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ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/cardiac-guideline.

Endorsed by the American Heart Association.

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ABSTRACT

Purpose

Cardiac dysfunction is a serious adverse effect of certain cancer-directed therapies that can interfere with the efficacy of treatment, decrease quality of life, or impact the actual survival of the patient with cancer. The purpose of this effort was to develop recommendations for prevention and monitoring of cardiac dysfunction in survivors of adult-onset cancers.

Methods

Recommendations were developed by an expert panel with multidisciplinary representation using a systematic review (1996 to 2016) of meta-analyses, randomized clinical trials, observational studies, and clinical experience. Study quality was assessed using established methods, per study design. The guideline recommendations were crafted in part using the Guidelines Into Decision Support methodology.

Results

A total of 104 studies met eligibility criteria and compose the evidentiary basis for the recommendations. The strength of the recommendations in these guidelines is based on the quality, amount, and consistency of the evidence and the balance between benefits and harms.

Recommendations

It is important for health care providers to initiate the discussion regarding the potential for cardiac dysfunction in individuals in whom the risk is sufficiently high before beginning therapy. Certain higher risk populations of survivors of cancer may benefit from prevention and screening strategies implemented during cancer-directed therapies. Clinical suspicion for cardiac disease should be high and threshold for cardiac evaluation should be low in any survivor who has received potentially cardiotoxic therapy. For certain higher risk survivors of cancer, routine surveillance with cardiac imaging may be warranted after completion of cancer-directed therapy, so that appropriate interventions can be initiated to halt or even reverse the progression of cardiac dysfunction.

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INTRODUCTION

Recent advances in cancer treatment and supportive care have resulted in a growing number of survivors of cancer.[1] With longer survival, attention to the chronic and long-term adverse treatment effects has become increasingly important. Heart failure (HF), presenting during or after completion of cancer treatment, is a well-recognized complication impacting survival and quality of life. The American College of Cardiology (ACC) and American Heart Association (AHA) describe HF as a progressive disorder.[2] This process begins with risk factors known to be associated with the development of HF, including the toxicity of chemotherapy and/or radiation (RT; stage A), and is commonly progressive after structural changes to the heart occur. The initial manifestation may be asymptomatic cardiac dysfunction (stage B), which precedes eventual development of overt signs and symptoms (stages C and D). In patients with cancer, onset of either asymptomatic or symptomatic disease may also be responsible for interruption or discontinuation of cancer-directed therapy, potentially reducing

THE BOTTOM LINE

Recommendations for Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Questions

This clinical practice guideline addresses the following five overarching clinical questions (Fig 1): Which patients with cancer are at increased risk for developing cardiac dysfunction? Which preventative strategies minimize risk before initiation of therapy? What strategies minimize risk during potentially cardiotoxic therapy? What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction? What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Target Population

The target population consists of adults with cancer for whom cardiotoxic anticancer therapies are being considered.

Target Audience

This clinical practice guideline is targeted to oncologists, cardiologists, primary care physicians, specialists, practice providers, and any other relevant member of a comprehensive multidisciplinary cancer care team, as well as patients and their caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature, with a focus on five overarching clinical questions.

1. Which patients with cancer are at increased risk for developing cardiac dysfunction?

Recommendation 1.1. It is recommended that patients with cancer who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2)
  - High-dose radiotherapy (RT; $\geq$ 30 Gy) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) in combination with lower-dose RT ($<$ 30 Gy) where the heart is in the treatment field
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors ($\geq$ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age ($\geq$ 60 years) at cancer treatment
  - Compromised cardiac function (eg, borderline low left ventricular ejection fraction [50% to 55%], history of myocardial infarction, $\geq$ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) followed by trastuzumab (sequential therapy)

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 1.2. No recommendation can be made on the risk of cardiac dysfunction in patients with cancer with any of the following treatment exposures:

- Lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) or trastuzumab alone and no additional risk factors (as defined in Recommendation 1.1)
- Lower-dose RT ($<$ 30 Gy) where the heart is in the treatment field and no additional cardiotoxic therapeutic exposures or risk factors (as defined in Recommendation 1.1)
- Kinase inhibitors

(Evidence based; Evidence quality: low)

2. Which preventative strategies minimize risk before initiation of therapy?

Recommendation 2.1. Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes.

(Consensus based; benefits outweigh harms; Strength of recommendation: strong)

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.2. Clinicians should perform a comprehensive assessment in patients with cancer that includes a history and physical examination, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram before initiation of potentially cardiotoxic therapies.
(Evidence and consensus based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

3. Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?

Recommendation 3.1. Clinicians should screen for and actively manage modifiable cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments.
(Informal consensus and evidence based; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate)

Recommendation 3.2. Clinicians may incorporate a number of strategies, including use of the cardioprotectant dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin, for prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2).
(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 3.3. For patients who require mediastinal RT that might impact cardiac function, clinicians should select lower radiation doses when clinically appropriate and use more precise or tailored radiation fields with exclusion of as much of the heart as possible. These goals can be accomplished through use of advanced techniques including the following:

- Deep-inspiration breath holding for patients with mediastinal tumors or breast cancer in which the heart might be exposed
- Intensity-modulated RT that varies the radiation energy while treatment is delivered to precisely contour the desired radiation distribution and avoid normal tissues

(Evidence based and informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

4. What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4.1. Clinicians should complete a careful history and physical examination in patients who are receiving potentially cardiotoxic treatments.
(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 4.2. In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following strategy is recommended:

- Echocardiogram for diagnostic workup

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

- Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Referral to a cardiologist based on findings.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 4.3. Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of developing cardiac dysfunction. In these individuals, echocardiography is the surveillance imaging modality of choice that should be offered. Frequency of surveillance should be determined by health care providers based on clinical judgment and patient circumstances.
(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 4.4. No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances and considering the risks and benefits of continuation of therapy responsible for the cardiac dysfunction.
(Informal consensus; benefits outweigh harms; Evidence quality: insufficient)

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THE BOTTOM LINE (CONTINUED)

Recommendation 4.5. Clinicians may use routine echocardiographic surveillance in patients with metastatic breast cancer continuing to receiving trastuzumab indefinitely. The frequency of cardiac imaging for each patient should be determined by health care providers based on clinical judgment and patient circumstances.
(Evidence based and informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.1. Clinicians should complete a careful history and physical examination in survivors of cancer previously treated with potentially cardiotoxic therapies.
(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.1.1. In individuals with clinical signs or symptoms concerning for cardiac dysfunction, the following approaches should be offered as part of recommended care:

- Echocardiogram for diagnostic workup

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Serum cardiac biomarkers (troponins, natriuretic peptides)

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Referral to a cardiologist based on findings

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction.
(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.2.1. Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI.
(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.3. Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management.
(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram.
(Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care.
(Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/cardiac-guideline. Patient information is available at www.cancer.net.

Qualifying Statements

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

the chance for long-term survival. In children (≤ 21 years old at diagnosis) with cancer, the short- and long-term risk of cardiac dysfunction associated with therapeutic exposures, such as anthracycline chemotherapy (eg, doxorubicin, epirubicin, daunorubicin) or use of chest-directed RT. is well described.[3] This led to the development of evidence-based guidelines to direct surveillance and prevention of cardiac dysfunction in survivors of childhood cancer.[4] The need for comparable screening guidelines in survivors of adult-onset cancers is paramount, so that proper interventions can be implemented to avert the risk of cardiac dysfunction during and after completion of therapy.

In recognition of the increasing need for guidance, the ASCO Survivorship Guidelines Advisory Group recommended this guideline topic as a high priority for development, requesting that the emphasis be on cardiac dysfunction (asymptomatic or symptomatic) and that the full scope of therapeutic exposures and health conditions impacting risk be considered. Although it is well established that cardiac dysfunction can present as systolic and/or diastolic impairment, there is a paucity of information on the incidence and risk factors for diastolic dysfunction in survivors of adult-onset cancers. Therefore, the focus of this document is on prevention and monitoring of systolic cardiac dysfunction, typically detected as low left ventricular ejection fraction (LVEF). Moreover, although assessment of coronary artery disease and/or other cardiac abnormalities (valvular or pericardial disease) may be an important aspect of the comprehensive evaluation of cardiac function, recommendations for prevention and monitoring of these complications fall outside the scope of this guideline. With regard to the medical management of cardiac dysfunction, reference will be made to existing treatment guidelines[2] as well as relevant studies that address this topic.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following five overarching clinical questions (Fig 1): (1) Which patients with cancer are at increased risk for developing cardiac dysfunction? (2) Which preventative strategies minimize risk before initiation of therapy? (3) Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy? (4) What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction? (5) What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

METHODS

Guideline Development Process

A multidisciplinary Expert Panel was formed and tasked with drafting the guideline (Appendix Table A1, online only). Expert Panel members had expertise in medical oncology, cardiology, RT oncology, imaging, exercise physiology, cancer prevention, and survivorship (Data Supplement). The Expert Panel included representatives from the ACC and AHA. In addition, a survivor of cancer was included to provide a patient perspective. The Expert Panel met in person and via teleconference and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The recommendations were informed by a systematic review (1996 to 2016) of randomized clinical trials (RCTs), observational studies, and clinical experience. Where evidence was lacking but there was a high level of agreement among the panel members (> 80% of panelists), informal consensus was used, as noted with the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline. All ASCO guidelines are ultimately reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication. The guideline also underwent formal review by the ACC and AHA and was approved for endorsement by both organizations.

Systematic Literature Review and Strategy

ASCO guidelines are based on systematic reviews. A protocol for each guideline defines the parameters for a targeted literature search including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for identified literature. For this guideline, the MEDLINE (Ovid: 1996 through May [week 2] 2014) database was searched for evidence reporting on outcomes of interest. An updated literature search (period: May 2014 to February 16, 2016) was conducted in PubMed to identify relevant studies that may impact the current recommendations. Reference lists from seminal articles and recent review articles were scanned for additional citations, and known updates of included evidence were obtained as available. The literature search strategy used in the MEDLINE and PubMed databases is available in the Data Supplement.

Study Selection Criteria

Articles were eligible for inclusion in this review of the evidence if they met the following criteria.

Question 1. Risk categorization.

- Population-based cohort studies with long-term and complete follow-up that included validated cardiovascular outcomes, treatment dose–specific information, comparison with no exposure, and multivariable regression analysis that adjusted for confounders.

Question 2. Prevention before initiation of cancer-directed treatment.

- Comparative studies that considered prevention strategies of interest.

Question 3. Prevention during cancer-directed treatment.

- Studies that considered prevention strategies of interest, including limitation of cardiotoxic antineoplastic dose or exposure, alternative drug administration schedules, use of less cardiotoxic analogs, limitation of total RT dose, precision of RT volume to avoid heart, use of cardioprotectants, and management of modifiable risk factors.
- Results were reported for development of asymptomatic or symptomatic cardiac dysfunction.

Question 4. Surveillance during treatment.

- Studies that described the incidence of cardiac dysfunction (asymptomatic or symptomatic) as a result of specific therapeutic exposures during treatment.
- Comparative studies that evaluated the utility and accuracy of surveillance with cardiac imaging (eg, echocardiography, strain, tissue Doppler, magnetic resonance imaging [MRI], multigated acquisition [MUGA] scan) or blood-based biomarkers for detection of cardiac dysfunction.

Question 5. Surveillance after treatment.

- Studies describing the incidence of asymptomatic or symptomatic cardiac dysfunction over time were collected to inform the frequency and duration of long-term surveillance.
- Comparative studies that evaluated the utility and accuracy of surveillance with cardiac imaging (eg, echocardiography, strain, tissue Doppler, MRI, MUGA) or blood-based biomarkers for detection of cardiac dysfunction.
- Studies that examined the effectiveness of interventions in asymptomatic cancer survivors for prevention of symptomatic disease.

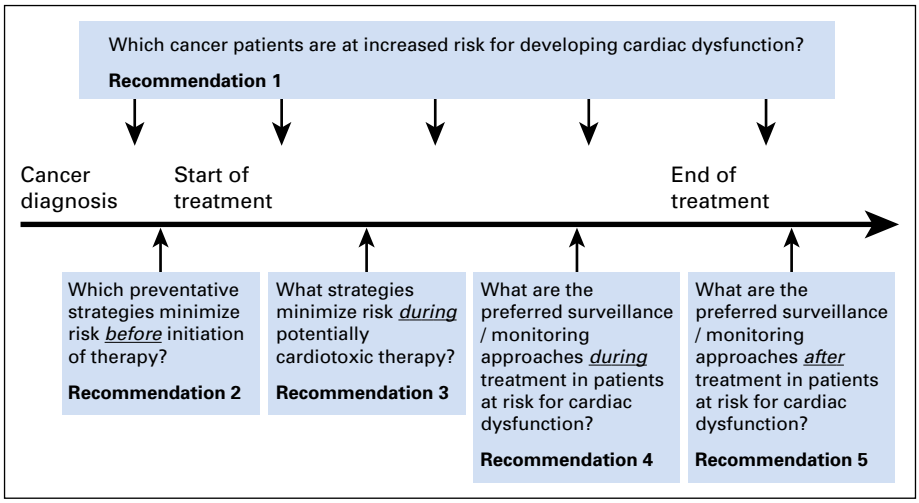

Fig 1. Overarching clinical questions addressed in the clinical practice guideline.

Articles were excluded from the systematic review if they were editorials, commentaries, letters, news articles, case reports, or narrative reviews; published in a non-English language; or described studies that included fewer than 20 participants. Meeting abstracts not yet published in peer-reviewed journals were generally excluded for review, except when there was uniform consensus from the Expert Panel regarding their importance for the formulation of recommendations. The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support methodology. In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (see Methodology Supplement for more information).

Study Quality Assessment

As seen in the Methodology Supplement, study quality was formally assessed for the 104 studies identified. Systematic reviews and meta-analyses were assessed for quality using the Assessing the Methodological Quality of Systematic Reviews tool.[5] Design elements, such as blinding, allocation concealment, placebo control, intention to treat, and funding sources, were assessed for RCTs. Methodologic criteria assessed for cohort studies and before-and-after studies included type of data collection, sampling method, representativeness of participants, objective outcomes, and appropriate statistical analyses. Assessment of cross-sectional studies was informed by the Modified Newcastle-Ottawa Scale.[6] Refer to the Methodology Supplement for ratings of overall potential risk of bias.

Data Extraction

Literature search results were reviewed and deemed appropriate for full-text review by an ASCO staff member in consultation with the co-chairs. Data were extracted by one ASCO staff member and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the co-chairs if necessary.

Revision Dates

The co-chairs determine the need for guideline updates or revisions based on periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an Update Committee is reconvened to discuss revisions to the document.

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/cardiac-guideline, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process, and quality assessment.

This is the most recent information as of the publication date. For updates, for the most recent information, and to submit new evidence, please visit www.asco.org/cardiac-guideline and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or

commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, and expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Studies Identified in the Literature Search

A total of eight systematic reviews,[7-14] 12 RCTs,[15-26] 49 cohort studies,[27-76], 32 before-and-after studies,[77-107] and three cross-sectional studies[108-110] met eligibility criteria and form the evidentiary basis for the guideline recommendations. The identified studies spanned from 1999 to 2016 and most often considered asymptomatic or symptomatic cardiac dysfunction as the primary outcome, although definitions of these varied across studies (eg, left ventricular dysfunction, HF, cardiomyopathy). There were 43 studies informing risk factors, 13 studies covering prevention during treatment, 34 studies on surveillance during treatment, and 15 studies on frequency and duration of surveillance after treatment (Table 1).

Study Quality Assessment

In general, most of the identified studies exhibited a low to intermediate potential risk of bias (Methodology Supplement). The Assessing the Methodological Quality of Systematic Reviews scores for the eight systematic reviews ranged from 5 to 10 out of a possible 11 points. The two low-scoring reviews[11,12] each showed deficiencies in the quality and publication bias assessments. The 11 included RCTs all received an intermediate potential risk of bias. Insufficient sample sizes, lack of reporting of intent-to-treat analyses, and missing statements regarding conflicts were the main concerns. Although the vast majority of cohort studies evaluated retrospective cohorts and the inherent limitations of retrospective designs should be taken into consideration, the collection of data did occur prospectively in all but one study.[42] The overall potential risk of bias was rated as low in 36 of the cohort studies, intermediate in 12 studies, and high in one study.[52] The vast majority of before-and-after studies were also assessed to have a low overall potential risk of bias. Finally, the three cross-sectional studies received scores of 5, 6, and 8 out of a maximum 10 points. Refer to the Methodology Supplement for extensive tables outlining formal quality assessment and for definitions of ratings for overall potential risk of bias.

Table 1. Included Studies

Question	No. of Studies
1. Risk determination*	43
2. Prevention before cancer treatment	—
3. Prevention during cancer treatment*	13
4. Surveillance during cancer treatment*	11 imaging; 23 blood biomarkers
5. Surveillance after cancer treatment*	15

*Summary of results available in Data Supplement.

RECOMMENDATIONS

Clinical Question 1: Which patients with cancer are at increased risk for developing cardiac dysfunction?

Recommendation 1.1. It is recommended that patients with cancer who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2)
  - High-dose RT ($\geq$ 30 Gy) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) in combination with lower-dose RT ($<$ 30 Gy) where the heart is in the treatment field
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors ($\geq$ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age ($\geq$ 60 years) at cancer treatment
  - Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, $\geq$ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) followed by trastuzumab (sequential therapy)

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 1.2. No recommendation can be made on the risk of cardiac dysfunction in patients with cancer with any of the following treatment exposures:

- Lower-dose anthracycline (eg, doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) or trastuzumab alone and no additional risk factors (as defined in Recommendation 1.1)
- Lower-dose RT ($<$ 30 Gy) where the heart is in the treatment field and no additional cardiotoxic therapeutic exposures or risk factors (as defined in Recommendation 1.1)
- Kinase inhibitors (KIs)

(Evidence based; Evidence quality: low)

Qualifying Statements

To date, a limited number of longitudinal cohort studies with long-term follow-up ($>$ 5 years after diagnosis) have evaluated the risk of anthracycline-related cardiac dysfunction by cumulative anthracycline dose; scant data are available on risk associated with certain anthracycline analogs (eg, daunorubicin, idarubicin) and mitoxantrone. Existing cohort studies have been mostly limited to patients with hematologic malignancies or breast cancer, with little

information on cardiac outcomes in survivors of other malignancies (eg, sarcoma), where anthracyclines are routinely used as part of first-line therapy. Although registry-based (eg, SEER-Medicare database, national registries) studies allow for characterization of cardiac dysfunction risk in large cohorts of survivors of cancer, they provide limited information regarding the dose-specific risk by therapeutic exposure.

Patients with breast cancer treated with anthracycline-based therapies, without trastuzumab, represent older cohorts of survivors for whom the risk of cardiac dysfunction may be markedly different than patients undergoing treatment with contemporary approaches. The initial alarming incidence of cardiac dysfunction and/or HF (up to 27%) associated with trastuzumab in women with breast cancer was largely a result of coadministration of the drug with doxorubicin.[38] Lower rates (2.8% to 3.4%) of cardiac dysfunction and/or HF were observed in subsequent clinical trials (North Central Cancer Treatment Group N9831 and National Surgical Adjuvant Breast and Bowel Project B-31) in which trastuzumab was given sequentially after doxorubicin.[17,26] It should be noted that patients treated in these trials were not allowed to receive trastuzumab if they developed symptomatic cardiac dysfunction during anthracycline-based therapy or demonstrated an absolute decline in LVEF of more than 15% from baseline before start of planned trastuzumab therapy. As such, the overall risk presented in these studies has to be interpreted in the context of the respective trials and current patterns of care.

Recent advances in the delivery of mediastinal RT (eg, shielding of the myocardium, lower total dose, more precise delivery to area of disease involvement) are often not accounted for in cohort studies describing long-term cardiovascular disease risk caused by RT in survivors of lymphoma. Mean heart dose described in studies has typically been estimated retrospectively from historically treated patients, making it difficult to establish an accurate cardiac dose-effect relationship.[111] Although mean heart dose is a straightforward and direct dose-volumetric parameter, treatment plans with the same mean heart dose could still result in different cardiac consequences depending on how much of the critical substructures are included in the volume.[111,112] Therefore, it is often difficult to generalize the risk of cardiac dysfunction by heart radiation volume alone or by the proportion of the heart that is included in the treatment field. Finally, few studies have differentiated between cardiac dysfunction as a first event and secondary cardiac dysfunction that develops after myocardial infarction or valvular disease.

Literature Review and Clinical Interpretation

Treatment-related modifiers of risk

Anthracyclines and/or mediastinal RT. The association between cumulative anthracycline dose and HF risk in adult patients with cancer was initially described in retrospective cohort studies, representing corollary analyses of acute cardiotoxicity rates reported on therapeutic clinical trials.[113,114] These studies suggested a doxorubicin dose threshold of 400 mg/m^2, after which the incidence of HF increased exponentially by cumulative anthracycline dose (5%, 26%, and 48% at cumulative doses of 400, 550, and 700 mg/m^2, respectively).[113,114] These authors speculated that the reported incidence in these studies may have been underestimated as a result of limitations of HF reporting on clinical trials and lack of long-term follow-up. A subsequent pooled prospective analysis of three clinical trials in patients with breast and lung cancer[115] found that the percentage of study participants who developed cardiac dysfunction was 9% at a cumulative doxorubicin dose of 250 mg/m^2, increasing to 18% and 38% at cumulative doses of 350 and 450 mg/m^2, respectively, suggesting a lower threshold for cardiac dysfunction risk in anthracycline-exposed survivors of cancer.

A recent population-based cohort study[64] with a median follow-up of 20 years reported a 4.5-fold risk of HF as a first event in survivors of Hodgkin lymphoma treated with $\geq$ 250 mg/m^2 of doxorubicin when compared with individuals treated without doxorubicin or mediastinal RT. Similarly, a nested case-control study[45] of long-term survivors of hematopoietic cell transplantation (n = 1,244) found a nearly 10-fold (odds ratio [OR], 9.9) risk of HF in survivors treated with $\geq$ 250 mg/m^2 of anthracyclines when compared with survivors treated with lower-dose ($<$ 150 mg/m^2) anthracyclines. These associations are in line with previous studies[22,31,43,53] that identified a significant and independent risk of cardiac dysfunction in individuals treated with higher dose (range, 200 to 400 mg/m^2) anthracyclines such as doxorubicin. After adjusting for anthracycline dose, sex, and comorbidities, higher dose ($\geq$ 30 Gy) mediastinal RT was associated with a 2.8- to 4.7-fold risk of HF as a first event when compared with no mediastinal RT exposure.[64] Individuals treated with mediastinal RT and lower-dose ($<$ 250 mg/m^2) doxorubicin had a 5.4-fold risk of HF when compared with survivors treated without mediastinal RT or doxorubicin.[64] In patients with breast cancer, a cumulative epirubicin dose $\geq$ 600 mg/m^2 has been associated with significant elevation of cardiac dysfunction risk when compared with lower-dose epirubicin exposure.[15,16,36,37]

Given the consistent and strong association between higher-dose doxorubicin ($\geq$ 250 mg/m^2) or epirubicin ($\geq$ 600 mg/m^2), higher-dose mediastinal RT ($\geq$ 30 Gy), or the combination of anthracyclines and mediastinal RT and risk of cardiac dysfunction,[15,16,22,31,36,37,43,45,53,64] survivors with past exposure to these therapies should be considered at increased risk for developing cardiac dysfunction.

There is conflicting evidence about whether lower-dose anthracycline therapy (eg, doxorubicin $<$ 250 mg/m^2), without an additional cardiotoxic exposure (eg, mediastinal RT, trastuzumab) or presence of comorbidities (eg, hypertension, diabetes), increases the long-term risk of cardiac dysfunction in survivors of cancer. In a recent report, van Nimwegen et al[64] did not observe a statistically significant risk of HF in survivors of Hodgkin lymphoma treated with lower-dose ($<$ 250 mg/m^2) doxorubicin without mediastinal RT, when compared with survivors treated without anthracyclines or mediastinal RT. These findings are supported by previous studies in survivors of lymphoma[43,53] that found a similar non-significant association between lower-dose anthracycline exposure and cardiac dysfunction risk. However, registry-based studies[67,68] of patients with breast cancer treated between 1999 and 2007 have reported a modest increase in risk (1.1- to 1.4-fold) of cardiac dysfunction for individuals receiving standard anthracycline-based therapy (without trastuzumab), when compared with those treated without anthracyclines.

With regard to mediastinal RT, although it is well established that there is a dose-dependent association between mediastinal RT

and certain cardiovascular diseases such as coronary artery disease or valvular disease,[116-118] there is little evidence that lower-dose (< 30 Gy) mediastinal RT alone can increase the long-term risk of developing cardiac dysfunction or HF as a first event. In the study by van Nimwegen et al,[64] individuals treated with 1 to 29 Gy of mediastinal RT had a nonsignificant increased risk (hazard ratio, 1.6; 95% CI, 0.5 to 5.6) of cardiomyopathy or HF as a first event. Similarly, studies[45,119] of survivors of hematopoietic cell transplantation treated with total-body irradiation found no association between lower-dose fractionated RT (12 to 13 Gy) and risk of HF as a first event.

Given the lack of studies demonstrating an increased risk of cardiac dysfunction in survivors treated with lower-dose anthracyclines or mediastinal RT (eg, doxorubicin < 250 mg/m^2, RT < 30 Gy) and no other risk factors, no recommendations can be made regarding the risk for cardiac dysfunction in survivors treated with these lower-dose therapies alone.

Trastuzumab. Large population-based studies have shown that treatment with trastuzumab after anthracycline-based chemotherapy (typically doxorubicin < 250 mg/m^2) can be associated with a significantly increased risk of cardiac dysfunction when compared with no anthracycline therapy (seven-fold risk[67]) or only standard anthracycline-based adjuvant therapy (range, two- to six-fold risk[14,65,68]). For the most part, these studies have relied on administrative data sets and have included patients with breast cancer who are typically older (≥ 65 years old) at the time of treatment.[35,68] Nevertheless, the risk of cardiac dysfunction in individuals treated with anthracyclines followed by trastuzumab is not negligible.

Clinical trials evaluating efficacy of non–anthracycline-based regimens for breast cancer have reported a low incidence of cardiac dysfunction in women receiving trastuzumab-based therapy. Dang et al[63] found the 3-year incidence of cardiac dysfunction in women treated with trastuzumab and paclitaxel to be 0.5%. This is consistent with the relatively low incidence reported from 10 years of follow-up of the docetaxel, carboplatin, and trastuzumab arm of the Breast Cancer International Research Group 006 trial[120,121] and a phase II trial by Jones et al,[69] which described risk associated with docetaxel, cyclophosphamide, and trastuzumab. Additional population-based studies are needed to describe the short- and long-term risk for cardiac dysfunction in women treated outside the clinical trial setting. Until then, no recommendations can be made regarding risk classification for individuals treated with trastuzumab without anthracycline and with no other risk factors.

KIs. Tyrosine and serine/threonine kinases are small-molecule inhibitors that are useful in the treatment of more than one type of cancer. However, these agents can be associated with a variety of cardiotoxicities, with the mechanisms and severity appearing to differ according to each KI.[122] Toxicities can be on target, where the intended target kinase also plays a role in the heart, or can be a result of off-target toxicity that can impact cardiac function.[122] Cardiac dysfunction associated with lapatinib, for example, may be a result of myocardial human epidermal growth factor receptor 2 (HER2) inhibition, whereas other KIs such as sunitinib can result in hypertension and/or thrombosis in addition to HF.[122] Given the differences in both mechanism of action and subsequent toxicities with KIs, it is currently unclear whether cardiotoxicity is a drug-specific or class-specific phenomenon. Consequently, there is insufficient evidence to guide clinicians about the safety of switching drugs within this class after cardiotoxicity occurs. Importantly, lack of longitudinal data in survivors treated with KIs precludes accurate assessment of long-term cardiac dysfunction risk. As such, no recommendation can be made regarding risk stratification for individuals treated with KIs alone.

Non–treatment-related modifiers of risk

Older age. Cutoffs used to define older age at treatment have varied across studies, with most associations for increased risk seen in individuals who were ≥ 60 years of age at treatment. Six studies[17,26,33,38,47,53] reported a significant and independent increased (1.6- to 6.8-fold) risk of cardiac dysfunction in older patients with cancer treated with anthracyclines and/or trastuzumab when compared with younger patients with cancer. Four additional studies[35,43,54,55] were limited to individuals who were ≥ 65 years of age at the time of treatment; nevertheless, there was an incremental risk for cardiac dysfunction by increasing age.

Comorbidities. Modifiable risk factors such as smoking, hypertension, diabetes, and dyslipidemia were significantly associated with increased risk of cardiac dysfunction in patients with cancer treated with anthracyclines and/or trastuzumab.[17,26,32,33,35,39,45,55,65,110,119] The most consistent association was with hypertension. The presence of multiple modifiable risk factors (≥ two factors) was associated with the highest risk of HF.[119,123]

Compromised cardiac function. Borderline low LVEF (50% to 54%), history of myocardial infarction, history of cardiac dysfunction, and presence of other cardiac comorbidities (eg, ≥ moderate valvular heart disease) before the start of anthracycline or trastuzumab therapy have been associated with an increased risk (3.6- to 11.8-fold) of cardiac dysfunction in three studies.[17,26,49,55]

Individuals treated with potentially cardiotoxic therapies (eg, anthracyclines, trastuzumab, or mediastinal RT) who have additional risk factors such as compromised cardiac function before treatment initiation, who have multiple cardiovascular risk factors (≥ two factors), or who are older (≥ 60 years) at the time of treatment should be considered as being at increased risk for developing cardiac dysfunction.

Clinical Question 2: Which preventative strategies minimize risk before initiation of therapy?

Recommendation 2.1. Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes.

(Consensus based; benefits outweigh harms; Strength of recommendation: strong)

Recommendation 2.2. Clinicians should perform a comprehensive assessment in patients with cancer that includes a history and physical examination, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram before initiation of potentially cardiotoxic therapies.

(Evidence and consensus based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Literature Review and Clinical Interpretation

Decisions pertaining to choice of anticancer therapies must balance the antitumor efficacy of the treatment with the potential for acute and long-term toxicities, including cardiotoxicity. Few studies have evaluated the efficacy of preventive strategies before initiation of cancer therapy. As such, any recommendation regarding prevention strategies before initiation of cancer-directed therapy is based on good clinical judgment and expert consensus. Therefore, we recommend avoidance or minimizing the use of potentially cardiotoxic therapies in individuals at moderate to high risk if established alternatives exist that would not compromise cancer-specific outcomes. Moreover, patients planning to receive potentially cardiotoxic therapies should undergo a comprehensive assessment that includes a history and physical examination, screening for cardiovascular risk factors, and an echocardiogram to ensure adequate cardiac function before initiation of potentially cardiotoxic therapy. These recommendations are based on the consistent epidemiologic evidence[33,35,38,39,43,45,47,49,53-55,65,110,119] that pretreatment cardiovascular disease risk status is an important prognosticator of future cardiac dysfunction risk.

Clinical Question 3: Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?

Recommendation 3.1. Clinicians should screen for and actively manage modifiable cardiovascular risk factors (eg, smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments.

(Informal consensus and evidence based; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate)

Recommendation 3.2. Clinicians may incorporate a number of strategies, including use of the cardioprotectant dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin, for prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2).

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 3.3. For patients who require mediastinal RT that might impact cardiac function, clinicians should select lower radiation doses when clinically appropriate and use more precise or tailored radiation fields with exclusion of as much of the heart as possible. These goals can be accomplished through use of advanced techniques including the following:

- Deep-inspiration breath holding for patients with mediastinal tumors or breast cancer in which the heart might be exposed
- Intensity-modulated RT that varies the radiation energy while treatment is delivered to precisely contour the desired radiation distribution and avoid normal tissues

(Evidence based and informal consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

Qualifying Statements

To date, several meta-analyses[7-10,124] have been performed demonstrating the efficacy of various cardioprotective strategies, especially with regard to anthracycline therapy (eg, coadministration of dexrazoxane, use of liposomal formulation, continuous infusion). However, many of the RCTs included in these meta-analyses were limited to patients who were undergoing treatment of advanced-stage or metastatic disease, representing a population of patients with cancer who had received a significant amount of anthracycline therapy (eg, doxorubicin $\geq$ 250 mg/m^2) before initiation of a cardioprotectant. Therefore, any information regarding the potential cardioprotective effect of these agents has to be considered in the context of the lifetime dose of anthracycline delivered to an individual as well as the individual's disease stage and status. Finally, studies evaluating other cardioprotective strategies (eg, use of angiotensin-converting enzyme [ACE] inhibitors, β-blockers, or angiotensin receptor blockers [ARBs] in normotensive patients or statins in patients without dyslipidemia) have been limited by small sample size, lack of long-term measures of clinical efficacy (eg, reduction in the risk of symptomatic cardiac dysfunction), and use of nonrandomized study design.

Literature Review and Clinical Interpretation

At least three meta-analyses,[7,9,10] pooling the findings from four clinical trials,[114,125-127] have examined the efficacy of dexrazoxane as a cardioprotectant in adult patients with cancer receiving anthracyclines. Although there is evidence that dexrazoxane can significantly reduce the risk (risk reduction, 0.21 to 0.31) of acute clinical and/or subclinical HF without compromising antitumor efficacy, two of the four clinical trials[126,127] included participants who had received high cumulative doses of anthracycline therapy before initiation of dexrazoxane. As such, the potential for risk reduction as a result of dexrazoxane must be considered in the context of the population in which it was evaluated.

A meta-analysis by Smith et al[7] included four RCTs[128-131] that compared bolus with continuous (range, 6 to 96 hours) infusion. One study[129] included participants previously treated with anthracyclines. The risk of both subclinical (OR, 3.04; 95% CI, 1.66 to 5.58) and clinical cardiotoxicity (OR, 4.13; 95% CI, 1.75 to 9.72) was significantly increased when anthracyclines (epirubicin or doxorubicin) were given as a bolus compared with continuous infusion. It is important to note that for subclinical cardiotoxicity, the pooled result was highly dependent on the choice of the summary statistic (random effects relative risk [RR], 1.93; 95% CI, 0.84 to 4.44), which may have been a result of the different definitions for LVEF reduction used in each of the studies.

Three meta-analyses[7,8,124] compared liposomal encapsulated doxorubicin with conventional doxorubicin. Smith et al[7] found that liposomal doxorubicin decreased the risk of clinical cardiotoxicity (OR, 0.18; 95% CI, 0.08 to 0.38) and subclinical cardiotoxicity (RR, 0.31; 95% CI, 0.20 to 0.48) when compared with conventional doxorubicin. Similarly, van Dalen et al[8] reported a significantly lower risk of clinical HF in patients treated with liposomal encapsulated doxorubicin compared with treatment with conventional doxorubicin (RR, 0.20; 95% CI, 0.05 to 0.75). Combining subclinical and clinical HF also resulted in a decreased risk (RR, 0.38; 95% CI, 0.24 to 0.59). These results mirrored the findings of Rafiyath et al,[124] who reported significantly lower risk of HF (OR, 0.34; 95% CI, 0.24 to 0.47) in patients receiving liposomal doxorubicin when compared with conventional anthracyclines. No

differences in cancer-specific outcomes were noted when the liposomal formulation was used. All patients included in these studies were adults with advanced cancers, predominantly breast cancer. As such, no conclusions could be made about the effects of treatment with liposomal doxorubicin versus doxorubicin for individuals being treated in the curative setting or with other malignancies.

These limitations notwithstanding, there is considerable evidence that for patients receiving higher-dose anthracyclines, a number of preventive approaches can result in a lower risk of cardiotoxicity, with low probability of compromising cancer-specific outcomes. Therefore, clinicians may consider incorporating the use of dexrazoxane, continuous infusion of anthracyclines, or liposomal formulation of doxorubicin for prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines. However, there is no evidence to suggest that these approaches would reduce risk of cardiotoxicity in patients receiving lower-dose anthracyclines (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2).[132,133] As a result, no recommendations can be made regarding these preventive strategies in patients planning to receive lower-dose anthracyclines.

Prophylactic use of ACE inhibitors, β-blockers, or ARBs for prevention of anthracycline-induced cardiotoxicity is an ongoing area of active investigation. Cardinale et al[133a] demonstrated that in high-risk patients, defined by an increased troponin I (TnI) value (> 0.07 ng/mL) during treatment, early initiation of enalapril (ACE inhibitor) resulted in decreased risk of cardiac dysfunction. With regard to β-blockers, two nonrandomized clinical trials[60,134] and one placebo-controlled[134] trial have suggested that prophylactic use of these agents may decrease the risk of subclinical cardiac dysfunction in patients receiving anthracycline-based therapy. In a subsequent study,[135] patients randomly assigned to receive enalapril and carvedilol (β-blocker) had preserved LVEF during 6 months of therapy, when compared with individuals randomly assigned to placebo. The Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA; ClinicalTrials.gov identifier: NCT01434134) study[136] randomly assigned 120 patients receiving anthracycline therapy with or without trastuzumab to candesartan (ARB), metoprolol (β-blocker), or placebo. The candesartan arm demonstrated a significant yet modest attenuation in the decline in LVEF when compared with metoprolol or placebo.[136] A more recent randomized placebo-controlled study[137] failed to demonstrate a cardioprotective effect of candesartan in patients with breast cancer treated with trastuzumab.

The Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial[138] randomly assigned patients with HER2-positive disease to perindopril (ACE inhibitor), bisoprolol (β-blocker), or placebo; of note, approximately 75% of patients received a trastuzumab regimen without anthracycline exposure. Although the study did not meet the primary end point of prevention of left ventricular remodeling, patients receiving either perindopril or bisoprolol had significantly fewer trastuzumab drug holds compared with the placebo group.[139] The Preventing Anthracycline Cardiovascular Toxicity With Statins (PREVENT; NCT01988571) trial is currently evaluating the efficacy of prophylactic atorvastatin (statin) to reduce the risk for cardiac dysfunction or HF. With greater maturity of these studies as well as completion of larger trials, use of these agents may be more broadly endorsed in the future.

There have been no studies to evaluate the efficacy of cardioprotective strategies in patients receiving KIs. However, it is well recognized that these agents markedly increase the risk of hypertension[122] and that aggressive monitoring and management of hypertension can significantly lower the incidence of cardiotoxicity. Therefore, it is important that patients receiving KIs have their blood pressure monitored as part of routine clinical care so that appropriate treatments can be initiated to reduce the risk of cardiotoxicity.[140]

For patients for whom RT is planned that might impact cardiac function, approaches to reduce cardiac radiation exposure include radiation dose reduction, radiation field or volume reduction, and use of modern RT planning and delivery techniques (eg, three-dimensional conformal therapy, accelerated partial breast irradiation). Patients with early-stage Hodgkin lymphoma or low-risk disease have benefited from dose reduction of RT (eg, 30 to 20 Gy), without compromising cancer-specific outcomes.[141] Although there is a paucity of information on cardiac outcomes after dose de-escalation, it is encouraging that a lower-dose strategy can be considered for subsets of patients with low-risk disease. With regard to field or volume reduction, the availability of more effective systemic therapy, improved staging and imaging studies, and computed tomography–based RT planning have resulted in marked reduction of field or volume (eg, extended-field RT, to mantle-field RT, to involved-field RT, to involved-node/involved-site RT) in patients with lymphoma, yielding lower radiation exposure to the heart. In a dosimetric study[142] of patients with Hodgkin lymphoma, mantle-field RT resulted in a mean heart dose of 27.5 Gy, compared with 7.7 Gy with involved-node RT; this corresponded to a reduction in the 25-year absolute excess risk of cardiac disease from 9.1% to 1.4%. Newer approaches, such as use of involved-node RT, can result in close to a 50% reduction in mean heart dose when compared with involved-field RT.[75,76] Modern RT approaches such as intensity-modulated RT and proton beam therapy have the potential to further decrease exposure to healthy organs. For example, a recent phase II study[73,74] on proton beam therapy for mediastinal Hodgkin lymphoma demonstrated dosimetric benefits to the heart, lungs, and breast using involved-node proton beam therapy. Additional studies are needed to evaluate the long-term cardioprotective effects of such strategies. Finally, maneuvers such as deep-inspiration breath-hold technique have been shown to further decrease RT doses to the heart and surrounding tissues[70-72] and should be incorporated as part of standard of care for patients receiving mediastinal RT.

Clinical Question 4: What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4.1. Clinicians should complete a careful history and physical examination in patients who are receiving potentially cardiotoxic treatments.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 4.2. In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following strategy is recommended:

- Echocardiogram for diagnostic workup

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Referral to a cardiologist based on findings.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 4.3. Routine surveillance imaging may be offered during treatment in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of developing cardiac dysfunction. In these individuals, echocardiography is the surveillance imaging modality of choice that should be offered. Frequency of surveillance should be determined by health care providers based on clinical judgment and patient circumstances.

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 4.4. No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances and considering the risks and benefits of continuation of therapy responsible for the cardiac dysfunction.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient)

Recommendation 4.5. Clinicians may use routine echocardiographic surveillance in patients with metastatic breast cancer continuing to receiving trastuzumab indefinitely. The frequency of cardiac imaging for each patient should be determined by health care providers based on clinical judgment and patient circumstances.

(Evidence based and informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Qualifying Statements

To date, the direct clinical impact of monitoring frequency on cardiovascular or oncologic outcomes remains unknown. Current guidelines[143] in select populations (eg, patients with early-stage HER2-positive breast cancer) recommend routine cardiac monitoring during therapy, although the supporting evidence, as well as the clinical and cost effectiveness on a population level, is unclear. Moreover, additional gaps in knowledge, as outlined in the discussion of Recommendation 1, include a precise and accurate determination of dose-specific risk of dysfunction by therapeutic exposure and individual patient characteristics. This limits our ability to make robust recommendations regarding repeated surveillance in all patients. Finally, there is a risk from overscreening that curative or palliative therapy will be inappropriately compromised in some patients.

Literature Review and Clinical Interpretation

A thorough history and physical examination are strongly recommended in patients receiving cardiotoxic therapies in whom there is a clinical concern for cardiac dysfunction. Referral to an oncocardiologist or a health care provider with expertise in this area is also recommended for these patients.[144]

With regard to surveillance of asymptomatic patients, a recent meta-analysis of studies conducted in nononcology populations found that the severity of left ventricular systolic dysfunction (measured by LVEF) was the strongest predictor of progression from asymptomatic (ACC/AHA stage B) to symptomatic (ACC/AHA stage C) HF; there was a 40% increase in risk per standard deviation change in LVEF. Therefore, screening for asymptomatic cardiac dysfunction may be important for certain high-risk cancer populations (Recommendation 1.1) so that interventions can be implemented to delay the onset of symptomatic disease.[27,49,120,145-147]

Two-dimensional echocardiography, coupled with Doppler flow studies, is the preferred imaging modality in the monitoring of asymptomatic patients because it is highly portable, readily available, noninvasive, and safe. Moreover, echocardiography provides valuable information regarding right and left ventricular structure, systolic and diastolic function, and valvular disease and hemodynamics.[145] It is important to emphasize that although LVEF is the most widely studied measure of cardiac function in patients with cancer, other echocardiographic parameters (eg, diastolic function, such as E/A ratio [peak early atrial velocity divided by peak late atrial velocity], tissue Doppler measures, or prolonged isovolumetric relaxation time; global longitudinal strain) may provide valuable information regarding cardiac function during and after completion of cancer-directed therapy.[146] Imaging should adhere to established imaging standards,[147] relying on consistent imaging technologies (eg, machine manufacturer, analysis software) to limit technical variability. Other imaging modalities such as cardiac MRI or MUGA may be considered if an echocardiogram is not available or technically feasible (eg, poor image quality as a result of body habitus, chronic lung conditions, or history of mediastinal surgery), with preference given to cardiac MRI. In this setting, three-dimensional echocardiography may also be considered, according to expertise and availability.

Measurement of serum natriuretic peptides (brain natriuretic peptide [BNP], N-terminal pro-BNP [NT-proBNP]), cardiac troponins (TnI, troponin T), or echocardiography-derived strain has been demonstrated to have some diagnostic and prognostic use in patients with cancer receiving cardiotoxic therapies. Studies have shown that early elevation in cardiac biomarkers such as troponin or changes in cardiac strain during cancer-directed therapy precede changes in LVEF, as assessed by two-dimensional echocardiography.[11,78-80,84,87,98,101,148,149] Cardiac troponins are sensitive and specific markers of myocardial injury and are widely used in cardiovascular medicine. Of the troponins, TnI has been the most widely studied blood biomarker of cardiotoxicity in patients with cancer. A large study (n = 703) evaluated the use of serial monitoring of patients with cancer with TnI at multiple time points (immediately after and 12, 24, 36, and 72 hours after each high-dose

chemotherapy cycle) and 1 month after completion of chemotherapy.[84] The highest incidence of cardiotoxicity was observed among patients with TnI elevation within 72 hours of chemotherapy that persisted at 1 month after treatment. A study by the same group performed in patients treated with trastuzumab demonstrated that an elevated TnI was associated with an increased risk of cardiotoxicity and a lack of LVEF recovery, indicative of a particularly high cardiovascular risk group with a poor prognosis.[81] Smaller studies from other groups[77,78] corroborate associations and predictive use of high-sensitivity TnI in patients receiving anthracyclines and trastuzumab, although these studies differed in study design and replication of findings. Although BNP and NT-proBNP are standard biomarkers used for the diagnosis and management of HF in the nononcology community,[2] their use in asymptomatic patients with cancer remains largely investigational. As such, there is a need for additional studies to clarify the role of cardiac troponins and natriuretic peptide assessment during cancer therapy.

Advances in echocardiographic imaging have facilitated the investigation of novel measures of cardiac function in patients with cancer. One of the most widely studied parameters for cardiotoxicity monitoring during cancer therapy is global longitudinal strain. Longitudinal strain is derived from apical images obtained via vendor-specific algorithms and reflects change in the distance between two segments of the heart relative to their baseline distance apart.[150] A prospective study of 81 patients with breast cancer evaluated the use of longitudinal strain assessed at baseline, after completion of anthracycline-based therapy, and every 3 months during trastuzumab.[78] Of note, the apex was excluded in all strain tracings secondary to poor visualization. A longitudinal strain value of greater than −19% (less negative or a lower negative number) after the completion of anthracyclines was predictive of cardiotoxicity, as defined by an asymptomatic decrease in LVEF of ≥ 10% to less than 55% or a symptomatic decrease in LVEF of ≥ 5% to less than 55%. Findings supporting the potential use of longitudinal strain have been corroborated by other investigators, whereby an 11% reduction in longitudinal strain was predictive of cardiotoxicity, as defined by a decrease in LVEF of ≥ 10%.[149] These two studies formed the basis for the development of the expert consensus for multimodality imaging in patients with cancer by the American Society of Echocardiography.[151] However, there have been no studies to demonstrate that early intervention based on change in strain alone can result in reduction of clinically significant (eg, symptomatic cardiac dysfunction) risk in patients with cancer. There are important studies under way that will provide insight into this question (eg, Strain Surveillance During Chemotherapy for Improving Cardiovascular Outcomes [SUCCOUR]). Such studies are needed to clarify the timing of screening and implementation of interventions based on change in strain alone in this population.

Clinical Question 5: What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.1. Clinicians should complete a careful history and physical examination in survivors of cancer previously treated with potentially cardiotoxic therapies.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.1.1. In individuals with clinical signs or symptoms concerning for cardiac dysfunction, the following approaches should be offered as part of recommended care:

- Echocardiogram for diagnostic workup

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Serum cardiac biomarkers (troponins, natriuretic peptides)

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Referral to a cardiologist based on findings

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction.

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.2.1. Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI.

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.3. Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram.

(Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care.

(Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Qualifying Statements

To make strong recommendations regarding the frequency and duration of long-term screening for a disease, there needs to be a clear understanding of the incidence and natural history of the

condition over time. There is currently a paucity of information regarding the true incidence and natural history of cardiac dysfunction after completion of cancer-directed therapy. Large longitudinal studies that have described the incidence of cardiac dysfunction have often relied on claims-based administrative data (eg, SEER-Medicare database, national registries).[35,43,54,55,68] However, this strategy may overestimate the true incidence of cardiac dysfunction because performance of a screening test to rule out HF may be falsely interpreted as a diagnosis of HF. In fact, a recent analysis[152] of the accuracy of such claims-based data revealed that the positive predictive value of HF or cardiomyopathy as a diagnosis ranged from 42% to 69% in survivors of cancer treated with potentially cardiotoxic therapies. Moreover, there are no studies that compare the efficacy of one cardiac surveillance timing or frequency to another in survivors of cancer. Finally, the existing AHA/ACC guidelines[2] for management of stage B disease recommend initiation of pharmacotherapy (eg, ACE inhibitors, β-blockers) for individuals with reduced LVEF, regardless of etiology. Therefore, it can be argued that repeated echocardiography is warranted for at-risk survivors of cancer to identify and intervene before onset of symptomatic disease (stage C or D).[153] However, it remains to be seen whether the full benefit of early detection and intervention will be realized in survivors of cancer whose cardiac insult was time limited rather than ongoing, such as in nononcology patients with myocardial injury as a result of coronary artery disease or progressive infiltrative disease. In survivors of cancer, there continue to be gaps in knowledge with regard to timing and choice of intervention (eg, pharmacotherapy, lifestyle modification, aggressive management of comorbidities), if any, for stage B disease.

Literature Review and Clinical Interpretation

Post-treatment history and physical examination (with attention to symptoms and signs of cardiac dysfunction, such as chest pain, shortness of breath, ankle swelling, decreased exercise tolerance, palpitations, and fainting/lightheadedness) are minimally burdensome and inexpensive. Clinical suspicion for cardiac disease should be high and the threshold for cardiac evaluation should be low in any survivor who has received potentially cardiotoxic therapy.

Although there is potential value to early diagnosis and treatment of cardiac dysfunction, it is important to note that screening for asymptomatic cardiac dysfunction using advanced imaging might lead to added distress in survivors of cancer. This may be especially true in survivors of cancer in whom the prevalence of cardiac dysfunction is expected to be low, because the positive predictive value of the screening test will be low as well. However, in certain higher risk (Recommendation 1.1) survivors, health care providers may consider imaging studies to evaluate cardiac function 6 ro 12 months after completion of therapy. This recommendation is based on knowledge that most cases of treatment-associated cardiac dysfunction develop within the first year after completion of therapy[27,65] and that the greatest improvement in cardiac function is likely to occur if pharmacotherapy is initiated closer to the cardiotoxic insult.[154]

Echocardiography has been the most widely used method for monitoring cardiac function after chemotherapy. In a 2014 guideline, the American Society of Echocardiography recommended three-dimensional echocardiograms, if available, because of a concern that two-dimensional echocardiography was only sensitive enough to detect changes in LVEF close to 10%.[152,155] However, the clinical relevance of detecting changes in LVEF less than 10% is questionable, and three-dimensional echocardiograms may not be widely available. Although one small study suggested that early decreases in contractile reserve during receipt of anthracycline seen by stress echocardiography might predict later cardiac impairment,[66] there is insufficient evidence for routine use of stress tests after treatment is completed in adult survivors of cancer.

Cardiac MRI–derived indexed left ventricular mass was found to be an independent predictor of a composite end point of cardiovascular death, implantable cardioverter-defibrillator placement, and admission for decompensated HF among 91 patients with reduced LVEF (mean, 35%) after anthracycline therapy.[28] A separate study[156] of cardiac MRI before, during, and after anthracycline-based chemotherapy for breast cancer reported that the magnitude of early gadolinium relative enhancement immediately after the first dose of anthracycline was predictive of later decline in LVEF by greater than 5%. Neither of these studies assessed the sensitivity or specificity of these parameters in survivors without known cardiac dysfunction. Thus, the clinical use of this test in asymptomatic survivors after completion of therapy remains to be determined. That said, in instances where echocardiography is not available or technically feasible (eg, poor image quality), cardiac MRI or MUGA may be considered for screening in higher-risk individuals; preference should be given to cardiac MRI because of its ability to provide detailed information regarding cardiac anatomy and systolic and diastolic function and lack of radiation emission.

TnI, troponin T, BNP, and NT-proBNP have shown promise as potential early biomarkers of cardiac dysfunction,[79,80,84,87,98,148,151] but the appropriate cutoff values for concern in the asymptomatic setting are not known. Moreover, whether there is any value to testing after completion of cancer-directed therapy in someone who did not have testing or evidence of biomarker changes during therapy is unclear.

Finally, although no randomized data are available to demonstrate that screening and aggressive management of cardiovascular risk factors (eg, smoking, hypertension, diabetes, dyslipidemia, physical inactivity, obesity) can result in improvement in long-term cardiac outcomes in survivors of cancer, studies in noncancer populations highlight the importance of vigilance and treatment of these modifiable risk factors,[2] a strategy strongly advocated in the current recommendations. A heart-healthy lifestyle, including the role of diet (healthy calories) and exercise, should be discussed as part of long-term follow-up care in at-risk survivors of cancer.

FUTURE DIRECTIONS FOR RESEARCH

Cardiac dysfunction developing during or after completion of cancer therapy is a growing heath concern that should be addressed in a multidisciplinary setting, taking into consideration the costs as well as risks and benefits of early screening and prevention. The Expert Panel endorses the recent collaborative effort by the

National Cancer Institute and the National Heart, Lung, and Blood Institute,[157] which has provided the framework for research to bridge the knowledge gaps highlighted in the current document. This call to action can set the stage for the next generation of studies to examine the cardiovascular pathogenic mechanisms associated with cancer treatment, as well as prevention of short- and long-term cardiovascular complications in survivors and cancer.

PATIENT AND CLINICIAN COMMUNICATION

Cardiac dysfunction is a serious adverse effect of certain cancer-directed therapies that can interfere with the efficacy of treatment, decrease quality of life, or impact the actual survival of the patient with cancer. It is important for oncologists and advanced care practitioners to initiate the discussion regarding the potential for cardiac dysfunction in individuals in whom the risk is sufficiently high before starting therapy. Hearing about potential complications from therapy early in the cancer journey can be difficult for patients with cancer to process, because their primary focus is surviving their malignancy. However, clear provider-patient communication may lead to appropriate monitoring and implementation of potential preventive strategies. A baseline cardiac dysfunction risk assessment by the oncology care provider(s) is important before therapy. For high-risk patients, a tailored and detailed plan for cardiac monitoring throughout treatment and beyond should also be established. Patients also need to be advised that cardiac dysfunction can be a progressive disorder and may initially be asymptomatic; therefore, early and late warning signs and symptoms should be discussed and reported to the primary oncology team or to a cardiologist. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed with all patients with cancer before and after completion of their cancer therapy.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[158] Racial and ethnic minorities with existing disparities in cardiovascular outcomes may have a substantially higher burden of cardiovascular complications during and after cancer treatment, in part because of inequities in the management of cardiovascular risk factors. African Americans, for example, have significantly higher rates of hypertension, diabetes, and cardiovascular disease–related complications when compared with nonminority groups.[159] At the same time, African American women with breast cancer have the poorest cancer-specific and overall survival, and a significant component of the disparity in mortality has been attributed to disparity in cardiovascular comorbidities.[159,160] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. These factors are especially relevant when developing population-based guidelines that call for advanced diagnostic technologies or subspecialty care that may not be readily available across all centers. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions (a situation in which the patient may have two or more such conditions, referred to as multiple chronic conditions [MCCs]) is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any surveillance and treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs, which highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

EXTERNAL REVIEW

The draft of this guideline was submitted to two ASCO external reviewers with content expertise. It was rated as high quality, and it was agreed that it would be useful in practice. In addition, the guideline was reviewed by two peer reviewers from the ACC and two reviewers from the AHA, as well as the AHA Science Advisory and Coordinating Committee. Their comments were reviewed by the Expert Panel and integrated into the final article before approval by the ASCO Clinical Practice Guideline Committee.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The

guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/cardiac-guideline. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers Guideline Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Saro Armenian	City of Hope	Co-chair, Steering Committee, Survivorship
Jean-Bernard Durand	The University of Texas MD Anderson Cancer Center	Co-chair, Steering Committee, Cardiology
Daniel Lenihan	Vanderbilt University	Steering Committee, Cardiology
Joseph Carver	University of Pennsylvania	Cardiology
Louis S. Constine	University of Rochester Medical Center	Radiation oncology
Susan Dent	The Ottawa Hospital Cancer Centre	Medical oncology
Pamela S. Douglas	Duke University	Cardiology/imaging
Michael Ewer	The University of Texas MD Anderson Cancer Center	Cardiology
Carol Fabian	University of Kansas Medical Center	Cancer prevention and survivorship
Melissa Hudson	St Jude Children's Research Hospital	Survivorship
Lee W. Jones	Memorial Sloan Kettering Cancer Center	Exercise physiology
Bonnie Ky	Hospital of the University of Pennsylvania	Cardiology/biomarkers
Kevin Oeffinger	Memorial Sloan Kettering Cancer Center	Family medicine
Neelima Denduluri	Virginia Cancer Specialists	Medical oncology, ASCO Practice Guidelines Implementation Network representative
Kathryn Ruddy	Mayo Clinic	Medical oncology
Erica L. Mayer	Dana-Farber Cancer Institute	Medical oncology
Javid Moslehi	Vanderbilt University	Cardio-oncology
Katharine Ray	Communications and Brand Professional	Patient representative
Ana Barac	Medstar Heart Institute, Medstar Washington Hospital Center	American College of Cardiology representative
Mariell Jessup	University of Pennsylvania	American Heart Association representative

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