

American Society of Clinical Oncology Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects

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A B S T R A C T

Purpose

To review the evidence on the incidence of long-term cardiac or pulmonary toxicity secondary to chemotherapy, radiotherapy, or trastuzumab in symptomatic and asymptomatic cancer survivors.

Methods

An American Society of Clinical Oncology Panel reviewed pertinent information from the literature through February 2006.

Results

Few studies directly addressing the benefits of screening for long-term cardiac or pulmonary toxicity in asymptomatic cancer survivors who received chemotherapy, radiotherapy, or trastuzumab were identified. The reviewed literature included primarily retrospective and cross-sectional studies describing the incidence of cardiac and pulmonary late effects. Anatomic and/or functional abnormalities have been associated with use of all currently available anthracyclines and their derivatives. Trastuzumab-related cardiac dysfunction rarely causes death, and in most cases is reversible with improvement in cardiac function on drug discontinuation and/or treatment with cardiac medications. The estimated aggregate incidence of radiation-induced cardiac disease is 10% to 30% by 5 to 10 years post-treatment, although the incidence may be lower with modern techniques. Radiation pneumonitis is reported in 5% to 15% of lung cancer patients receiving definitive external-beam radiation therapy. A minority of patients may develop progressive pulmonary fibrosis; late complications include cor pulmonale and respiratory failure. Bleomycin-induced pneumonitis is an acute rather than late effect of treatment. Late pulmonary complications in bone marrow or stem cell transplantation patients who develop interstitial pneumonitis include idiopathic pneumonia syndrome and bronchiolitis obliterans.

Conclusion

An increased incidence of cardiac and/or pulmonary dysfunction is observed in cancer survivors. Research is needed to identify high-risk patients, and to determine the optimal screening strategies and subsequent treatment.

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INTRODUCTION

LATE EFFECTS OF CANCER SURVIVORS: THE SCOPE OF THE PROBLEM

During the past three decades, the development of effective screening and treatment strategies for many cancers has resulted in an enormous population of long-term cancer survivors.^{1,2} Current figures estimate that 60% of adults newly diagnosed with cancer are expected to be alive 5 or more years later. According to estimates from the National Cancer Institute and the Centers for Dis-

ease Control and Prevention, there were more than 10 million cancer survivors in the United States alone in 2002.³

The impact of cancer and of cancer treatment on the long-term health of these survivors is substantial. Late effects include organ damage and functional disabilities that result from the disease, the treatment, or both, and include the development of second malignancies. In addition, a multitude of psychosocial issues confront adult cancer survivors. The prevalence of the range of late effects is uncertain, but there is growing recognition that these effects have become more

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common with the increasing use of more complex and intensive, multiagent and multimodality cancer interventions.

Presently, there is wide variation in the clinical care offered to long-term cancer survivors. There are gaps in patient and physician knowledge about the need for long-term follow-up, and evidence-based guidelines to direct surveillance to detect the late effects of treatment are lacking.

CARDIOVASCULAR AND PULMONARY LATE EFFECTS

Long-term cancer survivors are at risk for a variety of cardiac and/or pulmonary late effects. Chemotherapy-induced cardiovascular toxicity may include cardiomyopathy with or without overt congestive heart failure (CHF), endothelial dysfunction, and arrhythmias. Doxorubicin-induced cardiomyopathy is the most studied chemotherapy-induced cardiovascular toxicity. A similar entity is associated with all of the anthracyclines and mitoxantrone and may also be associated with high-dose cyclophosphamide. Radiotherapy-induced cardiovascular toxicity may include coronary artery disease (CAD), valvular disease, chronic pericardial disease, arrhythmias and conduction disturbances, cardiomyopathy, or carotid artery stenosis. Trastuzumab (Herceptin; Genentech Inc, South San Francisco, CA) therapy is associated with a specific type of cardiac dysfunction, which differs in many respects from anthracycline-induced myocardial damage. Cancer patients who have received trastuzumab represent a relatively new population and are addressed separately in this review. Pulmonary toxicity may be secondary to either chemotherapy or radiotherapy; these toxicities can include radiation pneumonitis, pulmonary fibrosis, and an overall decrease in pulmonary function. Stem-cell transplantation may also be associated with long-term pulmonary complications, including idiopathic pneumonia syndrome and bronchiolitis obliterans. In addition, carmustine (BCNU) pneumonitis occurs in 25% to 30% of patients receiving augmented regimens and frequently results in chronic pulmonary function testing abnormalities. Although a variety of chemotherapeutic agents may cause pulmonary toxicity, bleomycin has been the most studied.

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL EVIDENCE REVIEW

The American Society of Clinical Oncology (ASCO) convened an expert panel to develop guideline recommendations for the ongoing surveillance and care of adult and pediatric survivors of cancer to provide health professionals with the knowledge and expertise to decrease morbidity and to improve quality of life for adult survivors of cancer. Given the broad range of topics to address in a cancer survivorship guideline, the expert panel proposed to develop a series of practice guidelines. In late 2005, the expert panel began work on a cardiac and pulmonary late effects guideline. The purpose of the guideline was to develop screening recommendations for chemotherapy- and radiotherapy-induced cardiac and pulmonary late effects.

In June 2006, the expert panel submitted the guideline to the ASCO board of directors for their consideration. After extensive deliberation, the board voted to not approve the document as a guideline in light of the lack of direct, high-quality evidence on the benefits and harms of screening for cardiac and pulmonary late effects. The evidence identified from the systematic review of the literature was of cross-sectional or retrospective studies of the

incidence or prevalence and/or treatment of cardiac or pulmonary toxicity in cancer survivors. Few prospective studies were identified. None of these studies was designed to directly address the utility, benefits, or harms of screening for long-term toxicities in a population of asymptomatic cancer survivors.

Although the existing evidence was considered insufficient to form the basis for a practice guideline, the ASCO board of directors recognized the value of the systematic review of the literature completed for the guideline, in identifying gaps in the literature, and in providing the basis for a detailed agenda for future research. The board of directors therefore directed the panel to develop a new document—the clinical evidence review (CER)—that would review the identified literature without delineating specific guidelines. The CER reported here summarizes the results of that systematic review of the literature on cardiac and pulmonary late effects among cancer survivors. The CER is organized around the major questions originally addressed by the panel relating to screening for cardiac and pulmonary disease among asymptomatic cancer survivors who have received a range of therapies. The CER concludes with a discussion of the limitations of the research conducted to date and with a detailed research agenda for future investigation.

SYSTEMATIC REVIEW METHODOLOGY

PANEL COMPOSITION

The ASCO Health Services Committee (HSC) convened an expert panel consisting of experts in clinical medicine and research relevant to cancer survivorship and the long-term care of adult cancer survivors, including internal medicine, medical oncology, epidemiology, gynecological oncology, cardiology, health services research, oncology nursing, psychosocial oncology, and radiation oncology. Academic and community practitioners, an oncology fellow, and patient representatives were also part of the panel. The panel members are listed in online-only Appendix Table A1. The panel formed four subcommittees corresponding to the four major topic areas in the guideline series, and oversaw the conduct of the systematic review reported here.

LITERATURE REVIEW AND ANALYSIS

Literature Search Strategy

The following electronic databases were searched through February 2006: MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library. Results were supplemented with hand searching of selected reviews and personal files. The following MeSH terms and text words were used in a core search: “neoplasms,” “survivors,” “bone marrow diseases,” “antineoplastic agents,” “Herceptin,” “trastuzumab,” “radiotherapy,” “heart diseases,” and “respiratory tract diseases.” “Heart,” “lung,” “mediastinum,” and “cardiovascular system” MeSH terms were paired with the qualifiers “radiation effects” and “drug effects.” Focused searches were done using the term screening and the MeSH subheading “prevention and control.” Due to the expected limited number of randomized controlled trials for screening studies in the target population, study design was not limited to randomized controlled trials, but included any study type, including cohort designs, case series, evaluation studies, and prospective studies.

Case reports and non-English language articles were excluded. Letters, commentaries, abstracts not yet published in manuscript form, and editorials were reviewed for any new information. Existing practice guidelines from other organizations were also reviewed.

Articles were originally selected for inclusion in the systematic review of the evidence if they met the following criteria: the study examined a screening intervention for cardiovascular or pulmonary disease; the study population consisted of cancer survivors who had previously received chemotherapy and/or radiotherapy and/or trastuzumab; primary outcomes of interest included screen-detected cardiovascular or pulmonary disorders and the effect of screening on cardiovascular or pulmonary morbidity, quality of life, and overall survival. Primary consideration was given to studies with 50 or more patients and to studies published after 1994; however, studies not meeting these criteria were considered when they provided important additional data or data not available elsewhere. Additional review articles were obtained for reference.

ASCO Expert Panel Literature Review and Analysis

An initial abstract screen was performed by ASCO staff. The ASCO panel reviewed all remaining potentially relevant abstracts identified in the original literature searches to select studies pertinent to its deliberations. Two panel members independently reviewed each abstract for its relevance to the clinical questions, and disagreements were resolved by third-party review. Full-text articles were then reviewed for all selected abstracts. Evidence tables were developed based on selected studies that met the criteria for inclusion.

SUMMARY OF OUTCOMES ASSESSED

Originally, the primary outcomes of interest included: the incidence of screen-detected cardiovascular or pulmonary disease; the effect of screening on cardiovascular or pulmonary morbidity; quality of life; and overall survival. Also considered as secondary outcomes were disease-free survival, treatment risks, education or increased awareness, and cost effectiveness. Subsequent to the finding that there were insufficient data in these primary outcome areas, attention was focused on the incidence or prevalence of cardiovascular or pulmonary disease in long-term cancer survivors.

RESULTS

Preliminary searches identified 4,805 abstracts. The initial abstract screen performed by ASCO staff eliminated 3,696 abstracts that failed to meet any of the inclusion criteria. The ASCO panel conducted dual independent review of all remaining 1,109 potentially relevant abstracts identified in the original systematic review. The panel eliminated 745 abstracts at this stage of the review; the remaining 364 articles were reviewed in full for the interventions and outcomes described earlier.

Almost all of the studies reviewed presented data on the incidence or prevalence of cardiac or pulmonary toxicity in cancer survivors. Most of these studies were cross-sectional or retrospective by design and only a few prospective studies were identified. Other studies reported on the treatment of radiation- or chemotherapy-induced cardiac or pulmonary toxicity. Few of these studies were designed to directly address screening for toxicities in a population of asymptomatic cancer survivors.

Reviews were identified on the following topics: the long-term risk of cardiovascular disease after radiotherapy; a Surveillance, Epidemiology, and End Results (SEER) database review reporting on the cardiovascular effects of chemotherapy and radiotherapy in breast cancer patients; and a systematic review on the frequency and risk factors of subclinical cardiotoxicity in children after anthracycline use. A meta-analysis was not performed because the studies were judged to be too heterogeneous for meaningful quantitative synthesis.

CARDIAC DISEASE IN ADULT CANCER SURVIVORS WHO PREVIOUSLY RECEIVED ANTHRACYCLINES OR PLATINUM-BASED CHEMOTHERAPY

EVIDENCE SUMMARY

Anthracyclines are potent and effective drugs used in the treatment of a broad spectrum of pediatric and adult hematologic and solid organ cancers. Their use has improved survival rates and there is abundant evidence regarding their toxic effects on the heart in long-term survivors (defined as > 2 years after treatment completion) who received chemotherapy. Abnormalities in left ventricular size and function measured by noninvasive testing and/or overt CHF have been associated with the use of all of the currently available anthracyclines and their derivatives.¹⁻³ Patients may or may not have symptoms and measured abnormalities may be predominantly diastolic, systolic, or combinations of both.

Cisplatin-based chemotherapy has direct and indirect effects that impact on the cardiovascular system. Direct chronic endothelial damage⁴ commonly leads to Raynaud-like symptoms and less commonly has been associated with CAD. Indirectly, this chemotherapy impacts on the traditional cardiac risk factors to increase the survivors' risk of developing atherosclerosis. Long-term follow-up of survivors of germ cell tumors (GCT) treated with cisplatin-based chemotherapy have an abnormally high incidence of obesity, lipid abnormalities (low high-density lipoprotein and elevated low-density lipoprotein), and hypertension. The relative risk of developing atherosclerosis in the coronary and carotid arterial systems is increased compared with age-matched cohorts.⁴

No study has systematically evaluated the role of routine non-invasive testing for cardiac dysfunction or the role of specific treatment to prevent cardiac disease in a population of asymptomatic cancer survivors. Although the incidence and description of cardiac effects have been well documented and studied, there has been little investigation into the true incidence of asymptomatic disease in the survivor population and there is virtually no direct evidence regarding the value of any treatment in altering the natural history of cardiac disease in the asymptomatic survivor. There is a paucity of even observational studies that address serial changes in asymptomatic survivors with left ventricular dysfunction (LVD), and no screening schedule has been tested for efficacy or cost effectiveness.

REVIEW OF RELEVANT LITERATURE: CHEMOTHERAPY-INDUCED CARDIAC TOXICITY

Incidence

Anthracycline cardiomyopathy is characterized by a dose-dependent progressive decrease in systolic left ventricular function

often resulting in CHF. In the adult survivor, it is clinically indistinguishable from CHF due to other causes. Several factors increase the risk and are listed in Table 1. The development of cardiac toxicity is independent, for the most part, of the type of the underlying cancer treated⁵ and strictly related to treatment protocol. There is also evidence that the risk can be reduced but not eliminated with cardioprotective drug use (dexrazoxane)⁶ and with the use of epirubicin and pegylated preparations. It can also be reduced by alterations in administration schedule (eg, once per week *v* once every 3 weeks) or continuous infusion schedules.

The cardiomyopathy may also present as diastolic dysfunction that is either symptomatic or asymptomatic.⁷ In pediatric patients who received anthracyclines, both systolic and diastolic abnormalities may present with a latency period up to at least 25 years after the completion of therapy and the risk of cardiac failure clearly increases over time.⁵ It has become increasingly recognized that symptomatic CHF may be preceded by asymptomatic or subclinical cardiac dysfunction undetectable at bedside evaluation and/or defined by abnormalities measured by noninvasive imaging techniques (echocardiogram, multigated [MUGA], or radionuclide angiography) in presumed healthy survivors of cancer.⁸

The risk of developing cardiotoxicity is mainly related to the total cumulative dose of doxorubicin (1% to 5% up to 550 mg/m², 30% at 600 mg/m², and 50% at 1g/m² or higher) with individual variation. The risk increases proportionally to the total accumulated dose in a nonlinear fashion,⁹ so that there probably is no safe dose of doxorubicin.⁵ It is increasingly recognized that abnormalities in noninvasive studies can be found in greater frequency and at a lower cumulative dose than previously reported.^{10,11}

The prevalence of subclinical cardiotoxicity varies widely between studies with the majority of evidence coming from two separate sources: survivors of pediatric cancer, dominated by long-term follow-up studies of children treated for Hodgkin's disease (HD) and adult studies mainly focused on female survivors of breast cancer. Because the mechanism of disease and the approach to study have been different between the pediatric and adult populations, they will be discussed separately.

Adult Studies

Late cardiotoxicity in adults has been studied in breast cancer patients treated with anthracyclines (mainly doxorubicin and epirubicin), acute myeloid leukemia patients treated with idarubicin,

or patients treated with doxorubicin for various hematologic malignancies. A total doxorubicin dose of 550 mg/m² has been the traditional cutoff and most studies have looked at populations receiving doses between 450 and 550 mg/m². The incidence of subclinical cardiomyopathy in patients receiving lower doses of doxorubicin has been studied by Hequet et al,¹² and Table 2¹²⁻¹⁵ summarizes studies (with a variety of study designs) reporting on cardiotoxicity after treatment with anthracyclines.

Beginning at the 5-year mark after treatment completion, the relative risk of cardiotoxicity among patients who received doxorubicin increased compared with untreated patients.¹³ These results emphasize the importance of recognizing the late cardiac effects of treatment especially as the number of long-term survivors treated with anthracyclines continues to increase.

There are very few studies that have examined the risks of anthracyclines and radiation therapy. In one study, breast cancer patients randomly assigned to receive a total cumulative dose of 225 mg/m² with or without radiation had no increase in clinically significant cardiac events relative to the expected rates based on the Framingham heart study, whereas patients who received 450 mg/m² with radiation had significantly higher rates.¹⁶ The concurrent use of doxorubicin and radiation led to a significantly higher rate of CHF in left-sided breast cancers than those with right-sided breast cancers and concurrent use of these two treatments is no longer used in the clinic.¹⁷

Platinum-Based Chemotherapy

After cisplatin-based chemotherapy, survivors of testicular cancer have an increased risk of cardiovascular risk factors and an increased risk of cardiovascular disease compared with an untreated matched population (Table 3).¹⁸⁻²⁰ Survivors treated with cisplatin-based chemotherapy have an excess of cardiac risk factors and an increased risk of the development of premature atherosclerosis. No study has systematically evaluated the role of routine noninvasive testing or the role of specific prophylactic treatment in this population.

MONITORING

On the basis of risk factors, multiple strategies have been proposed for the early detection of anthracycline cardiomyopathy. These include serial endocardial biopsy, serial B-type natriuretic peptide (BNP) and troponin level testing, radionuclide MUGA or radionuclide angiography, exercise testing, and echocardiogram.^{21,22} Currently, none of these strategies has become standard monitoring for long-term survivors of cancer treated with anthracyclines and the majority of the published evidence describing the incidence of late asymptomatic cardiotoxicity has been based on data derived from echocardiogram and Doppler studies.

Echocardiography is the most widely used noninvasive tool to evaluate cardiac function. Primary parameters of systolic function are represented by measurements of ejection fraction (EF) and fractional shortening (FS). Additional parameters of afterload and contractility can be obtained, as well as accurate measurements of chamber size, pericardial integrity and function, and associated valvular disease. In the current large multicenter studies, most have used radionuclide angiography, MUGA, or echocardiogram to evaluate left ventricular function.

Several studies have suggested that diastolic dysfunction may be an early sign of anthracycline cardiotoxicity, and echocardiogram is particularly sensitive for measuring diastolic function in both adult and pediatric patients.

Table 1. Risk Factors for Anthracycline Cardiomyopathy

Patient Characteristic	
Young age (< 18 years) at treatment initiation	
Age > 65 years at treatment initiation	
Associated hypertension, pre-existing cardiac disease (coronary artery disease, left ventricular dysfunction)	
Pregnant or contemplating pregnancy	
Engaging in extreme/competitive athletics	
Treatment Characteristic	
Higher cumulative dose equal to ≥ 300 mg/m ² of doxorubicin or ≥ 600 mg/m ² of epirubicin	
Associated mediastinal radiation therapy	
Combination chemotherapy (trastuzumab, cyclophosphamide, etoposide, melphalan, paclitaxel, mitoxantrone, idarubicin)	
Longer duration of survival	

Table 2. Cardiotoxicity, Anthracyclines, Adult Studies

Reference	Malignancy (n)	Therapy	Follow-Up	Findings
Hequet et al ¹²	Lymphoma (n = 141)	Doxorubicin, cumulative median dose 300 mg/m ²	5-year post-treatment minimum; median, 8 years from diagnosis	Overt CHF, n = 1; cardiomyopathy, asymptomatic patients with evidence of LVD (based on FS < 25%), n = 39 (27.6%); cardiomyopathy, asymptomatic patients based on two of three variables (FS < 28%, EF < 50%, or wall motion abnormality), n = 29
Bonneterre et al ¹⁴	Breast cancer, node-positive (n = 150)	FEC (epirubicin at 50 or 100 mg)	Median, 102 months	FEC 100: EF < 50%, n = 5; overt CHF, n = 2; asymptomatic LVD, n = 18; FEC 50: asymptomatic LVD, n = 1
Doyle et al ¹³	Breast cancer, stage I-III (n = 31,748)	Doxorubicin v no chemotherapy	Diagnosed from 1992-1999	The hazard ratios for cardiomyopathy, CHF, and heart disease for patients treated with doxorubicin compared with patients who received no chemotherapy were 2.48 (95%CI, 2.10 to 2.93), 1.38 (95% CI, 1.25 to 1.52), and 1.35 (95% CI, 1.26 to 1.44), respectively
Shapiro et al ¹⁵	Breast cancer, stage I-III (n = 299)	AC (doxorubicin at 45 mg/m ²) for five cycles or 10 cycles	Median, 6 years	Estimated risk of cardiac events/100 patient-years: CA10, 1.7 (95% CI, 1.0 to 2.8); CA5, 0.5 (95% CI, 0.1 to 1.2); P = .02; CA10, incidence of cardiac events compared with the general female population of the Framingham heart study: relative risk ratio, 3.6; P < .00003; CA5, risk of cardiac events did not differ significantly compared with Framingham population

Abbreviations: CHF, congestive heart failure; LVD, left ventricular dysfunction; FS, fractional shortening; EF, ejection fraction; FEC, fluorouracil, epirubicin, and cyclophosphamide; AC, doxorubicin and cyclophosphamide.

The addition of tissue Doppler studies²²⁻²⁴ that allow measurement of regional myocardial wall motion velocity may be important in the early detection of local abnormalities before global function change is apparent. Tissue doppler may be more sensitive in characterizing diastolic left ventricular relaxation. These additional measurements increase the discriminating ability of the study and are currently part of the routine adult study in some institutions.

Stress testing and dobutamine stress echocardiogram have been studied extensively, with mixed value reported in their ability to enhance the diagnostic sensitivity in the survivor population.

Recently, there has been interest in serial measurements of BNP to detect changes in left ventricular function. At present, no study has validated this as a routine measurement or screening tool in this population.

TREATMENT

Although the incidence and description of cardiac effects have been well documented and studied, there has been little investigation into the true incidence of asymptomatic disease in the survivor population and there is virtually no direct evidence regarding the value of any treatment in altering the natural history of cardiac

Table 3. Cardiotoxicity, Platinum

Reference	Malignancy	Therapy	Follow-Up (years)	Findings
Nuver et al ¹⁸	Testicular cancer (n = 90)	PBCT	Median, 7	Increased frequency of impaired left ventricular relaxation demonstrated by echocardiography; high prevalence of risk factors (diastolic blood pressure elevation 22%), compared with matched controls who did not receive chemotherapy
Van den Belt-Dusebout et al ¹⁹	Testicular cancer (n = 2,512)	Cisplatin, vinblastine, bleomycin Bleomycin, etoposide, cisplatin	Median, 18.4	Cardiovascular events, n = 694; acute MI, n = 141 Associated with 1.9-fold increased MI risk (95% CI, 1.7 to 2.0) Associated with 1.5-fold increased cardiovascular risk, but not associated with increased MI risk (95% CI, 1.0 to 2.2)
Meeinardi et al ²⁰	Germ cell tumors (n = 87)	Cisplatin	9-16	Overt CAD, n = 5; MI, n = 2; angina, n = 3

Abbreviations: PBCT, cisplatin-based chemotherapy; MI, myocardial infarction; CAD, coronary artery disease.

disease in the asymptomatic survivor. Because cardiomyopathy in the adult survivor looks like the more commonly seen nonanthracycline-induced dilated cardiomyopathy, it is intriguing to speculate that the same treatment approach should be beneficial. There are scattered case reports of improvement in symptomatic anthracycline cardiomyopathy using standard therapy for CHF that includes combinations of beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, spironolactone, diuretics, nitrates, and hydralazine. Systematic study of these agents in asymptomatic survivors has not been undertaken.

SPECIAL CONSIDERATIONS: PEDIATRICS

In pediatric survivors of cancer, it is estimated that more than half of all patients exposed to anthracyclines will show abnormalities on echocardiogram or radionuclide angiography when tested 10 to 20 years after treatment completion and that the incidence of these abnormalities increases with time.²⁵ In asymptomatic survivors, the abnormalities reported include reductions in FS, EF, increased wall stress and afterload due to cardiomyopathy. In children, FS less than 28% or a decrease of 10 percentile units compared with the initial values define systolic dysfunction. Several studies have suggested that diastolic dysfunction may be an early sign of anthracycline cardiotoxicity, and the echocardiogram is particularly sensitive for measuring diastolic function in pediatric patients.

There is abundant literature regarding treatment, including prophylactic treatment, with ACE inhibitors in the pediatric population with no consensus on long-term therapeutic value.^{5,25-27} Likewise, there is abundant literature evaluating the late subclinical incidence of cardiac disease in survivors of pediatric cancer who have been observed for up to 20 years.^{7,10,28-31} These studies are important for the adult population because most of these patients are now or will be treated by providers who care for adults.

Compared with adult studies that mainly assess LVEF, pediatric studies have looked at parameters of systolic function with measurements of contractility and afterload. These measures have taken on more importance in pediatric patients because of the recognition that chronic afterload with inadequate ventricular mass is associated with a progressive decrease in contractility, reduced cardiac output, and features of restrictive cardiomyopathy,³² whereas in the adult survivor, dilated cardiomyopathy with decreased EF predominantly occurs.

In a comprehensive review published in 2002, Kremer and colleagues systematically reviewed the then-current literature and presented the results of 25 studies of asymptomatic survivors of pediatric cancer previously treated with anthracyclines.³⁰ Based mainly on two-dimensional echocardiographic abnormalities, they presented an incidence spectrum that varied from between zero and 57%, with 13 studies showing an incidence of more than 20%. Increased risk was found to be associated with higher cumulative dose, longer follow-up post-treatment, mediastinal radiation, and young age at diagnosis.

In a more recent article published in 2004, Pein et al³¹ studied 151 pediatric long-term survivors (up to 25 years) of solid tumors treated with anthracyclines. They performed a battery of studies that included ECGs, echocardiogram, exercise testing, metaiodobenzylguanidine imaging, and BNP levels. Overall, they found a

9% incidence of cardiac abnormalities in asymptomatic survivors that required treatment and close follow-up (four patients with severe FS < 20% and nine patients with mild FS > 20% to 25%). This pattern was linked to cumulative doxorubicin dose after adjustment for other factors. Similarly, the EF was reduced in 17 patients. In terms of afterload, 65 (43%) of 151 patients had some abnormality of systolic function (abnormal wall stress, hypertrophy, contractility).

Dexrazoxane, a free radical scavenger, may protect the heart from doxorubicin-associated damage. In a study of children with acute lymphoblastic leukemia, Lipshultz et al³³ showed reduced levels of troponin T liberation without any reduction in clinical efficacy. The routine use of dexrazoxane as a cardioprotective agent and BNP monitoring for acute toxicity still require more widespread investigation before being adopted clinically as the standard of care.

Conclusions

Abnormal cardiac function occurs with long-term follow-up of patients of all ages who received anthracycline-based chemotherapy for any cancer diagnosis. For purposes of future study, a higher risk population may be defined at the extremes of age, higher cumulative dose, association of mediastinal radiation, and female sex. In contrast with adults, comprehensive serial cardiac monitoring has been performed in pediatric cancer survivors who were treated with anthracyclines. The results show that late symptomatic decompensation is usually preceded by a latent period, often marked by asymptomatic or subclinical LVD. The incidence of abnormal cardiac function appears to increase with the length of follow-up after treatment, and this is particularly true in patients treated with higher total cumulative doses of anthracyclines.

There is a paucity of observational studies that address serial changes in EF in asymptomatic adult survivors, and no studies address cardiac treatment of long-term survivors with asymptomatic LVD. Of the noninvasive studies, echocardiogram may provide the most information in assessing overall cardiac function in this population.

CARDIOVASCULAR DISEASE AMONG ADULT CANCER SURVIVORS PREVIOUSLY TREATED WITH MEDIASTINAL, CHEST, MANTLE, OR LEFT BREAST RADIATION

EVIDENCE SUMMARY

The heart is susceptible to radiation injury. Pericardial damage is the most frequently described, but all structures are at risk. Several recent comprehensive reviews describe exquisite details of incidence, pathophysiology, and testing, and offer personal views of testing modalities and frequency.³⁴⁻³⁷ A summary of the late structural abnormalities is presented in Table 4.

Much of the information available on the late complications of mediastinal radiation comes from children treated for HD, who because of their young age at diagnosis and effective therapy that leads to long-term survival, are an informative group for evaluation of the late cardiac effects of mediastinal radiation.

Adult patients with a variety of hematologic and solid organ cancers have also benefited from effective therapy and live long enough to develop late cardiac sequelae of their radiation treatment. The most robust literature includes information on

Table 4. Spectrum of Radiation Damage to the Heart

Structure	Abnormality	Natural History	Pathology
Pericardium	Pericarditis	Chronic asymptomatic effusion and/or pericarditis with symptoms: hemodynamic compromise with either constriction or tamponade	Fibrous thickening and fluid production
Myocardium	Myocarditis	Progressive diastolic dysfunction and restrictive hemodynamics with symptoms: CHF	Diffuse interstitial fibrosis/microcirculatory damage leading to capillary obstruction/extensive fibrosis
Endocardium	Valvular damage	Over time, progressive stenosis and regurgitation	Cusp and/or leaflet fibrosis
Vascular System	Arteritis	Premature CAD/accelerated atherosclerosis Pulmonary hypertension	Ostial and proximal stenosis; LAD, RCA, and left main more than left circumflex Pathology similar to atherosclerosis
Conduction System		All forms of heart block and conduction delay	Fibrosis of the conduction system
Autonomic Dysfunction		Supraventricular tachycardia; heart rate variability	

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; LAD, left anterior descending [coronary artery]; RCA, right coronary artery.

survivors of adult malignancies of the breast and head and neck cancers, as well as lymphomas and seminomas.

As with the risk factors for anthracycline cardiotoxicity, there are a number of factors that increase the risk of cardiovascular sequelae after mediastinal radiation. These factors producing a potentially high-risk population are reviewed in Table 5.

Review of the literature consistently describes a watershed in radiation oncology beginning around 1985. Treatment after this year marks the beginning of the so-called “modern era” or era of treatment with modern techniques. Incidence rates of cardiac toxicity have decreased progressively when mediastinal radiation is delivered according to “modern techniques.” These include the use of more conformal techniques, image-guided therapy, lower radiation doses, and more limited radiation fields in selected diseases. The changes and advances that characterize “modern” techniques are listed in Table 6.

Because of the increased risk attached to young age, adult survivors of pediatric cancer who received mediastinal radiation (most commonly patients with HD) have a reported increase in the incidence of CAD and fatal myocardial infarction, and should be considered at higher risk for cardiac complications.

Table 5. Factors Increasing the Risk of Cardiac Sequelae After Mediastinal Radiation Therapy

Patient factors

- Associated anthracycline chemotherapy
- Location of tumor close to heart border*
- Age < 18 years
- Associated cardiac risk factors
- Baseline cardiac disease*
- > 10 year post-radiation therapy

Radiation factors

- Orthovoltage radiation (rarely used since the 1970s)
- Volume of irradiated heart*
- Total dose to the heart > 30 Gy
- Daily dose fraction > 2 Gy/day
- Absence of subcarinal blocking

*These factors are consensus based and not individually validated.

REVIEW OF RELEVANT LITERATURE: RADIOTHERAPY-INDUCED CARDIAC TOXICITY

Natural History

As with survivors of anthracycline treatment, all late sequelae are progressive so that the risk of having subclinical disease and/or symptomatic cardiac disease increases over time from initial treatment. Similar to anthracycline cardiotoxicity, there can be a latent period of up to 20 years until symptoms occur and, during that latent period, there can be subclinical disease that may have important implications for diagnosis and treatment.

Often there is more than one structure of the heart affected so that combinations of conditions occur together (eg, heart block and valvular disease, pericardial effusion and restrictive

Table 6. Modern Radiation Therapy Techniques

- Three-dimensional treatment planning
- Intensity-modulated radiation therapy in selected cases
- Positron emission tomography-computed tomography fusion planning in selected cases
- Reducing total dose (being tested in randomized trials)*
- Reducing treatment field size (ongoing trials testing further reducing involved-field radiation therapy to involved-node radiation therapy using conformal techniques)*
- Daily fraction size ≤ 2 Gy

*Pertains to the lymphoma patient population, in which MR is often employed.

cardiomyopathy, heart block, and aortic stenosis). This coexistence of diseases has major implications for screening, monitoring, and treatment.

Incidence

An estimate of the aggregate incidence of radiation-induced cardiac disease is between 10% and 30% by 5 to 10 years post-treatment. Up to 88% of patients have asymptomatic abnormalities of cardiac muscle, valves, pericardium, conduction system, and the vascular system. Because of the wide spectrum of cardiac toxicity and the linkage to specific cancer diagnoses, the incidence data will be presented in several formats that can be referenced by the clinician.

In general, in the premodern era of radiation oncology, higher doses of radiation were delivered to larger volumes of the heart leading to incidences of all complications that are magnitudes larger than in the modern era. It is important to establish the details of radiation not only by year, with 1985 as the watershed year, but with comprehensive details of past treatment protocols. This is especially important in identifying those survivors whose treatment can be characterized as "high-risk." The majority of these patients were children with HD treated with combined modalities who are now in their late 20s and early 30s.

Equally important is the elapsed length of time from treatment completion, since it is well documented that as the interval from therapy to evaluation increases, so does the risk for the development of radiation-induced cardiac sequelae. The third important principle is that when associated with chemotherapy and especially anthracycline use, the incidence of radiation-induced cardiac disease is increased even though these two treatments have different mechanisms of injury.

Hodgkin's disease. Mediastinal radiation causes inflammation and progressive fibrosis of all of the structures of the heart. Symptomatic heart disease has been well defined in survivors of mediastinal radiation for HD. In a landmark study published in 2003, Heidenreich and associates³⁸ defined the status of asymptomatic valvular and myocardial disease in long-term HD survivors. They prospectively performed echocardiogram screening in 294 asymptomatic patients (mean age, 42 ± 9 years) treated with mediastinal radiation (mean dose, 43 ± 3 Gy) who ranged from 2 to 33 years (mean, 15 years) from treatment completion and separated these patients into those surviving 2 to 10 years, 11 to 20 years, and longer than 20 years from treatment. They found frequent abnormalities in valvular function, left ventricular mass, and systolic function in this population. The prevalence of these abnormalities was compared to the Framingham population and was several-fold higher. All abnormalities increased over time elapsed from treatment completion. The most common valvular abnormality was aortic regurgitation, with less frequent involvement of the mitral and tricuspid valves. Sixty percent of patients that were followed in excess of 20 years had at least mild aortic insufficiency that would meet the criteria for endocarditis prophylaxis. Of interest, only 5% of these patients were recognized to have aortic insufficiency by physical examination performed by an experienced cardiologist. In addition to valvular disease, 36% of these patients had abnormal systolic function marked by a decreased fractional shortening. The development of valve disease is similar to the general population regarding hemodynamics, natural history, and progression.

The same group subsequently reported on diastolic function of the 294 prospectively screened asymptomatic patients.³⁹ They found a high prevalence of diastolic dysfunction in this asymptomatic group, with increased incidence related to older age, the presence of hypertension, diabetes, wall motion abnormalities, and those with a longer latency period from radiation treatment to screening. For patients who had completed radiation therapy for 11 to 20 years and longer than 20 years, 15% and 23%, respectively, had mild to moderate diastolic dysfunction. Diastolic dysfunction was seven-fold more common in this population than in community data from Rochester, MN. Moreover, on stress echocardiography, CAD was found to be significantly more common in patients with diastolic dysfunction than in patients with normal function (10% v 2%; $P = .005$). Deaths or events due to CAD were also significantly more common in patients with diastolic dysfunction compared with patients with normal function (25% v 8%; $P = .002$).

Multiple studies have shown that HD survivors treated with mediastinal radiation are at increased risk for fatal cardiovascular disease, with relative risk ranging from 2.2 to 7.2 compared with age- and sex-matched general population controls.⁴¹⁻⁴³ This risk becomes manifest 5 to 10 years after therapy completion^{44,45} and cardiovascular disease remains a major cause of morbidity and mortality after treatment for HD. The clinical presentation of radiation-induced CAD is similar to CAD in the general population. It may be silent, present with angina, or cause sudden death. Silent myocardial infarction may be more common due to the possible damage to nerve endings in and around the heart secondary to radiation. When CAD is due to radiation therapy, it more commonly affects the right coronary artery, the left anterior descending coronary artery, and the left main coronary artery, with relative sparing of the left circumflex system. A characteristic of radiation-induced disease is the proximal and often ostial distribution of disease.³⁷

Radiation-induced cardiovascular disease is responsible for one fourth of the deaths not directly attributable to HD itself with an increase in relative risk of 2.2 to 3.1. The risk is associated with treatment total more than 40 Gy. The relative risk for myocardial infarction is 4.2 and 6.7 for myocardial infarction or sudden death.³⁵ Hull et al³⁷ found a 10.4% incidence of CAD at a median follow-up of 11.2 years post-treatment in a survey of 415 patients. The results of at least one study³⁷ suggest that the major modifier in the development of ischemic heart disease is the presence of traditional cardiovascular risk factors³⁷ so that, at a minimum, a history of mediastinal radiation therapy could logically be added to that list.

The American College of Radiology⁴⁶ has developed appropriateness criteria for routine follow-up evaluation of HD survivors who are asymptomatic. Their expert panel recommended routine exercise tolerance testing and echocardiography in symptomatic patients and periodic screening in patients depending on the mediastinal radiation dose, cumulative anthracycline dose, and presence of other cardiac risk factors.

The data are similar for pediatric survivors of HD treated with radiation therapy alone or combined modalities. These are important because of the large potential number of adolescents/young adults who will transition to adult oncologists for long-term follow-up. A published review of 14 articles found that the cumulative incidence of clinical CVD assessed in nine studies

ranged from 0.3% to 22.8%.⁴⁷ In a prospective cardiac screening study, Adams et al⁴⁰ reported on the incidence of asymptomatic cardiac disease in survivors of childhood HD who were 5.9 to 27.5 years post-treatment (median, 14.3 years) that consisted of a median of 40 Gy (range, 27 to 51.7 Gy) at a median age of 16.5 years (range, 6.4 to 25 years). They found that 42% had significant valve defects, 75% had conduction defects, and 22% had echocardiographic changes suggestive of restrictive cardiomyopathy.

Breast cancer. Radiation therapy is an integral component of the locoregional management of breast cancer and has efficacy in reducing local recurrence. Breast and chest wall radiation treatment have been associated with an increase in cardiac toxicity, mainly manifested by ischemic heart disease with angina, myocardial infarction, or sudden death.

The early literature focused on women who were treated after mastectomy with adjuvant radiation therapy. Those with left-sided breast cancer were shown to have an increased incidence of fatal CVD that manifested with prolonged follow-up.⁴⁸⁻⁵¹ In studies published before 1990, reflecting premodern radiation oncology, the risk of radiation-induced CAD was thought to be increased in patients with left-sided breast cancer compared with right-sided, with the excess mortality balancing or exceeding the risk reduction gained by adjuvant radiation therapy. More recent meta-analyses have shown a survival benefit for radiation treatment after surgery (mainly breast conserving), and with modern techniques the incidence of cardiac disease for left and right breast radiation therapy is similar with an overall risk reduction compared with no radiation treatment.⁵²⁻⁵⁶ Whether or not there is a significant laterality effect, there is no question that coupled with risk factors for cardiovascular disease, radiation therapy of either side increases the risk of future events.

Data from the SEER database⁵⁴ on 8,363 patients with left breast cancer and 7,907 patients with right breast cancer treated from 1986 to 1993 with adjuvant radiation therapy at a mean follow-up time of 9.5 years (0 to 15 years) showed no laterality differences for the development of ischemic heart disease (9.8%), valvular heart disease (2.9%), and conduction disease (9.7%). Another study using SEER data⁵⁵ examined the risk of cardiac death in 27,283 women in three periods of radiation therapy that reflect the transition to modern radiotherapy: 1973 to 1979, 1980 to 1984, and 1985 to 1989. This study confirmed the lack of laterality in the incidence of ischemic heart disease that grew from changing radiation treatment delivery technique and, of equal importance, showed that the risk of death substantially decreased over time from 1973 to 1979 with the 15-year post-treatment risk of cardiovascular death decreased from approximately 13% in 1973 to 1979 to 5.5% in 1985 to 1989.

Pericardial disease. Radiation-induced late pericardial disease (months to years after treatment) may be silent, with the incidental discovery of asymptomatic pericardial effusions, or may present with hemodynamic compromise secondary to a reduction in ventricular filling and cardiac output. The latter can be due just to excess pericardial fluid with tamponade, purely constrictive without pericardial fluid, or a combination of both: effusive constrictive pericarditis. All of the latter are symptomatic, not silent, and present with typical signs and symptoms. There is no evidence that interventions can

alter the course of hemodynamically inconsequential and clinically silent effusions.

Approximately 20% to 25% of those with late pericarditis progress to develop chronic constrictive disease or acute tamponade 5 to 10 years post-therapy. The incidence of pericardial disease decreased from 20% to 2.5% at one center with the use of modern techniques.⁵⁷

Cardiomyopathy. Radiation-induced myocardial disease differs from the predominantly systolic dysfunction associated with anthracyclines. Instead, it presents with diastolic disease and restrictive hemodynamics (in the absence of combined treatment with an anthracycline). Modern techniques have reduced the risk of systolic dysfunction but have not changed the course of restrictive disease.⁵⁸ In a series of 21 asymptomatic survivors⁵⁹ treated with 20 to 76 Gy (mean, 35.9 Gy) for HD before 1983, 57% had an abnormal EF by radionuclide angiography 7 to 20 years after treatment (mean, 14.1 years) compared with a modern technique series⁶⁰ evaluating 50 HD survivors age 18.5 to 47.5 years (mean, 35.1 years), 1 to 30 years after treatment (mean, 14.1 years) in which 4% had an abnormal EF by radionuclide angiography and 16% had an abnormal filling rate consistent with diastolic dysfunction.

Arrhythmias and conduction system disease. Life-threatening arrhythmias and conduction disease occur years after treatment. There is a wide spectrum of abnormalities that include the sick sinus syndrome, all forms of atrio-ventricular block, and bundle branch block. All are easily identified by a routine ECG.

The frequency of serious conduction abnormalities in long-term asymptomatic cancer survivors ascribed solely to mediastinal radiation therapy is not known and is probably overstated in the literature since disturbances may not occur for years after treatment cessation, making causality a difficult assumption. There are few prospective studies reporting incidence.

Carotid disease and stroke. Carotid artery stenosis is a recognized late treatment effect of radiation therapy for head and neck tumors.⁶¹⁻⁶³ Hull³⁷ reported an incidence of carotid and/or subclavian artery disease of 7.4% at a mean of 17 years post-treatment cessation. This complication impacts the risk of stroke with reported actuarial stroke rate of 12% at 5 years⁶⁴ and a 10- and 15-year relative risk of 10.1% (95% CI, 4.4% to 20%) and 12.0% (95% CI, 6.5% to 21.4%),⁵⁴ respectively. Wai-man Lam⁶⁵ found greater than 50% stenosis in the extracranial carotid artery in 24 of 80 patients. Nine patients had historical evidence of a cerebrovascular accident or transient ischemic attack and 15 patients were asymptomatic. Only seven patients had a carotid bruit recognized by auscultation and no control patient had any stenosis more than 50%. Cheng et al⁶⁶ performed serial carotid ultrasound studies on 95 patients postexternal neck radiation therapy and found an accelerated progression rate from less than 50% at baseline over a 3-year period of 15.4% compared with a control group (nonirradiated) rate of increase of 4.8%.

Knowledge about the increased risk of carotid disease and its progression is important since there is definitive surgery that has been as successful in radiation-induced disease as in atherosclerotic disease⁶⁷⁻⁷¹ and has been shown to reduce the incidence of transient ischemic attack and stroke.

CARDIAC DISEASE AMONG ADULT CANCER SURVIVORS WHO PREVIOUSLY RECEIVED TRASTUZUMAB FOR THE TREATMENT OF BREAST CANCER

EVIDENCE SUMMARY

Trastuzumab-related cardiac dysfunction differs from anthracycline-induced myocardial damage in that it rarely causes death, is not dose related, and in most instances it is reversible with improvement in cardiac function when the drug is discontinued and/or the patient is treated with cardiac medications.^{72,73} Concurrent administration of trastuzumab and doxorubicin leads to an unacceptable rate of symptomatic CHF and should not be used.⁷⁴ In the four large adjuvant trastuzumab trials, symptomatic CHF occurred in 1% to 4% of patients depending on whether they received prior anthracycline or a nonanthracycline adjuvant regimen, and whether they received trastuzumab concurrently with or sequentially after the chemotherapy.⁷⁵⁻⁷⁷ The only prospectively defined risk factors for trastuzumab-related cardiac dysfunction are increasing patient age and decreasing LVEF post-treatment with anthracyclines.⁷⁸ The magnitude of the disease-free and overall survival benefit of trastuzumab-containing chemotherapy outweigh the small risk of mostly reversible symptomatic and/or asymptomatic cardiac dysfunction.

A limitation of the existing data is that the median follow-up in the trastuzumab adjuvant trials is between 2 and 3 years. Therefore, there is no information on the potential for late cardiac dysfunction, or if the short-term improvements in CHF or LVEF with medical treatment are permanent or will increase the risks of subsequent late cardiac dysfunction. Likewise, there is no information on whether breast or chest wall radiation therapy, especially to the left side, will increase late cardiac dysfunction in trastuzumab-treated patients. Finally, cardiac monitoring is based on sequential assessments of LVEF. The optimal interval and duration as well as the cost effectiveness of cardiac monitoring remain undefined. Alternative methods to detect cardiac dysfunction using serum markers are being evaluated, but their routine use outside of clinical trials is not supported.

REVIEW OF RELEVANT LITERATURE: TRASTUZUMAB-INDUCED CARDIAC TOXICITY

Incidence

Trastuzumab improves the outcome of women with HER-2/*neu* amplified and/or overexpressing breast cancers in the metastatic and adjuvant treatment settings (Table 7).^{68-71,79} The significant improvements in disease-free, progression-free, and overall survival are accompanied by a small increased risk of symptomatic CHF and a higher risk of asymptomatic declines in LVEF.⁸⁰ Although there are numerous phase II trials of trastuzumab as single agent or in combination with chemotherapy, the best sources for trastuzumab-related cardiotoxicity are the four prospective randomized controlled trials in the adjuvant setting (Table 7). In each of these trials, the end points reported were cardiac deaths; symptomatic CHF primary defined as New York Heart Association (NYHA) class III (marked limitation of physical activity comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea) and class IV (unable to carry out any physical activity without discomfort, symptoms of cardiac insufficiency at rest; if any physical activity is undertaken, discomfort

is increased); or asymptomatic declines in LVEF. In the pivotal trial of chemotherapy with or without trastuzumab in metastatic disease,⁷⁴ prospective measurements of cardiac function were not performed, but an independent cardiac evaluation committee retrospectively adjudicated the cases of cardiac dysfunction. Concurrent administration of trastuzumab with doxorubicin and cyclophosphamide (AC) resulted in a 16% incidence of NYHA classes III and IV relative to 3% with AC alone, and this combination is no longer used in the clinic. Preliminary experience with other anthracyclines, such as epirubicin or liposomal encapsulated doxorubicin and trastuzumab, is limited to small phase I and II trials^{81,82} in which the observed incidence of NYHA classes III and IV is lower. In contrast, paclitaxel or docetaxel and trastuzumab combinations⁸³ result in 1% to 2% incidence of NYHA class III or IV relative to $\leq 1\%$ with taxane alone, and taxane/trastuzumab alone or after AC has rapidly become the new standard for metastatic and adjuvant treatment, respectively.

Based on the incidence of CHF observed in the pivotal trial, the adjuvant trials included serial prospective measurements of LVEF by MUGA and/or echocardiogram performed pretreatment, after anthracycline-based chemotherapy, and typically every 6 to 12 months after randomization.^{75-77,79} In addition, patients with pre-existing heart diseases such as CHF, myocardial infarction, angina requiring medications, or arrhythmia requiring medications were excluded from the trials. The criterion for permanently stopping trastuzumab was the development of symptomatic cardiac dysfunction. The criteria for holding trastuzumab were based on LVEF decrements in asymptomatic patients with a repeat measurement of LVEF after 4 weeks. If there was no improvement in LVEF, trastuzumab was permanently discontinued.

In the combined analysis of the Intergroup and National Surgical Breast and Bowel Project (NSABP) trial B-31, LVEF was evaluated before and after AC, before receiving paclitaxel/trastuzumab.^{75,78,84} Only those patients with LVEF above the lower limit of the normal range or in whom it had decreased less than 16% from the baseline value were eligible to receive trastuzumab. Ninety-three percent of patients received trastuzumab after AC. Overall, the incidence of NYHA classes III and IV for the trastuzumab-containing treatment group was 4.1% (NSABP) and 2.9% (Intergroup) versus 0.8% and 0% in the respective control groups.

A more detailed analysis of adverse cardiac events (symptomatic and asymptomatic) in NSABP B-31 was recently published.⁷⁸ A cardiac event was defined as NYHA class III or IV CHF and cardiac death. The cumulative incidence of cardiac events at 3 years was 4.1% versus 0.8% (hazard ratio [HR], 5.9; 95% CI, 2.3 to 15.3; $P = .0001$) in the trastuzumab and control groups, respectively. There was one cardiac death in the entire cohort and that patient was in the control group. In a multivariate analysis, increasing age and decreasing LVEF after AC were independent risk factors for CHF.

In the Breast Cancer International Research Group (BCIRG) 006 trial, patients were randomly assigned to a nonanthracycline trastuzumab treatment (docetaxel, carboplatin, and trastuzumab) versus AC followed by docetaxel with or without trastuzumab.⁷⁷ Symptomatic cardiac events were defined as CHF; grades 3 or 4 ischemia/infarction and arrhythmia; and asymptomatic declines in LVEF of more than 15% or below the lower limit of normal. At a

Table 7. Randomized Controlled Trials of Trastuzumab

Trial	Design/Treatment	No. of Patients	Median Follow-Up (months)	Key Findings
Metastatic Slamon ⁷⁴	Open-label	469		TTP, 7.4 v 4.6 months; $P < .001$; OS, 25 v 20; $P = .05$
	AC \pm trastuzumab	281		TTP 7.8 v 6.1; $P < .001$; OS 27 v 21; $P = .16$; NYHA III, IV 16% v 3%
	Paclitaxel \pm trastuzumab	188		TTP, 6.9 v 3.0; $P < .001$; OS, 22 v 18; $P = .17$; NYHA III, IV 2% v 1%
Adjuvant HERA ⁷⁶	Open-label	3,387	12	DFS HR, 0.54; 95% CI, 0.43 to 0.67; $P < .0001$
	Trastuzumab: 1 year v observation after adjuvant chemotherapy that included anthracyclines (94%); taxanes (26%); and radiation (76%)			Distant DFS HR, 0.49; 95% CI, 0.38 to 0.63; $P < .0001$ OS HR, 0.76; 95% CI, 0.47 to 1.23; $P = .26$ Symptomatic CHF 1.7% v 0.06%; $P < .001$ NYHA III, IV CHF 0.5% v 0%, $P = .002$
Romond ⁷⁵	Open label	3,351	24	DFS HR, 0.48; 95% CI, 0.39 to 0.59; $P < .0001$; distant DFS HR, 0.47; 95% CI, 0.37 to 0.61; $P < .001$; OS HR, 0.67; 95% CI, 0.48 to 0.93; $P = .015$; NYHA III, IV: CHF, 4.1% v 0.8%; NSABPB B-31, 2.9% v N9831, 0%
	AC followed by paclitaxel \pm trastuzumab (1 year)			
Slamon ⁷⁷	Open label	3,222	23	DFS AC plus docetaxel v AC-DH: HR, 0.49; $P = .00000005$; SCE, 1.2% v 2.3%; $P = .05$
	AC followed docetaxel \pm trastuzumab (AC-DH) (1 year)			
Joensuu ⁷⁹	Open-label	232	36	DFS AC plus docetaxel v DCH: HR, 0.61; $P = .0002$; SCE, 1.2% v 1.2%; $P = 1.00$
	Docetaxel/carboplatin trastuzumab (DCH) (1 year)			
Joensuu ⁷⁹	Open-label	232	36	DFS docetaxel or vinorelbine + trastuzumab HR, 0.42; 95% CI, 0.21 to 0.83; $P = .01$; OS HR, 0.41; 95% CI, 0.16 to 1.08; $P = .07$; SCE, 0% v 3%
	Docetaxel or vinorelbine \pm trastuzumab (9 weeks) followed by FEC			

Abbreviations: AC, doxorubicin and cyclophosphamide; TTP, time to progression; OS, overall survival; NYHA III, IV, New York Heart Association; HERA, Herceptin Adjuvant Trial; DFS, disease-free survival; HR, hazard ratio; CHF, congestive heart failure; NSABP, National Surgical Breast and Bowel Project; SCE, symptomatic cardiac events; FEC, fluorouracil, epirubicin, and cyclophosphamide.

median follow-up of 23 months, the incidence of symptomatic cardiac events was 2.3% versus 1.2% ($P = .046$) for AC followed by docetaxel with or without trastuzumab, respectively; in the nonanthracycline-containing trastuzumab arm, it was 1.2% ($P = .99$ relative to the control arm). Likewise, asymptomatic declines in LVEF were 2.4% versus 0.6% (AC followed by docetaxel with or without trastuzumab, respectively $P = .001$) and 0.6% v 0.4% (relative to nonanthracycline trastuzumab arm, $P = .54$).

Unlike the Intergroup, NSABP, and BCIRG trials, patients in the Herceptin Adjuvant Trial (HERA) trial received trastuzumab after completion of adjuvant chemotherapy.⁷⁶ Ninety-four percent of patients received prior anthracyclines with or without taxanes, and approximately 50% of these patients received epirubicin. Using a more restricted definition of cardiac events, the overall incidence of symptomatic CHF (including NYHA class III or IV) or decrease from baseline of more than 10% below 50% was 1.73% v 0.06% ($P \leq .001$) for trastuzumab and control, respectively. Asymptomatic declines in LVEF were observed in 7.1% v 2.2% ($P < .001$). The HERA trial included a second random assignment

to 2 years versus 1 year of trastuzumab; however, no cardiac safety or efficacy results are available.

A recent subset analysis of a small number of HER-2–overexpressing breast cancers showed that a 9-week duration of trastuzumab with either adjuvant docetaxel or vinorelbine followed by epirubicin-containing chemotherapy reduced the HR for disease-free survival and was not associated with any cardiac dysfunction.⁷⁹ To our knowledge, this is the first such trial to suggest that a short duration of trastuzumab may be effective. However, larger trials are needed to confirm this result.

Natural History

The clinical course of trastuzumab-related CHF differs from anthracycline-induced CHF in several important ways: it very rarely causes death; does not cause myocyte drop-out or other changes observed in electron microscopy of endomyocardial biopsies typical of anthracycline-induced CHF; and is reversible with/without medical treatment.⁷³ In addition, there is evidence that cumulative dose and duration of trastuzumab do not

contribute to increasing the risk of CHF.⁸⁵ In fact, Ewer et al⁷² have proposed a new category of “Type II myocardial dysfunction” to describe trastuzumab-related CHF as opposed to “Type I myocardial damage” that results from anthracyclines. Based on the available experience, the majority of patients who developed trastuzumab-related CHF and discontinued trastuzumab had recovery of LVEF with subsequent follow-up.

Monitoring

The optimal duration, frequency, and method of cardiac monitoring during trastuzumab treatment remain unknown. Criteria for discontinuing anthracyclines on the basis of LVEF decrements evaluated by resting MUGA scans or echocardiograms were developed from retrospective studies. One small prospective blinded study of serial LVEF for cardiac monitoring in patients treated with epirubicin concluded that MUGA scans were too insensitive to predict CHF.⁸⁶ The same approach used for anthracycline cardiac monitoring with serial assessments has been applied in the adjuvant trastuzumab trials. Using cut-offs for transiently stopping or permanently discontinuing trastuzumab based on LVEF decrements from baseline, the incidence of CHF NYHA classes III and IV ranges from 3% to 4%. Plasma markers of cardiac dysfunction, such as cardiac troponin or BNP, have been collected in some adjuvant trastuzumab trials, but no results are available.

PULMONARY DISEASE AMONG ADULT CANCER SURVIVORS WHO PREVIOUSLY RECEIVED CHEMOTHERAPY OR RADIOTHERAPY

EVIDENCE SUMMARY

Studies of pulmonary function testing in long-term (≥ 2 years) cancer survivors who received chemotherapy and/or radiation therapy have been reported. A minority of HD and germ cell tumor survivors who received bleomycin as part of multiagent combination chemotherapy will have abnormal pulmonary function testing. A more substantial proportion of HD survivors treated with mediastinal radiation therapy will demonstrate abnormal pulmonary function testing, as will a minority of bone marrow transplantation (BMT) survivors. No study has demonstrated that identification of abnormal pulmonary function testing in the asymptomatic adult cancer survivor leads to an improved clinical outcome.

REVIEW OF RELEVANT LITERATURE: CHEMOTHERAPY- OR RADIOTHERAPY-INDUCED PULMONARY TOXICITY

Incidence

Although many chemotherapeutic agents may cause pulmonary toxicity (Table 8), bleomycin is the most studied and is the focus of this section of the review. Bleomycin is commonly used in the treatment of GCTs and malignant lymphoma, especially HD. Bleomycin-induced pneumonitis (BIP) is the most common form of bleomycin-related pulmonary toxicity. Risk factors that predispose to BIP include the cumulative dose of bleomycin, the patient's age, smoking, renal dysfunction, mediastinal radiation therapy, and administration of oxygen.^{87,88} The incidence of BIP ranges

Table 8. Chemotherapy Agents Associated With Pulmonary Toxicity

Bleomycin
Busulfan
Carmustine
Chlorambucil
Cyclophosphamide
Cytosine arabinoside
Docetaxel
Etoposide
Fludarabine
Gemcitabine
Methotrexate
Mitomycin
Paclitaxel
Procarbazine
Vinca alkaloids

from 0% to 46%, depending on the patient population being studied and the criteria used to diagnose this entity.⁸⁷

GCT patients receiving bleomycin-containing chemotherapy are an ideal population for examining the incidence of pulmonary toxicity. These patients are generally younger and do not receive mediastinal radiation therapy which is also associated with pulmonary toxicity (Table 9).⁸⁹⁻⁹³ As noted, in most GCT studies the incidence of clinically-significant BIP is quite low. In a large trial comparing mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (MOPP/ABV) with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in HD patients, acute pulmonary toxicity occurred in 25% to 31% of patients. However, unlike the GCT population, approximately 10% of these patients in this study also received radiation therapy.

Radiation pneumonitis has been reported in patients who have undergone mediastinal radiation therapy for lung cancer, HD, breast cancer, and other cancers that require radiation therapy to the thorax. Radiation pneumonitis is reported in 5% to 15% of patients receiving definitive external-beam radiation therapy for lung cancer.⁹⁴ Clinical factors that may increase the risk of radiation pneumonitis include concomitant chemotherapy, previous irradiation, and recent withdrawal of steroids.⁹⁴ A retrospective analysis of 1,911 patients who underwent combined-modality therapy for lung cancer demonstrated that the overall risk of radiation pneumonitis was 7.8%.⁹⁵ In a multivariate analysis, the daily fraction dose, number of daily fractions, and total dose were associated with radiation pneumonitis ($P < .001$; $P < .018$; and $P < .003$, respectively).

The incidence of radiation pneumonitis is lower in HD and breast cancer patients who received mediastinal radiation therapy compared with lung cancer patients. A series of 590 patients with stage IA-IIIB HD who received mantle radiation therapy alone demonstrated a 3% risk of radiation pneumonitis with radiation therapy alone. The risk of radiation pneumonitis was significantly increased to 11% when radiation therapy was combined with chemotherapy ($P = .0001$).⁹⁶ Patients with breast cancer who undergo breast radiation therapy as part of a breast conserving approach have less than 1% risk of radiation pneumonitis.⁹⁷

Table 9. Pulmonary Toxicity After Bleomycin

Reference	Malignancy	Therapy	Findings
Loehrer ⁸⁹	GCT	BEP, three cycles (cumulative bleomycin dose 270 units)	No clinically significant pulmonary toxicity
De Wit ⁹⁰	GCT	BEP, three cycles v BEP, three cycles + EP, one cycle	Acute grade 3-4 pulmonary toxicity: 1% of BEP patients, 2% of BEP + EP patients; grade 1-4 late pulmonary toxicity: 8% of BEP patients, 9% of BEP + EP patients; PFTs prior to and after therapy showed a median acute decline in DLCO of 19%
De Wit ⁹¹	GCT	BEP, four cycles (cumulative bleomycin dose 360 units) v EP, four cycles	FVC median decrease: BEP, 3.8%; EP, 0%; DLCO median decrease: BEP, 20%; EP, 2%; $P < .001$; late pulmonary toxicity (grade 1-2 dyspnea): BEP, 3%; EP, 0%
Nichols ⁹²	GCT	BEP, four cycles v VIP, four cycles	Pulmonary toxicity in < 1% of patients in each arm
Duggan ⁹³	Hodgkin's (n = 856)	ABVD v MOPP/ABV hybrid	Acute pulmonary toxicity: ABVD, 24.5%; MOPP/ABV, 30.6%; pulmonary toxicity at completion of therapy: ABVD, 8.3%; MOPP/ABV, 9.3%*

Abbreviations: GCT, germ cell tumors; BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; PFTs, pulmonary function tests; DLCO, diffusion capacity; FVC, forced vital capacity; VIP, etoposide, ifosfamide, and cisplatin; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine.

*Ten percent of patients also received radiotherapy

Pulmonary complications occur frequently after BMT. In one study of 311 patients with hematologic malignancies who underwent autologous, allogeneic, or syngeneic BMT, the 2-year risk of interstitial pneumonitis was 26.8%.⁹⁸ In 90% of these cases, cytomegalovirus was detected or the cases were considered idiopathic. Patients who underwent allogeneic BMT had the highest incidence of interstitial pneumonitis (34.1%). In patients who underwent allogeneic stem-cell transplantation, age older than 20 years, a history of chronic myelogenous leukemia, alloimmunized donor, prior splenectomy, and graft-versus-host disease were risk factors for the development of interstitial pneumonitis. Interstitial pneumonitis occurs more frequently after busulfan-conditioning regimens as compared with total-body irradiation. The use of lung compensators during total-body irradiation decreases the risk of interstitial pneumonitis.⁹⁹ Patients who receive BCNU as a part of augmented preparative regimens for high-dose chemotherapy and autologous peripheral blood progenitor cell transplantation are at risk for pulmonary toxicity. Up to 30% of these patients develop noninfectious pulmonary complications. BCNU pneumonitis may result in long-term pulmonary function testing abnormalities. In addition, patients may respond to corticosteroids.¹⁰⁰

Natural History

BIP usually starts insidiously during treatment, but the development of BIP up to 2 years after discontinuation has been reported.¹⁰¹ Most patients who experience BIP will recover with discontinuation of the agent and/or corticosteroid treatment. A minority will progress to pulmonary fibrosis.⁸⁷ The majority of patients who develop BCNU pneumonitis will respond to corticosteroid therapy.¹⁰⁰ Radiation pneumonitis is typically a delayed acute reaction, usually occurring 1 to 3 months after completing mediastinal radiation therapy.⁹⁴ Patients who experience acute radiation pneumonitis will often have a self-limited course, with complete resolution of this process. However, a minority of patients may develop progressive pulmonary fibrosis, usually 6 to 24 months after treatment. Late complications of pulmonary fibrosis include cor pulmonale and respiratory failure. Late pulmonary complications in BMT patients who develop interstitial pneumo-

nitis include the idiopathic pneumonia syndrome and bronchiolitis obliterans.

Monitoring

Pulmonary function testing includes measurement of lung volumes and oxygen diffusion capacity. Pulmonary function test monitoring has been reported in several populations of long-term (> 24 months) cancer survivors treated with chemotherapy and/or radiation therapy (Table 10).¹⁰²⁻¹¹⁰ Most of the studies have focused on HD survivors. Of interest, in many of these studies, early decline in pulmonary function testing is followed by subsequent improvement over time in most patients.

CONCLUSIONS

LIMITATIONS OF THE LITERATURE

There are several important limitations in estimating the risks of anthracycline or radiation-related cardiac toxicity in long-term survivors of adult cancers. The most reliable source of cardiac or other treatment-related events is the randomized trial. However, many individual trials are too small and lack sufficient statistical power to detect a rare treatment-related event. Meta-analyses of randomized trials are another reliable source for treatment-related events. Combining the results of all randomized trials in a meta-analysis of the literature increases the likelihood of detecting a rare event that may or may not occur in individual trials. However, the meta-analysis may include older trials such as outmoded radiation treatment techniques that are known to increase the dose/exposure of the heart and cardiac toxicity.

Data on the frequency and severity of treatment-related cardiac dysfunction often comes from retrospective case-control and registry studies. These studies are subject to various biases that may underestimate or overestimate the association between treatment exposure and adverse events. For example, the large dropout rate from follow-up may overestimate the true incidence of cardiac toxicity. In addition, underlying cardiac risk factors such as family history, hypertension, diabetes, and smoking were not assessed in

Table 10. Pulmonary Function Testing in Cancer Survivors

Reference	Malignancy	Therapy	Follow-Up	Findings
Horning ¹⁰²	Hodgkin's disease (n = 145)	MR (n = 50), MR + bleomycin (n = 36), bleomycin without radiotherapy (n = 33)	> 3 years	Decrease in FVC and DLCO in first 15 months, followed by recovery after 36 months in most patients; FVC < 80% predicted: MR, 32%; MR + bleomycin, 37%; bleomycin without radiotherapy, 19%; DLCO < 80% in 7% overall; MR associated with a greater reduction in pulmonary function and less complete recovery
Lund ¹⁰³	Hodgkin's disease (n = 129)	MR alone or as part of combined modality regimen	Median, 10 years	One third of patients with reduction in FVC and DLCO; 14% with moderate fibrosis on radiologic studies, associated with a decrease in pulmonary function values ($P < .05$)*
Jensen ¹⁰⁴	Hodgkin's disease (n = 142)	MR (n = 54), chemotherapy (n = 26), combined modality (n = 62)	Median, 8 years	MR associated with a more obstructive pattern of impairment, combined modality with a more restrictive pattern; dyspnea and abnormal CXRs associated with more severe abnormalities in pulmonary function
Hirsch ¹⁰⁵	Hodgkin's (n = 60)	ABVD, ABVD + MR	Median, 30 months	Persistent but mild pulmonary symptoms: ABVD, 18%; ABVD + XRT, 30% (did not greatly affect patients' functional status); acute pulmonary toxicity resulted in modification of bleomycin dose in 23% of patients and was fatal in 1.7% of patients; most patients experienced improvement of pulmonary status over time. Patients who received mediastinal radiation therapy had further FVC decline following completion of treatment
Theuvs ¹⁰⁶	Breast cancer (n = 69), lymphoma (n = 41)	XRT, XRT + chemotherapy	Serial PFTs before treatment and 3, 18, and 48 months after treatment	Initial reduction in PFTs at 3 months, with significant recovery noted in all patients at 18 months
Lehne ¹⁰⁷	GCT (n = 94)	Surgery alone v surgery + bleomycin-containing chemotherapy, three to four cycles		FVC, FEV1, and DLCO within normal limits in both groups, no difference between groups
Beinert ¹⁰⁸	Leukemia (n = 88)	Allogeneic BMT		Development of obstructive and restrictive lung defects during first 3-6 months after transplant, followed by partial recovery; busulfan in conditioning regimen was a predictor of long-term decline in PFT; TBI was not a significant predictor of pulmonary decline
Thomas ¹⁰⁹	Various (n = 478)	BMT with prior TBI	Median, 49 months	Restrictive abnormalities in 8%, abnormal DLCO in 12%; risk of abnormal function increased with chronic GVHD and XRT-specific factors
Gore ¹¹⁰	Various (n = 111)	BMT, with TBI in n = 103		Post-transplant FEV1, FVC, and TLC lower than pretransplant values at 6 and 12 months, but with subsequent recovery; DLCO significantly lower at all post-transplant intervals; delayed or incomplete recovery of function most frequent in patients with GVHD, pulmonary infection, and high-dose XRT to lungs

Abbreviations: MR, mediastinal radiation therapy; FVC, forced vital capacity; DLCO, diffusion capacity; CXR, chest x-ray; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; XRT, radiation therapy; PFTs, pulmonary function tests; GCT, germ cell tumors; FEV1, forced expiratory volume over 1 second; BMT, bone marrow transplant; TBI, total body irradiation; GVHD, graft-versus-host disease; TLC, total lung capacity.

*Chemotherapy was a significant predictor of pulmonary function impairment in this study.

many of these studies and therefore the impact of these factors on the risk of treatment related cardiac toxicity is unknown.

Additional methodological limitations include the lack of standard and universal definitions of cardiac dysfunction and the use of several noninvasive testing modalities. This problem has been compounded by the case mix of studies with respect to

cumulative anthracycline dosing, route of administration, role of associated mediastinal radiation therapy (technique, dosing, blocking), and the wide variation in time from treatment to cardiac assessment.

While data on the short-term incidence of trastuzumab-induced cardiac dysfunction is consistent and derived from randomized trials, median follow-up is 3 years or fewer. Therefore, the

optimal interval and duration of long-term cardiac monitoring is not defined and requires additional follow-up in the randomized adjuvant trastuzumab trials.

FUTURE STUDIES

While a large body of literature attempts to document the incidence of long-term cardiac and pulmonary effects in cancer survivors, there has been a lack of standardization in the definition of the problem; furthermore, various testing strategies and cutoff points have been employed, and studies vary in the amount of time elapsed from treatment. To date, no study has been designed to evaluate the utility and cost effectiveness of regular screening in asymptomatic cancer survivors.

The panel strongly recommends that future research focus on several critical areas: the adoption of a standard definition and a standard test to evaluate cardiac dysfunction; and the collection of standardized incidence data. A retrospective cohort study has been established that captures data on pediatric cancer survivors and such information is extremely valuable in establishing the true incidence of late-effects within adult survivors of pediatric cancer.¹¹¹ Although there are substantial differences between pediatric cancer patients—the majority of whom are treated on clinical trials and who have a fully developed set of follow-up guidelines¹⁶ and adult cancer survivors (in whom only a minority are treated on clinical trials), nonetheless the panel recommends that an effort similar to the Childhood Cancer Survivor Study¹¹² be undertaken in adults and the resources to accomplish this complex task be provided by governmental agencies, foundations, and the private sector.

Future research should include prospective long-term studies that are designed to directly determine the efficacy of screening in asymptomatic cancer survivors. At present, until these studies are done, not only are the optimal screening strategies not established, but

it remains unclear whether treatment of some of these subclinical conditions will prove to be of benefit.

The panel recognizes the potential that exists in available, large, multicenter, adjuvant, breast cancer studies. Longitudinal data may soon permit the research community to answer most of the outstanding questions regarding incidence, natural history, screening, and ultimately, treatment of cardiotoxicity in this population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

- Krischer JP, Epstein S, Cuthbertson DD, et al: Clinical cardiotoxicity following anthracycline treatment for childhood cancer: The Pediatric Oncology Group experience. *J Clin Oncol* 15:1544-1552, 1997
- van Dalen EC, van der Pal HJ, Bakker PJ, et al: Cumulative incidence and risk factors of mitoxantrone-induced cardiotoxicity in children: A systematic review. *Eur J Cancer* 40:643-652, 2004
- Von Hoff DD, Layard M: Risk factors for development of daunorubicin cardiotoxicity. *Cancer Treat Rep* 65:19-23, 1981 (suppl 4)
- Gietema JA, Sleijfer DT, Willemse PH, et al: Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated non-seminomatous testicular cancer. *Ann Intern Med* 116:709-715, 1992
- Lipshultz SE, Lipsitz SR, Sallan SE, et al: Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. *J Clin Oncol* 20:4517-4522, 2002
- Swain SM, Whaley FS, Gerber MC, et al: Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. *J Clin Oncol* 15:1318-1332, 1997
- Lipshultz SE, Colan SD, Gelber RD, et al: Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 324:808-815, 1991
- Shan K, Lincoff AM, Young JB: Anthracycline-induced cardiotoxicity. *Ann Intern Med* 125:47-58, 1996
- Lipshultz SE, Lipsitz SR, Mone SM, et al: Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 332:1738-1743, 1995
- Pinarli FG, Oguz A, Tunaoglu FS, et al: Late cardiac evaluation of children with solid tumors after anthracycline chemotherapy. *Pediatr Blood Cancer* 44:370-377, 2005
- Swain SM, Whaley FS, Ewer MS: Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. *Cancer* 97:2869-2879, 2003
- Hequet O, Le QH, Moullet I, et al: Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol* 22:1864-1871, 2004
- Doyle JJ, Neugut AI, Jacobson JS, et al: Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study. *J Clin Oncol* 23:8597-8605, 2005
- Bonneterre J, Roche H, Kerbrat P, et al: Long-term cardiac follow-up in relapse-free patients after six courses of fluorouracil, epirubicin, and cyclophosphamide, with either 50 or 100 mg of epirubicin, as adjuvant therapy for node-positive breast cancer: French adjuvant study group. *J Clin Oncol* 22:3070-3079, 2004
- Shapiro CL, Hardenbergh PH, Gelman R, et al: Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. *J Clin Oncol* 16:3493-3501, 1998
- Landier W, Bhatia S, Eshelman DA, et al: Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *J Clin Oncol* 22:4979-4990, 2004
- Valagussa P, Zambetti M, Biasi S, et al: Cardiac effects following adjuvant chemotherapy and breast irradiation in operable breast cancer. *Ann Oncol* 5:209-216, 1994
- Nuver J, Smit AJ, Sleijfer DT, et al: Left ventricular and cardiac autonomic function in survivors of testicular cancer. *Eur J Clin Invest* 35:99-103, 2005
- van den Belt-Dusebout AW, Nuver J, de Wit R, et al: Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol* 24:467-475, 2006
- Meinardi MT, Gietema JA, van der Graaf WT, et al: Cardiovascular morbidity in long-term survivors

of metastatic testicular cancer. *J Clin Oncol* 18: 1725-1732, 2000

21. Steinherz LJ, Graham T, Hurwitz R, et al: Guidelines for cardiac monitoring of children during and after anthracycline therapy: Report of the Cardiology Committee of the Childrens Cancer Study Group. *Pediatrics* 89:942-949, 1992

22. Ganz WI, Sridhar KS, Ganz SS, et al: Review of tests for monitoring doxorubicin-induced cardiomyopathy. *Oncology* 53:461-470, 1996

23. Kapusta L, Thijssen JM, Groot-Loonen J, et al: Discriminative ability of conventional echocardiography and tissue Doppler imaging techniques for the detection of subclinical cardiotoxic effects of treatment with anthracyclines. *Ultrasound Med Biol* 27:1605-1614, 2001

24. Kapusta L, Thijssen JM, Groot-Loonen J, et al: Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines. *Ultrasound Med Biol* 26:1099-1108, 2000

25. Smith SC Jr, Greenland P, Grundy SM: AHA conference proceedings: Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: Executive summary. *American Heart Association Circulation* 101: 111-116, 2000

26. Silber JH, Cnaan A, Clark BJ, et al: Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol* 22:820-828, 2004

27. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail* 12:10-38, 2006

28. Steinherz LJ, Steinherz PG, Tan CT, et al: Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 266:1672-1677, 1991

29. Bu'Lock FA, Mott MG, Oakhill A, et al: Left ventricular diastolic function after anthracycline chemotherapy in childhood: Relation with systolic function, symptoms, and pathophysiology. *Br Heart J* 73:340-350, 1995

30. Kremer LC, van der Pal HJ, Offringa M, et al: Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: A systematic review. *Ann Oncol* 13:819-829, 2002

31. Pein F, Sakiroglu O, Dahan M, et al: Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. *Br J Cancer* 91:37-44, 2004

32. Lipshultz SE, Lipsitz SR, Sallan SE, et al: Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol* 23:2629-2636, 2005

33. Lipshultz SE, Rifai N, Dalton VM, et al: The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 351:145-153, 2004

34. Adams MJ, Hardenbergh PH, Constine LS, et al: Radiation-associated cardiovascular disease. *Crit Rev Oncol Hematol* 45:55-75, 2003

35. Glanzmann C, Kaufmann P, Jenni R, et al: Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother Oncol* 46:51-62, 1998

36. Prosnitz RG, Chen YH, Marks LB: Cardiac toxicity following thoracic radiation. *Semin Oncol* 32:S71-S80, 2005

37. Hull MC, Morris CG, Pepine CJ, et al: Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA* 290:2831-2837, 2003

38. Heidenreich PA, Hancock SL, Lee BK, et al: Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol* 42:743-749, 2003

39. Heidenreich PA, Hancock SL, Vagelos RH, et al: Diastolic dysfunction after mediastinal irradiation. *Am Heart J* 150:977-982, 2005

40. Adams MJ, Lipsitz SR, Colan SD, et al: Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol* 22:3139-3148, 2004

41. Lee CK, Aeppli D, Nierengarten ME: The need for long-term surveillance for patients treated with curative radiotherapy for Hodgkin's disease: University of Minnesota experience. *Int J Radiat Oncol Biol Phys* 48:169-179, 2000

42. Mauch PM, Kalish LA, Marcus KC, et al: Long-term survival in Hodgkin's disease. *Cancer J Sci Am* 1:33, 1995

43. Hancock SL, Tucker MA, Hoppe RT: Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 270:1949-1955, 1993

44. Reinders JG, Heijmen BJ, Olofsen-van Acht MJ, et al: Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. *Radiother Oncol* 51:35-42, 1999

45. Hancock SL, Donaldson SS, Hoppe RT: Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol* 11:1208-1215, 1993

46. Ng AK, Constine LS, Deming RL, et al: American College of Radiology Appropriateness Criteria: Follow-up of Hodgkin's disease. Department of Quality and Safety, ACH, Reston, VA, 2005. Available online at http://www.acr.org/Secondary/MainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonRadiationOncologyHodgkinsWorkGroup/FollowUpofHodgkinsDiseaseDoc2.aspx

47. van der Pal HJ, van Dalen EC, Kremer LC, et al: Risk of morbidity and mortality from cardiovascular disease following radiotherapy for childhood cancer: A systematic review. *Cancer Treat Rev* 31:173-185, 2005

48. Cuzick J, Stewart H, Rutqvist L, et al: Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol* 12:447-453, 1994

49. Jones JM, Ribeiro GG: Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy. *Clin Radiol* 40: 204-208, 1989

50. Paszat LF, Mackillop WJ, Groome PA, et al: Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol* 16:2625-2631, 1998

51. Early Breast Cancer Trialists' Collaborative Group: Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. *Lancet* 355: 1757-1770, 2000

52. Nixon AJ, Manola J, Gelman R, et al: No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol* 16:1374-1379, 1998

53. Rutqvist LE, Liedberg A, Hammar N, et al: Myocardial infarction among women with early-stage breast cancer treated with conservative surgery and breast irradiation. *Int J Radiat Oncol Biol Phys* 40:359-363, 1998

54. Patt DA, Goodwin JS, Kuo YF, et al: Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol* 23:7475-7482, 2005

55. Giordano SH, Kuo YF, Freeman JL, et al: Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst* 97:419-424, 2005

56. Vallis KA, Pintilie M, Chong N, et al: Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. *J Clin Oncol* 20:1036-1042, 2002

57. Carmel RJ, Kaplan HS: Mantle irradiation in Hodgkin's disease: An analysis of technique, tumor eradication, and complications. *Cancer* 37:2813-2825, 1976

58. Cameron EH, Lipshultz SE, Tarbell NJ, et al: Cardiovascular disease in long term survivors of pediatric Hodgkin's disease. *Prog Pediatr Cardiol* 8:139-144, 1998

59. Burns RJ, Bar-Shlomo BZ, Druck MN, et al: Detection of radiation cardiomyopathy by gated radionuclide angiography. *Am J Med* 74:297-302, 1983

60. Constine LS, Schwartz RG, Savage DE, et al: Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 39:897-906, 1997

61. Cheng SW, Ting AC, Lam LK, et al: Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 126:517-521, 2000

62. Halak M, Fajer S, Ben-Meir H, et al: Neck irradiation: A risk factor for occlusive carotid artery disease. *Eur J Vasc Endovasc Surg* 23:299-302, 2002

63. Elerding SC, Fernandez RN, Grotta JC, et al: Carotid artery disease following external cervical irradiation. *Ann Surg* 194:609-615, 1981

64. Haynes JC, Machtay M, Weber RS, et al: Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 112:1883-1887, 2002

65. Lam VWW, Yuen HY, Wong KS, et al: Clinically underdetected asymptomatic and symptomatic carotid stenosis as a late complication of radiotherapy in Chinese nasopharyngeal carcinoma patients. *Head Neck* 23:780-784, 2001

66. Cheng SW, Ting AC, Ho P, et al: Accelerated progression of carotid stenosis in patients with previous external neck irradiation. *J Vasc Surg* 39: 409-415, 2004

67. Harrod-Kim P, Kadkhodayan Y, Derdeyn CP, et al: Outcomes of carotid angioplasty and stenting for radiation-associated stenosis. *Am J Neuroradiol* 26:1781-1788, 2005

68. Cazaban S, Maiza D, Coffin O, et al: Surgical treatment of recurrent carotid artery stenosis and carotid artery stenosis after neck irradiation: Evaluation of operative risk. *Ann Vasc Surg* 17:393-400, 2003

69. Friedell ML, Joseph BP, Cohen MJ, et al: Surgery for carotid artery stenosis following neck irradiation. *Ann Vasc Surg* 15:13-18, 2001

70. Hassen-Khodja R, Kieffer E: Radiotherapy-induced supra-aortic trunk disease: Early and long-term results of surgical and endovascular reconstruction. *J Vasc Surg* 40:254-261, 2004

71. Francfort JW, Gallagher JF, Penman E, et al: Surgery for radiation-induced symptomatic carotid atherosclerosis. *Ann Vasc Surg* 3:14-19, 1989

72. Ewer MS, Lippman SM: Type II chemotherapy-related cardiac dysfunction: Time to recognize a new entity. *J Clin Oncol* 23:2900-2902, 2005

73. Ewer MS, Vooletich MT, Durand J-B, et al: Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. *J Clin Oncol* 23:7820-7826, 2005

74. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001
75. Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 353:1673-1684, 2005
76. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1659-1672, 2005
77. Slamon D, Eiermann W, Robert N, et al: Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin, and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. *Breast Cancer Res Treatment* 94: 2005 (suppl 1, abstr 1)
78. Tan-Chiu E, Yothers G, Romond E, et al: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 23:7811-7819, 2005
79. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al: Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 354:809-820, 2006
80. Seidman A, Hudis C, Pierri MK, et al: Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 20:1215-1221, 2002
81. Buzdar AU, Ibrahim NK, Francis D, et al: Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 23:3676-3685, 2005
82. Ewer MS, Martin FJ, Henderson C, et al: Cardiac safety of liposomal anthracyclines. *Semin Oncol* 31:161-181, 2004
83. Marty M, Cognetti F, Maraninchi D, et al: Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 Study Group. *J Clin Oncol* 23:4265-4274, 2005
84. Perez EA, Suman VJ, Davidson NE, et al: Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial. *J Clin Oncol* 22:3700-3704, 2004
85. Tripathy D, Seidman A, Keefe D, et al: Effect of cardiac dysfunction on treatment out-
- comes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer. *Clin Breast Cancer* 5:293-298, 2004
86. Jensen BV, Skovsgaard T, Nielsen SL: Functional monitoring of anthracycline cardiotoxicity: A prospective, blinded, long-term observational study of outcome in 120 patients. *Ann Oncol* 13:699-709, 2002
87. Sleijfer S: Bleomycin-induced pneumonitis. *Chest* 120:617-624, 2001
88. O'Sullivan JM, Huddart RA, Norman AR, et al: Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol* 14:91-96, 2003
89. Loehrer PJ Sr, Johnson D, Elson P, et al: Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: An Eastern Cooperative Oncology Group trial. *J Clin Oncol* 13:470-476, 1995
90. de Wit R, Roberts JT, Wilkinson PM, et al: Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: A randomized study of the European Organisation for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. *J Clin Oncol* 19:1629-1640, 2001
91. de Wit R, Stoter G, Kaye SB, et al: Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: A randomized study of the European Organisation for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. *J Clin Oncol* 15:1837-1843, 1997
92. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *J Clin Oncol* 16:1287-1293, 1998
93. Duggan DB, Petroni GR, Johnson JL, et al: Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup trial. *J Clin Oncol* 21:607-614, 2003
94. McDonald S, Rubin P, Phillips TL, et al: Injury to the lung from cancer therapy: Clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys* 31:1187-1203, 1995
95. Roach M III, Gandara DR, Yuo HS, et al: Radiation pneumonitis following combined modality therapy for lung cancer: Analysis of prognostic factors. *J Clin Oncol* 13:2606-2612, 1995
96. Tarbell NJ, Thompson L, Mauch P: Thoracic irradiation in Hodgkin's disease: Disease control and long-term complications. *Int J Radiat Oncol Biol Phys* 18:275-281, 1990
97. Harris S: Radiotherapy for early and advanced breast cancer. *Int J Clin Pract* 55:609-612, 2001
98. Granena A, Carreras E, Rozman C, et al: Interstitial pneumonitis after BMT: 15 years experience in a single institution. *Bone Marrow Transplant* 11:453-458, 1993
99. Sampath S, Schultheiss TE, Wong J: Dose response and factors related to interstitial pneumonitis after bone marrow transplant. *Int J Radiat Oncol Biol Phys* 63:876-884, 2005
100. Alessandrino EP, Bernasconi P, Colombo A, et al: Pulmonary toxicity following carmustine-based preparative regimens and autologous peripheral blood progenitor cell transplantation in hematological malignancies. *Bone Marrow Transplant* 25:309-313, 2000
101. Uzel I, Ozguroglu M, Uzel B, et al: Delayed onset bleomycin-induced pneumonitis. *Urology* 66:195, 2005
102. Horning SJ, Adhikari A, Rizk N, et al: Effect of treatment for Hodgkin's disease on pulmonary function: Results of a prospective study. *J Clin Oncol* 12:297-305, 1994
103. Lund MB, Kongerud J, Nome O, et al: Lung function impairment in long-term survivors of Hodgkin's disease. *Ann Oncol* 6:495-501, 1995
104. Jensen BV, Carlsen NL, Groth S, et al: Late effects on pulmonary function of mantle-field irradiation, chemotherapy or combined modality therapy for Hodgkin's disease. *Eur J Haematol* 44:165-171, 1990
105. Hirsch A, Vander Els N, Straus DJ, et al: Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. *J Clin Oncol* 14:1297-1305, 1996
106. Theuvs JC, Muller SH, Seppenwoolde Y, et al: Effect of radiotherapy and chemotherapy on pulmonary function after treatment for breast cancer and lymphoma: A follow-up study. *J Clin Oncol* 17:3091-3100, 1999
107. Lehne G, Johansen B, Fossa SD: Long-term follow-up of pulmonary function in patients cured from testicular cancer with combination chemotherapy including bleomycin. *Br J Cancer* 68:555-558, 1993
108. Beinert T, Dull T, Wolf K, et al: Late pulmonary impairment following allogeneic bone marrow transplantation. *Eur J Med Res* 1:343-348, 1996
109. Thomas O, Mahe M, Campion L, et al: Long-term complications of total body irradiation in adults. *Int J Radiat Oncol Biol Phys* 49:125-131, 2001
110. Gore EM, Lawton CA, Ash RC, et al: Pulmonary function changes in long-term survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 36:67-75, 1996
111. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 355:1572-1582, 2006
112. Mertens AC, Yasui Y, Neglia JP, et al: Late mortality experience in five-year survivors of childhood and adolescent cancer: The Childhood Cancer Survivor Study. *J Clin Oncol* 19:3163-3172, 2001

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Appendix

Table A1. Panel Members	
Panel Member	Institution
Charles Shapiro, MD, Co-Chair*	Ohio State University Comprehensive Cancer Center
David Vaughn, MD, Co-Chair*	Abramson Cancer Center of the University of Pennsylvania
Noreen Aziz, MD, PhD, MPH	National Cancer Institute (NCI)
Joseph Carver, MD*	Abramson Family Cancer Research Institute
Patricia A. Ganz, MD	UCLA Jonsson Comprehensive Cancer Center
Linda Jacobs, PhD, RN*	Abramson Cancer Center of the University of Pennsylvania
Christine Laine, MD, MPH	Annals of Internal Medicine
Susan Leigh, BSN, RN, Patient Representative	Cancer Survivorship Consultant
Mary McCabe, RN	Memorial Sloan-Kettering Cancer Center
Andrea Ng, MD*	Brigham and Women's Hospital
Loria A. Pollack, MD, MPH	Center for Disease Control and Prevention (CDC)
Carolyn Runowicz, MD	University of Connecticut Neag Comprehensive Cancer Center
Cindy Schwartz, MD*	Brown University
Katherine S. Virgo, PhD, MBA*	Saint Louis University Medical Center & Department of Veterans Affairs Medical Center, Saint Louis
Robin Zon, MD	Michiana Hematology Oncology

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