

Long-term follow-up study and long-term care of childhood cancer survivors

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= Abstract =

The number of long-term survivors is increasing in the western countries due to remarkable improvements in the treatment of childhood cancer. The long-term complications of childhood cancer survivors in these countries were brought to light by the childhood cancer survivor studies. In Korea, the 5-year survival rate of childhood cancer patients is approaching 70%; therefore, it is extremely important to undertake similar long-term follow-up studies and comprehensive long-term care for our population. On the basis of the experiences of childhood cancer survivorship care of the western countries and the current Korean status of childhood cancer survivors, long-term follow-up study and long-term care systems need to be established in Korea in the near future. This system might contribute to the improvement of the quality of life of childhood cancer survivors through effective intervention strategies. (*Korean J Pediatr* 2010;53:465-470)

Key Words : Childhood cancer survivor, Survivorship, Long-term follow-up, Long-term care, Korea

Introduction

The treatment of childhood cancer patients in western countries has improved remarkably, and the current 5-year event-free survival of childhood cancer patients in these countries is approaching 80%¹⁾. This improvement in the survival of children with cancer has increased the population of childhood cancer survivors.

In USA, 1 out of 750 adults is a childhood cancer survivor, and this number is expected to grow to 1 out of 250 by 2020²⁾. Many studies on long-term complications and health behavior of childhood cancer survivors during the last 2 decades have emphasized the importance of long-term follow-up (LTFU) study and long-term care of childhood cancer survivors^{3, 4)}.

In Korea, annually about 1,700 children and adolescents are newly diagnosed with cancer. According to the nationwide cancer statistics of the National Cancer Center, the 5-year event-free survival rate of Korean children and adolescents with cancer between 2001 and 2005 was about

70%⁵⁾. Therefore, recently, the need for LTFU care of Korean childhood cancer survivors has become widely recognized. By reviewing the current status of LTFU study and care of childhood cancer survivors of western countries, we can understand recent progress in childhood cancer survivorship. In this report, we will discuss the current situation of Korean childhood cancer survivorship and propose a model of LTFU and care system that will facilitate the implementation of excellent Korean childhood cancer survivorship care in the near future.

Long-term follow-up studies of childhood cancer survivors

There are several reasons why we need to conduct a collaborative long-term childhood cancer survivor study⁶⁾. First, childhood cancer survivors have a long life expectancy. Second, the number of childhood cancer survivors is increasing. Third, the long-term effect of treatment of childhood cancer has a marked effect on the lives of these patients and on the society. Lastly, there are limitations when studying long-term effects within populations derived from a single institution. Hence, childhood cancer survivor studies have been mostly conducted as multicenter retrospective cohort studies on a nationwide scale. Until now, a few countries have performed similar studies. The Childhood

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Cancer Survivor Study (CCSS) of USA, Canadian Childhood Cancer Surveillance and Control Program (CCCSCP) of Canada, and British Childhood Cancer Survivor Study (BCCSS) of United Kingdom are the present ongoing studies.

The CCSS of USA is the first longitudinal cohort study on childhood cancer survivors^{6,7}. After submission of a grant application and completion of peer review, the National Cancer Institute (NCI) approved the funding for this study in 1994. Initially, 26 clinical centers from USA and Canada participated in the CCSS consortium. The eligibility criteria for inclusion into the cohort were as follows: the patient should be diagnosed with cancer between 1970 and 1986 at one of the participating institutions, the age at diagnosis should be less than 21 years, and the patient should have been alive 5 years from the date of diagnosis. These criteria were satisfied by 20,276 candidates who were contacted in August, 1994 and recruited in the study. Among those who were successfully contacted, 81.2% completed a 24-page questionnaire designed for collecting baseline data. This questionnaire included items related to medical conditions, health habits, education, insurance, income, etc. The participating institutions had to provide the medical abstracts pertaining to operation, radiation, chemotherapy, and cumulative dose of chemotherapeutic agents. Recruitment of sibling controls was started in July, 1996; 80.4% of the 4,782 eligible siblings participated in the study. All study surveys are available on the CCSS Web site (www.stjude.org/ccss). On the basis of the baseline information and medical abstracts, the occurrence of and the risk factors for adverse late-occurring events in the CCSS cohort were assessed. The CCSS investigators have published more than 120 articles in the scientific literature related to the long-term morbidity and mortality of childhood cancer survivors⁸⁻¹⁰. The results of CCSS have markedly influenced the well-being of cancer survivors, clinical practice, and research-related issues. CCSS has also served as a resource for addressing important future issues concerning treatment outcome, role of genetics, cause and mechanism of disease progression and the quality of life.

Four follow-up surveys (2000, 2003, 2005, and 2007) were conducted after the collection of baseline data from the study cohort. In addition to the biannual follow-up surveys, several topic-specific surveys were conducted within the cohort. To further enhance the scope of research within the CCSS, a biologic repository was established in which the

genomic DNA obtained from buccal cell samples of survivors and siblings was submitted in addition to the peripheral blood samples from survivors with a second or subsequent neoplasm. To ensure the scientific impact of the CCSS resource, efforts are underway to expand the existing cohort by adding the 5-year survivors diagnosed and treated between 1987 and 1999; 26,093 eligible 5-year survivors have been identified for this period⁷. Another priority for CCSS is the emphasis on the translation of the study findings into intervention strategies. To this end, it is necessary to develop and execute clinical trials to evaluate the feasibility and efficacy of the intervention.

Long-term follow-up guidelines

In 2000, the cooperative study groups of childhood cancer merged to form the Childrens Oncology Group (COG)¹¹. Next year, in 2001, the COG established the Late Effect Committee (LEC). The purpose of the LEC is to promote and facilitate research on adverse health-related outcomes that may arise after childhood cancer. This committee integrates studies in epidemiology, genetics, and molecular biology; it consists of 4 working groups: Outcomes research, Gene-environment, Education, and Methodological.

In 2003, the Institute of Medicine summarized the salient issues influencing health care for childhood cancer survivors in a report entitled "Childhood Cancer Survivorship: Improving Care and Quality of Life"¹². In response to the concerns raised in this issue and after the National Cancer Policy Boards meeting, the Institute of Medicine charged the COG-LEC with the development of comprehensive clinical guidelines for LTFU care of childhood cancer survivors¹³. These guidelines were developed by collaborative efforts among COG-LEC committee, Nursing Discipline, task force team, panels of experts, reviewers, Health Link authors, and members of the NCI-supported cooperative clinical trials group. A total of 62 individuals participated in the review process. The entire process was supported by COG with financial assistance from the NCI.

COG-LEC established the Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG-LTFU Guidelines) in 2004. These are clinical practice guidelines to optimize and standardize the care for childhood cancer survivors. These guidelines promote healthy life styles, provide for continuous monitoring of health status, facilitate early identification of late effects,

and provide timely intervention for late effects. The COG-LTFU Guidelines are risk-based, exposure-related, and evidence- and consensus-based clinical practice guidelines for screening and management of late effects resulting from therapeutic exposures used during the treatment of pediatric malignancies. The screening recommendations represent a statement of consensus from a panel of experts in the late effects of pediatric cancers. The guidelines are organized into 9 key categories: therapeutic agents, potential late effects, risk factors, highest risk, periodic evaluations, minimum recommended frequency, health protective counselling, considerations for further testing and intervention, and references.

This guideline is available to all primary care providers and subspecialists on the website www.survivorshipguidelines.org. Now, the revised version of LTFU Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, 2008, is also available.

Implementation of the COG-LTFU Guidelines, including the practicality and efficiency of applying these guidelines, in individual clinical situations is an important issue. These guidelines should be integrated to long-term care programs. Poplack, from the Baylor College of Medicine, and collaborators in the COG are developing Passport for Care, a web-based program that has incredible potential for enhancing the quality of life of long-term survivors¹⁴. This program is mainly based on an internet-based tool that outputs an individualized summary of the COG-LTFU Guidelines on the basis of the patients cancer treatment history.

Long-term follow-up care

The rationale for LTFU of survivors of childhood cancer is based on 2 assumptions: (1) screening and surveillance for late effects can lead to early diagnosis and intervention that will improve the treatment outcome and quality of life and (2) how and to what extent do radiation and chemotherapy alter the aging process of normal tissue and how does this effect influence the development of other common adult health problems associated with aging are largely unknown. Therefore, the LTFU care of childhood cancer survivors should be longitudinal risk-based care¹⁵.

Optimum care of childhood cancer survivors should include the following key components: (1) longitudinal care

that means care starting from the time of cancer diagnosis and continuing till death, regardless of age, (2) continual care, which can be achieved by partnership between the survivor and a single health provider, (3) comprehensive, anticipatory, and proactive care that includes a systemic plan of prevention and surveillance, (4) multidisciplinary team approach, (5) health care of the person and his family and safeguarding his cultural and spiritual values, (6) sensitivity to the issues of cancer experience, including expressed and unexpressed fears of the survivor and his family/spouse.

The first report on health care patterns of adult survivors in the CCSS cohort focused on 4 measures of self-reported outpatient health care in the 2 years preceding enrollment¹⁶. There were 3 important findings in this study. First, the likelihood of undergoing a general physical examination, cancer-related medical visit, or a visit to a cancer-center significantly decreased with the increasing age of the survivors or the time interval between cancer diagnosis and treatment. Among survivors who had been survived for at least 20 years after their cancer diagnosis, less than 30% reported a cancer-related medical visit and less than 14% reported a visit to a cancer center. Second, risk-based care was uncommon. Only 52% of the survivors who had been treated with $>300 \text{ mg/m}^2$ of an anthracycline reported a cancer-related medical visit in the previous 2 years. Third, subpopulations that were less likely to report either cancer-related or cancer center visits were identified. In addition to age and the interval from the time of cancer diagnosis, male gender, lack of health insurance, and no concern about future health were the primary factors associated with receiving less care.

Many potential barriers of LTFU care were identified^{15, 17, 18}. These barriers could be classified as follows: (1) survivor-related barriers, (2) physician-related barriers, and (3) health care system-related barriers. The following 2 primary survivor-related barriers were identified: first, most survivors were not aware of the potential late effects and future health risks, and second, survivors often did not know the details of their cancer and cancer therapy. The 3 physician-related barriers were as follows: lack of capacity for survivor care at the institutions that provide cancer treatments; unfamiliarity of the primary care physicians with the population; and poor communication between cancer centers and primary care physicians. Health insurance, health care policies, and health care system were

the 3 health care system-related barriers.

A comprehensive LTFU program is essential to provide optimal LTFU care. However, by 2002, there were only 28 programs in the US and Canada that provided comprehensive LTFU care, which is defined as care provided through a program with following attributes: (1) at least a single physician interested in late effects, (2) a nurse or a nurse practitioner or coordinator, (3) an LTFU clinic that meets at a specified time and place, (4) at least 2 follow-up visits to the clinics per month, (5) comprehensive care and screening for late effects based on the survivors treatment, (6) referral to appropriate specialists, and (7) prevention and wellness education²⁾. In a recent report published in 2006, 28 directors of well-established LTFU clinics have suggested an ideal model of LTFU program for childhood cancer survivors¹⁹⁾. This report indicated that even these leading programs encounter many challenges while providing what they believe is the standard care for their patients. The difficulties included financial and manpower restraints, lack of communication on the part of their institution, and increasing number of patients. The respondents also noted that identifying primary care physicians to care for this complex growing patient population is a challenge¹⁹⁾.

Status of childhood cancer survivor study and care in Korea

In Korea, annually, about 1,700 patients below the age of

20 are newly diagnosed with cancer. The number of children and adolescents receiving treatment for cancer are about 5,000. The 5-year survival rate between 2001 and 2005 is about 70%.

In Korea, the treatment of children with cancer became possible with the advent of the modern therapeutic approach from the 1970s. During the past 4 decades, the number of childhood cancer survivors in Korea has increased to approximately 20,000–25,000. However, the exact number of childhood cancer survivors in Korea is not known. The annual number of long-term survivors of cancer includes about 1,200 new childhood cancer patients; therefore, we could presume thus the cumulative number of childhood cancer survivors will increase every year, like in USA or UK²⁰⁾.

Several studies on childhood cancer survivors have been published. Most of them are single institutional, small-sized, and short-term follow-up studies^{21–23)}. However, with the increasing number of Korean childhood cancer survivors, the research scope has also increased. For the nationwide cohort study, a model of Korean childhood cancer survivors cohort was proposed (Fig. 1)²⁴⁾. The validity of the Korean versions of the instruments for measuring the quality of life of childhood cancer survivors was established^{25, 26)}, and the first nationwide Korean childhood cancer survivors meeting was held in February 2010.

We have a lot of questions about the status of Korean childhood cancer survivors: What is the number of child-

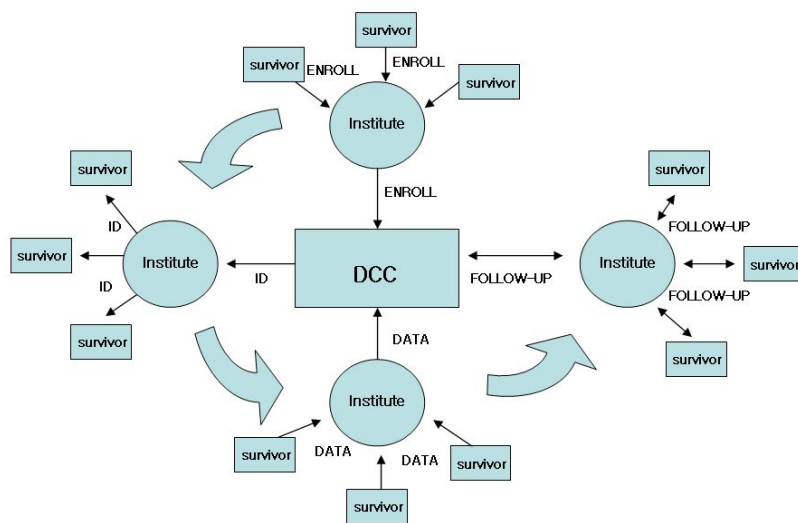


Fig. 1. Long-term follow-up process of Korean childhood cancer survivors. Abbreviation : DCC, Data Coordinating Center.

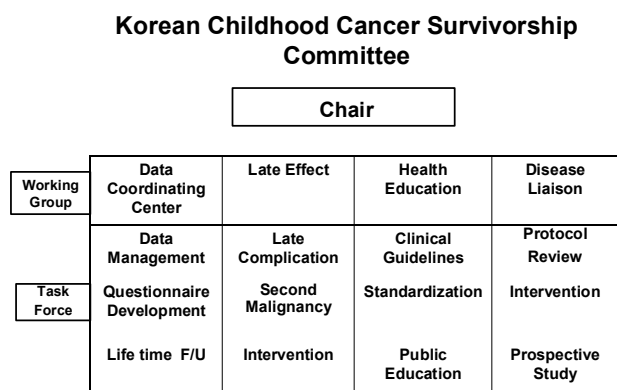


Fig. 2. Proposal for organization of Korean childhood cancer survivorship committee.

hood survivors in Korea? What are their sufferings? What measures should be taken so that these survivors can lead a new and normal life? Who is taking care of such patients? What kind of health services are provided to them? What are the obstacles in providing optimal long-term care to them?

For the care of Korean childhood cancer survivors, an expert committee of childhood cancer survivors should be established as soon as possible (Fig. 2)²⁴. Experts from several disciplines with interest in childhood cancer survivorship can take an initiative and play a significant role.

To evaluate the present situation of cancer survivors in our country, we need to urgently establish a childhood cancer survivor cohort. Although it is a difficult task, only studies on a Korean cohort can provide answers to our questions; further, the data collected for this cohort would be a very useful resource for data analysis, publication, and health policies²⁷. On the basis of the understanding of the CCSS in USA, we can build our cohort by adapting similar methodologies to our study design, assessing the exposure, evaluating the validity of the treatment outcome, and performing statistical analysis.

In spite of many difficulties, some institutions have conducted LTFU programs. However, the application of long-term care for pediatric survivors has not been investigated. Most pediatric oncologists try and schedule follow-up sessions for survivors. However, many survivors may not attend follow-up sessions 5 years after completion of the treatment. The patients do not visit the cancer center for reasons other than those related to cancer, for example, periodic examination for cancer centers.

Hence, maybe many pediatricians are taking care of

childhood cancer survivors in their community, and in the future this number is expected to increase. Therefore, pediatricians play very important role as health promoters of pediatric cancer survivors²⁸. In addition to screening for late effects on the basis of previous therapeutic exposures, health counseling and promotion of a healthy lifestyle are important aspects of LTFU care in this population.

We now need to define the Korean LTFU guidelines to provide information for health care providers in many fields. We should determine an effective way of communicating and educating the health providers in the community.

The current status of Korean LTFU program and LTFU care should be investigated. On the basis of these findings, we can define the problems faced in our medical situation, take steps to overcome these problems, and propose a model of long-term care.

Conclusion

Over the last 20 years, the CCSS and COG have significantly improved the understanding of childhood cancer survivorship. Until now, many intervention strategies for childhood cancer survivorship have focused on secondary-interventions. These interventions deal with the occurred or occurring problems.

Improvements in the treatment of childhood cancer patients can increase the number of long-term survivors. Childhood cancer survivorship care should be considered from the beginning of cancer treatment. Therefore, all treatment protocols should integrate primary intervention strategies to promote survivorship care.

In Korea, tremendous improvement has been achieved in the field of childhood cancer treatment. From now on, we should make more efforts to optimize the survivors physical and psychosocial health, ideally enabling them to enjoy the same quality of life as their peers. We can build a well-organized childhood cancer survivorship care system and provide the best care for childhood cancer survivors in the near future.

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