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Late effects of childhood cancer recorded at a single outpatient clinic over the course of one year: implications for follow-up care

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The paper provides a descriptive analysis of medical data and selected patient-reported outcomes from a group of 133 survivors of childhood cancer recruited at St. Anne's University Hospital in Brno, Czech Republic, over the course of one year. The participants were 18-53 years old (mean age 27.9 years) and had been diagnosed with childhood cancer in the period 1979-2016. Treatment data and data on relevant health outcomes were extracted from the medical records and categorized. Patient-reported outcomes were measured using the clinic's questionnaires completed by survivors prior to the medical examination. The most frequent adverse health outcomes in the study were dyslipidemia (50%) and overweight, obesity, and even morbid obesity (45%, 15%, and 1.5%, respectively). Endocrinopathies were observed in more than one-third (35.3%) of the survivors, followed by nephropathy (33.8%). Cardiovascular abnormalities were found in 9.7% of the survivors and fertility impairment in 9%. 38% of the survivors reported chronic fatigue and one-half (51%) reported pain. 20% of the cohort face mobility impairment. A remarkably high percentage of the survivors (70%) communicated some level of mental health issues. Moderate to severe anxiety and/or depression was reported by 25% of the survivors. 40% of the survivors experienced strong fears of disease recurrence, another 40% reported mild or moderate fears. Fear of late effects was communicated by 83% of the survivors, with 38% experiencing high levels of concerns. Only 8% of the survivors had no adverse health outcome. The rate of somatic and mental health outcomes identified in our sample is high. Some of the most frequent outcomes are mutually interconnected and modifiable, which highlights the need for patient education on a healthy lifestyle. There is also a clear need for improved psychological support for childhood cancer survivors to mitigate unnecessary anxieties resulting from unsubstantiated health concerns. Dissemination of personalized and positive messages should be part of routine follow-up care.

Key words: late effects of childhood cancer, follow-up care, personalized care, mental health, cancer survivorship

With increasing treatment success rates, the population of cured childhood cancer patients (survivors) reaching adulthood is steadily increasing. Previously incurable diseases have now become curable, but are often accompanied by chronic and, in some patients, lifelong physical and mental health complications that may consequently also have social and economic implications.

In the Czech Republic, we treat an average of 320 children and adolescents annually for various cancers, of whom 120 are treated at the Department of Pediatric Oncology in Brno. The chance of cure is nowadays higher than 90% for many childhood cancer diagnoses. Although these are still rare diseases, according to the Institute of Health Information and Statistics, there are currently more than 10,000 cured childhood cancer patients in the Czech Republic and the number will continue to grow [1]. The treatment results of pediatric oncology in the Czech Republic have improved steeply in the last few decades, which is why the majority of cured childhood cancer patients are currently under 40 years of age. Some serious late effects may manifest themselves with a long latency (even decades) after treatment for the primary childhood tumor. The most feared of these is the risk of secondary cancers, which is around 3–4% for the entire cohort of childhood cancer survivors, but in some survivor groups, the lifetime risk is more than 30% [2]. Research in the area of cancer survivorship has also led to the realization that cured patients are generally "frail" and age more rapidly, i.e. that they can often be in a similar state of health after the age of forty as the "healthy" population aged sixty and over [3]. Almost 80% of cured middle-aged patients have some adverse effects of treatment or medical conditions, and 10% have severe or combined effects of treatment and

comorbidities. The most commonly reported problems in this survivor population include endocrinopathies (growth disorders, infertility, hypopituitarism, hypothyroidism, metabolic syndrome, and nutritional disorders), organ dysfunctions (especially cardiac, lung, kidney), sensory impairments (especially ototoxicity after treatment with platinum derivatives, less often visual impairment), mobility disorders (including amputations or paresis), psychosocial issues including cognitive dysfunctions, and many other disorders that can affect virtually all organ systems [4, 5]. Early detection and long-term personalized monitoring and management of late effects, both physical and psychosocial, can ideally prevent or at least mitigate a severe impact on the quality of life of cancer survivors and their families. A better understanding of the pathogenesis of late effects can translate into desirable adjustments in therapeutical strategies to prevent these late effects.

As a result of the above-mentioned trends, there is a growing need for specialized outpatient clinics or follow-up care programs for childhood cancer survivors with a standardized process for transition of care from the primary pediatric oncology department. The follow-up care system in the Czech Republic works well until survivors reach the age of 19. Up until then, the follow-up care clinics are affiliated directly with the pediatric oncology centers that led the primary treatment. However, after reaching adulthood, many cured pediatric patients are lost from active follow-up at these centers [6]. Along with this, detailed information about the patient's cancer history and thus information about personal health risks worthy of attention is often lost from the patient's health care later in life.

Follow-up care must take into account the individual health risks arising from genetic predisposition, diagnosis, location, extent and stage of the disease, the treatment received, and occurrence of any serious complications after treatment. Thus, a pediatric oncology center should ideally provide each of its patients with a written summary of the type and extent of disease, treatment details, including cumulative doses of cytostatics, specification of the radiation field and doses of radiotherapy, and a list of relevant treatment-related toxicities and complications, as well as genetic predisposing factors. The transition from pediatric to adult specialist care would also be greatly facilitated by the delivery of an individualized follow-up care plan including personalized recommendations of diagnostic tests and screening for possible secondary malignancies and prevention of chronic health problems and psychosocial disorders [7]. From the perspective of the cured patient, this plan is also an important platform allowing for efficient collaboration between specialist clinics and general practitioners in providing personalized preventive care [8].

The adverse late effects of radiotherapy and administration of cytostatics that have been used in oncology for a long time (such as doxorubicin, methotrexate, cyclophosphamide, ifosfamide, and cisplatin) have been well described and there are evidence-based recommendations ("living guidelines") for follow-up after treatment with these drugs/radiotherapy [9]. Similarly, there are known adverse effects of long-term steroid administration, which is an important component in the treatment of acute leukemias and some lymphomas [10]. Long-term negative effects associated with surgical cancer treatment are well described (limb amputation or deformity, eye enucleation, brain surgery, nephrectomy, splenectomy, etc.) [11], and so are those associated with hematopoietic stem cell transplantation (e.g., renal and hepatic toxicities and low bone mineral density) [12]. In the last two decades, new innovative anticancer drugs (e.g., immunotherapeutics, biodifferentiating agents) have been gradually introduced into clinical practice and we do not yet have enough information about the long-term effects of these therapies. Similarly, the long-term effects of intrathecal therapy have not yet been sufficiently explored either.

Systematic, longitudinal, and structured registration of detailed treatment parameters and health outcomes in survivors in the follow-up care of late effects clinics is a necessary condition for future understanding of the possible unknown consequences of innovative treatments and new or insufficiently mapped therapies.

Therefore, in the present paper, we contribute with an overview of late effects of treatment and adverse health conditions observed in survivors in the care of the outpatient Late Effects Clinic at St. Anne's University Hospital in Brno for childhood cancer survivors over the course of one year. We will supplement this overview with a discussion of selected clinical implications of the detected health outcomes that are relevant for personalized care and targeted recommendations for survivors. We also focus on the mental health consequences of cancer treatment (particularly anxiety and depression), which are sometimes overlooked in clinical practice, yet can have comparable effects on the overall health and quality of life of cured patients to somatic late effects.

Patients and methods

This paper provides a descriptive analysis of medical data (on diagnosis, treatment, late effects, and health status) and selected patient-reported data (on mental health, psychosocial well-being, and selected aspects of the quality of life) from a sample of 133 survivors of childhood cancer who received follow-up medical care at the outpatient Late Effects Clinic at St. Anne's University Hospital in Brno, Czech Republic. From its establishment in 2016 to February 2022, the specialized outpatient clinic treated 540 childhood cancer survivors over 18 years of age. We recruited for the study a consecutive series of survivors who came to the outpatient clinic for medical examination and met the following criteria: 1/ had an appointment at the outpatient clinic between March 2021 and February 2022; were 2/ treated with chemotherapy and/or radiotherapy for cancer diagnosed at the age of 0–18 years; 3/ aged 18 years or older at inclusion in the study; 4/ at least

5 years from primary cancer diagnosis; 5/ at least 2 years off treatment for cancer; 6/ in complete remission of primary (or any subsequent) cancer; 7/ with available detailed cancer treatment data; 8/ signed an informed consent with the use of their health data for scientific and research purposes.

The survivors' medical data (both somatic and mental health data) were extracted from their medical records and categorized. Patient-reported outcomes were collected using selected items from the clinic's survivor screening questionnaire completed by the study subjects prior to medical examination at the clinic. The screening questionnaire is based on the Czech SF-36 measure, version 1, supplemented with questions on treatment-related late effects and survivors' concerns associated with late effects. The stratification of survivors into categories of risk of development of late effects was based on the Frobisher classification scheme [13]. This classification system is based on a combination of the diagnosis and treatment modality in solid tumors, lymphomas, and leukemias. The data were analyzed using basic descriptive statistical methods.

Results

Sample description. Survivors enrolled in the study are a relatively young cohort with an average age of 27.9 years. However, given the age range of 18–53 years and a tumor diagnosis between 0–18 years (mean age at diagnosis 10.4 years), the cohort covers almost four decades of experience with pediatric oncology in the Czech Republic: survivors in the study were diagnosed with cancer between January 15, 1979 and October 3, 2016. As of the date of analysis, survivors had been followed up for an average of 16.8 years (5–43 years) from the date of diagnosis. Females comprised 45% of the cohort, males comprised 54%, and one person identified as non-binary. The characteristics of the cohort in terms of demographic and treatment parameters are summarized in Table 1.

The largest group of the survivors (53.4%, n=71) underwent treatment for hemato-oncological malignancies (acute leukemia and malignant lymphomas), 46.6% for solid tumors (n=62). In the case of survivors of solid tumors, the disease was mostly localized (82.3%) and less often metastatic (17.7%). 13.5% of the survivors (n=18) experienced a relapse of the disease and we have also recorded 5 secondary malignancies (3.7%); all of the concerned patients subsequently achieved a second complete remission of the disease.

Almost all our survivors (98.5%, n=131) were treated with chemotherapy. As shown in Figure 1, they were exposed to 34 types of cytostatics used in different periods and in different treatment schedules and doses. Individual survivors were treated with a combination of at least 2 but also up to 13 different cytostatics. The most commonly used cytostatic drugs over the nearly 40-year period when the survivors were diagnosed (1979–2016) were the drugs vincristine (74%), doxorubicin (72%), cyclophosphamide (66%), etoposide (56%), and methotrexate (36%). A quarter of the survivors (25.6%, n=34) were also given the drugs intrathecally, and a fifth (19.5%, n=26) were given steroids (for more than 28 consecutive days, which is a threshold considered risky in terms of the development of late effects). 21 survivors (16%) were treated with 12 different innovative drugs (immunotherapeutics, biodifferentiating agents) or hormones. The (so far low) frequencies of use of these new drugs are also apparent from Figure 1.

Over half of our survivors (51.9%) underwent radiotherapy (n=69) and almost half (42.8%) underwent surgery (n=57). Fifteen survivors (11.3%) underwent hematopoietic

Table 1. Survivor characteristics.

Age, age at diagnosis, duration of FU (n=133)	**Mean (years)**	**Range (years)**
Age at study entry	27.9	18-53
Age at diagnosis	10.4	0-18
Duration of follow-up	16.8	5-43
Year of diagnosis	–	1979–2016
Sex (n=133)	**Number**	**%**
Females	60	45.1
Males	72	54.1
Non-binary	1	0.8
Primary tumor (n=133)	**Number**	**%**
Malignant lymphomas	44	33.1
Leukemias	27	20.3
Bone tumors	17	12.8
Central nervous system tumors	15	11.3
Germ cell tumors	9	6.8
Soft tissue tumors	6	4.5
Renal tumors	5	3.8
Neuroblastoma	3	2.3
Other malignant tumors	3	2.3
Liver tumors	2	1.5
Retinoblastoma	2	1.5
Treatment modality (n=133)	**Number**	**%**
Chemotherapy	131	98.5
Radiotherapy	69	51.9
Tumor surgery	57	42.9
Hematopoietic stem cell transplantation	15	11.3
Extent of disease in solid tumors (n=62)	**Number**	**%**
Metastatic	11	17.7
Localized	51	82.3
Treatment for relapse (n=133)	**Number**	**%**
Yes	18	13.5
No	115	86.5
Treatment for SPTs (n=133)	**Number**	**%**
Yes	5	3.8
No	128	96.2
Frobisher score - risk of late effects (n=133)	**Number**	**%**
Grade 1	13	9.8
Grade 2	59	44.3
Grade 3	61	45.8

Abbreviations: FU-follow-up; SPTs-subsequent primary tumors

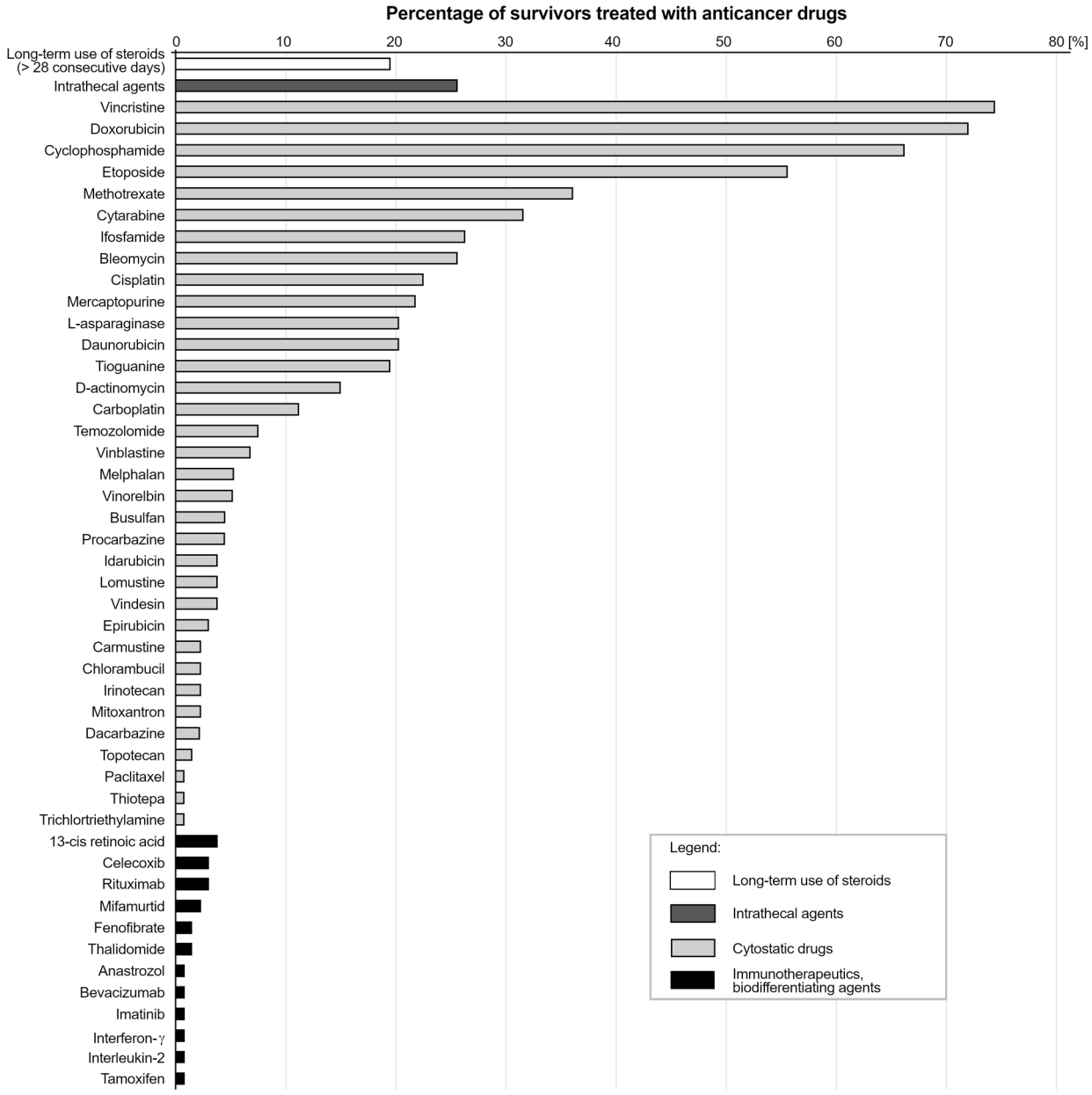

Figure 1. An overview of chemotherapy (steroids, 34 types of cytostatics, 12 types of immunotherapeutics or biodifferentiating agents) given to the study cohort in different periods and under different treatment schedules and doses, some also intrathecally. Individual survivors were treated with a combination of at least 2 but also up to 13 different drugs.

stem cell transplantation. Of these, two were after allogeneic sibling MSD BMT (matched sibling donor bone marrow transplantation) for acute leukemia, and the remaining were after autologous transplantation following treatment for childhood solid tumors or lymphomas. Regarding radiotherapy, the chest (mediastinum, lungs, chest wall) and neck were the most common areas irradiated, mostly in patients with lymphomas, but also some solid tumors (sarcomas), followed by head irradiation, especially in patients with brain tumors and leukemia. With regard to the risks of secondary tumors and severe late organ toxicity, we specifically monitor the risks after irradiation of the heart and, in women, of the breasts as key target organs. The irradiated areas are summarized in Table 2.

With respect to the diagnosis and treatment received, according to the Frobisher classification scheme, 91.2% of survivors in our cohort have a high (Frobisher 3, 45.8%, n=61) or moderate (Frobisher 2, 44.3%, n=59) risk of developing late effects, while the remaining 9.8% (Frobisher 1, n=13) have a low risk (Table 1).

Late effects of anticancer treatment and other adverse health outcomes. Our study shows a substantial burden of adverse health outcomes in the study cohort. As seen in Table 3, only 8% of the (young) cohort does not currently have any known medical condition. Medical records of 86% of cured patients show at least one adverse somatic health issue (either alone or in combination with a mental health outcome), likely – although not conclusively – associated with their cancer history. 9% of cured patients have a medical record of a mental health problem (again, either alone or in combination with a somatic health outcome).

A detailed overview of the late effects (and their clinical implications) is given in Table 4. As in the general population, in addition to the obvious late effects of treatment, there are also serious comorbidities independent of treatment or of unclear origin in the cohort of cured patients. For example, we observed sporadic cases of genetically determined diseases such as Down syndrome or congenital cryptorchidism, as well as other serious diseases such as multiple sclerosis and ulcerative colitis in our cohort. Some late effects cannot be reversed. These include permanent effects of surgical treatment of tumors (e.g., amputations), visual and hearing impairment, paraplegia, etc.

Within the scope of this publication, the paragraphs below summarize the occurrence of those selected late effects that are among the most common ones and at the same time can be influenced or prevented. Thus, they are an appropriate

Table 2. Radiotherapy (n=69).

Radiotherapy field	Number	%
Mediastinum/lung/chest	30	43
Neck	29	42
Head/cranial/facial	23	33
Spine	8	12
Abdomen/retroperitoneum	8	12
Pelvis	6	9
Spleen	5	7
Extremity	3	4
TBI (total body irradiation)	1	1
Selected relevant organs at risk for late effects in the radiotherapy field	**Number**	**%**
Heart	33	47
Breast (in females)	20	29

Table 3. The rate of somatic and mental health outcomes in medical records and as reported by survivors (n=133).

Outcome	Medical records		Patient-reported outcomes	
	Number	%	Number	%
Any somatic outcome alone	111	83	–	–
Any mental health outcome alone	8	6		
Any somatic and mental health outcome combined	4	3	93	70
No identified adverse health outcome	10	8	–	–

Table 4. Somatic and mental health outcomes in the study sample and implications for clinical care (n=133).

Outcome	Number	%	Implications for clinical care
Dyslipidemia	67	50	healthy lifestyle, education, nutritional counseling, appropriate health care (referral to the GP)
Endocrinopathies	47	35	education, appropriate health care (referral to the endocrinologist), psychological support if needed
Nephropathies	45	34	healthy lifestyle (fluid intake, avoiding nephrotoxic drugs), referral to the nephrologist, psychological support if needed
Hearing impairment	24	18	education, school and employment counseling, psychological support, hearing protection (hearing aids), referral to the audiologist
Cosmetic problems	21	16	education, school and employment counseling, psychological support, referral to appropriate specialists (orthopedic surgeon, plastic surgeon)
Neurological deficit	20	15	education, school and employment counseling, psychological support, referral to the neurologist or psychiatrist if appropriate
Mobility impairment	18	8	education, school and employment counseling, psychological support, referral to appropriate specialists (orthopedic surgeon)
Any cardiac outcome	13	10	education, referral to the cardiologist, psychological support if needed
Infertility	12	9	education, psychological support, referral to assisted reproduction clinic if so wished
Lung impairment	12	9	education, healthy lifestyle support (physical activities), psychological support if needed, referral to the pulmonologist
Hypertension	8	6	healthy lifestyle, education, appropriate health care (referral to the GP)
Severe dental problems	7	5	healthy lifestyle, education, appropriate health care (referral to the dentist)
Severe visual impairment	3	2	education, school and employment counseling, psychological support, referral to the ophthalmologist
Self-reported mental health outcomes	93	70	psychosocial support, referral to the psychiatrist if needed
Other=individual	51	38	a holistic person-centered approach needed

Notes: cosmetic problems-skeletal and connective tissue hypotrophy due to tumor, surgery and/or radiotherapy; any cardiac outcome-arrhythmia, valve problems, left ventricle function impairment; severe dental problems-dental problems due to tumor, surgery and/or radiotherapy; other-Down syndrome, congenital cryptorchidism, ulcerative colitis, diabetes mellitus, paraplegia, hemochromatosis, chronic anemia, osteopenia, avascular necrosis, chronic hepatopathy, psychiatric disorders (anxieties, phobias, depressions, suicidal ideations)

example of the space for effective early intervention and targeted recommendations to survivors.

As can be seen from Table 4, dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia) was the most frequent medical outcome. It was found in as many as half of the survivors (50%). Almost the same proportion of survivors was overweight (45%), another 15% were above the obesity threshold, and two survivors (1.5%) were even morbidly obese. Signs of endocrinopathy and nephropathy were also observed in large groups of survivors – more than one-third (35.3% and 33.8%, respectively). Cardiovascular abnormalities concerned 9.7% of survivors.

In our cohort, fertility disorders were found in the medical records of 9% of survivors (Table 4). As shown in Table 5, most of the men and women in our young cohort (81%) are still childless and do not currently plan to have children. Only five (4%) achieved parenthood with the help of assisted reproductive techniques. However, more than two-thirds (68%) already reported a moderate or even strong fear of infertility in the clinic's survivor questionnaire.

The survivor questionnaire covers selected aspects of survivors' mental health and psychosocial outcomes. The comparison of data from medical records and survivor-reported questionnaire data highlighted a major gap between the level of attention paid to this important area of health within the system of cancer follow-up medical care and the subjective need as reported by survivors themselves. While only 9% of survivors had a record of a mental health issue in their medical file (Table 3), as many as 70% of survivors self-reported some level of psychological distress, anxieties and/or depression through the questionnaire. Moderate to severe anxiety and/or depression was communicated by 25% of survivors. As seen also in Table 6 (and in Table 5 on fertility), psychosocial concerns are highly relevant for our target population. 20% of survivors said that they had sought professional psychological and/or psychiatric intervention at some point since their anticancer treatment. It is also clear that a significant proportion of survivors (some even long after completion of treatment) experience distress associated with their cancer-treatment history. 40% of survivors experienced strong fears of disease recurrence, another 40% reported mild or moderate fears. Concerns related to the risk of late effects were expressed by 83% of survivors, with 38% suffering from a considerable level of concerns.

To illustrate a broader psychosocial context of the lives of survivors, we can add that more than one-third (38%) reported chronic fatigue, and as many as one-half (51%) reported experiencing pain. One-quarter (27% and 24%, respectively) said that fatigue or pain compromised their ability to function in daily life. Mobility problems were reported by 20% of survivors in our cohort at the time of the survey.

Table 5. Fertility issues (n=133).

Fertility issues	Number	%
Fear of infertility (patient-reported)		
No concerns	42	32
Some concerns	40	30
Major concerns	50	38
Offspring		
Yes	25	19
No	108	81
Parenthood through ARTs		
Conceived through ARTs	5	4
Conceived naturally	20	15
No children, currently no family planning	108	81

Abbreviation: ARTs-assisted reproduction technologies

Table 6. Patient-reported concerns and mental health and psychosocial outcomes (n=133).

Concerns/Outcomes	Number	%
Anxiety/Depression		
No anxiety/depression	40	30
Mild anxiety/depression	60	45
Moderate or severe anxiety/depression	33	25
Fear of tumor recurrence		
No concerns	27	20
Some concerns	53	40
Major concerns	53	40
Fear of late effects		
No concerns	22	17
Some concerns	60	45
Major concerns	50	38
Mental health care received after treatment		
Yes	26	20
No	107	80
Chronic fatigue		
Yes	50	38
No	82	62
ADLs compromised by chronic fatigue		
Yes	36	27
No	97	73
Pain		
Yes	68	51
No	65	49
ADLs compromised by pain		
Yes	38	29
No	95	71

Abbreviation: ADLs-activities of daily living

Discussion

The paper aims to present structured data on the rates of late effects of anticancer treatment in a sample of childhood cancer survivors in their adulthood and to discuss the main associations between the observed health outcomes, known treatment modalities, and clinical implications for follow-up care. Systematic and long-term registration of these data is important for our ongoing understanding of treatment

toxicity, especially for innovative drugs for which there is not yet a sufficient evidence base in practice. At the same time, a good quality evidence base makes it possible to articulate targeted recommendations for specific survivors in terms of long-term management of their individual health risks. The presented work is the first review study in our outpatient follow-up clinic in Brno, Czech Republic, which maps objective health outcomes in 133 survivors and, at the same time, pays attention to the impact of cancer treatment on mental health (depressions, anxieties, concerns associated with the risk of disease recurrence, and the risk of developing treatment-related late effects).

The rates of somatic health outcomes identified in our sample of survivors (83%, with dyslipidemias, overweight, endocrinopathies, and nephropathies being the most prevalent) are broadly in line with expectations and published literature. For example, Oeffinger et al. [5] reported a 73.4% cumulative incidence of chronic health conditions in a large cohort of 10,397 survivors of childhood cancer with a mean age of 26.6 years (18–48 years) which is a cohort closely matching the age distribution in our group of study subjects. The slightly higher rate of somatic late effects in our study (83%) may be attributed to the fact that we did not enroll survivors with therapy by surgery only (with the least risk of late effects), compared with 6% of such survivors in the cohort of Oeffinger et al.

While some late effects are irreversible, other ones are modifiable or preventable and thus are a field of opportunity for intervention or cooperation with the survivor on health maintenance. Selected modifiable late effects and implications for clinical care will be discussed in more detail in the following paragraphs.

Dyslipidemia and overweight. An increased risk of dyslipidemia applies particularly to survivors after treatment of leukemia and those with whole-body irradiation and all types of hematopoietic stem cell transplantation.

Even in the general population of the Czech Republic, half of the adults have a higher than optimal weight [14]. However, given the low average age in our sample of survivors (Table 1), the data on our cohort appear more alarming. Obesity and dyslipidemia are important modifiable risk factors for the development of a number of major diseases such as heart disease and stroke, high blood pressure, diabetes, and some cancers. Obesity-related diseases are the second most common cause of death in the country, after smoking-related diseases. Obesity is multifactorial in survivors and is related not only to the treatment received and lifestyle, but also bidirectionally to psychosocial factors such as anxiety, depression, and economic status [15]. Its management is a good example of the need for a holistic approach and interdisciplinary cooperation, including psychological support.

At our late effects clinic, patients with documented dyslipidemia in younger age groups are provided with information about the health risks associated with overweight and dyslipidemia. In cases of mild disorders, we recommend non-pharmacological approaches, i.e., adherence to healthy lifestyle principles. In more severely affected cases, we refer the patient to lipid-lowering counseling or offer weight reduction and healthy diet counseling. We motivate survivors to actively participate in improving their health. In the case of a more significant disorder or familial lipid-spectrum disorders, treatment with hypolipidemic is indicated in collaboration with the general practitioner.

Endocrinopathy. The groups at increased risk are survivors of brain tumors, especially those who had brain irradiation, survivors who had their thyroid gland removed or irradiated, and survivors treated with hematopoietic tissue transplants.

The available literature suggests that the number of survivors with endocrinopathies will continue to increase as our cohort ages. In some large studies with longer follow-up periods, endocrinopathies were seen in up to 62% of survivors [16]. While in most survivors in our study group the symptoms were only mild (typically hypothyroidism well managed with levothyroxine), survivors after treatment for brain tumors in a hypopituitary region or after irradiation with a higher dose of radiotherapy or after allogeneic transplantation with a conditioning regimen containing whole-body irradiation often had combined endocrine disorders that significantly compromise their options for weight reduction and health risks reduction (e.g., those who have developed panhypopituitarism).

In the case of any endocrinopathy, we refer the patient to the care of an endocrinologist to set adequate treatment.

Nephropathy. Renal dysfunction is a subtle but significant adverse effect of treatment, especially in survivors who underwent nephrectomy or were treated with cisplatin or ifosfamide. Therefore, our findings are not surprising and are consistent with data published in other studies [17]. Nephropathies are associated with the risk of developing hypertension and chronic renal failure. These two health conditions in turn increase the risk of cardiovascular diseases in the future [18].

We recommend all our patients at risk or with a history of nephropathy to maintain a proper drinking regime and avoid potentially nephrotoxic drugs (e.g., especially non-steroidal antiphlogistic drugs such as commonly used ibuprofen or aminoglycoside antibiotics). In the case of severe renal dysfunction, we refer the patient to the care of a nephrologist.

Cardiovascular findings. Cardiotoxicity is mainly associated with the administration of anthracyclines (more than 70% of survivors in our cohort) – doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone – and radiotherapy to the heart region. Cardiovascular diseases include cardiomyopathies/heart failure, coronary artery disease, pericardial disease, heart rhythm disorders, valvular defects, and vascular disorders and are very relevant for survivors [19–21]. The population of childhood cancer survivors is

7 times more likely to die from late cardiovascular toxicity compared to the general population [22], making cardiovascular disease the most common cause of non-cancer death in our concerned population.

In our young cohort, the majority of affected survivors only had conditions that did not require pharmacological interventions or management (hemodynamically insignificant valvular defects, borderline reduced left ventricular function), but in some survivors, we have already observed cardiac rhythm disturbances requiring antiarrhythmic treatment and cardiac failure related to anticancer therapy.

Patients at risk are educated about cardiovascular risk factors and lifestyle strategies for prevention. In the case of more serious outcomes, the condition is managed in cooperation with cardiologists. The traditional risk factors for the development of cardiovascular disease are hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking tobacco products. All of these factors can effectively be targeted by interventions and patient education.

Fertility disorders. In our cohort (and in general), fertility disorders are less frequent than some of the other late effects mentioned above, but undoubtedly a great area of concern for survivors from a young age. In both women and men, fertility disorders are associated with treatment with alkylating agents (cyclophosphamide, chlorambucil, melphalan, mechlorethamine, ifosfamide, trofosfamide, prednimustine, bendamustine, temozolomide), as well as radiotherapy to the ovarian or testicular region and the whole-body irradiation. Survivors with a history of tumors in the hypothalamic-hypopituitary region and those with a history of hydrocephalus or insertion of a ventriculoperitoneal shunt are also at increased risk.

Fertility disorders deserve special attention given their significant impact on the quality of life of survivors. Here we would like to highlight an important aspect of fertility disorders in women, which is the risk of primary amenorrhea or premature menopause. Premature menopause in women increases the risk of comorbidities such as cardiovascular disease and osteoporosis. Fertility disorders in both sexes (ovarian failure in women and azoospermia in men) are closely linked to the psychological well-being of survivors and may directly translate into psychological problems such as depression.

In the case of any fertility disorder, we refer both women and men, if interested, to the care of specialized reproductive medicine centers. We also offer and provide psychological support.

Patient-reported concerns and mental health issues. The frequency of self-reported mental health problems (depression and anxiety) seen in our study is remarkably high and much higher than could be expected when looking at the rates registered in medical records (70% and 9%, respectively). The major discrepancy between the two rates shows how severely mental health issues are overlooked or underdiagnosed in childhood cancer survivorship.

Our survivors clearly have a considerable level of psychological care needs. In addition to the high rates of self-reported depression and anxiety, we have also observed profound concerns about disease recurrence even in those survivors where the risk of relapse is virtually nil. An unfounded level of concern was also seen with respect to fertility issues. This indicates an ongoing need for cured patients to receive positive reassuring information. One purpose of this paper is to provide data support for this reassuring information in a local setting. Many cured patients, for example, continue to worry about the return of their disease for a very long time after treatment. For a large proportion of childhood cancers, a five- or ten-year survival from a cancer diagnosis essentially means cure. Although the overall rate of late effects seen in our cohort may be high, not every risk applies to every survivor and the high rate also covers symptoms that are only mild and well manageable. It would seem that the common professional term used in medical records, "ongoing complete remission of disease", may not be well received by many survivors or may not give them the level of certainty they expect. Our findings indicate the need for our survivors to hear directly that "they are cured" [23].

We confront these issues by embracing the person-centered attitude to survivors at our clinic, by providing personalized and accurate risk information, emphasizing positive outcomes and conclusions wherever possible, offering support through the Brno survivor association Together Towards a Smile, and last but not least, offering psychological support.

To sum up the observed outcomes and touch on the limitations of our study, in the absence of a control group or population data in a comparable age group, we cannot say whether the prevalence of these adverse health outcomes is higher in our cohort compared to their healthy peers for example. However, at the individual level, any observed health risk is relevant. The high frequencies of preventable risk factors (dyslipidemia, overweight and obesity, endocrinopathy, nephropathy, and hypertension, as already mentioned) for the development of major diseases of civilization (namely cardiovascular diseases, diabetes, and secondary malignancies) and the interrelationship and interdependence of these factors, including mental health factors (depression, anxiety) seen in our cohort, highlight the importance of sustained motivation of survivors to a healthy lifestyle, including mental hygiene. That said, the rate of patient-reported mental health issues could be slightly elevated in our study due to two factors. Survivors at a higher risk for developing late effects (Level 2 or 3 according to the Frobisher classification) are a large group in our cohort (92%). These survivors usually attend our outpatient follow-up clinic at shorter intervals (once a year to once every two years), compared with low-risk survivors who attend our outpatient clinic once every 3–5 years or are followed up by general practitioners. The composition of our survivor sample (we included a consecutive series of survi-

vors who came in for a follow-up clinic visit over the course of one year and met the study entry criteria) may have also been influenced by the COVID-19 pandemic during which clinic visits took place. This may have selected the population towards more anxious survivors or those with higher levels of health problems. On the other hand, however, social distancing concerns may have prevented another group of anxious survivors from attending the clinic. We will seek insight into possible intervening factors and long-term trends by continuing to register data and repeating analyses in the future.

In conclusion, the identified rate of somatic health outcomes in our sample is high, yet broadly in line with expectations and published literature. There is a major discrepancy between the (very high) frequency of self-reported mental health issues and corresponding records of mental health problems in medical files (very few). Some of the most frequent somatic health outcomes are important modifiable risk factors for the development of major diseases such as cardiac disease and stroke, high blood pressure, diabetes, and some cancers. The identified somatic and psychological health outcomes are mutually interconnected and alterable and highlight the need for patient education on risk prevention and a healthy lifestyle. There is also a clear need for improved psychological support for childhood cancer survivors, including mitigation of unnecessary anxieties resulting from unsubstantiated health concerns by disseminating personalized risk information and positive messages.

Dispelling unfounded anxieties along with motivation to live a healthy life and take co-responsibility for one's own health is clearly the ideal ultimate goal. We aim at this goal with the motto of our outpatient clinic: "No one can change their genes or the history of cancer and its treatment, but everyone can change their lifestyle and thus positively influence their own health-related quality of life".

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