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Clinical characteristics and outcome of pediatric patients diagnosed with Langerhans cell histiocytosis in pediatric hematology and oncology centers in Poland

Anna Raciborska[1*], Katarzyna Bilska[1], Jadwiga Węcławek-Tompol[2], Olga Gryniewicz-Kwiatkowska[3], Małgorzata Hnatko-Kołacz[4], Joanna Stefanowicz[5], Anna Pieczonka[6], Katarzyna Jankowska[7], Filip Pierelejewski[8], Tomasz Ociepa[9], Grażyna Sobol-Milejska[10], Katarzyna Muszyńska-Rosłan[11], Olga Michoń[12], Wanda Badowska[13], Monika Radwańska[14] and Katarzyna Drabko[15]

Abstract

Background: Langerhans cell histiocytosis (LCH) affects 1–2 in 1,000,000 people. The disease is not associated with increased risk of treatment failure (especially among older children), but appropriate procedures implemented in advance can eliminate complications which might appear and significantly worsen the patients' quality of life. Thus, we sought to evaluate the clinical features, management, and outcome of children with LCH treated in Polish pediatric hematology-oncology centers.

Materials and methods: One hundred eighty two patients with LCH were treated according to the Histiocytic Society Guidelines between 2010 and 2017. The participating centers were requested to provide the following data: demographic, clinical, as well as local or systemic treatment data and patients' outcome. Overall survival (OS) and event free survival (EFS) were estimated by Kaplan-Meier methods and compared using the log-rank test.

Results: Sixty nine percent of children were classified as single system (SS). The patients with SS disease were significantly older as compared to the children with multisystem disease (MS), 6 vs. 2.3 years respectively (p 0.003). Bones were involved in 76% of patients. Systemic treatment was applied to 47% of children with SS disease and 98% with MS disease. Fourteen patients relapsed while two children died. OS and EFS in entire group were 0.99 and 0.91 respectively (with median follow-up 4.3 years).

Conclusion: The treatment of LCH in Polish centers was effective, however, new approaches, including mutation analyses and good inter-center cooperation, are needed to identify patients who might require modification or intensification of treatment.

Keywords: Histiocytosis, Treatment, Survival, Children

* Correspondence: anna.raciborska@hoga.pl
[1]Department of Oncology and Surgical Oncology for Children and Youth, Institute of Mother and Child, Kasprzaka 17a, 01-211 Warszawa, Poland
Full list of author information is available at the end of the article

Background

Langerhans cell histiocytosis (LCH) affects 5–9 in 10^6 children younger than 15 years and 1 in 10^6 older patients. At the origin of the disease lies the clonal proliferation of histiocytes called Langerhans cells. Its symptoms are the result of accumulation of the abnormal cells in tissues and organs. The disease is not associated with increased risk of treatment failure (especially among older children) However, appropriate procedures implemented preemptively can eliminate possible complications and so significantly reduce the risk of deterioration of patients' quality of life [1–6].

Currently, new approaches and procedures allow to identify the patients requiring modification or intensification of treatment. As part of routine diagnostics, the gene profile and targeted therapies are increasingly used in treatment regimens [7–13].

Unfortunately, the treatment of children with LCH in Poland continues to be limited by financial resources, legal restrictions to introducing new treatment protocols and clinical studies for children, as well as by the lack of national cooperative clinical trials. Owing to the aforementioned reasons, the Polish Children Oncology Group adopted the Histiocyte Society Guidelines for LCH III in 2010. This was the first attempt to unify the management of children with LCH in Poland. In spite of this early effort, none of the Polish oncological centers used randomization at the time. Instead, they determined the treatment arm independently. To our knowledge, there has been no prior clinical assessment of their decision.

Thus, in the present study, we sought to: 1) evaluate the efficacy of the managements adopted by each oncological center on their own, with no inter-center cooperation; 2) assess the outcome of children with LCH treated in Polish pediatric hematology-oncology centers. We believe that the ability to implement complex studies by centers and countries traditionally excluded from large cooperative groups is key to generalize the results of treatment to children with LCH globally.

Methods

Patients

Since 1962, by the decision of the Polish Minister of Health, the care for children with cancer is provided separately from adult oncology. Currently, there is a very well-functioning oncology care system for children and adolescents with 18 centers located in major cities throughout the country.

For the purpose of this study, all Polish child oncology centers were requested, based on national regulations, to provide the following data: demographic data, clinical data, local or systemic treatment data and outcome of the patients treated due to LCH between January 2010 and December 2017. As a result, we were able to retrospectively collect data from 14 out of 18 pediatric oncology centers in Poland. All patients had a histological confirmation of LCH at the time of diagnosis using immunohistochemical method without central verification, which was not implemented until 2018. Patients were assessed as single system disease (SS: defined as one organ or system involved) or as multi system disease (MS: defined as two or more organs or systems involved) [6]. The approval for this retrospective study was obtained from all relevant institutions in compliance with national law and international regulations for protection of Human research subjects.

Statistical methods

Overall Survival (OS) was defined as the time interval from the date of diagnosis to the date of death or to the date of last follow-up. Event-free survival (EFS) was defined as any of the following: the time interval from the date of diagnosis to the date of disease progression, recurrence, second malignancy, death of any reason or to the date of last follow-up for patients without above events. Results distributions were estimated using the method of Kaplan-Meier. Survival curves in groups were compared using log-rank test and $p \leq 0.05$ was regarded as significant. Statistical analysis was performed using Statistica 13.3 for Windows.

Results

Patients characteristic and treatment

One hundred and eighty-two patients with LCH were treated using Histiocyte Society Guidelines [14] during the period between 2010 and 2017. There were 71 (39%) boys and 111 (61%) girls. The majority of children (69%) were classified as single system. Median age at diagnosis was 4.2 years, however, the patients with single system disease (SS) were significantly older as compared to the children with multisystem disease (MS), that is 6 years vs. 2.3 years respectively (p 0.003). The most common site was bones (76% patients with SS). The next most common locations were skin (16%), followed by lymph nodes (3%). Only one patient had isolated CNS involvement. MS disease presented with more than two organs involvement was found in 33 (59%) out of 56 cases [15]. Molecular tests were performed in 26 (14%) of patients. BRAF mutation was found in 11 participants (42%).

Table 1 Patient Characteristics

	SS	MS	p
Number of patients	126 (69%)	56 (31%)	
Age			
years: median (range)	6 (0.1–18.1)	2.2 (0.2–16.5)	0.001
Sex			
Male	49 (39%)	22 (39%)	
Female	77 (61%)	34 (61%)	0.89
Chemotherapy			
Yes	59 (47%)	55 (98%)	
No	67 (53%)	1 (2%)	

SS Single system, *MS* Multisystem;

Systemic treatment was applied to 112 patients: 47% children with SS disease and 98% with MS disease. One hundred nine children received systemic chemotherapy according to Histiocyte Society Treatment Guidelines adopted by Polish Children Oncology Group [14]. As local therapy, radiotherapy was applied in two cases, and a surgery was performed with or without local steroids in seven patients. The patient clinical and treatment characteristics are shown in Table 1.

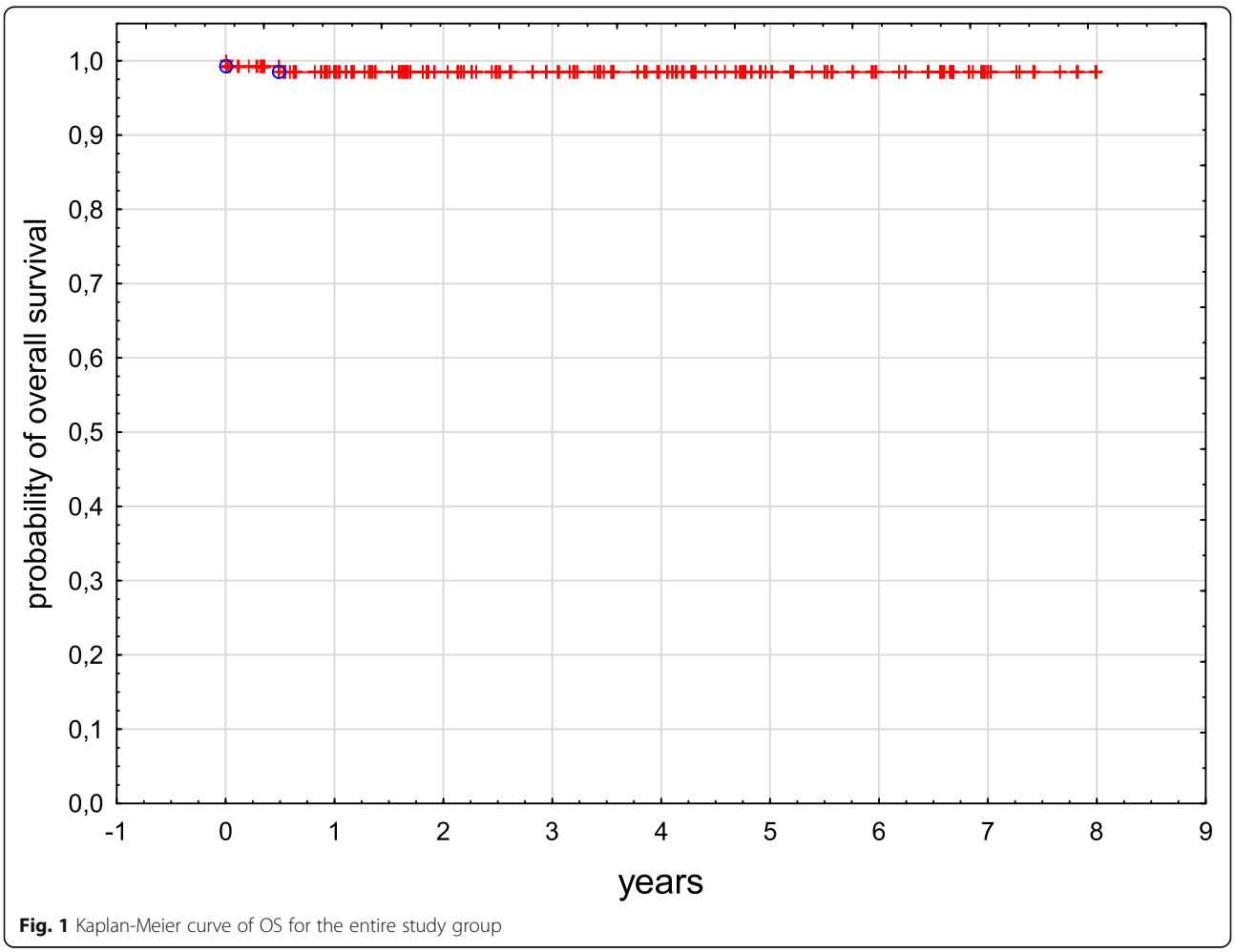

Fig. 1 Kaplan-Meier curve of OS for the entire study group

Follow-up and outcome

Six children were lost from the follow-up and three patients were still receiving treatment at the time of data collection. One hundred and seventy-one patients are alive with a median follow-up of 4.3 years from diagnosis (range from 0.1 to 18.1 years). Two children died, one infant prior to receiving treatment and one child due to a progressive disease 6 months post-diagnosis. Fourteen patients relapsed and are alive in second remission. Overall survival (OS) and event free survival (EFS) in the entire group were 0.99 and 0.91 respectively (Figs. 1 and 2). OS and EFS were significantly better in SS group as compared to MS group, p 0.03 and p 0.008, respectively (Figs. 3 and 4). Among 11 patients with BRAF mutation, one child relapsed and one progressed. The patient who relapsed was treated with second line chemotherapy (cytarabine and vincristine), while the patient who progressed received target therapy with vemurafenib. Both children are alive in complete clinical remission.

Discussion

Langerhans cells histiocytosis (LCH) is a rare disease with unclear etiology. It may affect different age groups, but is most often observed in the first decade of life [1–4]. It can affect different organs and systems i.e. bones, skin, lymph nodes, liver, lung, spleen, hematopoietic system, and central nervous system (CNS). The spectrum of clinical manifestations is broad, from single-focus to life-threatening symptoms. Current classification divides LCH into two groups: single system (single organ or system is involved; found in about 55% of patients), and multisystem (involves 2 or more systems / organs; with or without risk organs involvement) [1–6]. In our study, the single system disease was found in 69% of patients, which may be associated with multisystem underestimation, since the total number of patients was not known (no data from 4 centers). Bones were most involved which is consistent with other reports [2, 4, 6].

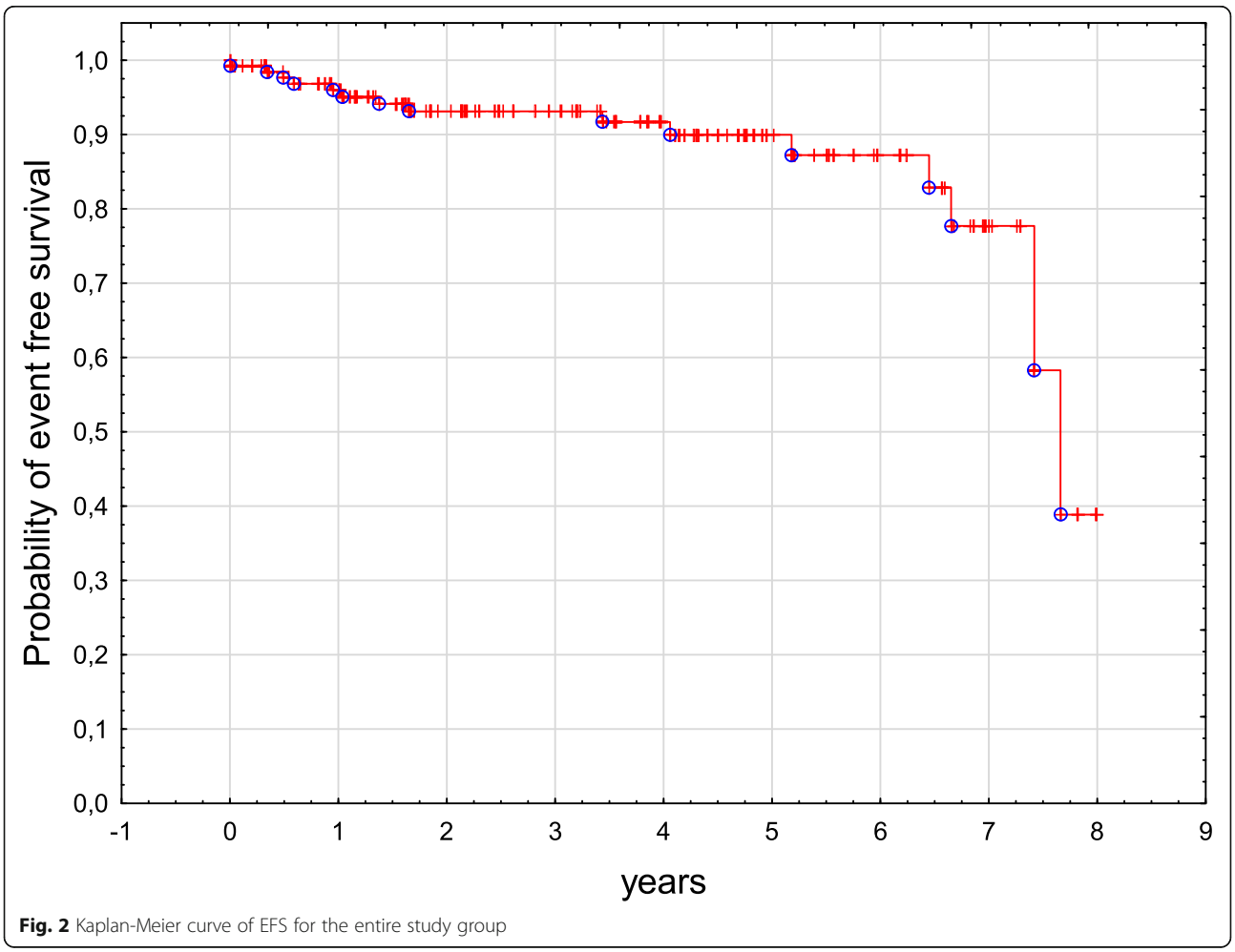

Fig. 2 Kaplan-Meier curve of EFS for the entire study group

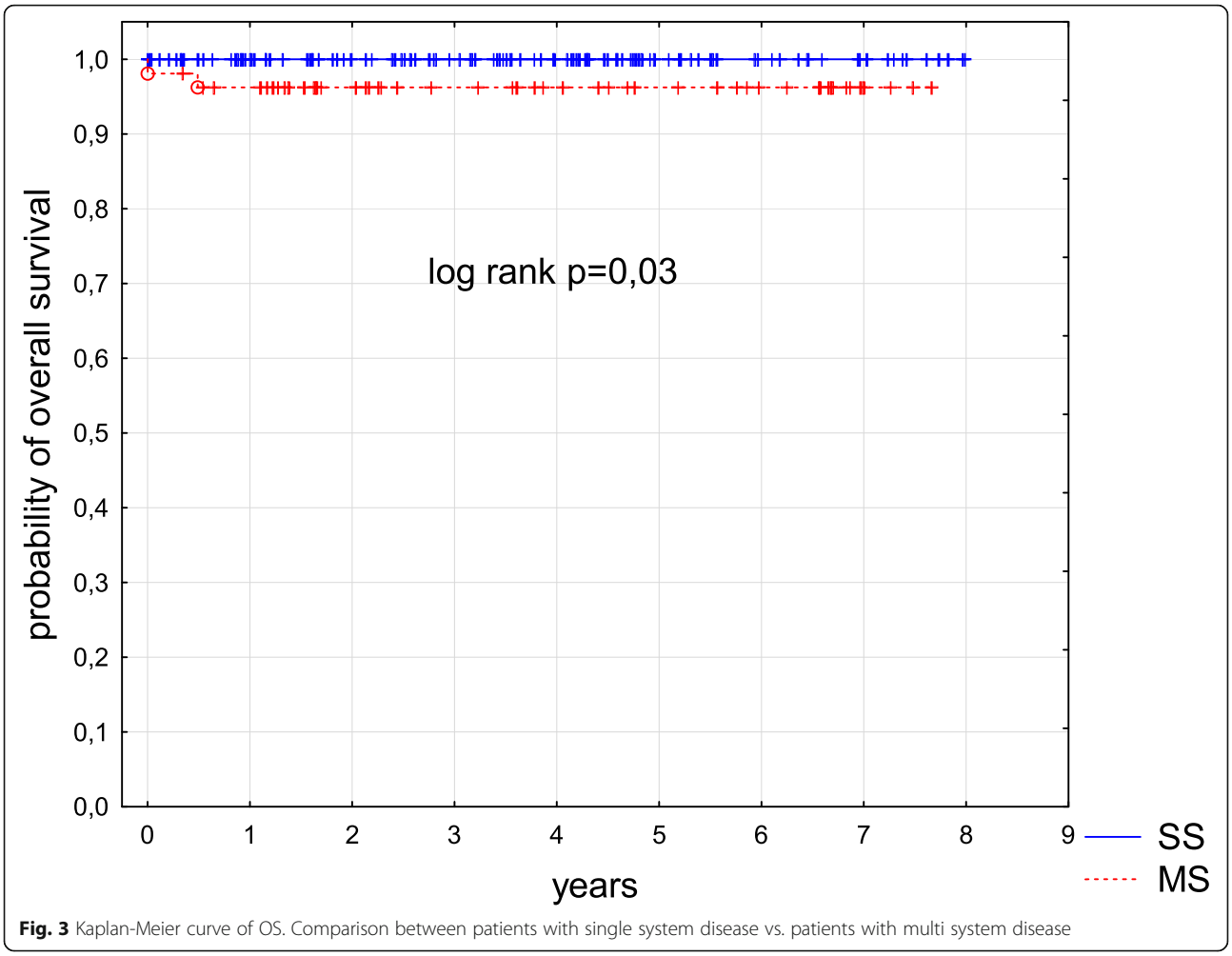

Fig. 3 Kaplan-Meier curve of OS. Comparison between patients with single system disease vs. patients with multi system disease

The course of LCH can be diverse and often is unpredictable. It oscillates from spontaneous regression, through a long-term period of exacerbation of the disease, to an aggressive form rapidly leading to death. In 2010, Badalian-Very published the study describing the presence of mutations in the $BRAF^{V600E}$ gene in histiocytes in patients with LCH [7]. Nowadays, it seems that the occurrence of mutations in the BRAF gene is usually associated with a more aggressive form of the disease, more frequent resistance to conventional chemotherapy, and with a higher probability of recurrence and progression [1, 6, 10–12]. For these reasons, molecular diagnostics is routinely carried out in many countries. In the present study, only 14% of patients underwent molecular tests and we strongly believe, it is necessary to introduce them for routine diagnostics in this group of patients in Poland.

The younger the child, the greater the risk of multisystem disease, and the greater the risk of the unfavorable course of LCH. In addition, the involvement of the risk organs (hematopoietic system, liver, spleen) is associated with a worse prognosis [1–4, 6]. In our material, both deceased patients had MS disease. What is more, first symptoms occurred before the age of 2 in both cases.

Although, the outcome of Polish patients can generally be considered as good, the need for the implementation of unified diagnostic procedures is clear. These must include molecular tests, treatment and other managements based on LCH guidelines. Furthermore, successful outcomes are dependent on the introduction of individualized aggressive local control measures. Thus, due to the rarity of appearances, a good inter-center cooperation is needed for a more thorough understanding of the nature of the disease, as well as for better treatment results.

Conclusion

The treatment of LCH in Polish centers was effective. However, successful long-term outcomes are dependent on good diagnostic approaches and very judicious use of chemotherapy. Identifying areas for improvement is

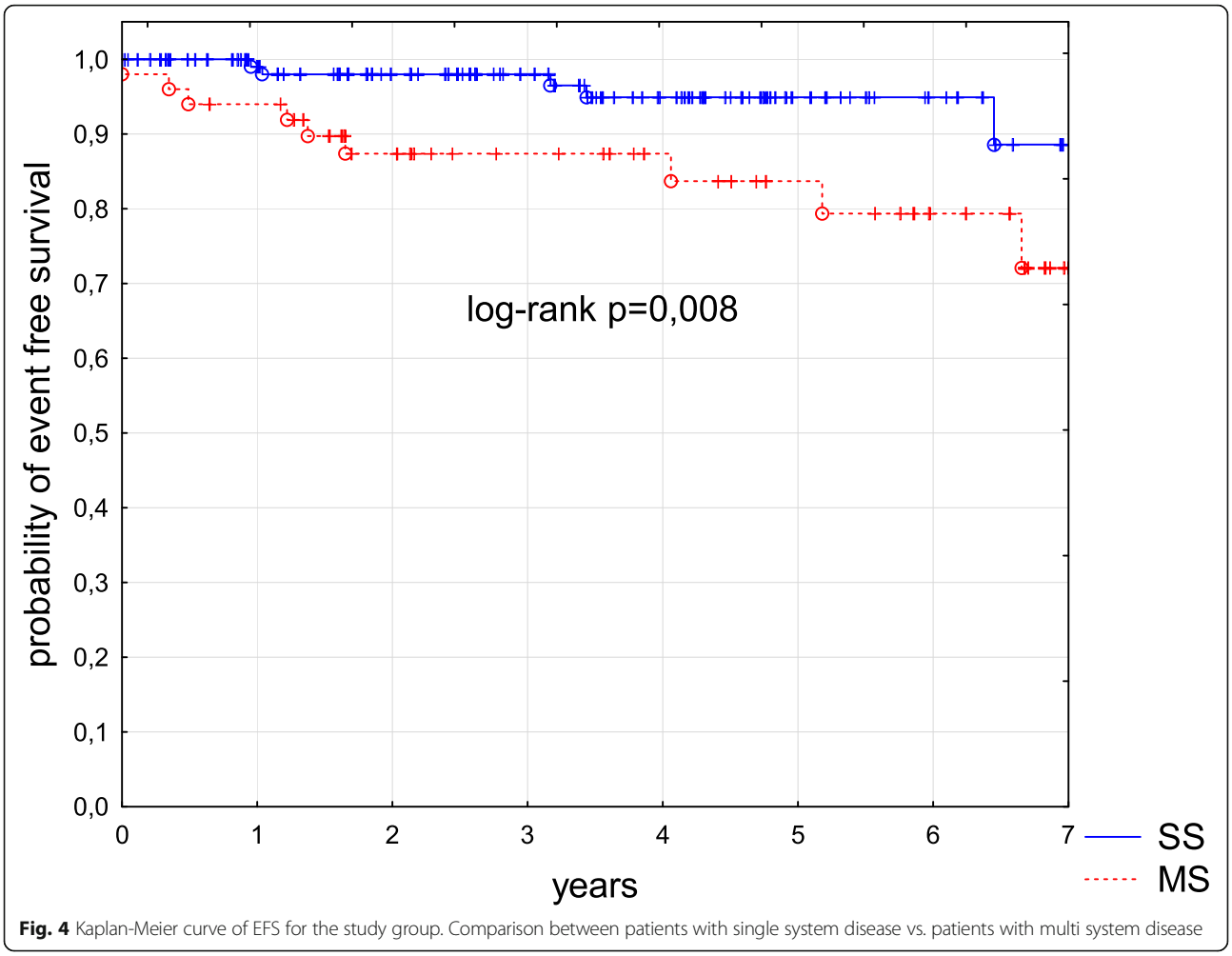

Fig. 4 Kaplan-Meier curve of EFS for the study group. Comparison between patients with single system disease vs. patients with multi system disease

needed in order to generalize outcomes. The development of national cooperative groups to coordinate and optimize resources, adapt treatment guidelines, and develop centralized centers of excellence is imperative in the advancement of care for children with cancer worldwide.

Abbreviations

LCH: Langerhans cell histiocytosis; OS: Overall survival; EFS: Event free survival; SS: Single system disease; MS: Multi system disease; CNS: Central nervous system

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The results were preliminarily presented by authors in the form of a poster during a session at the Histiocytic Society Annual Meeting in Lisbon in 2018 and published in *Abstracts from the 34th Annual Meeting of the Histiocyte Society* - citation 15.

Authors' contributions

AR and KD are responsible for the conception and design of the study. AR, KB, JW-T, OG-K, MH-K, JS, AP, KJ, FP, TO, GS-M, KM-R, OM, WB, MR, KD shared patients' clinical data and were responsible for the acquisition of literatures for manuscript. AR, KD were responsible for interpretation of data and preparation final manuscript for publication. The final manuscript was reviewed and approved by all authors.

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Availability of data and materials

Data and material are available upon request. Katarzyna Drabko katarzynadrabko@umlub.pl

Ethics approval and consent to participate

Written informed consent was obtained from all individuals included in the study and their parents or guardians on behalf of any participant under the age of 16. Additionally, retrospective studies from non-experimental data can be conducted in accordance with Polish national law (April, 30th 2010 regarding research institutes) to assess the efficacy and safety of treatment without specific consent, data can be reported to study coordinator in compliance with national law. Hence, explicit was not required in this instance, provided that only anonymous data is used in the publication (ref. the Polish legislation Dz.U. 1997 nr 28 poz. 152).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Oncology and Surgical Oncology for Children and Youth, Institute of Mother and Child, Kasprzaka 17a, 01-211 Warszawa, Poland.

[2]Department and Clinic of Pediatric Oncology, Hematology and Bone Marrow Transplantation, Wroclaw Medical University, Wrocław, Poland. [3]Department of Oncology, Children's Memorial Health Institute, Warszawa, Poland. [4]Department of Oncology and Hematology, University Children's Hospital of Cracow, Kraków, Poland. [5]Department of Pediatric Hematology and Oncology, Medical University of Gdansk, Gdańsk, Poland. [6]Department of Pediatric Oncology, Hematology and Transplantology, Medical University of Poznan, Poznań, Poland. [7]Department of Pediatric Hematology and Oncology Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland. [8]Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Łódź, Poland. [9]Department of Pediatrics, Hematology and Oncology, Medical University of Szczecin, Szczecin, Poland. [10]Unit of Pediatric Oncology, Hematology and Chemotherapy, Medical University of Silesia, Katowice, Poland. [11]Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Children's Clinical Hospital of L. Zamenhof, Białystok, Poland. [12]Department of Pediatrics, Hematology and Oncology, Medical University of Zabrze, Zabrze, Poland. [13]Department of Pediatric Oncology, Hematology, Medical University of Olsztyn, Olsztyn, Poland. [14]Department of Pediatric Oncology, Hematology, Medical University of Rzeszow, Rzeszów, Poland. [15]Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Lublin, Poland.

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