Meeting Report

Research Issues in Cancer Survivorship: Report of a Workshop Sponsored by the Office of Cancer Survivorship, National Cancer Institute

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Introduction

A scientific meeting sponsored by the NCI OCS was held in Bethesda, Maryland, on March 9–10, 1998. Announcements for the workshop were published in professional journals, and abstracts were solicited. The meeting was planned by the OCS Steering Committee. The aims of the workshop were to provide an up-to-date review of information concerning cancer survivorship and to assist the OCS in making recommendations for the support of future research. Almost 200 consumers and scientists attended.

Nine invited speakers joined 13 abstract authors in giving oral presentations. There were 43 posters; 22 of these were grouped according to topic into five poster discussions that were led by experts, who also added background information and previous research findings. Authors were instructed to focus on what was already known in their fields and, considering what was needed and not known, to speculate on the directions that research resources should take. For this report, invited speakers and poster discussants contributed summaries of their presentations in the following areas: psychosocial late effects; sexual, hormonal, and reproductive toxicity; medical late effects; cardiac toxicity; BMT; and second cancers. Steering Committee members briefly summarized other related oral presentations and posters.

Anna Meadows reviewed the history of the OCS. The OCS was established in 1996 to provide a focus at the NCI for the support of research and education aimed at professionals who deal with cancer patients and survivors and at the survivors themselves. In so doing, the NCI recognized the large number of individuals who are now long-term cancer survivors and their unique and poorly understood medical, social, and psychological needs. The primary mission of the OCS remains the development and support of a research agenda that explores the long- and short-term physical and psychological effects of cancer and its treatment. Four workshops were held to set the agenda for the OCS. Cardiovascular effects, renal function, cognitive function, reproduction, sexuality, early menopause, effects of hormone replacement therapy, second cancers, ongoing medical care, and assessment of interventions to improve QOL were highlighted as requiring further research. In addition, the OCS provides a focus for continuing education of professionals engaged in caring for and promoting the health and well-being of survivors. It is expected that changes in treatment and support for cancer patients will come about as a result of the research supported.

In addition to the scientific presentations, insight from the perspective of the survivors themselves was provided by Ellen Stovall and Susan Leigh, active advocates for increased research and a focus on public policy issues for survivors. Susan Leigh emphasized the need for prevention and surveillance of multiple cancers. Life-long surveillance would ideally include biomedical and psychosocial monitoring, a neglected area. She advocated minimum standards for continued follow-up. Survival is not only about cure, but it is about how patients survive for the rest of their lives. Ellen Stovall emphasized the need for an increase in funding for cancer research, as well as access to clinical trials for patients. She also discussed the study of behavioral and social sciences and their importance in formulating necessary changes in policies regarding cancer survivorship issues.

The Cancer Journey: Issues for Survivors, a new training program for health professionals, was presented by Katherine Crosson. Developed in partnership with the National Coalition for Cancer Survivorship and Ortho Biotech Inc., the program was designed to provide health professions with the tools and information needed to effectively respond to the many issues cancer survivors face. A key component of the training program, a 30-min videotape, was shown. The video features cancer patients from a wide variety of backgrounds speaking about their personal experiences, as well as their interactions with family and friends, during the course of their treatment and follow-up care. Additionally, the training program consists of a 28-page leader’s guide that suggests different ways to use the training program resources in a variety of settings to meet the needs of specific target audiences, such as nurses, social workers, physicians, health educators, patient advocates, and chaplains.

Programs to support minority survivors were described by the recipients of four awards from Bristol-Myers Squibb Oncology. These programs were developed by Catherine Logan-Carrillo, Karen Jackson, Andrell Sturdivant, and the Reverend Joseph Davis to serve survivors in New Mexico, Houston, Detroit, and Alabama, respectively. Details of the methods used and approaches taken have been incorporated into a guide for
psychosocial late effects. Recurrence of physical symptoms constitutes a reactivation of all of the psychological associations that have accompanied the initial treatment. Bad news tends to reactivate cognitive networks of stress, helplessness, fear, and pain that may have been stimulated earlier. Social support can function as a stress buffer, helping people to modulate the somatic effects of stress.

Energy problems persisted up to the 9th year of follow-up and affected almost one-half of the Hodgkin's disease patient sample studied by Dr. Spiegel. Although fewer patients experienced depression, >20% still suffered some depression 8 years later. Vocational problems nearly doubled from the initial year after treatment to the 9th year after treatment. Variables associated with the probability of being employed were sex (men were more likely to be employed than women), lower levels of depression, older age, return of energy, and lack of relapse. Job loss in patients and family members, denial of life or health insurance, higher insurance rates, and concerns about changing from one health insurance policy to another are all important issues.

Long-term survivors were anxious about imparting negative information about their medical status to physicians because of an unconscious conditioned expectation that such information will produce a new kind of punishment. People who tend not to admit to themselves or to others that they are distressed in any way tended to be more depressed and anxious. Dr. Spiegel found that good relationships tended to get better and bad relationships become worse in the face of illness. Patients who had social support resources had more difficulty both in maintaining the support they had and in forming new relationships after they had been ill; those who had the least in terms of social and emotional resources were at greatest risk.

A subset of long-term survivors who were socially isolated and who had social, family, or sexual problems and vocational insurance problems appeared to benefit from intensive structured interventions designed to provide guidance that includes building new networks of social relationships, expressing emotions, and detoxifying fears of dying and death. Included were patients with high levels of depression and anxiety. Exposure to others who are suffering the same problems, if handled properly, can help patients reorder their priorities in life, improve communication in families and with physicians, and teach specific techniques to control pain or other symptoms. In the future, it will be important to study the interaction among stressors, to identify those at risk, and to provide interventions suitable to the level of risk.

An intervention study for breast cancer survivors is also being developed by Betty Ferrell, who found that fatigue, continuing pain (experienced by 51%), and fear of recurrence were major factors in reducing the QOL. According to Joyce Guillory, who studied 135 African-American women, spirituality was positively associated with immunoglobulin levels, and social support provided the majority of variance in the life satisfaction score. A survey of 1200 National Coalition of Cancer Survivors by Karen Dow documented negative QOL changes in all domains, with the exception of spirituality.

The QOL of colorectal cancer survivors (n = 174) as a function of stage at diagnosis and time since diagnosis was evaluated by Scott Ramsey. He found that the patients fare comparatively well after diagnosis and that the QOL at diagnosis did not change substantially over time. Comorbidity, rather than stage and treatment, seems to have the most influence on health utilities index scores.

Early data on the prostate cancer QOL and patterns of care study of 3330 men were reported by Arnold Potosky. This study followed men at 6, 12, and 24 months postdiagnosis and assessed health-related QOL, treatment, and recurrence of the disease. In a substudy of 133 men, there was relatively good agreement between baseline and 6 months for incontinence and bowel and sexual functions, which suggested that recall is sufficiently reliable to permit assessment of change in functioning.

The employment problems of long-term cancer survivors were highlighted by Joan Bloom in her study of 403 survivors. Individuals who have limited energy as a result of their disease or treatment will spend less time in leisure activities to continue working. If, in addition to work time, leisure activities are not considered, the impact on survivors may be underestimated. She also suggested that there is evidence that cancer is still a stigmatizing condition in the workplace, despite the laws.

Pediatric and adolescent patients have unique problems that are not seen in adults because of developmental differences and parental involvement in their care. A review of several posters dealing with the importance of psychosocial aspects of adjustment to pediatric cancer survival also demonstrated the vulnerabilities of survivors and their parents to psychological disorders such as PTSD and ADHD. In a sample of 309 survivors of childhood cancer and their parents and 155 control participants and their families, Anne Kazak found that parents of childhood cancer survivors had higher levels of posttraumatic stress symptoms than control parents but that the child survivors did not differ in level of symptoms from the control sample. She outlined plans for a randomized program of intervention involving adolescent survivors and their family members. The program uses cognitive and behavioral intervention to reduce symptoms of posttraumatic stress by targeting anxiety, beliefs about cancer and its treatment, social support, and family communication.

In another study of 70 parents of childhood cancer survivors, Sharon Manne found that 6% of the parents met criteria for PTSD, although another 20% had sufficient symptomatology to be classified as “subclinical.” Grace Christ reported, in a slightly older sample (age range of 11–24 years during treatment for limb sarcomas), that one-third of a sample of 45 reported symptoms of psychopathology, based on quantitative and qualitative methodologies. The emphasis on QOL issues in pediatrics highlights the importance of attending to developmental concerns as survivors “grow up” and face the challenges of integrating their illness and treatment sequelae with the
demands of young adulthood. Kevin Krull, in a study of 40 6–17-year-olds off treatment for at least 2 years, found levels of impulseness comparable to a group of 20 children with ADHD. The cancer survivors gave evidence for more impulsive styles. Treatment strategies for cancer survivors that build on the knowledge gained in interventions for ADHD deserve study. A 41-item questionnaire developed by May Tao for patients whose disease and treatment involves the brain shows promise for meeting the complex and distinct needs of assessing this population.

**Sexuality and Hormonal and Reproductive Toxicity**

**Sexuality.** Sexual problems are some of the most common long-term sequelae of cancer treatment. Leslie Schover provided an overview of these issues, as well as hormonal and reproductive toxicity and associated psychosocial effects. About 50% of long-term breast and gynecological cancer survivors experience global and profound sexual dysfunction. For men with prostate cancer, the prevalence of sexual dysfunction is probably closer to 70%. The most common sexual problems include loss of desire for sexual activity in men and women, erectile dysfunction in men, and dyspareunia in women.

Self-reports of sexual satisfaction change less after cancer treatment than do reports of specific sexual problems. To be useful in addressing the particular problems of long-term cancer survivors, assessment instruments should measure a variety of aspects of sexual function, including desire, arousability, erection quality, vaginal lubrication, ability to reach orgasm, and pain with sexual activity. Research on assessment should include longitudinal, prospective studies of sexual function in specific groups of patients and controls to compare the impact of specific treatments on sexual QOL.

For sexual dysfunction after cancer, a variety of treatment modalities are available via books, pamphlets, CD-roms, videos, or Internet online interactions, but few have been tested. Effective programs that use cost-effective intervention strategies integrating medical and psychological modalities are needed but are unlikely to be available because of the problems in funding mental health interventions. With the advent of sildenafil, a new oral medication to treat erection problems, the need for good outcome studies on treatment for erectile dysfunction becomes even more acute.

**Hormonal Effects.** In women, premature menopause from cancer treatment typically causes sexual dysfunction and increases risks of cardiovascular disease and osteoporosis; the impact on mood, memory, and sexual desire remains controversial. Breast cancer survivors face the dilemma of whether or not to use estrogen replacement. Can we use new selective estrogen receptor modifiers to prevent osteoporosis? Are new, slow-release vaginal estrogen systems safe for breast cancer survivors? How can we encourage the use of estrogen replacement in women who are not breast cancer survivors but who associate estrogen with cancer risk and are unaware of the true risk-benefit ratio?

Men who have long-term hormonal therapy for prostate cancer have similar problems with profound sexual dysfunction and osteoporosis. More men will be exposed to hormonal therapy for prolonged periods if treatment for elevated PSA is instituted at younger ages. Delaying hormonal therapy for a better QOL, having intermittent therapy, or using treatments less destructive to sexual function such as androgen-blocking drugs or finasteride may be options.

**Reproduction.** Infertility is a concern for a small number of survivors, but it causes immense distress when it is present. More data are needed on prevalence with reference to age of diagnosis, disease site, and treatment. Support is needed for registries of children born after parents' exposure to cancer treatment, either before conception or during pregnancy. We also need better information on the health risks of pregnancy in women survivors. Many are unaware of possible cardiovascular and obstetric complications related to pregnancy after chemotheray or radiation but many have unnecessary fears that pregnancy will promote a cancer recurrence, an issue that is mainly restricted to young women who have had breast cancer.

There is almost no information on how survivors decide whether or not to have children and whether the experience of cancer promotes positive parenting in cancer survivors. Little is known about how a history of cancer in childhood or early adulthood affects the probability of finding a mate, financial ability to take care of a family, and ability to adopt or to afford infertiltiy treatment. How can survivors of childhood cancer avoid passing on genetic risk of cancer, if any, to their children?

The benefits of sperm-banking before cancer treatment have greatly increased with the advent of in vitro fertilization with intracytoplasmic sperm injection. We need to investigate how best to educate young men and their families about this option. Methods to cryopreserve oocytes are a high priority. Preliminary success in animal studies with autotransplantation of cryopreserved ovarian tissue may have some value in the future for humans. We need to make assisted reproductive technology more financially accessible to survivors as well.

Sexual functioning was also studied by Karen Syrjala and her colleagues. Using a self-report measure in 101 female patients prior to and after stem cell or marrow transplant, they assessed sexual behavior, satisfaction, menopausal symptoms, and other psychosocial functions. The measure developed to assess these functions appears to be an improvement over previous questionnaires. Hormone replacement therapy and higher hormone levels were related to greater sexual activity and satisfaction. Hormone assays may assist in determining treatments to improve sexual function and QOL.

Several posters dealing with gynecological dysfunction were reviewed by Carolyn Runowicz. In a 3-year longitudinal study of QOL in gynecological cancer patients, Susan Lutgendorf reported that coping strategies were found to be predictive of adjustment. At 12 months from diagnosis, there were significant declines in depression and anxiety and increases in functional well-being, compared to the scores at diagnosis. Not studied were the effects of age, diagnosis, and treatment.

Limitations on ovarian cancer survivors’ QOL were pain, fatigue, and problems with sexuality, as reported by Betty Ferrell. A case-control QOL study will be performed by Lari Wenzel in survivors of cervical cancer, lymphoma, and gestational trophoblastic disease. Reproduction and sexuality will be compared by disease site and with a control group of noncancer survivors. In a mail survey of 111 postmenopausal breast cancer survivors, Denise Oleseke found that the number of menopausal symptoms, some of which might have accounted for by Tamoxifen, and an increase in depression scores were associated with an increase in rates of hospitalization.

**Medical Late Effects of Cancer**

Physiological effects of treatment may depend upon the cancer itself or upon treatment with surgery, radiation, or chemotherapy. Patricia Ganz's review provided a summary of the potential problems relating to disease and treatment. For some types of tumors, survival exceeds 75%, results often obtained following complex and multimodal therapies that may increase long-
term toxicities. Chronic toxicities include pulmonary fibrosis, congestive heart failure, graft versus host disease, neurological syndromes, infertility, hypothyroidism, or serious risk of second malignancies.

Why should we study these outcomes now? The relationship of late effects to prior treatment is critical for prevention of late effects. The pediatric oncologists have made excellent use of knowledge of specific late effects to modify subsequent treatment regimens (e.g., elimination of craniospinal radiation in acute leukemia). Some important general considerations are that the risk of late effects depends on the tissue and age of the patient at the time of treatment. Furthermore, late effects are dose and modality specific (e.g., surgery, radiation, and chemotherapy), and combined modality therapy can have additive risks.

Late effects of surgery can result from limb amputation (e.g., functional changes and cosmetic deformity), abdominal surgery (e.g., intestinal obstruction from adhesions and short bowel syndrome), lymphadenectomy (e.g., lymphedema), splenectomy (e.g., immune dysfunction and sepsis), or pelvic surgery (e.g., impotence and incontinence). Many of these effects are immediate; however, some may not be apparent until many years after initial cancer diagnosis and treatment.

Chemotherapy can cause a wide range of late effects in a variety of tissues. For example, corticosteroids can cause cataracts, as well as avascular necrosis of bone. A variety of drugs can cause pulmonary fibrosis [e.g., bleomycin, methotrexate, and 1,3-bis(2-chloroethyl)-1-nitrosourea]. A number of drugs can cause central and peripheral nervous system changes that can impair functioning. Decreased renal functioning can occur with cisplatin, methotrexate, and the nitrosoureas. This may be so severe at times so as to require hemodialysis. Liver function abnormalities can be mild, or they could, in some instances, lead to hepatic failure [e.g., methotrexate and 1,3-bis(2-chloroethyl)-1-nitrosourea]. Finally, gonadal dysfunction can occur with both alkylating agents and procarbazine, resulting in premature menopause in women, as well as infertility in both men and women.

The late effects of radiotherapy are largely confined to the organs/tissues that are the target of treatment. Injuries to the bone and soft tissues are common, leading to abnormal growth and short stature in children, as well as atrophy, fibrosis, and cosmetic deformities at all ages. The oropharynx and teeth may be injured, leading to poor enamel and root formation, as well as a dry mouth. The eyes may be damaged, leading to premature cataracts, retinopathy, and keratoconjunctivitis. Cardiovascular injury from radiation can lead to pericardial effusion, constrictive pericarditis, and premature coronary artery disease. Radiation can also injure the lungs, leading to pulmonary fibrosis and decreasing lung volumes. CNS injury from cranial irradiation often leads to neuropsychological deficits in children and dementia in adults. Renal and genitourinary abnormalities can lead to hypertension, renal failure, and bladder fibrosis/contractures. Gastrointestinal irradiation may result in malabsorption syndromes, and adhesions with obstruction. There are endocrine consequences of radiation therapy, such as pituitary hormone deficiencies, hypothyroidism, and gonadal dysfunction with sterility and premature menopause.

It is unclear who is monitoring the late effects of cancer treatment on survivors. Although oncologists are the most knowledgeable about the potential late effects of treatment, they are not always able to follow their patients beyond 5 years after treatment. Primary care physicians, who are unfamiliar with these late effects, are increasingly becoming the caregivers for survivors. It is important for cancer survivors themselves to be aware of their past treatments and to review their symptoms with the physician in light of the cancer history and treatment. We need to prepare survivors for these potential late effects by providing them with information about potential toxicities and by openly discussing the need for long-term follow-up.

To make progress in this area, however, Dr. Ganz stressed the need for increasing our knowledge of the late effects of cancer treatments through the conduct of systematic research. We need to make better use of the cooperative groups and cancer registries to link the primary treatment with subsequent outcomes. She suggested that survivor clinics and registries be established to facilitate the systematic assessment of physical late effects using research funding. A knowledge of the prevalence of late effects is needed to accurately inform physicians and survivors about what to expect from treatments and the time course for late effects.

Ongoing studies of late effects of therapy were presented by several investigators. Cognitive deficits, such as difficulty with memory and concentration, were described by Tim Ahles. He plans to compare functional magnetic resonance imaging with other measures of cognition in an attempt to understand the relationship of chemotherapy to cognitive function. Because of continuing symptoms and signs, head and neck cancer survivors are primarily concerned about cancer recurrence, according to a report by Bruce Campbell. Documentation of late effects of radiation for prostate and head and neck cancers has been difficult. To deal with this problem, Charles Scott reported that the Radiation Therapy Oncology Group is developing a set of scales to measure subjective (S), objective (O), and management (M) aspects of late sequelae following radiation; research is planned to validate the SOM assessment scale prospectively. In a preliminary analysis of 59 survivors of childhood acute lymphoblastic leukemia who had been in complete continuous remission for at least 4 years after treatment, Sue Kaste and colleagues found that the frequency and severity of decreased bone mineral density are significantly less than those in age- and sex-matched normal controls.

Melissa Hudson noted a 4.5% prevalence of hepatitis C serum antibody in 119 of 2620 patients treated for childhood cancer who were transfused with red blood cells. Of these patients, 2 died of hepatitis C, 18 died of cancer, and 4 died of other causes. Liver biopsies performed in these 24 patients revealed that 20 (83%) had chronic hepatitis, 16 (67%) with fibrosis and 3 (13%) with cirrhosis.

Kathy Albain discussed the special problems of lung cancer survivors. Although lung cancer is the greatest cause of adult cancer mortality in both sexes, active research on issues in lung cancer survivorship has been scarce. Few patients are able to survive beyond 5 years. Other roadblocks include: (a) complex, nontraditional endpoints; (b) survivors' guilt and lack of advocacy; (c) competing major comorbidities in lung cancer survivors; and (d) therapeutic nihilism among primary physicians, with the lack of recognition that the pool of intermediate lung cancer survivors is, indeed, increasing. Some of this reluctance may be changing now because progress in recent years in the treatment of lung cancer has increased the pool of "intermediate" survivors. For metastatic non-small cell lung cancer, 2-year survivals approaching 15–20% were recently reported with third-generation chemotherapy regimens. Combined modality approaches (chemotherapy plus radiotherapy) have significantly improved the 3–5-year survival, including cures for patients with locally advanced (stage III) small cell and non-small cell lung cancer. Finally, earlier stage non-small cell lung cancer without nodal metastases is often curable with surgery, and trials with added chemotherapy are in progress to
increase the proportion alive at 5 years. Beyond the 5-year survival, death often occurs from competing illnesses, second primary cancers, or late treatment effects, rather than relapse of the initial disease.

Future lung cancer survivorship research might concern the growing pool of intermediate survivors and the cohort of young women with lung cancer (often nonsmokers, usually adenocarcinoma), incorporating molecular epidemiology. It might include research on how to monitor lung cancer survivors for second primaries, chemoprevention of second primaries, and interventions for comorbidities (chronic obstructive pulmonary disease and cardiac), including pulmonary rehabilitation trials after combined modality therapy and after surgery.

**Cardiac Late Effects**

In his review of cardiac effects following treatment, Steven Hancock presented the results of his studies in survivors of Hodgkin’s disease. Cardiac toxicity is primarily the result of anthracycline chemotherapy of cardiac irradiation. Acute toxicity occurs occasionally, but the greater problem after anthracycline treatment is a subacute decline in contractility that may lead to congestive heart failure, the risk increasing with increasing doses and longer follow-up times. Cumulative doses >550 mg/m² have been associated with cardiac dysfunction in 1.6% of 6500 children and adolescents in the Pediatric Oncology Group studies. In other studies, up to 27% of patients have had impairment in left ventricular systolic function and peak wall stress. Strategies to decrease these effects include the use of cardiac protectants, such as dexrazoxane and the substitution of idarubicin, epirubicin, and mitoxantrone for doxorubicin. Radiation-associated delayed toxicity, especially after doses of >3000 cGy, including constrictive pericarditis with tamponade, myocardial fibrosis, and acute myocardial infarction (with a 3.4-fold increased risk of death), were less affected by early changes in radiation technique. Age, time from radiation, and treatment before 1972 were also factors. Patients who were <40 years of age had a 2–6-fold greater risk than did those over 40. The risk increases 2–9-fold beginning 5 years from treatment. Silent ischemia with coronary artery disease occurs in at least 7% after irradiation.

Important research questions include: will lower doses of anthracyclines and irradiation or cardiac protectants avoid or merely delay the onset of toxicity, and what else can be done to modify future risks? Other questions include: will exercise testing be of benefit in detecting asymptomatic survivors at risk for late toxicity, and will afterload reducers be able to prevent long-term damage? To predict the late effects of interventions, one would ideally have quantifiable and early endpoints, and these are not yet available.

**Bone Marrow Transplant**

The problems specific to bone marrow transplant survivors were described by Susan Parsons and were reviewed in a poster discussion session. Dr. Parsons and her colleagues developed a child-scored BMT-specific instrument to evaluate children’s health status following transplantation. Preliminary findings using this instrument include a strong association between the physicians’ assessment of clinical severity and children’s self-reported health status, lower parental assessments of their child’s health status than that reported by the child, and lower physical functioning and overall QOL for children with chronic graft versus host disease.

Cindy Schwartz reviewed five abstracts demonstrating that serious effects can emerge long after therapy with cytotoxic agents; four concerned survivors of BMT. Because follow-up of patients beyond 5 years after diagnosis is limited, reports of long-term therapeutic toxicity rarely extend beyond this time frame. But the 5-year mark by which tumor control is measured does not reflect an end to the consequences of therapy.

A study by George McDonald evaluated patients after BMT. Thirty-one of 2287 (1.45%) had cirrhosis detected >3 years from diagnosis. The prevalence was higher in those studied >10 years after treatment. Nineteen of 645 (2.9) in this cohort with longer follow-up had cirrhosis. The median time to diagnosis was 10.2 years (1.2–24.9 years). Univariate analysis suggested that the following were risk factors: hepatitis C (P = 0.004) and venocclusive disease (P = 0.045). Although a greater prevalence of cirrhosis in longer-term survivors may reflect changes in transfusion practices over the years, detection primarily during longer-term follow-up care suggests that this may be an injury that will manifest its effects many years after treatment.

For very young children, it may be more than 10 years before the extent of developmental effects becomes apparent. Jean Sanders reported the impact of prior CNS irradiation and BMT preparative regimens on long-term growth and development. Final adult height was directly related to the age at the time of BMT and was most affected by prior CNS radiation and nonfractionated total body irradiation. Puberty progressed normally after cyclophosphamide alone in 90% of patients. In contrast, normal pubertal development occurred in only 34–50% of those with additional cranial radiation. CNS irradiation also affected the subsequent intellectual outcome. As the outcome of cancer therapy extends beyond survival at 5 years, encompassing longer-term medical effects, the importance of the QOL also becomes more apparent.

Richard McQuellon noted that, although many aspects of life were improving in patients who were 1 year post-BMT (e.g., depression), fatigue was persistent. Marcia Grant evaluated 311 patients after BMT using a QOL instrument that measured “well-being” via measures of physical, psychological, social, and spiritual status. Fatigue remained a notable concern for patients after treatment. Because many patients will experience toxicity long after treatment is complete, there is a need for very long-term follow-up of patients after cancer therapy. Few programs now exist for the very long-term follow-up of adult survivors of either pediatric or adult cancer therapy. Programs designed specifically for very long-term survivors are essential to understand the very long-term consequences of survival, the “later late effects.”

**Second Cancers**

Second primary cancers are another serious long-term problem for survivors. Fred Li provided an overview of what is now known concerning specific factors associated with the development of new cancers and the magnitude of the increased risk. Second cancers develop as a consequence of carcinogenic exposures with pleiotropic effect, inherited susceptibility to cancers of multiple sites, and/or radiotherapy and certain chemotherapeutic agents.

Cigarette smoking accounts for ~30% of cancer deaths in the United States. Smokers are at increased risk of cancers of the lung, oral cavity, urinary bladder, pancreas, and other sites. Smokers who survive their first cancer are at high risk of developing second cancers within the same organ or other susceptible organs. Additionally, most inherited cancer susceptibility genes predispose to the development of neoplasia in
multiple organ sites. For example, the BRCA1 and BRCA2 genes predispose not only to breast cancer but also to ovarian and, perhaps, other cancers. Cancer occurrence at unusually early ages and bilateral or multifocal neoplasms can be indicative of predisposition and future second cancer risk. Genetic testing can identify carriers at high risk of future cancers for early interventions, including increased medical surveillance, enrollment in chemoprevention trials, and prophylactic surgery.

Ionizing radiation is well established as a human carcinogen. The carcinogenic effect increases with dose and field size. Radiation-induced cancers can be of diverse types, whereas most chemotherapy-associated cancers are acute myelocytic leukemia. Success in therapy of cancer has substantially increased the number of cancer survivors worldwide. Identifying and avoiding risk factors for second cancers can improve both the duration and quality of survival of cancer patients.

Second cancers have been studied by Alfred Neugut and Philip Rowlings, and their posters were summarized by Smita Bhatia. Of the 1.4 million new cancers diagnosed every year, 95,000 are second cancers. The second cancers comprise 6–11% of all cancer diagnoses, and second cancers are rapidly becoming the fourth or the fifth most common cancer in the United States. In general, patients diagnosed with one cancer have twice the risk of a new primary cancer than do others in the population. For those diagnosed with their first cancer at <15 years of age, the risk is increased 8-fold. The risk is not increased for patients over the age of 30 years at first diagnosis. Women treated with radiation therapy for breast cancer had a 2–3-fold increased risk of lung cancer in the ipsilateral lung after 10 years, and with smoking, the risk was increased to 40-fold. Esophageal squamous cell carcinoma also was increased. Posttransplant lymphoproliferative disease was identified in 78 of 18,000 patients in the International Bone Marrow Transplant Registry or the Fred Hutchinson Center between 1964 and 1992. The rates were highest within 6 months of transplant. When Hodgkin’s disease occurs following BMT, it is usually of the mixed cellularity subtype, occurs later than PTLD, and is not associated with T-cell depletion, mismatched marrow, or the use of antithymocyte globulin for graft-versus-host disease prophylaxis.

High priority needs to be given to characterizing and preventing second neoplasms because they are often associated with high levels of morbidity and mortality. Several issues remain unresolved, and these include the latencies between specific cancer treatments and subsequent cancers; age at diagnosis; sex preference; and the role of specific therapeutic agents and the interactions between all of these. To quantify the influence of family history in the development of subsequent neoplasms, a study from Finland reported that patients who had a family history of early-onset cancer were at 4.7-fold higher risk of developing a subsequent neoplasm, as compared to those who did not have a positive family history. Moreover, adjustment for radiation did not alter this risk. Thus, the authors concluded that both genetic factors and exposure to ionizing radiation increase the risk of a subsequent neoplasm. In a matched case-control study of 30 patients with secondary lung cancer following Hodgkin’s disease, radiation was associated with an increased risk. In addition, there was a significant dose-response relationship between smoking and the risk of developing secondary lung cancer, with a positive interaction between smoking and radiation exposure.

Throughout this workshop, the speakers and discussants emphasized the gaps in our knowledge concerning cancer survival and recommended opportunities for further research. The ultimate goal is clear: to successfully treat and cure children and adults with cancer, while maximizing their chances of a long and healthy life, using both primary prevention strategies (modification of treatment) and secondary prevention strategies (identification of high risk populations and institution of screening measures).

Acknowledgments
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Appendix
Workshop Participants
K. Albain, Loyola University Medical Center. Survival following lung cancer and late mortality.
S. Bhatia, City of Hope National Medical Center. Poster discussion: second cancers.
B. Campbell, and P. M. Layde. The Medical College of Wisconsin. Persistent symptoms and fear of cancer recurrence in long-term head and neck cancer survivors.
J. Davis, and S. Churchill, National Black Church Family Council, Tuscaloosa County, AL. The spiritual journey of surviving cancer for women in the black community.
P. A. Ganz, Jonsson Comprehensive Cancer Center, UCLA Schools of Medicine and Public Health. Medical late effects in cancer survivors.
M. Grant, L. Rivers, B. Ferrell, and C. King, City of Hope National Medical Center and University of Rochester. The impact of fatigue on quality of life in bone marrow transplant survivors.
J. A. Guillory, Morehouse School of Medicine. Relationships of physi-ological, psychosocial and spiritual variables and survivorship in African-American women with breast cancer.
S. Hancock, Stanford University Medical Center. Long-term cardiac toxic-ity in cancer survivors.
K. E. Jackson, and C. Harris, Houston, TX. Sisters Network, Inc.; guide for new chapters.
S. A. Leigh, National Coalition of Cancer Survivorship, Tucson, AZ. Living with cancer.
F. P. Li, Dana-Farber Cancer Institute. Second cancers.
C. Logan-Cartillo, People Living Through Cancer, National Coalition of Cancer Survivorship, Albuquerque, NM. People living through cancer.


P. A. Rowlings, R. E. Curtis, D. Kingma, E. S. Jaffe, G. Socie, H. J. Deeg, L. Travis, and M. M. Horowitz, Medical College of Wisconsin, National Cancer Institute, and Fred Hutchinson Cancer Research Center. *Hodgkin's disease following allogeneic bone marrow transplantation: long latency and association with Epstein-Barr virus*.


C. Runowicz, Albert Einstein College of Medicine, Montefiore Medical Center. *Poster discussion: after gynecologic cancer*.

J. E. Sanders, Fred Hutchinson Cancer Research Center. *Impact of prior central nervous system irradiation and marrow transplant preparative regimens on long-term growth and development*.

L. R. Schover, The Cleveland Clinic Foundation. *Sexuality, hormonal, and reproductive toxicity*.

C. Schwartz, Johns Hopkins University. *Poster discussion: late effects after marrow transplant*.

C. Scott, C. Scarantino, D. W. Bruner, K. Fu, W. Shipley, and J. Cooper, RTOG, Fox Chase Cancer Center, University of California, Massachusetts General Hospital, and New York University. *Late effects of normal tissues in head and neck and prostate cancer patients treated with radiation therapy*.

D. Spiegel, Stanford University School of Medicine. *Psychosocial long-term effects*.

E. Stovall, National Coalition for Cancer Survivorship. *Policy issues for survivors*.


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