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RESEARCH ARTICLE

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Rhabdomyosarcoma-Like and Non-Rhabdomyosarcoma-Like in Children: Assessment of Outcomes in Combination Cancer Therapy

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ABSTRACT

Soft tissue sarcomas (STS) are rare malignant neoplasms, accounting for approximately 7-8% of childhood cancers. The 5-year survival rate varies from 15-90% depending on the severity of the disease. The purpose of our study was to assess the therapeutic results of patients who received combined treatment, according to CWS Protocols implemented at the Department of Pediatric Oncology, Hematology and Transplantology (DPOHT) in Poznan (2007: 2017). The study group consisted of 29 children, although the final analysis of treatment outcomes was completed in 25 children, 18 (72%) boys and 7 (28%) girls. Combined treatment according to the regimens of VAIA III, CEVAIA, O-TIE, radiotherapy and surgery was applied. After first-line treatment, 17/25 (68%) patients achieved remission and 7/25 (28%) died due to disease progression without achieving remission. One child (4%) received palliative care with disease progression. In 3/17 (18%) children, the disease relapsed. The pOS for the RMS-like group is 0.530 and the non-RMS-like group is 0.621. The pEFS for the RMS-like group is 0.578 and the non-RMS group is 0.505. The 5-year survival probability of RMS-like and non-RMS-like patients, despite intensive treatment, is lower than other childhood cancers. In the study group, treatment failures were mainly due to treatment resistance.

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Introduction

Soft tissue sarcomas (STS) are malignant neoplasms originating from the second germ layer, which are the cells of the primary mesenchyma.

Every year in Poland, about 80-100 children are diagnosed with soft tissue sarcomas. In about 20% of the cases, the disease is already disseminated at diagnosis. Despite the use of very intensive treatment, the 5-year survival is currently from 15% in disseminated disease to about 90% in children with localized disease with favorable prognostic factors [1].

Due to the histopathological differences, different biology of neoplasms and the projected response to the treatment of soft tissue sarcomas, they are divided into three therapeutic groups:

1. Group of myosarcoma tumours: rhabdomyosarcoma (RMS)
2. Group of RMS-like tumours: rhabdomyosarcoma-like (RMS-like)
3. Group of non-rhabdomyosarcoma-like tumours (non-RMS-like)

The RMS-like group includes the extraosseous Ewing sarcoma family (EES), syno-vial sarcoma (SySa) and undifferentiated sarcoma (UDS).

Non-RMS-like is a heterogeneous group of rare mesenchymal soft tissue neoplasms, which account for 50% of all childhood sarcomas [2-4]. Non-RMS includes over 50 different histopathological subtypes.

Treatment of these neoplasms is multi-stage and multi-directional where surgery, polychemotherapy and radiotherapy are used. One of the factors responsible for therapy failures is the high heterogeneity of the group of childhood sarcomas.
The aim of the study is to evaluate the treatment outcomes of patients diagnosed with RMS-like and non-RMS-like who received combined treatment (multidrug chemotherapy, surgery and radiotherapy) according to the CWS Protocols, carried out at the Department of Pediatric Oncology, Hematology and Transplantology at Poznan University of Medical Sciences in Poland during the years of 2007: 2017.

Materials and Methods

Originally, 29 children were enrolled in the study group, of which 4 (1 with RMS-like and 3 with non-RMS) continued treatment in other centers during the study. Ultimately, the study analyzed the treatment outcomes of 25 children, 18 (72%) boys and 7 (28%) girls, presented in Table 1.

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Table 1: Distribution of patients and patient characteristics.

Therapeutic group	Number of patients	Male gender	Female gender	Age distribution (median) in years
RMS-like	12	7	5	0-17 and 8/12 (10 and 4/12)
Non-RMS-like	17	12	5	0-17 and 9/12 (3 and 1/8)

Legend: RMS-Like: Rhabdomyosarcoma-Like, Non-RMS-Like: Non Rhabdomyosarcoma-Like.

The diagnosis of soft tissue sarcoma was based on a histopathological examination of a biopsy or resection of the complete lesion performed at a reference center.

The study was approved by the Bioethics Committee of the Poznan University of Medical Sciences: KB nr 215/17.

Treatment

Patients were initially treated according to the CWS 2006 protocol followed by CWS guidance [5,6]. As these programs do not differ in their risk group classification and proposed treatment principles, patients were analyzed together.

First-line Treatment

Treatment complementary to surgery included multi-drug chemotherapy based on the VAIA III regimen (Ifosfamide, Vincristine, Adriamycin, Actinomycin-D) and radiotherapy. In disseminated disease, patients received CEVAIE chemotherapy (Ifosfamide, Vincristine, Actinomycin-D, Carboplatin, Epirubicin, Etoposide) followed by oral O-TIE maintenance treatment (Trophosphamide, Etoposide, Idarubicin) according to the CWS 2006 treatment protocol [5].

Due to frequent treatment failures in the non-RMS-like group, patients were treated with the EU-RHAB 2010 program (Doxorubicin, Ifosfamide, Carboplatin, Etoposide, Vincristine, Actinomycin and Cyclophosphamide) or with the use of highdose megachemotherapy Carboplatin followed by Thiotepa autotransplantation of bone marrow stem cells [7].

Radiotherapy

In cases of disease progression, relapse, or failure to respond to first-line treatment, patients were eligible for second-line treatment. Based on first-line treatment and response to treatment, the appropriate therapeutic management was selected out of chemotherapy VAIA, CEVAIA, SL, radical resection, RTX, TECC (Topotecan, Carboplatin, Cyclophosphamide, Etoposide), O-TIE, and/or participation in phase II/III clinical trials [5,6].

Statistical methods

The statistical analysis was based on the Statistica ver. 9.0 by StatSoft. The Kaplan-Meier method was used to calculate the survival curves and the log-rank test was used to compare the curves between the groups.

Results

Table 2 shows the histopathological characteristics of the study group.

Table 3 shows the clinical stage of the tumor according to International Rhabdomyosarcoma Study (IRS) at diagnosis.

In the study group, no remission was achieved in 8 out of 25 (32%) patients, including RMS-like with 2/11 (18.2%) patients and non-RMS with 6/14 (43%) patients. After first-line treatment, 17/25 (68%) patients achieved remission, and 7 (28%) patients died due to disease progression without achieving remission. 3/17 (18%) children relapsed. One patient was provided with palliative care during the progression of the disease.

Table 2: Distribution of histopathological diagnoses in the entire study group.

Histopathological diagnosis	Number of patients	%
ESa	9	31.0%
SySa	3	10.3%
MPNST	4	13.8%
MRT	3	10.3%
RAT	1	3.4%
DSRCT	1	3.4%
Histiocytic Sarcoma	1	3.4%
cFS	1	3.4%
Fibromatosis	1	3.4%
HPC	1	3.4%
Embryonic Sarcoma	1	3.4%

ESa: Ewing sarcoma family, SySa: Synovial sarcoma, MPNST: Malignant peripheral nerve sheath tumor, MRT: Malignant rhabdoid tumor, RAT: Pigmented neuroectodermal tumor of childhood, DSRCT: Small round desmoplastic tumor, HPC: Haemangiopericitoma, PPB: Pleural, AS: Vascular sarcoma, UPS: High grade undifferentiated pleomorphic sarcoma.

Table 3: IRS tumor stage in the study group.

IRS	Number of RMSlike patients	%	Number of non- RMS-like patients	%
I	0	0	3	17.7
II	3	25	3	17.7
III	5	41.7	6	35.3
IV	4	33.3	5	29.3

IRS: International Rhabdomyosarcoma Study.

Table 4: Treatment results in the study group.

	RMS-like	Non-RMS-like	Overall
Number of patients	11	14	25
Number of children with 1st remission	9	8	17
Number of children with primary resistance	2	6	8
Number of children with relapses	2	1	3
Number of children with 2nd remission	0	1	1
Number of children living in 1st and 2nd remission	7	8	15
Deaths due to illness	4	5	9
During treatment	0	1+1-palliative	2

Table 5: First-line treatment in the study group.

First-line treatment	Number of patients	%
	Surgery	
	RMS-like	
R0	0	0
R1	3	25
R2	9	75
	Non-RMS-like	
R0	3	17.6
R1	3	17.6
R2	11	64.8
	Chemotherapy	
	RMS-like	
VAIA	7	63.6
CEVAIE	3	27.3
2 VAC blocks (newborn)	1	9.1
	Non-RMS-like	
Not applied	6	40
VAIA	4	26.6
CEVAIE	1	6.7
EU-RHAB 2010	3	20
VAC + PAX	1	6.7
	Radiotherapy	
	RMS-like	
50.4 Gy (max dose)	7	63.6
48.6 Gy	1	9.1
45 Gy	1	9.1
30 Gy	1	9.1
Not applied	1	9.1

First-line treatment	Number of patients	%
	Non-RMS-like	
Not applied	10	71.4
50.4 Gy	3	21.4

R0: Microscopic radical resection, R1: Microscopic residue or no microscopic residue, but regional lymph node involvement, R2: Macroscopic residue, VAIA: chemotherapy VAIA (Ifosfamide for 2 days, Vincristine, Actinomycin + Ifosfamide for 2 days, Vincristine, Adriamycin), CEVAIE: Chemotherapy (Carboplatin, Epirubicin, Vincristine, Actinomycin Ifosfamide, Etoposide), EU-RHAB 2010: EUROPEAN RHABDOID REGISTRY (Doxorubicin, Ifosfamide, Carboplatin, Etoposide, Vincristine, Actinomycin, Cyclophosphamide), VAC + PAX: Chemotherapy (Vincristine, Cyclophosphamide, Adriamycin + Paclitaxel), Gy: Gray.

Table 6: Primary Resistance to Treatment.

Primary resistance to treatment			
Diagnosis	**Location**	**Treatment**	**Treatment outcome**
		RMS-like	
congenital biphenotypic PNET	area of the shoulder girdle	2 VAC blocks	death
PNET/saEwing	sub-scapular area bones	9 CEVAIE + radiotherapy for metastatic foci → PACE→ VIT, TC, Gemcitabine with Docetaxel	death
congenital biphenotypic PNET	area of the shoulder girdle	2 VAC blocks	death
		Non-RMS-like	
DSRCT	abdominal cavity	CEVAIE (5 blocks) → SL → RTX → Irinotecan + Carboplatin → Cyclophosphamide + Vinorelbine	death
MPNST*	Posterior mediastinal peripheral nerves	VAIA (5 blocks) → RTX 50,4Gy + Vincristine, yclophosphamide (6 blocks) → TECC	death
MRT**	liver Kidney, tk. subcutaneous in the browbone vicinity, cerebellar worm	CEVAIE (2 blocks) → EU-RHAB 2010 (3 blocks)	death
MRT	liver	EU-RHAB 2010 (3 blocks) → complicated tumor resection	death
MRT	head tumor in the area of the left cheek with penetration into the skull lungs	Partial resection → EU-RHAB 2010 → complicated resection attempt	death
undifferentiated germ cell sarcoma	jejunum	VAIA (5 blocks) → CWS 2006 → Irinotecan + Daxarbazine / Vincristine + Dacarbazine with Actinomycin / Etoposide + Ifosfamide + Carboplatin / Cisplatin + Doxorubicin → Chemoembolization with Irinotecan in microspheres	disease progression and palliative care

PNET: Primitive neuroectodermal tumor, DSRCT: Desmoplastic small round cell tumor, MPNST: Malignant peripheral nerve sheath tumor, MRT: Malignant rabdoid tumor, VAC: chemotherapy (Vincristine, Cyclophosphamide, Adriamycin), CEVAIE: chemotherapy (Carboplatin, Epirubicin, Vincristine, Actinomycin, Ifosfamide, Etoposide), PACE: chemotherapy (Cisplatin, Doxorubicin, Cyclophosphamide, Etoposide), VIT: chemotherapy (Vincristine, Irinotecan, Temozolomide), TC:
Topotecan, Carboplatin), SL: second line, RTX: radiotherapy, VAIA: chemotherapy (Ifosfamide for 2 days, Vincristine, Actinomycin + Ifosfamide for 2 days, Vincristine, Adriamycin), TECC: chemotherapy (Topotecan, Etoposide, Carboplatin, Cyclophosphamide), EU-RHAB: EUROPEAN RHABDOID REGISTRY (Doxorubicin, Ifosfamide, Carboplatin, Etoposide, Vincristine, Actinomycin, Cyclophosphamide).

* Previously treated with RTX on the mediastinum for Hodgkin's lymphoma
** Primary diagnosis: malignant neuroectodermal tumor with muscular differentiation; treated according to the scheme for children with CNS tumors < 3 years of age: Cyclophosphamide, Vincristine, Etoposide and Cisplatin, Etoposide, Vincristine
→ next stage of treatment
+ treatment carried out in parallel metastases

Table 7: Treatment of Relapse.

Diagnosis	Primary location	Relapse		
		Type of relapse	Treatment of relapse	Treatment outcome
		RMS-like		
ESa: Askin's tumor	chest wall	local	SL → IVADo → mega-chemotherapy + autotrans-plantation	death
PNET/saEwing	retroperitoneal space	local, pulmonary	SL → TECC	death
		non-RMS		
Histiocytic sarcoma	area of the mammary gland	local, pulmonary	CEVAIE → Methotrexate + Vinblastine	remains in 2nd remission

PNET: Primitive neuroectodermal tumor, SL: second line, IVADo: chemotherapy (Ifosfamide, Vincristine, Actinomycin, Adriamycin), TECC: chemotherapy (Topotecan, Etoposide, Carboplatin, Cyclophosphamide), CEVAIE: chemotherapy (Carboplatin, Epirubicin, Vincristine, Actinomycin, Ifosfamide, Etoposide).

Treatment methods

Table 5 shows first-line treatment performed in the study group.

Primary resistance to first-line treatment

Primary resistance to first-line treatment was reported in 8/25 (32%) patients, including 2 (25%) girls and 6 (75%) boys.

Treatment of Relapse

Recurrence of the disease was noted in 3/17 (18%), including 2 (67%) girls, 7 and 17 months after the 1st remission, respectively, and 1 (33%) boy 7 months after the 1st remission. Median time was 7 months. Relapse characteristics and treatment outcomes are presented in Table 7.

Statistical Analysis of Treatment Outcomes

The probability of overall survival (pOS) for RMS-like study group was 0.530 and for non-RMS-like study group was 0.621; p=0.922, presented in Figure 1.

The probability of 5-year event free survival (pEFS) for the RMS-like study group was 0.578 and for the non-RMS-like study group was 0.505; p=0.521, presented in Figure 2.

The probability of overall survival (pOS) for children under 10 years of age was 0.692 and for children above 10 years of age was 0.350; p=0.590, presented in Figure 3.

The probability of 5-year event-free survival (pEFS) for children under 1 year of age was 0.286 and for children above 1 year of age was 0.627; p=0.020, presented in Figure 4.

There is the statistical relevance for pEFS between previously mentioned groups.

The probability of overall survival (pOS) for patients who underwent radiotherapy was 0.481 and for patients without radiotherapy was 0.6; p=0.759, presented in Figure 5.

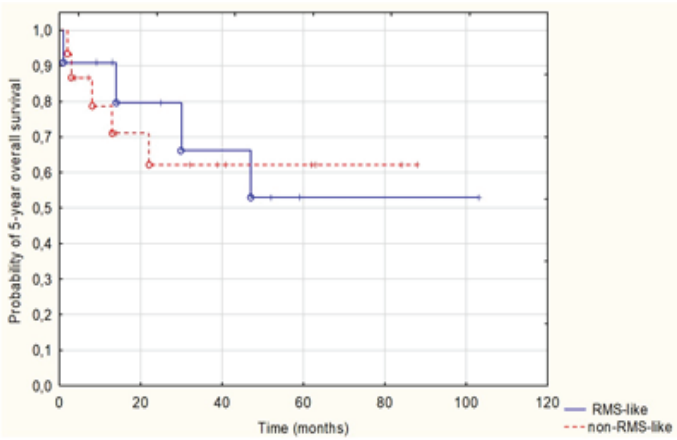

Figure 1: Probability of 5-year overall survival (pOS) for the study group depending on the diagnosis (pOS RMS-like = 0.530 and non-RMS-like = 0.621); p = 0.922.

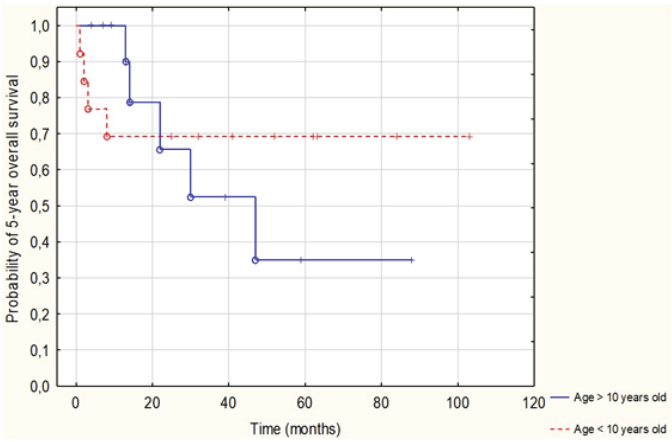

Figure 2: Probability of 5-year event-free survival (pEFS) for the study group depending on the diagnosis (pEFS RMS-like = 0.578, non-RMS-like = 0.505); p = 0.521.

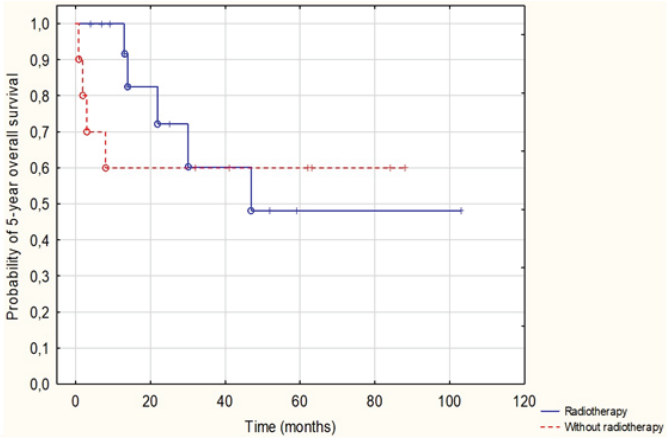

Figure 3: Probability of 5-year overall survival (pOS) for the study group depending on the age of the child (<10 years of age pOS = 0.692, >10 years of age pOS = 0.350); p = 0.590.

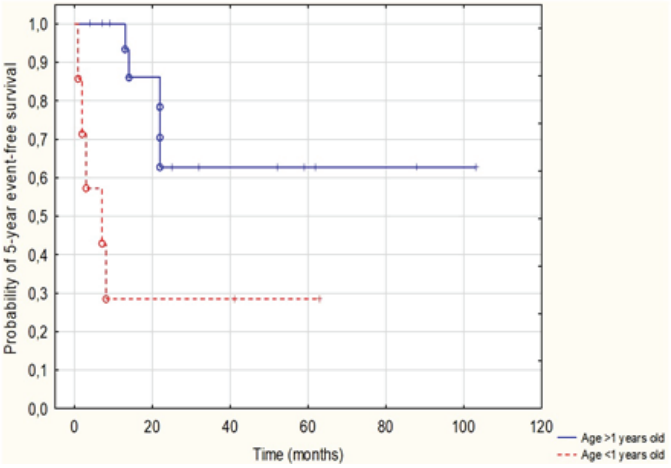

Figure 4: Probability of 5-year event-free survival (pEFS) for the study group depending on age (<1 year of age pEFS = 0.286, >1 year of age pEFS = 0.627); p = 0.020.

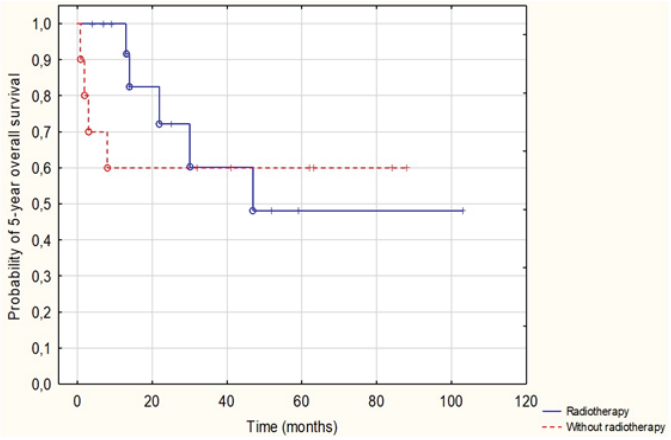

Figure 5: Probability of 5-year overall survival (pOS) in the study group depending on the use of radiotherapy. (pOS radiotherapy = 0.481; pOS without radiotherapy = 0.6); p = 0.7594.

Discussion

Soft tissue sarcomas are a very rare and diverse group of cancers. The small size of the study group indicates the need for multicenter observations. The analysis of the survival curves for the entire study group shows lower values of these parameters for soft tissue sarcomas, compared to other childhood cancers where the survival rate exceeds 70%.

The pOS and pEFS for the RMS-like group was 0.530 and 0.578, respectively. In literature, these indicators are analyzed separately for individual diagnoses and in the CWS analyses for tumors located in the Ewing sarcoma group that amount to 69% and 62%, respectively and for SySa, 90% and 84%, respectively [8]. Cash et al. analyzing non-disseminated Ewing sarcoma found even higher percentages of overall and eventfree survival rates with a pOS of 85% and pEFS of 76% [9]. However, in the analyses of synovial sarcoma, these values exceed the threshold of 80% [2,10].

The 5-year pEFS for the non-RMS-like group described by Dasgupta et al. differs depending on the surgical procedure performed from 15-20% in stage IV to 90% in patients in the low-risk group [11]. In the study group, this percentage was about 50% but as this group is very small, it is difficult to relate to it in statistical terms (Figure 2). The recurrence rate was also lower (12.5%), which was observed in one child. In the literature, this percentage is higher and reaches 15-45% [11]. In the analyzed group, the percent-age of patients with primary disease resistance was high, i.e., as much as 75%.

The patient's age is an important prognostic factor for STS. According to various analyses, older children had worse prognoses comparing to younger [1,8,11,12]. In the analysis carried out in the study group, pOS for children under 10 years of age was higher than for the group over 10 years of age (pOS = 0.692 vs. pOS = 0.350), but no statistically significant difference was found. On the other hand, the pEFS for children under 1 year of age was statistically significantly lower than for children over 1 year of age (pEFS = 0.286 vs pEFS = 0.627). This situation results from difficulties in achieving remission, as well as the inability to use radiotherapy in this age group of patients, which leads to local recurrences.

There was no statistically significant difference in the pOS score for patients treated with radiotherapy (pOS = 0.481) and those treated without radiation (pOS = 0.6). Radiotherapy is seen as an important part of combination therapy and its abandonment may contribute to local disease recurrence and treatment failure. However, based on prospective studies conducted on 529 patients, it was found that in the group of low-risk patients, adjuvant radiotherapy should be minimized [13]. This strategy minimizes the possibility of long-term side effects of radiation therapy.

Thanks to the introduction of combined treatment, i.e., multi-drug chemotherapy, modern radiotherapy, improvement of surgical techniques and the introduction of auto transplantation, treatment outcomes have improved significantly in recent

decades. Early diagnosis of the disease as well as immediate initiation of diagnosis and introduction of intensive treatment remain a challenge. Despite the wide therapeutic possibilities, the prognosis in patients with soft tissue sarcoma with the disease refractory and relapsing is still quite poor. Therefore, it is worth considering the diagnosis of soft tissue sarcomas based on genetic testing, which would enable the use of targeted therapy. The ongoing research on modern pharmaceuticals, with different target points than classic chemotherapy, gives a chance to further improve the results of treatment in the most difficult cases of soft tissue sarcomas. Attention is drawn to the wide and detailed attempts to use cytoreductive procedures in the treatment of advanced cancer forms with subsequent washing of the body cavities with cisplatin in a hyperthermic state. It is not a method that guarantees cure, but in the literature, it significantly extends the survival and comfort of patients [2,14-17].

References

1. Hawkins DS, Spunt SL, Skapek SX. COG Soft Tissue Sarcoma Committee. Children's Oncology Group's 2013 blueprint for research: soft tissue sarcomas. Pediatr Blood Cancer. 2013; 60(6): 1001-1008.
2. Hayes-Jordan A. Recent advances in non-rhabdomyosarcoma soft-tissue sarcomas. Semin Pediatr Surg. 2012; 21(1): 61-67.
3. Peinemann F, Smith LA, Kromp M, Carmen Bartel. Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas. Cochrane Database Syst Rev. 2013; 16(8).
4. Qureshi SS, Prabhu A, Bhagat M, Seema K, Tushar V, et al. Re-excision after unplanned resection of nonmetastatic nonrhabdomyosarcoma soft tissue sarcoma in children: Comparison with planned excision. J Pediatr Surg. 2017; 52(8): 1340-1343.
5. CWS 2006 A guidance for risk adapted treatment of soft tissue sarcoma in children, adolescents, and young adults, Version 1.3 vom 15.12.2006.
6. CWS-guidance for risk adapted treatment of soft tissue sarcoma and soft tissue tumours in children, adolescents, and young adults, Version 1.6.1. from 24.05.2014.
7. A multinational registry for rhabdoid tumors of any anatomical site EUROPEAN RHABDOID REGISTRY EU-RHAB, v. 2010.
8. Dantonello TM, Int-Veen C, Harms D, Ivo L, Bernhard FS, Manfred H, et al. Cooperative trial CWS-91 for localized soft tissue sarcoma in children, adolescents, and young adults. J Clin Oncol. 2009; 27(9): 1446-1455.
9. Cash T, McIlvaine E, Krailo MD, Stephen LL, Elizabeth RL, et al. Comparison of clinical features and outcomes in patients with extraskeletal versus skeletal localized Ewing sarcoma: A report from the Children's Oncology Group. Pediatr Blood Cancer. 2016; 63(10): 1771-1779.
10. Scheer M, Dantonello T, Hallmen E, Bernd B, Monika SS, et al. Synovial Sarcoma Recurrence in Children and Young Adults. Ann Surg Oncol. 2016; 23: 618-626.
11. Dasgupta R, Rodeberg D. Non-rhabdomyosarcoma. Semin Pediatr Surg. 2016; 25(5): 284-289.
12. Galyfos G, Karantzikos GA, Kavouras N, Argiri S, Konstantinos P, et al. Extraosseous Ewing Sarcoma: Diagnosis, Prognosis and Optimal Management. Indian J Surg. 2016; 78(1): 49-53.
13. Spunt SL, Million L, Chi YY, James A, Jing T, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020; 21(1): 145-161.
14. Hayes-Jordan A. Cytoreductive Surgery Followed by Hyperthermic Intraperitoneal Chemotherapy in DSRCT: Progress and Pitfalls. Curr Oncol Rep. 2015; 17(8): 38.
15. Angarita FA, Hassan S, Cannell AJ, Dickson BC, Gladdy RA, et al. Clinical features and outcomes of 20 patients with abdominopelvic desmoplastic small round cell tumor. Eur J Surg Oncol. 2017; 43(2): 423-431.
16. Honoré C, Atallah V, Mir O, Orbach D, Ferron G, et al. Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery? PLoS One. 2017; 12(2).
17. Fan HS, I'Ons B, McConnell R, Varahini K, Saleh A, et al. Peritonectomy and hyperthermic intraperitoneal chemotherapy as treatment for desmoplastic small round cell tumour. Int J Surg Case Rep. 2015; 7: 85-88.