research article

Treatment of rhabdomyosarcoma in children and adolescent from four low health expenditures average rates countries

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Background. Survival of children with cancer in Eastern and Central Europe is 10–20% lower than in high income European countries. We evaluated outcome of children and adolescents with rhabdomyosarcoma (RMS) in Slovenia, Croatia, Slovakia and in Romania.

Patients and methods. We retrospectively analysed event-free survival (EFS) and overall survival (OS) for all patients treated in Slovenia and Croatia. Slovakia included patients from two centers, representing half of expected cases. Romania included patients from single institution, representing only 10% of expected patients. Joint database for analysis was established.

Results. One hundred seventy-eight children and adolescent with RMS diagnosed from January 2000 to December 2015 were included. Mean patient age at diagnosis was 7.7 years, one third was older than 10 years. Twenty-five percent had alveolar histology and 72% unfavorable location. Higher than expected proportion of patients had nodal involvement (24%) or metastatic disease (27%). All patients received systemic chemotherapy, 57% had radiotherapy and 63% surgery as local control. Kaplan- Meier estimates for 5-year EFS and OS were 50.7% and 59.6%, respectively. Five-year OS for patients with localised disease was 72% compared to 24% for metastatic disease.

Conclusions. Children with RMS treated in Eastern and Central Europe have inferior outcome compared to their counterparts treated in high income European countries. Active participation of low health expenditures average rates (LHEAR) countries in international clinical trials may improve outcome of paediatric oncology patients.

Key words: rhabdomyosarcoma; low income country; outcome

Introduction

Cancer is diagnosed in more than 35.000 children and young adults across Europe each year.[1] Despite great improvement in treatment and care over last decades, cancer is still leading cause of death due to disease in this population. While 5-year survival rates are around 80% with best available therapy[2], survival in Eastern and Central Europe is 10–20% lower than in high income European countries.[3]

European Society of Pediatric Oncology (SIOPE) study confirmed lack of health care resources to ensure minimal standards of care for children with cancer as one of the main reasons for existing inequalities.[4]

ALL IC BFM 2002 trial is a role model for international collaboration between centers with limited resources and lower level of experience. Improved management of children with acute lymphoblastic leukemia was achieved with detailed treatment agenda and supportive care guidelines.[5]

Outcome of patients with soft tissue sarcomas is improved, if patients are treated according to established guidelines and in expert centers.[6] Quality of local control is critical point in therapy and is increased in specialized centers with high expertise.[6] We report outcome of children and adolescent with rhabdomyosarcoma in four low health expenditure average rate (LHEAR) countries.

Patients and methods

Patients

Study presents data from 178 patients aged 0–17 years with rhabdomyosarcoma treated in four LHEAR countries (Slovenia, Slovakia, Croatia, Romania) from January 2000 to December 2015. Data from Slovenia were extracted from National Cancer Registry and are population based. Data from Croatia were collected from all pediatric oncology hospitals in Croatia (two in Zagreb, Rijeka, Split) and cover entire population. Slovakia provided data from two centers (Department of Pediatric Oncology/Hematology, Children University Hospital, Bratislava and Kosice) and Romania from single center (Oncology Institute Cluj Napoca). Data were collected by first author in joint database.

We estimated expected number of patients from WHO International Incidence of Childhood Cancer 3 report (IICC-3).[7] In IICC-3 Slovenia has an annual average of 2.2; Croatia an annual average of 4.9; Slovakia an annual average of 5.9 and Romania an annual average of 28 children with soft-tissue sarcoma. Present study includes 25 cases from Slovenia (annual average 1.6), 73 cases from Croatia (annual average 4.5), 40 cases from Slovakia (annual average 2.5) and 39 cases from Romania (annual average 2.4). Number of cases reported in study from Croatia and Slovenia correspond to expected in population, approximately 50% of cases are reported from Slovakia and 10% from Romania. Slovenia has 2 million, Croatia 4 million, Slovakia 5,4 million and Romania 19 million inhabitants. Patients were eligible for this analysis, if diagnosis of rhabdomyosarcoma was confirmed by local pathologist. Disease staging included postsurgical tumor stage (IRS), age and size, histology, site, presence of nodal involvement or distant metastasis.

Treatment in Slovenia was based on Cooperative Weichteilsarcom Studiengruppe protocol (CWS); from 2011–2015 patients were enrolled in European Pediatric Soft Tissue Sarcoma Group protocol (5 cases) (EpSSG RMS 2005). Patients from Slovakia were treated according to International Society of Pediatric Oncology malignant Mesenchymal Tumor Group (MMT) guidelines; from 2006 patients were enrolled in EpSSG RMS 2005 protocol (16 cases). Croatia and Romania treated patients according to CWS protocols. Five patients from Croatia were treated according to RMS 2005 recommendations and 3 patients from Romania according to MMT protocols. Patients from Romania and Croatia did not participate in clinical trials.

Statistical methods

Disease staging included postsurgical tumor stage (primary complete resection (R0), microscopic residual (R1) or macroscopic residual/biopsy only (R2)), patient age and tumor size (favorable = tumor size < 5 cm and age < 10 years, unfavorable = tumor size > 5 cm and age > 10 years or < 1 year), histology (favorable = embryonal, spindle cell, botryoid, unfavorable = alveolar), primary tumor site (favorable = orbit, para-testicular, vagina/uterus, head/neck, unfavorable = para-meningeal, extremities, genitourinary bladder/prostate and other), presence of nodal involvement or distant metastases. Treatment included surgery (yes/no) and quality of resection (complete resection [R0], microscopic residual [R1] or macroscopic residual [R2]), chemotherapy (yes/no) and radiotherapy (yes/no).

Follow up was performed by pediatric oncologist at least 5 years after completed therapy or until 18 years old, whatever comes later.

Five-year overall survival (OS) and event-free survival (EFS) were estimated using Kaplan-Meier method with Pandas, Phyton data analysis library. The statistical significance of each variable was tested by log-rank test.

Results

Local pathologists classified 111 tumors (62%) as embryonal, 45 (25%) as alveolar, 10 (5%) spindle or botryoid RMS; for 12 cases histology subtype was unknown. Fusion status was determined in 21 (11%) tumors.

Mean patient age at diagnosis was 7.7 years (range 3 months to 17.9 years) (Figure 1). Fifty-

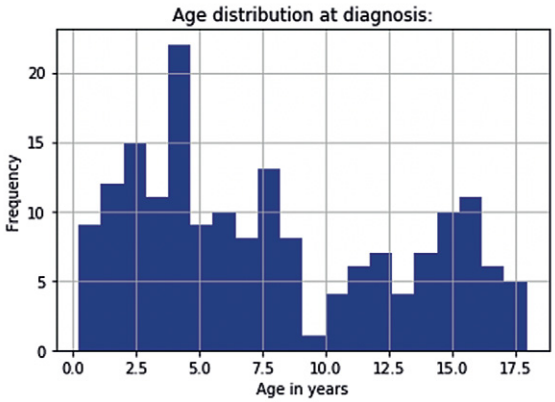

FIGURE 1. Age distribution at diagnosis.

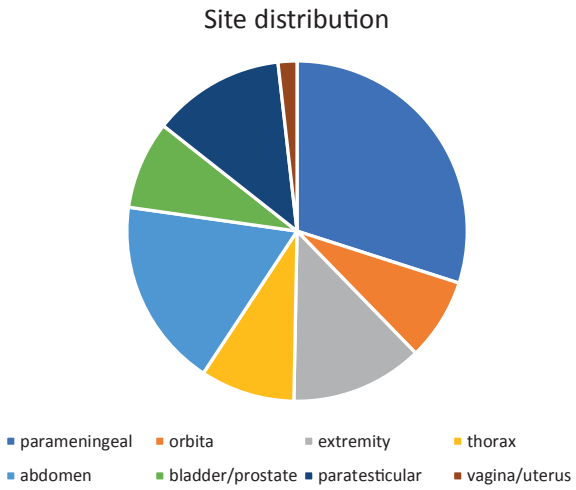

FIGURE 2. Site distribution.

eight patients (32%) were older than 10 years, 9 were infants.

Sixty-three patients (35%) presented with small tumors (< 5 cm) and favorable age. Nodal involvement was present in 67 patients (37%), 31 had localized disease. Metastases were diagnosed in 48 patients (27%), 9 had pulmonary metastases only.

Eleven patients had head/neck (6%), 50 parameningeal (28%), 13 orbit (7%), 21 extremity (12%), 15 thoracic (8%), 30 abdominal (16%), 14 bladder/prostate (8%), 21 para-testicular (12%) and 3 vaginal primary tumors (Figure 2).

All patients received chemotherapy.

Biopsy was only surgical procedure for 124 patients (70%) at diagnosis. Remaining 54 patients (30%) had primary surgery; 33 primary complete resection, 15 microscopic and 6 macroscopic residual disease. Secondary surgery was performed in 66 patients, 62 had biopsy at diagnosis, 4 patients had primary R1 resection. Complete resection was achieved in 24 patients, 23 had microscopic and 15 macroscopic residual disease. For 4 patients result of surgery is not known. Complete resection was most commonly achieved in patients with para-testicular, prostate/bladder, extremity and head and neck primary.

Radiotherapy was part of primary treatment in 102 patients (57%). Radiotherapy was omitted in 17/21 patients with para-testicular, 8/13 orbit, 11/14 bladder/prostate and 6/11 head/neck primary. Fourteen metastatic patients and fifteen (50%) with abdominal primary had no radiotherapy. Local control with radiotherapy was applied in 27 patients for the first time at relapse. Patient and disease characteristics are shown in Table 1.

For whole group 5-year OS was 59.6% (95% CI 51.8–66.6%) and 5-year EFS 50,7% (95% CI

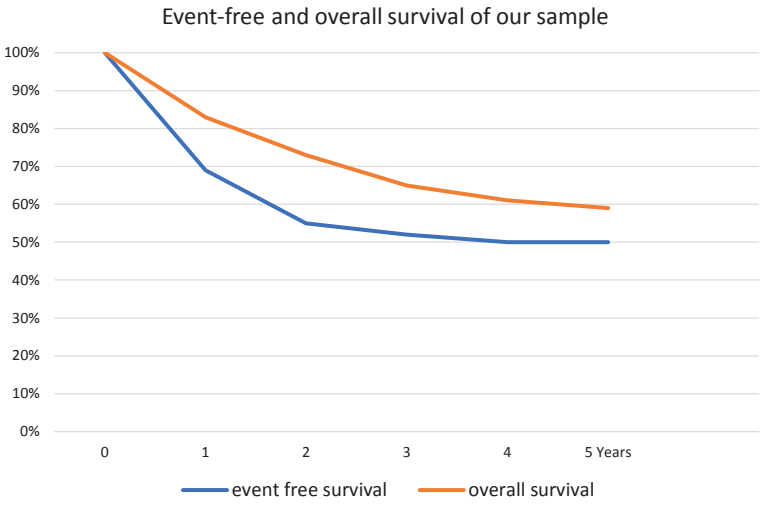

FIGURE 3. Event-free (EFS) and overall survival (OS) of investigated sample.

43.0–58.0%) (Figure 3). At median follow up of 5 years 106 patients were alive, 69 dead due to disease relapse or progression and 3 from toxic death. Patients with bladder/prostate (92%), orbit (72%) and para-testicular (81%) primary had highest OS and those with thoracic primary poorest outcome (40%). Survival in patients with head and neck (54%), para-meningeal (55%), extremity (47%), abdominal and pelvic primaries (48%) was around 50%.

In the study 15/21 of children with para-testicular rhabdomyosarcoma were older than 10 years and had additional poor prognostic signs (6 alveolar histology, 9 lymph node involvement, 4 metastatic disease). Only 6 children with para-testicular RMS fulfilled criteria for low risk group and had

TABLE 1. Patient and disease characteristics

Country	Slovenia	Croatia	Slovakia	Romania
Number (pt)	25	72	40	41
Age < 1 year	1	2	3	3
Age > 10 years	8	21	12	17
Favourable histology	19	41	31	30
Unfavourable histology	5	21	8	11
Primary surgery				
Biopsy	20	50	28	26
R0	2	19	4	8
R1	1	3	8	3
R2	2	NA	NA	4
Site				
Orbit	2	3	7	1
Paratesticular	1	6	8	6
Vagina/uterus	1	1	1	NA
Head/neck	NA	3	2	6
Parameningeal	12	22	3	13
Extremity	NA	7	9	5
Abdomen	NA	19	6	5
Thorax	7	5	1	2
Bladder/prostate	2	6	3	3
Size (> 5 cm)	13	44	32	24
Nodes +	6	31	12	18
Metastases +	6	24	13	5
RT	21 (84%)	39 (54%)	21 (52%)	21 (51%)
RTsalvage	2	13	5	7
Secondary surgery	7	29	18	12
R0	1	11	9	3
R1	5	6	4	8
R2	1	12	1	1
Primary+secondary surgery	12 (48%)	51 (70%)	26 (65%)	27 (65%)
Alive	**16 (64%)**	**44 (61%)**	**23 (57%)**	**23 (56%)**

Pt = patients; RT = radiotherapy; RTsalvage = salvage radiotherapy

excellent 5-year OS (100%). Local control in parameningeal primaries was not optimal, since nobody had surgery and 10/50 had no radiotherapy. Radiotherapy was not part of primary therapy in 8/13 of patients with orbital RMS. Radiotherapy at relapse salvaged only 1/4 patient, 3 died despite further treatment with chemoradiotherapy. Outcome for patients with bladder/prostate primary was excellent, but extent of surgery and mutilation was not reported. Last 3 patients in the study patients were managed in expert foreign centre with combined organ preservation surgery and brachytherapy.

Patients with embryonal histology (5-year OS 62% embryonal *vs.* 48% alveolar, P = 0.003) and favorable size and age (5-year OS 76% favorable *vs.* 51% unfavorable, P = .001) had better outcome.

5-year OS for 130 patients with localized disease was 72% compared to 24% for metastatic patients. Survival of subgroup of patients with pulmonary metastases only was better compared to other metastatic patients (33% *vs.* 21%, P = 0.02). All metastatic patients treated without radiotherapy died.

Twelve patients out of 27 irradiated as salvage at relapse survived; patients had either orbit, head and neck, para-meningeal, para-testicular, bladder/prostate or vaginal primary.

5-year OS of patients with localized disease treated with or without radiotherapy (77% *vs.* 72%, P = 0.53) was similar. Outcome of patients with surgical resection was better (5-year OS 70 *vs.* 48%, P = 0.001) and depended on quality of surgical resection (R0 90% *vs.* R1 66% and R2 50% 5-year OS, P = 0.001). Complete resection was most commonly achieved in patients with para-testicular, prostate/bladder, extremity and head/neck primary. There are no data regarding mutilation after surgery.

Discussion

Our study supports previous reports of lower survival of pediatric cancer patients in Eastern and Central Europe.[3] OS for the whole group was close to 60%, with high proportion (27%) of metastatic patients and patients with advanced localized disease (24%). Nodal involvement in localized disease was almost two times higher compared to MMT 89 (13%)[8] and RMS 2005 study (15%).[9] In large cohorts approximately 15% of patients with rhabdomyosarcoma had metastases.[10,11] Survival rate of patients with metastatic disease in our study was also lower from published analysis of pooled metastatic patients from Europe and United States (24% *vs.* 34% 5-year OS).[12]

Survival of patients with localised disease (72%) is almost 10% lower than in recently presented RMS 2005 study, where 5-year OS reached 80%.[9] Patients with localized disease have comparable survival to high-risk patients treated in recent RMS 2005 study[13] or with survival in MMT 89 study (5-year OS 71%) where 50% of survivors were treated without significant local therapy.[8]

Less than two thirds of the patients (57%) were treated with radiotherapy as part of primary treatment. Results from previous studies and recent RMS 2005 show that about 30% of children with RMS can be cured without radiotherapy.[11,14-17] Omitting radiotherapy in patients with para-testicular, bladder/prostate, head/neck and orbital primary was in line with MMT protocols. Patients with abdominal, thoracic or para-meningeal primary and metastases were not eligible for radiotherapy due to progressive disease, unacceptable toxicity for local radiotherapist or unavailable general anesthesia for small children. Without radiotherapy adequate local control cannot be achieved in substantial proportion of children with soft tissue sarcoma.[14-17] There is difference between participating countries in number of patients irradiated (Table 1). High percentage (84%) of irradiated patients in Slovenia is consequence of longstanding tradition of pediatric radiotherapy and site distribution. Multidisciplinary team for pediatric cancer patients in Slovenia (pediatricians, radiation oncologist, cytologist/pathologist, surgeons) was established in 1960s by founding member of SIOP, prof. B Jereb.[18]

Small proportion of children with orbital, head and neck, para-meningeal, testicular, bladder/prostate and vaginal primary tumor were salvaged with use of radiotherapy at relapse.

Majority of patients had biopsy only at diagnosis. Primary surgery was less common than secondary. Two thirds had surgery for local control at any point of treatment. Most patients with unfavorable site (para-meningeal and trunk location) had no surgery. Surgical resection was performed in 2/3 of patients in Croatia, Slovakia and Romania and only in half of patients in Slovenia; unfavorable site distribution precluding surgery (80% para-meningeal and thoracic primary). Quality of resection, with 84% of patients achieving R0 or R1 resection, is comparable with data in MMT 89 study.[8] Para-testicular, prostate/bladder, extremity and head/neck primaries were most common accessible for complete excision.

Distribution according to site was as expected, with half of the patients presenting with tumor in head and neck region, majority being para-meningeal. Genitourinary region was second most frequent site (20%). Outcome of patients with para-testicular, orbit and para-meningeal primary was lower than expected. Children with para-testicular RMS in our study were older, with unfavourable histology and disseminated disease. Those in low risk group had excellent survival as expected.[19,20] Poor local control compromised outcome of patients with para-meningeal RMS.[21-23] In RMS 2005 study there was substantial gap between EFS (77%) and OS (94%) for patients with orbit primary, most patients were salvaged by additional chemoradiotherapy. This was not repeated in our study, since only 1/4 patients survived. Outcome for bladder/prostate primary was comparable to published results, probably more mutilating surgeries were performed without concomitant radiotherapy.[24]

Relation of local control modality on outcome was not assessed for other variables, such as tumor site and size, nodal or metastatic disease and is thus of limited value.

This study has major limitations. Data for Slovakia and Romania are not population based and are thus source of selection bias, precluding firm conclusions. Lack of standardized diagnostic and therapeutic protocol reflects in poor quality of the data and therefore suboptimal statistical analysis.

Improved outcome for patients with rhabdomyosarcoma observed in high income European countries over the last three decades is the result of well-designed protocols based on a multidisciplinary approach and prospective data collection[25], which results in standardization of diagnostic procedures, chemotherapy protocols, radiotherapeutic and surgical guidelines and supportive measures. Unfortunately substantial number of children from member states of European Union are not included in academic (therapy optimization) trials. This results not only in inferior treatment outcomes, but also loss from scientific standpoint as data from this group of patients are not used for therapy optimization trials. Our retrospective analysis of data from four countries should be seen as a step towards activation and motivation of pediatric oncology centers in LHEAR European countries to more active participation and involvement in clinical research work in the field of pediatric oncology.

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