones and lungs if this is doable. Radiotherapy may be delayed, especially in respect to neoplastic

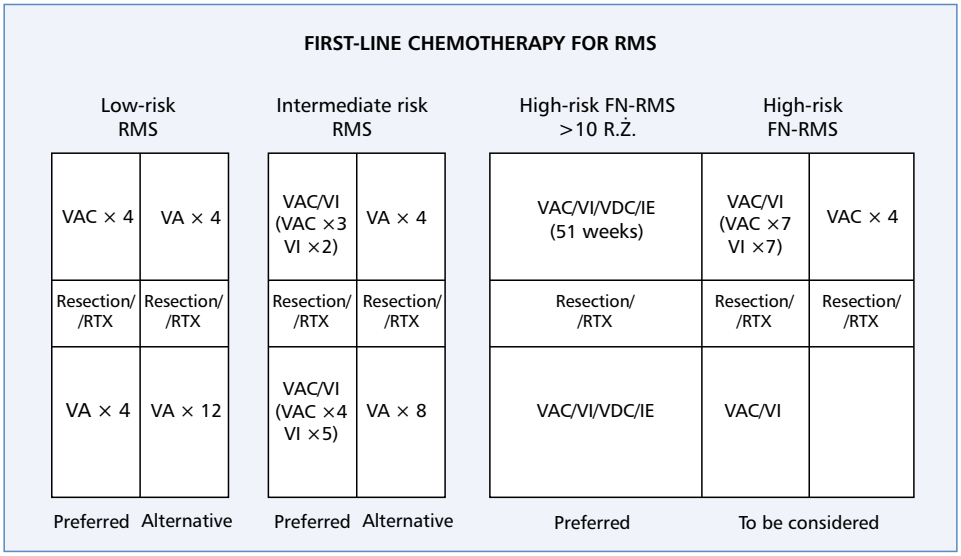

Figure 8. Proposed rhabdomyosarcoma (RMS) treatment regimens in children and young adults. Based on [51]; RTX — radiotherapy; VA — vincristine, actinomycin; VAC — vincristine, actinomycin, cyclophosphamide; IE — ifosfamide and etoposide; VI — vincristine and irinotecan; VDC — vincristine, doxorubicin, deksrazoksan

metastases, to evaluate the response to chemotherapy and to avoid myelosuppressive complications due to systemic cytotoxic treatment. Currently, it is particularly important to include patients with RMS recurrence or progression into clinical trials and to use chemotherapeutics with proven activity against RMS. There are no data permitting comparison of the effectiveness of treating with specific chemotherapy regimens, thus the decision about the choice of a given type of therapy in patients with RMS recurrence depends on many factors, including among others the first-line treatment protocol, the patient's general status, and the tolerance of earlier therapy. As a rule, second-line chemotherapy is used containing previously mentioned active drugs (platinum derivatives, camptothecin, etoposide, doxorubicin, vinorelbine). In patients with recurrence or primarily generalized RMS, attempts at high-dose chemotherapy have also been made. Phase III trials with a random selection of patients were conducted, in which standard chemotherapy was compared with myeloablative treatment. There are insufficient data to determine the optimum length of chemotherapy duration in the case of recurrence/progression. Patients, in general, receive at least 8 cycles of chemotherapy, if a complete response to therapy and acceptable tolerance of therapy occurs [51]. In the MMT89 and MMT91 trials, a group of 52 patients from a high-risk group who had undergone myeloablative therapy after standard induction chemotherapy were nonrandomly compared with 44 patients treated only with standard inductive and supplementary chemotherapy. The percentages of progression-free survivals were 30% for myeloablative chemotherapy and 19% for standard treatment. In this group of patients, a more significant prognostic factor associated with treatment turned out to be the response to initial inductive chemotherapy. The percentage of OS in patients who were in complete remission after surgery and chemotherapy up to week 18 was 41% in comparison with 14% in patients in whom a complete response had not been obtained ($p = 0.0001$). The available data do not allow a valid evaluation of myeloablative treatment in young adults and suggest the resistance of RMS cells to mega chemotherapy, as most recurrences after treatment occurred in sites previously occupied by the neoplasm [196, 197]. The effectiveness of chemotherapeutics commonly used in treating other types of soft tissue sarcomas in adults such as gemcitabine, docetaxel, or pazopanib, has so far not been sufficiently evaluated in RMS. Moreover, few published data are indicating a good effect of using tyrosine kinase inhibitors in the therapy of patients with RMS. Also, the role of the increasingly popular immunotherapy, including checkpoint inhibitors (antibodies directed against PD-1, PD-L1, or CTLA-1), immunomodulating drugs, or CAR-T cell therapy, has not yet been verified in the context of RMS treatment, but there are single cases of complete response to treatment with drugs from these groups [198].

The algorithm of the procedure to follow if recurrence or progression of rhabdomyosarcoma is suspected is presented in Figure 9 [51].

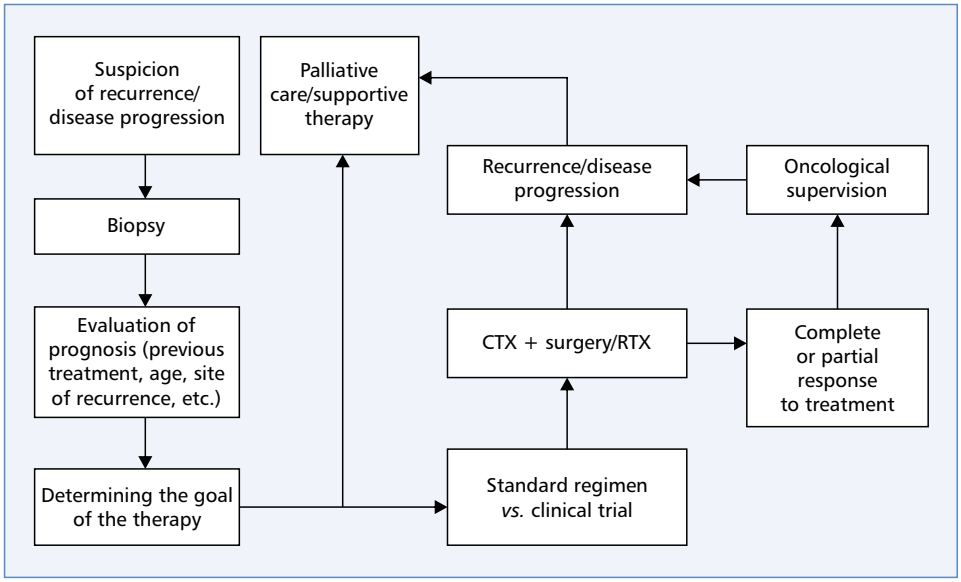

Figure 9. Algorithm of procedure for suspicion of rhabdomyosarcoma recurrence or progression. After [51]; CTX — chemotherapy; RTX — radiotherapy

RMS in adult patients — selected aspects

Due to the rare occurrence of RMS in the adult population, there are no unequivocal guidelines concerning the treatment of this neoplasm. There are no published results of clinical trials with randomization which could be the basis of uniform principles of care for such patients. So far experience in treating adult patients with RMS is based on small groups collected in retrospective analyses [144, 147, 178]. The used treatment regimens differ considerably depending on the center in which the patients are treated and the therapy standards in that center.

In the largest meta-analysis published so far including 533 adult patients with RMS in a localized stage, a large variety of treatment protocols chosen by specialists for patients with RMS was presented [5]. Currently, three main methods are used for the treatment of localized RMS, which include oncological surgery, radiotherapy, and chemotherapy. In the mentioned meta-analysis, the most used methods were surgery plus chemotherapy (27.5%), a combination of the 3 methods (25.1%), and surgery alone (19.0%). The combination of surgery and radiotherapy (1.2%) and radiotherapy and chemotherapy (13.2%) were slightly less common. Monotherapy, that is chemotherapy or radiotherapy, was the least common (3.8%). The median radiation dose used in the case of radiotherapy and surgery was 54 Gy (from 14 to 110 Gy), while when radiotherapy was the only method used the median was slightly higher, namely 56.5 Gy (from 36 to 110 Gy). The most common chemotherapy was as an adjuvant treatment (42.9%) or as primary therapy (15.3%). The protocols were mainly based on cyclophosphamide (22.5%), a combination of cyclophosphamide with anthracycline (21.2%), and a combination of ifosfamide with anthracycline (13.9%). Another study which included 82 patients with locoregionally advanced RMS, had a 5-year overall survival index of 44% [155]. The treatment was most commonly a combination of surgery, radiotherapy, and chemotherapy (30 persons), a combination of radiotherapy and chemotherapy (28 persons), and a combination of radiotherapy and surgery (15 persons). Radiotherapy in the case of a preoperative procedure included irradiation with a median of 50 Gy, whereas postoperative radiotherapy and radiotherapy without surgery had a median of 60 Gy. Chemotherapy was given to 58 patients and included administering doxorubicin or actinomycin D in combination with vincristine or cyclophosphamide. Disease recurrence occurred in 47 patients (57%), most commonly in the form of distant metastases (22 persons), less frequently as a local (11 persons) or loco-regional recurrence (11 persons). In the retrospective study of Noujaim et al. [7] 32 patients with localized RMS were described in whom in 26 cases radical surgery — removal of the primary tumor — was performed. Frequently in as many as 15 patients, postoperative radiotherapy was applied, whereas only 3 persons received chemotherapy or preoperative radiotherapy. Local and distant recurrence was present in 4 and 10 persons, respectively. In a study from another center, including 16 patients with RMS in a localized stage, the most common procedure was ra-

diotherapeutic treatment combined with chemotherapy (11 persons) and chemotherapy alone (2 persons) [6]. Three persons were treated by primary surgery supplemented by chemotherapy or/and radiotherapy. The most frequently chosen chemotherapy regimen (regardless of the stage of the disease) was vincristine, actinomycin D, cyclophosphamide (VAC) alternating with ifosfamide and etoposide (IE). During radiotherapy in 10 patients, simultaneous chemotherapy was used in the vincristine and cyclophosphamide (VC) regimen. Among patients treated with non-palliative radiotherapy, the median radiation dose was 56 Gy. Among 16 persons treated for primary localized RMS, 4 had local recurrence, whereas metastases or regional dissemination were observed in 6 persons. Treatment with radiotherapy ($p = 0.009$) and chemotherapy lasting longer than 19 weeks ($p = 0.009$), as well as adding a simultaneous regimen of VC chemotherapy to radiotherapy ($p = 0.01$), was associated with a longer OS. In the next group of patients including 111 adults with localized RMS, surgery of the primary tumor was performed in 80% (89 persons), radiotherapy in 73% (81 persons), and chemotherapy was administered to 75% of patients (83 persons) [147]. CT, MRI, and PET-CT can be used to evaluate the periodic effectiveness of the treatment.

Because RMS is rare in adults there is a limited number of papers reporting the results of treating this neoplasm, and their main limitation is their retrospective character (Tab. 10). The lack of unequivocal guidelines concerning the treatment of metastatic disease leads to a large variety of chemotherapy regimens in studies from large centers, which, moreover, differ in their standards of oncological care. Survival of adults with RMS is still much lower than the results obtained in pediatric populations, where 5-year overall survival is OS = 77–87% in children and OS = 20–40% in adults [5, 144, 167, 178]. This fact can probably be explained by several aspects. First, age was shown to be an independent prognostic factor for patients with RMS [200]. A significant difference is the use of lower doses of supportive chemotherapy components in adults in comparison to children, due to the high frequency of serious complications, including bone marrow suppression, infections, and neurotoxic effects, among others [174]. Additionally, the more common histopathological RMS subtypes in adults are pleomorphic and alveolar RMS, they are associated with a poorer prognosis [13]. Five-year overall survival in RMS patients is in the range of 40–50% for localized disease and is from zero to 30% in the case of metastatic disease based on available analyses from large centers [7, 14, 147, 178]. Nevertheless, retrospective studies have shown that initiation of pediatric protocols of localized disease treatment is associated with a better prognosis and obtaining 5-year survivals of patients at the level of 61.5% [144, 147]. The use of radiotherapy was also associated with better survival of the patients both in the local disease stage, as well as for disseminated disease [147, 200, 201]. Including chemotherapy was found to be an independent prognostic factor causing lower mortality due to the progress of the neoplastic disease according to the analysis of patients from a center in Thailand [202]. There are, however, also reports on the lack of improvement of survival of patients subjected to chemotherapy in comparison to a control group [201]. Moreover, tumors smaller than 5 centimeters in size correlate with longer patient survival regardless of other factors [155, 178]. Favorable tumor localization has been distinguished in some elaborations of retrospective studies as an independent factor affecting survival [4]; however, there are also opposite conclusions that multifactorial analysis indicates that this aspect is not statistically significant [5, 203]. In the case of tumors of the urinary tract, localization within the prostate gives a better prognosis as compared to the urinary bladder or kidney RMS [204]. It is worth underlining that obtaining negative surgical margins after tumor resection was distinguished as a prognostic factor in the context of disease recurrence and progression [147, 178]. Surgical resection of the primary tumor remains the standard in localized disease, but it has been shown that this procedure improves survival in disseminated disease in adults [147, 205]. After treatment careful control of recurrences is necessary. Medical visits should take place every 3 months for the first year, every 4–6 months during the second and third year, and subsequently once a year. Among analyses performed during control visits are interview and physical- examination, peripheral blood morphology and biochemistry (parameters of liver and kidney function), imaging studies — CT every 3–6 months for the first 2 years, subsequently once a year for the next 3 years, bone scintigraphy (every 6 months for the first 2 years, subsequently once a year for the next 3 years), the remaining examinations (ultrasound/CT/MRI) of the area of the primary tumor and PET-CT depending on the decision of the multi-specialist team [206].

Selected aspects of pediatric RMS

Rhabdomyosarcoma is the most diagnosed soft tissue sarcoma in children. It constitutes about 5–7% of all pediatric neoplasms and 60% of soft tissue sarcomas. Over one-half of the cases appear in small children aged 2–6 years. In the group of pediatric patients, ERMS (55–70%) and ARMS (25–30%) are the most common [13, 209–211]. The most frequent localization of the disease in children is the head and neck area (eye socket, parameningeal area, soft tissues of the face and neck; about 36%). These are generally cases of ERMS, diag-

Table 10. Studies describing the treatment of adult patients with diagnosed rhabdomyosarcoma

References	Number of patients	Patients' age (median)	mOS		5-OS		Median PFS/DFS/RFS/EFS	
			M(–)	M(+)	M(–)	M(+)	M(–)	M(+)
[7]	45	71.5 (28.4–92.8)	12.8	7.1	–	29%	7.3 (RFS)	2.3 (PFS)
[6]	20	34 (19–79)	53.2	21.7	–	20% (3–year)	19.8 (DFS)	20.4 (DFS)
[147]	157	37 (18–86)	40.0	13.0	43%	5%	9.3 (RFS)	–
[147]	292	55 (18–99)	40.0 (whole cohort)	40.0 (whole cohort)	–	–	–	–
[178]	84	31 (16–76)	35.0	15.0	50%	22%	–	–
[200]	36	29 (21–72)	–	–	–	–	22.4 (PFS)	13.3 (PFS)
[207]	59	56 (38–72)	11.0	9.0	–	–	–	–
[14]	39	26 (16–82)	–	–	44%	0%	–	–
[155]	82 (M–)	27 (17–81)	38	–	44%	–	6.5 (PFS)	–
[144]	171	27 (19–83)			45.7%	4.3%		
[13]	1071	> 19	–	–	47%	–	–	–
[4]	138	28 (16–86)	–	–	45%	approx. 18%	–	–
[180]	8	24 (18–60)	27.3	–	–	–	17.0 (PFS)	–
[203]	66	28 (18–71)	30.0	11.0	36%	11%	17.0 (EFS)	–
[208]	239	19 (10–102)	45.6	16.8	44.1%	18%	22.8 (RFS)	10.8 (PFS)
[203]	66	28 (18–71)	30.0	11.0	35%	11%	–	–

DFS — disease free survival; EFS — event free survival; M(–) — non-metastatic disease; M(+) — metastatic disease; m-OS — median overall survival; OS — overall survival; PFS — progression free survival; RFS — relapse free survival; 5-OS — 5 years overall survival

nosed before the age of eight years, rarely metastasizing to regional lymph nodes [166]. The urogenital tract is also a frequent site of RMS occurrence in children (approx. 23%). In respect to prognosis, this localization can be divided into the area of the bladder and prostate, and the area without the bladder and prostate (testes, epididymis, the peritesticular area, penis, vulva, vagina, ovary, uterus) [212]. Vaginal RMS deserves particular attention in this group; it occurs, in general, in small girls and has a very characteristic clinical presentation of botryoid masses "falling out" of the vaginal vestibule, causing bleeding and/ or discharge [124, 203]. Uterine tumors are generally oligosymptomatic and are thus diagnosed in advanced stages [166, 212]. Extremities are a less common localization in children (approx. 20%). The neoplasm, in general, develops in the form of a painless tumor, often giving metastases to regional lymph nodes (50%) [166]. In about 15% of RMS cases in children, at the moment of diagnosis generalized disease is found (stage four of clinical progression according to TNM for RMS) with metastases to the lungs (50%), bone marrow (30–40%), bones (10%) and/or lymph nodes (depending on the localization 5–50%) [166, 212].

Treatment of soft tissue sarcomas in children is based on international protocols of the Cooperative Weichteilsarkom Studiengruppe (CWS) and the European Paediatric Soft Tissue Sarcoma Group (EpSSG), recommended by the Polish Pediatric Solid Tumor Group. The basis for the treatment strategy is appropriate stratification to risk groups based on the following prognostic factors: the disease stage according to the IRSG classification, histological type, age of the patient, size, and localization of the tumor. The risk stratification system is periodically updated. Taking into consideration the most recent data on the prognostic value of the genetic status of ARMS, it should be kept in mind that the current system of stratification will need to be verified in the near future. Currently, this system assumes a division into risk groups. The assignment to a given risk group determines the choice of a specified therapeutic regimen. The American system of risk stratification elaborated by the Children's Oncology Group-Soft-Tissue Sarcoma (COG-STS), differs slightly from the European system created by EpSSG. A detailed description of both systems of risk stratification is presented in Tables 11 and 12.

Recent studies have confirmed the importance of PAX3/7-FOXO1 fusion status as a critical prognostic biomarker following M status [215–217]. Other molecular factors of potential prognostic significance, which have not yet been used in RMS risk stratification, are under investigation. The INternational Soft Tissue SaRcoma

Table 11. Stratification to rhabdomyosarcoma (RMS) risk groups according to *Children's Oncology Group-Soft-Tissue Sarcoma*. Based on [131, 213, 214]

Risk	Histology	Grade	Clinical group
Low	ERMS	1	I, II, III
	ERMS	2, 3	I, II
Standard	ERMS	2, 3	III
	ARMS	1, 2, 3	I, II, III
High	ERMS	4	IV
	ARMS	4	IV

ARMS — alveolar rhabdomyosarcoma; ERMS — embryonic rhabdomyosarcoma

Table 12. Stratification to risk groups for the localized form of rhabdomyosarcoma (RMS) according to the European Paediatric Soft Tissue Sarcoma Group. Based on [131, 213, 214]

Risk	Histology	Clinical stage	Localization	N Status	Tumor size and patient's age
Low	ERMS	I	All	N0	≤ 5 cm and ≤ 10 years
Standard	ERMS	I	All	N0	> 5 cm or > 10 years
	ERMS	II, III	Favorable	N0	all
	ERMS	II, III	Unfavorable	N0	≤ 5 cm and ≤ 10 years
High	ERMS	II, III	Unfavorable	N0	> 5 cm or > 10 years
	ERMS	II, III	All	N1	All
	ARMS	I, II, III	All	N0	All
Very high	ARMS	II, III	All	N1	All

ARMS — alveolar rhabdomyosarcoma; ERMS — embryonic rhabdomyosarcoma

Table 13. Modified risk stratification system including the PAX3/7-FOXO1 fusion [219]

Risk	IRSG TNM stage	Clinical group	Age	Rearrangement FOXO1 (fusion)
Low	1	I, II, III (only eye socket)	Any	FOXO1-
	2	I, II		
Standard	1	III (without eye socket)	Any	FOXO1-
	1, 2, 3	I, II, III		FOXO1+
	2, 3	III		FOXO1-
	3	I, II		FOXO1-
	4	IV	< 10 years	FOXO1-
High	4	IV	≥ 10 years	FOXO1-
			Any	FOXO1+

ConsorTium will supervise the coordination of further research work and combining clinical and molecular data from different research studies from various medical centers. A modification of the current risk stratification system by including the PAX3/7-FOXO1 fusion status is a subject of several prospective clinical trials [COG (ARST1431) and EpSSG Frontline and Relapsed-Rhabdo-MyoSarcoma (FaR-RMS)] (Tab. 13) [218].

Unfavorable localization encompasses limbs, the parameningeal area, the bladder, and the prostate. The alveolar type of sarcoma, the patient's age > 10 years, and tumor size > 5 cm are also associated with a poorer prognosis [13, 170, 209–211].

Currently, in about 70% of children with locally advanced disease, a permanent cure is obtained after using combined treatment [209, 210]. The optimal time for initiating local therapy is controversial. European protocols recommend surgery and/or radiotherapy after the 3rd cycle, i.e. in week 13 from starting chemotherapy, and for metastatic disease from week 22 [209, 210].

The modality of surgical treatment of RMS is due to the possibility of infiltration of various sites by the tumor, and the course of the disease may be different depending on the tumor localization. Radical surgery is an important prognostic factor, but because of the localization and size of the tumor, it is generally difficult to perform. However, only in 10% of the patients at the moment of diagnosis, the extent of neoplastic disease allows radical surgical resection [212]. In the remaining patients, the surgical intervention is limited to a biopsy. Analysis of survival did not indicate the superiority of debulking surgery as compared to a biopsy [56]. After performing non-radical tumor resection, a second evaluation by the surgeon is recommended to determine the possibility of radicalization and to consider performing such a procedure before initiating systemic therapy (PRE, pre-treatment re-excision). The premise of the surgical protocol is complete (macroscopic and microscopic) removal of the neoplastic tumor with the margin of the surrounding tissues, without a significant cosmetic effect nor perturbation of function [56, 212, 214]. The surgery before initiating systemic treatment affects risk stratification, allowing classification of the patient to a better group compared to the classification of the primary surgery [220]. The subject of safe tissue margins during primary resection in children remains controversial. Most frequently obtaining a margin of about 0.5 cm is recommended [56]. In the case of locally advanced disease, surgical treatment is only considered after completing induction chemotherapy (DPE, delayed primary excision) when imaging studies show a residual tumor qualifying for radical resection.

Histopathological verification of regional lymph nodes is recommended in patients with the suspected occupation of lymph nodes in a clinical investigation or imaging study and primary RMS localization within the limbs and the peritesticular area (≥ 10 years). This procedure is also recommended in children with ARMS with the PAX/FOXO1 translocation [56]. The recommended method is a biopsy of the sentinel node [56]. Confirmation of regional lymph node involvement is an indication for radiotherapy, as radical lymphadenectomy was not found to improve survival [56].

Rhabdomyosarcoma is a neoplasm with high sensitivity to chemotherapy, therefore, current regimens are based on neoadjuvant chemotherapy. Despite many studies on the intensification of this treatment, the standard in Europe is still the regimen using three drugs: ifosfamide, vincristine, and actinomycin D [209–211]. In turn, COG recommends the VAC regimen composed of vincristine, actinomycin D, and cyclophosphamide. The European group explains the substitution of cyclophosphamide by ifosfamide by a decreased risk of toxicity to the gonads. The treatment of patients qualified to the low-risk group is shorter, and a reduction of the dose of cyclophosphamide is also possible without affecting overall survival. In patients from the moderate risk group, a reduction of the cyclophosphamide dose requires adding the next drug (e.g. irinotecan) to the basic treatment regimen. The greatest challenge is the treatment of patients from the high-risk group and patients with disease recurrence, as for years no improvement of survival indices has been observed. In these groups, attempts are made to introduce new drugs into the treatment regimens now in force and to introduce new treatment methods.

Radiotherapy, except for cases from the low-risk group, is standard supplementary treatment after surgery. However, there are premises for including this treatment before surgery: an easier and more precise definition of the target for irradiation, limiting the volume of normal tissues receiving a high dose, decreasing the risk of secondary tumors (most of the irradiated tissues will be removed), and the radiobiological advantage of irradiating tissues which are better oxygenated. So far little data have been published on this subject. In a group of 17 children with diagnosed RMS of the urogenital tract, Seitz et al. [221] obtained a 5-year EFS of 82%, which is a very promising result. However, the basic advantage of such a treatment sequence is the decrease in the risk of late toxicity. Radiotherapy in the pelvic or parameningeal area, especially in children under 3 years of age, is a treatment associated with a high risk of hindering the development of irradiated tissues and serious toxicity depending on the dose administered to normal organs. The fear of initiating such aggressive treatment in neonates probably contributes to the poorer survival indices in this age group [214]. Hence modern treatment methods utilizing volumetric modulated arc therapy (VMAT) or proton therapy, with a greater possibility of protecting healthy tissues, are currently recommended as the treatment of choice [170, 221, 222]. To further improve the conformality of the distribution and to decrease the dose outside the target volume, the technique of simultaneous irradiation is used, in which different doses are given in different areas of the target volume simultaneously. For a selected group of patients, especially with RMS localized in the organs of the pelvis minor, brachytherapy may be used as part of the procedure together with sparing surgery. This is, however, a form of treatment performed only in a few reference centers [210].

In irradiation of children with an RMS diagnosis a broad range of doses from 36 to 54 Gy is used and, in the case of monotherapy, even up to 59.4 Gy. This depends on the localization and histological type of the sarcoma and, above all, on the extent of the residual disease [209–211]. Research on the use of doses escalated to 59.4 Gy in all patients with tumors exceeding 5 cm in size is ongoing [223].

There are many contradictory data on procedures in metastatic disease. In choosing the optimal type of treatment criteria, identifying 4 prognostic factors may be helpful: age, localization of the primary focus, occupation of the bone marrow, and metastases to at least 3 localizations. Patients with the presence of only one

factor attain a 3-year EFS of 44% in comparison to 14% of patients with 2–4 factors [209]. There are no unequivocal guidelines as to the role of surgery in treating generalized neoplastic disease. The recommended procedure is a biopsy, performed to confirm the presence of a metastatic focus, and surgical resection of the persisting focus after chemotherapy [56, 224].

Despite significant improvements in treating children diagnosed with RMS from the low and standard risk group (3-year EFS > 70%), the effects of treating more advanced diseases are still unsatisfactory, especially in the presence of factors with adverse effects on the prognosis [209–211]. In 20–30% of pediatric patients with localized RMS and 70% with metastatic disease, a recurrence of the disease will occur [225, 226]. Despite gradual improvement in the treatment of such patients, indices of 5-year post-relapse survival (PROS) in this group do not exceed 30% [227].

There are still many questions regarding, among others, the optimal time for introducing radiotherapy, the benefit of escalating the dose, or the role of radiotherapy in persistent disease, especially with a poor prognosis. The possibilities of conventional treatment intensification are limited by complications, and the low survival indices in the group of patients with recurrence and generalized disease indicate that new safer methods of targeted therapy must be sought. Among substances with proven activity against RMS, which have been tested in vitro and in vivo, are monoclonal antibodies against IGF-1R (cixutumumab and robatumumab), IGF-1R inhibitor (BMS-754807), VEGFR inhibitor (cediranib), RTK inhibitor (sunitinib), AAK inhibitor (alisertib), and mTOR kinase inhibitor (rapamycin). Cixutumumab (IMC-A12), temsirolimus (mTOR kinase inhibitor), and bevacizumab (monoclonal antibody against VEGF) are being tested in clinical trials in combination with chemotherapy in patients with RMS recurrence and generalized neoplastic disease [228–230]. New reports on the efficacy and good tolerance of the combination of vinorelbine with the histone deacetylase inhibitor mocetinostat in RMS is interesting [231].

Conclusion

Most of the data concerning survival and prognostic factors of adults with RMS come from retrospective, single-center analyses including several dozen to several hundred patients (Tab. 10). Despite the development of diagnostic techniques and new technologies in radiotherapeutic treatment, the spectacular improvement in survival attained in the pediatric population has not been possible for adults. This fact indicates that the course of the disease is considerably different in children and teenagers in comparison with adults. In care for the patient with local tumor development, the greatest role is played by oncological surgery combined with radiotherapy and chemotherapy. The evaluation of the effectiveness of these combinations of methods in patients with disseminated RMS is crucial in the context of elaborating an optimal sequence of treatment and chemotherapeutic and radiotherapeutic regimens in adults. The standardization and verification of procedures used in treating patients with RMS metastases are particularly important to prolong and improve their quality of life. Taking into consideration the rarity and the complexity of this disease, patients with RMS should be treated in highly specialized hospital wards with long-term practice in care for persons with soft tissue sarcomas. Cooperation within a multidisciplinary team is crucial. That team should be composed of an oncological surgeon, a clinical oncologist, a radiotherapist, and, depending on the need, physicians of other specializations (e.g. a gynecologist or an ear and throat specialist). Multidirectional treatment and the experience of oncological teams in large specialist centers allow us to obtain the best results of treatment. The need to include adult patients into multicenter clinical trials has been repeatedly stressed, as their results may be the basis for elaborating uniform standards of care for patients with RMS.

Current clinical trials for adult patients with RMS are presented in Table 14.

Table 14. Current clinical trials of adult patients with rhabdomyosarcoma (RMS)

Clinical phase	Intervention	Primary endpoints of the clinical trial	Age of patients recruited for the trial
I/II	AMG479 antibody (Ganitumab) against IGF-1R receptor combined with Src family kinase inhibitor (Dasatinib)	Phase I Determining a safe dose of dasatinib combined with ganitumab in patients with recurrent RMS or resistant-to-treatment embryonal or alveolar RMS Phase II Number of patients with ORR (CR or PR)	> 2 years
III	VAC alternating with vincristine and irinotecan (VI) *vs.* VAC/VI plus temsirolimus	EFS	< 40 years

→

Table 14 cont. Current clinical trials of adult patients with rhabdomyosarcoma (RMS)

Clinical phase	Intervention	Primary endpoints of the clinical trial	Age of patients recruited for the trial
III	VAC *vs.* VAC alternating with vincristine and irinotecan (VI)	EFS RR OS	< 49 years
II	Cabozantinib-s-malate (XL184) — small-molecule tyrosine kinase inhibitor (c-Met, VEGFR2, AXL, RET)	ORR (CR and PR)	2–30 years
I	NK cells from donors without compatibility in HLA system combined with ALT803 (IL-15 analog increasing NK cell cytotoxicity)	Establishing maximum tolerated dose of NK cells in combination with ALT803 administration	18–100 years
II	Vemurafenib (BRAF inhibitor)	ORR (CR and PR)	1–21 years
II	Nab-paclitaxel combined with gemcitabine	RR PFS	12–30 years
I	Vorinostat, vincristine, irinotecan, temozolomide	Establishing maximum tolerated dose of vorinostat (combined with other chemotherapeutics)	1–30 years
I/II	Eribulin and irinotecan	Phase I: Establishing maximum tolerated dose of eribulin combined with irinotecan and establishing the appropriate dose of a combination of drugs for phase II of a clinical trial Phase II: ORR (CR and PR)	5 months– –25 years
I	Mocetinostat combined with vinorelbine	Determining the toxicity of the drug combination Establishing maximum tolerated dose of drug combination	> 13 years
I	Immunotherapy using B7H3 CAR-T cells and B7H3 x CD19 CAR-T cells	Establishing maximum tolerated dose of CAR-T cells Evaluation of immunotherapy toxicity Evaluation of the technology of preparing bispecific B7H3 x CD19 CAR-T cells	< 26 years
II	Regorafenib	PFS	> 5 years
I	Palbociclib combined with temozolomide and irinotecan	Evaluation of toxicity and adverse effects of drug combination RR	2–20 years
I	Lyso-thermosensitive liposomal doxorubicin	Establishing maximum tolerated dose of the drug Evaluation of drug toxicity Evaluation of drug pharmacokinetics	< 30 years
I	Immunotherapy using EGFR806 CAR-T cells	Maximum tolerated dose Evaluation of drug toxicity and adverse effects Evaluation of the yield of the process of obtaining CAR-T cells	< 26 years
I	CLR131	Evaluation of drug toxicity	2–21 years
I/II	Prexasertib combined with irinotecan	Establishing recommended dose of prexasertib combined with irinotecan for phase II trial Evaluation of response to treatment among	> 1 year
I	Olaparib combined with temozolomide or olaparib in combination with temozolomide and irinotecan	Maximum tolerated dose of drug combinations	> 16 years
I/II	Infusion of haploidentical activated NK cells	RR	< 80 years
II	Vincristine and irinotecan or vincristine, irinotecan and temozolomide	PR or CR	6 months —50 years

CR — complete response; EFS — event free survival; IGF-1R — insulin growth factor 1; NK — natural killers; ORR — objective response rate; OS — overall survival; PR — partial response; RR — response rate; VAC — vincristine, dactinomycin, cyclophosphamide

Conflict of interest

Authors declare no conflict of interest.

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