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Research Article

Treatment results in childhood cancer between 1996-1999 in a Cancer Center in Romania – A transition period

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Abstract. Objective: Improved diagnostic and treatment methods in childhood cancer determined a significant increase in survival in the last decades. Despite these important progresses there is still a significant difference in survival between developed countries compared to developing and underdeveloped countries. For more insight in these differences we studied treatment results of the Pediatric Department of the Institute of Oncology "Prof. Dr. I. Chiricuta" from Romania between 1996-1999. Material and Methods: We included 202 patients under the age of 18 treated for malignant tumors. Data about diagnosis, treatment, acute toxicities, treatment response, relapse, second cancer were extracted from patient files. Results: From the 202 patients included in our study 84 (41.6%) were diagnosed with malignant blood disorders and 118 (58.4%) with solid tumors. After completing the primary treatment, 146 patients (72.3%) showed complete response, 14 patients (6.9%) showed partial response, 6 patients (3%) showed stable disease, and 36 patients (17.8%) showed progressive disease. The median follow-up was 245.9 months (20.5 years). OS at 20 years was 58% for the entire studied group (CI: 51-64%), while DFS was 53% (CI: 46-60%). The second neoplasia was diagnosed in 3 patients (1.48%) of the studied group. Conclusion: Our data show promising results, however lower than in developed countries in the same period. Our results might be helpful to National Health Care providers in order to establish policies to improve access to treatment and implementation of therapeutic protocols in order to improve survival in transition periods.

Key Words: childhood cancer, survival, developing countries, middle-income, second malignancy

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Introduction

Pediatric cancers represent a rare pathology, but at the same time they represent the main cause of children's death in developed countries. According to GLOBOCAN, in 2018, 200.166 new cases were diagnosed worldwide in children between 0-14 years, with higher rates of incidence being recorded in developed countries. The reported incidence by the National Register of Childhood Cancer in Romania for the same year was of 11.03 per 100.000 children (National Childhood Cancer Registry 2019). The overall age-standardized rate of childhood cancer is 155.8 per million person-years in children aged 0–19 years (Steliarova-Foucher et al 2017). Registration and reporting are deficient in developing and underdeveloped countries, reason why accurate measuring of incidence in these countries is difficult.
The main pathologies in pediatric oncology are represented by leukemia and lymphomas (41%), central nervous system tumors (17%), soft tissue and bone sarcomas (8%), and neuroblastomas (5%) according to literature (Wang et al 2011).
Early diagnosis is in many cases not possible due to unspecific symptoms, similar to those found in common pediatric pathology. Parents and medical professionals have to have a high grade of suspicion so that early diagnose and treatment can be possible (Fragkandrea et al 2013).
Treatment in pediatric oncology is multimodal (chemotherapy, radiotherapy, surgery) and it depends on histological subtype and stage of the disease. Taking into account that this is a rare pathology, the best results are obtained in highly specialized-centers with experience in treatment of pediatric cancers. In developed countries treatment is managed by a team formed by pediatric oncologist, radiation oncologist, surgeon, specialist nurses, social workers and psychologist (Dobrozsi et al 2019).
Improving diagnostic and treatment methods determined a significant increase in survival in the last decades. In 1970 survival rates of approximately 50% were reported, today long-term survival rates higher than 80% are reported in the literature(Jamal et al 2010, Howlader et al 2013; Ward et al 2014, Stiller et al 2018). Despite the important progresses recorded in the last decades, there is a significant difference between specific mortality recorded in developed countries (under 20 in one million children) compared to those recorded in developing countries

(approximately 50 in one million children) and underdeveloped countries (approximately 70 in one million children) according to data from Ferlay et al (2010).

The purpose of this paper was to evaluate results of oncologic treatments applied to children between 1996-1999 in the Institute of Oncology "Prof. Dr. Ion Chiricuta" Cluj-Napoca (IOCN). The main objective was to evaluate overall survival and progression free survival. Secondary objectives were to evaluate the interval between symptom onset and first medical consult and time between first medical consult and establishment of the diagnosis; evaluation of acute toxicities, incidence of the second cancer.

Patients and methods

We included in this retrospective study patients under the age of 18 diagnosed with malignant tumors and who were treated on the Pediatric Department of IOCN between January 1996 and December 1999. Patients were excluded from the study if their primary treatment was performed in other cancer centers, if patients' files were incomplete or lost, if parents refused oncologic treatment or if treatment was abandoned prematurely. The study was approved by the Ethics Committees of Iuliu Haţieganu University of Medicine and Pharmacy.

The following information were extracted from patient files:

- Demographic data
- Clinical data
- Oncologic diagnosis
- Oncologic treatment: therapeutic sequence, chemotherapy protocol used (optimal/suboptimal doses and timing), radiotherapy (optimal/suboptimal dose and fractionation), optimal/suboptimal surgery
- Acute toxicities
- Treatment response: clinical and imagistic evaluation
- Relapse
- Treatment for relapse
- Response to relapse treatment
- Late toxicities
- Long term sequels of the treatment and disease
- Second cancer
- Date of last follow-up visit and treatment response status at last follow-up visit
- Date of death and cause of death

Out of the patients examined in IOCN between 1996 and 1999, 403 were identified as potentially eligible for this retrospective analysis. We excluded from this study: seventy patients that received primary treatment outside IOCN (in our Institute they received only the radiotherapy sequence or treatment for relapse); 83 patients with incomplete or missing files; 8 patients older than 18 years at diagnosis; 11 patients for which the parents refused treatment, 27 patients who abandoned primary treatment; 2 patients for whom the diagnosis of malignancy was not confirmed. After the exclusion of ineligible patients, 202 patients were included in the final analysis.

Adverse events of grades 3 and 4 - in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 - were recorded.

Survival curves were calculated with the Kaplan Meier method, considering the interval from the date of beginning of treatment until death or end of study (5 July 2018). The statistical analysis was performed with the STATA package (2013, STATA Statistical Software 13 ed; Stata Corporation, College Station, Texas, USA).

Results

The study includes 202 patients who were treated in the Pediatric Department of IOCN between January 1996 and December 1999. Median age at diagnosis was 8, with an age interval of 0 to18. A number of 103 males (51%) and 99 females (49%) were treated.

Types of cancers present in the studied group

Eighty-four patients, representing 41.6% of all patients included in the study, were diagnosed with malignant blood disorders. Forty-two patients (20.8%) were diagnosed with lymphomas. The proportion between Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL) was equal (21 patients each). Thirty-four patients (16.8%) were diagnosed with acute lymphoblastic leukemia (ALL) and only eight patients (4%) with acute myeloblastic leukemia (AML).

One hundred eighteen patients, representing 58.4% of all patients included in this study, were treated for solid tumors. Most frequent solid tumors in our patients were central nervous system tumors – 35 patients (17.3%), nephroblastoma – 17 patients (8.4%), soft tissue sarcomas – 13 patients (6.4%), of which 7 with rhabdomyosarcomas (RMS), bone sarcomas – 12 patients (5.9%), of which 5 with osteosarcomas and 5 with Ewing sarcomas, thyroid carcinomas – 10 patients (5%). Other solid tumors diagnosed and treated were: germinal testicular tumors – 8 patients (4%), nasopharynx carcinoma – 8 patients (4%), neuroblastoma – 6 patients (3%), retinoblastoma – 5 patients (2.5%). Out of the studied group, three patients (1.5%) were diagnosed with adult oncologic pathology: one patient with polyposis was diagnosed and treated for a mucinous adenocarcinoma of the colon, one patient for kidney carcinoma with clear cells, while the third one was treated for spinocelular carcinoma of the skin.

Interval between symptom onset and diagnostic

The time between symptom onset and first medical consult, and the interval between first medical consult and diagnosis was analyzed. One hundred and forty-seven (72.8%) patient files that included these data were identified.

The time interval between symptom onset and first medical consult varied largely between 0 and 1129 days, with a median of 14 days and a mean of 45 days.

The time interval between the first medical consult and the diagnosis varied between 0 and 906 days, with a median of 34.5 days and a mean of 67.6 days.

Of the 34 patients who were diagnosed and treated at IOCN for ALL, 26 had data in their files about symptom onset, the first medical consult and the date of the diagnosis. The majority (12 patients) presented to the doctor in the first 7 days from symptom onset, 3 patients at 8 to 14 days from symptom onset, and 10 patients at more than 2 weeks after symptom onset. For 10 patients the time between the first medical consult and diagnosis was less than 7 days, for 6 patients the interval was between 8 and 14 days, and for 10 patients it was greater than 14 days.

Twenty-four out of 35 patients with CNS tumors had data about symptoms onset, first medical consult and date of diagnosis recorded in their files. Six patients had the first medical consult in less than 24 hours from symptom onset, 4 patients between

Table 1. Grade 3 and 4 adverse reactions to chemotherapy depending on malignancy type

Adverse reactions	ALL[1]	Lymphoma	Nephroblastoma	Soft tissue sarcoma	CNS[2]	Others	Total
Anemia	18 (36%)	10 (20%)	4 (8%)	1 (2%)	2 (4%)	15 (30%)	50
Neutropenia	25 (37.9%)	15 (22.7%)	8 (12.1%)		4 (6.1%)	14 (21.2%)	66
Leucopenia	20 (38.5%)	11 (21.2%)	6 (11.5%)	1 (1.9%)	4 (7.7%)	10 (19.2%)	52
Thrombocytopenia	25 (59.5%)	5 (11.9%)	3 (7.1%)		3 (7.1%)	6 (14.3%)	42
Neurotoxicity	1 (33.3%)	1 (33.3%)	1 (33.3%)				3
Febrile neutropenia	1 (20%)	2 (40%)			1 (20%)	1 (20%)	5
Elevated liver enzymes	6 (54.5%)	1 (9.1%)	1 (9.1%)			3 (27.3%)	11
Paralytic ileus	4 (50%)	2 (25%)		1 (12.5%)		1 (12.5%)	8
Hyponatremia	3 (100%)						3
Allergic reaction	4 (36.4%)	4 (36.4%)				3 (27.3%)	11
Acute kidney failure		1 (50%)			1 (50%)		2
Nausea		1 (16.7%)			1 (16.7%)	4 (66.7%)	6
Mucositis		1 (33.3%)	1 (33.3%)		1 (33.3%)		3

[1] ALL - acute lymphoblastic leukaemia; [2] CNS - central nervous system

24-72 hours. For seven patients the interval between symptom onset and first medical consult was less than 30 days and for 6 patients between 30 days and one year. One patient sought medical attention only after 1129 days from symptom onset. Diagnosis was established in less than 7 days for 7 cases, between 7 and 30 days for 5 cases, between 31and 123 days for 11 cases. One patient was diagnosed after 906 days from the first medical consult.

Performance status

One hundred twenty-two patients (65.3%) had the performance status (ECOG Scale) at admission documented in the files. Sixty-four patients (48.3%) had a performance status of 0 or 1, and 68 patients (51.7%) had a performance status equal or greater than 2.

Treatment

Acute lymphoblastic leukemia

Patients diagnosed with ALL were treated according to ALL-BFM (Acute Lymphoblastic Leukaemia – Berlin-Frankfurt-Muenster) 90 protocol. Until the beginning of the year 1999, the consolidation phase consisted of administration of 6-mercaptopurine and oral low dose Methotrexate associated with prophylactic cranial irradiation (27 patients). Starting with 1999, the consolidation phase consisted of the administration of 6-mercaptopurine and high-dose intravenous methotrexate (7 patients).

Lymphoma

Eleven (52.4%) patients with HL were diagnosed with early stage (3 patients with stage I and 8 patients with stage II) and 10 patients (47.6%) were diagnosed with advanced disease (4 patients with stage III and 6 patients with stage IV).All patients were treated with the ABVD protocol (doxorubicin, bleomycin, vinblastine, dacarbazine). Patients with stages III and IV received external radiotherapy after chemotherapy.

Patients diagnosed with NHL represent a heterogenous group. Of the 21 patients diagnosed with NHL, seventeen (80%) had aggressive and very aggressive forms (10 patients with Burkitt Lymphoma, 5 with precursor B cell lymphoblastic Lymphoma, 1 patient with diffuse large B cell lymphoma, 1 patient with immunoblastic lymphoma with T cells). The treatment regimens used were Bleo-CHOP, CHOP, NHL-BFM-90.

Nephroblastoma

Of all patients diagnosed with Nephroblastoma, 2 had stage I disease, 8 patients stage II disease, 5 stage III and 2 patients had metastatic disease at diagnosis. All patients were treated according to the SIOP (Society of Pediatric Oncology) 93 protocol using the following cytotoxic agents: vincristine, doxorubicin, actinomycin.

Central nervous system tumors

The study included 35 patients with tumors of the central nervous system.

Twelve were diagnosed with posterior fossa Medulloblastoma, a majority of these patients (10 patients) receiving multimodal treatment (surgery, adjuvant craniospinal radiotherapy and chemotherapy), while two patients didn't undergo adjuvant treatment after surgery.

Six patients were diagnosed with low grade astrocytoma and underwent surgery followed by adjuvant radiotherapy.

Eight patients were diagnosed with anaplastic astrocytoma and received adjuvant radiotherapy and chemotherapy with vincristine and lomustine.

One patient was diagnosed with glioblastoma and received adjuvant radiotherapy after surgery. Seven patients had unresectable tumors (5 in the brainstem and 2 patients had thalamic tumors). Four patients underwent external radiotherapy and three patients received radiotherapy associated with chemotherapy.

Soft tissue sarcomas

Thirteen patients with soft tissue sarcomas were included in this study and 7 (53.8%) of them were diagnosed with RMS. Of the latter, 4 patients had unfavorable histology (alveolar) and 3 had favorable histology (embryonal). All patients received chemotherapy according to the CESS 91 protocol. With regard to the local treatment: three patients received combined local treatment - surgery followed by adjuvant radiotherapy, two patients underwent only surgery, and two patients received only

Table 2. Response to primary treatment based on diagnosis

Diagnosis/Response	CR[1]	PR[2]	SD[3]	PD[4]	Total
ALL[5]	27 (79.4%)		1 (2.9%)	6 (17.6%)	34
AML[6]	4 (50%)			4 (50%)	8
Lymphoma	36 (85.7%)	2 (4.8%)		4 (9.5%)	42
CNS[7] tumors	21 (60%)	7 (20%)	2 (5.7%)	5 (14.3%)	35
Nephroblastoma	14 (82.4%)	1 (5.9%)		2 (11.8%)	17
Soft tissue sarcoma	10 (76.9%)			3 (23.1%)	13
Thyroid carcinoma	8 (80%)		1 (10%)	1 (10%)	10
Bone sarcoma	7 (58.3%)	1 (8.3%)		4 (33.3%)	12
Neuroblastoma	3 (50%)	1 (16.7%)		2 (33.3%)	6
Nasopharyngeal carcinoma	5 (62.5%)	1 (12.5%)	2 (25%)		8
Germ cell tumors	6 (75%)	1 (12.5%)		1 (12.5%)	8
Malignant neurofibroma				1 (100%)	1
Retinoblastoma	3 (60%)			2 (40%)	5
Rectum adenocarcinoma				1 (100%)	1
Clear cell kidney carcinoma	1 (100%)				1
Spinocellular carcinoma	1 (100%)				1
	146 (72.3%)	14 (6.9%)	6 (3%)	36 (17.8%)	202

[1] CR - complete response; [2] PR - partial response; [3] SD - stable disease; [4] PD - progressive disease; [5] ALL - acute lymphoblastic leukaemia; [6] AML - acute myeloblastic leukaemia; [7] CNS - central nervous system

radiotherapy with curative intent. The patients with non-RMS tumors represent a heterogenous group: 3 patients with fibrosarcoma, 1 with synovial sarcoma, 2 with alveolar sarcoma, and 1 with liposarcoma. Only local treatment (surgery) was performed for incipient stages of the disease, while for the advanced stages adjuvant radiotherapy was associated, in accordance with the CESS-91 protocol.

Thyroid cancer

All the patients included in the study underwent total thyroidectomies followed by the administration of radioactive iodine.

Adverse events to chemotherapy

The most common acute adverse events to chemotherapy were related to haemato-toxicity: 66 patients (32.6%) presented at least one episode of 3rd or 4th degree neutropenia, 52 patients (25.7%) presented at least one episode of 3rd or 4th degree leukopenia, 50 patients (24.7%) presented at least one episode of 3rd or 4th degree anemia, and 42 patients (20.7%) presented at least one episode of 3rd or 4th degree thrombocytopenia.

Chemotherapy was stopped for 11 of the patients as they presented 3rd or 4th degree allergic reactions to the cytostatic medication (asparaginase, carboplatin, etoposide).

Two patients suffered from acute renal failure, requiring dialysis: the first one following the treatment with cisplatin, and the second one following the treatment with high-dose methotrexate (Table 1).

Response to treatment

After completing the primary treatment, 146 patients (72.3%) showed complete response, 14 patients (6.9%) showed partial response, 6 patients (3%) showed stable disease, and 36 patients (17.8%) showed progressive disease. The results of the primary treatment based on diagnosis are shown in Table 2.

Overall survival and disease-free survival

The median follow-up was 245.9 months (20.5 years) with an interval between 2 and 273.7 months. Of the 202 patients included in the study, 114 (56,4%) patients are alive. There were 88 (43.5%) registered deaths, 85 of which (42%) were due to the oncologic pathology.

The overall survival (OS) at 20 years was 58% for the entire studied group (Confidence interval (CI): 51-64%), while the disease-free survival (DFS) was 53% (CI: 46-60%) - Figure 1. OS and DFS were analyzed for the main treated sites. The best results were obtained in patients diagnosed with thyroid carcinoma, with an OS of 100% and a DFS of 80%. Patients treated for lymphomas had an OS of 76% and a DFS of 67%. For nephroblastoma patients the OS was 71% and the DFS was 65%, while patients with tumors of the CNS had an OS of 50% and a DFS of 48% at 20 years. Soft tissues sarcomas had an OS of 58% and a DFS of 51%. The lowest OS and DFS of the entire group were recorded for patients treated for ALL – 38%.

The second neoplasia

The second neoplasia was diagnosed in 3 patients (1.48%) of the studied group.

A patient who had previously been treated for mandibular Ewing Sarcoma, was diagnosed 8 years after the first diagnosis with Ewing Sarcoma of the proximal third of the right femur (stage IV with pulmonary metastases) for which he received palliative chemotherapy, but died later due to the second neoplasia.

The second patient has been first diagnosed with a tumor in the brainstem which was treated with radio-chemotherapy. After 3

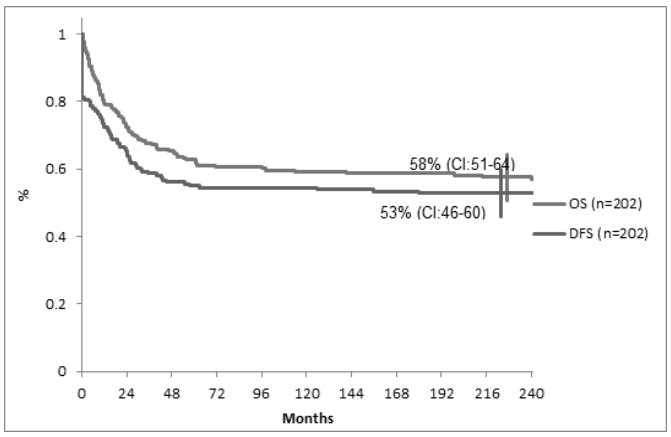

Fig. 1. Overall survival and disease-free survival for the entire studied group

years he was diagnosed with advanced loco-regional thyroid papillary cancer which was treated surgically with a complete thyroidectomy followed by treatment with radioactive iodine which resulted in a complete response and is alive.

The third patient had been diagnosed during childhood with NHL for which he received chemotherapy. Six years after the diagnosis of the first neoplasia, he was diagnosed with stage IV non-differentiated Nasopharyngealcarcinoma which was treated with radio-chemotherapy, but he later died due to the second cancer.

Discussion

Pediatric cancers represent an important health issue around the world. In developed countries pediatric cancers represent the first cause of death for children between 5 and 14 years of ageaccording to GLOBOCAN (2018), however, 84% of pediatric cancers are diagnosed in developing and under-developed countries as shown by Magrath et al (2013).

The difference between the results obtained in developed versus developing countries in the treatment of pediatric cancers is well known in the literature. There are multiple causes for these differences, some of the most important among them being: difficult access to specialized centers, lack of multimodal teams, lack of cheap medication which is essential for long term treatment, lack of radiotherapy centers, migration of specialists to the developed countries, low adherence of parents to treatment schemes due to financial difficulties (Magrath et al 2013). Many of these causes can be found in our country.

The Pediatric Department of IOCN was established in 1983 by Prof. Dr. Ion Chiricuță and in the beginning few of the treated patients survived. The use of European protocols for the treatment of pediatric oncology patients was started in 1996, as such the period analyzed in this study is, in fact, the implementation and learning period for these new protocols. This period was marked by issues independent of the will of the medical staff: the prolonged lack of essential medication, such as doxorubicin, bleomycin, dacarbazine, vincristine, vinblastine, calcium leucovorin, as well as the reduced patients' adherence to the prescribed treatments.

It is often considered that prolonging the time interval between the first symptoms and establishing the diagnosis of malignancy negatively influences the patients' survival, due to diagnosis at an advanced stage. However, quantifying the negative impact on survival and mortality is difficult (Neal et al 2009). The length of the interval depends on multiple factors with the main ones being tied to:tumor type and localization, factors which are dependent on the patient/family (these influence mainly the interval between the first symptoms and the first medical consultation) and factors which are dependent on the medical system (these influence the interval between the first medical consultation and the diagnosis date). Other studies show similar results, with large time intervals between the symptom onset and the oncologic diagnosis: a study performed in Sweden reported an interval of 1 to 1393 days with a median of 35 days from symptom onset to the first consultation, and a median of 21 days from the first consultation to diagnosis according to Thulesius et al (2000); another study performed in Singapore reported an interval of 1to 1982 days between symptom onset and diagnostic with a median of 21 days between the first symptoms and the first consultation and a median of 8 days between the first consultation and the diagnosis(Loh et al 2012). No limit was established for the interval between symptom onset and the diagnosis of malignancy, over which time will be to the detriment of the patient as shown by Lethaby et al (2012).

Over 50% of the patients in the studied group had a performance index greater of, or equal to two at admission in the IOCN, which often demonstrates a prolonged interval between the onset of symptoms and the start of treatment.

The results of oncological treatments in children show large variations across Europe. Several population studies were carried out based on the national and regional registries of several European countries in order to evaluate the OS at the level of the entire Europe and to compare the results in various regions. Worth mentioning is the fact that Romania is not present in any of these population studies. Data from Eastern Europe are represented in the majority of studies by the cancer registries of Estonia, Poland, Slovenia, and Slovakia.(Gatta et al 2005, Gatta et al 2014)

In 2005 the EUROCARE study group reported for the period 1983-1994 an increase in OS at 5 years for the entire Europe from 65% between 1983-1985 to 75% between 1992-1994; in Eastern Europe the overall survival increased from 50% to 66%; the best results were obtained in the Nordic countries (Finland, Norway, Sweden) according to data from Gatta et al (2005).

Another study reported for the period 1990-1994 survival rates of 60-70% at 5 years in Eastern Europe and over 75% in the Nordic countries. While Nordic countries represent a golden standard with survival rates at 5 years of 92% for nephroblastoma, 85% for ALL, 73% for cerebral tumours, and 62% for AML, the eastern countries (represented in this study by Estonia, Poland, Slovenia, Slovakia, and Czechia) have the lowest survival rates at 5 years: 89% for Hodgkin Lymphoma, 71% for nephroblastoma, 68% for ALL, 57% for cerebral tumors (Gatta et al 2003).

The results of the EUROCARE-5 study published in 2014 reports an OS for children diagnosed in the period 2000-2007 of 77.9% for the entirety of Europe and mentions the greatest improvements in Eastern Europe, where overall survival at 5 years increased from 62.5% between 1991-2001 to 70.2% between 2005-2007 (Gatta et al 2014).

In this study we present the results of the PediatricDepartment of IOCN during the implementation period of the European protocols. The OS of 58% for all cancers at 20 years can be

considered as an encouraging result considering the learning curve and the difficulties faced at the time. The lowest survival rates were observed in the studied group for the patients diagnosed with ALL (OS of 38% at 20 years). The interpretation of this result should consider the fact that only since the beginning of 1999 has high-dose methotrexate treatment been in use, which is why a significant increase in overall survival is expected in the next years.

For other types of cancers, the results we report are not strikingly different from does reported in other eastern European countries (represented only by Poland and Czech Republic) for the same period of time according to the EUROCARE-4 study, however there is still an important difference in OS. For CNS tumors we report an OS at 20 years of 50% versus 57.6% at 5 years. Patients with nephroblastoma had a 71% OS at 20 years versus 83% at 5 years for Eastern Europe in EUROCARE-4 study (Gatta et al 2009). These comparations must be viewed with caution due to the major difference in the studied populations: single institution vs cancer registries, ages 0-18 years vs 0-14 years, overall survival at 20 years vs 5 years.

Thyroid cancer has similar OS and DSF and those reported in the literature (Hesselink et al 2016).

It is worth mentioning that a large proportion of patients in the studied group presented at least one 3rd or 4th degree adverse reaction during chemotherapy, but there were no treatment related deaths.

Most cancers in children are curable. The most important factors influencing their survival are: the access to treatment and the application of current therapeutic protocols.

The objective at institutional and national levels is to continue improving results by implementing European treatment protocols.

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