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

• With longer survival, attention to the chronic and long-term adverse treatment effects has become increasingly important in cancer treatment and supportive care.

• Heart failure (HF), presenting during or after completion of cancer treatment, is a well-recognized complication impacting survival and quality of life.

• In recognition of the increasing need for guidance, the American Society of Clinical Oncology (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.
ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/cardiac-guideline
Clinical Questions

This clinical practice guideline addresses five overarching clinical questions:

(1) Which cancer patients are at increased risk for developing cardiac dysfunction?

(2) Which preventative strategies minimize risk *prior to* 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 / monitoring approaches *during* treatment in patients at risk for cardiac dysfunction?

(5) What are the preferred surveillance/ monitoring approaches *after* treatment in patients at risk for cardiac dysfunction?
Target Population and Audience

Target Population
Adults with cancer for whom cardiotoxic anti-cancer therapies are being considered

Target Audience
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.
Summary of Recommendations

CLINICAL QUESTION 1
Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation 1.1
It is recommended that cancer patients 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 (e.g. ≥250 mg/m² doxorubicin, ≥600 mg/m² epirubicin)
• High dose (≥30 Gy) radiotherapy where the heart is in the treatment field
• Lower dose anthracycline (e.g. <250 mg/m² doxorubicin, <600 mg/m² epirubicin) in combination with lower dose radiotherapy (<30 Gy) where the heart is in the treatment field

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Summary of Recommendations

• Treatment with lower dose anthracycline (e.g. <250 mg/m² doxorubicin, <600 mg/m² epirubicin) or trastuzumab alone, and presence of any of the following risk factors:
  – Multiple (≥2) cardiovascular risk factors, including: smoking, hypertension, diabetes, dyslipidemia, obesity during or after completion of therapy
  – Older (≥60 years) age at cancer treatment
  – Compromised cardiac function (e.g. borderline low LVEF [50-55%], history of myocardial infarction, >moderate valvular heart disease) at any time prior to or during treatment
• Treatment with lower dose anthracycline (e.g. <250 mg/m² doxorubicin, <600 mg/m² epirubicin) followed by trastuzumab (sequential therapy)
  (Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of the Recommendation: Moderate)
Summary of Recommendations

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

- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin, <600 mg/m² epirubicin) or trastuzumab alone, and no additional risk factors (as defined in 1.1)
- Lower dose radiotherapy (<30 Gy) where the heart is in the treatment field, and no additional cardiotoxic therapeutic exposures or risk factors (as defined in 1.1)
- Kinase inhibitors

*(Evidence-based; Evidence quality: Low)*
Summary of Recommendations

CLINICAL QUESTION 2
Which preventative strategies minimize risk prior to 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 cancer patients that includes a history and physical examination, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram prior to initiation of potentially cardiotoxic therapies (Evidence and consensus-based; Benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong).

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Summary of Recommendations

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 (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, or continuous infusion, or liposomal formulation of doxorubicin for prevention of cardiotoxicity in patients planning to receive high-dose (e.g. ≥250 mg/m2 doxorubicin, ≥600 mg/m2 epirubicin) anthracyclines (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:

• Deep inspiration breath-holding for patients with mediastinal tumors or breast cancer in which the heart might be exposed.

• Intensity modulated radiation therapy that varies the radiation energy while treatment is delivered in order 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)
Summary of Recommendations

CLINICAL QUESTION 4
What are the preferred surveillance / 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 work-up (Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Strong)
- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (e.g. 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)
Summary of Recommendations

**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 healthcare providers based upon 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/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/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 healthcare providers, based upon clinical judgment and patient circumstances (Evidence-based and Informal Consensus; Benefits outweigh harms; Evidence quality: Low; Strength of Recommendation: Moderate).
Summary of Recommendations

CLINICAL QUESTION 5
What are the preferred surveillance/monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.1
Clinicians should complete a careful history and physical examination in cancer survivors previously treated with potentially cardiotoxic therapies (Informal Consensus; Benefits outweigh harms; Evidence quality: Insufficient; Strength of Recommendation: Strong).

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Summary of Recommendations

**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 work-up (*Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Strong*).
- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (e.g. 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*).

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Summary of Recommendations

**Recommendation 5.2**
An echocardiogram may be performed between 6 to 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 (e.g. 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 for further assessment and management (*Informal consensus; benefits outweigh harms; Evidence quality: Insufficient; Strength of Recommendation: Strong*).
Summary of Recommendations

**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 during their 6-12 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*).
Future Directions for Research

• Cardiac dysfunction developing during or after completion of cancer therapy is a growing health concern that should be addressed in a multi-disciplinary 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 (NCI) and the National Heart, Lung, and Blood Institute (NHLBI)\(^1\) 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 cancer survivors.

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Patient and Clinician Communication

• Cardiac dysfunction is a serious side 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 cancer patient.

• It is important for oncologists and advanced care practitioners to initiate the discussion regarding the potential for cardiac dysfunction in individuals where the risk is sufficiently high, prior to start of therapy.

• For high risk patients, a tailored and detailed plan for cardiac monitoring throughout treatment and beyond should be established.

• A heart-healthy lifestyle including the role of diet and exercise should be discussed with all cancer patients prior to and following completion of their cancer therapy.
Health Disparities

• Racial and ethnic minorities with existing disparities in cardiovascular outcomes may have a substantially higher burden of cardiovascular complications during and after cancer treatment, due in part to 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 to non-minority groups.²

• 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.²,³

• Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities.

• 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.
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/cardiac-guideline

Patient information is available at www.cancer.net
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References


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