

Pediatric Cancer Survivors: Past History and Future Challenges

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Introduction

Modern therapy for childhood cancer began about 1970, and by the middle of that decade, many children who had discontinued treatment continued to remain in remission. Survival curves of children and adolescents treated during the 1970s remained flat following a period specific to each tumor type; for embryonal tumors, this generally occurred two years after diagnosis, while for leukemia and brain tumors, the period of risk extended for several years after therapy had been discontinued. The concept of cure followed the recognition that many children with cancer could achieve long-term survival. At the same time, concern regarding the prospects for the continuing health of these survivors began to be expressed. Research was conducted initially by interested investigators at single institutions and then, because of the need to study more subjects, consortia, such as the Late Effects Study Group (LESG), comprised of several institutions were formed. The Children's Cancer Group (CCG) and others also began to study the physical and psychologic health of surviving children who had been enrolled on cooperative group trials. In more recent times, more precise analyses of treatment and outcome have been performed, and finally, efforts have been made to initiate and study surveillance and intervention in the clinical setting. (Table 1)

Clinical trials have confirmed that there are large numbers of youngsters and young adults who are cured and who have many years of productive life ahead of them. That growing body of knowledge has also revealed a wide range of outcomes: while many survivors are leading normal lives with no apparent disability, some have been left with long-term sequelae, ranging from mild cosmetic changes to life-threatening cardiac and renal disease. The past 20 years have witnessed further improvements in the cure rates; it is now believed that 3 of every 4 children treated for cancer will be long-term survivors. At the same time, many more studies of health-related outcomes began to link specific aspects of therapy to certain undesirable consequences. The psychologic consequences of having survived a life-threatening illness also began to emerge as a significant research endeavor in a number of treating institutions. This knowledge led to numerous clinical trials testing the effectiveness of treatment modifications designed to reduce or eliminate late complications, and to recommendations for surveillance and follow-up of survivors. Questions have also been raised concerning the optimal method of gathering non-biased data regarding the

health and quality of life of long-term survivors. Numerous practical and ethical issues have been raised regarding research methodology in light of the reluctance of large numbers of subjects to return for ongoing care. Absence of adequate medical coverage for follow-up studies can lead to problems in providing necessary clinical care and in assuring that bias does not influence research results.

Certain landmarks in the history of survivorship research in pediatric oncology are worth reviewing. (Table 2) In the decade of the 1970s, pediatric oncologist began to recognize that cure was possible and, through randomized trials, investigators developed effective protocols. As more became known regarding prognostic factors in the 1980s, therapy could be reduced for some patients. During the last decade, we began to understand the relationship between dose and outcome, and initiated efforts to educate survivors. The record of these accomplishments, and the difficulties inherent in conducting high quality research and providing appropriate follow-up care to long term childhood cancer survivors that is evidence-based, is the subject of this paper.

The Early Years

Reports of a sea change in survival for children with cancer during the last three decades fail to acknowledge that the major gains began when changes in therapy occurred in the late 1960s and early 1970s. As early as 1960, pediatric oncologists recognized that chemotherapy could induce remissions in leukemia, lymphoma, and Wilms' tumor. (1) Later on, it was learned that chemotherapy could effectively shrink embryonal tumors, such as rhabdomyosarcoma rendering them amenable to cure with surgery and radiation therapy. (2) Before that watershed era, solid tumors in children were treated primarily with surgery (sometimes mutilating) and radiotherapy (often in doses used to treat adults without consideration of normal tissue tolerance in children). When chemotherapy was employed, rarely in the treatment of solid tumors, more often for leukemia and lymphoma, it was with one or at most two agents, the second agent being added when the patient failed to respond to the first drug.

As pediatric neoplasms responded to chemotherapy during the latter part of the 1960s, some principles governing the rational use of chemotherapy began to be elucidated. The most

important of these resulted from an awareness of the development of resistance to a single, specific class of drugs and led to the recommendation that multiple agents whose mechanisms of action differed could be used together to prevent emergence of resistant strains. An additional benefit of using multiple agents was that one could use more total chemotherapy but less of any single agent with less dose-dependent specific toxicity. In the treatment of solid tumors by utilizing adjuvant therapy with multiple agents, and by combining chemotherapy with radiation therapy and surgery, it soon became apparent that many children were able to remain in remission even when treatment was discontinued. In childhood leukemia, the introduction of so-called prophylactic treatment to the central nervous system and the use of multiple drugs given simultaneously rather than sequentially, also resulted in sustained remissions. (3)

Recognizing that radiation and the drugs used to treat cancer could themselves be responsible for creating new neoplasms, the same individuals began to express concern regarding the subsequent carcinogenic risks. In 1972, Drs. Giulio D'Angio, a pediatric radiation oncologist and Audrey Evans, a pediatric oncologist, were awarded a contract from the National Cancer Institute with Drs. Robert Miller, Joseph Fraumeni, and Curtis Harris as Project Officers. I was recruited as the Research Fellow on the study to review the records of children who had successfully discontinued therapy at the three major pediatric cancer treatment centers in Philadelphia, Boston, and Columbus, Ohio for the purpose of recording additional benign and malignant neoplasms. Although the National Cancer Institute was primarily concerned with carcinogenesis, many of us felt that there were likely to be other serious long-term disabilities for which these survivors were at risk. During the planning phases of the study, and in view of the extensive effort required in identifying and abstracting the records, a decision was made, therefore, to record all disabilities and any dysfunction that might be a consequence of treatment. (4,5)

Shortly after beginning the record review at the Children's Hospitals of Philadelphia, Boston and Columbus, 8 more institutions were recruited and the Late Effects Study Group was officially launched. The chart review was interesting and revealing. Although many records contained only the notation "NED" without reference to educational or vocational status, psychosocial adjustment, timeliness of secondary sexual development, marital status, or any other aspects of survival that could impact the quality of that survival, significant late effects were

reported. (6) Second malignant neoplasms (SMN) were reported and it was possible to relate the SMN to treatment and, sometimes to genetic predisposition. (7, 8,9) For the purpose of publishing more precise incidence data regarding SMN, it was essential that information regarding certain clinical characteristics of the patients and the therapy given to all patients at risk at each of the LESG institutions be accurately recorded and analyzed. Margaret Tucker traveled to each of the institutions and recorded data on over 9,000 survivors. Analysis concerning the prevalence and risk of second cancers were carried out with the assistance of others at the Epidemiology Branch of the National Cancer Institute. (10) Subsequently, publications analyzing the relationship of bone cancer, leukemia, and thyroid cancer to treatment were published. (11, 12,13)

Some of the LESG institutions were also members of the Children Cancer Group (CCG). Spearheaded by investigators at these institutions, efforts to study survivors who had been enrolled in the CCG clinical trials began, and a number of cohort and case control studies dealing with endocrine function, school performance, and second tumors were initiated. (14, 15,16) Studies of cohorts of survivors and of specific functional systems, such as intellect and growth, some using a variety of factors, including age, sex, chemotherapy, and radiation dose, to construct models for the end results, were reported. (17, 18, 19) The National Wilms' Tumor Study Group has also reported on several long term effects of therapy in the patients they have been able to contact through their Late Follow-up Study. (20,21,22)

Coincident with the development of these studies of survivors, clinical trials in Wilms' tumor, acute lymphocytic leukemia, early stage neuroblastoma, lymphomas, and sarcomas began to incorporate therapeutic questions for selected groups of patients whose survival was excellent that sought to reduce therapy with the potential for adversely affecting the quality of survival. The earliest critical questions tested whether the elimination of radiation or reduction in the radiation dose adversely affected survival with the implicit, if not proven, contention that radiation therapy was deleterious to growing children. Those clinical trials proved successful in that chemotherapy could be substituted for radiation without adversely affecting survival and with significantly fewer late effects. (23,24) By substituting cyclophosphamide for mechlorethamine in the treatment of Hodgkin's disease, and by altering the schedule of administering etoposide, the risk of secondary leukemia was greatly reduced. (25, 26) (Table 3)

Survivors

By the decade of the '90s, it was estimated that, overall, 75% of children and adolescents with cancer could be cured. (27) Similar projections are now possible for youngsters with acute lymphocytic leukemia, the diagnosis that comprises one-third of childhood cancer. The expectation is better for Wilms' tumor, non-Hodgkin's lymphoma and Hodgkin's disease patients with at least 85% expected to be cured. The outlook is not so good for children with brain tumors, neuroblastoma and non-lymphoid leukemia, and efforts are underway to improve this by utilizing yet more aggressive therapy. Approximately 20 years ago, based on a 60% long term survival rate, we estimated that 1 in 1000 young adults would be a survivor of childhood cancer. (6) We can now modify that prediction, utilizing the more recent results, and including adolescents as well. Since cancer occurs in 1/300 children and adolescents from birth to 20 years of age, and 75% can be expected to survive long-term, survivors will comprise 1/450 individuals in the population.

The term "survivor" emerged in the 1970s and since then the definition has been surrounded by some controversy. Some people propose that a survivor is an individual with cancer who is alive from the day of diagnosis forward. However, if one is studying the quality of survival, and long term survival can result in as many as 70 years of life following successful treatment, it seems best to separate the effects that occur at the time of treatment or shortly thereafter from those that will be present throughout the life of an individual. Children with cancer have few competing conditions that are likely to prove fatal, and surviving cancer can be considered synonymous with cure. It is the quality of the long lives that lie ahead for childhood cancer survivors that is the focus of pediatric late effects research. We have recommended the following definition of a pediatric cancer survivor: someone who has survived for at least five years from the last evidence of disease and is at least two years from discontinuation of therapy since we believe that patients who are likely to be cured are the most relevant subjects for study of late effects. This definition, or a minor variation of it, is now accepted by most pediatric oncologists who are engaged in outcomes research.

Late Effects

In the last 20 years, there have been many reviews describing the consequences of treatment and some have even recommended that certain follow-up evaluations be performed with varying periodicity. (28-30) Complications, disabilities, or adverse outcomes that are persistent and are the result of the disease process, the treatment or both, are generally referred to as 'late effects.' They may be clinically obvious and consist of functional or cosmetic disturbances that interfere with activities of daily living such as amputation or severe cognitive impairment. These are usually immediately apparent from the history and physical examination. Some are subtle and apparent only to the trained observer, such as asymmetry of the trunk or scoliosis, and some are sub-clinical and detectable only by lab screening or imaging techniques, such as infertility, hypothyroidism or malabsorption. The problem of attribution of effects is relatively easy in pediatrics, since the childhood years are generally free of the morbidity that follows therapeutic intervention for cancer, such as congestive heart failure, infertility, and a decline in cognitive function.

Surgery, radiation therapy and chemotherapy are capable of causing changes that qualify as late effects in every organ and system of the body. Procedures and agents, under certain circumstances and following particular doses, have been identified as having tissue-specific late effects. A summary of potential late effects in children needs to consider the changes that take place during the developmental stages from infancy to adulthood. Physiologic and psychologic changes occur and are especially impacted by agents that inhibit the growth of tissues, such as radiation and certain drugs. Since children are most severely affected by these agents, and since they were the earliest recipients of treatment with chemotherapy combined with radiation, it was possible to organize and summarize the late effects following treatment for childhood cancer. Table 4 presents an outline for categorizing these late effects.

Second cancers, or new malignancies that are clearly not recurrences of the original neoplasm, are a late effect that has been well-studied by many groups and often reviewed.(7-13,16, 20, 31-43) Several etiologic factors are now well known to contribute to an increase in risk of developing more than one malignant disease. Therapy with radiation and certain classes of drugs are the most frequent of these factors, although a small subset of children is genetically predisposed. This latter group includes all children with neurofibromatosis, type 1, and children

with the genetic form of retinoblastoma.(9, 44,45)A syndrome characterized by sarcomas in children and breast cancer in young adult women, the Li-Fraumeni syndrome, may also be responsible for multiple cancers in few susceptible individuals. (46-48) Together these groups comprise less than 3% of the childhood cancer population. As is the case with the study of other late effects, the study of second cancers has enabled researchers to find genes whose mutations are in somatic cells associated with cancer even in non-predisposed individuals.

The problem of quantifying the severity of sequelae is one that has not yet been solved. At the Children's Hospital of Philadelphia, in studies of quality of life, including school performance and psychologic adjustment, we have used a three-point scale that we believe is valid and describes the severity of most physiologic changes that occur as a result of therapy. (49) In more recent work, we have expanded to a four-point scale that permits somewhat more precision. (Appendix) There is an ongoing effort by the Cancer Therapy Evaluation Branch of the NCI to modify the Common Toxicity Criteria (CTC) manual now on-line to include all effects of therapy, both acute and late. As is the CTC, it is expected that this system would be used by cooperative groups and others. Precision in quantifying effects of treatment over the entire life of a patient would be a valuable tool and provide an additional dimension to the evaluation of therapeutic efficacy.

Research in a Clinical Care Setting and Clinical Care in a Research Setting

There is general agreement regarding two important functions that a follow-up program for cancer survivors should accomplish: to provide clinical care and to conduct high quality research. Although pediatric oncologists have become accustomed to this duality of function in connection with clinical trials and therapy for cancer, and they are able to perform both functions well, it may present major challenges in the context of follow-up after therapy is complete. An essential component of a successful program in which both are taking place is awareness on the part of the clinician and the researcher that the objectives and methods of providing excellent clinical care and of conducting quality research are different.

Clinical care of childhood and adolescent cancer survivors requires a focus on potential adverse late effects based on relevant demographic factors, the initial diagnosis, site(s) of disease, and specific therapies in order to provide counseling and guidance for the future. (Table 5)

Evaluations, including radiographs, laboratory studies, and interventions should be based on the data concerning potential late effects of the therapy received. Often, the assistance of dedicated and knowledgeable subspecialists is required. Follow-up also needs to include attention to the principles of good preventive medicine and screening as appropriate based on the age, sex, length of follow-up and other characteristics of the individual.

On the other hand, research requires that the investigator articulate testable hypothesis and specific aims prior to initiating a study. Attention to methodologic issues, such as ascertainment of cases and exposures, and care in selecting the most appropriate instruments for evaluating outcomes, is required. Since pediatric survivors grow up, leave their families, marry and change their names, it is often difficult to secure a representative, non-biased population for research. Added to this is the problem of reluctance on the part of the survivor to return to the site of former trauma. This avoidance is one of the manifestations of a post-traumatic syndrome. (49) The selection of appropriate controls, therefore, for a given outcome may be difficult, with unaffected and well survivors either not returning or choosing not to participate in research that does not bear on their own problem. On the other hand, without controls, there is a risk of overestimating adverse outcomes. For studies of intervention, there is the ethical problem of withholding from the control group something that may be viewed as important to health. Some groups have solved this problem by having a "wait-list" control group, assessing both before and after the intervention in question.

Nevertheless, if attention is paid to methodologic issues, research regarding late effects can best be carried out successfully in the context of a clinical survivorship program. Clinics offer the opportunity of evaluating standardized approaches to follow-up, of conducting pilot studies and of testing interventions. Since pediatric cancer is rare, research regarding late effects has required the collaborative efforts of many investigators and institutions. The cooperative efforts of these consortia will continue to be useful in two areas that require many subjects: research regarding the value of interventions to prevent disability and research concerning the most appropriate venue and method of long term follow-up care.

Transition from Pediatric Acute Care to Lifetime Adult-Oriented Care

Pediatric oncologists have been pioneers in developing programs that provide multidisciplinary, coordinated care to survivors of childhood and adolescent cancer, and there have been reports of several institutional models for follow-up. (50) However, pediatric oncologist cannot continue to provide follow-up care for all patients once they have reached maturity so long as their risk of recurrence is negligible. Limited resources and the mind-set devoted to "stamping out disease" is in conflict with that of "wellness and health promotion" that needs to be intrinsic to a survivor program.

The transition from the childhood and adolescent years to adulthood is often delayed in survivors of childhood cancer, but as the number of survivors of childhood cancer is expected to increase, the importance of transition care for this population is now recognized. In other conditions in which children with chronic diseases require transition to an adult care setting, several models of care have been proposed. (51-54) Survivors of childhood cancer do not quite fit any of these models, although they can be utilized with modifications in our population. Our patients are generally well, and often require the expertise of any one or more of the following subspecialists cardiologist, nephrologist, pulmonologist, gynecologist, neurologist or gastroenterologist. None of the models proposed for children with chronic diseases can assure a smooth transition from the pediatric acute care setting to the adult setting in which prevention and general well-being are paramount, and few institutions have sufficient resources to draw upon the expertise of the numerous subspecialties in adult medicine required to tend to the needs of all cancer survivors.

General pediatricians and internists encourage care to continue with pediatric oncologists. If they undertake such follow-up, they either subject patients to excessive monitoring or, due to their inadequate knowledge base, provide inadequate follow-up. However, it is these very practitioners who are trained to promote good health practices and avoidance of risk-taking behaviors, such as smoking, excesses of food and alcohol consumption, and unsafe sex..

An ideal model might be one in which pediatric oncology and general practitioners, internists, or gynecologists share future care. The patient might be discharged from the Pediatric Oncology Follow-up Clinic armed with information concerning previous treatment, complications of treatment, and the risks to long term health. The patient remains the guardian of this information, is counseled to be aware of signs and symptoms of health problems, and is able to convey this information to the practitioner who is responsible for instituting the health-promoting and early detection practices intended to prevent more serious disease.

Conclusion

One of the most salutary improvements during the last two decades in treating children with cancer has been the emphasis on so-called "prognostic factors" in selecting treatment appropriate to the risk of recurrence. This has spared those children who derive no added benefit from more aggressive regimens and from their potential late effects. This process needs to continue, and concern for long-term deleterious effects should enter into consideration of future protocols. Unhappily, however, children who now are expected to fare poorly are being subjected to ever more intensive therapy, and should they survive, they can be expected to suffer from more serious complications as they age, complications that will not become known for many years.

The majority of surgical procedures, radiation therapy practices, and drug combinations offered now have been in use for many years and will continue to be in the future. Most pediatric oncologists have adequate knowledge of the specific potential morbidity associated with cancer and various treatment modalities. But not all are capable of imparting this information in a way that provides long-term survivors with the tools to manage their own health. Early detection and prevention of serious illness can best be accomplished if survivors are encouraged to be responsible for their own care. Achieving this realistic goal should be an objective.

There are several challenges for the future. (Table 6) Follow-up care for pediatric cancer survivors should be a coordinated effort of the pediatric oncologist and the generalist. It is exceedingly important to establish mechanisms by which primary care providers become knowledgeable about the late sequelae of anti-cancer treatment and its potential consequences on adult health. They also need to be informed regarding the value or lack of value of certain

screening measures. Survivors need to be educated regarding their risks and about what they can do to prevent or detect serious illness. Our present health care system does not provide a way to accomplish this goal and many survivors do not undergo appropriate screening and interventions for their prior treatment exposures, while some are subject to excessive intervention. Research should provide data on which to base decisions concerning the optimal system of follow-up care delivery in a variety of communities and institutions. It will not be easy to conduct that sort of research without the biases and inequities intrinsic to our present health care system, and with the other methodologic problems inherent in research for this growing and aging population.

It is especially important to continue to provide all survivors with appropriate follow-up care based on their expected risks, and to conduct research that can inform subsequent generations of oncologists responsible for designing clinical trials. As new treatments become widely accepted, follow-up intended to keep track of late-occurring toxic events should be incorporated into the clinical care of patients receiving therapy. In this way future generations of clinicians will be able to assess the impact of these treatments on long-term quality of life. The combined efforts of pediatric oncologists and general practitioners will be required to observe, catalog, and report the consequences of these newer agents and combinations. As our appreciation of the life long effects of treatment and life-style in older survivors increases, we will be able to rationally determine long-term risk-benefit ratios, and to increase our knowledge of the mechanisms of the diseases that we produce.

Table 1: Evolution of Late Effects Research

Anecdotal reports

Case series

Prospective studies

Dose-response relationships

Modifications of therapy

Surveillance recommendations

Intervention/prevention

Table 2: Landmarks in Pediatric Oncology by Decade

1970s

Recognition that cure was possible

Proliferation of randomized clinical trials

Effective multi-modality protocols

1980s Tailoring therapy to risk factors

Defining late effects

Reducing radiation dose

Substituting effective drugs for radiation

1990s

Understanding the relationship of dose to late effects

Distinguishing research from clinical care

Initiating efforts to track and educate survivors

Table 3: Modifications of Therapy Resulting from Late Effects Research

Elimination or reduction in dose of radiation in acute leukemia, Wilms' tumor and lymphomas

Substitution of cyclophosphamide for mechlorethamine in the treatment of Hodgkin's disease

Alteration in schedule for administration of etoposide

Guidelines for counseling and surveillance of long term survivors

Development of educational materials for childhood cancer survivors

Table 4: Late Effects in Pediatric Oncology

Growth and Development

Linear growth

Skeletal maturation

Intellectual function

Emotional and social maturation

Sexual development

Fertility and Reproduction

Fertility

Health of Offspring

Vital Organ Function

Cardiac

Pulmonary

Renal

Endocrine

Gastrointestinal

Vision/Hearing

Second Neoplasms

Benign

Malignant

Table 5: Functions of a Follow-up Program

Provides support, counseling, anticipatory guidance
Directs multidisciplinary, coordinated health care
Facilitates health education and early detection based on therapy
Enables research regarding health-related outcomes
Standardizes follow-up to study effects of therapy modification

Table 6: Childhood Cancer Survival: Opportunities and Challenges for the New Millennium

Surveillance, counseling and intervention based on risk of future disease
Education of patients to share responsibility for their own care
Evaluation of intervention to reduce and/or prevent late effects
Modification of protocols based on studies of long term survivors
Research on the effects of new agents and the aging process
Improvement in tracking and follow-up into adulthood
Reducing the economic and other barriers to follow-up care

References

1. Farber S. Chemotherapy in the treatment of leukemia and Wilms' tumor. *JAMA* 198:826, 1966.
2. Wilbur JR. Combination chemotherapy for embryonal rhabdomyosarcoma. *Cancer Chemother Rep* 58:281, 1974.
3. Simone J, Aur RJ, Hustu HO, et al. "Total therapy" studies of acute lymphocytic leukemia in children. Current results and prospects for cure. *Cancer* 30:1488-1492, 1972.
4. Meadows AT & D'Angio GJ. Late effects of cancer treatment: Methods and techniques for detection. *Semin Oncol* 1:87-90,1974.
5. Meadows AT, D'Angio GJ, Evans AE, Harris CC, Miller RW, Mike V. Oncogenesis and other late effects of cancer treatment in children. *Radiology* 114:175-180,1975.
6. Meadows AT, Krejmas NL, Belasco JB for the Late Effects Study Group. The medical cost of cure: Sequelae in survivors of childhood cancer. In: Status of the Curability of Childhood Cancers, van Eys J and Sullivan MP, (Eds), Raven Press: New York, 1980, pp. 263-276.
7. Meadows AT, D'Angio GJ, Mike V, Banfi A, Harris C, Jenkin RDT, Schwartz A. Patterns of second malignant neoplasms in children. *Cancer* 40:1903-1911, 1977.
8. Mike V, Meadows AT, D'Angio GJ. Incidence of second malignant neoplasms in children: Results of an international study. *Lancet* 2:1326-1331, 1982.
9. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RDT, Marsden B, Nesbit ME, Newton W, Oberlin O, Sallan SG. Second malignant neoplasms in children: An update from the Late Effects Study Group. *J Clin Oncol* 3:532-538, 1985.
10. Tucker MA, Meadows AT, Boice JD, Hoover RN, Fraumeni JF. Cancer risk following treatment of childhood cancer. In Radiation Carcinogenesis: Epidemiology and Biological Significance, Fraumeni, J.F., & Boice, J.D. (Eds). Raven Press, NY pp 211-224, 1984.
11. Tucker MA, Meadows AT, Boice JD, Stovall M, Oberlin O, Stone BJ, Birch J, Voute PA, Hoover RN, Fraumeni JF. Leukemia after therapy with alkylating agents for childhood cancer. *JNCI* 78:459-464, 1987.
12. Tucker MA, D'Angio GJ, Boice JD, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 317:588-593, 1987.
13. Tucker MA, Morris-Jones PH, Boice JD Jr, Robison LL, et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. *Cancer Res* 51:2885-2888, 1991.

14. Robison LL, Nesbit ME, Sather HN, Meadows AT, Ortega JA, Hammond GD. Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. *Am J Pediatr Hematol/Oncol* 6:115-121, 1984.
15. Hamre MR, Robison LL, Nesbit ME, Sather HN, Meadows AT, Ortega JA, D'Angio GJ, Hammond GD. Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol* 5:1759-1765, 1987.
16. Neglia JP, Meadows AT, Robison LL, Ruymann F, Newton W, Kim T, Sather H, Hammond D. Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 325:1330-1336, 1991.
17. Meadows AT, Gordon J, Massari DJ, Littman P, Fergusson J, Moss K. Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. *Lancet* 2:1015-1018, 1981.
18. Silber JH, Littman PS, Meadows AT. Stature loss following skeletal irradiation for childhood cancer. *J Clin Oncol* 8:304-312, 1990.
19. Silber JH, Radcliffe J, Peckham V, Perilongo G, Kishnani P, Fridman M, Goldwein JW, Meadows AT. Whole-brain irradiation and decline in intelligence: The influence of dose and age on IQ score. *J Clin Oncol* 10:1390-1396, 1992.
20. Breslow NE, Takashima JR, Whitton JA, et al. Second malignant neoplasms following treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 13:1851-1859, 1995.
21. Ritchey ML, Green DM, Thomas PRM, Smith GR, Haasse G, et al. Renal failure in Wilms' tumor patients: A report from the National Wilms' tumor Study Group. *Med and Pediatr Oncol* 26:75-80, 1996.
22. Greene DM, et al. Congestive heart failure after treatment for Wilms' tumor: A report from the National Wilms' Tumor Study group. *J Clin Oncol* 19:1926-34, 2001.
23. D'Angio DJ, Breslow N, Beckwith B, Evans A, et al. Treatment of Wilms' tumor: Results of the Third National Wilms' Tumor Study. *Cancer* 64:349-360, 1989.
24. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: A Children's Cancer Group Phase III trial. *J Clin Oncol* 11:527-537, 1993.
25. Schellong G, Potter R, Bramswig J, et al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: the German-Austrian multicenter trial DAL-HD-90. The German-Austrian Pediatric Hodgkin's Disease Study Group. *J Clin Oncol* 17:3736-44, 1999.

26. Smith MA, Rubinstein L, Anderson JR, et al. Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol* 17:569-77, 1999.
27. Ries LAG, Smith MA, Gurney JG, et al. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*. Bethesda, National Cancer Institute SEER Program, 1999.
28. Meister LA, Meadows AT. Late effects of childhood cancer therapy. In: Current Problems in Pediatrics, Fost N, Winter RJ (Eds), Mosby Year Book, p. 102-131, 1993.
29. Schwartz CL, Constone LS, Hobbie WL. Algorithms of late effects by disease, in *Survivors of childhood cancer: assessment and management*, C.L. Schwartz, et al., Editors. 1994, Mosby: St Louis. p. 7-21.
30. Blatt J, Copeland DR, Bleyer WA. Late Effects of Childhood Cancer and Its Treatment in Principles and Practice of Pediatric Oncology. Pizzo and Poplack (eds): Lippincott-Raven Publishers, Philadelphia, 1997.
31. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows AT. Breast cancer and other second neoplasms following childhood Hodgkin's disease: a report from the Late Effects Study Group. *N Engl J Med* 334:745-751, 1996.
32. Metayer C, Lynch CF, Clark A, Glimelius B, et al. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 18(12):2435-43, 2000.
33. Sankila R, Garwicz S, Olsen JH, et al. Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in the five Nordic countries. *Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. J Clin Oncol* 14(5):1442-1446, 1996.
34. Dunst J, Ahrens S, Paulussen M, Rube C, et al. Second malignancies after treatment for Ewing's sarcoma: a report of the CESS-studies. *Internal J of Rad Oncol* 42(2):379-84, 1998.
35. Heyn R, Haerberlen V, Newton WA, et al. Second malignant neoplasms in children treated for rhabdomyosarcoma. *J Clin Oncol* 11:262-270, 1993.
36. Kuttesch, Jr. JF, Wexler LH, Marcus RB, Fairclough D, et al. Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas. *J Clin Oncol* 14:2818-2825, 1996.
37. Dalton VMK, Gelber RD, LiF, Donnelly MJ, et al. Second malignancies in patients treated for childhood acute lymphoblastic leukemia. *J Clin Oncol* 16:2848-2853, 1998.

38. Loning L, Zimmermann M, Reiter A, Kaatsch P, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 95:2770-2775, 2000.
39. Walter AW, Hancock ML, Pui C-H, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St. Jude Children's Research Hospital. *J Clin Oncol* 16:3761-3767, 1998.
40. Swerdlow A.J, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol* 18(3):498-509, 2000.
41. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL. Second Malignant Neoplasms in Five Year Survivors of Childhood Cancer: Report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 93:618-629, 2001.
42. Kingston JE, Hawkins MM, Draper GJ, et al. Patterns of multiple primary tumors in patients treated for cancer during childhood. *Br J Cancer* 56(3):331-338, 1987.
43. Olsen JH, Garwicz S, Hertz H, et al. Second malignant neoplasm after cancer in childhood or adolescence. *Br Med J* 307:1030-1036, 1993.
44. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. *Br J Cancer* 53:661-671, 1986.
45. Wong FL, Boice JD, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *JAMA* 278(15):1262-67, 1997.
46. Li FP, Fraumeni JR, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 48:5358-5362, 1988.
47. Malkin D, Jolly KW, Barbier N, et al. Germ line mutation of the p53 tumor-suppressor gene in children and young adults with second malignant neoplasms. *N Engl J Med* 336:734, 1997.
48. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with the Li-Fraumeni syndrome. *J Natl Cancer Inst* 90:606-611, 1998.
49. Hobbie WL, Stuber M, Meeske K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *J Clin Oncol* 18(24):4060-4066, 2000.
50. Hobbie WL, Ogle S. Transitional care for young adult survivors of childhood cancer. *Seminars in Oncol Nursing* 17(4):268-273, 2001.
51. Schidlow DV, Fiel SB. Life beyond pediatrics. Transition of chronically ill adolescents from pediatric to adult health care systems. *Medical Clinics of North America* 74(5):1113-

20, 1990.

52. MacLean WE, et al. Transitions in the care of adolescent and young adult survivors of childhood cancer. *Cancer* 78(6):1340-4, 1996.
53. McAnarney ER. Social maturation. A challenge for handicapped and chronically ill adolescents. *J Adol Health Care* 6(2):90-101, 1985.
54. Blum RW. Transition to adult health care: setting the stage. *J Adol Health* 17(1):3-5, 1995.