"Solid Tumor Second Malignant Neoplasms as a Late Effect of Childhood Cancer Therapy"

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Biographic Information

Dr. Orlino completed a combined Internal Medicine/Pediatrics residency at The Ohio State University Hospitals and Columbus Children's [now Nationwide Children's] Hospital in 2002, then served as Pediatric Chief Resident in 2003. After a year in general internal medicine practice and newborn nursery call in rural Oklahoma with the Choctaw Nation Health Service, she relocated to Dallas, TX, where a year after working *locum tenens* for a regional primary care network, she joined the Division of General Internal Medicine at UT Southwestern in 2006 as a clinician-educator. In 2007 the opportunity for clinical work with the After the Cancer Experience ("ACE") survivorship program arose, and she has had the pleasure of collaborating in clinical and research ventures with Dr. Dan Bowers, Cindy Cochran, PNP, and the Children's Health Center for Cancer and Blood Disorders ever since. Her main clinical interests remain general internal medicine primary care, resident and student education, and of course long-term follow-up of childhood cancer survivors. She looks forward to collaborating with the nascent Internal Medicine/Pediatrics residency program at UT Southwestern Medical Center, slated to match its inaugural class in 2016.

Purpose and Overview

Current long-term survival of children with is now greater than 80%. As these young adults advance in age, they have unique medical needs and health risks that may go unheeded as they transition from pediatric care into general medical care. Their greatest risk of early mortality after short-term survival (5 years) of their original cancer is secondary malignancy related to their cancer therapy.   This presentation attempts to demonstrate the heightened risk of subsequent cancer in this adult population throughout their lifespan, and to outline a clinical framework with which to approach that risk.

Educational Objectives

-       Recognize that the childhood cancer survivor population is growing in number every year, and is at risk of developing subsequent neoplasms across their lifespan.

-       Recognize that any radiation exposure confers an additional risk of subsequent cancer for childhood cancer survivors.

-       Recognize that in females treated with radiation for childhood Hodgkin Lymphoma, their risk of breast cancer parallels that of BRCA(+) women.

-       Recognize that specific cancer screening guidelines exist for this high-risk population.

Abbreviations:

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CAD/ASCVD, coronary artery disease/atherosclerotic cardiovascular disease; CI, confidence interval; CI*, cumulative incidence; CKD, chronic kidney disease; CNS, central nervous system; EAR, excess absolute risk; GCT, Germ Cell Tumor; Gy, Gray (unit of delivered dose of radiation – cGy, centigray; mGy, milligray); HL, Hodgkin lymphoma; LTFU, Long-term follow-up; NBL, neuroblastoma; NHL, non-Hodgkin lymphoma; NICM, nonischemic cardiomyopathy; PNET, primitive neuroectodermal tumor; Rb, Retinoblastoma; RMS, rhabdomyosarcoma; RR, relative risk; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End-Results; SIR, standard incidence ratio [or O:E, observed to expected number of cancers]; SMN, second malignant neoplasm; SPN, subsequent primary neoplasm; SN, subsequent neoplasm; STS, soft tissue sarcoma

INTRODUCTION

Childhood cancer: the very thought of it induces a visceral horror in parents and physicians alike. The fight against it garners more philanthropic funds equaling or exceeding nearly all other human conditions or endeavors. And it is one of the true success stories of modern medicine. Childhood cancer was uniformly a death sentence across the history of man until recent times. With the advent of combination chemotherapy and therapeutic radiation, the 5-year survival rate for patients treated for childhood cancer has increased from less than 30% in the mid-20th century to 50-60% in the mid-1970's to greater than 80% currently. [1]

But as nearly every cancer survivor of any age can attest, achieving long term remission or "cure" is hardly the end of his or her journey. To varying degrees each survivor has a unique set of future health risks related specifically to the type of cancer treatment he or she received – and much of this corpus of knowledge is a work in progress. Newer evidence on cellular aging suggests that cell media exposed to radiation and chemotherapy produce inflammatory factors comparable to that of aging cells *in vivo* [2]. As such, one might postulate that the reaction of a child's body when subjected to chemotherapy and radiotherapy is one analogous if not similar to accelerated aging [3].

This paradigm of accelerated aging has also reached the mainstream media – a December 2013 article in the Wall Street Journal [4] described the experience of several childhood cancer survivors experiencing clinical "fragility" with decreased muscle mass and bone density leading to increased risk of hip fracture in the 4th decade of life, as well as early onset of Mild Cognitive Impairment 30 years earlier than expected, as a result of cranial irradiation as a child.

A short list of potential late effects to childhood cancer survivors includes:

- NICM – from anthracycline chemotherapy and chest radiation
- Premature CAD/ASCVD – from chest or neck radiation
- Impaired fertility – central or peripherally mediated

- CKD – radiation or platinum-based chemotherapy, single kidney
- Hepatitis C – from remote blood transfusions
- Radiation enteritis – with malabsorption & dysmotility
- Neurocognitive – from CNS radiation, intrathecal chemotherapy (methotrexate)
- Bone – from steroid or methotrexate chemotherapy and/or radiation
- Metabolic Syndrome & Obesity – ALL & cranial radiation

But the main cause of early mortality in childhood cancer survivors is second (or subsequent) malignancies. Though certainly known hereditary syndromes of cancer (such as Li-Fraumeni, Hereditary Retinoblastoma) account for some of the increased risk of metachronous cancers, most of the cases involve subsequent neoplasms as a result of exposure to carcinogenic treatment of the original cancer.

In an impassioned 2005 editorial from the Journal of the National Cancer Institute, Dr. Dan Longo of the National Institute on Aging calls the apparent triumph of long-term remission rates of Hodgkin Lymphoma a Pyrrhic victory – a victory coming at the expense of the future health of is survivors, particularly the females treated with mantle radiation, who at age 25 have a nearly 1 in 3 chance of developing breast cancer by age 55 [5].

Today, it is estimated that one in every 640 young adults is a childhood cancer survivor [6] and this population is growing in number as well as age. The first long term survivors of Hodgkin Lymphoma are now in their 6th and 7th decades and facing the ravages of an aging body on top of their comorbid risks from remote cancer treatment. The long-term side effects decades after exposure of young children's tissues to radiation, chemotherapy, and surgery are just now being elucidated with the help of longitudinal studies within and across many countries and ethnicities, many of which are entering their 2nd and 3rd phases.

HISTORICAL BACKGROUND

It was not until the 1940's that chemotherapy was developed to effect some degree of remission in acute lymphoblastic leukemia (ALL), the most common pediatric cancer. In 1948, Dr. Sidney Farber described the use of aminopterin (an antifolate, similar to methotrexate) to induce temporary remission of ALL. 6-mercaptopurine and the vinca alkaloids were developed in the 1950's and 1960's, respectively with cooperation from the pharmaceutical industry. This ushered in the new era of combination chemotherapy, and the POMP (Prednisone, Oncovin™, Methotrexate, Purinethol™) regimen was one of the first to help achieve long-term remission of ALL.

The colorful history of Hodgkin disease befits its mysterious histology. Once thought infectious in nature, it wasn't until 1902 when Dorothy Reed shed clarity on the pathognomonic cell from tissue described by British physic (and abolitionist) Thomas Hodgkin 70 years prior as "morbid glands". Though it had been known since the early 20th century that "glandular" lymphatic tissue was particularly radiosensitive, it

was not until the 1960's that radiation could be delivered in a curative manner by taking advantage of the contiguous pattern of Hodgkin disease spread -- radiation oncologist pioneer Vera Peters described cures in 35% of patients she treated, and her findings helped develop the initial staging systems of Hodgkin disease. In 1965 the famous multidisciplinary meeting in Paris, France *"La Radiotherapie de la Maladie de* Hodgkin" led to one of the earliest cancer treatment and surveillance consortia, and the scepter of treatment-induced second malignancies acknowledged. These risks were mitigated in part with the concomitant novel application of combination chemotherapy, allowing radiation therapy to be pared down in dose and in area. Eventually the original MOPP (Mechlorethamine, Oncovin™, Prednisone, Procarbazine) regimen was supplanted by the less leukemogenic and gonadotoxic ABVD (Adriamycin™, Bleomycin, Vinblastine, Dacarbazine).

In the mid-1970's, the 5 years overall survival of Childhood Cancer approached 60% and by 2000 had reached 80% such that 1 in every 640 young adults between the ages of 20 and 39 was a childhood cancer survivor.[6] Today, 5-year survivorship approaches 90% for many of the most common pediatric cancer diagnoses such as ALL or HL [1].

The term "Late Effects" was coined in the medical literature by pediatric oncologist and survivorship medicine pioneer Dr. Anna Meadows and radiation oncologist Dr. Giulio D'Angio, who in 1974 proposed a methodology in the medical literature for studying this growing population of long-term survivors [7]. These two practitioners were amongst the earliest to recognize morbidity past remission, and insist that "cure is not enough" – Dr. D'Angio's clinical mantra [8].

One of the first specific references to Childhood Cancer Survivors in the medical literature was by none other than legendary cancer epidemiologist (and eponymal source of the TP53 Li-Fraumeni Syndrome) Dr. Frederick P. Li, who in a 1976 Annals of Internal Medicine article described one of the first series of survivors and their late term sequelae [9]: a single center report (Sidney Farber Cancer Center in Boston) employing a retrospective case study methodology with combined patient questionnaire and medical record review that would become the model for future studies – the cohort comprising 164 eligible patients and 142 respondents from age birth through 17 years of age, with 137 of them at least 2 years off therapy, and the majority of which were 5-year survivors treated prior to 1968. Seventy-four of the 142 (52%) had "major defects in treated organs" and 17 of the 142 (12%) developed subsequent neoplasms – numbers not dissimilar to those found in more formally recruited cohorts in the subsequent decades.

In the 1980-1990's nascent consortia such as the Late Effects Study Group began to systematically pool studies and resources in order to investigate long-term sequelae of childhood cancer survivors, mainly those of Hodgkin Lymphoma -- one of the first childhood/young adult cancers achieving long-term remission.

In 2002, The Institute of Medicine in its report of Childhood Cancer Survivors [10] articulated the need for long-term follow-up of these young cancer survivors, and called upon the Children's Oncology Group (COG) to develop clinical practice guidelines for surveillance of this patient population for late effects of

therapy. The first iteration was released in 2003, and subsequent revisions in 2008 and 2013 [11] have further refined and expanded the initial recommendations, incorporating the increasing body of evidence from survivor cohorts around the world.

These latter revisions of the COG survivorship guidelines were greatly influenced by the ongoing findings of the landmark North American Childhood Cancer Survivor Study (CCSS), a cohort of nearly 20K childhood cancer survivors first identified in the early 2000's [12] which also identified a sibling cohort as a control group. This study is to childhood cancer survivorship what The Framingham Study was to cardiovascular disease in America.

International cohorts have also been formed, and underrepresented countries and ethnicities continue to publish in the medical literature on late effects of childhood cancer. Formally identified international cohorts include [15]:

- Life after Childhood Cancer in Scandinavia (ALiCCS) 5 Nordic cancer registries; 33K 1-year survivors; 22% followed past age 40 y
- BCCSS - British Childhood Cancer Survivor Study
- GPOH-HD-Spaetfolgen - German Hodgkin Late Sequelae Study
- Dutch Childhood Oncology Group (DCOG) LATER
- Swiss Childhood Cancer Survivor Study (SCCSS).
- French Childhood Cancer Survivor Study (FCCSS)
- French Childhood Cancer Survivor Study for Leukaemia (LEA)
- Italian Study on off-therapy Childhood Cancer Survivors (OTR).

SECONDARY MALIGNANCIES DURING EARLY SURVIVAL

The Surveillance, Epidemiology, & End-Results (SEER) database is administered by the National Cancer Institute (NCI), and is the largest cancer registry in the United States; 17 cancer registries comprise SEER, covering a geographic area containing 26% of the US population. As a true population-based registry, it is less affected by the selectivity that may occur in cohort identification at certain treatment centers, and provides important information about the incidence of second malignancies in the pediatric population.

A 2007 analysis [14] of SEER data for both short- and long-term survivors looked at nearly 26K children treated between 1973 and 2002 and surviving at least 2 months. About 15K were 5-year survivors, 10K were 10-year survivors, and 3.5K were 20-year survivors; the maximum age was 47 years. They found 433 SMNs in 400 individuals, giving a SIR (or observed:expected) of 5.9 and EAR of 16.9 cancers per 10K person-years. The most common SMNs were breast, CNS, and leukemia, with thyroid and bone tumors rounding out the top 5. A biphasic risk was also noted: an SIR increase in the first 5 years for SMN's like AML, and a SIR increase only after 10 years for breast & GI cancers. HL gave rise to 26% of the SMN's, and the following trends of SMN after primary malignancy were significant:

- AML following ALL, NHL, Ewing, Osteosarcoma, RMS, Wilms
- Breast CA following HL, NHL, Ewing, Osteosarcoma, RMS, GCT
- CNS CA following ALL or CNS CA
- Sarcoma following ALL, CNS CA, sarcoma, Rb, Wilms
- Thyroid CA following ALL, CNS, NBL
- Oropharyngeal CA following ALL & STS
- CML following CNS astrocytoma
- ALL following Rb, PNET

Also in regards to secondary acute leukemia, the overall SIR and EAR for AML peaked between years 1 & 5, but in the contemporary group treated between 1995-2002 the EAR was in excess of 100 cancers per 10K person-years, coincident with the decrease in overall radiotherapy use with time (from 56% in 1973-79 to 28% in 1995-2002), and increase of potentially leukemogenic chemotherapy.

A 2010 SEER analysis published in the surgical literature [15] examined the incidence and characteristics of second malignancies following the primary solid tumors in pediatric patients. Over 31K cases of pediatric solid malignancies (excluding leukemia or lymphoma) diagnosed between 1973 and 2005 and younger than 20 years of age at treatment were identified, with 177 (0.56%) developing a second malignancy. During this time period, leukemia was the most common second malignancy (35.5% of SMN) with CNS tumors comprising 22.5%; soft tissue sarcoma, retinoblastoma, and bone tumors rounded out the top 5 causes of second malignancy in this adolescent/early young adult period. Notably, carcinomas were most common in the age 15-19 group, and whereas the latency period from initial diagnosis to SMN diagnosis for secondary leukemia was only 3.9 years, the latency for secondary solid tumor SMNs was greater than 11 years – thus suggesting a trend toward the emergence of adult-type tumors occurring toward late adolescence and adulthood.

These and other analyses of SEER data suggested that in the pediatric population, second malignancies came in two general types: leukemia, usually chemotherapy-related and occurring generally within the first 5-10 years of initial treatment; and solid tumors, nearly always radiation-induced and occurring after a longer latent period of at least a decade or more. And whereas secondary leukemias usually made themselves manifest while a child was still under pediatric care, the solid tumors were more likely to arise after the child had attained adult age. Therefore the remainder of our focus here is narrowed to the solid tumor secondary malignancies, which internists are more likely to encounter in clinical care.

SOLID TUMOR SECONDARY MALIGNANCIES IN THE CCSS

As previously mentioned, the North American Childhood Cancer Survivor Study (CCSS) cohort involved in the Long-Term Follow-Up (LTFU) Study is a retrospective cohort comprising 25 institutions across the United States and Canada; cohort members have all survived at least 5 years after diagnosis and treatment of pediatric cancer at less than 21 years of age, between 1970 and 1986 inclusive. Of the original 20K+ identified as eligible for the cohort, 13-14K have participated in at least one or more

periodic questionnaires or interviews collecting information including interim diagnosis of a new cancer [12, 16, 17, 18, 19].

One of the first analyses of second malignancies of the CCSS cohort was done 2001 [16], where amongst 13581 eligible study subjects, 314 second malignancies were diagnosed in 298 survivors, excluding nonmalignant meningioma and non-melanoma skin cancer (NMSC). Breast, thyroid, and CNS cancers comprised the majority of the solid organ cancers, giving rise to 19%, 14%, and 11% of second malignancies, respectively, in this cohort of median age 23 years, diagnosed with their second malignancy after a median latent period of 11.7 years. The overall cumulative incidence of a second cancer was found to be 3.2% at 20 years of follow-up, with risk trends toward significance of female sex, younger age at treatment, primary diagnoses of HL or STS, and initial therapy including alkylating agents such as cyclophosphamide.

An interim analysis of the same cohort 7 years later in 2009 [17] revealed 802 secondary malignancies in 730 survivors – a 2.3-fold increase from the initial 2001 report – with an increase in the cumulative incidence of second malignancy to 9.3% at 30 years of follow-up. One particular highest-risk population was identified in female survivors of childhood HL radiotherapy – with a cumulative incidence of breast cancer at age 40 found to be 12.9% -- comparable to the incidence of the BRCA population.   This was also the first analysis to also note a measurable incidence of meningioma and NMSC. With the addition of 66 cases of meningioma and 1007 NMSC cases, a total of 1875 subsequent neoplasms (SN) were detected, and a new trackable category was formed.

The next major statistical analysis of SN/SMN incidence in the CCSS cohort occurred in 2010 [18], at which time 2703 SNs (including 806 SMNs) were found amongst 1402 survivors, whose median age was now 30 years. In this analysis, the first to fully include nonmalignant meningioma and NMSC, the median time between original and SN diagnosis was 17.8 years. The overall risk was consistent with that found in the original 2001 analysis, with a SIR of 6.0. The overall incidence at 30 years of follow-up was 20.5% for all SN's, 7.9% for SMN, 9.1 for NMSC, and 3.1 for nonmalignant meningioma. Of the 806 SMNs, 252 were breast cancer, 128 were thyroid cancer, and 77 were malignant CNS cancers. Statistically significant trends of risk included initial diagnoses of HL and Ewing Sarcoma, as well as female sex, older age at diagnosis, treatment in earlier era (i.e. 1970's), and radiotherapy exposure.

In 2015, for the first time, analysis of the CCSS cohort reaching at least 40 years of age was feasible – in data published just in August, 3171 survivors over 40 were analyzed for cumulative incidence of SN/SMN's [19]. This group had attained a median age of 44 years (maximum 58 years of age), and of these survivors, fully 21% had been diagnosed with an initial subsequent neoplasm, 8% of them for the first time only after age 40. For this over-40 population, the 15-year cumulative incidence of SN was 34.6%, and SMN 16.3%, far exceeding that of the general population at age 40 years.

Those survivors with the highest cumulative incidence were initially treated with radiotherapy – with a history of SN prior to age 40, the 15-year cumulative incidence for developing subsequent neoplasm was 62.3% after the age of 40; conversely, the lowest incidence was noted in those survivors without history

of radiotherapy treatment and without history of SN prior to age 40 – their 15-year cumulative incidence was only 13.3%.

Of the 470 survivors previously diagnosed with a subsequent neoplasm before age 40, 121 were diagnosed with at least one additional SN after the age of 40, including 42 occurrences of SMN.

SECONDARY BREAST CANCER – A PARADIGM FOR SCIENTIFIC INQUIRY AND CLINICAL CARE

Breast Cancer is one of the most common and best characterized solid tumors seen in childhood cancer survivors in the literature. As such, the way we apply our current knowledge to clinical practice can serve as a paradigm for other secondary cancers (such as thyroid cancer and colorectal cancer), which themselves are just now becoming better characterized as this survivor population approaches middle age and beyond. As these survivor cohorts age and are serially analyzed, not only we will also have a better picture of the incidence of specific secondary malignancies but hopefully we as medical practitioners can collaborate on an international level to utilize resources in a cost effective manner in order to discern the highest-risk survivors and screen them for second malignancy.

As early as the late 1990's and early 2000's, an increased risk of breast cancer was noted in childhood cancer survivors, particularly in Hodgkin Lymphoma and Wilms Tumor survivors, and this risk was described across several international cohorts, such as the North American, British, Dutch, and Nordic. While it became clear that exposure to radiotherapy, particularly chest radiotherapy, was the most common risk factor, some studies also demonstrated an increased risk in childhood cancer survivors who received no radiotherapy at all.

One of the first analyses of entire childhood cancer survivors cohorts, and not just HL survivors, was that of the CCSS – a 2004 report from the Annals of Internal Medicine elucidated some of the more specific risk factors leading to an increased risk of secondary breast cancer [20]. As expected, history of chest radiation prior to the age of 21 was the most common risk factor, but a few surprising findings included increased relative risks in non-irradiated patients treated for bone and soft tissue sarcoma (i.e., osteosarcoma and rhabdomyosarcoma), as well as decreased risk in patients who had received pelvic irradiation (presumably from de facto ovarian oblation). Also of interest was the finding that patients who had received anthracycline chemotherapy as part of their initial treatment were not necessarily protected from the increased risk of breast cancer from their radiation exposure, as was originally postulated. One-quarter of the cancers were in situ tumors, and 60% were stage I or II tumors. Estrogen Receptor status was able to be confirmed in only half of the confirmed cases, and of those, 76% were found to be ER-positive. In all, 24% (23/95) women with secondary breast cancer died during the course of the study, 15 (16%) from breast cancer related causes.   The overall cumulative breast cancer incidence by age 40 for this survivor cohort was nearly 13% for HL survivors who had received chest radiotherapy, a number comparable to the incidence seen in BRCA-positive individuals.

With chest radiotherapy clearly established as a consistent risk factor in breast cancer risk after treatment of childhood cancer, efforts were turned to determine more sophisticated risk stratification

for particular doses received, as well as to further clarify specific chemotherapeutic agents which could be implicated for secondary breast cancer risk (the data to date had been rudimentary and contradictory to that point). For the North American CCSS, a breast dosimetry study in 2009 [21] calculated a 0.27 odds ratio increase per Gy of breast RT dose/exposure; they were also able to demonstrate an apparent relative protective effect of ovarian ablation that had been observed but never quantified in the previous literature – patients who had received > 5 Gy ovarian dose of RT had an odds ratio of only 0.06 per Gy, which was a significant difference. These data translated to an 11-fold risk at a dose of 40 Gy, a risk that then decreased to 3.4-fold when a radioablative ovarian dose of >5 Gy had been received. While no chemotherapeutic agents were specifically implicated in breast cancer risk, there were a few agents whose exposure approached significance in both higher-risk (doxorubicin, carmustine, dactinomycin, and dacarbazine) and lower-risk (mechlorethamine & procarbazine) directions – the latter category possibly through a gonadal chemosterilization effect.

After this trend toward a linear RT dose-response for breast cancer was demonstrated, attention was turned to defining this in a more clinically relevant way, taking into account the contemporary treatment trends of involved-field radiation and decreased radiation doses considered sub-threshold by many current screening guidelines. Another CCSS study published in 2014 [22], not only confirmed again a cumulative incidence in the highest-risk irradiated patients as comparable to genetically predisposed breast cancer (i.e. BRCA 1 and BRCA2), but also demonstrated an increased breast cancer risk of intermediate chest radiotherapy doses between 10 & 19 Gy, previously considered sub-threshold for screening, and used in common childhood cancer radiotherapy regimens – including whole lung, mantle, TBI, and mediastinal RT.

Outside of the North American CCSS, other countries with their cohorts have corroborated the data of the North American CCSS, but have also noted different and sometimes conflicting data (or interpretation thereof). The British CCSS, an older cohort than the North American CCSS reported a cumulative incidence of invasive breast carcinoma (not including in situ tumors) in irradiated patients of 1.4% by age 40 and 3.2% by age 50. HL survivors comprised 22% (18/81), and 63% (63/81) had received radiotherapy of any kind [23]. Certain initial cancer diagnoses were found to be at risk: HL, Hereditary Rb, Wilms, and sarcoma. The cumulative incidence numbers are considerably less than the North American CCSS, which included in situ carcinomas, but are still elevated compared to the British general population during that time period. Notably, they did note a plateau in risk after age 40 and hypothesized a convergence of risk at age 50, leading to their national recommendation of screening mammography after age 50 every three years, regardless of childhood cancer history. The difference in interpretation of findings across international studies has led to considerable heterogeneity in high-risk screening practices.

In recognition of this heterogeneity of practice, an effort is under way to harmonize all childhood cancer survivor screening guidelines on an international level [24]. In the Americas, high risk breast cancer guidelines mirror those of other high-risk genetic groups such as BRCA1 or BRCA2 positive population. These are outlined and modified periodically (most recently in 2013) by the Children's Oncology Group (COG) Long-Term Follow-Up Guidelines Task Force. For breast cancer screening it is strongly recommended that those survivors at "highest risk", i.e. females who had received > 20 Gy of chest RT

start breast cancer screening with yearly MRI and mammogram starting at age 25 or 8 years off therapy, whichever occurs later. According to the internationally harmonized guidelines in 2013, high-risk screening regimens are now recommended on a graded level, analogous to those pioneered in the cardiac literature in conjunction with the American Heart Association. Whereas in our COG guidelines, only the highest-risk stratum was recommended for screening, now in the harmonized guidelines there is a gradation of screening such that high-risk screening "is reasonable" (grade B) or "may be reasonable" (grade C) in patients such as those female survivors who received 10-19 Gy of chest RT (including TBI and upper abdominal RT). Therefore, the fine tuning of high-risk breast cancer screening in this survivor population is a demonstration of ongoing accumulated survivorship data serving to refine clinical practice at a population as well as individual level.

FUTURE of LATE EFFECTS SCREENING AND PREVENTION

In a Journal of Clinical Oncology editorial published in August 2015, Drs. Appelbaum and Cohn of the University of Chicago comment on the accompanying study summarizing the state of second neoplasms in the oldest cohort of the CCSS -- those diagnosed between 1970 and 1986, and now entering their fifth and sixth decades [25]. The article verifies some well-established tenets of surveillance of increased SMN risk (such as the high risk of breast cancer in chest-irradiated females), and also notes that the risk factors for certain high-risk populations are being further refined even at the genetic level, such as the presence of genomic variants in PRDM1 in HD survivors treated with radiation [26]. It also points out certain treatment practices which have been phased out, reduced in intensity, or used much more judiciously -- such as cranial irradiation for ALL patients and body radiation for HL or Wilms' patients -- that have led to measurable decrease in late mortality rates. In a sense, the future is already here, insofar as the late effects literature informs development of current treatment protocols, nearly to the same degree as efficacy does. Newer modalities of radiation therapy such as proton radiation and highly-conformal radiotherapy hold promise for minimizing risk of devastating late toxicities such as second malignancies. Researchers and clinicians such as Dr. Longo, who first labeled successful HL treatment a Pyrrhic victory, advocate further study of preventive and prophylactic approaches such as those seen in other high-risk breast cancer, such as use of tamoxifen and prophylactic mastectomy [5]. Studies looking at the prevalence of HPV in secondary malignancies of survivors may make future targeted use of cancer prevention modalities already in existence [27]. In all, Dr. "Dan" D'Angio's clarion call of "cure is not enough" is finally starting to permeate the medical field in attitude and practice.

CONCLUSION

While childhood cancer is a relatively rare disease, the cumulative numbers of survivors per year are growing and will continue to grow, given the ongoing improvements in long-term cure of the pediatric malignancies. These patients deserve our attention as internists and our high index of suspicion for potentially devastating late effects, such as remote secondary malignancies, which may become clinically manifest several decades after treatment. These patients also give valuable insight into the

long-term risks of cancer treatment in our adult population as well as patients of all ages whose non-neoplastic chronic conditions call for treatment with traditional antineoplastic agents. Additionally, the systematic study of the remote late effects of childhood cancer therapy has given a methodologic framework with which to study the late effects of the widely varied types of adult malignancy. In other words, just as pediatric malignancy blazed the trail for treatment of all malignancies, so too could childhood cancer survivorship inform care of adult survivors. They have shown us that it is possible for us as researchers and clinicians to progress from being satisfied merely with benchmark survival statistics to searching out ways we can help improve the long-term quality of life for themselves and future cancer patients.

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