Chapter 26
Chemotherapy, Cardiovascular Disease, and Cardiac Tumors

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Cardiotoxicity of Common Chemotherapy (Anthracyclines, Trastuzumab, and Anti-VEGF Treatments)

Background: New treatment strategies in oncology have greatly improved prognosis and survival of cancer patients [1–3]. As the utility of these chemotherapeutic drugs increases, the possible cardiotoxic effects of these agents become more apparent [4]. Chemotherapeutic agents can cause acute and chronic cardiovascular toxicity including hypertension, thromboembolism, pericarditis, coronary artery disease resulting in early and late myocardial ischemia, cardiomyocyte damage (immune and non-immune mediated) leading to cardiomyopathy, myocarditis, early and late conduction abnormalities, and valvular abnormalities [5–10] (Figure 26.1 showing an overview of the cardiovascular side effects of chemotherapy and radiation).

Anthracyclines: Highly effective antibiotic-based chemotherapeutic agents commonly used in the treatment of solid-tumor and hematologic malignancies including leukemias, lymphomas, and sarcomas [11]

- Initially discovered in the late 1950s from *Streptomyces* bacterium species (*Streptomyces peucetius* var. *caesius*)
- Anti-tumor effects [12]
  - Occur by preventing DNA and RNA synthesis by intercalating between nucleic acid base pairs, thereby inhibiting replication of rapidly proliferating cancer cells

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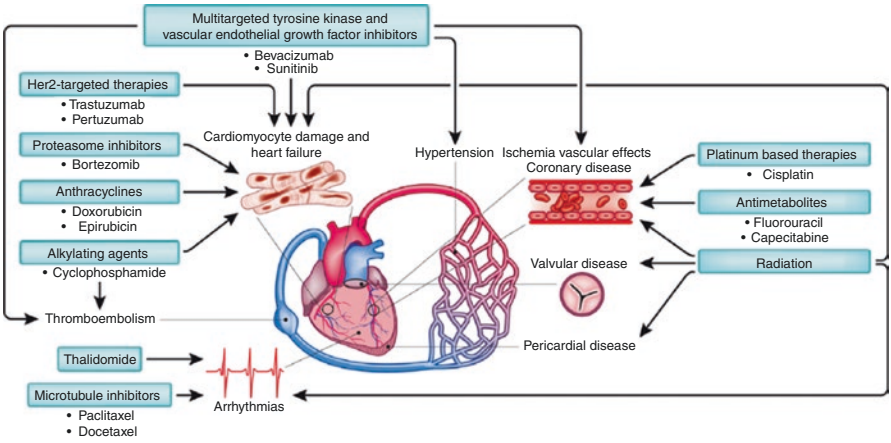

Fig. 26.1 An overview of the cardiovascular side effects of chemotherapy and radiation. Reproduced with permission from Carrie GL [13] Circ Res. 2016 Mar 18;118(6):1008–20, Copyright © Wolters Kluwer Health, Inc.

  - May inhibit the action of topoisomerase II enzyme, which in turn prevents relaxation of supercoiled double-helix DNA, thus blocking DNA transcription and replication
  - Seem to generate free oxygen radicals that may damage DNA, proteins, and cell membranes

- Possible mechanisms of anthracycline-induced cardiotoxicity [13]
  - May impair removal of cytosolic calcium
  - Reduce loading of the sarcoplasmic reticulum
  - Induce defective calcium release leading to impaired myocyte contraction and relaxation
  - Alteration of SERCA2 pump—leading to calcium mishandling
  - Promotion of free radicals leading to apoptosis (Fig. 26.2a–c)

Cardiotoxicity remains the major limitation for use of anthracyclines.

1. **Epidemiology of anthracycline-induced cardiotoxicity** [14, 15]**:**
   (a) 5–23% of patients expose to anthracycline will develop short- and/or long-term left ventricular dysfunction and heart failure.
   (b) The risk for cardiotoxicity and subsequently heart failure depends on the cumulative exposure dose.
      - 5% risk of heart failure at 400 mg/m [2]
      - 25% risk of heart failure at 700 mg/m [2]
   (c) Other risk factors for cardiac toxicity:
      - Both extreme of age (<18 or >60)
      - HTN
      - LVH

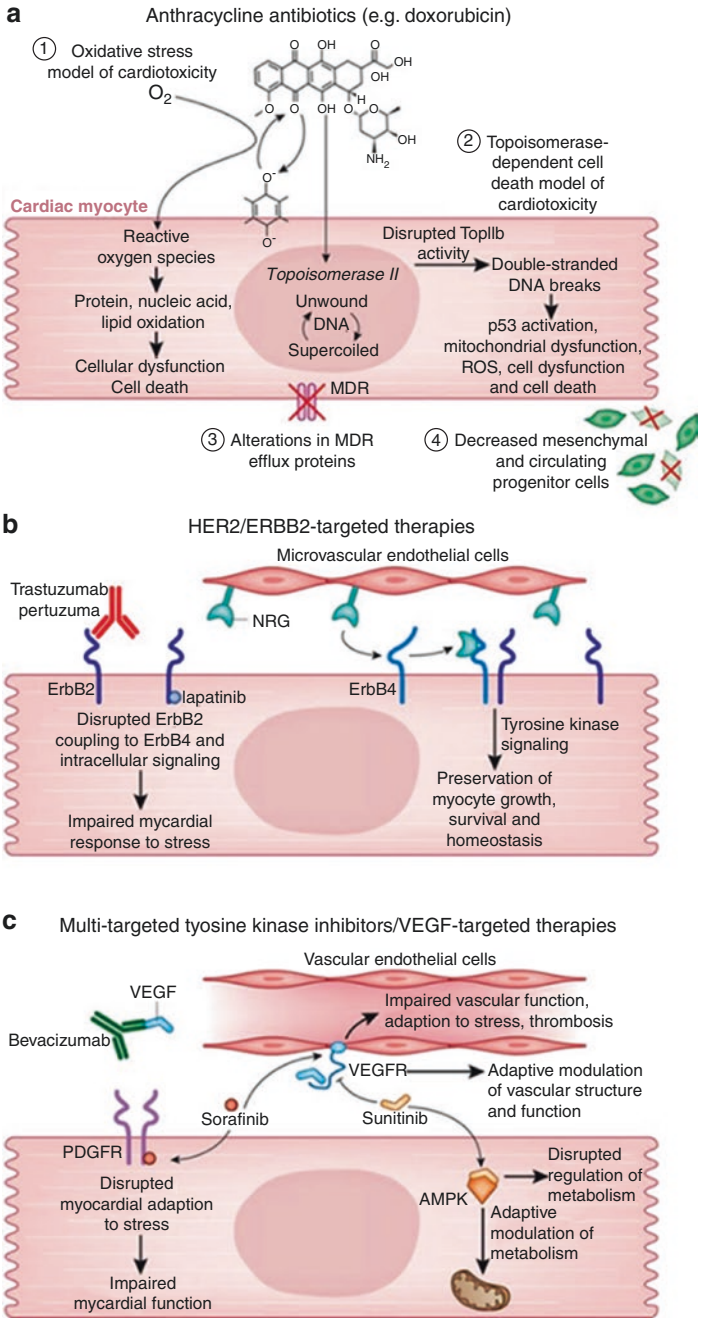

Fig. 26.2 Molecular pathways involved in cardiotoxicity related to anthracyclines and HER2-targeted and tyrosine kinase inhibitors/vascular endothelial growth factor (VEGF) inhibitors. Reproduced with permission from Carrie GL [13] Circ Res. 2016 Mar 18;118(6):1008–20, Copyright © Wolters Kluwer Health, Inc.

- Type II DM
- Prior or concomitant chemo/XRT
- Hematopoietic cell transplantation
- Tobacco habituation

(d) Timing:
- Acute cardiotoxicity: occurs at the time of infusion
- Early cardiotoxicity: occurs within 1 year of exposure
- Late cardiotoxicity: occurs within 1–20 years of exposure

2. Examples of anthracyclines and tumors they treat [11]:
   (a) *Doxorubicin and epirubicin*: breast cancer, pediatric solid tumors, sarcomas, and lymphomas
   (b) *Daunorubicin*: acute lymphoblastic or myeloblastic leukemias
   (c) *Idarubicin*: multiple myeloma, non-Hodgkin's lymphomas, and breast cancer
   (d) *Nemorubicin*: hepatocellular carcinoma
   (e) *Pixantrone*: non-Hodgkin's lymphomas
   (f) *Sabarubicin*: non-small cell lung cancer, metastatic prostate cancer, and ovarian cancer
   (g) *Valrubicin*: bladder cancer

Molecularly Targeted Chemotherapeutic Agents

Her-2 Receptor [16]

- A receptor kinase involved in normal cell growth.
  - Also called ERBB2, human EGF receptor 2, and human epidermal growth factor receptor 2.
  - Overexpressed in subset of breast, ovarian, and possibly colon cancers.
  - May be a target for cancer treatment.
  - Inhibition of ERBB2 in cardiomyocytes interferes with growth, repair, and survival of cardiomyocytes.
    May result in ATP depletion and contractile dysfunction
- A signaling pathway independent of ERBB2 signaling may also exist in which there is immune-mediated destruction of cardiomyocytes (see Figure 26.3 showing ERBB2 signaling and inhibition in breast cancer and cardiomyocytes).

Epidemiology

1. Close to 30% of women treated initially with anthracyclines and subsequently with HER-2 neu-targeted agents have developed cardiotoxicity.
2. Patients identified as at increased risk for developing cardiotoxicity include:
   (a) Standard risk factors for developing structural heart disease

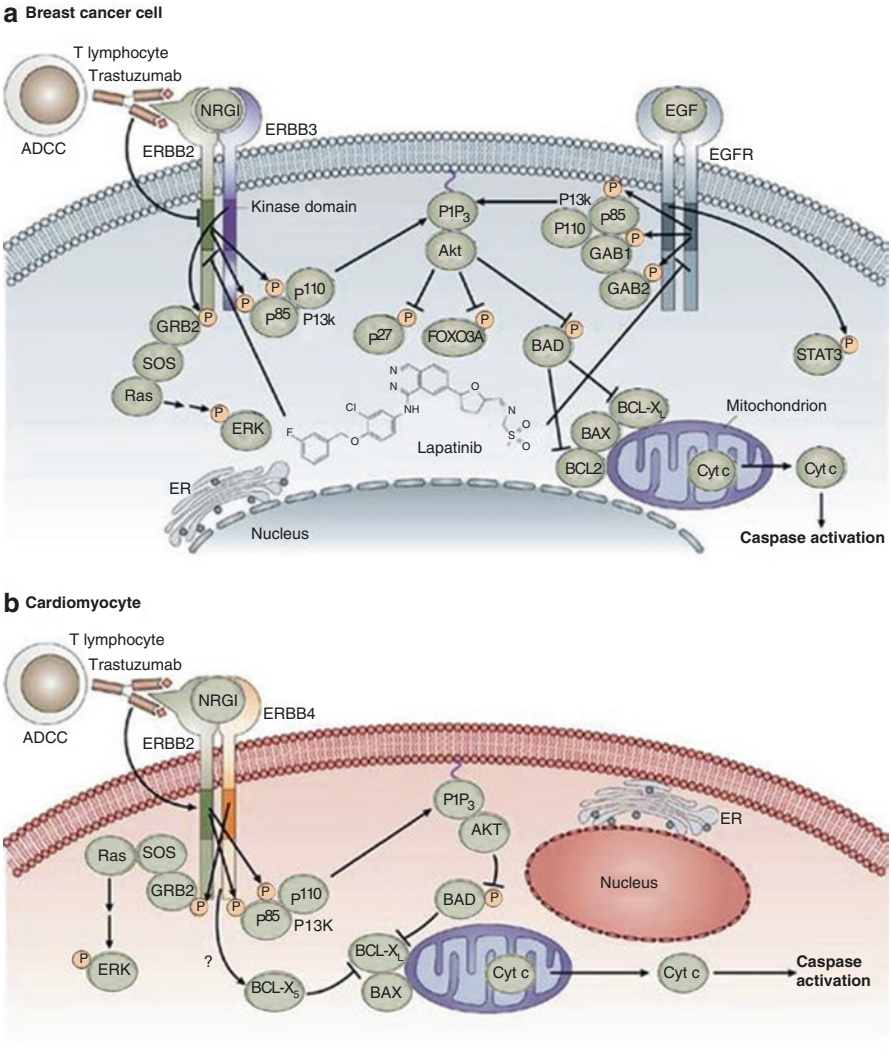

Fig. 26.3 ERBB2 signaling and inhibition in breast cancer and cardiomyocytes. Reproduced with permission from Force, T. et al. Nature Reviews Cancer 7, 332–44 (May 2007), Copyright ©

(b) Previous doxorubicin exposure
(c) Previous chest wall irradiation
(d) Obesity

3. Reversibility—largely possible but not necessarily 100%

Inhibition of Vascular Endothelial Growth Factor (VEGF) Signaling Pathways [17]

1. VEGF is expressed in endothelin cells and within the kidney and plays a role in producing nitric oxide and prostacyclin and decreasing production of endothelin-1, a potent vasoconstrictor.
2. VEGF is secreted by tumors and plays a key role in angiogenesis by binding to VEGF receptors and activating VEGF signaling pathways.
   (a) Chemotherapeutic agents that inhibit VEGF (monoclonal antibodies or small molecules) appear to downregulate nitric oxide and prostacyclin production and increase endothelin production (see Fig. 26.4, mechanisms of VEGF-/VEGFR-mediated protection of cardiomyocytes).
3. Cardiovascular side effects of VEGF signaling inhibitors:
   (b) Hypertension
   - Appears to occur within 1 week of initiation and seems to occur in a dose-dependent and transient manner.
   - The overall incidence of HTN ranges from 20 to 25% with bevacizumab and sunitinib to >50% with newer agents.

   (c) Vascular thrombosis
   (d) Cardiomyopathy
   - **Detection** [18–21]: At present, there are no consensus guidelines for early detection for adults undergoing chemotherapy. However, there are surveillance strategies being developed to identify patients at risk for developing

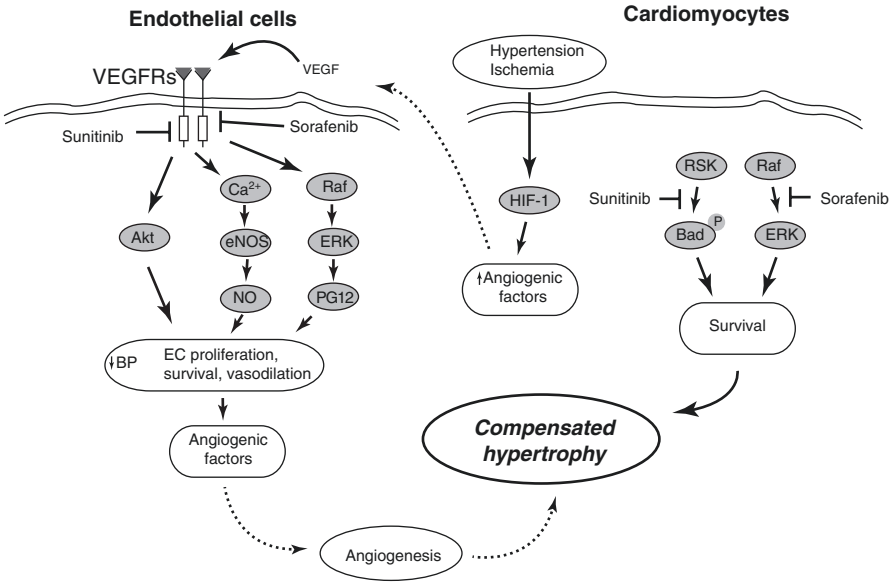

Fig. 26.4 Mechanisms of VEGF-/VEGFR-mediated protection of cardiomyocytes from pressure stress and ischemia and potential interactions of sunitinib and sorafenib. Reprinted with permission Circulation. 2008;118:84–95, Copyright ©

subclinical cardiotoxicity. These include ECG, multimodality imaging strategies, and novel biomarkers that may be useful in the early identification of patients developing subclinical chemotherapy-induced cardiotoxicity.

- **Electrocardiography:**
  - Early predictor of drug-induced cardiomyopathy
  - Limb lead QRS voltage decrease by ≥30%
- **Imaging:**

  Echocardiogram:
  - The preferred imaging modality to monitor LVEF pre- and postexposure to cardiotoxic chemotherapy agents.
    - Widespread availability and absence of radiation exposure
  - 3D echo produces additional benefit over 2D.
    - Improved accuracy and reproducibility
  - Tissue Doppler and Strain:
    - Global longitudinal strain may provide early detection of myocardial dysfunction by measuring the degree of myocardial deformity.
    - Measurement of left ventricular systolic function not left ventricular ejection fraction

  Nuclear imaging:
  - An alternative to echocardiography especially when results are suboptimal.
  - MUGA scans provide a more precise measure of LVEF compared with an echocardiogram.

  Cardiac MRI:
  - Indicated when echocardiography or nuclear results are inconclusive or inconsistent

- **Biomarkers:** may provide earlier detection of cardiac damage before LV dysfunctions take place. Serum troponin release is a marker of cardiac microscopic and/or macroscopic injury with some correlation with the dose of chemotherapy. It has been monitored in high-risk patients undergoing doxorubicin treatment and shown to potentially identify patient at risk for developing subsequent LV dysfunction. BNP is an established biomarker of LV dysfunction/heart failure and may be followed serially prior to development of LV dysfunction on less-sensitive modalities such as cardiac imaging. Once left ventricular dysfunction occurs, the compensatory mechanism of the myocardium has already been compromised. Biomarkers may provide earlier detection of cardiac damage before LV dysfunctions take place.

  Serum troponins:
  - Marker of cardiac injury that may have some correlation with the dose of doxorubicin used
  - If troponins remain positive, may predict long-term development of left ventricular dysfunction

  BNP:
  - Although an established biomarker of heart failure, its use in identifying asymptomatic left ventricular dysfunction is controversial.

- **Treatment:** Currently, there are no guidelines from the ACC, AHA, and HFSA regarding the treatment and management of chemo-induced cardiotoxicity. The general consensus from experts is the initiation of angiotensin-converting enzyme inhibitor, beta blocker, and statin for patients who develop left ventricular dysfunction or to prophylactically treat patients that are deemed to be at high risk of developing cardiotoxicity. Classes of medications that may increase SERCA2 expression/function include angiotensin-converting enzymes and beta blockers.
  - **ACEi:**
    - Showed in prospective studies to improve LVEF in women treated with epirubicin for metastatic breast cancer
  - **Beta blocker:**
    - Small randomized trials have suggested the use of carvedilol or nebivolol that may have a protective effect.
      - Carvedilol
        - May be important in upregulating mitochondrial SERCA2 expression and function thereby preventing intracellular calcium mishandling
        - May prevent mitochondrial dysfunction and alleviate oxidative stress
  - **Statins:**
    - Appear to exert their effects by decreasing oxidative stress and inflammation
    - May have cardioprotective effects against chemotherapy induced cardiotoxicity
  - **Dexrazoxane (Zinecard)**
    - A derivative of EDTA found to be a potent intracellular chelating agent
    - The only drug approved by the FDA to prevent cardiotoxic effect of anthracycline
    - May help prevent cardiotoxicity in selected cardiovascular high-risk breast cancer patients treated with doxorubicin

Take-Home Message: Cardioprotective strategies include general cardiovascular risk factor modifications (treatment of hypertension, diabetes, hyperlipidemia, coronary artery disease).

ASCO Guidelines Cardiotoxicity

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American Society of Clinical Oncology Clinical Practice Guideline recommendations for prevention and monitoring of cardiac dysfunction before, during, and after treatment with potentially cardiotoxic agents:

1. Minimize risk before therapy (ASCO *Clinical Practice Guideline* **Recommendation 2**)
   - Avoid or minimize potentially cardiotoxic therapies if alternative therapy exists and that would not compromise outcomes.

- Perform a comprehensive assessment with a history and physical examination, screening for cardiovascular disease, and an echocardiogram before initiating therapy.

2. Minimize risk during therapy (ASCO *Clinical Practice Guideline* **Recommendation 3**)
   - Screen for and actively manage cardiovascular risk factors.
   - Incorporate strategies, including the use of dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin, for prevention of cardiotoxicity in patients planning to receive high dose of anthracyclines.
   - Select lower radiation doses when clinically appropriate and exclude as much of the heart as possible for patients who require mediastinal radiation therapy.
3. Surveillance and monitoring during treatment (ASCO *Clinical Practice Guideline* **Recommendation 4**)
   - Complete a careful history and physical examination in patients who are receiving potentially cardiotoxic treatments.
   - If patients develop clinical signs or symptoms that are concerning for cardiac dysfunction during treatment, perform a diagnostic echocardiogram.
   - Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (preference given to cardiac MRI).
   - Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging.
   - Referral to a cardiologist.
4. Surveillance and monitoring after treatment (ASCO *Clinical Practice Guideline* **Recommendation 5**)
   - Complete history and physical examination on cancer patient who were previously treated with cardiotoxic therapies.
   - If patients develop clinical signs or symptoms that are concerning for cardiac dysfunction after treatment, perform a diagnostic echocardiogram.
   - Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible.
   - Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging.
   - Referral to a cardiologist.
   - Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is available or technically feasible (preference given to cardiac MRI).

Cardiac Tumors

- **Background and Epidemiology** [22–24]
  - Occur in 1 per 300–100,000 autopsies.
  - In adults, ~75% of all primary cardiac tumors are benign.
  - In children, ~90% of the primary cardiac tumors are benign.

  - Most common in adults:
    - Myxoma (40% of all primary cardiac tumors)
    - Papillary fibroelastoma (8%)
    - Rhabdomyoma
    - Lipomatous hypertrophy
  - Most common in pediatric:
    - Rhabdomyoma
    - Fibroma
    - Teratoma
  - Secondary cardiac tumors:
    - 20–40 times more common than primary tumors.
    - Occurs mainly with extensive metastatic cancer.
    - See Fig. 26.5 for common distribution of cardiac masses.
    - See Fig. 26.6 for a diagnostic algorithm for evaluation of a cardiac mass.
- **Clinical Presentation** [25–27]
  - Determined by location rather than histopathology
  - Can present with both cardiac and non-cardiac manifestations
  - Obstruction (valvular), embolic (TIA/CVA), and constitutional (weight loss, fever, fatigue, dyspnea, and malaise)

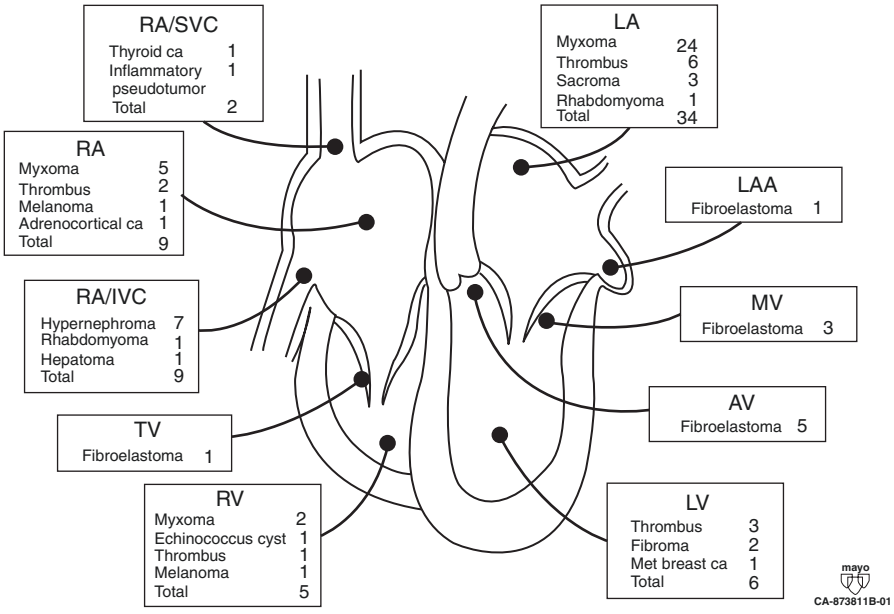

Fig. 26.5 Distribution of cardiac masses. Reprinted from Dujardin KS, Click RL & Oh TK, The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal, J Am Soc Echocardiogr 13: 12, 1080–1083, Copyright © (2000), with permission from Elsevier

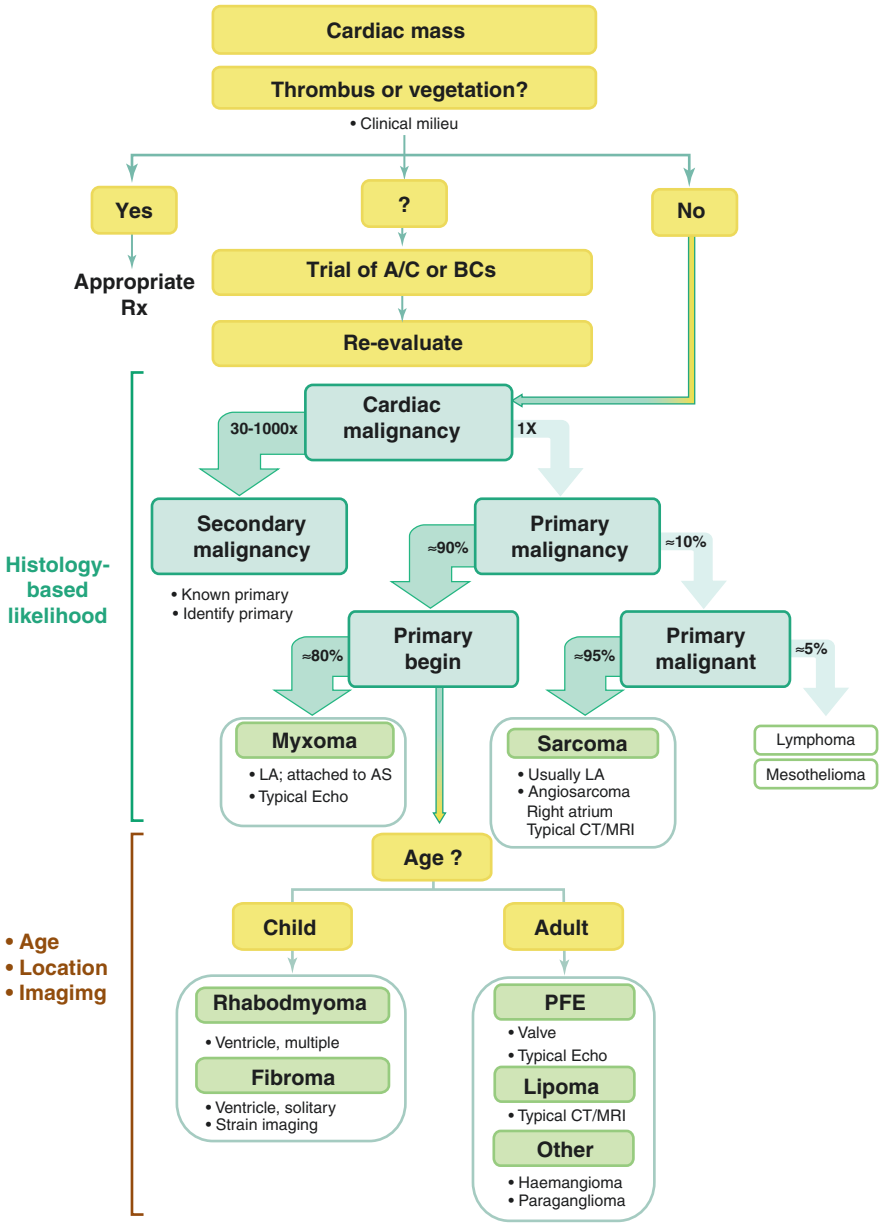

Fig. 26.6 Diagnostic algorithm for evaluation of a cardiac mass. Reproduced from Cardiac tumours: diagnosis and management, Charles JB, Heart 2011; 97:151–160, Copyright © 2011 with permission from BMJ Publishing Group Ltd. [22]

- **Detection**
  - **Echocardiography** [28, 29]
    - Initial imaging method of choice
    - Noninvasive, inexpensive, simple, and widely used
  - **CT** [30–34]
    - When MRI is not available
  - **MRI** [32]
    - ECG-gated MR is the imaging modality of choice.
    - Can offer clues as to the type of tumors.
    - Provides high temporal resolution and excellent soft-tissue contrast.
- **Primary Benign Cardiac Tumors** [22]
  - **Myxoma**
    - Most common primary tumor
    - Sporadic: 90% occur in atria, 80% on left side
    - Pedunculated tumors
    - Usual symptoms: due to obstruction, emboli, and constitutional
    - Familial with Carney syndrome: 10% of the cases, autosomal dominant with extra-cardiac manifestation (blue nevus, schwannomas, skin pigmentation, and endocrine dysfunction)
    - Treatment: excision
  - **Lipomatous hypertrophy**
    - Rare cardiac tumors.
    - Usually confined to atrium with sparing of the fossa ovalis.
    - Septal thickness is 2–7 cm.
    - Usual symptoms: congestive heart failure, atrial fibrillation, supraventricular tachycardia, syncope, dysthymias, and sudden cardiac death.
    - Treatment: none.
  - **Lambl excrescence**
    - Filamentous strands seen originating from the aortic valve.
    - Also called valvular strands.
    - Usually in the elderly population.
    - Associated with stroke.
    - Looks very fragile and delicate.
    - Generally, there is absence of any clinical evidence of valvular dysfunction.
    - Treatment:
      - If no history of TIA/CVA, conservative management
      - If TIA/CVA (no anticoagulation), warfarin, or ASA and clopidogrel
      - If TIA/CVA (on anticoagulation), surgical debridement
  - **Fibroma**
    - Rare in adults but very common in the pediatric population
    - Found in 10% of Gorlin syndrome patients (nevoid-basal cell carcinoma syndrome)
    - Treatment: excision or possibly transplant

  - **Rhabdomyoma**
    - 50–90% of primary tumors in the pediatric population
    - May present with valvular obstruction or sudden cardiac death
    - Treatment: Usually regresses spontaneously, surgical intervention only if outflow obstruction or dysrhythmia
- **Primary Malignant Cardiac Tumors** [22]
  - Constitute 15% of primary cardiac tumors; most common are the sarcomas.
  - **Angiosarcoma**
    - Most common primary malignancy in adults
    - Mostly atrium (right more than left)
    - Male predominance
    - Treatment: very poor prognosis and death usually within months
  - **Rhabdomyosarcoma**
    - Most common cardiac malignancy in infants and children
    - Usually metastases to the lung, GI tract, and kidney
    - Treatment: surgical resection and chemotherapy
  - **Leiomyosarcoma**
    - Usually very poor prognosis
    - Arises from the pulmonary veins and arteries
    - Associated with EBV in cardiac transplantation
  - **Lymphoma:**
    - Associated with immunocompromised states
    - Usually diffuse large B cell lymphoma
    - Poor prognosis
  - **Posttransplant lymphoproliferative disorder**
    - Lymphoid proliferations that occur in the setting of organ transplantation as a result of immunosuppression
    - Mostly related to B cell proliferation secondary to infection with Epstein-Barr virus
    - Treatment: antiviral prophylaxis and early tapering immunosuppressive therapy
- **Secondary Cardiac Tumors** [22]
  - Metastatic involvement of the heart is relatively common.
  - Reflects the aggressiveness of the individual malignancy.
  - Virtually any primary malignancy may metastasize to the heart, however, the most often encountered primaries comprise:
  - They may arise from:
    - Lung, breast, kidney, and thyroid carcinomas and malignant melanomas.
    - Other common sources are lymphomyeloproliferative types, lymphoma, and leukemia.

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