



Childhood cancer survivors: improving our practice today to reduce late, major surgical interventions tomorrow

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Approximately 35,000 children and adolescents in Europe (1), and 450,000 in the US (2) are diagnosed with cancer every year. With more new technologies, advances in surgical techniques and innovative drug therapies being developed, childhood cancer survivors (CCSs) to date account for more than 80% of the patients treated for pediatric tumors (3-5). As these patients age and reach middle and late ages, they are at high risk of long-term side effects, including secondary cancers, and premature mortality (6).

Recently, Dieffenbach *et al.* (7), analyzing data from the Childhood Cancer Survivor Study (CCSS, retrospective cohort study with longitudinal prospective follow-up of 25,656 5-year survivors of childhood cancer, who were diagnosed between 1970 and 1999, and matched with a group of 5,045 siblings), conducted a full examination of the associations between specific childhood cancer treatments and the burden of late surgical interventions.

The authors observed a significant burden of late major surgical interventions: cardiovascular, spine, endocrine, central nervous system (CNS), respiratory, genitourinary, gastrointestinal, musculoskeletal, head and neck, breast interventions. The rate of these interventions was higher compared with that of their siblings (7) and these happened at a younger age (more than 10 year earlier than in the comparison group). The authors reported detailed risk categories. The risk of cumulative burden of major surgical interventions was higher in female versus male survivors, in those diagnosed in the 1990s versus those diagnosed on

the 1970s, in those treated with locoregional surgery or radiotherapy, and in Hodgkin lymphoma and bone sarcoma patients (7).

Surgery plays a fundamental role in the treatment of childhood cancer, also in the management of long-term sequelae (8), and the result of high cumulative late major interventions was expected due to these reasons. Treatment of secondary malignancies, bowel obstruction after surgical adhesions or abdominal radiotherapy, the shunt replacement or revision in CNS survivors, correction of spinal deformity subsequent to radiotherapy or laminectomy, many limb salvage procedures, prosthetic substitutions, complications of amputations, and surgical treatment of osteonecrosis are some of the long lists of these late surgical interventions.

The greatest merit of this work (7) is the detailed information available, to underline the extent of the issue (28,202 surgical intervention versus 4,110 in the siblings' cohort), which had been poorly quantified up to this point.

When comparing data from survivors treated in the 1970s and those treated in the 1990s, an increasing cumulative burden of late major surgery emerges in the more recent group; this is probably due to an increased number of survivors of high-risk disease who underwent intense multimodal therapy, with subsequent occurrence of late, treatment-related complications (7). Moreover, Dieffenbach *et al.* shows how the cumulative burden of major surgical interventions is higher among female

(versus male) survivors (7-12). Overall, female survivors were more frequently submitted to surgeries regarding breast, endocrine and cardiovascular systems, especially among those with Hodgkin's lymphoma [this is true for all cancer diagnoses except acute lymphocytic/lymphoblastic leukemia (ALL), soft tissue sarcomas, and Ewing sarcoma]. Data for early menopause was not available in these series, but it is well recognized that early menopause increases the risk of comorbidities such as cardiovascular disease and osteoporosis, and could be a cause of further late surgeries in female survivors. It was confirmed that women CCSs were particularly at risk for poor physical quality of life (QoL) (9), and in German female survivors, the worst QoL was described in all domains of the EORTC QLQ-C0, when compared to general population (10). The patients suffering most from the burden of major surgical interventions were survivors of Hodgkin's lymphoma, Ewing sarcoma and osteosarcoma (7). The development of new techniques and the knowledge acquired on late effects is expected to translate into a future lesser burden, particularly in selected groups of patients. In recent years, some treatments have been implemented by using lower anthracycline dosages and avoiding/reducing radiotherapy (i.e., avoiding prophylactic radiotherapy in ALL, reducing the indication of radiotherapy in Hodgkin's lymphoma, using proton beam radiotherapy instead of photons in some subtypes of CNS tumors), where possible (7). Therefore, we would hope for a decrease in the burden of late surgical intervention in Hodgkin's survivors as compared to this old cohort.

The same cannot be said for patients in other disease or higher risk subgroups for which the main objectives are still an increased event-free survival and overall survival regardless of long-term toxicities.

Dieffenbach *et al.* reported that locoregional surgery or radiotherapy were associated with late surgical intervention in the same body region or organ system (7).

For example, in bone sarcomas, it is still necessary to perform extensive surgeries involving prosthetics and requiring further surgical adjustments during adult age. In most of these patients, when surgery fails or is impossible (i.e., axial localizations), radiotherapy cannot be avoided or may be necessary in combination with other treatments, such as in cases of Ewing sarcoma. This combination of surgery and radiotherapy can cause further hypotrophy and dysmetries with consequent need for other future surgical procedures to correct the deformity. Speaking about late surgery in CCSs, we must certainly not forget the important

role that reconstructive surgery plays in particular groups of patients (i.e., patients who have undergone previous demolitive surgery). In this context, many patients who would usually be treated with photons could be treated with protons or carbon ions, ideally reducing late effects. However, data on very long-term late effects of these relatively new techniques are not yet available in the childhood cancers (CCs), and we cannot predict with certainty whether these may cause a reduction of burden in the late, major surgical intervention.

These patients could be also at risk for low bone mineral density (BMD), caused by disturbances in bone metabolism, that may develop as a consequence of many factors (i.e., treatments, cancer itself, wrong diet, genetic susceptibility), and reduced physical activity during and after the disease (13). In addition, BMD may be a final result of gonadal failure after exposure to abdomino/pelvic radiation or alkylating agents, or as a result of hypothalamic-pituitary deficiencies after CNS irradiation. Although reduced BMD is usually asymptomatic, data in general population has shown that it leads to an increased risk of fractures, which results in acute and sometimes long-term morbidity, and in selected cases may require surgical interventions (13).

To date, there is now a great attention to promote exercise and its related benefits (14-17). Being long-term survivors, therefore, cancer patients are always encouraged to live a normal life (17). Regular exercise can help reduce the deterioration of physical function (15-17). The benefits of exercise for patients with cancer are increasingly being investigated; the inactivity could be a contributor of death, and probably has a relevant role in the rising incidence of non-communicable diseases, including certain types of cancer and cancer-related acute and late morbidity (17). Survivors who exercise are exposed to a lower risk of further major surgeries, cardiovascular interventions, or bariatric surgeries. Exercise should be supervised and tailored to the individual to avoid the necessity of orthopedic intervention (i.e., traumatic fractures, muscular strains). This concept is particularly relevant considering the high prevalence and severity of bone density deficits observed in CCSs.

Due to these considerations, it is essential to encourage survivors to adopt a healthy lifestyle (i.e., the avoidance of smoking, alcohol, physical inactivity, and caffeine consumption). Strain *et al.* (18), showed that the health benefits of weight loss are well established. If other methods previous failed, we have no evidence that weight loss surgery cannot be offered to patients who have had a previous diagnosis and successful treatment of cancer.

As a final point, the economic aspect must certainly be taken into account for single patient in terms of the economic and social consequences of the disease as well as for Health systems. Fidler-Benaoudia *et al.* (19) observed that compared with those in the UK, CCSs in the United States had worse outcomes as the time since diagnosis increased. This could be related to a suboptimal follow-up care for survivors, due to the lack of insurance, identified as an important predictor: CCSs are more likely to skip a necessary examination or medical treatment due to cost issues, and surgical procedures could be particularly expensive. In Health systems, this burden of late surgeries undoubtedly also represents an economic burden both for the individual and the society (20). There is, therefore, a situation whereby, both the individual patient and the economic system in general, suffer. This is not true for other health systems, in which the economic cost of late surgeries may only be covered by a few. It is also important to remember that frequently, due to the health burden, CCSs are individuals who have some difficulties in finding jobs, who most often live with their native family, have limited independency and, therefore, may represent a burden.

In conclusion, CCSs are complex patients and, thanks to new cancer therapies, their numbers will increase more and more in the coming years. Evidence-based guidelines for the management of CCSs are offered in many issues. The outstanding work, initiated in 2010, by International Late Effects of Childhood Cancer Guideline Harmonization Group allows a shared and common strategy for the surveillance of late effects in CCs (21) to be established, and awareness on this topic to grow. The CCSS study focuses on a sometimes poorly quantified burden of survivorship, adding a new important insight on the already complex needs of long-term cancer survivors. Moreover, up-to-date guidelines, e.g., from the IGHG (International Late Effects of Childhood Cancer Guideline Harmonization Group), exist, the problem being that they are not broadly implemented (22).

We must, therefore, help physicians and educate CCs in recognizing early late effects requiring major surgeries, inform the medical communities of this high-cost need and evaluate changes, if any, in the recent CCs cohorts of this long-term burden.

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References

1. Childhood Cancer International Europe [Internet]. Available online: <https://ccieurope.eu/> (accessed 24 July 2023).
2. Cure Search. Available online: <https://curesearch.org/> (accessed November 3, 2023).
3. Landier W, Skinner R, Wallace WH, et al. Surveillance for Late Effects in Childhood Cancer Survivors. *J Clin Oncol* 2018;36:2216-22.
4. Landier W, Armenian S, Bhatia S. Late effects of childhood cancer and its treatment. *Pediatr Clin North Am* 2015;62:275-300.
5. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review (CSR) 1975–2014. Updated April 2, 2018. https://seer.cancer.gov/archive/csr/1975_2014/ (accessed November 03, 2023).
6. Ernst M, Hinz A, Brähler E, et al. Quality of life after pediatric cancer: comparison of long-term childhood

- cancer survivors' quality of life with a representative general population sample and associations with physical health and risk indicators. *Health Qual Life Outcomes* 2023;21:65.
7. Dieffenbach BV, Murphy AJ, Liu Q, et al. Cumulative burden of late, major surgical intervention in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS) cohort. *Lancet Oncol* 2023;24:691-700.
 8. Henderson TO, Nathan PC. Childhood cancer survivors: considerations for surgeons in the transition from pediatric to adult care. *Semin Pediatr Surg* 2015;24:93-9.
 9. van Erp LME, Maurice-Stam H, Kremer LCM, et al. Health-related quality of life in Dutch adult survivors of childhood cancer: A nation-wide cohort study. *Eur J Cancer* 2021;152:204-14.
 10. Geue K, Sender A, Schmidt R, et al. Gender-specific quality of life after cancer in young adulthood: a comparison with the general population. *Qual Life Res* 2014;23:1377-86.
 11. Krawczuk-Rybak M, Panasiuk A, Stachowicz-Stencel T, et al. Health status of Polish children and adolescents after cancer treatment. *Eur J Pediatr* 2018;177:437-47.
 12. Prasad M, Goswami S, Chinnaswamy G, et al. Long-Term Outcomes in Survivors of Childhood Cancer: A 30-Year Experience From India. *JCO Glob Oncol* 2022;8:e2200044.
 13. van Atteveld JE, Pluijm SMF, Ness KK, et al. Prediction of Low and Very Low Bone Mineral Density Among Adult Survivors of Childhood Cancer. *J Clin Oncol* 2019;37:2217-25.
 14. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409-26.
 15. Braam KI, van der Torre P, Takken T, et al. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev* 2013;(4):CD008796.
 16. Wurz A, McLaughlin E, Chamorro Viña C, et al. Advancing the Field of Pediatric Exercise Oncology: Research and Innovation Needs. *Curr Oncol* 2021;28:619-29.
 17. Spreafico F, Gattuso G, Nigro O, et al. Recommending exercise for children with a single kidney. *Nat Rev Urol* 2022;19:65-6.
 18. Strain GW, Cooley V, Ebel F, et al. Weight loss after bariatric surgery in cancer survivors. *Surg Obes Relat Dis* 2020;16:670-3.
 19. Fidler-Benaoudia MM, Oeffinger KC, Yasui Y, et al. A Comparison of Late Mortality Among Survivors of Childhood Cancer in the United States and United Kingdom. *J Natl Cancer Inst* 2021;113:562-71.
 20. Bejarano-Quisoboni D, Panjo H, Fresneau B, et al. Excess healthcare expenditure in adults treated for solid cancer in childhood: a cohort study in France. *Eur J Health Econ* 2023. [Epub ahead of print]. doi: 10.1007/s10198-023-01606-6.
 21. Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 2013;60:543-9.
 22. International Guideline Harmonization Group [Internet]. Available online: <https://www.ighg.org/guidelines/> (accessed on November 3, 2023).

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