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ORIGINAL ARTICLE

Follow-up of long-term cancer survivors in the Nordic countries

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Abstract

Cancer survivors are at increased risk of developing different co-morbid conditions. With an increasing number of long-term cancer survivors in the Nordic countries, the need for recommendations for long-term follow-up has become necessary. However, at present there are no general guidelines for follow-up in the Nordic countries. Three steps of follow-up should be distinguished and the objectives associated with each: 1) Follow-up research done as clinical studies in cancer survivors and as registry-based epidemiological investigations. Whenever possible these approaches should be combined with translational research relating clinical observations with findings from biological material for increased understanding of pathophysiology and aetiology. Such investigation has to provide evidence-based knowledge of late effects associated with the malignancy itself and its treatment. The Nordic countries have excellent possibilities for conducting such follow-up research; 2) Creation of guidelines, in an attempt to put results from research into clinical practice, should take the local situation and resources into consideration. Provision of an individualized Survivorship Care Plan is a first step; 3) Implementation of guidelines into daily health care. Guidelines have little influence on long-term cancer care if they do not reach the practitioners and convince them to comply. There is a need for well-planned follow-up to manage and reduce possible treatment-related morbidity and mortality in cancer survivors. The Nordic countries provide excellent possibilities for relevant research, but lack, so far evidence-based guidelines. In agreement with the initiatives of ASCO the development of Survivor Care Plans is the first step to improve on this situation.

Each year more than 100 000 people are diagnosed with cancer in the Nordic countries (www.ncu.un). Each of the Nordic national cancer registries report of increasing incidence rates, and there are no sign this tendency will change within the next decades. Today about 60% of all cancer patients can expect to live for at least five years and between 30% and 40% live for at least 20 years [1]. Thus approximately 800 000 individuals live in the Nordic countries with a prior diagnosis of cancer and its consequences.

Much information on long-term effects after cancer and its treatment is based on studies of survivors after childhood cancer and cancer in young adults. Today, between 75% and 95% of these patients are rendered tumour-free [2]. However, in comparison to age-matched controls, increased mortality rates have been demonstrated in survivors

after childhood cancer, especially due to second malignancies and cardio-vascular events [3–8]. Other health-related problems include gonadal dysfunction, metabolic syndrome, cognitive impairment and growth problems [9–15].

Solid second tumours usually start to occur 10 years or more after irradiation, whereas the risk of secondary leukaemia peaks after 5 to 10 years after chemotherapy and declines steadily thereafter [16,17]. Long-term cardiovascular effects are described after both chemotherapy and radiotherapy in tumour-free survivors after testicular cancer, Hodgkin's lymphoma and breast cancer [18–20]. Other well-documented late effects include hearing reduction, tinnitus and peripheral neuropathy after cisplatin-based chemotherapy [21]. Oncological surgery is also associated with specific long-term

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effects. Examples are lymph oedema in the arm after extensive lymph node dissection for breast cancer or urinary incontinence and erectile dysfunction after radical prostatectomy [22,23]. Except probably for female breast cancer much limited research has been done in long-term cancer survivors above the age of 50 years (bladder and prostate cancer, gynaecological and GI cancer). Though the risk of second cancer sometimes has been explored [24,25] sparse data are available about non-malignant late sequelae for these cancer survivors. The recent decade's research on quality of life has, however, drawn the attention to previously unrecognised somatic and psychological late effects, which can have significant impact on cancer survivors' lives. The recognition on such objective and subjective late treatment-related morbidity has contributed to several important treatment modifications such as the reduction of target fields and target doses in Hodgkin's lymphoma [26], seminoma [27] and improved radiotherapy techniques for breast cancer [20]. For other cancer sites the overall treatment intensity has admittedly rather increased by combining "standard surgery" with radiotherapy and chemotherapy, as for example in case of rectum cancer. The long-term effects of such combination treatment represent important issues of today's clinical research [28]. Overall, the awareness of late effects after cancer and their prevention and treatment is increasing, but there are still many questions to be answered, such as the overall burden of late effects for the individual or the interaction between aging and late adverse effects. The severity of late effects shows a considerable inter-patient variability. At present it is impossible to predict at start of cancer treatment to what extent an individual patient will develop late effects. Assessment of genetic susceptibility for radiation or chemotherapy effects may in the future contribute to increase our understanding of this interpatient variability [29–31]. The principal aims of long-term follow-up after cancer care are prevention, early diagnosis and treatment of morbidity related to cancer or its treatment, including evidence-based counselling. Further, insight into development and aetiology of the late effects after cancer treatment will assist toxicity-reducing modification of therapy in future cancer patients. However, oncologists and cancer patients should always bear in mind that the primary goal of cancer treatment is cure or at least long-lasting palliation. Today's research on long-term effects after cancer will hopefully enable the establishment of an optimal balance between this goal and the risk of inevitable long-term sequelae. Cost-effective guidelines have to be written for follow-up of the

different cancer types, based on the individual patient's risk of long-term toxicity and having in mind that the absolute number of long-term survivors with severe problems is low.

One major problem to establish cost-effective guidelines for long-term follow-up of cancer survivors is the fact that many severe late effects become clinically recognizable after latency of 10 years or more, at the time when the patient no longer is seen by the responsible oncological unit. Due to the relatively stable population in the Nordic countries and the high quality of population-based registries the Nordic countries have particular advantages to overcome this problem and to perform long-term research in cancer survivors in order to reach the above aim. A further challenge is to involve the primary health care service in the follow-up of cancer patients.

The present situation on follow-up of long-term cancer survivors in the Nordic countries

At present, there are no general guidelines for follow-up of long-term cancer survivors in the Nordic countries, though multiple studies performed at Nordic hospitals or Cancer Registries have provided valuable results concerning long-term morbidity after cancer.

In Sweden, the National Board of Health and Welfare (www.socialstyrelsen.se) has published regional as well as national cancer treatment programs for most tumour groups. These treatment programs discuss to some extent possible late effects related to treatment, but most of the recommendations are directed towards the detection of relapse and improvement of cancer-free survival.

The Danish National Cancer Plan II [32] recommends not only a general improvement in cancer health care services, but also an improved health care for cancer survivors. Cooperation between the primary care sector and oncologists is suggested to strengthen the quality of long-term rehabilitation for cancer survivors.

In 2004 the Directorate for Health and Social Affairs of Norway published National Cancer Plan [33], which also focused on long-term cancer survivors and possible late effects. The report suggested a national follow-up centre for long-term cancer survivors. In 2005, a National Centre for Long-Term Studies after Cancer was established at Rikshospitalet – Radiumhospitalet Medical Centre by the Norwegian Ministry of Health and Care Services. The main objectives of this division are to perform research on diagnosis, prevention and treatment of long-term side-effects and, if possible, to provide medical care to those experiencing such

adverse effects. The centre should also provide relevant guidelines to be used in future cancer patients.

How should follow-up of long-term cancer survivors in the Nordic countries be designed?

Recommendations for follow-up of long-term cancer survivors should be based on three steps:

1. Follow-up research: The type of long-term effects, their incidence and relation to previous cancer and their pathophysiology should be assessed. As not all morbidity in cancer survivors is related to their cancer experience, but may be a consequence of aging or an unhealthy life style comparison with age- and gender-matched normal population cohorts is essential.
2. Development of guidelines: Guidelines should be created in an attempt to put evidence from research into practice. Guidelines should address time schedules and type of examinations and determine which health care level is responsible for the follow-up. The guidelines should also outline essential features of a written Survivorship Care Plan to be given to the patient at the end of specialist oncological care. A Survivorship Care Plan should contain information on his/her treatment, complications and risk of adverse long-term effects and how the latter can be prevented or reduced.
3. Implementation: Communication with the community health care professionals and their appropriate post-graduate education are essential pillars of these phase when guidelines are to be transferred into clinical practice.

Step 1 Follow-up research

Patient- and treatment-related heterogeneity is a major challenge in follow-up research: A multitude of factors contributes to morbidity in cancer survivors such as environmental factors, life style (smoking, nutrition, physical activity) and patient-related variables such as age, gender and hormones [34,35]. In addition, the variability of tumour sites, variable treatment and responsiveness to treatment increase the complexity of follow-up research in cancer survivors.

Follow-up research may consist of retrospective cross-sectional studies, but should also be based on longitudinal investigations with repeated examinations of cohorts of interest. Cross-sectional studies in cancer survivors generally require the establishment of an age- and gender-matched control group in

order to identify the cancer-specific late toxicity. Cross-sectional studies are used for generating new hypotheses, whereas longitudinal studies contribute to a more casual evaluation of long-term trends in the development of late effects. One model for the longitudinal studies are repeated surveys among clearly defined large populations [36,37]. The cancer patients in such cohorts can be identified by merging with the Cancer Registry by the personal identification number given to each citizen in the Nordic countries. Such studies allow comparison of cancer survivors' incidence and prevalence of late effects with a cancer-free population. An example for such study is research done by Nord et al. [38,39], identifying cancer survivors in the Nord-Trøndelag Health survey [40]. The authors compared health problems in cancer patients with those of the cancer-free individuals based on data as registered in the Cancer Registry of Norway. However, information on treatment data and extent of the disease as recorded to the National Cancer Registries is often incomplete. Registry-based studies need therefore to be supplemented by more detailed clinical studies evaluating the impact of overall treatment, pre-treatment co-morbidity and major post-treatment health events. Questionnaire-based surveys among cancer survivors from population-based studies should be combined with clinical examinations which also provide the possibility to collect biological material for the assessment of genetic and biochemical profiles thus increasing the understanding of pathophysiological pathways.

A third option of long-term cancer research would be to use data from large phase III clinical trials [37]. In such studies, a large cohort is usually identified characterized by relatively similar pre-treatment eligibility criteria and standardised treatment modalities. Another benefit of this approach is that cancer survivors from large phase III trials are regularly monitored resulting in longitudinal data which could be helpful in the understanding of intermediate steps leading to possible late effects.

Step 2 Development of guidelines for follow-up of cancer survivors

Clinical guidelines are systematically developed statements to assist specialists, general practitioners and patients to decide about appropriate health care for cancer survivors [41]. The intention should be to decrease adverse health effects related to cancer and to increase quality of life. Evidence-based guidelines are based on linkage between the therapeutic exposure and observed late effects and their risk factors including screening recommendations considering clinical experience.

Guidelines for follow-up care of long-term cancer survivors should at least include recommendations for a) monitoring of health status, b) early detection of late effects, c) treatment of late effects and d) life style adjustments.

As cancer therapy differs in relation to the type of cancer, the patient's age, the calendar year period of treatment guidelines have to take into account this variability [42].

Step 3 The implementation of guidelines

The implementation of guidelines should take the local situation and resources into consideration. The general practitioners' adherence to guidelines is critical when translating recommendations into clinical practice [41]. Many clinicians may be unwilling to change their routine due to "no interest", or they may have concerns about patient or peer resistance. Implementation of guidelines means a permanent change of the way work is done previously [43]. One way of changing is to follow the plan-do-study-act-cycle (PDSA-cycle) (www.ihl.org) which tests a change in the real work-setting by 1) planning the change, 2) trying it, 3) observing the results and 4) acting on what is learned. After testing the change in a small scale and refining the change through several PDSA cycles, the change is ready for use on a broader scale. Thus implementation of guidelines should for example start with one malignancy gradually expanding the task to other cancer types.

Caring for long-term cancer survivors

Care across the cancer continuum implies longitudinal care from diagnosis until death, regardless of the patient's age [34]. The first phase of caring for long-term survivors includes treatment planning which considers individual patients balance between responsiveness to treatment and the risk of acute and late complications. When long-term survival is achieved maintenance of "health as good as possible" and prevention of cancer-related morbidity is the intention of the second phase. In this phase care should include physical, psychological, social services as well as information to and education of cancer survivors concerning their risk and how to reduce it by i.e. change of life style.

Models of care are needed, which take into account the required frequency and intensity of follow-up for the individual survivors [44]. High-risk cancer survivors and low-risk cancer survivors should be identified according their risk of developing late effects. Low-risk cancer survivors may be referred to the primary care for further follow-up

care, whereas high-risk cancer survivors may need follow-up at late effect clinics. The referral to primary care requires an ongoing guidance from the cancer centre with respect to the monitoring and management of late effects within a shared care model [45]. Contact between the primary care and the late effects clinic should be on at least an annual basis either phone, mail or electronic contact. The complexity of long-term late effects makes the care for cancer survivors time-consuming, which may make it difficult to integrate follow-up care into a busy primary care practice.

The introduction of a Survivorship Care Plan may be the first step to implement long-term care for cancer survivors into the community care. This document is a brief summary of what happened during the phase of primary intervention and eventually during treatment of relapse and the control period at the oncological unit. Furthermore, an outline should be given about possible late effects and how to monitor and prevent them. This document is provided to the cancer survivor when he/she is dismissed from regular follow-up by oncologists and should be shown to any new physician contacted by the cancer survivor.

One important aspect is whether cancer survivors will comply with guidelines of regular follow-up during many years, sometimes for life time. Some cancer survivors may have reservations about the benefits of follow-up care. Barriers of attendance may also be due to negative emotions associated with being reminded of the cancer experience by each follow-up visit. Though it has been postulated that the experience of cancer increases the willingness to make life style changes [46] the persistence of such psychological attitude over years remains unclear. Cancer organisations should be involved when discussing appropriate models for follow-up. Finally, ethical considerations should not be overlooked. It is, for example, by no means clear when and how the cancer survivors should be informed about possible late effects.

Conclusions

The overall burden of late effects in the individual long-term survivor after adult cancer is still unclear, though recent years' research has documented considerable late toxicity in malignancies of young individuals with for example Hodgkin's lymphoma and testicular cancer. Continuous retrospective and prospective follow-up research is needed not only to evaluate the treatment of yesterday but also to evaluate the possible late effects of cancer therapy used today and of tomorrow. Development and implementation of guidelines are necessary to put

the achieved evidence from research into practice and to increase the quality of long-term follow-up care. A first and feasible step is the design of Survivorship Care Plan for the larger cancer types.

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Appendix I: Survivorship research in the USA from the perspective of ASCO

Cancer survivors in the USA represent an important and growing constituency, with over 10.5 million survivors today, representing about 3.5% of the population [47]. With the aging of the population, this number will increase dramatically. In recognition of this problem, the American Society of Clinical Oncology (ASCO) established a Survivorship Task Force in 2005 with the goal of surveying what activities ASCO was involved in related to survivorship and to develop strategies to incorporate survivorship into educational and clinical goals of the organization. To this end, ASCO participated in the dissemination activities for the Institute of Medicine report on adult cancer survivors. "From Cancer Patient to Cancer Survivor: Lost In Transition," published in 2005 and followed by a one day symposium to elaborate on the findings from the report [48,49]. ASCO also established a "Patient and Survivor" track within its annual meeting program in 2006, and has begun to develop a series of survivorship focused guidelines. A central recommendation of the Institute of Medicine report was the identification of the need for an end of treatment summary and survivorship care plan. To this end, ASCO is developing model templates for these reports, with a plan for their dissemination in 2007.

Appendix II: Late effects and follow-up care needs among cancer survivors in the US, National Cancer Institute

There are an estimated 10.5 million cancer survivors in the United States today, and worldwide figures stand at approximately 24 million. Current trends indicate that the majority of those diagnosed with cancer will survive for extended periods of time.

However, most widely used cancer treatments are known to carry substantial risk of adverse long-term or late treatment related effects [50,51]. These adverse consequences among the sizeable population of cancer survivors are challenging – how is long-term follow-up care to these individuals best provided [52,53]. Given the median age at diagnosis (67–68 years) and length of time projected for survival, co-morbid conditions also may exert an impact on post treatment follow-up care [54,55].

It is increasingly being acknowledged in the USA the necessity to develop effective research priorities and recommendations for clinical care, education, and policy related to care for survivors of cancer. Two points may act as driving principles when achieving this goal: (a) the population of cancer survivors consists of individuals with varying needs and issues – those cured of their disease and no longer undergoing active treatment, as well as those with recurrences or resistant disease requiring ongoing treatment; and (b) regardless of disease status, any survivor may experience lasting adverse effects of treatment [56].

Research conducted with cancer survivors indicates that long-term adverse outcomes are more prevalent, serious, and persistent than expected [50–53]. However, the late effects of cancer and its treatment in survivors, especially among those diagnosed as adults, and/or those belonging to ethno culturally diverse or medically underserved groups, remain poorly documented [50–53]. In addition, it has been shown that survivors of cancer have significantly poorer health outcomes on multiple burden-of-illness measures than do people without a history of cancer. These health decrements may occur or continue many years after diagnosis [57]. Compared with matched controls with no history of cancer, it has been reported that it is more likely that survivors would not receive recommended care across a broad range of chronic medical conditions (e.g., angina, congestive heart failure, and diabetes) [56]. Quality-of-life issues in long-term survivors of cancer differ from their problems at the time of diagnosis and treatment [58,59]. Thus, the recognition that interventions with the potential to treat or ameliorate late and chronic effects of cancer and its treatment must be developed, evaluated for efficacy, and disseminated [46,52].

In a recent study, Aziz et al. provided a detailed description of comprehensive long-term follow-up (LTFU) programs for paediatric cancer survivors in the USA [60]. The primary benefits of providing health care to survivors through formal LTFU programs included the following:

- a. Health care delivered by clinicians familiar with long-term risks of survivors;
- b. Provision of risk-based screening and surveillance for late effects; and
- c. Targeted education for risk reduction and healthy lifestyles.

Key system-driven and survivor-driven barriers to the functioning of existing LTFU programs included the following:

- a. Inadequate resources to sustain programs (system-driven);
- b. Low institutional commitment toward the provision of survivorship care (system-driven);
- c. Lack of capacity to care for the growing population of survivors (system-driven);
- d. Difficulties with regular communication with community physicians (system-driven);
- e. Lack of interest (survivor-driven); and
- f. Lack of awareness of cancer-related risks (survivor-driven).

Consequently, the critical challenges, as survivorship care evolves, will include integrating a structured process of program evaluation and building capacity for care [60].

The larger scientific community has begun to champion the need for cancer survivorship research, and to call for solutions that will lead to both increased length and quality of life for all cancer survivors. This demand is reflected in the language of several Institute of Medicine (IOM) reports, PRG documents, and US National Cancer Institute bypass budgets. The IOM Report on cancer survivors diagnosed as adults articulates key areas for research and care delivery, especially with respect to the development of a formal care plan for survivors that integrates, within one document, key treatment relevant variables, exposures, late effect risks, and management/follow-up care needs [49]. The recent IOM report on childhood survivorship cites the need to create and evaluate standards and alternative models of care delivery, including collaborative practices between paediatric oncologists and primary care physicians as well as hospital-based long-term follow-up clinics [61]. Another IOM Report, *Ensuring Quality Cancer Care*, recognized that attributes of high quality care could be linked to optimal outcomes such as enhanced length and quality of survival, and that continued medical follow-up of survivors should include basic standards of care that address the specific needs of long-term survivors [52].

In the USA, the majority of cancer survivors return to their primary care providers for medical follow-up once treatment ends, many of whom may be unaware of the additional health risks of cancer treatment. Provider education and training is thus necessary. Extant published international long-term follow-up care guidelines provide a logical basis for

informed practice, but are not truly evidence based and must be updated regularly and communicated optimally to providers and survivors to be truly effective and useful [62,63].

The lack of evidence base that can help tailor optimal care strategies needs to be addressed. The relative roles of primary care providers and specialists in the care of cancer survivors are not clear. Developing and testing interventions that examine outcomes among groups of survivors managed under different follow-up care settings is a critical need. The recommendations arising out of the Acta Oncologica Meeting are an important step in deli-

neating potential directions we could follow in order to add to the growing knowledge base of cancer survivorship and to facilitate the development of evidence based follow-up care and surveillance strategies in this health vulnerable group of individuals diagnosed with cancer. Findings from methodologically rigorous studies will improve our understanding of the nature and extent of the burden of illness carried by cancer survivors, yield key information regarding follow-up care, and facilitate future efforts focusing on the development of standards or best practices for such care, especially when notable health disparities might exist.